FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

Addressing the Threat of Drug-Resistant Tuberculosis

A Realistic Assessment of the Challenge

WORKSHOP SUMMARY

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Addressing the Threat of Drug-Resistant Tuberculosis

A Realistic Assessment of the Challenge

W O R K S H O P S U M M A R Y

Robert Giffin and Sally Robinson, *Rapporteurs*

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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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 over-

seen by **Barry R. Bloom,** Harvard School of Public Health. 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

ACH	air changes per hour
ACT	artemisinin combination therapy
ACTG	AIDS Clinical Trial Group
AFRO	African regional office
AIDS	acquired immune deficiency syndrome
ANRS	French National Agency for AIDS Research
ATP	adenosine triphosphate
CDC	U.S. Centers for Disease Control and Prevention
CGD	Center for Global Development
DOTS	directly observed treatment, short course
DST	drug susceptibility testing
EMEA	European Medicines Agency
FDA	U.S. Food and Drug Administration
FIND	Foundation for Innovative New Diagnostics
GDF	Global Drug Facility
GLC	Green Light Committee
GLI	Global Laboratory Initiative
HIV	human immunodeficiency virus

IDA	International Dispensary Association
IHR	International Health Regulations
IOM	Institute of Medicine
IT	information technology
IUATLD	International Union Against Tuberculosis and Lung Disease
LIMS	laboratory information management system
MDR TB	multidrug-resistant tuberculosis
MEND	Medicine in Need
MIRU	mycobacterial interspersed repetitive unit
MRSA	methicillin-resistant *Staphylococcus aureus*
MSH	Management Sciences for Health
NGO	nongovernmental organization
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PCR	polymerase chain reaction
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PETT	CDC's Preserving Effectiveness of TB Treatment study
PHLIP	Public Health Laboratory Interoperability Project
POC	point of care
PRV	priority review voucher
R&D	research and development
RFLP	restriction fragment length polymorphism
SA	*Staphylococcus aureus*
SRL	Global Supranational Reference Laboratory
TB	tuberculosis
UNICEF	United Nations Children's Fund
USAID	U.S. Agency for International Development
UV	ultraviolet
WHO	World Health Organization
XDR TB	extensively drug-resistant tuberculosis

Summary

Tuberculosis (TB) kills more than 4,500 people each day worldwide; approximately 1.7 million TB deaths occurred in 2006 alone (WHO, 2008a). TB is second only to AIDS as the leading infectious disease–related cause of adult deaths. Although antibiotic treatment for TB was discovered more than half a century ago, an estimated one-third of the world's population is currently infected with *Mycobacterium tuberculosis* (Keshavjee and Seung, 2008), and 9.2 million new cases of active TB are estimated to occur around the world annually (WHO, 2008a).

A large percentage of TB cases can be treated effectively with available antibiotics. But multidrug-resistant TB (MDR TB)—strains of TB that are resistant to the two principal first-line TB drugs—is a major and growing global problem. While MDR TB has been under control in the United States since it was first recognized, worldwide an estimated 4.8 percent of all new and previously treated TB cases diagnosed in 2006—nearly half a million cases—were MDR according to the World Health Organization (WHO, 2008b). These cases are considered by many to be a substantial underestimate. Moreover, some strains of TB—termed extensively drug-resistant TB (XDR TB)—are resistant even to second-line therapies, and strains of TB that are totally resistant to all drugs are now emerging.

The combination of HIV and TB has proven to be especially deadly. At least one-third of the 33 million people living with HIV worldwide are coinfected with TB (WHO, 2008c). As a result of their weakened immune system, HIV-positive patients often develop active TB. In 2000, TB was identified as the cause of 11 percent of all AIDS-related deaths (Corbett et al., 2003).

The global health apparatus has been slow to respond to the transformation of TB into highly drug-resistant forms. Outmoded techniques for diagnosis and treatment are still common throughout the world, and only a small fraction of MDR TB worldwide is currently diagnosed and treated. The characterization and epidemiology of MDR TB have been slow to emerge. Only 11 of the 22 highest-burden TB countries provide data on drug-resistant TB, and even fewer have the capability to assess patients' susceptibility to the second-line drugs used to treat MDR TB. Severe problems exist in the supply of drugs, and adequate health systems for delivering treatment to patients are lacking. When treatment is delivered, moreover, it is often inappropriate or incomplete. The failures of the system are themselves adding to the problem—when treatment is inadequate or interrupted, drug resistance accelerates.

WORKSHOP OBJECTIVES

To examine these issues and explore strategies for enhancing the global response to MDR TB, the Institute of Medicine's (IOM's) Forum on Drug Discovery, Development, and Translation held a workshop in Washington, DC, on November 5, 2008. The goals of this workshop were to understand the magnitude and nature of the drug resistance problem; to assess the adequacy of the current global response; and to examine key obstacles to effective diagnosis and treatment, including inadequate diagnostic capacity, a lack of new drugs, bottlenecks in the supply chain of existing drugs, drugs that are counterfeit or of poor quality, suboptimal treatment regimens and patient management practices, inadequate infection control, inadequate in-country health systems, and a lack of resources. The workshop brought together a wide range of experts and organizations engaged in the global effort to combat TB to share information, develop an understanding of the challenges, and consider opportunities and strategies for confronting the problem. Speakers from around the world presented data and described firsthand their experiences with MDR and XDR TB in multiple countries, including China, Cambodia, Ethiopia, Russia, and South Africa. In addition, to provide baseline information on MDR TB and outline the issues for discussion during the workshop, the IOM commissioned a white paper from Partners In Health.

The workshop presentations and discussions focused attention on seven key issues:

1. Limitations of global TB estimates,
2. The role of HIV in the spread of MDR TB,
3. The importance of infection/transmission control,
4. Limited diagnostic capacity,
5. Low rates of treatment,

6. Bottlenecks in the procurement and distribution of high-quality drugs, and
7. The need for new TB drugs.

ISSUES

Limitations of Global TB Estimates

WHO has estimated that of the more than 9 million cases of TB in 2006, approximately half a million (or 4.8 percent) were MDR TB, and about 40,000 (or 0.4 percent) were XDR TB (Nunn, 2008) (see Table S-1). Many consider these to be underestimates of the actual incidence of drug-resistant TB, however, for several reasons. First, drug resistance surveys have not been conducted in 25 of the 46 countries in Africa. Second, in many countries, the availability of diagnostic laboratories is limited; for example, 9 African countries lack even a single reference laboratory capable of culturing TB and making a diagnosis. Further, current drug resistance surveys include only smear-positive TB cases, yet not all MDR TB cases are smear positive. In particular, in many countries with a high TB burden, the incidence of HIV infection is also very high, and HIV-positive TB patients are more likely than other TB patients to be smear negative. It was pointed out during the workshop that underreporting of rates of infection may have serious consequences, since it may weaken the political will to take appropriate measures to combat the MDR TB threat.

Role of HIV in the Spread of MDR TB

As noted, individuals who are HIV positive have compromised immune systems and are thus more susceptible than the general population to TB

TABLE S-1 Estimated Number of TB Cases and Number of Deaths, by Type, 2006

Form of TB	Estimated Number of Cases	Estimated Number of Deaths
All forms	9,200,000	1,650,000
Multidrug-resistant (MDR TB)	489,000	120,000
Extensively drug-resistant (XDR TB)	40,000	20,000
HIV-associated	700,000	200,000

SOURCE: Nunn, 2008. (The data on total cases and deaths are from WHO, 2008a; the number of MDR TB cases is from WHO, 2008b; the deaths from MDR and XDR TB were estimated by Nunn's team from published literature using the case numbers listed in the table; and the number of XDR TB cases [according to the revised October 2006 definition of XDR TB] was estimated from the MDR TB number listed in the table using the percentages from CDC, 2006.)

infection. Coinfection with HIV and MDR TB has received particular attention in Africa, although it is also a growing problem in Eastern Europe. The progression of the TB epidemic in KwaZulu-Natal, South Africa, for example, has been closely intertwined with that of HIV. A large percentage of the province's residents now have compromised immune systems that make them increasingly vulnerable to infection and the progression of disease.

The coincidence of TB and HIV has both accelerated TB drug resistance and contributed to the rapid transmission of HIV. Limited infection control facilities and practices compound the problem. Health care facilities routinely house patients who are HIV positive with those who have drug-resistant TB, creating opportunities for nosocomial transmission. Recent efforts have been aimed at deinstitutionalizing and decentralizing care by focusing on community-based treatment in people's homes, thereby reducing such opportunities.

Importance of Infection/Transmission Control

There are two pathways for infection with drug-resistant TB. Acquired, or amplified, resistance typically emerges in settings where TB treatment is inadequate, patients fail to adhere to proper treatment regimens, or incorrect or non-quality-assured drugs are used for treatment. Transmitted, or primary, resistance results from the direct transmission of drug-resistant strains from one person to another. Neel Gandhi of the Tugela Ferry Care and Research Collaboration stated that this latter mechanism has largely been neglected during the development of TB control programs.

Drug-resistant strains of other diseases typically are not as resilient as drug-susceptible strains and therefore tend to die out. While acquired or amplified resistance due to inadequate treatment may explain how the cases of MDR and XDR TB first emerged in South Africa and other parts of the world, however, speakers presented substantial evidence of transmitted rather than acquired TB. In one study, for example, about half of those patients who died from highly resistant forms of TB had never before been treated for the disease, and 85 percent had a genetically similar strain, indicating that resistance was likely transmitted rather than acquired. Other studies using molecular fingerprinting have shown that patients who relapsed with MDR or XDR TB had different genotypes in their relapse isolate compared with their initial isolates, suggesting that their relapses occurred as a result of primary transmission rather than acquired resistance. Gandhi suggested several lessons from these studies:

- Efforts must focus on creating infection control programs to prevent the further transmission of drug-resistant strains.

- Early diagnosis of MDR and XDR TB cases, which is currently hampered by a lack of laboratory capacity and rapid diagnostic tests (see below), will be critical to infection control.
- Further studies are needed to better characterize transmission patterns both in hospitals and in communities so that other means of curbing the epidemic can be devised.

Implementing effective transmission control in resource-limited settings, however, presents major challenges. For example, establishing community-based treatment outside a hospital is not currently feasible in some settings because the tradition and infrastructure for community care do not exist. Transmission control can be very expensive, particularly when elaborate ventilation systems are required, and the necessary technical expertise is often lacking. Furthermore, the importance of undiagnosed and unsuspected cases in the spread of disease is often underappreciated. Edward Nardell of Brigham and Women's Hospital described a number of potential strategies for reducing the transmission of drug-resistant TB, including hospital triage and separation; ventilation; and research on novel interventions, such as the use of germicidal ultraviolet (UV) air disinfection and the development of inhaled antibiotics.

Limited Diagnostic Capacity

WHO recommends that countries maintain at least one culture laboratory per 5 million people and one facility capable of conducting drug susceptibility testing per 10 million. Only a handful of high-burden countries meet these standards, and many countries lack even a national reference laboratory to perform some of the most basic surveillance. Furthermore, many experts consider the recommended numbers to be wholly inadequate. It is estimated that a mere 5 percent of all MDR TB cases are currently being detected.

While current global capacity allows for the conduct of approximately 10 million culture tests, WHO has estimated that the actual need is at least 60 million (Weyer et al., 2007). According to John Ridderhof of the U.S. Centers for Disease Control and Prevention (CDC), to meet current needs, hundreds or even thousands of new laboratories would have to be developed worldwide, representing an investment in laboratory capacity of $1 billion or more. WHO and the Stop TB Partnership created the Global Laboratory Initiative (GLI) in 2007 to begin to address this gap, but the GLI's modest goal is to diagnose 74,000 new MDR TB patients by 2011.

Cost-effective point-of-care TB testing is also critically important. Ideally, such tests would be performed during a patient's visit so that appropriate treatment could begin immediately. There have been recent breakthroughs

in the development of point-of-care systems, and two portable systems were presented and discussed at the workshop. But such technology is likely to remain unattainable for those in resource-poor settings.

An example of the type of test envisioned by many is the dipstick test used in HIV diagnostics. That test, which costs US$1.00 and is 99 percent sensitive and specific, revolutionized HIV testing and was a key element in the scale-up of antiretrovirals worldwide. As Mark Harrington of the Treatment Action Group noted, "In some ways [point-of-care testing] is even more important than a new drug or a new vaccine. There is a cure for most cases of TB, and there is reasonable treatment for MDR. But if it can't be diagnosed, millions of people will die of a treatable and curable disease." To achieve the goal of a rapid, inexpensive, and effective point-of-care diagnostic test, support will be needed from large organizations such as the National Institutes of Health and the Bill and Melinda Gates Foundation, along with small-scale innovative efforts supported by smaller donors.

Low Rates of Treatment

Only a small proportion of newly diagnosed cases of MDR TB are being treated either through Green Light Committee (GLC)–approved or non-GLC-approved treatment programs (see Figure S-1). Even among the small proportion of patients who are being treated, many are not receiving drugs that are quality assured through the GLC program. For others, treatment may not address their drug resistance profile, making their treatment ineffective.

Furthermore, the public health infrastructure needed to deliver TB care cost-effectively is inadequate in many resource-poor environments. Current programs are often fragmented and limited in scale, and it is frequently difficult to scale up successful programs to the regional or country level. Effective public health models, such as providing patients with housing as an alternative to hospitalization and training villagers to serve as community health workers, have yet to be widely adopted. Technical assistance, when available, often lacks coordination.

It was noted that experience with the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) could be instructive for the fight against TB. Substantial funding for HIV/TB programs was an important factor in the success of PEPFAR—funding increased from $18.8 million in 2005 to $169 million in 2008, more than 700 percent. In addition, PEPFAR established a supply chain management system for both forecasting demand and delivering drugs, fast-tracked U.S. Food and Drug Administration (FDA) approval of new and generic antiretroviral drugs, fostered community-based delivery of care, invested in improved laboratory surveillance systems, built a tiered

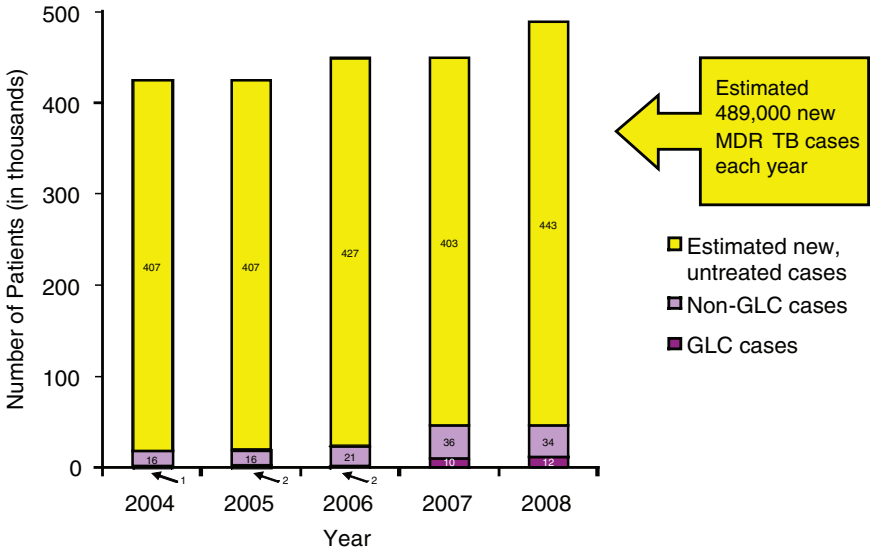

FIGURE S-1 MDR TB burden and patients in treatment.
NOTES: The bars represent the number of new MDR TB cases in each year. Data for 2007 and 2008 are WHO estimates. The lavender portions indicate the number of patients treated in non-GLC-approved projects; the purple portions indicate the number of patients treated in GLC-approved projects; and the yellow portions represent patients receiving no treatment. GLC = Green Light Committee.
SOURCE: Zintl, 2008 (based on unpublished data from GLC Secretariat, Geneva 2008).

public health laboratory network and transport system for samples, and set specific performance targets.

Bottlenecks in the Procurement and Distribution of High-Quality Drugs

Continuing problems constrain the procurement and distribution of high-quality TB drugs worldwide. Treatment and drug quality vary tremendously across programs and countries. The markets for second-line drugs in priority countries are large and growing rapidly, but they are fragmented, and regulation is inconsistent. The absence of accurate demand forecasting creates financial risks for both suppliers and programs and disrupts the flow of drug supplies.

Ruth Levine of the Center for Global Development discussed the critical role of accurate demand forecasting, drawing on lessons learned from

dealing with malaria. WHO's malaria drug demand forecasts have been off by orders of magnitude. For example, the original demand for Coartem was estimated to be 55 million doses; the actual orders turned out to total 14 million. The following year, WHO estimated that 100 million doses would be demanded and purchased; the actual number turned out to be 55 million. Likewise, the manufacturer had to discard 10 million tablets of artesunate because of overforecasts. There are also serious problems with the quality of TB drugs, and countries are not sufficiently insistent that their MDR TB patients be treated with second-line drugs that are of high quality—meaning in most cases that they are potent enough. Anecdotal reports of quality issues are widespread, but actual data on the quality of many drugs being used are limited. Paul Nunn of WHO described current WHO efforts to collect data on drug quality by looking randomly at TB drugs from various sites in different countries and measuring their active ingredients—similar to what was done with AIDS and malaria. But results from those studies are months away.

To ensure the quality of second-line drugs being supplied to high-burden countries and to improve the reliability of supply, the GLC was formed in 2000. Substantial growth has occurred in the number of GLC-approved projects and the numbers of patients treated. In 2006, just over 5,500 patients were enrolled in 32 approved projects; by 2007, 30,000 patients were enrolled in 104 projects. The latter figure includes a rapid ramp-up in the African region from 0 to 15 projects, as well as a large number of projects in Eastern Europe.

Despite this recent growth, GLC projects represent only a tiny fraction of the more than 400,000 MDR TB cases estimated to occur each year. The vast majority of patients are being treated through non-GLC-approved projects under programmatic conditions that may not be ideal for treatment of MDR TB and with drugs that are not quality assured. But the requirements for GLC participation can be onerous and costly, and as a result, many countries and suppliers prefer to circumvent the GLC process. With one exception, only one quality-assured supplier exists for each of the second-line drugs for GLC projects.

Workshop participants offered a number of suggestions for improving the procurement and distribution of TB drugs. These included improving forecasting, aligning the incentives for key stakeholders along the supply chain, and ensuring that the GLC procurement process is clear and straightforward.

Need for New TB Drugs

The global fight against TB has been impeded by the lack of new drugs and vaccines. The current classes of both first- and second-line TB drugs were all discovered between the 1940s and the 1960s. The last approval for

a newly developed drug to treat TB—rifampicin—occurred in the 1970s. The root of the drug resistance problem is the complexity and length of drug-sensitive regimens. Thus it is critically important to develop a pipeline of new drugs with shorter, simpler regimens for drug-sensitive TB, and ideally, novel mechanisms of action that are equally effective against MDR and XDR and drug-sensitive strains of TB. Ideal TB drugs would be taken once a day or less, and orally. They would have minimal drug–drug interactions for both HIV-positive and HIV-negative patients and would be obtainable at low cost.

While some promising drug development efforts are under way—and far more drugs are in the pipeline than was the case even in 2000—both the time frames for such efforts and the probabilities of ultimate success for any given candidate are discouraging. A compound that has progressed to preclinical development from among the thousands of compounds that enter the discovery phase has about a 1 in 10 chance of making it to registration and therefore to patients. Only in Phase III development do the odds become fairly good. About two-thirds of drugs that make it all the way to pivotal clinical trials will ultimately be registered.

Ann Ginsberg of the TB Alliance identified a number of strategies for addressing the challenges facing TB drug development:

- Focus on developing multidrug regimens rather than individual drug candidates.
- Improve biomarkers and validate surrogate end points to streamline clinical development.
- Validate animal models.
- Strengthen clinical trial capacity, including the development of sites, staff, and investigators who can work to current global registration standards.
- Harmonize regulatory guidance for TB drug development across the FDA, the European Medicines Agency (EMEA), and regulatory authorities in high-burden countries.
- Enter drug candidates with novel mechanism of action into simultaneous clinical development programs for both drug-sensitive and drug-resistant strains of TB, since they involve very different patient populations and study designs.

Among the variety of candidates currently being pursued, the majority are cell wall active, which means they work well against the most rapidly replicating mycobacteria but are not likely to be effective against persistent organisms that are replicating slowly or not at all. These drugs are consequently unlikely to shorten therapy, an objective requiring drugs that act against other kinds of targets. A number of new discovery projects are focused on energy

metabolism, and if these candidates are successfully developed, they will likely contribute to shortening therapy.

Research Priorities at the National Institutes of Health

Anthony Fauci of the National Institute of Allergy and Infectious Diseases discussed important lessons to be drawn from the experience with AIDS research. Solid funding and the resulting research efforts have led to a number of extraordinary advances over the 27 years since AIDS was first recognized in 1981. Today there are more antiretroviral drugs for HIV/AIDS than the total of all drugs available for all other viral diseases combined. This achievement was possible because of a serious investment in biomedical research, partnerships with industry, and the pharmaceutical industry's realization that the development of antiretroviral drugs promised a large return on investment and would significantly impact the lives of patients in the United States and globally. Compared with the current National Institutes of Health (NIH) budget for HIV/AIDS, the budget for TB is modest. Fauci highlighted five priorities for expanded research:

1. Development of rapid and reliable diagnostic methods that can be used at the point of care;
2. Investment in the pipeline of new drugs, as well as proper use of existing first- and second-line therapies;
3. Investment in research to understand the epidemiology that contributes to the spread of drug-resistant and drug-sensitive strains of TB;
4. Understanding of the relationship between and comorbidities of HIV/AIDS and TB; and
5. Development of effective vaccine and chemotherapy prevention strategies for all forms of TB.

Fauci cited several critical success factors for accelerating the development of new TB drugs and vaccines: a commitment of substantial financial resources, enlistment of the best and brightest investigators, engagement of the affected communities, collaboration with industry and global organizations, and support from leaders and policy makers. He noted the importance of coordinating research efforts among government agencies such as NIH, CDC, and the U.S. Agency for International Development (USAID) and global partners such as other international government agencies, federal programs such as PEPFAR, philanthropic organizations such as the Gates Foundation, pharmaceutical and biotechnology companies, and public–private partnerships and research consortia. Fauci also emphasized the need to ensure the integration of scientific disciplines within infectious disease

research and immunology and state-of-the-art technological approaches, as well as the importance of balancing fundamental research and product development efforts.

Economic Incentives

Workshop participants discussed the types of economic incentives that are needed to accelerate the discovery and development of new therapies, including both push and pull mechanisms. Push mechanisms stimulate the supply or production side of the market, while pull mechanisms stimulate the demand side. The Orphan Drug Act of 1983 is an example of a push mechanism because it is aimed at making the development of an orphan product easier, less costly, or less risky for a company.[1] BioShield[2] represents another form of push mechanism that involves directly funding research and development for terrorism countermeasures. A third push approach is the development of a public–private partnership such as the TB Alliance. These partnerships are effective because they organize strategies within the field and facilitate the sharing of scientific knowledge and effort. Pull mechanisms include the use of advance market commitments, through which market demand—e.g., a price and a certain number of units to be purchased—is guaranteed in advance (typically by government or a philanthropic organization). Other pull incentives include extended patent life guarantees and priority review vouchers, which a company can use to receive priority review for another drug or can sell to another company.

CONCLUDING REMARKS

The workshop presentations and discussions highlighted a basic tension between the need to focus global health programs on drug-susceptible TB versus drug-resistant TB. While the current epidemic of TB is at risk of being replaced by an epidemic of drug-resistant strains, Nunn argued that

[1] A therapy may be designated as an orphan product if one of the following conditions is met: (1) the disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year as specified in 21 CFR Sec. 316.21(b); or (2) for a drug intended for diseases or conditions affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 200,000 or more persons per year in the United States, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States as specified in 21 CFR Sec. 316.21(c).

[2] The Project BioShield Act was passed in 2004. This bill gave the U.S. Department of Health and Human Services authority to support the development and acquisition of medical countermeasures as part of a national strategic effort to prepare for threats to public health from chemical, biological, radiological, or nuclear events.

the first priority in addressing MDR TB is preventing its occurrence in the first place, which places the emphasis on basic control of TB. Gail Cassell of Eli Lilly and Company countered that, with MDR and XDR TB being nearly out of control, simply focusing on susceptible strains will not be sufficient. Kenneth Castro of CDC suggested that both Nunn and Cassell were correct and affirmed the need for both types of interventions. A multipronged approach is necessary, he argued, which should include focusing on MDR TB infection control, laboratory capacity building, and rebuilding of the infrastructure for basic TB control.

Several participants noted that the U.S. and global response to the MDR TB crisis has been more incremental than transformative, and some advocated for bolder action. A possible presidential initiative to combat drug-resistant TB, similar to the PEPFAR initiative, was discussed. It was also suggested that the debate over WHO's emphasis on health sector strengthening versus priority diseases should be resolved through a comprehensive plan. It was noted that the 2000 IOM report *Ending Neglect: The Elimination of Tuberculosis in the United States* recommended important strategies, a number of which have yet to be addressed (IOM, 2000).

Cassell, the workshop chair, reflected on the proceedings of the day and reminded the audience that not only are MDR and XDR TB growing, but also between 30 and 40 percent of patients diagnosed with XDR TB are totally untreatable with existing drugs. She remarked on the workshop presentations indicating the high degree of primary transmission, in stark contrast to what has generally been believed in the past about the ability of these organisms to spread. Despite these growing concerns, she observed that the diagnostic capabilities, resources, treatment and infection control policies, data collection mechanisms, and research capacity needed to understand the MDR and TB crisis effectively still are not in place. Said Cassell, "What we have also heard is the great need to directly confront MDR TB and XDR TB, whereas emphasis in the past has been on strengthening TB control programs per se, believing we could [thereby] control the problem of MDR and XDR TB."

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1

Introduction

Tuberculosis (TB) kills more than 4,500 people each day worldwide; approximately 1.7 million TB deaths occurred in 2006 alone (WHO, 2008a). TB is second only to AIDS as the leading infectious disease–related cause of adult deaths. Although antibiotic treatment for TB was discovered more than half a century ago, an estimated one-third of the world's population is currently infected with *Mycobacterium tuberculosis* (Keshavjee and Seung, 2008), and 9.2 million new cases of active TB are estimated to occur around the world annually (WHO, 2008a).

A large percentage of TB cases are susceptible to available effective TB antibiotics. Nonetheless, multidrug-resistant TB (MDR TB) is a major and growing global threat.[1] An estimated 4.8 percent of all new and previously treated TB cases diagnosed worldwide in 2006—a total of 489,139 cases (95 percent confidence level, 455,093–614,215)—were MDR TB (WHO, 2008b). However, many consider this global figure to be a significant underestimate, and in many regions around the world the rates are much higher. Drug resistance is perpetuated for a number of reasons, including the failure to ensure regular treatment with high-quality existing drugs and the fact that only a few drugs to treat TB are available, and they are very old. The rifamycins, the last new treatments for TB, were developed in the 1960s. Because patients with MDR TB are resistant to treatment with first-line drugs, they must be treated with second-line drugs that are more expensive, have more side effects, often require injection, and involve longer treatment

[1] MDR TB is a form of TB that is resistant to the two principal first-line drugs used to treat TB—isoniazid and rifampicin.

regimens. Moreover, some strains of TB—termed extensively drug-resistant TB (XDR TB)—are resistant even to these second-line therapies.[2] According to estimations by the World Health Organization (WHO), the incidence of XDR TB worldwide is 0.4 percent (Nunn, 2008).[3] While this is a rough global estimate, it is important to note that, as with MDR TB, in many regions of the world the rates are much higher.

The combination of HIV and TB has proven to be especially deadly. At least one-third of the 33.2 million people living with HIV worldwide are coinfected with TB (WHO, 2008c). As a result of their weakened immune system, HIV-positive patients often develop active TB. In 2000, TB was identified as the cause of 11 percent of all AIDS-related deaths, most of which occurred in Africa (Corbett et al., 2003); even higher percentages have also been reported (Mohar et al., 1992; Lucas et al., 1993; Nelson et al., 1993).

OBSTACLES TO TREATMENT

The fight against drug-resistant TB faces many obstacles. These include inadequate diagnostic capacity, a lack of new drugs, bottlenecks in the supply chain of existing drugs, drugs that are counterfeit or of poor quality, suboptimal treatment regimens, suboptimal patient management practices, inadequate infection control, inadequate in-country health systems, and a dismal lack of resources.

Until recently in most parts of the world, TB diagnosis was reliant on technologies dating back to the nineteenth century. Sputum smear microscopy has played an important role in diagnosis, but drug-resistant TB requires faster and more specific diagnostic tools. To this end, the Global Laboratory Initiative (GLI), part of the Stop TB Partnership,[4] has launched a program to scale up rapid mycobacterial culturing using liquid media and rapid molecular testing for drug-resistant TB. While these developments have been significant, large gaps remain in the availability of appropriate TB diagnostics, primarily in the area of rapid point-of-care diagnostics—tests that can yield quick and accurate results on site without the need for a laboratory.

After decades with no new TB drugs, there are now a handful of promising compounds in the pipeline. If clinical trials yield clear results demonstrating effectiveness, these new drugs may be developed within the next 10 years. However, even new drugs must be used only in combination,

[2] XDR TB is MDR TB that is also resistant to any one of the fluoroquinolones and any one of the second-line injectable drugs.

[3] Using MDR TB figures reported in WHO's fourth report on anti-tuberculosis drug resistance (WHO, 2008b) and XDR TB percentages determined according to CDC (2006), WHO estimated that the global prevalence of XDR TB is 0.4 percent.

[4] The Global Laboratory Initiative was launched to promote the detection of TB and drug-resistant TB.

or they, too, will quickly become ineffective because of the development of resistance. Thus a minimum of three to four new drugs are needed immediately to avert the escalation of drug-resistant TB.

The delivery of drugs to the populations that need them is impeded by several factors, including burdensome procurement mechanisms, inadequate demand forecasting, bottlenecks in country-level distribution, and inadequate public health infrastructure. Without accurate forecasting, manufacturers may have to dispose of unsold drugs; donors face uncertain supplies and prices; and shortages of quality-assured drugs may occur, resulting in incomplete treatments and increased drug resistance. Significant care-delivery problems exist as well, ranging from difficulties with infection control in congregate settings to inadequate capacity to deliver care over the 2-year course of treatment.

WORKSHOP OBJECTIVES

To address the issues outlined above, the Institute of Medicine's (IOM's) Forum on Drug Discovery, Development, and Translation held a workshop in Washington, DC, on November 5, 2008. This was the first in a series of anticipated workshops to be held in the United States and in countries with the highest TB burden—South Africa, China, Russia, and India. Those future workshops will be organized by and represent a broad range of stakeholders. The goals of the workshop summarized in this report were to understand the magnitude and nature of the drug resistance problem; to assess the adequacy of the current global response; and to examine in depth three primary areas of concern—diagnosis, drug supply, and treatment delivery. The workshop brought together a wide range of experts and organizations engaged in the global effort to combat TB so they could share information, develop an understanding of the challenges, and consider opportunities and strategies for confronting the problem. Key organizations and stakeholders in the global fight against TB were represented, including WHO, the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH), the TB Alliance, the Bill and Melinda Gates Foundation, the U.S. Centers for Disease Control and Prevention (CDC), the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), and many others (see Appendix A for a full listing of organizations represented at the workshop).

Speakers from around the world presented data and described firsthand their experiences with MDR and XDR TB in multiple countries, including China, Cambodia, Ethiopia, Russia, and South Africa. To provide baseline information on MDR TB and outline the issues for discussion during the workshop, the IOM commissioned a white paper from Partners In Health (see Appendix C). This paper provides updated information on the epidemiology and treatment of MDR TB and describes the barriers to effective

global response.[5] The original intent of the workshop was primarily to release the white paper and to discuss its conclusions and recommendations with an expert audience. As the workshop agenda was being developed, however, the scope expanded significantly.

Gail Cassell of Eli Lilly and Company, who served as chair of the workshop, said that the reporting of MDR TB (approximately 500,000 new cases annually) is a gross underestimate of the true burden. Only 11 of 22 high-burden TB countries provide data on drug-resistant TB, and even fewer have the capability to assess patients' susceptibility to the second-line drugs used to treat MDR TB. To exploit the opportunity offered by having multiple major stakeholders present at the workshop, she encouraged all participants to engage in a frank discussion of the emerging crisis.

Paul Farmer of Partners In Health discussed the lack of urgency and attention that has characterized the response to TB in the past three decades. Since the 1980s, public health officials have wrongly assumed that the tools necessary to combat TB were already available, that current drugs were safe and effective, and that the proper strategies for eliminating TB were at hand. In 1992, an editorial published in *Science* attempted to dispel these incorrect assumptions. The editorial argued that the world lacked proper drugs, diagnostics, and strategies for combating the disease (Bloom and Murray, 1992). Today the world stands on the precipice of a TB pandemic, the full extent of which is not known, and Farmer argued that the tools needed to combat the problem are still lacking.

ORGANIZATION OF THIS REPORT

This report is intended to provide a faithful summary of the presentations and discussions that took place during the workshop, although remarks have been substantially abbreviated and reorganized to improve the report's readability and usefulness. It should be noted that, while a number of presenters and participants expressed opinions and recommendations, these should in no way be interpreted as attributable to the Forum or the IOM.

Chapter 2 provides an overview of the global spread of MDR TB. The ensuing chapters address in turn MDR TB transmission, HIV coinfection, and transmission control (Chapter 3); diagnosis (Chapter 4); infrastructure and health care delivery systems (Chapter 5); global systems for the purchase and delivery of TB drugs (Chapter 6); and research on the global control of TB and the role of drugs, vaccines, and funding (Chapter 7). The final chapter summarizes strategies put forth by workshop participants for confronting the global crisis of drug-resistant TB.

[5] It should be noted that this paper represents the views of its authors and not those of the IOM.

2

The Global Spread of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis

SCOPE OF THE PROBLEM

Paul Nunn of WHO summarized the available surveillance data on TB, MDR TB, and XDR TB. WHO, together with the International Union Against Tuberculosis and Lung Disease (IUATLD), regularly collects and analyzes global TB surveillance data. WHO has estimated that in 2006, the most recent year for which data are available, the total number of cases of TB worldwide was just still growing—from 9.1 million in 2005 to 9.2 million in 2006 (WHO, 2008a; see Figure 2-1), although the global incidence of TB per capita fell slightly, continuing the trend since 2003 (see Figure 2-2). The most dramatic reductions in per capita incidence appear to have occurred in Africa, apparently as a result of reductions in the prevalence of HIV (Figure 2-2). As noted in Chapter 1 and shown in Table 2-1, WHO estimated that of the approximately 9.2 million cases of TB in 2006, approximately 489,000 (95 percent confidence level, 455,093–614,215), or 4.8 percent, were MDR TB, and about 40,000 (or 0.4 percent) were XDR TB (Nunn, 2008).

Limitations of Global TB Estimates

Nunn stated that the WHO surveillance data on MDR and XDR TB have large confidence limits. To determine the percentages of MDR and XDR TB among all cases of TB, WHO first estimates the percentage of cases that are MDR, and then within those cases, the percentage that are XDR. A number of factors complicate the WHO estimates. First, no data

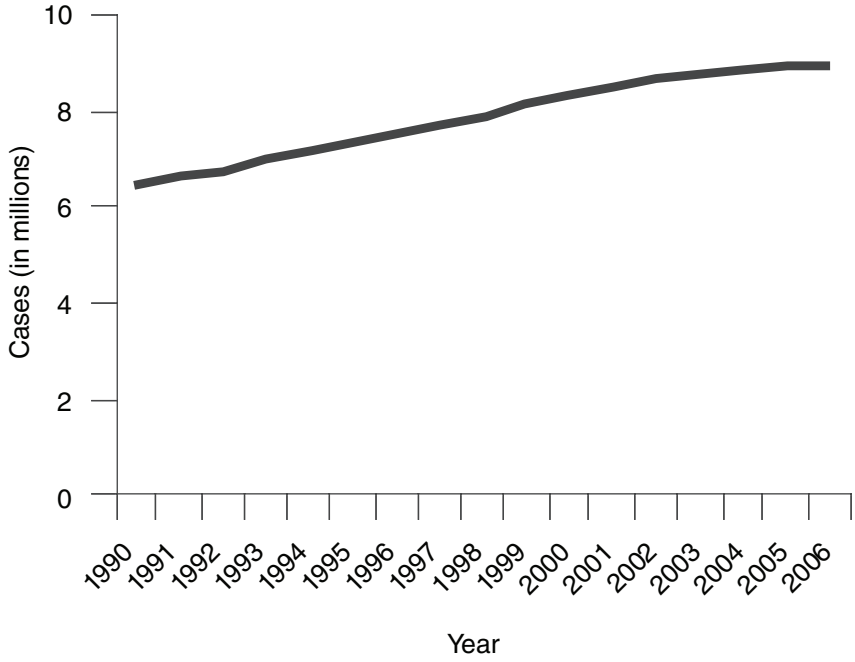


FIGURE 2-1 Global incidence of TB.
SOURCE: Nunn, 2008 (based on data from the WHO TB database, October 2008).

are available for many locations, particularly in sub-Saharan Africa. Second, in many countries, the availability of diagnostic laboratories is limited; nine African countries lack even a single reference laboratory capable of culturing TB and making a diagnosis. Finally, mortality data are unreliable because little is known about the long-term outcomes of the MDR cases that are reported. Megan Murray of Brigham and Women's Hospital added that the WHO survey data represent surveillance samples of incident cases in which drug resistance was measured through drug sensitivity testing. The data come from two different sources: either newly presenting TB patients or retreatment cases. The data do not capture patients who develop MDR TB during the course of therapy, and therefore may yield considerable underestimates. The degree of underestimation will depend on when in the course of an epidemic the data are sampled. At the beginning of an epidemic, when many of those cases arise from people who fail therapy and amplify their drug resistance, the estimates will be especially low. Later, when transmission of drug resistance dominates most of those cases, the reported MDR TB rates will be higher.

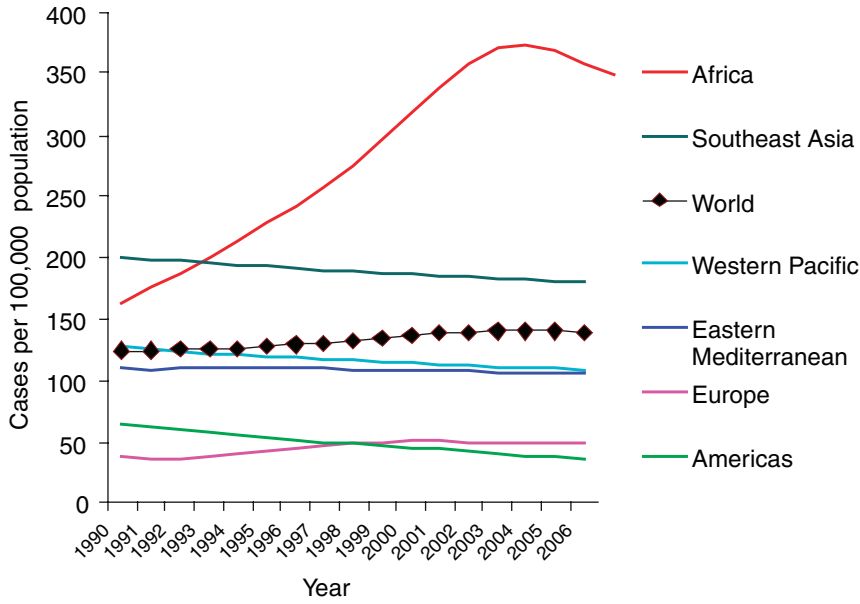


FIGURE 2-2 Per capita incidence of TB.
SOURCE: Nunn, 2008 (based on data from the WHO TB database, October 2008).

TABLE 2-1 Estimated Number of TB Cases and Number of Deaths, by Type, 2006

Form of TB	Estimated Number of Cases	Estimated Number of Deaths
All forms	9,200,000	1,650,000
Multidrug-resistant (MDR TB)	489,000	120,000
Extensively drug-resistant (XDR TB)	40,000	20,000
HIV-associated	700,000	200,000

SOURCE: Nunn, 2008. (The data on total cases and deaths are from WHO, 2008a; the number of MDR TB cases is from WHO, 2008b; the deaths from MDR and XDR TB were estimated by Nunn's team from published literature using the case numbers listed in the table; and the number of XDR TB cases [according to the revised October 2006 definition of XDR TB] was estimated from the MDR TB number listed in the table using the percentages from CDC, 2006.)

Burden of MDR and XDR TB

Fifty-seven percent of the MDR TB burden is found in just three countries: as of 2006 China had about 131,000 cases per year, India about

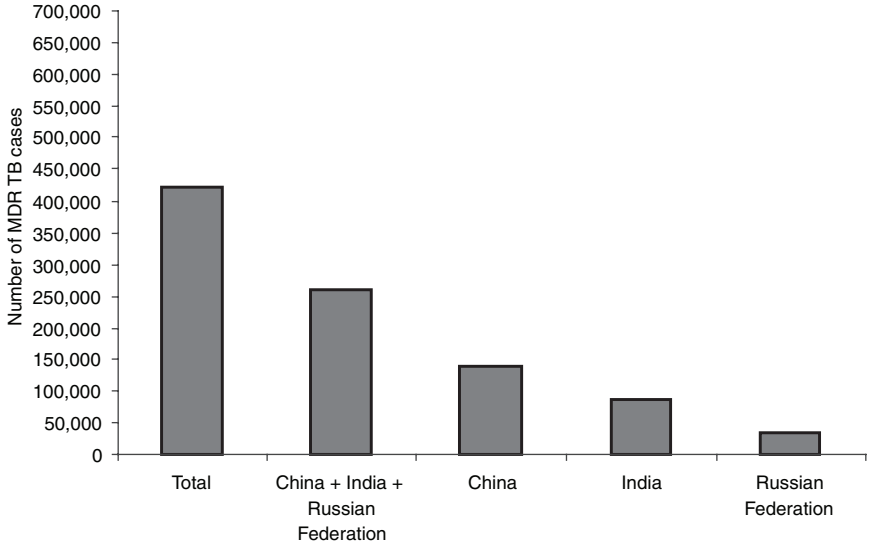


FIGURE 2-3 Two-thirds of the MDR TB burden is located in just three countries.
NOTE: As of 2006 China had about 131,000 cases per year, India about 110,000, and the Russian Federation about 36,000.
SOURCE: Nunn, 2008 (based on data from WHO, 2008b).

110,000, and the Russian Federation about 36,000 (see Figure 2-3). South Africa is a close fourth (WHO, 2008b). While a significant number of new TB cases are being diagnosed as MDR, most MDR TB occurs in previously treated patients. The incidence of MDR TB among previously treated patients is particularly high in Eastern Europe and in the eastern Mediterranean. In fact, the percentage of MDR TB among retreatment cases is approaching or exceeding 60 percent in three oblasts of the Russian Federation (Arkhangelsk, Tomsk, and Ivanovo) (Nunn, 2008). Nunn presented data comparing Estonia and Tomsk Oblasts following investments in TB and MDR TB control. Estonia's notification rate for TB is decreasing, and the percentage of MDR TB is decreasing slightly. Although the TB notification rate in Tomsk is decreasing as well, the percentage of MDR TB among new cases is rising. These data demonstrate that investments in TB control alone will not be sufficient to combat the problem and that new drugs will be needed.

To investigate rates of XDR TB throughout the world and in a few selected regions, WHO and CDC surveyed the global Supranational Reference Laboratory (SRL) international network of laboratories using data for

2000–2004.[1] The samples analyzed had been collected, tested for resistance to at least three second-line drugs, and stored. These data were compared with samples from the U.S. National Surveillance System (collected during 1993–2004); samples taken from a cohort of MDR TB patients in Latvia's National MDR TB Registry during 2000–2002; and samples from South Korea's National Reference Laboratory. With the exception of those from South Korea, the samples were not population based. The researchers found that, among the 49 countries included in the SRL network, 2 percent of cases were XDR TB; in the United States 4 percent were XDR TB, in Latvia 19 percent, and in South Korea 15 percent (CDC, 2006). Isolated incidents such as that which occurred in Tugela Ferry, South Africa (discussed below) demonstrate that pockets of dramatically higher rates are possible.

TB in the United States

Kenneth Castro of CDC discussed the status of TB in the United States. In 2007, 13,299 cases were reported in the United States. Until the mid-1980s, the incidence of TB in the United States had declined steadily—about 5–6 percent annually—for three decades. Concurrent with this decline in TB cases, categorical federal funds for TB control were progressively reduced, until they were eliminated in 1972 (IOM, 2000). From 1972 until 1980, federal funds were provided to the states in the form of block grants for control of communicable diseases, including TB. The result was the dismantling of many TB programs. An unprecedented resurgence of TB ensued, fueled by the association between TB and HIV and the occurrence of MDR TB. From 1985 to 1992, the incidence of TB increased by 20 percent in the United States. Because so many programs had been cut, the nation was ill prepared for this sudden resurgence. A federal TB task force was created in 1991 to coordinate the development of a national action plan to combat MDR TB, and Congress appropriated new funding for the effort. These new resources enabled many programs that had been dismantled to be reconstituted. As a result of this new investment, focused on rebuilding laboratory capacity, instituting infection control measures, and reinvigorating research capacity, the incidence of TB has again declined—by about 40 percent in the past 15 years. Unfortunately, according to Castro, renewed complacency has resulted as well. From 1993 to 2000, the rate of decline in the incidence of TB in the United States was 7.3 percent annually;

[1] The goal of the SRL network, which comprises 25 reference laboratories on 6 continents, is to collaborate with national reference laboratories to increase culture and drug susceptibility testing capacity and to provide quality control for global surveys assessing resistance to anti-TB drugs.

from 2000 to 2007, however, that figure fell to 3.8 percent—an early sign of stagnation in the country's progress against TB.

Among U.S.-born populations, the rate of TB in non-Hispanic blacks is eight times higher than in non-Hispanic whites. In 2007, fully 58 percent of U.S. cases were foreign born, reflecting the global nature of TB within the United States. Of these foreign-born cases, 24 percent were from Mexico, 12 percent from the Philippines, 8 percent from India, 7 percent from Vietnam, and 5 percent from China.

Fortunately, MDR TB has been under control in the United States since it was first recognized. In 1993, there were about 400 cases of MDR TB, which represented almost 3 percent of all culture-positive cases. That figure has since declined to about 100 cases of MDR TB—about 1 percent—and has remained steady over the past 4–5 years.

Castro referred to the IOM report *Ending Neglect* (IOM, 2000), which offers five recommendations for addressing TB in the United States: (1) continue to maintain control by investing in the basic program activities that have yielded results; (2) accelerate the rate of decline, because the current rate is insufficient to achieve the goal of eliminating TB in the foreseeable future; (3) invest in research and development necessary to produce new tools (e.g., rapid and reliable diagnostics, new safe and effective drugs and vaccines); (4) invest in global control of TB because of its impact on the United States; and (5) advocate for and monitor progress toward the elimination of the disease. Castro also noted the imminent release of an article in the *Journal of the American Medical Association* describing the epidemiology of MDR TB (Shah et al., 2008).

Relationship Between HIV and TB

As noted, individuals who are HIV positive have compromised immune systems, and they are thus more susceptible to reactivation of their latent TB infection as their CD4 T lymphocyte counts fall. Although coinfection with HIV and MDR TB has received particular attention in Africa—especially in Tugela Ferry—it is also a threat in Eastern Europe. For example, Donetsk Province in the Ukraine has a high rate of MDR TB, and HIV was found to be a risk factor for MDR TB in a survey of all 4.7 million of its residents. Similar data exist for Latvia. Despite the prevalence of HIV and TB coinfection throughout the world, however, scientists have yet to determine conclusively whether there is a correlation between HIV status and transmission of TB (Escombe et al., 2008).

Lack of Adequate Treatments

Of even greater concern is that only about 10 percent of MDR TB patients are receiving any treatment, and only about 3 percent are being

treated under Green Light Committee (GLC) programs—according to WHO standards (WHO, 2008a).[2] The remainder are probably being treated with drugs and programs of unknown quality, a particular concern in Eastern Europe.

Summary

Nunn summarized his remarks by noting that drug-resistant patients in 2004 were resistant to significantly more drugs than they were in 1994. MDR TB is increasing in several countries and decreasing in others. But MDR rates among new cases are approaching 25 percent in many Eastern European countries, and XDR TB is clearly emerging. Moreover, the overlap between TB and HIV infection is increasing the risk for MDR TB (WHO, 2008b).

UNDERREPORTING OF MDR TB IN AFRICA

Lack of Data

Yanis Ben Amor of the Earth Institute argued that the WHO data severely underestimate the problem of MDR TB in Africa. He stressed that WHO's claim that rates in Africa are low is especially problematic because the TB community is willing to accept the WHO data, so appropriate measures to tackle the MDR TB threat in Africa are not taken. Although all of the African countries that have been surveyed, with the exception of Côte d'Ivoire, Mozambique, and Rwanda, show rates of MDR TB below 3 percent (see Figure 2-4), drug resistance surveys have never been conducted for more than half of Africa's countries (25 of 46), so there are no data for these countries to support claims that MDR TB prevalence is low. Defenders of the WHO data justify these claims by arguing that national TB programs are operating effectively, and because of rifampicin's later introduction to Africa relative to the rest of the world, there has been less time for resistance to develop.

Ben Amor compared the performance of national TB programs in the AFRO (African regional office) region with that of national TB programs in six countries of Eastern Europe that currently have the highest MDR TB rates (Estonia, Kazakhstan, Latvia, Lithuania, Russian Federation, and Uzbekistan). He reviewed data for the past 10 years and found that neither case detection nor treatment success rates offer strong evidence that the African programs have performed better than their counterparts in Eastern Europe, where MDR TB rates have already reached alarming levels (see

[2] The GLC program works to enable access to affordable, high-quality second-line anti-TB drugs for the treatment of MDR TB and to provide a strategy for administering treatment.

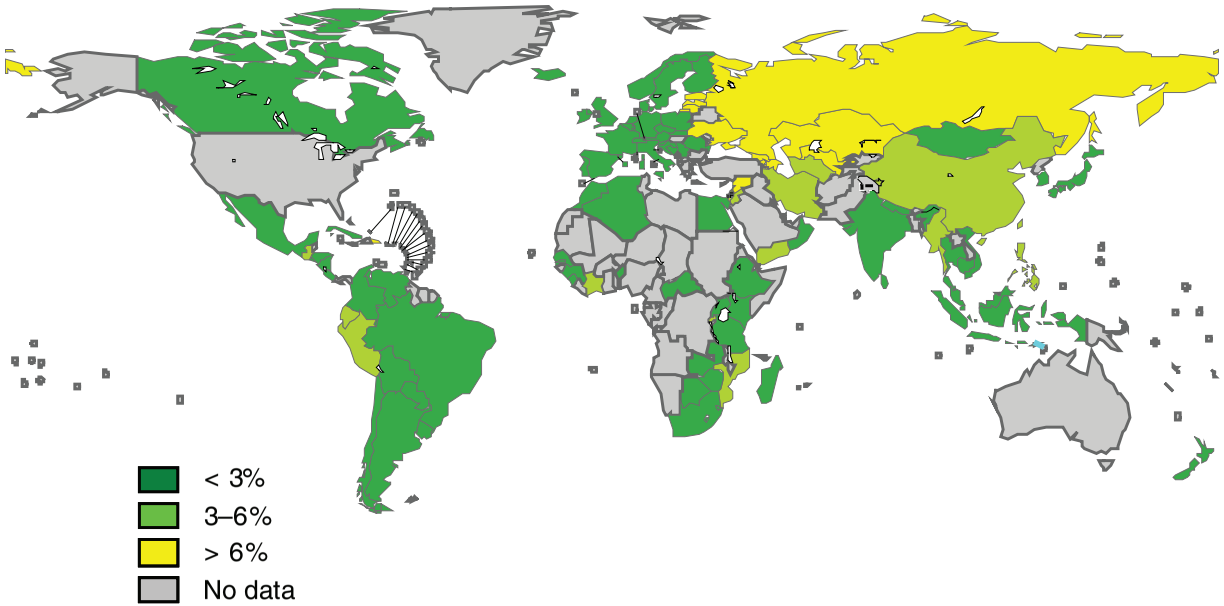


FIGURE 2-4 Percentage of MDR TB among new TB cases (1994–2007).
NOTE: Subnational averages were applied to China, Russia, and Indonesia. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city, or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines on which there may not yet be full agreement.
SOURCE: WHO, 2008b. Copyright 2008 WHO, reprinted with permission from WHO, 2008b.

Table 2-2). He suggested that the rifampicin argument is also invalid. For example, Mozambique introduced rifampicin roughly 10 years after South Africa, yet Mozambique's MDR TB rate is already higher than South Africa's. In addition, the MDR TB rate in Mozambique, which introduced rifampicin at the same time as Gambia, is 10 times higher than that in Gambia. Ben Amor further argued that countries identified as having the capability to conduct drug resistance surveys (WHO, 1997, 2000, 2004, 2008b) are more likely to have a well-functioning national TB program, laboratory structure, and transport network and therefore lower rates of MDR TB than those countries without these capabilities.

Old Data

Ben Amor discussed the credibility of the limited data that are being collected in Africa, arguing that there is compelling evidence that these data are misleading. The first and second maps of Africa shown in Figure 2-5 illustrate MDR TB data from the third WHO/IUATLD global report in 2004 and the fourth global report in 2008, respectively. The shading on the maps divides the countries into three categories on the basis of MDR TB rates (0 to 1.7 percent = low, 1.8 to 2.1 percent = moderate, and greater than 2.2 percent = high) (Ben Amor et al., 2008). In comparing these two maps, it is clear that over the past 4 years, all countries newly surveyed already had either moderate or high MDR TB levels, further suggesting that rates of MDR TB may not be as low as previously estimated. Furthermore, 14 of the 21 surveys illustrated on map 2 used data that were more than 5 years old. In the few settings where there were new surveys—for example, Botswana—MDR TB was found to be on the rise. According to Ben Amor, it is reasonable to assume that if new surveys were conducted in countries where the data are more than 5 years old, MDR TB rates would be higher. Using a formula developed by Zignol and colleagues (2006), map 3 shows

TABLE 2-2 Performance of National TB Programs

Country	Case Detection (%)	Treatment Success (%)
Estonia	69	68
Kazakhstan	76	76
Latvia	73	70
Lithuania	78	78
Russian Federation	43	64
Uzbekistan	42	79
AFRO region	51	70

NOTE: AFRO = African regional office.
SOURCE: Ben Amor et al., 2008 (based on data compiled from WHO, 2008a, for the years 1997–2008).

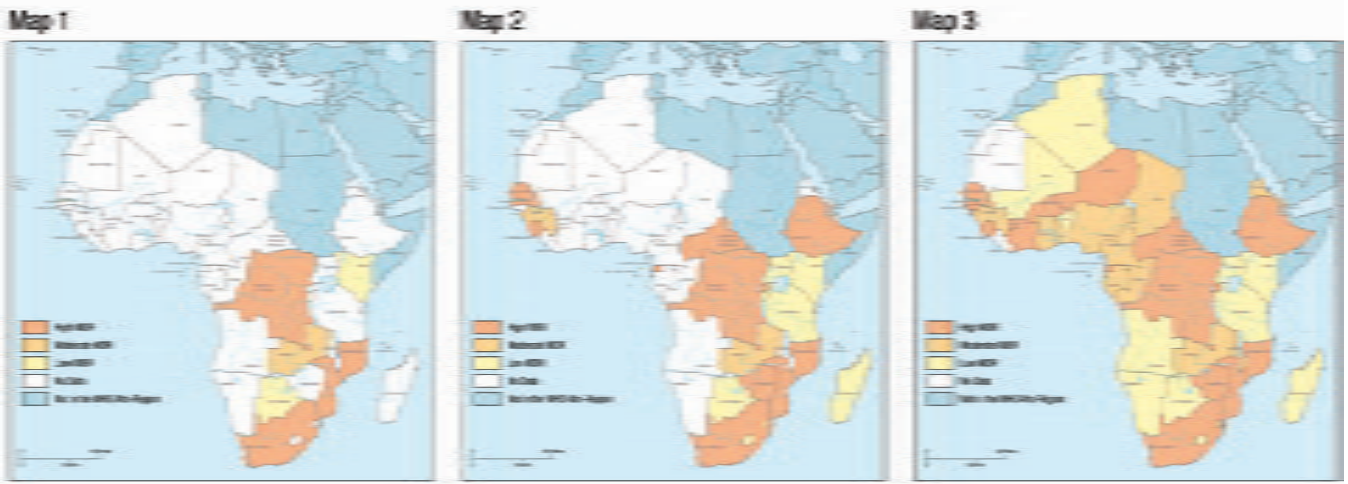


FIGURE 2-5 African countries with a known MDR TB rate.
NOTE: The first map represents data from the third global WHO/IUATLD report, published in 2004 (WHO, 2004); the second map represents data from the fourth WHO/IUATLD global report, published in 2008 (WHO, 2008b), as well as other sources; and the last map is based on a formula developed by Zignol et al., 2006, to estimate the MDR TB rate in countries in which a drug resistance survey was never conducted.
SOURCE: Updated from Ben Amor et al., 2008.

estimates of the MDR TB rates in those countries that have not yet conducted a drug resistance survey. This map shows a clustering of MDR TB in central Africa and South Africa. The formula used in map 3 suggests that, although Kenya's last drug resistance survey was conducted in 1995 and the reported incidence was zero percent, a drug resistance survey conducted in Kenya today would not yield the same result.

Methodological Problems

The methodology used to conduct drug resistance surveys has a serious flaw that may result in underreporting. Current drug resistance surveys include only smear-positive TB cases, yet not all MDR TB cases are smear positive. In Latvia and the Ukraine, for example, where MDR TB rates are segregated on the basis of HIV status, it has been shown that there is a significant association between HIV positivity and MDR TB. Furthermore, HIV-positive TB patients are more likely than other TB patients to be smear negative. Given the high prevalence of HIV in many parts of Africa, current drug resistance protocols may substantially underestimate MDR TB levels.

Further underreporting may result from the fact that because MDR TB is underestimated in Africa, tools for its proper diagnosis in the region are not widely available. Even in settings where a national reference laboratory is in place to conduct drug resistance surveys, it is considered unethical to diagnose patients if second-line drugs capable of treating MDR TB are not available, which is the case in most countries where Ben Amor's project, the Millennium Villages Project, has sites.

An Example: KwaZulu-Natal Province in Rural South Africa

Gerald Friedland of the Tugela Ferry Care and Research Collaboration provided a perspective on the MDR TB epidemic based on his experience in KwaZulu-Natal Province in rural South Africa, specifically Tugela Ferry. This rural area with a traditional Zulu population has an extraordinarily high incidence of TB—more than 1,000 per 100,000 population. The incidence of MDR TB, by Friedland's calculation, is 100 per 100,000 population, much higher even than nonresistant TB in most parts of the world. Among MDR and XDR TB patients, the rate of HIV coinfection is greater than 90 percent. When this catastrophe was reported several years ago (Gandhi et al., 2006), many thought it was an outbreak that would dissipate over time. As indicated in Figure 2-6, however, from 2005 to 2007, both MDR and XDR TB cases continued to increase, and the ratio of XDR to MDR remained very high. In 2007, there were 102 MDR and 146 XDR cases. By comparison, in the United States, 124 cases of MDR

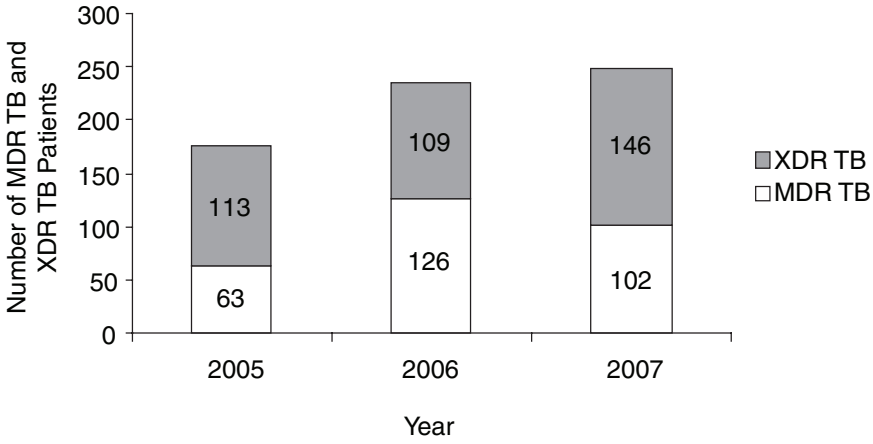


FIGURE 2-6 Numbers of MDR TB and XDR TB patients in Tugela Ferry, 2005–2007.
NOTE: The numbers of both MDR and XDR TB cases have continued to increase, as has the ratio of XDR to MDR.
SOURCE: Friedland, 2008.

TB were diagnosed in 2005, and from 1993 to 2005, 83 XDR cases were diagnosed.

Because of the data limitations discussed above, the full extent of the presence and consequences of MDR and XDR TB is unknown. According to Friedland, however, this outbreak is not limited to Tugela Ferry, but is much more widespread. By mid-2007, XDR TB had been reported by 60 health care facilities in KwaZulu-Natal; more than 4,700 cases of TB had been reported, 6 percent of which were XDR TB. The majority of the cases no longer came from Tugela Ferry. Neighboring countries—Botswana, Mozambique, Lesotho, Namibia, and possibly Zimbabwe—as well as all of the provinces in South Africa had reported cases as well.

Figure 2-7 demonstrates the limited knowledge of the extent of MDR TB in KwaZulu-Natal. At the beginning of the epidemic, the one facility in the province that had access to second-line drugs treated 686 patients for MDR TB, a mere 28 percent of the nearly 2,500 cases of MDR TB that were diagnosed. Behind these numbers, however, are an unknown number of patients who were seen and not diagnosed because of both the paucity of laboratory facilities and a policy of not doing cultures for individuals when they first present with TB, but only when they have failed treatment with first-line drugs. Finally, according to Friedland, the largest group is likely those who have never been diagnosed or treated because they have not visited a health care facility.

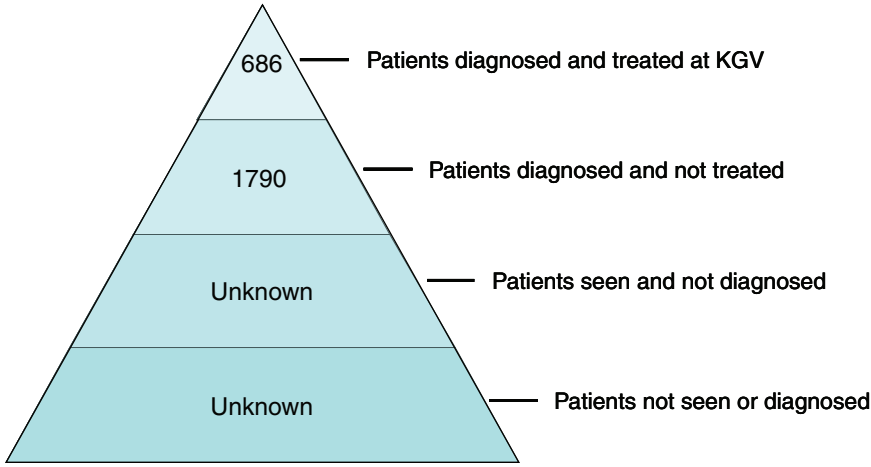


FIGURE 2-7 A representation of the limited knowledge of the extent of MDR TB in KwaZulu-Natal Province, 2006.
NOTE: KGV = King George V Hospital.
SOURCE: Friedland, 2008.

Impact of MDR and XDR TB on Mortality

Very high mortality is associated with the cases of MDR and XDR TB in Tugela Ferry. More than two-thirds of patients diagnosed with MDR TB and about 82 percent of patients with XDR TB die (Gandhi et al., 2009). Figure 2-8 shows the differences in mortality between MDR and XDR TB for Tugela Ferry; the top curve represents MDR TB mortality and the bottom curve XDR TB mortality. There is also a relationship between drug resistance and mortality. Rapid mortality is seen within the first 30 days; after 30 days, the rate of mortality increases with an increase in the number of drugs to which patients' organisms are resistant.

Martie Van der Walt of the Medical Research Council South Africa addressed the impact of MDR and XDR TB on mortality in South Africa. She stated that while the problem of XDR TB in South Africa was quite grave in 2005, the Medical Research Council believes the situation has stabilized with regard to prevalence and early mortality. She presented preliminary results based on data gathered in the Eastern Cape Province of South Africa, just south of KwaZulu-Natal Province, demonstrating the progress that has been made since 2005. Data collection efforts involved two cohorts of XDR TB patients—the first started in October 2006 and the second in October 2007. Preliminary results indicated improvement in the survival rates of patients diagnosed with XDR TB between the 2006

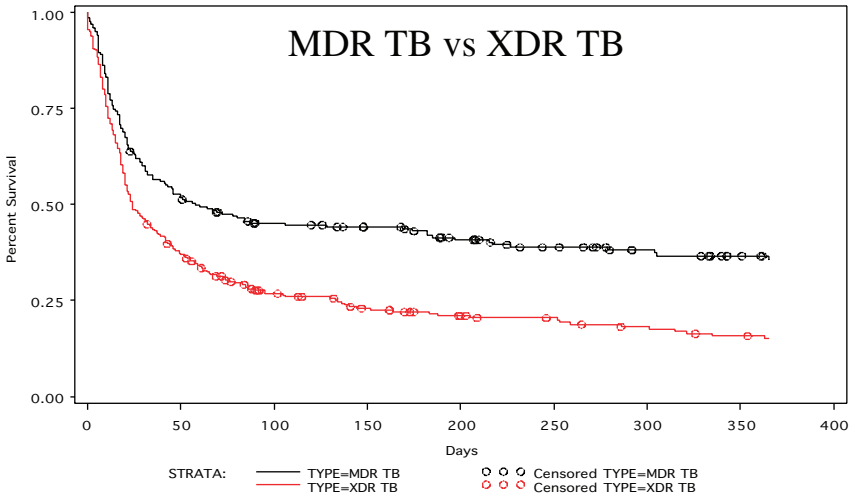


FIGURE 2-8 High mortality due to MDR and XDR TB in Tugela Ferry (2005–2007).
NOTE: The top curve represents MDR TB mortality (67 percent), and the bottom curve represents XDR TB mortality (82 percent).
SOURCE: Gandhi et al., 2009.

and 2007 cohorts. Van der Walt attributed these results to intensified case identification of and screening for drug resistance among treatment failures and patients with MDR TB. Despite this improvement, however, early mortality remains very high, perhaps because of baseline morbidity or additional drug resistance.

Using data from CDC's Preserving Effectiveness of TB Treatment (PETT) study, Van der Walt examined the drug resistance of baseline isolates among MDR TB patients enrolled in 2005 and found that 1 percent of the 800 cases screened were resistant to all drugs tested. She explained that, just as the emergence of XDR TB strains is in some cases a natural consequence of treating MDR TB patients, fully resistant strains can be expected to be the next threat, and may be a cause of XDR TB patients not responding well to treatment for XDR TB. She hypothesized that some of the high mortality among XDR TB patients could be due to the emergence of fully resistant TB. She also cited as part of the problem patients' lack of adherence to proper treatment protocols. As discussed later in this report, Neel Gandhi of the Tugela Ferry Care and Research Collaboration attributes this high mortality rate to high coinfection with HIV.

There are currently limited options for dealing with patients with drug-resistant disease in a country such as South Africa where the current

burden of MDR and XDR TB translates into limited bed capacity. Social and ethical issues arise with respect to keeping patients in lifelong isolation in hospitals, yet they cannot be sent home without treatment. Van der Walt stressed the importance of acting now to develop new drugs. Until new drugs are approved, she favors compassionate use of new drugs that are in development for the treatment of XDR or fully resistant TB.

THE THREAT OF TOTALLY DRUG-RESISTANT TB

Sarita Shah of the Tugela Ferry Care and Research Collaboration presented data based on ongoing surveillance for drug-resistant TB in Tugela Ferry demonstrating the steady progression of drug resistance in XDR TB patients over a 2-year period. Between 2005 and 2007, approximately 300 XDR TB cases were diagnosed. By 2007, the percentage of cases in South Africa resistant to all tested drugs—including all four of the first-line drugs and two second-line drugs—had risen from approximately 30 percent to approximately 95 percent.

Shah also presented data from a survey of the SRL network that first defined and quantified XDR TB. In this survey of more than 17,000 isolates, 234 that met the criteria for XDR TB were identified, and it was found that many of these XDR TB isolates had resistance to drugs beyond the minimum number required to be defined as XDR TB. Half of the XDR isolates were resistant to all four of the first-line drugs; many of these had additional second-line drug resistance, resulting in isolates with resistance to up to 10 drugs (Shah et al., 2007). This level of resistance severely limits treatment options based on the WHO guidelines for the programmatic management of drug-resistant TB, which require treatment with at least four effective drugs.

Alexander Sloutsky of the University of Massachusetts provided additional evidence for the potential emergence of totally resistant TB. Data from the Central Tuberculosis Research Institute in Moscow demonstrate the existence of one case of total drug resistance as early as 1997, with three additional cases in the following year. Sloutsky also showed data from Tomsk prison collected before the beginning of the Institute's MDR TB treatment project, revealing that of 91 MDR TB patients tested, 2 had a fully drug-resistant form of the disease (Sloutsky, 2008).

IMPORTANCE OF BETTER DATA

The true incidence and prevalence of drug-resistant TB are poorly characterized. Mark Harrington of the Treatment Action Group suggested that, while the data presented throughout the workshop suggest a crisis of significant magnitude, the paucity and limitations of those data are severe:

- Most countries do not even report on their drug-resistant TB situation.
- Data sets for most cohorts are incomplete, unpublished, or unvalidated.
- There is no rigorous, randomized evidence for the standard of care for MDR TB.

Harrington noted that data are crucial to mounting the necessary response to the crisis. He cited data as one of the key elements that enabled activists to transform the struggle against HIV, saying, "We brought data to policy makers and scientists, and we used the data to demand money, services, and the nation's attention."

3

MDR TB Transmission, HIV Coinfection, and Transmission Control

The spread of drug-resistant TB has been accelerated by several factors, including ineffective and interrupted treatment, coinfection with HIV, and inadequate infection control. Evidence suggests that there are two pathways through which the prevalence of drug-resistant TB increases—acquired resistance, discussed in the preceding chapter, and transmitted resistance, discussed here.

COINFECTION WITH HIV

Friedland expanded on his remarks, summarized in Chapter 2, regarding the progression of the TB epidemic in KwaZulu-Natal, South Africa, and its catastrophic relationship with HIV. The emergence and progression of the HIV/AIDS epidemic have dramatically affected the population in the region. A large percentage of the region's residents now have compromised immune systems that make them increasingly vulnerable to infection and the progression of disease. The coincidence of TB and HIV has both accelerated drug resistance and contributed to the rapid transmission of HIV. Friedland suggested that the present situation, characterized by recent increases in MDR and XDR TB, illuminates past and current deficiencies in existing knowledge of TB, as well as the practices, programs, and strategies used to combat the disease. Areas with high TB and HIV rates threaten the success of both the Stop TB Partnership and historic antiretroviral rollout programs.

Compounding the problem are the limitations of infection control facilities and practices in health care institutions. Health care institutions

routinely house patients who are HIV positive with patients who have drug-resistant TB, creating opportunities for nosocomial transmission and perhaps tangentially increasing community transmission. Recent efforts are aimed at deinstitutionalizing and decentralizing care by focusing on community-based treatment in people's homes and huts, thereby reducing the probability of nosocomial transmission.

TREATMENT

Murray discussed the inadequacies of current TB treatment strategies and how these inadequacies lead to increases in drug resistance and transmission. She cited estimates that of the half million MDR TB cases and 40,000 XDR TB cases newly diagnosed in 2006, only a small proportion are being treated through either GLC-approved or non-GLC-approved treatment programs (see Figure 3-1). Even among the small proportion of patients that are being treated, many are not receiving drugs that actually address their drug resistance profile, and therefore their treatment is ineffective. A recent review of treatment outcomes for MDR TB cases across 23 studies in 15 different countries (including high-, moderate-, and low-income countries) found that long-term cure rates ranged between 33 and 83 percent. It was found that MDR TB patients coinfected with HIV had lower cure rates than patients with MDR TB alone. Use of fluoroquinolone and surgical resection were associated with better cure rates. Programs that systematically included fluoroquinolone in treatment protocols tended to have cure rates ranging from 60 to 85 percent (Chan and Iseman, 2008). Murray presented pooled data from Partners In Health in Peru and Russia showing that while no particular second-line drug is absolutely necessary for success, the use of injectables (i.e., kanamycin, capreomycin, or amikacin) and fluoroquinolone is associated with better cure rates.

Murray also presented XDR TB outcome data published over the past year. These data showed that the failure rate for treatment of XDR TB ranges from about 35 percent to about 80 percent, mainly in non-HIV-prevalent populations. Murray hypothesized that the failure rates in Africa and in parts of Eastern Europe where HIV is more prevalent would likely be even higher. She noted that XDR TB cases, which are not treatable with fluoroquinolone, usually are not treatable unless a second injectable drug is available. Further, although cycloserine and ethionamide may have some impact, there is a strong potential for treatment to fail if the XDR TB strains are resistant to capreomycin, kanamycin, or amikacin.

The implications of the data presented by Murray for the epidemic potential of MDR and XDR TB are troubling. Without a vaccine and without early, accurate case detection and proper treatment, the MDR/XDR TB epidemic will be driven by transmission.

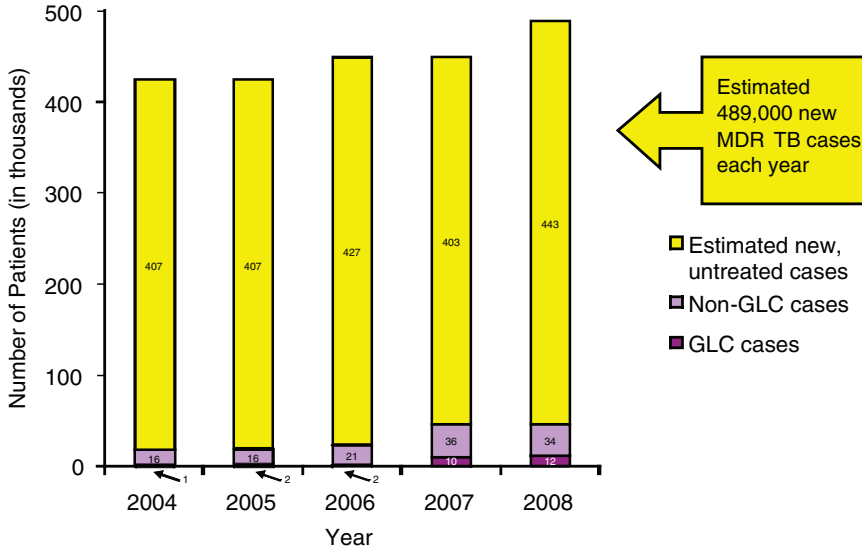


FIGURE 3-1 MDR TB burden and patients in treatment.
NOTES: The bars represent the number of new MDR TB cases in each year. Data for 2007 and 2008 are WHO estimates. The lavender portions indicate the number of patients treated in non-GLC-approved projects; the purple portions indicate the number of patients treated in GLC-approved projects; and the yellow portions represent patients receiving no treatment. GLC = Green Light Committee.
SOURCE: Zintl, 2008 (based on unpublished data from GLC Secretariat, Geneva 2008).

TRANSMISSION OF XDR TB

Jeffrey Drazen of the *New England Journal of Medicine* noted that drug-resistant strains of other diseases typically are not as resilient as drug-susceptible strains and therefore tend to die out. By contrast, in the MDR TB epidemic that occurred in New York City in the early 1990s, which affected mainly HIV-infected persons, the strains were readily transmissible. The recent experience in Africa and elsewhere provides further evidence of this phenomenon.

Murray discussed a study from the 1950s that exposed animals to laboratory TB strains selected for resistance to isoniazid. The isoniazid-resistant strain was found to be less virulent than susceptible strains in the animals. When the experiment was repeated with clinical strains, however, those strains were observed to be much more heterogeneous in their behavior in animals than were the laboratory strains. The results of these experiments

have been confirmed in recent years by multiple laboratories and are consistent with what is now known about MDR TB drug resistance. It is thought that the setting in which strains are transmitted acts as an "evolutionary" barrier: the less fit mutants are weeded out, and those mutants with greater fitness are selected. It is also likely that compensatory mutations[1] take place after an initial drug-resistance mutation. The sequencing of a set of evolved strains is now under way to identify such compensatory mutations.

Edward Nardell of Brigham and Women's Hospital stated that he and colleagues at the South African Medical Research Council and CDC have been researching the transmission of MDR TB from patients directly to sentinel guinea pigs to replicate and expand upon some of the early research of Richard Riley discussed by Murray. Although Nardell's group has observed higher rates of transmission than were reported in the past, rates of progression to active disease have been low. Nardell stated that from these studies, it is apparent that although the strains that are transmitted among normal hosts are likely to retain fitness, even attenuated strains likely survive and are transmitted in HIV-infected populations.

Gandhi added that colleagues in Durban have demonstrated that in South Africa over the past 10 years, certain predominant strains have been overrepresented among MDR and XDR TB cases (Pillay and Sturm, 2007). Principal among these are the Beijing strain and the KwaZulu-Natal strain. Until the mid-1990s, the KwaZulu-Natal strain existed in a fully susceptible form, but as drug-resistant forms of this strain emerged, they began and continue to be overrepresented in MDR and XDR TB patients.

Gandhi gave further evidence that XDR TB is being transmitted rather than acquired in Tugela Ferry by expanding on Friedland's comments regarding the Tugela Ferry epidemic. In 2006, Gandhi's group recorded the first 53 cases of XDR TB in South Africa. The study received international attention because of two notable factors (Gandhi et al., 2006). First, the XDR TB was highly fatal, with 98 percent of patients dying within a median of just 16 days after sputum collection. (More recent data presented in Chapter 2 indicate that the mortality rate has dropped to 82 percent [Gandhi et al., 2009].) This severe mortality was explained in part by the fact that all the patients were HIV infected (Gandhi et al., 2006). Second, because about half of these patients had never before been treated for TB, and 85 percent had a genetically similar strain, resistance was likely transmitted rather than acquired. The progression of XDR TB from June 2006 to 2007 is depicted in Figure 3-2, which shows facilities within KwaZulu-Natal Province where at least one XDR TB case was described or diagnosed. There were 6 such

[1] A compensatory mutation occurs when the fitness loss caused by one mutation is corrected by that mutation's epistatic interaction with a second mutation at a different location within the genome.

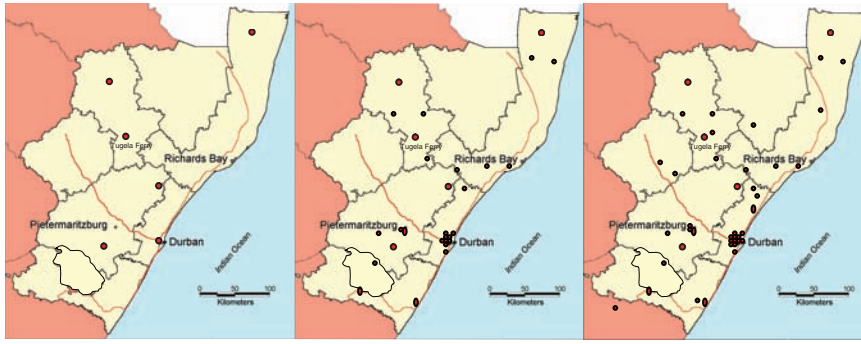


FIGURE 3-2 Facilities in KwaZulu-Natal Province where at least one XDR TB case was described or diagnosed from June 2005 to March 2007.
NOTE: There were 6 such facilities as of June 2005, a figure that had increased to 32 by June 2006 and 42 by March 2007. More than 60 facilities in KwaZulu-Natal have now reported cases of XDR TB.
SOURCE: Moodley et al., 2007.

facilities as of June 2005; by March 2007, that number had increased to 42, and it is now above 60 (Moodley et al., 2007). This situation is not limited to Tugela Ferry or to KwaZulu-Natal Province. In fact, cases of XDR TB have been found throughout South Africa, and prevalence rates have been roughly similar among the various provinces. XDR TB cases have also been reported from all of South Africa's neighbors.

Gandhi said it is generally thought that selection for drug-resistant strains, usually termed acquired or amplified resistance, occurs in settings where TB treatment is inadequate, patients fail to adhere to proper treatment regimens, or incorrect or non-quality-assured drugs are used for treatment. The other mechanism through which resistance is perpetuated is the direct transmission of drug-resistant strains, called primary or transmitted resistance. Gandhi stated that this latter mechanism has largely been neglected in the development of TB control programs. While acquired or amplified resistance due to inadequate treatment may explain how the very first cases of XDR TB emerged in South Africa and other parts of the world, it is difficult to say that the current magnitude of the epidemic could be attributable to acquired resistance alone. Gandhi reported that at his site in Tugela Ferry, there have been nearly 400 XDR TB cases in the past 3 years (Moll et al., 2007), and it is highly likely that the majority of these cases developed as a result of primary or transmitted resistance. But he hypothesized that even among those who had received prior TB treatment and relapsed (a majority of whom had documentation that their TB had been

cured or that they had completed their treatment course), the vast majority probably represented new infections rather than acquired resistance.

To better understand the role of acquired versus transmitted resistance among relapsed patients with MDR and XDR TB, molecular fingerprinting was used. Seventeen patients were identified for whom both initial susceptible isolates and follow-up MDR or XDR TB isolates were available. The results (shown in Figure 3-3) indicated that all 17 patients who relapsed with MDR or XDR TB had different genotypes in their relapse isolates compared with their initial isolates. Because the initial and relapse isolates differed in genotype, all 17 relapses occurred as a result of new infections and primary transmission, not acquired resistance. Additionally, while there was diversity among the TB strains in the initial isolates, only a few TB strains were seen among the MDR and XDR TB relapses (Andrews et al., 2008). This finding suggests not only that the relapses were due to new infections, but also that common sources of primary transmission are likely. High rates of HIV coinfection and hospitalization probably contributed to the risk for reinfection.

Figure 3-4 shows four different TB strains that were isolated from a single patient. The initial spoligotype pattern at the top is the baseline isolate, which was totally drug susceptible. Seventy days later, a follow-up culture indicated a different TB strain (second row) that was resistant to isoniazid and rifampicin. After second-line therapy was initiated, two additional TB strains were isolated, both of which were XDR TB. Genotyping, however, demonstrated that these two new XDR TB isolates resulted from new infections due to primary transmission, not acquired resistance to second-line therapy.

Gandhi suggested that three important lessons should be learned from these findings:

- Efforts must focus on creating infection control programs to prevent the further transmission of drug-resistant strains. Currently, most health care and congregate settings worldwide utterly lack infection control facilities.
- Early diagnosis of MDR and XDR TB cases is critical to facilitate infection control measures. Diagnosis of MDR and XDR TB is currently severely hampered by a lack of laboratory capacity and by the unavailability of a simple rapid diagnostic test that could be used in resource-limited settings (see the discussion in the next chapter).
- Further studies are needed to better characterize transmission patterns both in hospitals and in communities so that other means of curbing the epidemic can be devised.

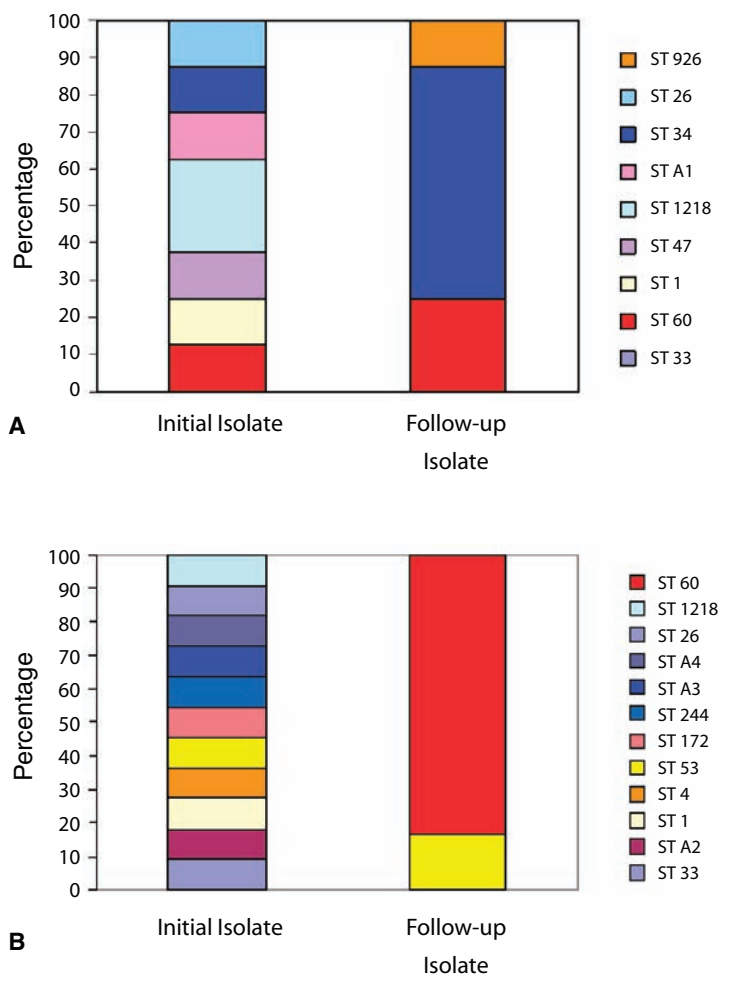


FIGURE 3-3 Genotypes of 17 patients with MDR and XDR TB relapse.
NOTE: Image A shows the genotypes of initial susceptible isolates and the follow-up MDR TB isolates for 7 patients. Image B shows the genotypes of initial susceptible isolates and the follow-up XDR TB isolates for 10 patients. All 17 patients had different genotypes in their relapse isolates compared with their initial isolates. Although there was diversity among the TB strains in the initial isolates, only a few TB strains were seen among the MDR and XDR TB relapses.
SOURCE: Andrews et al., 2008.

FIGURE 3-4 Four TB strains in a single patient.
SOURCE: Andrews et al., 2008. Copyright 2008 by the Infectious Diseases Society of America. All rights reserved.

PERSPECTIVE FROM RUSSIA

Nardell began his remarks by stressing that because a third of the world's population is already infected with TB, a static condition, the term "transmission control" is more appropriate than "infection control." Transmission denotes the process of an organism's going from one person to another, a dynamic process that needs to be interrupted if the epidemic is to be combated successfully.

Nardell presented his perspective on transmission in Tomsk, Russian Republic, a setting that has different characteristics from those of Africa: the climate in Tomsk is very different from that in Africa, highly effective treatment for MDR TB is available, and HIV infection is not widespread. Despite these differences, however, there is evidence of unrestrained transmission of MDR TB, and its rates are currently rising. To understand why MDR TB case rates were increasing despite the availability of effective treatments, a retrospective study was conducted. The investigators hypothesized that substance abuse was a strong predictor of nonadherence to TB treatment protocols and would therefore be correlated with MDR TB. However, the study results did not support this hypothesis. Instead, hospitalization (either early or later in the course of TB treatment) was correlated with MDR TB. A patient in Tomsk was six times more likely to develop MDR TB if hospitalized for drug-susceptible TB than if not hospitalized (Gelmanova et al., 2007). These results strongly suggest that transmission rather than resistance acquired predominantly by nonadherence is increasingly responsible for the rising MDR TB case rates in Russia and many other places. Nardell stated that the data presented by Nunn showing that the majority of new MDR TB cases occur among previously treated persons do not mean that these cases do not represent transmission and reinfection with a strain that is already drug resistant. Nardell argued that data from both Africa and China support the theory that cases of MDR and XDR TB are increasing because of transmission and reinfection. (Information on the current situation in Shanghai, China, presented by Qian Gao of Shanghai Medical College, is provided in Box 3-1.)

MITIGATING TRANSMISSION

Nardell stated that, given a setting with appropriate resources for transmission control strategies and more effective treatment, it is possible to cure and control the spread of MDR TB. This was convincingly demonstrated during the 1985–1992 resurgence of TB in New York City and Miami. With the infusion of many millions of dollars, MDR TB cases were effectively treated, and institutional spread was sharply decreased through the implementation of effective transmission control measures (this experience is dis-

BOX 3-1
Transmission of MDR and XDR TB in Shanghai

Each year 1.3 million new cases of TB are diagnosed in China. Based on a nationwide survey conducted in 2000, roughly 18.6 percent of these new cases are drug resistant, and 7.6 percent are MDR (Ministry of Health of the People's Republic of China, 2000). A more recent survey in Shanghai indicated that about 5.6 percent of TB patients had MDR TB; of these, 6.3 percent were XDR TB, and 31.4 percent were considered pre-XDR TB* (Zhao et al., 2009). More than 50 percent of the MDR and XDR TB cases are new, indicating that transmission may be a very important factor.

To better understand the cause of drug resistance among treated patients, a prospective study was conducted using genotyping technology. The goal of the study was to determine whether propagation of MDR and XDR TB was through acquired or transmitted resistance. The researchers sought to identify patients having two or more isolates with different drug susceptibility results. From their original patient pool they identified 32 patients that met their criteria. Strains were isolated and genotyped from patients both before and after treatment. Then using MIRU (mycobacterial interspersed repetitive unit) and IS6110 (insertion sequence 6110), the isolates were genotyped. Resistance could be classified as acquired if both isolates from the same patient had identical MIRU or RFLP (restriction fragment length polymorphism) patterns. Among the 32 patients, 84 percent had a pair of isolates with discordant patterns, and 16 percent had a pair of isolates with identical patterns. Thus, the researchers concluded that among treated patients, 84 percent of drug resistance was transmitted and 16 percent acquired. Gao stated that new strategies are needed to block the transmission of MDR and XDR TB.

*Pre-XDR TB is defined by Gao as resistant to isoniazid, rifampicin, and either fluoroquinolone or a secondary injectable drug (i.e., kanamycin, capreomycin, or amikacin), but not both.
SOURCE: Gao, 2008.

cussed in more detail below). However, implementing effective transmission control in resource-limited settings globally presents major challenges:

- Establishing community-based treatment outside a hospital currently is not feasible in some settings because the tradition and infrastructure for community care do not exist.
- Transmission control is expensive in many climates. For example, it is expensive to install and maintain ventilation systems in regions where natural ventilation is not sufficient.

- Technical expertise is often lacking to implement building design and engineering strategies.
- Health care workers and patients are stigmatized by wearing respirators, and therefore may neglect to do so.
- In many high-burden countries, health care workers are already infected and fail to see the rationale for transmission control practices.
- Many TB programs and hospitals do not fully appreciate the magnitude of the MDR TB problem or lack the will (and resources) to address it head-on. For example, some programs were under the impression that directly observed treatment, short course (DOTS)[2] alone would prevent the emergence of MDR TB and that MDR TB strains are less virulent than susceptible TB strains.

Nardell commented that, while the need for transmission control appears obvious, as recently as 2006 the current global plan from the Stop TB Partnership,[3] a roadmap for global TB control efforts, failed to mention it in any detail. Another factor in transmission control is the underappreciated importance of undiagnosed and unsuspected cases to the spread of disease. While the current focus of TB transmission control is on known cases, unsuspected cases may be responsible for a high proportion of transmission. A survey conducted in a hospital ward in Peru screened female patients that entered the ward for active cases of TB for an entire year. Of the 250 female patients treated in that ward, 40 (16 percent) were positive for TB by culture, 27 (11 percent) were positive by smear, and 8 (3 percent) had MDR TB. Thirteen of the 40 culture-positive patients were unsuspected cases, and 6 (46 percent) of those (i.e., the 13 unsuspected cases) actually had MDR TB, compared with 2 (7 percent) of the 27 suspected cases. Of the 8 patients that had MDR TB, 5 were smear positive, meaning they were highly infective (Willingham et al., 2001).

Congregate settings also have an impact on the propagation of MDR TB. As mentioned earlier, between 1985 and 1992 there was a somewhat focal MDR TB epidemic in the United States. Studies showed that MDR TB was being spread in hospitals, jails, prisons, homeless shelters, and residential AIDS facilities, among other congregate settings where both HIV-positive and -negative persons were exposed. In their retrospective review of how the New York City epidemic was brought under control, Frieden and colleagues (1995) credit more effective case finding and treatment and

[2] DOTS is an internationally recommended strategy for TB control. More information about the program and its five components can be found at http://www.who.int/tb/dots/en/.

[3] The Stop TB Partnership, established in 2000, consists of almost 1,000 organizations from around the world. The primary goal of this alliance is to eliminate TB as a public health problem. More information about the organization can be found at http://www.stoptb.org/.

effective institutional transmission control. The recent outbreak of XDR TB in KwaZulu-Natal in the absence of any transmission control interventions is reminiscent of these earlier outbreaks, not only in New York City and Miami, but also in Buenos Aires, Italy, and elsewhere in the world. Based on that experience, epidemic control will require interrupting transmission as well as providing effective treatment. Nardell attributed the extent of the epidemics in KwaZulu-Natal and China to ineffective transmission control strategies.

Potential Strategies

Nardell described a number of potential strategies with the potential to reduce the transmission of drug-resistant TB.

Hospital Triage and Separation. Over the past 15 years, Partners In Health has designed and implemented an effective transmission control program in Haiti that may be a useful model for other resource-poor settings. This is a community-based treatment program with relatively few patients requiring hospitalization. When hospitalization is required, however, a baseline triage and separation strategy is implemented. Patients are admitted to either the general medical ward, a TB pavilion, or very basic isolation rooms based on smear results and HIV status (see Figure 3-5). Although this approach is not ideal, Nardell argued that implementing this simple baseline strategy globally would help in combating the TB epidemic. The strategy is imperfect for several reasons: sputum smear-positive patients can transmit their disease, smear-positive patients in the TB pavilion can reinfect one another, and unsuspected cases pose a threat. Compared with current conditions, however, this baseline strategy could be highly effective if adapted and widely implemented in settings where no transmission control currently exists. At the same time, while apparently effective in Haiti, this model might not have the same success in Africa, where in many settings 85–90 percent of individuals infected with MDR TB are coinfected with HIV: It is more difficult to triage patients effectively when HIV infection is so dominant.

Ventilation. The rooms used in Haiti have natural ventilation supplemented by exhaust fans in isolation rooms. Under optimal design and climatic conditions, natural ventilation can be very effective in increasing the number of air changes per hour (ACH). Nardell presented data from KwaZulu-Natal to support this claim. Moll and colleagues (2007) reported at the recent IUATLD meeting in Paris that in a recently renovated ward, the rate of air replacement with windows closed and no ventilation equaled 0.3 ACH; the rate with closed windows plus ventilation equaled 16 ACH; and the rate with windows open and mixer fans on was much greater, equaling 67 ACH.

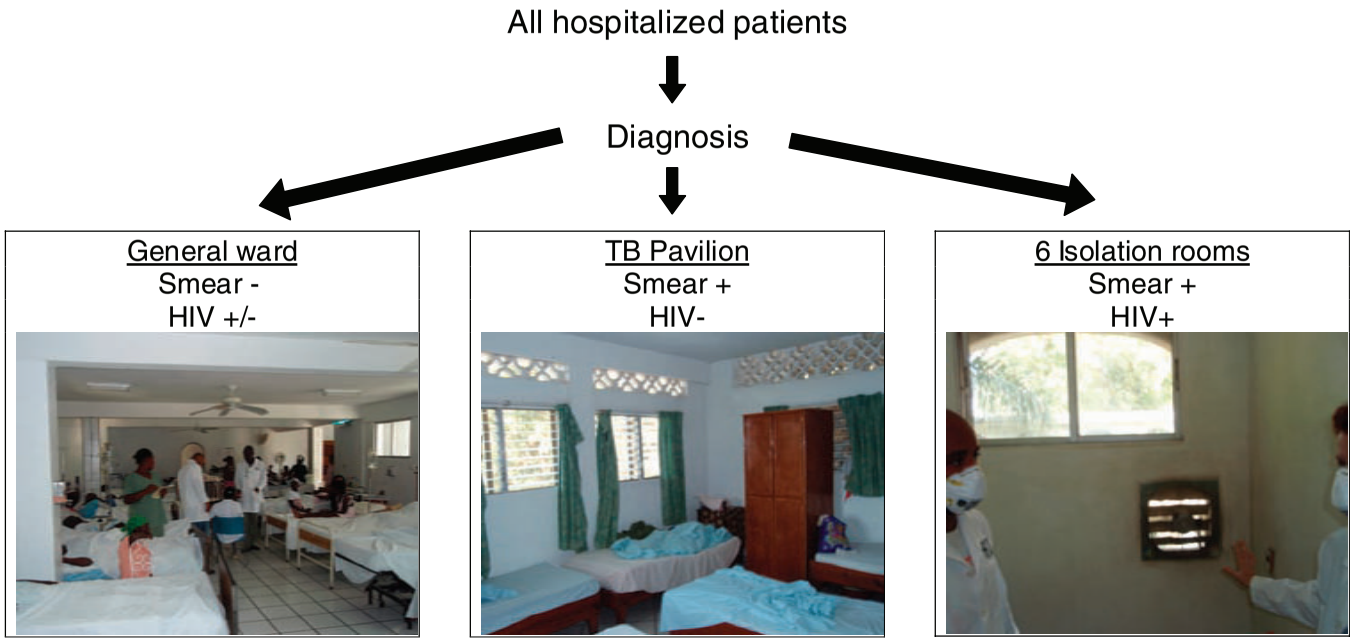


FIGURE 3-5 Partners In Health's community-based TB treatment triage strategy in Haiti.
NOTE: The general medical ward has natural ventilation and ultraviolet (UV) air disinfection; the TB ward has natural ventilation with fenestrated brick and more UV fixtures to disinfect the air than the general ward has; the six isolation rooms are off a common corridor, and each has a large exhaust fan built into the wall that draws air into the room from the corridor, as well as a UV fixture.
SOURCE: Nardell, 2008.

Respirators. The role of respirators in TB transmission control in resource-poor settings is controversial both because the equipment is costly and because the opportunities for transmission are legion. Respiratory protection is used optimally to reduce industrial risks for filterable airborne hazards—settings where the risky exposure activities are relatively few and can be identified for use of the equipment. In regions with high TB prevalence, exposure to the disease is commonplace, from unsuspected as well as from known sources. Moreover, because properly fitting disposable respirators are costly, they tend to be used for prolonged periods, and protection may deteriorate because of leaky face seals. Better respirators that are cleanable and reusable are needed for the developing world. A new program sponsored by the U.S. Veterans Administration is aimed at developing better respirators for health care workers requiring prolonged protection during a possible influenza pandemic. These nondisposable respirators may also be appropriate for use in resource-limited settings. At present, available nondisposable respirators interfere with speech, among other limitations. At the Partners In Health Lesotho MDR TB hospital, however, nurses and doctors have been using nondisposable respirators despite these limitations with the expectation of better protection at lower cost.

New Resources. New resources have been invested in several programs. The WHO infection control sub-working group (under TB-HIV) was established to provide guidance for and monitoring of transmission control interventions. New funding for TB transmission control has been made available through a number of major global funders, including PEPFAR and the Global Fund for AIDS, Tuberculosis, and Malaria. Multiple organizations, including the TB Control Assistance Program, CDC, and others, have launched training programs to develop the needed expertise. Harvard School of Public Health, for example, recently held a 2-week summer course for engineers and architects on design and engineering aspects of airborne infection control. Despite this infusion of new resources, however, the expertise needed to implement these interventions is lacking.

New Research. New research is under way on several novel interventions to enhance transmission control:

- Nardell stated that installation of upper-room UV air disinfection in a hospital and TB/HIV ward in Lima has been shown to reduce transmission by 72 percent. Additional experiments with upper-room UV disinfection are being conducted at an MDR TB hospital in South Africa, with sentinel guinea pigs being used to determine whether the intervention is effective in preventing transmission. That study is also showing excellent efficacy.

- The Harvard-based nonprofit organization Medicine in Need, or MEND, is developing inhaled antibiotics—specifically dry powder inhaled capreomycin that is aimed at improved therapy in the lung but may also provide a new approach to contagion control.

Summary

Farmer closed the discussion of infection control by stating that the apparent magnitude of transmitted MDR and XDR TB has profound implications for infection control, yet attention to this issue throughout the developing world is currently inadequate. Treating drug-resistant TB patients in hospitals is inherently problematic because it is difficult to prevent noninfected patients from being exposed. Rather than managing patients as inpatients in a hospital setting, it is important to establish effective community-based care that offers the potential to deliver higher-quality care, yield better outcomes, and reduce transmission.

IMPLICATIONS FOR HEALTH CARE WORKERS

As discussed earlier in this chapter, during the XDR TB epidemic in Tugela Ferry in 2006, 53 patients were diagnosed with XDR TB. Gandhi elaborated on the impact of that occurrence on health care workers in the region. Among health care workers involved in treating those afflicted by the XDR TB epidemic, there were four in whom XDR TB was suspected; all four were HIV infected, and all four died with a rapid course similar to that of the 53 patients. Since the initial cases were described, additional health care workers have been infected with both MDR and XDR TB. Strategies to protect health care workers have now been implemented, but the risk has not been eliminated. Friedland estimated that, at least in Tugela Ferry, about 75 percent of expected cases in health care workers could be averted if simple measures were instituted. He added that infection in health care workers has consequences for health care systems as well as individuals. The former consequences can be dire beyond those immediately affected, as they can deter other workers from providing care to TB patients or from working in an environment where TB patients are being treated.

4

Diagnosis

John Ridderhof of the GLI provided an overview of the state of TB diagnosis around the world and highlighted major gaps. Because of the worldwide shortage of laboratories capable of detecting drug resistance, a mere 5 percent of all MDR TB cases are detected. Table 4-1 shows results of a WHO survey of those countries with a high burden of TB. WHO recommends at least one culture laboratory per 5 million population and one facility capable of conducting drug susceptibility testing (DST) per 10 million. Ridderhof argued that, while these numbers may be adequate for the United States, they are inadequate for high-burden countries. Furthermore, as the survey results indicate, actual capacity is far less than even these recommended levels. Many countries lack a national reference laboratory to perform some of the most basic surveillance, and only a handful of countries meet the original recommended standard for culture laboratories. While there is additional capacity in the private sector and in some research institutions, it is generally not available to public health providers. The laboratories that are available are distributed disproportionately around the world; there is a particularly acute lack of supranational laboratories in sub-Saharan Africa. However, it is expected that the GLI will provide technical assistance and proficiency testing programs to help build this capacity.

ACTUAL NEED

Current global capacity allows for the conduct of approximately 10 million culture tests for the diagnosis of TB, although much of that capacity is centered in developed countries. In a recent effort led by WHO, it was

TABLE 4-1 Laboratory Capacity in High-Burden Countries, 2006

Country	National Reference Laboratory	No. of Culture Laboratories per 5 Million Population	No. of DST Laboratories per 10 Million Population
India	Yes	0.03	0.07
China	Yes	1.4	2.7
Indonesia	No	0.9	1.8
South Africa	Yes	1.3	2.7
Nigeria	No	0.0	0.0
Bangladesh	Yes	0.1	0.2
Ethiopia	Yes	0.1	0.1
Pakistan	No	0.1	0.2
Philippines	Yes	0.2	0.3
Congo	Yes	0.1	0.2
Russian Federation	No	34	68
Vietnam	Yes	1.0	2.1
Kenya	Yes	0.3	0.5
Tanzania	Yes	0.4	0.8
Uganda	Yes	0.5	1.0
Brazil	Yes	5.1	10
Mozambique	Yes	0.2	0.5
Thailand	Yes	5.1	10
Myanmar	Yes	0.2	0.4
Zimbabwe	Yes	0.4	0.8
Cambodia	Yes	1.1	2.1
Afghanistan	No	0.2	0.4

NOTE: DST = drug susceptibility testing.
SOURCE: Ridderhof, 2008 (based on data from WHO, 2008a, and Stop TB data from Mohamed Abdel Aziz, private communication; used with permission).

estimated that the actual need is at least 60 million culture tests (Weyer et al., 2007). There is also a critical need for enhanced DST capacity. To meet these needs, hundreds or thousands of new laboratories would have to be instituted around the globe. Considering just the centralized facilities needed to conduct molecular procedures for initial screening, many new facilities would be required. At least a $1 billion investment in laboratory capacity is necessary according to Ridderhof, not counting the training and systems that would have to be implemented in the facilities.

There is general agreement among partner organizations, including U.S. government agencies, that an expanded global effort is needed to address this issue. At the same time, a significant coordination challenge exists because so many different implementing organizations are involved. Within PEPFAR, for example, at least 20 U.S.-based organizations are developing laboratory capacity in Africa. The result can be duplication of effort and conflicting recommendations from multiple technical assistance consultants.

DIAGNOSTIC QUALITY

If patients are smear positive, at least 95 percent of these-smear positive specimens should also have a positive culture since the culture test is more accurate than microscopy (Kent and Kubica, 1985). But the experience of the Japanese TB Institute in working with national reference laboratories in a number of countries indicates extremely low yields, and these results were obtained using older, more forgiving methods, such as solid culture. A number of factors—for example, transport problems—could explain these results. Historically, however, there has been limited quality assurance for drug resistance surveillance.

CURRENTLY AVAILABLE DIAGNOSTICS

Although the development of line probe assays[1] and subsequent WHO approval have created a promising diagnostic tool for TB, scaling up the capacity to implement this tool widely will be challenging. Ridderhof outlined key strategic priorities for overcoming these challenges. The first is to establish a country-specific roadmap to determine the sequence of events for strengthening laboratory capacity and coordinating all of the implementing partners so they have a common strategic plan. The second is to develop the human resources, both consultants and qualified individuals at the country level, needed to direct and implement additional capacity. These resources will be especially important for implementing methodologies more complex than microscopy, such as molecular procedures, cultures, and DST. The third priority is to focus on improving biosafety. Infection control is an issue not just in the clinic (see Chapter 3), but also in the laboratory. Growing evidence indicates high rates of transmission in laboratories performing cultures and DST.

Van der Walt discussed South Africa's experience when the country investigated requirements for implementation of the line probe assay for routine diagnosis of MDR TB in 2008. An evaluation revealed that more than mere implementation of a new test in the laboratory was necessary; the approach to case finding—the systematic surveying of the population to identify all cases of infection—also needed to be changed to derive the full benefit of the new technology. Because of the issues identified above, South Africa decided to pursue a revised strategy for case finding of drug-resistant TB, in which screening for drug resistance takes place simultaneously with case finding. With this strategy, all specimens that are smear positive proceed immediately to a drug resistance screening with a

[1] For more information on line probe assays, refer to WHO's policy statement on Molecular Line Probe Assays for Rapid Screening of Patients at Risk of MDR TB, issued in 2008, available at http://www.who.int/tb/dots/laboratory/lpa_policy.pdf.

line probe assay. If there is any indication of resistance to rifampicin or isoniazid, a specimen proceeds to a full range of resistance tests while the patient is also referred for initiation of appropriate treatment. This strategy will be effective for early case finding of patients with resistant disease, and it has major implications for laboratories, as well as for patient referral processes. Currently, molecular assays are available in South Africa only at two provincial laboratories and the one national reference laboratory. The new strategy requires that (molecular) screening for drug resistance occur at the much lower-level primary health care facilities; this in turn means that far more molecular tests will be performed, but the number of unnecessary culture-based tests will be reduced.

Salmaan Keshavjee of Partners In Health discussed current strategies used by WHO and others to address issues of diagnostic capacity. In 2005, the World Health Assembly passed a resolution requesting the Director General to implement and strengthen strategies for the effective control and management of patients with drug-resistant TB.

In 2006, the Foundation for Innovative New Diagnostics (FIND), WHO, and Partners In Health collaborated to build a laboratory in Lesotho, a country with very rudimentary laboratory facilities. FIND's strategy was to provide the laboratory with a full-time technical assistance consultant and the right equipment, and to work with the laboratory to develop capacity, conduct training, and help establish the laboratory network. This strategy was effective in converting the laboratory to an effective state-of-the-art facility capable of performing both cell culture and DST. Since this pilot effort, the initiative has grown. In 2007, WHO and the Stop TB Partnership created the GLI, which will be active in 16 additional countries in Africa, South Asia, the Western Pacific, and Eastern Europe. The GLI's goal is to diagnose 74,000 new MDR TB patients by 2011.

A critical component of such an effort is securing sustainable funding from bilateral and multilateral donors to support the construction of in-country DST and rapid testing laboratories, as well as ongoing external quality assessments by supranational reference laboratories. The Lesotho example demonstrates that instituting ongoing quality assurance is a critical component of establishing new laboratories. Until these new laboratories are built, however, there is an immediate need for laboratory support to diagnose and treat MDR TB. Keshavjee suggested that excess laboratory capacity in the developed world should be used for this purpose.

POINT-OF-CARE (POC) DIAGNOSTICS

In addition to building comprehensive laboratories to conduct extensive diagnosis and analysis, there is a great need for cost-effective POC testing, such as a TB dipstick test or blood test, so that diagnosis can take place

during the patient's visit, and appropriate treatment can begin immediately. Two POC diagnostic systems that have been developed were discussed during the workshop: the GeneXpert cartridge system from Cepheid and another model from Akonni Biosystems Inc.

The Geneva-based FIND, with support from the Bill and Melinda Gates Foundation and NIAID, worked with Cepheid to develop a cartridge system specifically geared to the detection of TB and the simultaneous prediction of rifampicin resistance directly from the sputum of suspected TB cases. David Persing of Cepheid described the GeneXpert cartridge system as having the following characteristics:

- It is able to process both macrofluidics—specimens such as sputum, blood, stool, and pus (up to 4.5 milliliters)—and microfluidics.
- It has the ability to concentrate and purify samples from large volumes before they are processed for polymerase chain reaction (PCR) detection, so it does not require preprocessing of sputum specimens by centrifugation.
- It is a closed system, with no opportunity for contamination.
- The analysis can be performed in an on-demand, stat basis as soon as specimens have been collected.

Cepheid already has GeneXpert cartridge systems on the market for such pathogens as Group B streptococcus, enterovirus, methicillin-resistant *Staphylococcus aureus* (MRSA), and MRSA/SA (i.e., *Staphylococcus aureus* that is methicillin-sensitive). In addition, the system has been deployed for 3 years in 265 U.S. Postal Service mail sorting centers to detect the presence of *Bacillus anthracis*—the largest biothreat detection program in the country. To date, more than 7.5 million GeneXpert cartridges have been used to test 100 billion letters, with no false positives.

To customize the kit for use in detecting TB, scientists needed to develop an efficient method for working with sputum samples. Using a combination of sodium hydroxide, alcohol, and detergents, Cepheid developed a method for filtering and concentrating TB organisms from sputum without the use of a centrifuge. Once the TB organisms have been processed, sonic lysis, in the presence of glass beads, is used to blast them open inside the cartridge and release the DNA. This is followed by a nested PCR protocol, which is risky if performed in a laboratory because of contamination; as noted, however, the cartridge is completely contained, and the nested amplification yields about a 10,000-fold increase in sensitivity compared with conventional single-stage amplification of the same target. The PCR process used can detect a single genome of TB about 30–40 percent of the time and can consistently detect five genomes about 95 percent of the time. The PCR process amplifies the rifampin resistance locus, which carries the mutations that specify rifampin

resistance, and this is used as a surrogate marker for MDR TB because all the circulating MDR and XDR strains are rifampin resistant.

FIND is currently managing a clinical evaluation of the GeneXpert TB cartridge in five countries—Peru, Germany, Azerbaijan, India, and three sites in South Africa—which will be completed in December 2008. Those data will then be correlated with molecular data. Preliminary results for TB detection from Peru and Latvia indicate about 99 percent sensitivity for smear-positive, culture-positive cases. Sensitivity for smear negatives was approximately 87.5 percent, with a specificity of 97.3. Although the number of samples was small, preliminary findings indicate that 100 percent of all rifampin-resistant and rifampin-sensitive strains were correctly identified.

Charles Daitch of Akonni Biosystems Inc. described an alternative technology developed by his company in the early 1990s through a collaboration involving the U.S. Department of Energy, the Defense Advanced Research Projects Agency, and the Russian government. This system performs both genetic and immuno-based assays using a technology that is scalable and costs as little as US$8.00 per test. The technology, developed by the Engelhardt Institute of Molecular Biology in Moscow, is called three-dimensional gel drop arrays, and provides a hydrogel environment. A nano test tube can be loaded with a nucleic acid or an antibody for sample screening and detection. The assay can detect TB to very low limits, can hold hundreds of nano test tubes, and is adaptable to the addition of future sequences as they become available for MDR and XDR TB.

The system has the capability to process large samples (milliliters), avoiding the risk of not capturing and detecting the TB in a smaller sample. There are microarray screens for 75 different probes for profiling drug resistance, including two probes for TB complex—IS-6110 and IS-1245—and a probe for *Mycobacterium avium*, an organism that is resistant to most anti-TB drugs and can be mistaken for TB. Quality controls have been built into the assay. For example, everything on the array is replicated in quadruplicate, and the analysis automates interpretation to eliminate technician error.

The system looks at the difference between the wild-type signal and the mutation signal and can detect resistance, but only if the mutations are screened for in the assay. The assay's sensitivity depends on having the ability to screen for a wide array of mutations from throughout the world; sensitivity could be enhanced by creating a repository of markers or sequences that could be used to develop the test profile. Akonni Biosystems is currently working with collaborators to expand the chip coverage for sequences related to XDR TB.

Harrington offered some additional observations on the need for POC diagnostics and a commitment to research addressing the problem of diagnostic capacity. While the recent development of complex and expensive

technology is an important breakthrough, this technology is ill suited to resource-poor settings and is likely to remain unattainable for those most in need. Harrington advocated for the development of a TB dipstick test similar to the HIV pinprick test. That test, which costs US$1.00 and is 99 percent sensitive and specific, revolutionized HIV testing and was a key element in the scale-up of antiretrovirals worldwide. A TB dipstick would revolutionize TB care by providing a POC test that would reduce or eliminate delay. Harrington asserted, "In some ways it is even more important than a new drug or a new vaccine. There is a cure for most cases of TB, and there is reasonable treatment for MDR. But if it can't be diagnosed, millions of people will die of a treatable and curable disease."

Harrington outlined what needs to be done to achieve the goal of an effective dipstick test. First, there must be support from large organizations such as NIH and the Bill and Melinda Gates Foundation, as well as small-scale innovative efforts supported by smaller donors. Funding for TB diagnostics research currently represents only 6 percent of NIH's TB research investment and only 11 percent of its global TB research and development investment. Development of a TB dipstick test will also require a larger effort to identify biomarkers for active disease; platform development; and large, well-characterized clinical specimen banks more widely available than those in use today. Harrington suggested that meeting these needs will depend to some degree on effective advocacy.

5

Infrastructure and Health Care Delivery Systems

The structures of both in-country health care delivery systems and international donor programs are not optimal for the effective delivery of TB treatment, especially for drug-resistant forms, in many high-burden countries. Problems include underdeveloped general public health systems; an overemphasis on institutionalized care; fragmented funding and service delivery, which impede scale-up; inadequate training and technical expertise; inconsistent and sporadic technical assistance; ineffective diagnostic and referral networks; limited information technology (IT) and data collection; and inadequate financial resources. Following a review of the merits of vertical versus horizontal programs, the workshop turned to an examination of approaches that can be taken to address these infrastructure problems and the role that can be played by IT. In addition, a detailed case study of health care delivery programs in Cambodia and Ethiopia was presented (see Box 5-1 at the end of the chapter).

VERTICAL VERSUS HORIZONTAL PROGRAMS

A debate exists on the relative merits of vertical and horizontal programs. Vertical programs are donor driven and focus on a single disease, such as HIV or TB. Farmer stated that some in the global health community have criticized vertical programs, saying that they may fragment care, cannibalize funding and resources, and create inefficiencies, resulting in missed opportunities to treat multiple issues in an integrated fashion. Horizontal programs strengthen health systems so that they are able to address a broad range of needs, or at least to coordinate related disease

BOX 5-1
Universal Access for MDR Care:
The Cambodian and Ethiopian Perspectives

In Cambodia, the incidence of TB is currently approximately 500 per 100,000 population; MDR TB represents about 1.6 percent of new TB cases and accounts for about 2 percent of treatment-naïve coinfected TB/HIV patients. The Cambodian Health Committee (CHC) launched a pilot community directly observed treatment, short course (DOTS) program (community DOTS) in two rural provinces of the country, Svay Rieng and Kampot. The program served approximately 1 million people in 2006 and demonstrated a new-case detection rate of 75 percent and a cure rate of 95 percent. This community DOTS initiative was based on approaches the nongovernmental organization (NGO) has pioneered for the past 15 years. With scale-up of this pilot to the entire country of Cambodia and its population of 15 million, the detection rate for TB in the country as a whole is currently about 65.4 percent, and the cure rate is about 85 percent. Roughly one-quarter of HIV patients who present for AIDS outpatient care in CHC programs in Svay Rieng and Kampot have TB.

CHC has undertaken several initiatives and developed effective TB detection and treatment programs and AIDS prevention and care programs throughout Cambodia since initiating activities in 1994 in the highly impoverished and TB-burdened Svay Rieng Province:

- A large rural AIDS program was launched to develop urban centers of excellence for TB and AIDS care, and the CAMELIA (Cambodian Early versus Late Introduction of Antiretrovirals) clinical trial (to determine optimal timing of antiretroviral treatment for AIDS patients with TB) was initiated with the support of NIH and the French National Agency for AIDS Research (ANRS).
- In 2006, CHC made the first application to the Green Light Committee (GLC) for approval for second-line drug therapy for CAMELIA patients. CHC then made a second application on behalf of the country of Cambodia to expand treatment to another 100 MDR TB patients; this application was submitted in June 2007. In the interim, patients were treated with drugs purchased through privately raised donations to CHC.

These programs have proven effective. For example, Svay Rieng previously had the highest prevalence of TB in the country (about 700 cases per 100,000 population), and compliance with treatment was approximately 30 percent in 1994. Since these programs were undertaken, approximately 17,000 TB patients have been cured after receiving mainly rural community–based care or delivery of care by patient supporters and community-based health workers, as well as food supplementation. CHC uses approaches centered on pretreatment patient education, signing of treatment contracts, and linking of microfinance projects, and works closely with the National TB Program to create sustainability. In addition, the CHC Svay Rieng AIDS program was one of the first rural-based antiretroviral treatment sites in Cambodia and the first to integrate TB and AIDS services. In

2006, the CAMELIA clinical trial was launched in collaboration with NIH, the Comprehensive International Program of Research on AIDS (CIPRA), and ANRS. In addition, studies to determine the immune basis of immune reconstitution or paradoxical reactions are under way. This nesting of basic research in CHC delivery networks has been a powerful approach that has yielded basic insights about TB/AIDS pathogenesis.

The MDR TB program initiated by CHC in the CAMELIA trial was expanded to achieve universal access to MDR TB care in Cambodia: That program currently has 90 patients. While waiting for GLC drugs from UNITAID (GLC approval in October 2007, drugs ordered in November 2007, drugs arrived in May 2008), 38 patients were initiated on drugs purchased by CHC, and operational costs of the MDR TB program were shouldered by CHC. Thus, CHC filled the technical and procurement gap. CHC continues to manage the MDR TB program in partnership with the Cambodian National Tuberculosis Program and is actively searching for MDR TB cases from all treatment failures in Cambodia (approximately 800 patients).

The situation in Ethiopia is quite different. That country has a very large population (roughly 90 million); 129,000 new cases of TB are diagnosed per year, and the case finding rate is low (about 34 percent). Roughly 1.6 percent of new cases are MDR TB, and it is estimated that 12 percent of retreatment cases have MDR TB. This translates to about 6,000 new MDR TB cases per year in Ethiopia. In June 2008, Ethiopia submitted a GLC application for treatment for 45 patients, which was approved in November 2008.

CHC, known as the Global Health Committee (GHC) in Ethiopia, has initiated a new approach to south-to-south partnership with Ethiopia that involves working in collaboration with that country's Federal Ministry of Health to initiate MDR TB care. This collaboration is being accomplished through on-site training by the Cambodian team and visits by the Ethiopian team to CHC's MDR TB program in Cambodia. CHC is thereby transferring to Ethiopia procedures and operational community-based approaches to MDR TB and TB control that have proven extremely successful in Cambodia. CHC is also helping to fill the gap while Ethiopia waits for its GLC drugs by obtaining drugs to treat MDR TB.

In conclusion, an integrated approach to hospital- and community-based treatment has proven very successful in Cambodia, and it is hoped that such a program can be successfully transferred to Ethiopia. The power of a south-to-south partnership using approaches developed in similarly resource-poor and heavily TB-burdened countries and leveraging the resources of an NGO to fill technical and drug supply gaps is proving highly effective for dealing with the MDR TB emergency in both countries. In general, more rapid access to MDR TB drugs and on-the-ground technical support are necessary, as is large-scale funding for MDR TB similar to that furnished by the PEPFAR initiative, to make an impact on MDR TB.

SOURCE: Goldfeld, 2008.

programs. For example, establishing a diagnostic program only for TB is clearly inefficient. Yet the counterargument is that building public health infrastructure takes too long, and in the interim treatment will be denied to those in need. Farmer suggested that this debate is unnecessary: vertical programs, including those funded by such sources as PEPFAR and the Global Fund, can accomplish their immediate disease-specific goals while at the same time strengthen health systems and primary health care.

APPROACHES TO ADDRESSING INFRASTRUCTURE PROBLEMS

Addressing infrastructure problems at the local or national level in high-burden countries could have a positive impact on the global TB epidemic. Harrington suggested that one major problem to be overcome is the institutionalization of drug-resistant TB patients in improper settings, which may increase the risk of transmission (see Chapter 3), lower the morale of health care workers, and diminish patients' quality of life. In addition, many high-burden countries fail to use and expand existing human resources to provide ongoing follow-up and treatment support for people with all forms of TB. Through its community-based treatment program in Haiti, Partners In Health has demonstrated the need not only for trained doctors and nurses, but also for community health workers, treatment supporters, and laboratory technicians—all of whom need to be paid for their work. Farmer stated that investing in community health workers is what makes success sustainable. Many high-burden countries have high unemployment rates and a substantial supply of educated people who could take on these roles. Harrington suggested that creating systems that pay for treatment support needs to be a top priority.

Carol Nacy of Sequella, Inc., suggested a mechanism for training health care workers in high-burden countries. Developed countries could create curricula based on existing medical technology programs in the United States that could be formatted for distance education. Such programs could train individuals to perform clinical laboratory work and bring workers in developing countries up to the same skill levels as those in developed nations. Nacy also suggested creating a health volunteer corps, modeled after the Peace Corps, which would provide TB treatment in developing countries.

Finally, Farmer discussed the need for standards with respect to treatment and the organization of health care delivery, as well as metrics for measuring effectiveness and quality. The IOM and other academic and standards-setting bodies could play an important role in establishing such metrics, which would enable aid organizations to learn, for example, how vertical programs can strengthen health systems, how TB programs can deal optimally with complex forms of the disease, and how best to institute infection control programs.

ROLE OF INFORMATION TECHNOLOGY

Dale Nordenberg of Brigham and Women's Hospital addressed the role of IT in dealing with the global TB crisis. An information management infrastructure providing systems that support the disparate work of the laboratory technician, clinician, and public health program manager is essential. Globally, the demand for cultures and DST is great—on the order of 60 million cultures and 6 million DSTs annually (see Chapter 4). Thousands of new laboratories are needed, but so, too, are sound information systems. As laboratory volume and complexity increase, a laboratory information management system (LIMS) is needed to manage specimens and data effectively. These laboratory data are then transmitted to (1) medical record systems that provide physicians with a complete medical record to support care optimization, and (2) surveillance systems that support public health program management, such as prediction of medication requirements for particular programs. The challenges of building such systems, and doing so cost-effectively, are substantial in any setting, but are particularly daunting in resource-poor environments.

One vital role of IT in dealing with the TB crisis is enabling countries and projects to share data. Yet the costs involved in creating such a capability are a tremendous barrier to be overcome. In the United States, the estimated cost to establish a LIMS in a state public health laboratory is about $1–1.5 million per laboratory in the first year alone, with annual maintenance costs of approximately $500,000. In addition to the cost, however, complexities are involved in the implementation of a LIMS that are most pronounced when there is interest in and a need to share data among laboratories and programs.

A strategy for developing such a system has certain essential elements. Standards for effective data sharing must be formulated—a difficult task when technologies change rapidly, resulting in differences in case definitions, tests, manufacturers, and sensitivities and specificities. Nordenberg shared some of the lessons learned from the ongoing Public Health Laboratory Interoperability Project (PHLIP)—a collaboration between the Association of Public Health Laboratories and CDC. The objective of the project is to build a community of laboratories that can work collaboratively to help meet the challenges of building a national laboratory data sharing network. The laboratories recognized that each had different approaches and capabilities to generate diagnostic data for specific diseases because of differing public health priorities, disparate methodologies used by their scientists, and implementation of a variety of technology solutions depending on their budgets and expertise. By working as a community, PHLIP continues to lead the development of public health use cases for laboratory data, supporting data requirements, and a data sharing scheme that will

enable laboratories to support public health practice. The project is driven by a recognition that the creation of an efficient data sharing network is the product of close collaboration and harmonization of public health goals.

Harnish Fraser of Brigham and Women's Hospital described a system developed in Peru to illustrate the challenges associated with building what was ultimately a successful medical record system for MDR TB used both by the nonprofit Socios En Salud and the Peruvian Ministry of Health. The standard laboratory structure in Peru is hierarchical. Information typically passes from a small clinical laboratory that may do only smears to a larger regional laboratory that performs cultures and DST, to a national reference laboratory. Results from the larger laboratories return to the smaller laboratories in hard copy—a process that can result in long delays and loss of information. Before the project began, a median of 143 days elapsed between reporting of laboratory results and initiation of a revised second-line treatment regimen for a patient.

Peru's MDR TB electronic medical record system was also designed to assist in predicting drug supply needs. The system made it possible to model how long each patient was likely to be in treatment and to estimate what medications would be required for a group of patients. By combining the information on recruitment rate, time in treatment, and proportion of patients taking each drug based on the regimen that had been entered into the system, supply requirements for 6 months or longer could be predicted within about 5 percent or better.

Fraser also described a new open-source free electronic medical record system, OpenMRS.[1] This system is designed to support the collection and management of data on any medical condition, using a data dictionary to add new items. Partners In Health has now created a version of this system that supports the treatment of MDR TB as well as HIV. OpenMRS is also designed to support electronic data exchange with other information systems for laboratory, pharmacy, and reporting purposes. Open-source software is particularly useful because it allows multiple countries and projects to share in the system development process and maintain control over the data and the system; it can eliminate delays normally encountered when one is learning to build a system and make it easy to build individual implementations on top of an existing system. To illustrate the benefits of such an approach, Fraser described an HIV treatment project that created a data dictionary, which made it possible to share data among different projects and compare outcomes across sites without the need to program the system. Following the dictionary's creation, the source code was released with a public license so it could be downloaded. With some funding from WHO, a similar system was

[1] Information about OpenMRS and the program itself is available at http://www.openmrs.org.

developed for managing TB and MDR TB patients. This effort was part of a much larger initiative that is being supported by a number of organizations, including CDC, the Rockefeller Foundation, the Canadian International Development Research Centre, and a number of other funders, to create common standards and foster collaboration.

6

Global Systems for the Purchase and Delivery of TB Drugs

Paul Zintl of Partners In Health reported that in fall 2007, largely as a result of problems with GLC-approved projects around the world, the Working Group on Multidrug-Resistant Tuberculosis formed a Drug Management Subcommittee to help identify and quantify shortages of second-line drugs for such projects. The working group has worked with UNITAID, the Global Drug Facility (GDF) hosted through WHO, to resolve delivery and logistical issues. While the situation has improved, there is still a significant shortage of quality-assured drugs for GLC-approved projects. With the growth of diagnostic capacity and the increase in both projects and numbers of patients now being approved by the GLC, this shortage could be a real bottleneck.

The working group identified a combination of delivery and logistical problems. The GDF and the GLC were very understaffed to handle these problems, and the problems persist. But the real issue is the lack of consistent demand for quality-assured drugs. Suppliers are producing drugs on order because the demand is sporadic and unpredictable. In addition, once a project has been approved, actual enrollment often lags behind projected enrollment, and payments are slow.

As seen in Table 6-1, there has been substantial growth in the number of GLC-approved projects and the numbers of patients treated. In 2006, when WHO changed its global TB policy to recommend treatment of MDR TB patients under proper programmatic conditions, there were just over 5,500 patients enrolled in 32 approved projects. By 2007, there were 104 projects with 30,000 patients enrolled, including a rapid ramp-up in the

TABLE 6-1 Green Light Committee Projects and Patients, 2006–2009

	2006		2007–2009	
	Projects	Patients	Projects	Patients
AFRO	0	0	15	2,800
AMRO	6	3,305	16	4,575
EMRO	5	122	7	650
EURO	15	1,672	50	15,000
SEARO	3	210	9	1,500
WPRO	3	240	7	5,500
Total	32	5,549	104	30,025

NOTE: AFRO = African regional office, AMRO = American regional office, EMRO = Eastern Mediterranean regional office, EURO = European regional office, SEARO = South East Asia regional office, WPRO = Western Pacific regional office.
SOURCE: Zintl, 2008 (based on unpublished data from GLC Secretariat, Geneva 2008).

African region—from 0 to 15 projects. The large number of projects and patients in Eastern Europe, which includes Russia and the countries of the former Soviet Union, is also notable.

Despite the growth in GLC projects, they represent only a tiny fraction of the more than 400,000 MDR TB cases estimated to occur each year, as shown in Figure 3-1 in Chapter 3. The vast majority of patients are being treated through non-GLC-approved projects under programmatic conditions that may not be ideal for treatment of MDR TB and with drugs that are not quality assured. As shown in Figure 3-1, in 2008 there were an estimated 500,000 MDR TB cases worldwide. Of these, only 12,000 were expected to receive GLC-approved treatment; 34,000 were expected to be treated with a non-GLC regimen; and the remainder represent new, untreated cases.

The non-GLC market for second-line drugs is substantial. IMS Health has given WHO and the Drug Management Subcommittee data that show quite robust sales of all second-line TB drugs. There are, for example, a large number of manufacturers of second-line drugs in Russia, both domestic and foreign. In the *Pathway to Patients* report, the TB Alliance also confirms a very large and growing market for second-line drugs (TB Alliance and the Global Alliance for TB Drug Development, 2007).

PROCUREMENT PROBLEMS

Zintl noted that the increased incidence of MDR TB has already led to a significant growth in the world supply of second-line TB drugs. Unfortunately, however, most of this increased production and consumption is of second-line drugs that are not quality assured.

As countries confront their epidemics of MDR TB, there will be a significant expansion of public-sector treatment programs, as well as growth in the government- and donor-sponsored purchase and procurement of second-line TB drugs. This expansion could help boost the desperately short supply of quality-assured drugs if efforts to stimulate demand for such drugs in MDR TB priority countries are successful. This is likely to happen only if the GLC/GDF approval and procurement processes are overhauled. The existing GLC approval and GDF/International Dispensary Association (IDA) procurement processes were, appropriately, designed for the pilot project era when DOTS-Plus[1] was being evaluated, before WHO had revised its TB control policy calling for treatment of patients with MDR TB in the context of a strong DOTS TB control program. But the pilot project approval and procurement model is no longer appropriate, practical, or effective. The approach is too fragmented and has failed to achieve necessary scale. There is only one quality-assured supplier for each of the second-line drugs for GLC projects (except for one drug that has two quality-assured suppliers). All GLC-approved projects go through a single procurement agent, IDA, and there is only one source of supply. Such limited supply depth carries risks, as evidenced by a recent manufacturing bottleneck. Manufacturers of two key drugs shut down their plants—one because of a batch problem, the other because of factory expansion. As a result, deliveries of those drugs were put on hold for a considerable period of time, causing serious supply shortages and stock-outs in treatment projects.

THE DRUG QUALITY ISSUE

It is important that MDR TB treatment projects follow WHO treatment guidelines and that they use drugs that are quality assured. Poor treatment or treatment with poor-quality drugs will not cure patients and will ultimately generate XDR TB. For some countries and projects, the existing GLC/GDF approval and procurement mechanisms will still be adequate, but this will not be the case for other countries—notably those with the highest burdens of MDR TB. To address this shortcoming, countries could be enlisted to participate in a revamped system that would monitor their compliance with WHO treatment guidelines and the extent of their use of (or failure to use) quality-assured drugs. Not all quality-assured second-line TB drugs can be channeled through the GLC, nor do they need to be.

At the same time, calling for the existing GLC/GDF approval and procurement system to be revamped is not to minimize the seriousness of the challenge posed by nonstandard treatment protocols and poor-quality

[1] DOTS-Plus is a supplement to the standard DOTS therapy that takes into account specific issues that need to be addressed where there is a high prevalence of MDR TB.

drugs. Treatment and drug quality vary tremendously across programs and countries. The markets for second-line drugs in priority countries are large and growing rapidly; they are fragmented, and regulation and monitoring of these markets is nonexistent or inconsistent at best. The problem stems from largely insufficient insistence by countries that their MDR TB patients be treated with second-line drugs that are quality assured. In some cases, there are significant disagreements among regulators in different countries about what constitutes quality assurance.

A workshop participant from Management Sciences for Health asked whether suppliers face any risk associated with not participating in the prequalification process. Zintl replied that it should be made clear that the market is moving toward becoming totally quality assured through requests for national commitments from all high-burden countries. The expanding epidemic and increasing diagnostic capacity are creating a very attractive market for manufacturers, and there will be an incentive for both domestic markets and export production. If demand forecasting is reliable, companies such as Lupin Limited and Cipla will be eager to expand and to seek prequalification. But unless manufacturers see a growing market for quality-assured drugs—and, consequently, a declining market for drugs that are not quality assured—they will have no incentive to become prequalified. Thus if India, China, Russia, and the other priority countries continue to be willing to buy and treat patients with drugs of uncertain quality, it is the market for drugs of uncertain quality that will continue to grow, and manufacturers will see little return on investments in ensuring quality. Zintl added that in the short term, it may be necessary to sacrifice pricing objectives to achieve quality objectives, particularly in those high-burden countries where companies need a financial incentive to raise their quality standards.

Nacy asked whether there is a way to reward companies for bearing the expense of quality assurance. Zintl replied that there certainly is, and that such rewards are important interim steps. It is necessary to work with funders such as UNITAID to develop incentives. One such proposal is to provide, for example, a 25 percent premium over 2 years or to offer a minimum-purchase contract. The Center for Global Development, the Clinton Foundation, and others are already exploring such ideas.

Iain Richardson of Eli Lilly and Company noted the wide discrepancy between prices in local private markets, where many manufacturers are competing, and the prices of drugs provided through the GDF. To ensure that these companies produce drugs of high quality, it is necessary both to assure them of a good return on their investments in quality and to let them know that unless drugs are quality assured, they will not be able to be sold.

Need for Better Data on Drug Quality

Data on the quality of second-line drugs that have not gone through GLC prequalification are limited. Keshavjee noted that Management Sciences for Health studied this issue in Brazil—a market that is reasonably well regulated—and found that there have been problems with drugs. Nunn added that unpublished data from more than 10 years ago on first-line drug fixed-dose combinations show that many products, particularly from the Indian market, were substandard. Looking at the high rates of MDR TB in the former Soviet Union, one of the major hypotheses is drug quality. Cassell added that anecdotal evidence from Kazakhstan, for example, makes clear that substandard products are contributing to resistance and poor patient outcomes.

Sloutsky discussed what is really meant by "quality" and "assured." The ultimate issue regarding the quality of an antibiotic drug is its potency. In package inserts, drug manufacturers do not provide data on exact potency but list the potency within a range of concentrations. This range can be rather wide, with the minimum and maximum values being significantly different. For example, a drug may be listed as active in the range of 0.5–20.0 micrograms per milliliter. When one is dealing with second-line drugs and working close to critical concentrations, each drug dilution is meaningful, and such a wide range does not help in assessing the real potency. Sloutsky suggested that, if the drug manufacturer's package insert cannot be relied upon as a measure of quality assurance, this assessment must be conducted by an independent laboratory, and the test must be performed anonymously to ensure the integrity of the process. This testing can be requested by the GLC, the GDF, or other governing bodies, which can make it mandatory for drug manufacturers.

Nunn described current efforts to collect data on drug quality by looking randomly at TB drugs from various sites in different countries and measuring their active ingredients—similar to what was done with AIDS and malaria. But results from those studies are months away. Nunn added that much more data is needed, not only on first-line but also on second-line drugs, for which there are reasons to suppose the quality may be worse. Castro emphasized the need for a strong data collection effort going forward. He noted that intuitively, the contribution of poor-quality drugs to drug resistance appears clear, but data are needed to make an airtight case for the link—both baseline data and ongoing monitoring as progress is achieved. Cassell added that the private sector is making a strong commitment of effort and dollars to address the issue of counterfeit and substandard drugs as a result of contamination of heparin and other incidents. She suggested that this would be a fruitful area for collaboration between the private sector and the global health community.

Quality Enforcement

Observing that TB epidemics are spreading across borders, Jim Yong Kim of the Harvard School of Public Health and Harvard Medical School inquired about the possibility of the International Health Regulations (IHR) being invoked to address the cross-border spread of MDR and XDR TB. Nunn noted that the possibility of XDR TB being brought under the IHR had been discussed by the first of the task forces on XDR TB only a couple of years ago. He said, "The feeling then was that [XDR TB] doesn't easily fall under the IRH because it is not a question of a disease going from A to B. The likelihood is that the disease is already [at] B." The issue arose again in 2007 when a U.S. civilian who was thought to have XDR TB traveled internationally. Nunn added that to make a stronger case for invoking the IHR, it is first necessary to prove that drug quality is poor. This represents both a challenge and a strategic opening, as the results of quality assessments are beginning to emerge.

Quality Strategies

Zintl suggested that, to address the challenges raised above, countries must first commit to the purchase of quality-assured drugs. A proposal has been made to the GLC and the GDF to allow some large countries to purchase directly from manufacturers as long as they can demonstrate that the drugs are quality assured. This proposal raises a major economic issue, as indicated by the high prices of these drugs in Russia. Economic interests can be expected to cause countries to fight this proposal—particularly countries with very high burdens that will want to buy drugs from domestic manufacturers. It is essential, Zintl said, first to obtain evidence that products from manufacturers are already or on their way to being quality assured and then, over time, begin the difficult work toward further regulatory harmonization. Large, high-priority countries are not likely to commit immediately to procuring drugs only from an approved GDF list. But once they become willing to commit to quality-assured drugs, they may be cautiously willing to shift more and more of their second-line TB drug procurement to products that meet stringent regulatory standards.

In addition to quality assurance of drugs, it is important to obtain commitments to appropriate treatment of MDR TB. Such a commitment will include proper programmatic treatment and the use of drugs that are quality assured, and it will require engaging large, priority countries in pressing their pharmaceutical companies to become prequalified or, at a minimum, to be approved by stringent national regulatory authorities. A ministerial meeting is being held in Beijing in April 2009 to urge countries to make these commitments.

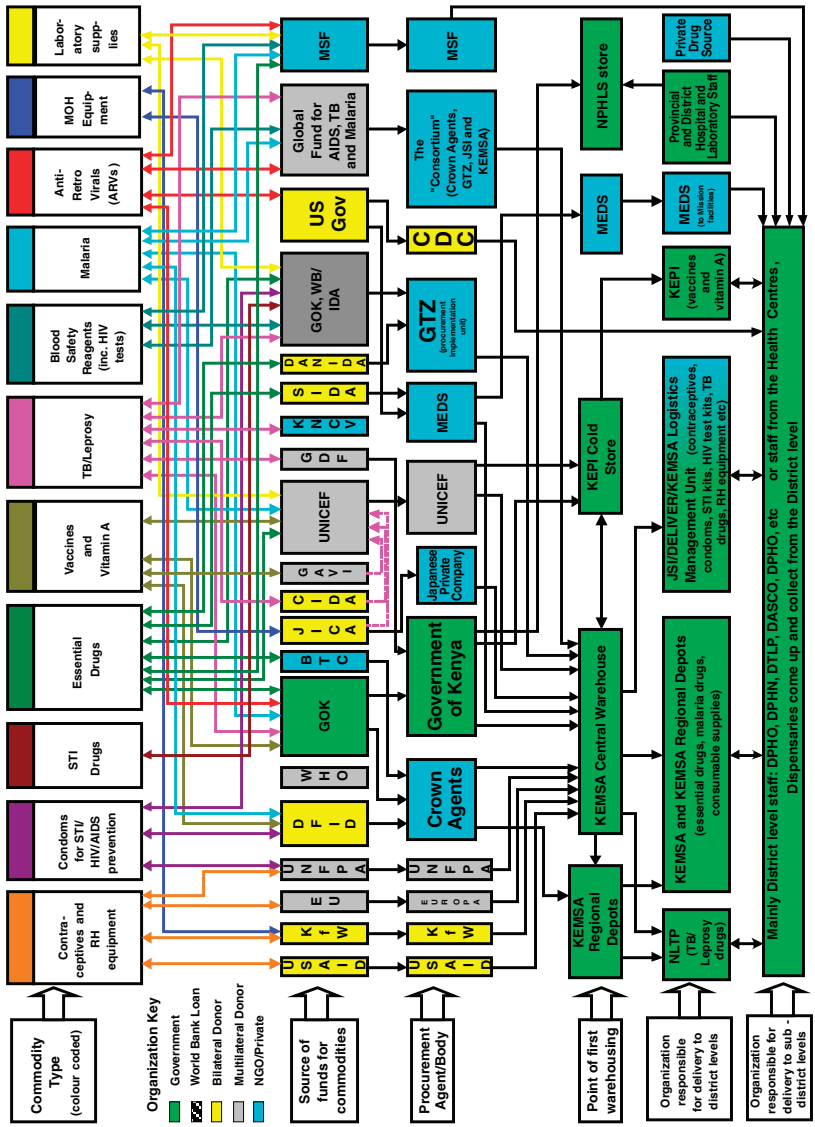
Countries are rapidly scaling up MDR TB treatment, but they are doing so mainly with drugs of unknown quality and without proper programmatic management. According to Zintl, it will be difficult to change this situation without a significant financial commitment and a willingness to alter the dynamics of the robust markets that are selling drugs of unknown quality. It is critical to engage countries in this process and then to track their progress over time. This effort should begin even before the Beijing meeting in 2009.

NEED FOR ACCURATE DEMAND FORECASTING

Levine discussed the critical role of accurate demand forecasting, drawing on lessons learned from dealing with malaria. In a recent report, a CGD global health working group examines issues related to demand forecasting, analyzing the underlying incentives and risks borne by the various parties involved with providing or using information for demand forecasting (CGD, 2007).

The past 5–7 years have seen major changes not only in the absolute volume of resources, but also in their use. While donor funding for the development and purchase of vaccines, diagnostics, and drugs traditionally represented a relatively small portion of donor contributions, it now accounts for approximately 60–65 percent of the total. While greater access to modern medicines benefits millions of people around the world, there is a discontinuity between demand and supply as manufacturers attempt to understand the current demand for their products and how to respond. Complicating matters is the entry of a range of new suppliers into the market, including both innovative multinational and emerging firms. With respect to the pipeline for malaria drugs, the good news is that, after a long period with limited new prospects, a large number of new products are now poised to come on line. While public–private partnerships have been working hard to develop new molecules into viable products, however, they have paid little attention to whether there will be a sustainable market for all of those products in the future and what the capacity requirements will be.

Companies face growing but fragmented demand, a dynamic supplier landscape, and an accelerating pipeline. As a result, they are finding it difficult, according to Levine, to estimate demand with sufficient clarity to make a strong business case for investment within the firm or to know how to engage with the global health players, whether in a commercial or a corporate social responsibility capacity. To illustrate one aspect of the complexity these companies face, Figure 6-1 depicts the procurement process in Kenya. It details the fragmentation of funders, the diversity of service providers, and the range of commodities that are being purchased in varying amounts at varying times, mainly from international sources.


Commodity Type (colour coded)
Contra-ceptives and RH equipment
Condoms for STI/ HIV/AIDS prevention
STI Drugs
Essential Drugs
Vaccines and Vitamin A
TB/Leprosy
Blood Safety Reagents (inc. HIV tests)
Malaria
Anti-Retro Virals (ARVs)
MOH Equip-ment
Labor-atory supp-lies
Organization Key
Government
World Bank Loan
Bilateral Donor
Multilateral Donor
NGO/Private
Source of funds for commodities
USAID
SKAfW
UNFPA
DFID
WHO
GOK
BTC
JICA
GAVI
UNICEF
GDF
KNCV
SIDA
DANIDA
GOK, WB/ IDA
US Gov
Global Fund for AIDS, TB and Malaria
MSF
Procurement Agent/Body
USAID
SKAfW
EUROPA
UNFPA
Crown Agents
Government of Kenya
Japanese Private Company
UNICEF
MEDS
GTZ (procurement implementation unit)
CDC
The "Consortium" (Crown Agents, GTZ, JSI and KEMSA)
MSF
Point of first warehousing
KEMSA Regional Depots
KEMSA Central Warehouse
KEPI Cold Store
JSI/DELIVER/KEMSA Logistics Management Unit (contraceptives, condoms, STI kits, HIV test kits, TB drugs, RH equipment etc)
NPHLS store
MEDS
KEPI (vaccines and vitamin A)
Private Drug Source
Provincial and District Hospital and Laboratory Staff
MEDS (to Mission facilities)
Organization responsible for delivery to district levels
NLTP (TB/ Leprosy drugs)
KEMSA and KEMSA Regional Depots (essential drugs, malaria drugs, consumable supplies)
Organization responsible for delivery to sub - district levels
Mainly District level staff: DPHO, DPHN, DTLP, DASCO, DPHO, etc or staff from the Health Centres, Dispensaries come up and collect from the District level

Each of these funders has its own budget cycle, and unpredictable increases or decreases in the willingness or ability to procure products have obvious implications for reliable supply.

Levine highlighted disconnects between the information suppliers receive about demand and the amounts for which there is money to purchase needed products, as well as the supply actually offered by the firms. In the case of malaria, WHO's demand forecasts have been off by orders of magnitude. For example, the original demand for Coartem was estimated to be 55 million doses; the actual orders turned out to total 14 million doses. The following year, WHO estimated that 100 million doses would be demanded and purchased; the actual number turned out to be 55 million. Sanofi had to discard 10 million tablets of artesunate because of overforecasts. Likewise, Uganda ended up with $1–2 million worth of expired AIDS drugs and other donor-purchased items because of overforecasts. Similar stories exist for other products. One possible exception is many vaccine products, for which demand is somewhat easier to project and UNICEF has a longer track record.

Many of those within industry with a strong commitment to participating in the global health effort identify weak demand forecasting as one of

FIGURE 6-1 Commodity logistics system in Kenya (as of April 2004).
NOTE: BTC = Belgian Technical Cooperation, CDC = Centers for Disease Control and Prevention, CIDA = Canadian International Development Agency, DANIDA = Danish International Development Agency, DASCO = District AIDS/STD Coordinator, DFID = UK Department for International Development, DLTP = District Leprosy and TB Program, DPHN = district public health nurse, DPHO = district public health officer, EU = European Union, GAVI = Global Alliance for Vaccines and Immunization, GDF = Global Drug Facility, GOK = Government of Kenya, GTZ = Deutsche Gesellschaft für Technische Zusammenarbeit, IDA = International Dispensary Association, JICA = Japan International Cooperation Agency, JSI = John Snow Inc., KEMSA = Kenya Medical Supplies Agency, KEPI = Kenya Expanded Program on Immunization, KFW = Kreditanstalt für Wiederaufbau, KNCV = Koninklijke Nederlandse Centrale Vereniging tot bestrijding der Tuberculose (Dutch Tuberculosis Foundation), MEDS = Mission for Essential Drugs and Supplies, MOH = Ministry of Health, MSF = Médecins sans Frontières (Doctors Without Borders), NGO = nongovernmental organization, NLTP = National Leprosy and TB Program, NPHLS = National Public Health Laboratories Services (Kenya), RH = reproductive health, SIDA = Swedish International Development Cooperation Agency, STI = sexually transmitted infection, UNFPA = United Nations Population Fund, UNICEF = United Nations Children's Fund, USAID = U.S. Agency for International Development, WB = World Bank.
SOURCE: Global Health Forecasting Working Group, 2007. Constructed and produced by Steve Kinzett, JSI/Kenya. Copyright 2007 CGD, reprinted with permission.

the leading, if not the greatest, challenges in providing global health products. It is difficult for a company to make the case for investing in either research and development or manufacturing capacity because of the poor track record of demand forecasting.

According to Levine, one of the central problems is that industry, public health specialists, and others in the global health community define needs differently. Governments, donors, funders, and procurement intermediaries in global health often think in terms of estimated need—how much one would ideally like to provide—as opposed to genuine demand, or how much one realistically expects will be purchased. Translating need to actual demand is complex, and involves applying multiple layers of information about both the available financing and the capacity of the health system to provide drugs and scale up when new products are being introduced or new programs are being initiated.

Demand forecasts, then, are an essential link in the supply chain and play five critical roles:

1. Facilitate the matching of supply with demand and eliminate lag time that often occurs.
2. Lead to new products because manufacturers have a realistic picture of future market potential.
3. Enable developing-country health systems to expand to meet changing supply and demand requirements.
4. Permit funders to plan purchases and allocate resources more efficiently.
5. Make bottlenecks more transparent so they can be addressed through advocacy and policy.

If all stakeholders would benefit from better demand forecasting, one might ask why it does not improve. To answer this question, one must examine incentives that drive behavior. Figure 6-2 shows the different stakeholders and the different kinds of risks they face, such as batch failure and leakage of funds. The one stakeholder that consistently faces the most risk is the manufacturer. Given this risk environment, Figure 6-3 shows the various incentives the different players have. Many of the stakeholders along the supply chain have an incentive to overestimate potential demand. In contrast, suppliers—who face the greatest risk—have an incentive to underestimate demand and reduce their exposure. According to Levine, while this example focuses on the artemisinin combination therapy (ACT) supply chain for malaria, similar incentives apply to the supply chain for TB drugs.

Levine offered three recommendations. One was to take forecasting seriously as critical to having a functioning global health system and to

	Supply-side facilitators	Suppliers	Quality regulators	Global technical agencies	Aggregate demand forecasters	Funding agencies	Procurement agents	Logistics providers	National buyers
Supply-side risks									
Batch yield risk	No risk	Low risk	No risk	No risk	No risk	No risk	No risk	No risk	No risk
Excess inventory risk									
Economic	No risk	High risk	No risk	No risk	No risk	Low risk	No risk	No risk	Moderate risk
Reputational	No risk	No risk	No risk	No risk	Low risk	No risk	No risk	No risk	No risk
Long-term overcapacity risk									
Economic	No risk	High risk	No risk	No risk	No risk	No risk	No risk	No risk	No risk
Reputational	Low risk	No risk	No risk	No risk	Low risk	No risk	No risk	No risk	No risk
Shortage risk									
Economic	No risk	Moderate risk	No risk	No risk	No risk	No risk	No risk	No risk	No risk
Reputational	No risk	High risk	No risk	Low risk	Moderate risk	Low risk	No risk	No risk	Moderate risk
Demand-side risks									
Price increase	No risk	No risk	No risk	No risk	No risk	Moderate risk	No risk	No risk	Moderate risk
Price decrease	No risk	Moderate risk	No risk	No risk	No risk	No risk	No risk	No risk	Low risk
Budget and purchasing power risks									
Grant approval and disbursement timing	No risk	High risk	No risk	No risk	No risk	Moderate risk	No risk	No risk	High risk
Sustainability of funding	Low risk	Moderate risk	No risk	No risk	No risk	High risk	No risk	No risk	High risk
Obsolescence risk	Low risk	Moderate risk	No risk	No risk	No risk	No risk	No risk	No risk	Moderate risk
Regulatory and quality risks									
Lack of approved drugs	No risk	No risk	Low risk	No risk	No risk	No risk	No risk	No risk	No risk
Regulatory enforcement risks									
Counterfeit product	No risk	Moderate risk	No risk	No risk	No risk	No risk	No risk	No risk	Moderate risk
Safety of approved drugs	No risk	High risk	High risk	No risk	No risk	Low risk	No risk	No risk	Moderate risk
Logistical risks									
Nontimely delivery	No risk	Moderate risk	No risk	No risk	No risk	No risk	Moderate risk	Moderate risk	Moderate risk
Losses in the distribution chain	No risk	No risk	No risk	No risk	No risk	Low risk	No risk	Moderate risk	Moderate risk

FIGURE 6-2 Artemisinin combination therapy (ACT) supply chain risk map.
SOURCE: Global Health Forecasting Working Group, 2007. Copyright 2007 CGD, reprinted with permission.

	Supply-side facilitators	Suppliers	Quality regulators	Global technical agencies	Aggregate demand forecasters	Funding agencies	Procurement agents	Logistics providers	National buyers
Supply side									
Develop innovative products	Incentive	Incentive	Indifferent	Indifferent	Indifferent	Indifferent	Indifferent	Indifferent	Indifferent
Increase size of the supply market	Incentive	Disincentive	Indifferent	Incentive	Indifferent	Incentive	Disincentive	Indifferent	Incentive
Decrease supply chain lead time	Incentive	**Indifferent**	Indifferent	Incentive	Indifferent	Indifferent	Incentive	Indifferent	Incentive
Overforecast in the short term	Indifferent	Disincentive	Indifferent	Indifferent	**Incentive**	**Incentive**	**Incentive**	Indifferent	**Incentive**
Underforecast in the short term	Indifferent	Indifferent	Indifferent	Indifferent	Disincentive	Disincentive	Disincentive	Indifferent	Disincentive
Overforecast in the long term (1-5 years)	**Incentive**	Disincentive	Indifferent	**Incentive**	Indifferent	**Incentive**	Indifferent	Indifferent	**Incentive**
Underforecast in the long term (1-5 years)	Disincentive	Disincentive	Indifferent	Disincentive	Indifferent	Disincentive	Indifferent	Indifferent	Disincentive
Sharing information on demand, inventory…	Incentive	Disincentive	**Indifferent**	**Indifferent**	Incentive	**Indifferent**	**Indifferent**	**Indifferent**	**Indifferent**
Demand side									
Decrease wholesale price of artemisinin-based combination therapy drugs	Incentive	Disincentive	Indifferent	Incentive	Indifferent	Incentive	Indifferent	Indifferent	Incentive
Decrease retail or end-customer price of artemisinin-based combination therapy drugs	Incentive	Incentive	Indifferent	Incentive	Indifferent	Incentive	Indifferent	Indifferent	**Indifferent**
Expedite grant approval and disbursement	Indifferent	Incentive	Indifferent	Indifferent	Indifferent	Incentive	Indifferent	Indifferent	Incentive
Rapid adoption of artemisinin-based combination therapy drugs	Incentive	Incentive	Indifferent	Incentive	Indifferent	Incentive	Indifferent	Indifferent	**Indifferent**
Enhance the level and sustainability of funding	Incentive	Incentive	Indifferent	Incentive	Indifferent	Incentive	Indifferent	Indifferent	Incentive
Regulatory and quality									
Ensure regulatory compliance and safety	Incentive	Incentive	Incentive	Indifferent	Indifferent	Incentive	Indifferent	Indifferent	Incentive
Expedite regulatory approval of new drugs	Incentive	Incentive	**Indifferent**	Incentive	Indifferent	Incentive	Indifferent	Indifferent	Incentive
Logistical and miscellaneous									
Improve efficiencies in distribution chain	Indifferent	Indifferent	Indifferent	Incentive	Indifferent	**Incentive**	Indifferent	Incentive	Incentive
Ensure availability of complementary inputs	Indifferent	Disincentive	Indifferent	Incentive	Indifferent	Incentive	Indifferent	Indifferent	Incentive
Achieve long lasting success (eradication)	Incentive	Indifferent	Indifferent	Incentive	Indifferent	Incentive	Indifferent	Indifferent	Incentive
Have rigorous accountability in funds usage	Indifferent	Indifferent	Indifferent	Indifferent	Indifferent	Incentive	Indifferent	Indifferent	**Incentive**

FIGURE 6-3 Artemisinin combination therapy (ACT) supply chain incentives map.
NOTE: The shading indicates the most powerful incentive effects.
SOURCE: Global Health Forecasting Working Group, 2007. Copyright 2007 CGD, reprinted with permission.

apply some good-practice principles that have been used in other sectors. The second was to create a global health infomediary—basically a clearinghouse for key demand information that would be completely separated from any advocacy functions and would be viewed as credible by industry. The third was to ensure that those who are providing the money and the information about demand have a clear stake in accurate forecasting. It is essential to redistribute risk to those who are paying for products so they share some of the risks associated with incorrect forecasts; currently, these risks are borne exclusively by suppliers.

Reflecting on Eli Lilly's experience with its MDR TB initiative over the past 5 years, Richardson suggested that greater transparency in the supply chain is needed. Second-line drug manufacturers are unsure of how to get drugs approved, who is going to pay for them, and what the demand is. It is important to ensure that this system is simple and that companies understand how to get their drugs procured. Standards to which suppliers will be held must be clear and unequivocal. And there must be some mechanism for dealing efficiently with changes once a manufacturer has been prequalified. Prequalification testing is only a partial solution to ensuring continued supply—there must be ongoing monitoring of both manufacturers and drugs. Ongoing monitoring of Good Manufacturing Practices at facilities is just as critical, or even more critical, than prequalification in ensuring a sustainable drug supply. Companies must learn how to navigate approval and procurement both at a local level and through an entity such as the GDF. It is important to engage people who are capable of steering a path through both sets of regulations. It is also important that the amount of uncertainty in the forecast and demand management aspects of procurement be reduced. If companies understand the path forward and know who will be paying, they will be better able to manufacture and supply the drugs that are needed.

7

Research on the Global Control of TB: Understanding the Role of Drugs, Vaccines, and Funding

The lack of new drugs is a major gap in the global fight against TB. Harrington observed that there has been a long period of stagnation in TB drug development: As noted in Chapter 1, the last new drug approved for TB was rifampin in the 1970s.

Currently, five new compounds are in Phase I or II clinical development, and two "repurposed" drugs are in Phase III development. Progress has been made, particularly with the drug candidate TMC207, which has shown preliminary efficacy in patients with MDR TB in South Africa. Off-label use of drugs such as the quinolones has played an important role in the management of drug-resistant TB.

Harrington compared the aggressive development of drugs for HIV with the lack of serious progress on drugs for TB. He cited the lack of biomarkers and surrogate end points as one of the major obstacles to TB drug development. As a result, getting drugs into the field is difficult for companies because they do not understand the critical path by which drugs can be approved quickly. In addition, Harrington suggested that TB drug manufacturers should take advantage of the U.S. Food and Drug Administration's (FDA's) accelerated approval mechanism, which was used effectively for HIV drug development in the 1990s. Further, research is focusing on only few classes of drugs. Harrington expressed his view that the number of drugs in the pipeline is inadequate to revolutionize treatment of TB, whether drug-sensitive or drug-resistant. He suggested further that "neither the background regimen nor how to use the new drugs with it is yet well defined, and there is no clinical trials infrastructure available to carry out the needed strategy trials, even as industry carries out its own

registrational studies." Finally, Harrington said that even as work on developing biomarkers proceeds, it may be possible to use indicators such as time to sputum smear conversion or culture conversion as surrogate markers to accelerate approval of new drugs for drug-resistant TB, given the unmet medical need.

THE PIPELINE FOR NEW DRUGS

Ann Ginsberg of the TB Alliance gave an overview of the pipeline for new TB drugs. The current drug classes—both first- and second-line drugs—were all discovered between the 1940s and the 1970s (see Figure 7-1). From then until 5 years ago, there was little work on TB drug development.

To find effective treatments for MDR and XDR TB, it is important to establish treatment regimens that are better tolerated, more efficacious, and more affordable. The root of the drug resistance problem is the complexity and length of drug-sensitive regimens. Thus it is critical to have shorter, simpler regimens for drug-sensitive TB. To meet this need, it will be necessary to develop new drugs that will shorten and simplify treatment. They must be effective against those mycobacteria that persist now in the face of drugs to which they are genetically susceptible. Ideally, one wants drugs with novel mechanisms of action that are equally effective against MDR and XDR and drug-sensitive strains of TB. They must also be effective and have minimal drug–drug interactions for both HIV-positive and HIV-negative patients. Additionally, they should be able to be delivered orally once a day or less frequently if possible, and obviously be low cost.

Ginsberg discussed the strategies that are being explored to achieve these goals. Figure 7-2 shows the variety of targets being pursued. One can see that the bulk of current drugs—listed in black—are cell wall active. This means they work well against the most rapidly replicating mycobacteria, but are probably not effective against persistent organisms that are replicating slowly or not at all. Cell wall active drugs are consequently unlikely to shorten therapy, an objective that requires drugs acting against other kinds of targets. Many new discovery projects—listed in red—are focused on energy metabolism. TMC207 from Tibotec (a subsidiary of Johnson & Johnson) is the most developed drug candidate that has targeted that pathway successfully and will likely contribute to shortening therapy.

The ideal is to find new drugs that simultaneously will be effective in drug-resistant TB using novel mechanisms of action and will shorten treatment. Current drugs that shorten treatment include rifampin, which combined with pyrazinamide is the most effective of the current drugs in shortening therapy and which inhibits RNA polymerase. The fluoroquinolones, which have the potential to shorten therapy, work against DNA gyrase. TMC207 works against adenosine triphosphate (ATP) synthase.

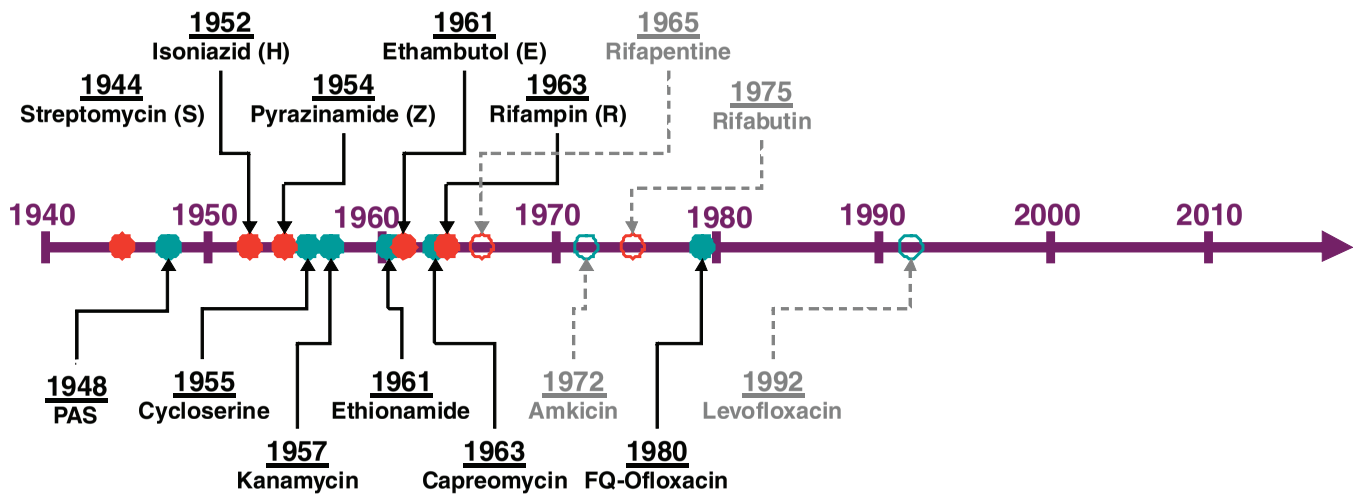


FIGURE 7-1 Discovery timeline of currently available TB drugs.
NOTE: The dotted lines indicate that these drugs are not first in class.
SOURCE: Ginsberg, 2008.

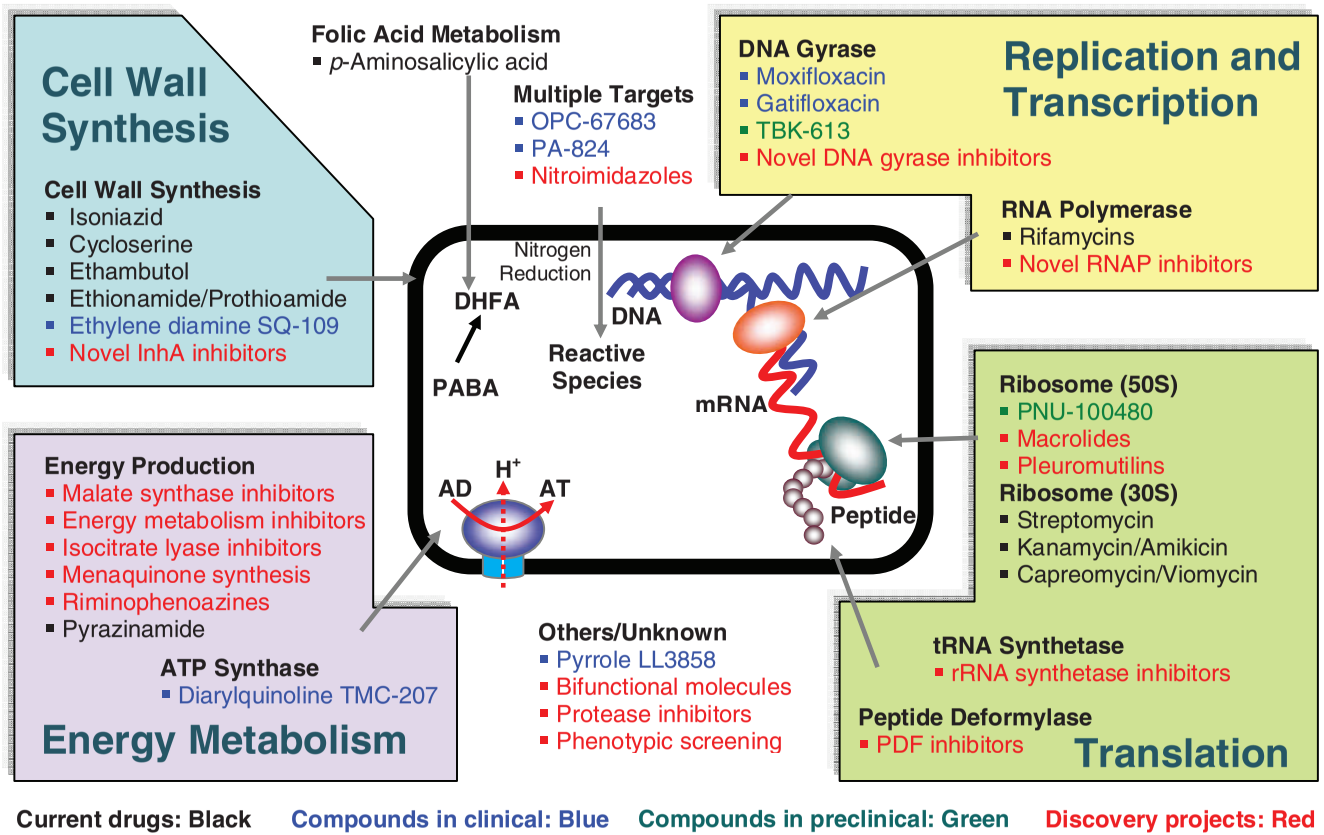


FIGURE 7-2 Distribution of TB drug targets.
SOURCE: Ginsberg, 2008.

The most desirable drugs act against targets that are new to the TB drug arsenal so the drugs will be active against drug-resistant TB and targets that are in pathways essential in persistent bacilli so the drugs will also shorten therapy.

Figure 7-3 shows the portfolio of drugs for TB currently in clinical trials, aimed toward registration. Ginsberg said that the first two, gatifloxacin and moxifloxacin, belong to the same chemical class; they are 8-methoxy-fluoroquinolones. Because they are so similar and have exactly the same mechanism of action, it will make sense for only one of them to be incorporated into any regimen. TMC207 brings a completely novel mechanism of action to the TB armamentarium; as noted, it is an ATP synthase inhibitor. The next two drugs in Figure 7-3 are both nitroimidazoles—OPC67683 from Otsuka Pharmaceutical Group, which is currently in Phase II trials in MDR TB patients, and PA-824, which is being developed by the TB Alliance. Again, only one of these would ultimately be incorporated into any given regimen because they have very similar if not identical mechanisms of action. Finally there are two compounds, SQ109 from Sequella, Inc., and LL-3858 from Lupin Limited, which are both in Phase I development.

PROBABILITY OF SUCCESS

While promising drug development efforts are under way, and there are far more drugs in the pipeline than was the case even in 2000, it is important to keep in mind both the time frames for such efforts and the probabilities of success. A typical drug takes at least 10–15 years to be developed from discovery to registration. Drugs for TB may take even longer than this average because the clinical trials for these agents can be very lengthy as a result of the efficacy end points that are currently required. The Phase III timelines could be shortened for MDR TB if regulators were to accept surrogate end points, such as sputum smear conversion rates at 4 or 6 months.

In general, however, the probability of ultimate success for any given candidate is discouraging. A compound that has progressed to preclinical development out of the thousands of compounds that enter the discovery phase has about a 1 in 10 chance of making it to registration and therefore to patients. Only in Phase III development do the odds become fairly good. About two-thirds of drugs that make it all the way to pivotal clinical trials will ultimately be registered.

Ginsberg identified a number of strategies for addressing the challenges facing TB drug development:

- A focus on developing multidrug regimens rather than individual drug candidates is needed. Combating drug resistance requires

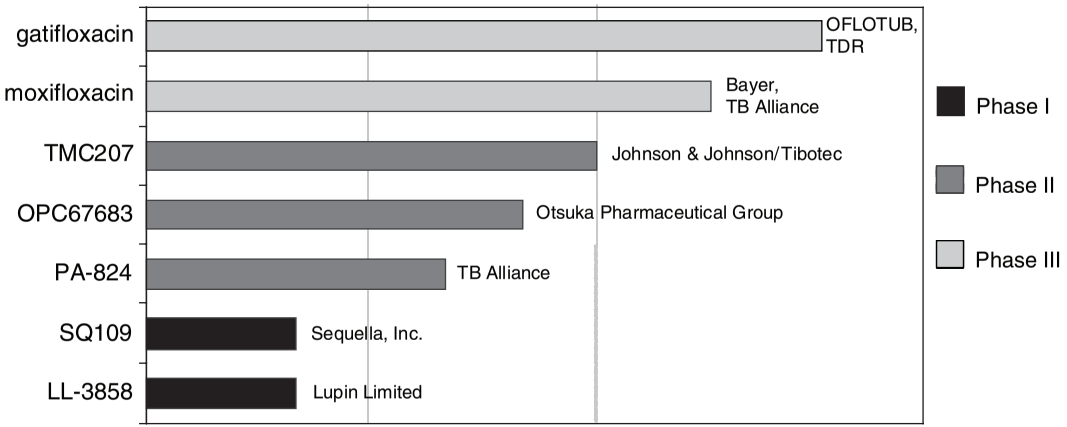


FIGURE 7-3 Global clinical portfolio of TB drugs in development.
NOTE: The OFLOTUB project (Ofloxacin-containing, short-course regimen for the treatment of pulmonary TB) is an ongoing study designed to simplify and shorten TB treatment from 6 to 4 months. TDR is an independent global program for research and training in tropical diseases.
SOURCE: Ginsberg, 2008.

cocktails of drugs with different mechanisms of action administered together. None of the current first-line TB drugs were developed in the modern regulatory era, and none have an ideal safety, pharmacokinetic, and efficacy profile for TB treatment, so entirely novel regimens will likely be required to markedly shorten and simplify TB treatment.

- Improved biomarkers and validated surrogate end points are essential to streamline clinical development, and although research is progressing in this area, it will be a multiyear process.
- Validated animal models that are predictive of drug efficacy and pharmacokinetic–pharmacodynamic relations in humans are needed.
- POC trial designs that can predict not only which drugs are likely to be efficacious but also which ones will help shorten therapy would also streamline the development process.
- Clinical trial capacity needs to be strengthened, including the development of sites, staff, and investigators who can work to current global registration standards.
- Clear, harmonized regulatory guidance for TB drug development in both drug-sensitive and drug-resistant TB are needed. Both the EMEA and the FDA are working to meet this need, and significant advances may soon be achieved. Globally harmonized guidance would significantly simplify the challenge of development as registration for TB drugs is required not only by the EMEA and the FDA, but also by regulatory authorities in high-burden countries.
- For any given drug candidate with a novel mechanism of action, simultaneous clinical development programs should be carried out to evaluate the drug for treatment of drug-sensitive and drug-resistant TB. Clinical trials for these two indications involve very different patient populations and study designs, so the resources required to do both are essentially double those required to pursue either indication alone.

Ray Woosley of The Critical Path Institute described recent discussions between the FDA and NIH, in association with the IOM, regarding formulation of a critical path for TB drug development. He also described the new TB data standards being developed by the Clinical Data Interchange Standards Consortium[1] for use in drug development. In addition to new drug development, the codevelopment of drugs and diagnostics can be facilitated by sharing data to create quantitative disease progression models and biomarker assays that evolve to become FDA-approved diagnostic

[1] For more information on these standards, visit http://www.cdisc.org/standards/.

tests. In this case the goal is not just approval of a new drug or diagnostic but a therapeutic strategy that includes both, as well as how they can be used together effectively.

Cassell discussed the broad strategy for drug development. Based on data from Tomsk and Peru, it is apparent that only 60–70 percent of patients with XDR TB can be cured. Consequently, an urgent concern in the development of new drugs is treatment of MDR and XDR TB. Echoing a point made by Ginsberg, Cassell noted that, unlike MDR staph infections or malaria, which in some cases can be treated effectively with one antibiotic, TB requires a cocktail of drugs to be treated effectively. Treating and stopping the spread of MDR and XDR TB will require a minimum of three to four new antibiotics immediately.

Fauci spoke about research needs for TB. He suggested that there are important lessons to be drawn from the experience with AIDS research—a discipline that did not exist prior to 1981 and yet became one of the best funded in the history of biomedical research.

An estimated 1.7 million deaths annually are attributed to TB, which ranks fourth among the highest-burden infectious diseases globally. In terms of mortality, TB follows diarrheal and respiratory diseases, which cause approximately 4.3 and 2.2 million deaths, respectively, and HIV/AIDS, which causes approximately 2 million deaths. Fauci stated that one of the reasons for the extraordinary response to HIV/AIDS and the large increase in funding was the impact of the disease on the U.S. population. Although federal funding for HIV/AIDS increased slowly at first, it eventually began to grow exponentially (see Figure 7-4). The U.S. federal government as a whole has spent a total of $233 billion on HIV/AIDS, and in fiscal year 2008 alone spent approximately $23 billion. The NIH research component has shown a similar increase, reaching a cumulative total of $36 billion and nearly $2.9 billion per year. While the overall NIH budget has not increased for several years, HIV/AIDS funding constitutes a stable 11 percent of the entire NIH research budget. Solid funding and the resulting research efforts have led to a number of extraordinary advances over the 27 years since AIDS was first recognized. There are more antiretroviral drugs for HIV/AIDS than the total of all drugs available for all other viral diseases combined. The extent of product development that took place in HIV/AIDS was possible because of a serious investment in biomedical research, partnerships with industry, and the pharmaceutical industry's realization that the development of antiretroviral drugs promises a large return on investment and significantly impacts the lives of patients in the United States and globally.

In addition to a significant pharmaceutical industry investment in the development of antiretroviral drugs, there has been a profusion of governmental and privately funded global programs directed at the prevention of

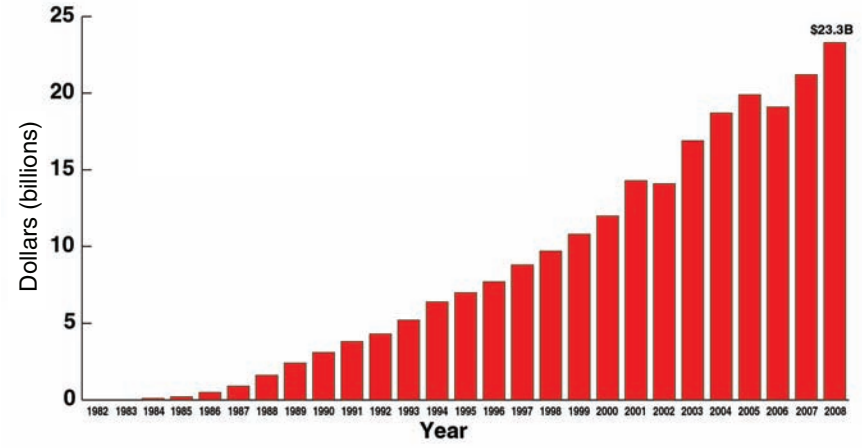


FIGURE 7-4 Federal funding for HIV/AIDS, 1982–2008.
NOTE: Through fiscal year 2008, more than $233 billion in federal funding has been spent on HIV/AIDS.
SOURCE: Fauci, 2008 (based on data from the Kaiser Family Foundation [KFF], unpublished analysis of data from the Office of Management and Budget, Congressional Research Service, federal agency documents, and congressional legislation; used with permission from KFF).

HIV/AIDS and treatment and care of HIV/AIDS patients (e.g., PEPFAR and the Global Fund for AIDS, Tuberculosis, and Malaria). A variety of other philanthropic organizations have also proven critical to helping HIV/AIDS patients worldwide. Since 2002, the number of HIV/AIDS patients in the developing world receiving antiretroviral drugs has grown from about 200,000 to more than 3 million.

Fauci noted that many of the challenges faced in combating HIV are similar to those for TB, and that lessons learned from biomedical, clinical, and operational research in HIV/AIDS may apply to TB. These lessons include the need to commit substantial financial and human resources, to enlist the best and brightest investigators in basic and clinical research, to engage the affected communities, to foster cross-collaboration with industry and global organizations, and to garner the support of leaders and policy makers.

Compared with the NIH budget for HIV/AIDS, the budget for TB is relatively modest. The current budget, shown in Figure 7-5, is roughly $152 million, $131 of which is NIAID funding. In fiscal year 2007, NIAID funding for biomedical TB research amounted to approximately $60 million for fundamental research; approximately $47 million for drug development; and approximately $8.5 and $15 million for vaccine and diagnostic

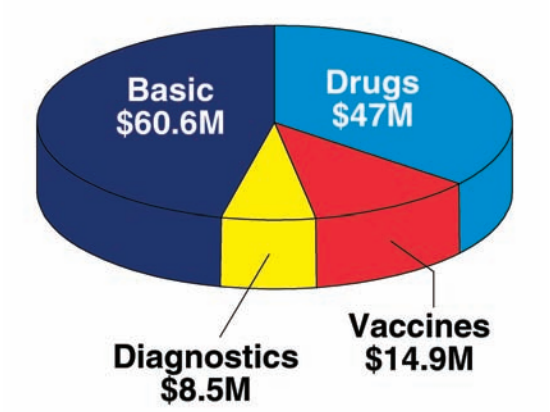


FIGURE 7-5 Funding for TB from the National Institute of Allergy and Infectious Diseases in fiscal year 2007.
NOTE: Total funding in 2007 was $131.1 million.
SOURCE: Fauci, 2008.

research, respectively. NIAID published a research agenda for MDR and XDR TB in June 2008 (Fauci, 2008). Fauci highlighted five areas of the research agenda that, in NIAID's view, require major consideration:

- Development of rapid and reliable diagnostic methods that can be used at the point of care;
- Investment in the pipeline of new drugs, as well as proper use of existing first- and second-line therapies;
- Investment in research to understand the epidemiology that contributes to the spread of drug-resistant and drug-sensitive strains of TB;
- Understanding of the relationship between and comorbidities of HIV/AIDS and TB; and
- Development of effective vaccine and chemotherapy prevention strategies for all forms of TB (see Table 7-1 for a list of the most advanced international vaccine development efforts).

NIH and several nongovernment organizations have launched initiatives in these areas.

Fauci reflected on the steps that must be taken to move the science forward. He first noted the extraordinary importance of coordinating research efforts among government agencies such as NIH, CDC, and the

TABLE 7-1 Four of the Eight TB Vaccine Candidates in Clinical Trials That Have Moved into Phase II Studies

Agent	Type	Description	Sponsor	Status
MVA85A	Prime boost	MVA vector	Oxford University	Phase II
GSK M72	Prime boost	Recombinant protein	GlaxoSmithKline	Phase II
Mycobacterium vaccae	Prime boost	Heat-killed NTM	Silence Therapeutics	Phase II
AERAS-402/Crucell Ad35	Prime boost	Adenovirus vector	Aeras/Crucell NV	Phase II

NOTE: MVA = Modified Vaccinia Ankara, NTM = nontuberculous mycobacterial.
SOURCE: Chou et al., 2008. Copyright 2008 Treatment Action Group, modified and reprinted with permission.

U.S. Agency for International Development (USAID) and global partners such as other international government agencies, international development entities such as PEPFAR, philanthropic organizations such as the Bill and Melinda Gates Foundation, pharmaceutical and biotechnology companies, public–private partnerships and research consortia such as those at Eli Lilly, and a variety of others.

In addition, Fauci noted that it is essential not to treat TB in isolation because it almost invariably occurs in the context of other diseases. An obvious connection is seen in the coepidemics of HIV and TB in many areas of sub-Saharan Africa and other low- and middle-income regions of the world.

Finally, Fauci emphasized the need to balance fundamental research efforts with product development to ensure proper integration of scientific disciplines within infectious disease research, immunology, and state-of-the-art technological approaches. Multidisciplinary research must also include robust partnerships with various product developers and sustainable investment in the development and retention of human capital.

Cassell asked Fauci to share his experience with advances in accelerated review and licensure of new antiretroviral drugs and whether they offer any lessons applicable to product development for TB. Fauci explained that, while the concept of accelerated review was a paradigm shift for regulatory authorities in the 1990s, regulators are now amenable to this strategy. Researchers need to engage the FDA early in discussing the possibility of and requirements for expedited review as well as expedited or conditional approval. The same could be said of the parallel-track concept for clinical trial design (i.e., those who cannot be enrolled because of geographic

constraints or enrollment criteria could still receive a drug contemporaneously with the clinical trial). Regulators have now embraced this concept, which has proven to be a productive mechanism for clinical evaluation of experimental therapies while making therapies available to approved patients who lack other therapeutic options. As for moving forward without animal models, Fauci noted that there is a much better possibility of gaining important research and preliminary efficacy data from current and emerging models of TB infection and disease than was the case with HIV since HIV/AIDS is a uniquely human disease.

Woosley asked whether a national clinical research infrastructure comparable to the AIDS Clinical Trial Group (ACTG) network would be effective for TB.[2] Castro replied that the ACTGs were in fact used for TB research in the context of HIV/AIDS coinfection, specifically to study the efficacy of rifampin and pyrazinamide for latent TB infection in HIV-infected patients.

Drazen asked Fauci what he would consider the highest priorities if new resources became available for TB research. Fauci replied that the development of quick, sensitive, and affordable point-of-care diagnostics is paramount, as are translational studies to discover and evaluate new drug and vaccine candidates.

Citing the significant advances in HIV once validated surrogate end points were available to aid in drug evaluation and regulatory approval, Castro asked Fauci to comment on immune correlates of protection for TB. Fauci responded that for HIV/AIDS, as is the case for TB, this was a difficult effort that took years and required the involvement of investigators from a variety of disciplines.

Ginsberg asked whether the market incentives for antiretroviral drugs and the extent of activism leveraged for HIV could make lessons learned less relevant to TB. Fauci asserted that there is potential for growth of TB activism. Because TB is a health crisis that is still unfolding, growing awareness of issues surrounding the global TB epidemic will likely lead to increased activism.

With respect to financial incentives for the development of health care interventions, there is a greater difference between HIV and TB. With HIV, there is a large patient population in the developed world willing and able to pay $17,000–18,000 a year for effective therapies; this is not the case with TB. TB occurs primarily in low- and middle-income countries, where patients are less likely to be able to afford expensive drugs. This disparity

[2] The ACTG network of investigators had both intellectual and supportive capacity infrastructure, together with funding to conduct individual clinical trials. It greatly expedited the ability to ask questions about efficacy and safety because there was uniformity in clinical trials across a network throughout the entire country. Woosley stated that the ACTG network was probably one of the most successful programs in advancing the drug development pipeline for HIV/AIDS.

calls for a greater role for government involvement in the development and distribution of affordable curative and preventive measures. A large, multilateral initiative may be the appropriate way to share risks and financial returns to provide the financial incentive for the development of new drugs (see the discussion of financial incentives below). Friedland asked about operational research strategies, such as cost-effectiveness studies, which enhance clinical and public health decision making. Fauci replied that for HIV/AIDS and TB alike, many studies in this area have yet to be conducted. Both infrastructure and operational research often receive less attention since they are peripheral to but highly integrated with basic and clinical science. The importance of operational research—of learning whether what is being done is the right thing—is still underappreciated. However, PEPFAR programs recently have become involved in several operational research projects for HIV, and similar attention is warranted for TB.

ECONOMIC INCENTIVES FOR DRUG DEVELOPMENT

Jeffrey Moe of Duke University described the various incentives that influence the decisions of companies to develop new drugs for TB. There are two important types of incentives in global health—push and pull mechanisms. Some examples of each are listed in Box 7-1. Push mechanisms stimulate the supply or production side of the market, while pull mechanisms stimulate the demand side.

The Orphan Drug Act of 1983 is an example of a push mechanism because it is aimed at making it easier, less costly, or less risky for a company to develop an orphan product.[3] The specific incentives include the use of research and development (R&D) tax credits and grant support. BioShield[4] represents another form of push mechanism that involves directly funding R&D for terrorism countermeasures. A third approach is the development of a public–private partnership such as the TB Alliance.

[3] A therapy may be designated as an orphan product if one of the following conditions is met: (1) the disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year as specified in 21 CFR Sec. 316.21(b); or (2) for a drug intended for diseases or conditions affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 200,000 or more persons per year in the United States, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States as specified in 21 CFR Sec. 316.21(c).

[4] The Project BioShield Act was passed in 2004. This bill gave the U.S. Department of Health and Human Services authority to support the development and acquisition of medical countermeasures as part of a national strategic effort to prepare for threats to public health from chemical, biological, radiological, or nuclear events.

BOX 7-1
Examples of Push and Pull Mechanisms for Stimulating Drug and Vaccine Development

Push Mechanisms (fund inputs—research and development [R&D] costs)	Pull Mechanisms (fund outputs—drugs, vaccines)
• Orphan Drug Act: R&D tax credits and grant support • BioShield: funds R&D investments for terrorism countermeasures • Public–private partnerships: consolidate R&D effort and facilitate information exchange	• Orphan Drug Act: market exclusivity • Advance market commitment: guaranteed price and number of units to be purchased • Transferable voucher for extended patent life: reward for development of treatments for diseases of developing countries or bioterrorism agents • Priority review voucher: reward for developing a new treatment for a neglected disease (e.g., TB, malaria)

SOURCE: Moe, 2008.

These partnerships are effective because they organize strategies within the field and facilitate the sharing of scientific knowledge and effort.

Pull mechanisms include the market exclusivity provisions of the Orphan Drug Act. However, market exclusivity for a TB drug in the United States would not be particularly attractive because the incidence of the disease, and therefore the market, are very limited. Another pull mechanism is the use of advance market commitments, through which market demand—e.g., a price and a certain number of units to be purchased—is guaranteed (typically by government or a philanthropic organization) in advance. A third pull mechanism is patent extension for an existing medicine as a reward for developing a drug to treat a disease of the developing world or a bioterrorism agent. The benefit to a company is clear: Extended patent life and therefore increased profitability of a drug constitute a highly tangible reward, which if applied to a blockbuster drug would be worth billions to a manufacturer. However, such an incentive singles out a group of patients and their insurers, by disease state, to bear the burden of the incentive. When such an incentive was discussed for inclusion in BioShield II, significant objections were raised by the generic pharmaceutical industry and patient advocacy groups.

Another type of incentive has actually been instituted in the form of the priority review voucher (PRV) concept included as Sec. 524 of the 2007 Food

and Drug Administration Amendments Act. In exchange for developing a new treatment for a neglected disease, such as TB or malaria (there are 16 qualifying diseases), a company receives a voucher that can be used to receive priority review by the FDA for another drug that is being developed or can be sold to another company.[5] In 2006, Moe and colleagues published their estimate that priority review is accomplished on average 12.6 months more quickly than standard review (Ridley et al., 2006). If this speed to market is applied to a blockbuster drug for the period studied, the value, on average, is $322 million to the manufacturer.

Moe cited five criteria that must be met for such incentives to be effective (Towse and Kettler, 2005):

1. The incentive must be efficient. For this reason, a program for an individual disease may not be as valuable as one that targets multiple diseases.
2. Target diseases must be carefully specified in advance.
3. The incentive must be credible in the eyes of potential developers, as drug development is a long and risky process that may span multiple administrations and regulatory regimes. If there is any question about the incentive's being honored over a long time period, its value will be negated.
4. The definition and treatment of new chemical entities as opposed to follow-on drugs or new combinations of existing drugs must be carefully specified to avoid any concern that the rules of the game may change or be enforced capriciously.
5. There must be some assurance that the product will be used by patients.

Moe argued that, if the incentive is to be effective, the application of these five criteria is critical to motivate private industry to direct R&D monies toward highly risky development efforts for neglected diseases, including TB.

[5] The FDA issued its guidance on the administration of the PRV incentive in October 2008 and is receiving public comments.

8

Strategies for Confronting the Global MDR and XDR TB Crisis

Throughout the workshop, problems with the current approaches to the diagnosis and treatment of MDR and XDR TB were highlighted and discussed. Participants suggested potential strategies for dealing with these problems, ranging from incremental adjustments to systemic changes in the global health system.

RECOMMENDATIONS PRESENTED BY DR. KESHAVJEE

Keshavjee summarized recommendations presented in a white paper commissioned for the workshop; the full text of the paper is presented in Appendix C. The paper offers 15 recommendations in three areas: diagnosis, drug supply, and treatment delivery (see the detailed listing in Box 8-1).

Diagnosis

Keshavjee discussed the urgent need for investment in in-country laboratory capacity and point-of-care testing. Smear microscopy, though useful, is increasingly inadequate. Keshavjee argued that it works just over half the time, it fails to detect extrapulmonary TB, it does not work well in patients with HIV, and it does not aid in diagnosing drug-resistant disease. Of the 22 high-burden countries, only 7 have one culture facility per 5 million population, and only 9 have one DST facility per 10 million population. Recent experience in Lesotho, discussed in Chapter 4, demonstrates how laboratory capacity can be expanded effectively in a resource-deprived area.

BOX 8-1
Specific Recommendations from the Report *Stemming the Tide of Multidrug-Resistant Tuberculosis: Major Barriers to Addressing the Growing Epidemic*

Diagnostics

- Sustainable funding from bilateral and multilateral donors must be increased to support construction of in-country drug-sensitivity testing/rapid-testing laboratories and ongoing external quality assessments by supranational reference laboratories.
- Creation of a system of long-term on-site technical assistance would help countries build and/or rapidly expand their capacity to perform mycobacterial culture, DST, and rapid molecular genetic tests for drug-resistant tuberculosis.
- In-country laboratory networks for specimen transport, data management, and certification and coordination of private laboratories need improvement.
- Use of excess laboratory capacity for mycobacterial culture and drug-susceptibility testing in wealthy nations should be encouraged while laboratories are being built in poorer regions.
- Priority must be given to research on—and funding for—the immediate development and rapid deployment of point-of-care testing for drug-susceptible and drug-resistant tuberculosis.

Drug Supply

- WHO and international partners should take immediate and rapid steps to increase the number of manufacturers of quality-assured second-line anti-tuberculosis drugs. A mechanism needs to be developed to make these drugs available at pre-negotiated prices to programs purchasing via the GDF and through direct-purchase by countries.
- The GDF should create a tiered system of approval for manufacturers of second-line drugs—and purchase of product by the GLC mechanism—consistent with a manufacturer's progress in WHO's Essential Drugs Monitoring (EDM) prequalification process. Large countries operating within the GLC mechanism should be allowed to purchase second-line anti-tuberculosis drugs from domestic manufacturers who have entered the EDM prequalification process.
- The GLC mechanism should institute a transparent system for quantification of demand for second-line drugs.
- The GDF should maintain a second-line anti-tuberculosis drug buffer stock (at minimum, enough to treat 5,000 patients) in order to facilitate rapid delivery of drugs to programs (less than 1 month).
- There should be a global effort to increase the options available for treating MDR TB and XDR TB, by optimizing current regimens and by developing at least three new anti-TB drugs. Increased TB clinical trial capacity needs to be created, and mechanisms developed to fast-track new anti-TB drugs through the regulatory process.

Treatment Delivery

- Universal treatment for drug-resistant tuberculosis within national TB control strategies—side by side with drug-susceptible disease—has to be clearly and actively promoted by multilateral and bilateral agencies, nongovernmental organizations, and within countries. Universal TB treatment also must be well integrated with current HIV treatment initiatives.
- The system of international technical assistance provision is currently inadequate. It must be transformed in order to better draw on the experience of successful regional MDR TB treatment programs, to include the provision of on-site, long-term technical assistance, and where necessary, to involve on-site implementation teams.
- Community-ambulatory-based MDR TB treatment, and where appropriate, active collaboration with private-sector laboratories and tuberculosis treatment providers, should be actively promoted as a safe means of rapidly treating the largest number of patients. Delivery systems that support this will need to be strengthened and/or built.
- Infection control to prevent transmission of TB strains has to be integrated fully into national TB control strategies, with appropriate resources, training, implementation strategies, and monitoring.
- Large global health initiatives—such as PEPFAR—and bilateral and institutional donors for global health should make improving the capacity to deliver MDR TB treatment an important priority. The Global Fund and UNITAID have done so, and others should follow this lead with their influence and resources.

SOURCE: Keshavjee and Seung, 2008, pp. 2–3.

Several lessons were learned from this experience. For example, in addition to setting up the laboratory, it is essential to have ongoing quality assurance; long term on-site technical assistance; a laboratory system capable of interacting with the clinical system; systems for specimen transport, data management, and certification; and coordination of private laboratories.

While laboratory capacity is being built in the high-burden countries, this process is lengthy, and officials in many countries are waiting until new laboratory capacity is available before treating MDR TB patients. At the same time, there is substantial untapped excess capacity for mycobacterial culture and DST in the developed world. One option would be to create a consortium of laboratories that could process samples from developing countries so that patients could begin receiving treatment while in-country laboratory capacity was being developed.

Perhaps no other single step could radically improve treatment of MDR

TB more than effective point-of-care testing. Because of the remoteness of many high-burden areas and the complexity of treatment, laboratory testing almost always leads to long delays in treatment, and delays represent one of the most critical factors in the development and spread of MDR TB. If a patient cannot be immediately diagnosed with TB, an antibiotic trial with first-line antibiotics needs to be conducted; this is a common cause of delay for patients beginning treatment. Data from Rwanda show that antibiotic trials delay treatment on average by 39 days. Other delays are due to routine health service and patient issues. In Rwanda, these issues result in an average 57-day delay in treatment. The problem is illustrated in Figure 8-1, which shows a patient being carried by a family member down a steep incline to get to a health clinic. It takes about 5–6 hours to walk to this village. When patients arrive, they are told to get an x-ray, then go home, and then return for the antibiotic regimen.

The advantages of point-of-care testing are obvious—the delay in the start of treatment is only 1 day. Ideally point-of-care testing will detect disease during the patient's initial visit, even if the patient has extrapulmonary TB, and will determine whether the TB is drug-resistant so the appropriate regimen can be initiated.

FIGURE 8-1 A patient being carried by a family member to a clinic.
SOURCE: Keshavjee, 2008. Copyright 2008 Open Society Institute/Pep Bonet, reprinted with permission.

Drug Supply

Keshavjee next addressed the urgent need to increase the number of manufacturers of quality-assured second-line anti-TB drugs. Meeting this need will require addressing a number of bottlenecks in the supply chain, including poor demand forecasting, problems in obtaining GLC prequalification, poor-quality and counterfeit drugs, and the high risks and limited incentives facing suppliers.

A number of different approaches can be used to address these issues. One is to shift the current focus from individual programs and to reduce barriers to countries' direct purchase of drugs. Another is to enable manufacturers of second-line drugs to begin to sell the drugs conditionally early in the GLC prequalification process. Large countries operating within the GLC mechanism should be allowed to purchase second-line anti-TB drugs from domestic manufacturers that have entered the system. In addition, a more transparent system for forecasting demand and a larger buffer stock of second-line TB drugs are needed to smooth out demand and supply, reducing risk for both programs and manufacturers. Currently, programs wait up to 6 months for drugs, keeping patients waiting, transmitting disease, and potentially dying. Finally, there is a need for additional options for treating MDR and XDR TB by optimizing current regimens and by developing at least three new anti-TB drugs.

Treatment Delivery

As new drugs and diagnostic capabilities become available, the demands on the existing delivery system will increase dramatically. Meeting these demands will require substantial investment, as well as new approaches.

Keshavjee described cost-effective approaches to improving the delivery of care in resource-poor environments. One program in South Africa, for example, provided patients with housing and found that it cost far less than hospitalization. In addition, ambulatory-based treatment can be more effective than hospitalization, which can lead to nosocomial transmission. Training villagers to be community health workers is another highly cost-effective approach.

Technical assistance is an area that lacks coordination and needs improvement. The system for providing international technical assistance should draw on the experience of successful programs to include long-term on-site assistance and implementation teams. One of the limitations of current programs is that they tend to be fragmented and limited in scale. It is not always clear how to scale up successful programs to the regional or country level. Scaling up sometimes requires that stakeholders achieve a critical mass and share a belief in the future. Currently, effective strategies

for diagnosis and treatment are being deployed only for a small proportion of patients. It will be necessary to increase the number of patients being treated to create demand for increased supplies of drugs and diagnostics. Large bilateral and institutional donors for global health will have to make improving the capacity to deliver MDR TB treatment a priority. Perhaps this scale-up will require a PEPFAR-like initiative for TB.

Michael Kimerling of the Bill and Melinda Gates Foundation reinforced the idea that scaling up requires a shift from project-level to country-level funding and planning. He cited Kazakhstan as an example of a government program that has transitioned from encompassing 300 MDR TB cases to covering 3,000 cases, based on the experiences of a model site in Almaty city that became GLC-approved recently. Scale-up is occurring at the national level, entirely within the government system and within a legislative framework, based on a smaller Almaty model project that was running for 5 years. Despite the success of this model, the Global Fund will not be able to sustain it over the long term since Kazakhstan exceeds the income index cutoff for further support. Hence, the concept of government ownership and commitment is key to both scaling up and sustainability. As for technical assistance, Kimerling noted that there are really two issues—the global capacity to provide technical assistance and the regional and in-country capacity to implement and sustain whatever assistance is given over the long haul. The critical need in this regard is human resource development planning at the global level that translates into regional and country-level capacity development that addresses both technical and managerial issues.

Charles Wells of Otsuka Pharmaceutical Development and Commercialization suggested that the white paper expand on the need for the capacity of global programs to conduct clinical trials. Given the paucity of new drugs, that capacity is now limited, and it will be critical for scale-up once new drugs and new diagnostics become available. Research capacity, he argued, should be built along the way, and such that it can be harnessed for new drug development.

LESSONS LEARNED FROM THE PRESIDENT'S EMERGENCY PLAN FOR AIDS RELIEF (PEPFAR)

A theme throughout the workshop was the relationship between PEPFAR and efforts to combat MDR TB. Caroline Ryan of the U.S. Department of State presented some observations from the PEPFAR experience that could be useful in the fight against TB. She first noted that HIV/TB has been a priority area for PEPFAR from the beginning, and that funding for HIV/TB programs increased from $18.8 million in 2005 to $169 million in 2008—more than 700 percent. Ryan outlined some of the approaches

that have been effective and that could represent opportunities for further leveraging TB care at the community level:

- Establishing a supply chain management system, which is a central mechanism for forecasting both demand and delivery—similar in some ways to the GLC,
- Fast-tracking FDA approval of new and generic antiretroviral drugs,
- Investing in surveillance to ensure that information is readily available,
- Investing in improved laboratory surveillance systems in six countries to enable detection of outbreaks of MDR and XDR TB,
- Developing a strong tiered public health laboratory network,
- Developing effective transport systems to improve the utility of diagnostics at both regional and central laboratories,
- Establishing specific performance targets and metrics for assessing progress in antiretroviral treatment programs, and
- Expanding both testing and treatment at the community level through home-based delivery of care.

Nacy observed that treatment strategies for MDR TB have become more systems oriented and less oriented toward individual patients. Farmer responded that while the focus has inevitably shifted to populations because of the scope of the crisis, programs remain patient-centric. Nacy added that there appear to be two different perspectives on diagnostics, one focused on epidemiologic tools and population metrics and the other on patient care—diagnosing and treating individuals. The current tests in development address the epidemiology of MDR TB (i.e., test for characteristic isoniazid and rifampin resistance), but little attention is currently being paid to identifying and developing clinical diagnostic tools that can identify to which drugs a particular patient is susceptible—a critical need in patient care.

Friedland offered a number of suggestions for reducing the impact of the TB epidemic:

- A rapid and massive infusion of resources,
- Enhanced epidemiological characterization,
- Strengthened TB programs,
- Integration of TB and HIV efforts,
- Implementation of infection control strategies to reduce airborne transmission,
- Improved TB and drug resistance diagnosis, and
- Expansion of MDR and XDR TB treatment.

Given the critical factor of immunosuppression due to HIV coinfection, Friedland suggested the need to continue to fast-track antiretroviral rollout

and provide improved access to current antiretroviral therapies. In addition, he argued for a shift in focus to the prevention of new infections. This would include earlier diagnosis with new rapid diagnostic tests, active intensive case finding, implementation of airborne infection control, and decreased reliance on hospital care. In the long term, the critical need is for new diagnostics, drugs, and vaccines.

Kim reflected on the progress that has been made through PEPFAR, the largest public health program in history, and noted that the opportunity exists to extend its reach farther than ever before. He discussed the importance of consolidating the many efforts to build on one another and utilize resources effectively. This is already happening, he noted, in other areas of public health. For example, nine universities, civil society organizations, WHO, and the Italian government are leading an effort called Positive Synergies to examine how global health initiatives, such as PEPFAR, the Global Fund, and the Global Alliance for Vaccines and Immunization, can be harnessed to strengthen health systems. This kind of operational research is difficult and is rarely carried out, but is essential to determine how to capitalize on all these efforts within a functioning health system. One of the challenges going forward will be to link these vertical programs to health systems that serve the critical public health needs in these countries.

POLICY FOCUS ON DRUG-RESISTANT VERSUS NON-DRUG-RESISTANT TB

A major theme of the workshop was the need to shift focus from the control of drug-susceptible TB to MDR and XDR TB. The discussion elicited pros and cons on this view. Nunn acknowledged the possibility that the current epidemic of mainly susceptible disease is at risk of being replaced by an epidemic of mainly resistant disease. But the question is how to change the approach to address this risk. Nunn argued that the first priority in addressing MDR TB is preventing its occurrence in the first place, which places the emphasis on basic control of TB. This, of course, is partly a resource issue: Does it make sense in resource-limited countries to emphasize laboratory strengthening just for drug-resistant disease? The capacity of laboratories needs to be increased in a number of ways, including the initial diagnosis for TB. Also, with respect to infection control, Nunn argued that such initiatives should be integrated with other efforts. PEPFAR, for example, was at first focused just on HIV, but now the TB–HIV connection is a central element of the program.

Cassell countered that, with MDR and XDR TB being nearly out of control, simply focusing on the susceptible strains will not be sufficient. It is in fact because of some countries' very limited resources that this issue is so important. Unless it is addressed directly, they will focus on TB control first, while MDR and XDR TB continue to spread.

Castro suggested that both Nunn and Cassell were correct and affirmed the need for both types of interventions. This combined focus is in fact part of a national action plan to combat MDR TB that resulted in new resources being appropriated by Congress. A multipronged approach is needed, which should include focusing on MDR TB infection control, laboratory capacity building, and rebuilding of the infrastructure for basic TB control.

Congressman James McDermott (D-WA) suggested that the need for medical infrastructure is perhaps even greater than what had been discussed already by workshop participants—that in addition to laboratories and medication, more people doing the work are required. He suggested that any major proposal should include U.S. involvement in training. He addressed the potential for an increased federal response to the crisis and the prospects for additional legislation. He noted that before the election, President Obama had expressed strong interest in reauthorization of the PEPFAR bill, which calls for $4 billion over 5 years to address TB. The legislation includes the requirement that USAID craft a plan and start setting targets to treat 90,000 MDR TB patients and 4.5 million standard TB patients. But this bill has not yet been funded. McDermott concluded that what is needed is a clear message as to what the plan should be, and he believes that Congress, working with the new administration, can get the plan implemented.

THE LEVEL OF RESPONSE

A substantial portion of the discussion focused on the level and nature of the U.S. and global response to the TB crisis. Nacy observed that the range of options discussed tended to be more incremental than transformative in terms of approaching the problem in innovative and creative ways. Matthew Cavanaugh of RESULTS encouraged the group to take a cue from the HIV/AIDS world and act boldly: "Most recently, it seems really clear that we have got only about half the funding we need to be tackling TB care around the world. We are short about $2.5 billion a year. The vast majority of funding is coming from countries themselves, meaning that the gap is really about wealthy countries doing their fair share." The level of funding requested must be adequate to respond in a degree commensurate with the magnitude of the crisis.

Harrington discussed lessons learned from AIDS activism that could be applied to TB. He acknowledged that AIDS is very different from TB, and that there may never be a grassroots movement for TB like that for AIDS. The question then becomes how to fill that gap and create the political will. He discussed the elements missing in the fight against drug-resistant TB: data, diagnosis, drug resistance testing and DST, drugs, delivery, dollars, determination, demand, and demonstration.

Data were essential in transforming the struggle against HIV. Data were used to support requests for money, services, and the nation's attention. Certain data are critical to making these arguments for TB—for example, data on the full extent of MDR and XDR TB and the degree to which transmission is acquired.

Another missing ingredient is dollars. Increases in spending on TB since the launch of the Stop TB global plan have actually decelerated since 2005–2006. Spending increased by only 6 percent, or $26 million, from fiscal years 2006 to 2007. Domestically, investment in TB research has been almost stagnant since the flat NIH budget in 2005, which declined by 20 percent in real dollars. NIH invested $2.9 billion in HIV research last year compared with only $157 million in TB research, despite the fact that TB kills almost as many people.

Unlike HIV and malaria, TB has no U.S. presidential initiative. In contrast with the United Nations–endorsed goal of universal access to treatment for HIV, the Stop TB global plan fails to set universal access targets for any kind of TB. Even if its goals were achieved, it would not reverse the TB epidemics in Africa or Europe—the continents most affected by HIV, TB, and drug-resistant TB. Harrington attributed this to the lack of political will, urgency, leadership, vision, and determination to address the problem. Even WHO, he argued, is not providing the leadership needed to determine how to solve the problem, not just control it.

As noted, there is little grassroots activism for TB, and consequently there is inadequate political pressure to demand results. Yet Harrington believes that activism is needed at all levels—increased scientific investment, strong political leadership, and greatly increased resources. He recommended a combination of top-down and bottom-up approaches. A key step would be to launch a Presidential initiative to stop TB, whether integrated into the Office of the U.S. Global AIDS Coordinator; the President's Malaria initiative; the new State Department–level Office of AIDS, TB, and malaria; or a new Office of Global Health. Most appropriate would be an integrated global scale-up for all forms of TB, including but not limited to MDR TB. Roy Widdus from the Global Forum for Health Research noted that while there are no activist groups involving patients in industrialized countries, there are groups that have dealt historically with TB and lung disease at the national level in Japan, the Netherlands, the United States, and Denmark. There is probably a role for the IUATLD in advocacy.

In addition, Harrington argued that WHO must rewrite the global plan and cease its internal argument on whether health sector strengthening or priority diseases should receive the greatest attention. It is important to integrate universal access to treatment for HIV and TB and other priority diseases into a comprehensive and universal plan. Said Harrington, "We need political leadership at the national level in countries, and we need to

strengthen community-based science and policy literacy to enable affected communities to participate effectively in fighting TB. I think that is one of the key differences between AIDS and TB—in that in AIDS we have treatment and research and policy literate communities in many countries around the world, and as a result many of the AIDS activists are leading efforts against TB in their countries." A combination of stronger grassroots efforts and stronger leadership from the scientific and political communities is needed.

Peter Hartsock from the National Institute on Drug Abuse discussed the concept of a PEPFAR equivalent for TB, and noted that TB's national security implications make this concept compelling. In Russia, HIV and XDR TB have already collided, especially in the prison and military populations. Hartsock asserted that the Russian military is concerned about the epidemic, and therefore it is a threat to the United States. As a result, it is in the United States' national security interests to press for an international TB initiative that is either similar to or part of PEPFAR.

Friedland added that there is substantial stigma associated with TB, HIV, and drug-resistant TB in most environments and cultures, and this has blunted the response both nationally and globally. Some of the populations that are at risk for and acquire drug-resistant TB by transmission or by treatment failure—particularly in the former Soviet Union and in parts of Asia—are themselves stigmatized because of issues of substance abuse or mental illness. That is part of the context in which TB and drug-resistant TB occur. Therefore, addressing stigma and resultant ethical issues must be an integral part of the response to the crisis.

Kim reflected on a recent article by Michael Porter in *Business Week* arguing that the U.S. government should not scrimp on its investments in such areas as education, science, and health care that will enhance the nation's future productivity (Porter, 2008). Although the national debt has almost doubled in the last decade, investments in TB are urgently needed. Unlike investments that are focused on meeting current needs created by the financial crisis at the end of 2008, investment in TB is an investment in the future. Policy makers should be bold about combating global health threats and about investing money for that purpose.

SUMMARY OF KEY POINTS

Castro provided a brief distillation of key points from the workshop presentations and discussions:

- There is collective ignorance about the true magnitude of the drug-resistant TB problem, as well as the numbers of persons undergoing treatment.

- It is recognized that transmitted rather than acquired resistance is driving this epidemic. This recognition highlights the key role of infection control and possibly isolation precautions in the community.
- A dramatic investment is needed in research into new drugs for individuals who are now relatively untreatable with available drugs.
- A renewed sense of urgency is needed to combat the relative complacency and lack of activism with respect to TB.

Castro mentioned two studies that he considered relevant to the discussion. First, he noted that the IOM issued a report in 2000, *Ending Neglect: The Elimination of Tuberculosis in the United States*, which recommends strategies for the elimination of TB. A number of those recommendations have never been addressed (IOM, 2000). Also relevant is an interagency plan to respond to XDR TB that was developed by the Federal TB Task Force and published in the *Morbidity and Mortality Weekly Report* in February 2009 (CDC, 2009). Ongoing work on TB is also being conducted by the National Security Council and Homeland Security Council. Cassell added that other activities within the National Academies address TB and other infectious agents in terms of both security and global public health.

CLOSING REMARKS

Cassell, the workshop chair, closed by reflecting on the proceedings of the day. She reminded the audience that two studies published in the last 2 months indicate that anywhere from 30 to 40 percent of patients diagnosed with XDR TB are untreatable with existing drugs. Gao presented information indicating that drug-resistant TB has been acquired from other infected patients, in stark contrast to what has generally been believed in the past about the ability of these organisms to spread. Gandhi and Friedland demonstrated that XDR TB is not limited to KwaZulu-Natal, but has spread to most of its southern African neighbors. Despite these growing concerns, the diagnostic capabilities, resources, treatment and infection control policies, data collection mechanisms, and research capacity needed to understand and effectively manage this crisis still are not in place. Said Cassell, "What we have also heard is the great need to directly confront MDR TB and XDR TB, whereas emphasis in the past has been on strengthening TB control programs per se, believing we could [thereby] control the problem of XDR TB and MDR."

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Appendix A

Agenda

8:00–8:10 **Objectives of the Workshop**

Gail Cassell, *Eli Lilly and Company*

Workshop Chair

8:10–9:40 **Panel I: SETTING THE STAGE**
10-minute presentations followed by a 30-minute panel discussion

Moderator: **Kenneth Castro,** *Centers for Disease Control and Prevention*

Paul Nunn, *World Health Organization*
Global Incidence of MDR TB

Yanis Ben Amor, *Earth Institute*
Underreported Threat of MDR TB in Africa

Gerald Friedland, *Tugela Ferry Care and Research Collaboration*
HIV/MDR-XDR TB: Implications

Megan Murray, *Brigham and Women's Hospital*
Number of MDR TB and XDR TB Patients Receiving Treatment Today: Successes/Failures/Consequences

Qian Gao, *Shanghai Medical College*
Transmission of MDR TB

Neel Gandhi, *Tugela Ferry Care and Research Collaboration*
Transmission of XDR TB

9:40–9:50 **Break**

9:50–11:30 **Panel II: HOW DID WE GET TO WHERE WE ARE TODAY: DIFFERENT PERSPECTIVES**
10-minute presentations followed by a 40-minute panel discussion

Moderator: **Richard Chaisson,** *Johns Hopkins University*

Edward Nardell, *Brigham and Women's Hospital*
Lack of Infection Control

John Ridderhof, *Centers for Disease Control and Prevention*
Laboratory Capacity: A Global Analysis

Anne Goldfeld, *Harvard School of Public Health*
Drug and Health Care Delivery: Cambodian and Ethiopian Perspectives

Wieslaw Jakubowiak, *WHO Country Office Russian Federation*
Fighting Drug Resistance in Russia: Challenges and Achievements

Paul Zintl, *Partners In Health*
Drug Supply: The Stop TB Partnership Perspective

Ruth Levine, *Center for Global Development*
Critical Role of Accurate Demand Forecasting: Lessons Learned from Malaria

11:30–12:30 **Lunch**

12:30–1:20 **Keynote Address: The Research Path to Tuberculosis Control: An NIH Perspective**

Anthony Fauci, *National Institute of Allergy and Infectious Diseases*

1:20–3:00 **Panel III: ESSENTIAL BUILDING BLOCKS**
10-minute presentations followed by a 20-minute panel discussion

Moderator: **Leonard Sacks,** *Food and Drug Administration*

Dale Nordenberg and **Hamish Fraser,** *Brigham and Women's Hospital*
Knowledge Management (IT): What Do We Need and What Do We Have?

David Persing, *Cepheid*, and **Charles Daitch,** *Akonni Biosystems*
Point-of-Care Diagnostics: How Close Are We?

Ann Ginsberg, *TB Alliance*
TB Drug Development: Realities of the Pipeline

Raymond Woosley, *The Critical Path Institute*
Critical Path for Parallel Development of TB Point-of-Care Diagnostic and Drug Development

Jeff Moe, *Duke University*
What Are the Odds? Who Will Pay? What Are the Incentives?

3:00–3:15 **Break**

3:15–4:15 **Panel III: A BLUEPRINT FOR ACTION**

Moderator: **Peter Cegielski,** *Centers for Disease Control and Prevention*

Salmaan Keshavjee, *Partners In Health*
The Plan: From Powder to Patient

Discussants:
Michael Kimerling, *Bill and Melinda Gates Foundation*
Carol Nacy, *Sequella, Inc.*
Iain Richardson, *Eli Lilly and Company*
Caroline Ryan, *U.S. Department of State*
Sarita Shah, *Tugela Ferry Care and Research Collaboration*
Alexander Sloutsky, *University of Massachusetts*
Martie Van der Walt, *Medical Research Council South Africa*
Charles Wells, *Otsuka*

4:15–5:30 **Panel V: THE NEED FOR URGENCY**
15-minute presentations followed by 45-minutes of discussion

Moderator: **Jim Yong Kim,** *Partners In Health*

Mark Harrington, *Treatment Action Group*
Lessons from HIV

Paul Farmer, *Partners In Health*
Lessons from MDR TB

5:30 **SYNTHESIS AND NEXT STEPS**

Gail Cassell, *Eli Lilly and Company*
Workshop Chair

Appendix B

Participant Biographies[1]

Yanis Ben Amor, Ph.D., is an Associate Research Scientist at the Earth Institute and the Tuberculosis Coordinator for the Millennium Villages Project (MVP). The TB initiative at MVP focuses on delivering a comprehensive package of TB interventions in remote health centers in rural settings across 10 African countries. By promoting community-based directly observed treatment, short course (DOTS), the TB initiative aims to decrease death rates by improving case detection and treatment success rates. Dr. Ben Amor's TB-related research is focused on finding ways to improve TB diagnosis in developing countries. He analyzes new, rapid diagnostic tools being investigated, and develops ways to allow their implementation in resource-poor settings, where electricity and clean water can be limiting factors. In 2006, Dr. Ben Amor validated the use of line probe assays in Rwanda for the detection of multidrug-resistant TB in that country. In October 2008, he launched Mali's first national drug resistance survey, to be conducted throughout the country in 2009.

Gail H. Cassell, Ph.D., is currently 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

[1] At the time of printing, biographies were not available for Caroline Ryan and Alexander Sloutsky.

the decade of her leadership. She obtained her B.S. 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. Dr. Cassell is past President of the American Society for Microbiology (the oldest and 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 (NIAID). Dr. Cassell was named to the original Board of Scientific Councilors 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 editorial 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.

Kenneth G. Castro, M.D., is Assistant Surgeon General, U.S. Public Health Service, and Director of CDC's Division of Tuberculosis Elimination (Sep-

tember 2008). Since January 1993, he has served as Director of the Division of Tuberculosis Elimination in CDC's National Center for HIV, STD, and TB Prevention (NCHSTP). In this role, Dr. Castro leads the team of technical experts devoted to TB elimination efforts in the United States: his division sponsors TB prevention, control, and research activities throughout the nation and other parts of the world. Since 1995, he has served as Co-chair of the U.S. Federal Tuberculosis Task Force. Recognizing the importance and magnitude of global TB, Dr. Castro has advanced U.S. involvement in global TB control efforts, serving as an expert advisor to the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Diseases (IUATLD). He is a founding member of the global Stop TB Partnership and member of its Coordinating and Executive Boards. In an unusual distinction afforded to a division director, Dr. Castro, who is a Commissioned Corps Officer in the U.S. Public Health Service, was promoted to the flag rank of Assistant Surgeon General (RADM, 0-7) in May 2000. Since the 2006 description of extensively drug-resistant (XDR) TB, he has provided national and global leadership in the development of a coordinated response to this urgent health problem. Prior to serving as director of CDC's Division of TB Elimination, Dr. Castro worked as the Assistant Director for TB and HIV, Office of HIV/AIDS at CDC, from May to December 1992. In May 1992, he was appointed to the office of Associate Director of HIV/AIDS to coordinate CDC-wide HIV-associated TB activities, after serving for almost 2 years as the Assistant Chief of the Epidemiology Branch in the Division of HIV/AIDS in the National Center for Infectious Diseases. From July 1989 until August 1990, he served as Special Assistant to the Director for Science in the Division of HIV/AIDS. Dr. Castro began his career with CDC in 1983 as an Epidemic Intelligence Service (EIS) officer with the AIDS Program, where he became a staff medical epidemiologist after completing the EIS training in 1985. A physician-scientist trained in epidemiology, he has a specialty in internal medicine and subspecialty in infectious diseases. He received his bachelor's degree in 1974 from the University of Puerto Rico; completed postgraduate biology studies at Northeastern University in Boston in 1976; and received his medical doctorate from the State University of New York at Stony Brook School of Medicine in 1980. Dr. Castro went on to complete his internal medicine postgraduate training in 1983 in the residency program in social medicine at the Montefiore Medical Center, Albert Einstein College of Medicine in New York. From 1988 until 1989, he continued his education, completing a fellowship in infectious diseases at the Emory University School of Medicine, where his work focused on describing the increase in the number of people with TB and its association with the HIV/AIDS epidemic. Since 1988, Dr. Castro has served as an adjunct clinical faculty member of the Division of Infectious Diseases,

Emory University School of Medicine, and at the infectious diseases clinic at Grady Memorial Hospital in Atlanta.

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 at 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 2 years of the fellowship he was posted to Muhimbili Medical Center, University of Dar es Salaam, Tanzania, where he was a Lecturer and Consultant Physician. From 1991 to 1994, Dr. Cegielski was an Assistant Professor in 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 held a joint appointment as Chief of Medical Services and Research, Center for Pulmonary Infectious Disease Control, and as an Assistant Professor in the Department of Medicine, both at the University of Texas Health Center at Tyler, Texas. At the end of 1996, he took a faculty position in the Department of Epidemiology at the Johns Hopkins University School of Public Health. In this capacity, he moved to Chiang Mai, Thailand, where he served as field director of the Johns Hopkins HIV/AIDS research program at Chiang Mai University. Then in 1998, he joined the International Activity of the Division of TB Elimination at CDC. In 2001, the International Activity became the International Research and Programs Branch, and Dr. Cegielski was promoted to Team Leader for Drug-Resistant TB. His work focuses on the epidemiology, prevention, diagnosis, and treatment of TB, especially drug-resistant TB.

Richard E. Chaisson, M.D., is Professor of Medicine, Epidemiology and International Health and Director of the Center for Tuberculosis Research at The Johns Hopkins University. He received his B.S. and M.D. degrees from the University of Massachusetts, and trained in internal medicine and infectious diseases and epidemiology at the University of California, San Francisco, where he conducted research on the HIV epidemic in injection drug users and initiated early studies on the interaction of TB and HIV. He then served as Director of the Johns Hopkins AIDS Service from 1988 to 1998, where he pioneered the use of observational cohort studies for understanding the natural history, treatment, and outcomes of HIV disease. Dr. Chaisson became Director of TB Preventive and Treatment Services for the Baltimore City Health Department in 1992, and built a productive clinical research program focusing on molecular epidemiology and TB clinical trials. In 1998 he founded the Johns Hopkins Center for Tuberculosis Research, a multidisciplinary research and training center with more than $120 mil-

lion in grants for the study of TB from bench to bedside. Dr. Chaisson's research interests focus on TB and HIV infection, including global epidemiology and control, prevention, clinical trials, and public health interventions. He is currently principal investigator for multiple research grants for studies of the treatment, prevention, and control of TB and HIV. He is also principal investigator of the Consortium to Respond Effectively to the AIDS/TB Epidemic (CREATE), an international research consortium funded by the Bill and Melinda Gates Foundation to assess the impact of novel strategies for controlling HIV-related TB. Dr. Chaisson has published more than 350 scientific papers and book chapters. He was awarded the World Lung Health Award in 2006 by the American Thoracic Society for his scientific contributions to global control of pulmonary infections.

Charles Daitch, Ph.D., is CEO of Akonni Biosystems Inc., which he founded in 2003. Dr. Daitch has diagnostic product development and R&D experience from NIH, the U.S. Department of Agriculture, and Sandia National Laboratories. He has held senior-level management positions at Veridian Corporation and at HandyLab Inc. Since 1987, Dr. Daitch's career has focused on automated and miniaturized biological detection systems.

Jeffrey M. Drazen, M.D., attended Tufts University with a major in physics and Harvard Medical School, and served his medical internship at Peter Bent Brigham Hospital in Boston. Thereafter, 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 finally as Chief of Pulmonary Medicine at Brigham and Women's Hospital. Through his research, he defined the role of novel endogenous chemical agents in asthma. This work led to four new licensed pharmaceuticals for asthma, with more than 5 million people treated worldwide. In 2000, Dr. Drazen 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 papers modifying the treatment of cancer, heart disease, and lung disease. The journal, which has more than a million readers each week, has the highest impact factor of any journal publishing original research.

Paul Farmer, M.D., Ph.D., is a Founding Director of Partners In Health, an international charity organization that provides direct health care services and undertakes research and advocacy activities on behalf of those who are sick and living in poverty. Dr. Farmer's work draws primarily on active clinical practice (he is an attending physician in infectious diseases and Chief

of the Division of Social Medicine and Health Inequalities at Brigham and Women's Hospital in Boston, and Medical Director of a charity hospital, the Clinique Bon Sauveur, in rural Haiti) and focuses on diseases that disproportionately afflict the poor. Along with his colleagues at Brigham and Women's Hospital, in the Program in Infectious Disease and Social Change at Harvard Medical School, and in Haiti, Peru, and Russia, Dr. Farmer has pioneered novel, community-based treatment strategies for AIDS and TB (including multidrug-resistant TB). Dr. Farmer and his colleagues have successfully challenged the policy makers and critics who claim that quality health care is impossible to deliver in resource-poor settings. Dr. Farmer has written extensively about health and human rights, and about the role of social inequalities in the distribution and outcome of infectious diseases. He is the author of *Pathologies of Power* (2003), *Infections and Inequalities* (1998), *The Uses of Haiti* (1994), and *AIDS and Accusation* (1992). In addition, he is co-editor of *Women, Poverty, and AIDS* (1996) and of *The Global Impact of Drug-Resistant Tuberculosis* (1999). Dr. Farmer is the recipient of the Duke University Humanitarian Award, the Margaret Mead Award from the American Anthropological Association, the American Medical Association's Outstanding International Physician (Nathan Davis) Award, and the Heinz Humanitarian Award. In 1993, he was awarded a John D. and Catherine T. MacArthur Foundation "genius award" in recognition of his work. Dr. Farmer is the subject of Pulitzer Prizewinner Tracy Kidder's *Mountains Beyond Mountains: The Quest of Dr. Paul Farmer, a Man Who Would Cure the World* (2003). He received his bachelor's degree from Duke University and his M.D. and Ph.D. from Harvard University. He is Presley Professor of Medical Anthropology in the Department of Social Medicine at Harvard Medical School.

Anthony S. Fauci, M.D., is Director of NIAID at NIH. Since his appointment to that position in 1984, he has overseen an extensive research portfolio devoted to preventing, diagnosing, and treating infectious and immune-mediated diseases. Dr. Fauci also is Chief of the NIAID Laboratory of Immunoregulation, where he has made numerous important discoveries related to HIV/AIDS; he is one of the most-cited scientists in the field. In addition, he has served as a key advisor to the White House and the Department of Health and Human Services on global AIDS issues, and on initiatives to bolster medical and public health preparedness against emerging infectious disease threats such as pandemic influenza. Dr. Fauci, a member of the National Academy of Sciences, has received numerous awards for his scientific accomplishments, including the National Medal of Science, the George M. Kober Medal of the Association of American Physicians, the Mary Woodard Lasker Award for Public Service, and the 2008 Presidential Medal of Freedom. He has been awarded 32 honorary doctorate degrees

and is the author, coauthor, or editor of more than 1,100 scientific publications, including several major textbooks.

Hamish S. F. Fraser, MBChB, MRCP MSc, is an Assistant Professor of Medicine at Harvard Medical School and Associate Physician at the Brigham and Women's Hospital. As Director of Informatics and Telemedicine at Partners In Health (PIH), he directs the development of web-based electronic medical record (EMR) systems and data analysis tools to support the treatment of drug-resistant TB and HIV in Peru, Haiti, Rwanda, Lesotho, Malawi, and the Philippines. The first system developed, the PIH-EMR, currently supports the management and monitoring of more than 6,500 patients in treatment for MDR TB in Peru and 1,000 patients in the Philippines. Dr. Fraser also led the development of the HIV-EMR, which is used to support the treatment of HIV patients in rural Haiti. Both of these systems include data analysis tools, as well as components that track the current use of medication and predict future medication needs. The EMR systems used by Partners In Health were designed as part of an international collaboration to develop flexible, open-source medical record systems in developing countries. The first version of this OpenMRS system, of which Dr. Fraser is a co-founder, went live in February 2006 in Kenya and in August 2006 in Rwanda. OpenMRS is now also used to support the Partners In Health projects in Lesotho and Malawi and will soon be used to support MDR TB care in Haiti.

Gerald Friedland, M.D., is Director of the AIDS Program at Yale New Haven Hospital and Professor of Medicine and Epidemiology and Public Health at Yale School of Medicine. He is a former member of the Governing Council of the International AIDS Society, National Advisory Council, National Institute on Drug Abuse, and Advisory Council, Office of AIDS Research, and currently serves on the WHO HIV/TB Working Group and as Chairman of the Board of Directors of the Aaron Diamond AIDS Research Center in New York City. Dr. Friedland has been directly involved in the development of comprehensive HIV care programs since the beginning of the HIV epidemic in 1981. His work was initially in the Bronx, New York, and has continued since 1991 in New Haven, Connecticut. He has developed and directed large-scale clinical and epidemiologic studies among vulnerable populations with and at risk for HIV disease. His group presented the first convincing evidence of lack of transmission of HIV by close personal contact, and defined the predictors of HIV transmission and natural history of HIV disease among injection drug users and the risk of reactivation of TB among those coinfected with HIV. More recently, Dr. Friedland has worked on clinical trials of antiretroviral therapies. He is currently Principal Investigator of New England ProACT, a regional

AIDS clinical trials network specializing in antiretroviral therapy trials. In this work he has focused on recruitment, enrollment, retention, and special issues with respect to HIV therapeutics among injection drug users and other marginalized populations, including the definition of pharmacokinetic drug interactions between HIV and substance abuse therapies. Dr. Friedland's research also has focused on studies at the interface of biology, clinical care, and behavior, including adherence to HIV therapies and the integration of prevention strategies and clinical care, notably in the development and testing of interventions to reduce the risk of HIV transmission among HIV-positive persons in clinical care. Dr. Friedland is also actively involved in HIV/AIDS international research aimed at providing access to antiretroviral therapy in resource-limited settings. The major focus of this work is the integration of HIV and TB care and treatment in coinfected patients, with the aim of improving diagnosis, treatment, and outcomes for both diseases. This work has led to the discovery of XDR TB as a major cause of death among HIV/TB coinfected patients in South Africa and now focuses on the diagnosis, treatment, and reduction of transmission of MDR and XDR TB in HIV coinfected patients. Dr. Friedland directs and participates in several research projects addressing these issues in rural and urban South Africa, supported by charitable research foundations and NIH. He is a Visiting Professor at the Nelson R. Mandela School of Medicine of the University of KwaZulu-Natal in Durban, South Africa, and the Mailman School of Public Health of Columbia University.

Neel Gandhi, M.D., is Assistant Professor of Medicine and Epidemiology at Albert Einstein College of Medicine and Montefiore Medical Center. He graduated from Brown Medical School and received training in primary care internal medicine at Columbia-Presbyterian Medical Center, clinical epidemiology in the Robert Wood Johnson Clinical Scholars Program at Yale University, and infectious diseases at Emory University. Dr. Gandhi has been engaged in clinical research in TB/HIV coinfection since 1998, when he performed his first research study in India. Since 2002, he has been performing epidemiology and operational research in rural South Africa in an effort to address the converging epidemics of HIV and TB. In November 2006, he was the lead author on a study describing high rates of mortality in patients with XDR TB and HIV coinfection. This study has been credited with uncovering a rapidly expanding MDR TB and XDR TB epidemic in South Africa. Dr. Gandhi is currently funded through a Clinical Scientist Development Award and an Operations Research on AIDS Care and Treatment in Africa Award (ORACTA) from the Doris Duke Charitable Foundation. These grants provide support to elucidate risk factors for developing MDR and XDR TB, to test the MODS assay (a rapid TB drug-resistance assay) in a high HIV-prevalence setting, to create a community-based treat-

ment program for MDR TB in HIV coinfected patients, and to develop a comprehensive airborne infection control program in a rural district hospital. Additionally, Dr. Gandhi is a co-investigator on grants to expand TB/HIV integration efforts in rural South Africa (President's Emergency Plan for AIDS Relief [PEPFAR], CDC), to examine the risk of household transmission of MDR and XDR TB in rural South Africa (NIH Fogarty Institute), and to elucidate the molecular epidemiology of drug-resistant TB in rural South Africa (Einstein Center for AIDS Research).

Qian Gao, Ph.D., is Professor at Fudan University, Shanghai Medical College. He received his Ph.D. in 2000 from the University of Southern California, and was a postdoctoral fellow at the School of Medicine, Stanford University, in 2003. His research interests are in the identification and characterization of new virulence genes of *M. tuberculosis*, the molecular epidemiology of TB, and anti-TB drug discovery.

Ann Ginsberg, M.D., Ph.D., is Head of Clinical Development for the TB Alliance. Prior to joining the TB Alliance in June 2004, she was Director, Project Management at Merck & Co., Inc. for 2 years. Dr. Ginsberg also brings 15 years of experience at NIH to this position. She began her NIH career in the National Cancer Institute as a Medical Staff Fellow and Resident in Anatomic Pathology. She subsequently joined the National Institute of Diabetes, Digestive and Kidney Diseases as a Senior Staff Fellow in the Laboratory of Cellular and Developmental Biology. In 1995 she joined NIAID as Program Officer for Tuberculosis, Leprosy and Other Mycobacterial Diseases; she was appointed Chief of the Respiratory Diseases Branch in 2000. Trained as a molecular biologist, Dr. Ginsberg is a board-certified anatomic pathologist. She holds a B.A. from Harvard University, an M.D. from Columbia University, and a Ph.D. from Washington University. She is the author of numerous scientific publications and recipient of several prominent awards, including the Department of Health and Human Services Secretary's Award for Distinguished Service in 2000. She has served on multiple global health committees and is currently a member of the Board of Directors of the Aeras Global TB Vaccine Foundation.

Anne Goldfeld, M.D., is Associate Professor of Medicine at Harvard Medical School, Senior Investigator at the Immune Disease Institute, Associate Professor of Immunology and Infectious Disease at the Harvard School of Public Health, and a member of the Infectious Disease Division at Brigham and Women's Hospital in Boston. Work in her laboratory focuses on basic gene regulation and on new understanding of how the immune system responds to TB and AIDS. Her laboratory has discovered basic mechanisms of cell type and inducer-specific gene regulation using the TNF gene and

HIV as model systems and genes and described new T cell responses associated with TB susceptibility and latency. As co-founder of the Cambodian Health Committee and the Global Health Committee, she has helped pioneer new models of TB and AIDS care and treatment while integrating basic research methods to improve care and to discover new approaches to and therapies for these diseases in Cambodia and globally.

Mark Harrington is Executive Director of the Treatment Action Group (TAG) in New York City. He graduated from Harvard with a B.A. in 1983, and organized many demonstrations as a member of ACT UP/New York (AIDS Coalition to Unleash Power), 1988–1992, including "Seize Control of the FDA" in 1988 and "Storm the NIH" in 1990. In 1992 he co-founded TAG. In 1997 he won a MacArthur Foundation "genius award" for his AIDS activism. He is a member of the WHO Strategic and Technical Advisory Committee for HIV, the WHO Strategic and Technical Advisory Group for Tuberculosis, and the writing group on WHO Guidelines for Antiretroviral Therapy for HIV Infection in Resource-Limited Settings, and he served for 12 years on the Department of Health and Human Services' Panel on Clinical Practices for Treatment of HIV Infection in Adults and Adolescents. Mr. Harrington has been an ad hoc member of the FDA Antiviral Drugs Advisory Committee three times and served on the NIH AIDS Clinical Trials Group (ACTG) Opportunistic Infections and Primary Infection Committees and Community Constituency Group (CCG) between 1989 and 1993. He has presented four plenary talks at International AIDS Conferences in Amsterdam ("Pathogenesis and Activism," 1992), Geneva ("Cure: Myth or Reality?," 1998), Durban ("Epidemiology and Activism," 2000), and Mexico City ("Moving from Universal Access to Comprehensive and Universal Primary Health Care for All," 2008). He published a chapter on AIDS activism in *Tactical Biopolitics: Art, Activism, and Technoscience* (2008) and co-authored recent articles in *PLoS Medicine* and *The Lancet* on the need for better drugs and diagnostics to treat and diagnose TB (2007). He has also written many articles and reports for ACT UP and TAG.

Salmaan Keshavjee, M.D., Ph.D., is Assistant Professor of Social Medicine and Medicine at Harvard Medical School and at Brigham and Women's Hospital. Since 2001, he has been working with the Boston-based nonprofit Partners In Health, treating drug-resistant TB in Tomsk, Russian Federation. In Tomsk, he has worked extensively on expanding MDR TB treatment from the penitentiary to the civilian sector and from urban to rural areas. Since 2004, he has also led the Harvard/Partners In Health research efforts in Tomsk and has been a driving force behind Partners In Health's Russia-wide MDR TB training programs. In addition to his work in Russia, Dr. Keshavjee was central to the 2006 launch of Partners

In Health's HIV and TB work in Lesotho. These efforts led to the development of a community-based treatment program for patients coinfected with HIV and MDR TB, aimed not only at dramatically improving care throughout Lesotho but also at extending this coordinated treatment model to coinfected patients throughout sub-Saharan Africa and other regions with high levels of HIV/TB coinfection. In September 2007, Dr. Keshavjee was appointed Chairman of the Green Light Committee (GLC) for MDR TB. The GLC is a mechanism of WHO and the Stop TB Partnership that assists countries faced with MDR TB in accessing concessionally priced, quality-assured second-line anti-TB drugs for use in projects providing care in accordance with WHO and international guidelines.

Jim Yong Kim, M.D., Ph.D., holds appointments as François Xavier Bagnoud Professor of Health and Human Rights at the Harvard School of Public Health and Professor of Medicine and Social Medicine at Harvard Medical School. He is Chief of the Division of Global Health Equity at Brigham and Women's Hospital, a major Harvard teaching hospital; director of the François Xavier Bagnoud Center for Health and Human Rights; and Chair of the Department of Global Health and Social Medicine at Harvard Medical School. Dr. Kim is currently leading a new Harvard University–based initiative in global health delivery, which is designed to discover and widely share knowledge about the effective implementation of health programs in resource-poor countries. Dr. Kim returned to Harvard in December 2005 after a 3-year leave of absence at WHO. While on leave, he was Director of WHO's HIV/AIDS Department, a post to which he was appointed in March 2004 after serving as advisor to the WHO Director-General. He oversaw all of WHO's work related to HIV/AIDS, focusing on initiatives to help developing countries scale up their treatment, prevention, and care programs, including the "3×5" initiative, designed to put 3 million people in developing countries on AIDS treatment by the end of 2005. Dr. Kim has 20 years of experience in improving health in developing countries. He is a founding trustee and the former Executive Director of Partners In Health, a not-for-profit organization that supports a range of health programs in poor communities in Haiti, Peru, Russia, Rwanda, Lesotho, and the United States. An expert in TB, Dr. Kim has chaired or served on a number of committees on international TB policy. He has conducted extensive research into effective and affordable strategies for treating strains of TB that are resistant to standard drugs. While at WHO, he was responsible for coordinating HIV efforts with the TB department. Dr. Kim trained dually as a physician and medical anthropologist and received his M.D. and Ph.D. from Harvard University. He has been recognized on numerous occasions as a global leader and distinguished professional. He received a MacArthur "genius award" in 2003, was named one of America's 25 best leaders by

U.S. News & World Report in 2005, and was named one of the 100 most influential people in the world by *Time* magazine in 2006. He was a contributing editor to the 2003 and 2004 *World Health Report*, and his edited volume *Dying for Growth: Global Inequity and the Health of the Poor* analyzes the effects of economic and political change on health outcomes in developing countries.

Michael E. Kimerling, M.D., M.P.H., serves as a Senior Program Officer for TB in the Global Health Program at the Bill and Melinda Gates Foundation, working closely with established grantees and new partners on translational and operational research, and technology delivery issues urgently required to intervene in the global TB and MDR/XDR epidemics. Trained as an internist, he started his medical career working with nongovernmental organizations in refugee medicine and rebuilding primary health services in chronic conflict zones. He comes to the foundation from the University of Alabama at Birmingham, where he was a Professor of Medicine in the Division of Infectious Diseases and in the Department of Epidemiology, School of Public Health. He is an expert in MDR-TB programmatic management and global TB control, TB-HIV program integration, TB in prisons, and issues regarding public-private mix, particularly around the inclusion of hospitals. He is a member of the Core Group of the WHO Stop TB Partnership's MDR-TB Working Group and also a member of the Technical Review Panel of the Global Fund. Michael has extensive field, program, and operational research experience in Asia, Africa, Latin America, Russia, and other former Soviet Republics.

Ruth Levine, Ph.D., is an internationally recognized expert on global health and health policy. She is a health economist with more than 15 years of experience in designing and assessing the effects of social-sector programs in Latin America, eastern Africa, the Middle East, and South Asia. In addition to serving as the Center for Global Development's (CGD's) Vice President for Programs and Operations, she leads the center's work on global health policy, including chairing a series of working groups on key policy and finance constraints on the effective use of donor funding for health programs in low-income countries. Before joining CGD, Dr. Levine designed, supervised, and evaluated loans at The World Bank and the Inter-American Development Bank. Between 1997 and 1999, she served as Advisor on the Social Sectors in the Office of the Executive Vice President of the Inter-American Development Bank. Dr. Levine holds a doctoral degree in economic demography from The Johns Hopkins University. She is co-author of the books *The Health of Women in Latin America and the Caribbean* (2001) and *Millions Saved: Proven Successes in Global Health* (2004, updated as *Cases in Global Health: Millions Saved* [2007]), as well

as the major reports *Making Markets for Vaccines: Ideas to Action* (2005), *When Will We Ever Learn: Improving Lives Through Impact Evaluation* (2006), and *A Risky Business: Saving Money and Improving Global Health Through Better Demand Forecasting* (2007).

Jeffrey L. Moe, Ph.D., Executive in Residence, joined the Health Sector Management program, Fuqua School of Business, in 2001. His research interests include new incentives for innovation in neglected tropical and infectious disease research, private-sector responses to the global health care worker shortage, and the use of business intelligence as a basis for competitive advantage among life sciences firms. Dr. Moe is co-author of "Developing Drugs for Developing Countries" (*Health Affairs*, March/April 2006), which led to the Sec. 524 amendment in the Food and Drug Administration Amendments Act of 2007. The article recommended, and the legislation now establishes in law, a new incentive for neglected tropical disease medicines: the priority review voucher (PRV). A PRV is awarded for U.S. registration of a new medicine (new chemical, biologic, or diagnostic) for a tropical disease (one of 16 diseases, including TB and malaria), termed the "tropical drug." The holder exercises the voucher by receiving priority review of a second drug, the "voucher drug," for FDA approval to market to U.S. patients. The FDA issued its guidance in October 2008 to administer the new voucher program, and the first tropical drug applications for the program were submitted beginning September 28, 2008. Dr. Moe is Chief Executive Officer of the Institute for Global Disease Medicines, Inc. (IGDM). IGDM utilizes a proprietary proteome capture discovery technology that combines focused chemical libraries with parallel affinity capture screens. The drug discovery engine enables new drug candidates to be identified in large combinatorial chemical libraries en masse and rapidly progressed to Phase I clinical trials through directed iterative chemistry. The platform first identifies the use of drug candidates that are preselected based on such criteria as solubility profile, likely pharmacokinetic profile, ability to be derivated, and distinctiveness relative to known compounds. IGDM is structured as a not-for-profit/for-profit hybrid business model and will become a self-sustaining biotechnology organization that is funded by philanthropic donations and grants. Its initial research program will focus on malaria and cancer. Dr. Moe is Director, Private Sector Task Force (TF), which operates under the aegis of the Global Health Workforce Alliance (managed by WHO). The TF identifies and promotes the expansion of private-sector initiatives that are increasing the supply, effectiveness, and retention of health care workers. Dr. Moe leads the research and administration of the Technical Working Group, which carries out analysis, interventions, and evaluation for the TF. The TF is using an innovative social/business "incubator" approach to increase the

scaling and cross-border movement of effective private-sector responses to the worker shortage. Before coming to Duke, Dr. Moe was an executive at GlaxoSmithKline. During a 15-year career he held positions in business development, corporate strategy, marketing, market economics, and human resources. He received his Ph.D. in organization development and behavior in 1981 from the University of North Carolina at Chapel Hill. He graduated from the Kellogg School, Northwestern University, Executive Development Program, in 1997.

Megan Murray, M.D., Ph.D., is an Assistant Professor of Epidemiology at the Harvard School of Public Health and an Assistant Professor of Medicine at Harvard Medical School. She is an Instructor with both the DGHE and the Infectious Disease unit at Massachusetts General Hospital. Dr. Murray's research group has the following major areas of interest: within-species comparative genomics of M. tuberculosis strains, modeling the transmission dynamics of emerging infectious diseases, including MDR TB, West Nile virus, SARS, and various sexually transmitted diseases, human iron metabolism and tuberculosis susceptibility, identifying risk factors for the transmission of drug-sensitive and drug-resistant tuberculosis transmission using molecular and conventional epidemiologic methods, outcomes research in tuberculosis treatment and control programs, pedagogy in interdisciplinary research and emerging infectious disease, and exhaled particles and their relationship to infectivity of infectious agents.

Carol A. Nacy, Ph.D., is currently Founder and Chief Executive Officer of Sequella, Inc., a 10-year-old privately held biopharmaceutical company that commercializes new and more effective products for diagnosis and treatment of TB and other infectious diseases. Sequella has a late-stage diagnostic product completing its clinical evaluation in 2008 and a new TB drug completing Phase I clinical trials. The company has secured several large pharma commercial partners that will market and sell its lead diagnostic, and recently in-licensed a promising new TB drug from Sanko, Ltd. It has raised nearly $38 million to date from institutional and qualified investors and peer-reviewed grants. Prior to joining Sequella, Dr. Nacy was Executive Vice President and Chief Scientific Officer at EntreMed, Inc., from 1993 through the company's successful public offering in June 1996. She left EntreMed in November 1996 to establish Sequella, and was part-time Chief Scientific Officer (1997–1998) for Anergen, Inc., a California company focused on autoimmune diseases. There she reorganized the scientific staff and approach and positioned the company for acquisition by Corixa Corporation in December 1998. Dr. Nacy became full-time CEO and Chair of the Board of Sequella in January 1999. She is a member of the Board of Directors of both companies (ASM Resources, Social and

Scientific Systems) and nonprofit agencies (Sequella Foundation, Women in Bio, Sloan Biotechnology Industry Organization), and serves on a number of committees in global health organizations. Prior to her business experience, Dr. Nacy was career Scientist and Science Manager at the Walter Reed Army Institute of Research, Washington, DC, where she studied tropical infectious diseases and published more than 140 scientific papers. She was elected to the American Academy of Microbiology in 1985. She maintains strong ties to the scientific research community, and was President of the American Society for Microbiology (1996) and the Society for Leukocyte Biology (1993) and served on the Board of the National Academy of Sciences, National Research Council (1996–2001). She is an adjunct faculty member of the Department of Biology, Catholic University of America, and Department of Tropical Diseases, The George Washington University. She earned her A.B., M.S., and Ph.D. degrees from the Catholic University of America, and in 2002 was awarded the Lifetime Achievement Award in Science from that institution. Dr. Nacy was singled out as a Top 50 Innovator in the United States by *Inc. Magazine* in 2002, named Entrepreneur of the Year by Women in BIO in 2004, named by the state of Maryland among its Top 100 Business Women in 2005, and named by the *Washington Business Journal* as a top 25 female executive in the Washington, DC, metropolitan area in 2005. In 2006, she received a National Leadership Award in Healthcare from the National Urban Technology Center in New York City, and in 2007 she was honored with a Special Outstanding Achievement Award for Clinical Trials by Women in BIO.

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 Tuberculosis 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 Tuberculosis Control for the Massachusetts Department of Public Health, a position he held for 18 years. In 2002 he joined Partners In Health as Director of Tuberculosis Research. In 2005 he left Cambridge Hospital to assume a full-time research position in the Department of Social Medicine and Health Inequalities, Brigham and Women's Hospital, the hospital arm of Partners In Health. He is also a member of the Pulmonary Division at the hospital, where he serves on the pulmonary consult service. Dr. Nardell's research interests include the control of MDR TB in Peru, Russia, and

other high-burden countries. His special research interest is airborne TB transmission and control. He currently has a project in South Africa, funded by the National Institute for 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, IUATLD. He was the 2005 recipient of the Chadwick Medal of the Massachusetts Thoracic Society.

Dale Nordenberg, M.D., is a health care consultant currently working as the Senior Scientist supporting the National Biosurveillance Advisory Subcommittee (NBAS) Task Force on Diagnostic and Laboratory Information Exchange. In this role, his focus is on leveraging the regulatory process to accelerate the development of data exchange standards for diagnostic tests and the governance for the National Biosurveillance Enterprise for Human Health. From 2001 through 2007, Dr. Nordenberg held various positions at CDC, including Associate Director and Chief Information Officer (CIO), National Center for Infectious Diseases (NCID), and Senior Advisor for Strategic Planning, Office of the CIO, CDC. During this time, he led the development of CDC's agency-wide information technology (IT) strategic plan (2008–2012) and was responsible for informatics for NCID. At NCID, he initiated the implementation of a single laboratory platform for the center's laboratories and launched the Public Health Laboratory Interoperability Project (PHLIP) in collaboration with the Association of Public Health Labs to create a standards-based national laboratory data sharing network. Dr. Nordenberg was involved in many disease surveillance, outbreak response, and bioterrorism preparedness and response activities and informatics programs. Prior to joining CDC, he was a founding executive of a company that launched VeriSign affiliates in Latin America and Asia. Before that he was a member of the faculty in the Emory School of Medicine, where founded and directed the Office of Medical Informatics for the Emory University Children's Center. Dr. Nordenberg has served on the boards of numerous companies. Most recently he was a member of the board for Coventry Health Care of Georgia. 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; he completed his training in pediatrics at McGill University, Montreal Children's Hospital, and a fellowship in epidemiology and public health in the Epidemic Intelligence Service program at CDC.

Paul Nunn, M.D., is Coordinator of the WHO team in the Stop TB Department that is concerned with TB and HIV, anti-TB drug resistance, infection

control, and laboratory strengthening. He led the team that prepared the WHO policy on collaborative TB/HIV activities, as well as a number of guidelines on how to address the problem of the impact of HIV on TB. Since September 2006, his responsibilities have included coordinating the global response to XDR TB. Previously, Dr. Nunn was Chief of TB research and surveillance in WHO's Global TB Program, in which he set up the Global TB Research Initiative and established the WHO/IUATLD anti-TB drug resistance surveillance project. Before joining WHO, he was with the London School of Hygiene and Tropical Medicine in Kenya. He researched the impact of HIV on TB in Nairobi; was a visiting scholar at the University of California, Berkeley; and was Coordinator of the Diploma in Tropical Medicine and Hygiene course. He trained as a respiratory physician at the Royal Postgraduate Medical School, London, following clinical studies at University College, London, and received a degree in physiological sciences from Oxford. He has published more than 50 peer-reviewed papers.

David Persing, M.D., Ph.D., is Executive Vice President and Chief Medical and Technology Officer at Cepheid in Sunnyvale, California. He obtained a B.A. degree in biochemistry from San Jose State University in 1979, and an M.D.–Ph.D. from the University of California, San Francisco, in 1988. His doctoral research was conducted in the Department of Biochemistry and Biophysics. He completed his residency in laboratory medicine at the Yale University School of Medicine and then joined the Laboratory Medicine and Pathology Staff at the Mayo Clinic, where he developed extramurally funded research programs on hepatitis viruses and tick-borne infections. In 1992 Dr. Persing established and directed the Molecular Microbiology Laboratory at the Mayo Rochester campus, which became one of the preeminent molecular diagnostic laboratories of its type in the country. In 1999, he joined Corixa Corporation in Seattle, where eventually as Chief Scientific Officer he headed research groups focused on innate immunity, vaccine development, and molecular diagnostics. From 2001 to 2005 he was principal investigator for two grants totaling $18 million in the area of Toll-like receptor agonists and antagonists. He is currently supported by $11 million in grants from NIAID and the Bill and Melinda Gates Foundation via the Foundation for Innovative New Diagnostics (FIND) for the development of MDR TB diagnostics. Dr. Persing has authored more than 260 peer-reviewed articles, book chapters, and reviews; served as editor-in-chief for 3 books on molecular diagnostics; and is an inventor on 16 issued or pending U.S. patents.

Iain Richardson is Director, Global Supply Chain and Logistics at Eli Lilly and Company. A graduate in chemical engineering from the University of Edinburgh with a masters in biochemical engineering from University

College London, he has worked for Eli Lilly for more than 20 years in the Manufacturing Division. A native of Scotland, he joined the company at its Liverpool facility in Technical Services before relocating to the United States in 1991. During 9 years in the United States, he held leadership positions in the company's Animal Health division before becoming Director of Manufacturing Strategy in 1998. In 2000, Mr. Richardson moved to Geneva, Switzerland, where he had manufacturing responsibility for Contract Manufacturing operations in Europe, the Middle East, and Africa, and Lilly and Contract Manufacturing operations in the Asia-Pacific area. It was in this assignment that he first began working on Lilly's MDR TB philanthropic initiative, with particular responsibility for the transfer of technology for Cycloserine and Capreomycin to the identified manufacturing partners. He relocated back to the United States in 2006. Since that time he has been responsible for Lilly's contract manufacturing processes globally, and he is now responsible for global supply chain and logistics operations for the company. He continues to lead Lilly's transfer of technology and product supply initiatives for the MDR TB program.

John Ridderhof, Ph.D., is Associate Director of Laboratory Science, National Center for Preparedness Detection and Control of Infectious Diseases (NCPDCID/CCID), CDC. He began his career as a microbiologist from 1979 to 1984 in the Virginia State Mycobacteriology and Mycology Laboratory. After attending graduate school at the University of North Carolina, Chapel Hill School of Public Health (UNC-SPH), he held an American Society of Microbiology–sponsored postdoctoral fellowship in clinical and public health microbiology from 1987 to 1988 at the Medical College of Virginia/Virginia Commonwealth University. He then served from 1988 to 1992 as Deputy Director of the Delaware State Public Health Laboratory. Dr. Ridderhof came to CDC in 1992 as Chief of the Laboratory Standards Branch, with responsibility for developing and supporting laboratory regulations (Clinical Laboratory Improvement Amendments [CLIA]). From 1994 to 2000, he served as Assistant Director, DLS, responsible for coordinating and conducting all mycobacteriology laboratory training, performance evaluation, and research activities in addition to coordinating the Clinical Laboratory Improvement Advisory Committee. In his recent position as Chief of the Laboratory Systems Development Branch (LSDB), he coordinated various international activities, including those focused on international TB laboratory strengthening, and the National Laboratory Systems initiative. The LSDB activities also included international and domestic laboratory training activities and research and guidelines in laboratory quality assurance in resource-limited countries. DLS has developed many of the international guidelines and training materials for TB and HIV in collaboration with many organizations. A DLS priority is to promote a

quality management systems framework and approach to strengthening laboratory systems. DLS/LSDB activities and responsibilities involve close partnerships with the Association of Public Health Laboratories (APHL), WHO, IUATLD, and other organizations to facilitate consensus and develop programs, training products, and guidelines that promote quality laboratory testing standards in support of public health in the United States and globally. Dr. Ridderhof is currently serving as Chair of the WHO/Stop TB Partnership Global Laboratory Initiative for 2006–2008. In August 2007 he was appointed Associate Director for Laboratory Science for NCPDCID. Dr. Ridderhof received a B.S. degree in biology at Virginia Commonwealth University. He holds master's and doctorate degrees in public health laboratory practice from UNC-SPH and certification as High Complexity Laboratory Director (HCLD/ABB).

Leonard Sacks, M.D., was born in Johannesburg, South Africa, where he received his medical education at the University of the Witwatersrand, graduating MBBCh in 1979. He completed his medical residency at Baragwanath Hospital in Johannesburg, becoming a Fellow of the College of Physicians (South Africa) in 1984. In 1988 he moved to the United States, completing a fellowship in immunopathology at Upstate Medical Center in Syracuse, New York, followed by a fellowship in infectious diseases at the Veterans Administration Medical Center in Washington, DC. Since that time he has worked as an attending physician in infectious diseases both in Washington, DC, and in South Africa, with particular interests in antimicrobial therapy, TB, and tropical diseases. Since joining the FDA in 1998, Dr. Sacks has served as a medical reviewer and team leader in the Division of Special Pathogens and Immunological Drug Products, Center for Drug Evaluation and Research; he is currently Deputy Director of the FDA's Office of Critical Path Programs. Dr. Sacks holds an academic position as Associate Clinical Professor of Medicine at The George Washington University.

Sarita Shah, M.D., M.P.H., is Assistant Professor of Medicine and Epidemiology/Population Health at Albert Einstein College of Medicine, New York. She completed her internal medicine residency at Columbia-Presbyterian Hospital, New York, and earned her M.D. degree from the Johns Hopkins School of Medicine, Maryland. She completed an M.P.H. degree at Columbia Mailman School of Public Health, New York. Dr. Shah spent 2 years in the Division of Tuberculosis Elimination at CDC, where she served as an Epidemic Intelligence Service (EIS) officer from 2004 to 2006. She was project officer for a variety of TB epidemiologic and program-building efforts in Ethiopia, Venezuela, and Southeast Asia. Dr. Shah served as lead investigator for the first survey that described the global emergence of XDR TB, a collaboration that involved CDC, WHO, and the international network of

TB reference laboratories. Since completing the EIS program at CDC, she has been working in Tugela Ferry, South Africa, where her research focuses on improving diagnosis and treatment of drug-resistant TB. In 2007, she received a 3-year Clinical Scientist Development Award from the Doris Duke Charitable Foundation to support this work. Additional funding from the Howard Hughes Medical Institute is supporting a study to improve TB diagnosis in children. Dr. Shah has also received funding from the Einstein Center for AIDS Research for research in the molecular epidemiology of MDR and XDR TB in Tugela Ferry. She complements her research with providing care for HIV/AIDS patients in the Bronx, New York, and teaching residents on the inpatient wards.

Martie Van der Walt, Ph.D., Interim Director for the TB Epidemiology and Intervention Research Unit, joined TB research at the Medical Research Council South Africa in 1998. Her basic training is in microbiology (MScAgric); she obtained a Ph.D. in biotechnology (vaccine development for livestock) and also holds an M.B.A. Dr. Van der Walt has been responsible for the unit's operational research program and for projects in such areas as program implementation, DOTS evaluation, and drug-resistant TB and epidemiology. The unit was tasked with implementing the programmatic management of MDR TB under DOTS-Plus, and oversaw this effort until it became a control program activity. Through the unit's operations research activities, Dr. Van der Walt has a network of TB control programs on both the national and provincial levels, thereby having access to all types of TB patients at all levels of the control program. She has worked extensively in all nine provinces of South Africa. She has worked in close collaboration with the Ministry of Health in research translation, policy development, and policy implementation, especially for drug-resistant TB and uptake of new diagnostics for the program. She has been responsible for the large-scale rapid MDR TB diagnosis project, providing evidence to WHO leading to new policy for the diagnosis of drug-resistant TB. Dr. Van der Walt has also been overseeing the 5-year Cooperative Agreement between CDC and the unit. She has performed program review in Swaziland. She is a member of the Stop TB New Diagnostics Working Group, the Drug-Resistance Working Group, and the WHO Global XDR-TB Task Force; served on the Green Light Committee from 2005 to 2007; and is a member of the Global Alliance Shareholders Association.

Charles D. Wells, M.D., currently serves as Medical Director for the Tuberculosis Products Unit at Otsuka Pharmaceutical Development and Commercialization (OPDC), having joined the company in May 2007 to support efforts to develop the compound OPC-67683 for TB treatment. Prior to joining OPDC, he served as Chief of the International Research and Pro-

grams Branch within the Division of Tuberculosis Elimination at CDC, 2001–2007, which has been a leading technical group for epidemiologic, clinical, and diagnostics research on TB and provided direct technical assistance internationally for the implementation and scale-up of programs for TB, TB/HIV (within PEPFAR), and MDR TB. Dr. Wells attended North Carolina State University, where he received a B.S. in chemical engineering in 1987. He then completed his medical studies at the University of North Carolina, Chapel Hill in 1992. After medical school, he completed a residency in internal medicine at Emory University in 1995; an EIS fellowship at CDC in 1997; and a clinical fellowship in infectious diseases, also at Emory University, in 1998. He is board certified in both internal medicine and infectious diseases. Dr. Wells began his research in TB in 1995 upon joining EIS and has remained in the field since that time. In addition to his previous work at CDC, he spent nearly 2 years working on new drug development for TB at PathoGenesis Corporation, 1998–1999. Additionally, while he was at CDC, his group successfully launched a 2,000-patient clinical trial in Botswana in November 2004, evaluating the optimal duration for isoniazid preventive therapy for persons living with HIV in TB-endemic settings. During his 13 years working in TB, TB/HIV, and MDR TB, he has worked in many countries, including Vietnam, Cambodia, Thailand, the Philippines, India, Russia, the Baltic countries, South Africa, Botswana, Ethiopia, Brazil, and Mexico, among others.

Raymond L. Woosley, Ph.D., earned his Ph.D. in pharmacology from the University of Louisville and an M.D. from the University of Miami. He specialized in internal medicine and clinical pharmacology at Vanderbilt University, where he rose to the rank of Professor of Medicine. At Georgetown University, he served as Chairman of the Department of Pharmacology and in 2000 was appointed Associate Dean for Clinical Research. In 2001 he became Vice President for Health Sciences at the University of Arizona and Dean of the College of Medicine. In January 2005 he assumed the position of President of The Critical Path Institute (C-Path), a nonprofit corporation formed by the FDA and the University of Arizona to accelerate the development of safe, innovative medicines. Since 1999, Dr. Woosley has directed 1 of 14 federally funded Centers of Education and Research on Therapeutics (CERTs). His research has been published in more than 260 publications and has investigated the basic and clinical pharmacology of drugs for the treatment of arrhythmias and the cardiac toxicity of drugs. His research revealed the mechanism of the toxicity of the antihistamine Seldane, which contributed to its subsequent removal from the market. For his contributions to medicine, he received the Rawls-Palmer Award from the American Society of Clinical Pharmacology and Therapeutics and the FDA Commissioner's Special Citation for his work to advise the

agency on the toxicity of dietary supplements containing ephedra. In addition, Dr. Woosley is a past President of the Association for Medical School Pharmacology and the American Society for Clinical Pharmacology and Therapeutics. He holds faculty appointments at the BIO5 Institute of the University of Arizona and the Biodesign Institute at Arizona State University. His research investigates the mechanisms responsible for adverse drug interactions and means of prevention.

Paul Zintl, M.P.A., is Chief Operating Officer for Partners In Health and Senior Advisor for Planning and Finance for the Program in Infectious Disease and Social Change (PIDSC) at Harvard Medical School. He joined Partners In Health and Harvard Medical School in January 2002. Previously, he was 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 an M.P.A. degree from the John F. Kennedy School of Government at Harvard. From 2000 to 2007, Mr. Zintl served as Chairman of the Board of Directors of Federated Dorchester Neighborhood Houses, Inc. He served as a trustee of St. Luke's-Roosevelt Hospital in New York City from 1988 to 2000 and on the Board of the Neighborhood House Charter School in Dorchester, Massachusetts, from 1996 to 2004. Mr. Zintl earned an undergraduate degree from the University of Virginia and a master of divinity degree from Harvard University.

Appendix C

Partners In Health White Paper—Stemming the Tide of Multidrug-Resistant Tuberculosis: Major Barriers to Addressing the Growing Epidemic

STEMMING THE TIDE OF MULTIDRUG-RESISTANT TUBERCULOSIS:

MAJOR BARRIERS TO ADDRESSING THE GROWING EPIDEMIC

A WHITE PAPER FOR THE
INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

HARVARD MEDICAL SCHOOL

PARTNERS IN HEALTH

FRANÇOIS–XAVIER BAGNOUD CENTER FOR
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IMS Health

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EXECUTIVE SUMMARY

Every year nearly 500,000 people worldwide fall ill from newly-acquired disease caused by multidrug-resistant tuberculosis (MDR-TB), adding to an estimated global burden of at least 1.5 million prevalent cases. This infectious disease is spread through the air and is caused by strains of *Mycobacterium tuberculosis* that are resistant to the two most effective first-line anti-tuberculosis drugs. Before they die from the disease, people infected with MDR-TB often transmit the mycobacterium to others. More ominously, tuberculosis strains now deemed extensively drug-resistant (XDR-TB) threaten the progress made to date in the treatment of resistant disease and necessitate an urgent call to action. Though aggressive treatment with second-line drugs has yielded a range of positive outcomes for patients with XDR-TB, the widespread emergence of totally drug-resistant strains (TDR-TB) would return us to the pre-antibiotic era.

Confronting MDR-TB is a core goal stated in the WHO's *Global Plan to Stop TB: 2006-2015.* Under the original plan, at least 800,000 people with active MDR-TB were to be treated by 2015. A subsequent revision, reflecting the concern over XDR-TB, made a more ambitious call for universal access to treatment for all active MDR-TB patients; this will require the treatment of nearly 1.6 million patients by 2015. At present, only ten percent of new MDR-TB cases are treated each year, and less than two percent are receiving verifiable, quality-assured, second-line anti-TB drugs through WHO's Green Light Committee (GLC) mechanism. Preventing the further emergence of strains of tuberculosis with broad-spectrum resistance—including those resistant to all first- and second-line anti-tuberculosis drugs—is dependent upon identifying and addressing barriers to effective diagnosis and treatment of drug-resistant tuberculosis without delay.

While multidrug-resistant strains of tuberculosis may have first emerged from inadequate treatment and control programs in the recent past, continued spread of this airborne pathogen is directly affected by the following barriers to large-scale, effective treatment delivery:

1. Exceedingly limited capacity to rapidly diagnose drug-resistant TB. True point-of-care testing is practically nonexistent, especially in the areas with the highest tuberculosis burden.
2. Limited supply of quality-assured second-line anti-tuberculosis drugs. The current supply is insufficient, even for the estimated two percent of MDR-TB patients being treated through the GLC mechanism. This is exacerbated by limited demand for quality-assured second-line anti-tuberculosis drugs in countries with high burdens of MDR-TB. These countries are using local manufacturers who often do not meet quality-assurance standards as defined by the WHO.
3. Ambiguous messaging about the importance of integration of MDR-TB into national tuberculosis control programs, perpetuated by a "pilot-program" mentality that has not been encouraging a push for universal access.

4. Inadequate mechanisms for delivering technical assistance to countries in a manner that sufficiently addresses the need and builds local capacity to effectively and safely treat and manage MDR-TB.
5. Lack of focus on interrupting transmission of the tuberculosis bacilli in congregate settings both in the community and in institutions such as hospitals, clinics, and prisons.

This paper provides several recommendations to facilitate the expansion of global treatment and prevention of multidrug-resistant tuberculosis. These include: promoting universal access to treatment as part of national tuberculosis control programs; improving and expanding laboratory capacity, including rapid point-of-service testing; reforming the current procurement system to ensure an adequate and accessible supply of quality-assured second-line drugs; providing ongoing, on-site technical assistance; and expanding the delivery of ambulatory-based MDR-TB treatment. It also includes recommendations concerning the development of effective transmission-control programs in resource-limited settings.

SPECIFIC RECOMMENDATIONS:

Diagnostics

- Sustainable funding from bilateral and multilateral donors must be increased to support construction of in-country drug-sensitivity testing/rapid-testing laboratories and ongoing external quality assessments by supranational reference laboratories.
- Creation of a system of long-term on-site technical assistance would help countries build and/or rapidly expand their capacity to perform mycobacterial culture, DST, and rapid molecular genetic tests for drug-resistant tuberculosis.
- In-country laboratory networks for: specimen transport, data management, and certification and coordination of private laboratories need improvement.
- Use of excess laboratory capacity for mycobacterial culture and drug-susceptibility testing in wealthy nations should be encouraged while laboratories are being built in poorer regions.
- Priority must be given to research on—and funding for—the immediate development and rapid deployment of point-of-care testing for drug-susceptible and drug-resistant tuberculosis.

Drug Supply

- The WHO and international partners should take immediate and rapid steps to increase the number of manufacturers of quality-assured second-line anti-tuberculosis drugs. A mechanism needs to be developed to make these drugs available at pre-negotiated prices to programs purchasing via the GDF *and* through direct-purchase by countries.
- The GDF should create a tiered system of approval for manufacturers of second-line drugs—and purchase of product by the GLC mechanism—consistent with a manufacturer's progress in the WHO's Essential Drugs Monitoring (EDM) prequalification process. Large countries operating within the GLC mechanism should be allowed to purchase second-line anti-tuberculosis drugs from domestic manufacturers who have entered the EDM prequalification process.
- The GLC mechanism should institute a transparent system for quantification of demand for second-line drugs.
- The GDF should maintain a second-line anti-tuberculosis drug buffer stock (at minimum, enough to treat 5,000 patients) in order to facilitate rapid delivery of drugs to programs (less than one month).
- There should be a global effort to increase the options available for treating MDR-TB and XDR-TB, by optimizing current regimens and by developing at least three new anti-TB drugs. Increased TB clinical trial capacity needs to be created, and mechanisms developed to fast-track new anti-TB drugs through the regulatory process.

Treatment Delivery

- Universal treatment for drug-resistant tuberculosis within national TB control strategies—side by side with drug-susceptible disease—has to be clearly and actively promoted by multilateral and bilateral agencies, non-governmental organizations, and within countries. Universal TB treatment also must be well integrated with current HIV treatment initiatives.
- The system of international technical assistance provision is currently inadequate. It must be transformed in order to better draw on the experience of successful regional MDR-TB-treatment programs, to include the provision of on-site, long-term technical assistance, and where necessary, to involve on-site implementation teams.
- Community/Ambulatory-based MDR-TB treatment, and where appropriate, active collaboration with private-sector laboratories and tuberculosis treatment providers, should be actively promoted as a safe means of rapidly treating the largest number of patients. Delivery systems that support this will need to be strengthened and/or built.
- Infection control to prevent transmission of TB strains has to be integrated fully into national TB-control strategies, with appropriate resources, training, implementation strategies, and monitoring.
- Large global health initiatives—such as PEPFAR—and bilateral and institutional donors for global health should make improving the capacity to deliver MDR-TB treatment an important priority. The Global Fund and UNITAID have done so, and others should follow this lead with their influence and resources.

GLOSSARY OF TERMS:

Term	Definition*
Multidrug-resistant TB (MDR-TB)	TB that is resistant to at least two of the best anti-TB drugs, isoniazid and rifampicin. These drugs are considered first-line drugs and are used to treat all persons with TB disease.
Extensively drug-resistant TB (XDR-TB)	TB that is resistant to isoniazid and rifampin, plus resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).
First-line drugs	The most common medicines used to treat newly diagnosed drug- susceptible TB are: isoniazid (INH); rifampin (RIF); ethambutol; and, pyrazinamide.
Second-line drugs	Drugs included in the treatment regimen for MDR TB are amikacin, capreomycin, ciprofloxacin, cycloserine, ethionamide, kanamycin, levofloxacin, ofloxacin, para-**a**minosalicylic acid, and prothionamide.

* Source: US Centers for Disease Control

SECTION I: THE PROBLEM OF DRUG-RESISTANT TUBERCULOSIS

1 INTRODUCTION

Tuberculosis (TB) is one of the leading causes of death in the world today. The World Health Organization (WHO) estimates that *Mycobacterium tuberculosis* caused active disease in 9.15 million people across the globe, killing 1.6 million of them. More people carry the bacillus today—one-third of the world's population—than at any other period in history.[1]

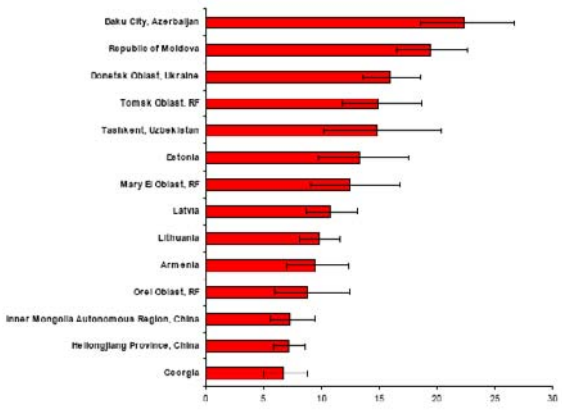
Known to medical science since earliest antiquity, TB has proven to be a remarkably hardy and resourceful foe. Its trademark symptoms—a hacking, productive cough, chest pain, fever—were accurately identified by Hippocrates in the fifth century BC; its contagiousness was established as early as the eleventh century AD; and the bacterium that causes it was isolated by Robert Koch in 1882. Antibiotics to treat the disease have been available for over half a century. But unlike earlier plagues that yielded readily to advances in medical science, TB has earned a fearsome reputation as one of the most tenacious and resilient threats to public health in recorded history.

That resiliency arises in part from the bacterium's ability to mutate and acquire drug resistance. In order to provide comprehensive TB care to some of the world's poorest populations, in 1993 the WHO created the DOTS strategy—directly observed therapy, short-course—as a global programmatic strategy. Developed by the British Medical Research Council (MRC) and the International Union Against Tuberculosis and Lung Disease (IUATLD) in the 1970s and 1980s, DOTS was an attempt to provide effective tuberculosis (TB) treatment in the shortest possible time, and thereby prevent the development of drug-resistant TB and large numbers of "chronic cases."[2,3,4,5,6,7,8] DOTS was rolled out with great fanfare in 1993. For the first time, TB treatment was to be delivered to patients under uniform programmatic conditions, which involved the direct observation of therapy. Despite its huge success as a program, the early DOTS strategy had several key shortcomings that limited its effectiveness and necessitated a different approach. Firstly, DOTS was originally designed for settings and conditions in which resistance to first-line anti-TB drugs was minimal.[9,10] However, in settings where a significant proportion of patients are infected with strains of *M. tuberculosis* that are already resistant to one or more of the first-line anti-TB drugs, short-course chemotherapy (the drug regimen in DOTS) is of limited utility.[11,12,13,14,15,16,17,18] In fact, in some places, use of the DOTS approach alone was contributing to poor outcomes and preventable mortality.[19,20,21,22,23,24,25,26,27,28]

According to the WHO, the amount of drug resistance has been trending upward in many parts of the world (at least one country in each of WHO's six regions reports an MDR-TB incidence of greater

than 3 percent among new patients [see Figure 1]).[29] Of particular concern are strains that are resistant to the two main first-line anti-TB drugs that form the back-bone of short-course chemotherapy, isoniazid and rifampin. Known as multi-drug resistant TB (MDR-TB), these strains have been found throughout the world,[30,31] and are a significant cause of global TB morbidity and mortality.[32,33,34,35,36,37] The total global burden of MDR-TB is estimated at almost 490,000 new cases per year, or over 4 percent of all TB cases; an estimated 120,000 of these patients die annually.[38,39,40] MDR-TB has been implicated in institutional outbreaks in the United States, Europe, Asia and Latin America, outbreaks that produced high case fatality rates among immunosuppressed people, as well as high rates of transmission to other patients, caregivers, and family members.[41,42,43,44,45,46,47,48,49] Because no new anti-TB drugs have been discovered or developed for decades, the antibiotic armamentarium with which to treat MDR-TB is surprisingly small. Patients who develop MDR-TB or XDR-TB require treatment for 18 to 24 months, sometimes hospitalization, and in some cases, surgical resection of infected lung tissue.

Figure 1: Countries and settings with MDR-TB prevalence higher than 5 percent (2002 to 2007)[50]



The problem of drug-resistance has become all the more frightening over the last half decade with the emergence of MDR-TB strains with broad-spectrum resistance to both first- and second-line anti-TB drugs. Some of these strains—known as extensively drug-resistant tuberculosis (XDR-TB)—have been found to be resistant to the most effective second-line anti-TB drugs: fluoroquinolones and parenteral anti-TB agents. A recent nosocomial outbreak of XDR-TB among HIV-positive patients in South Africa resulted in a case fatality rate of almost 100 percent.[51] According to the World Health Organization, there are an estimated 40,000 cases of XDR-TB each year, half of whom die in short-order.

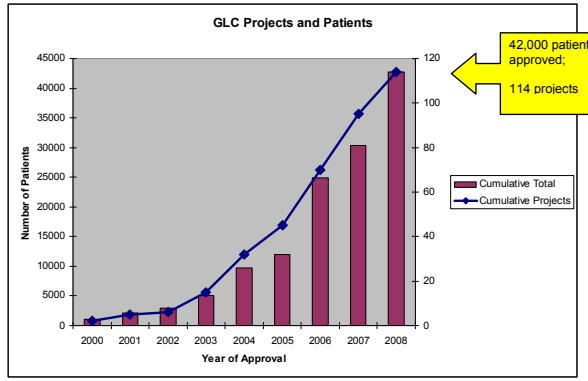
How drug-resistant TB emerges and spreads is best understood as two interlinked processes. Initially, a patient infected with drug-susceptible TB seeks treatment with standard, first-line medications. Under proper conditions—and assuming only quality-assured antibiotics are used—the patient will likely be cured and not relapse.[52] However, if the patient is treated with an inadequate number of effective drugs for an appropriate length of time, does not complete her treatment regimen, or has problems absorbing the treatment regimen (as is often the case in patients with HIV), the treatment can fail.[53] Although patients who fail treatment may have developed some drug resistance, most programs continue to prescribe multiple cycles of first-line anti-TB therapy. With each iteration of unsuccessful treatment, the number of drugs to which the patient becomes resistant increases (this process is called "amplification of resistance").[54,55] Newly infected patients are often not identified as having a drug-resistant strain of *M. tuberculosis*, and enter the same cycle as above, in which they are inadequately managed from the onset of treatment. Thus, in many ways, the recently recognized increase in global MDR-TB prevalence reflects serious deficiencies in both the programmatic approach to treating TB (drug-susceptible) and TB treatment delivery at the country-level. When MDR-TB strains appear in a given setting, the situation is exacerbated by: (1) constraints on the ability of local practitioners to diagnose drug-resistance, largely due to the absence of laboratory infrastructure; (2) the lack of a consistent and sufficient supply of quality-assured, second-line anti-TB drugs; and (3) programmatic challenges to delivering TB treatment for the requisite treatment length.[56]

Concern over the high burden of MDR-TB faced by many countries has recently led to major changes in the international TB community's approach to the treatment of resistant strains in resource-poor settings. In 1998, global TB partners, including the WHO, created "DOTS-Plus," which attempted to address the most glaring deficiencies of DOTS vis-à-vis treatment of drug-resistant TB. DOTS-Plus was greeted with skepticism by many TB experts and practitioners, who were concerned that the use of second-line anti-TB drugs would lead to expanded drug resistance. In 2000, to reassure those critics, the WHO and its partners established a multi-agency task force called the Green Light Committee (GLC) Housed at the WHO headquarters in Geneva, the GLC was assigned to improve access for programs to concessionary-priced second-line anti-TB drugs, while promoting the rational use of these drugs through appropriate programmatic management.[57] The initial five projects approved by the GLC became known as DOTS-Plus pilot projects, and provided essential information for the development of the WHO's global drug-resistant TB guidelines (*Guidelines For The Programmatic Management Of Drug-Resistant Tuberculosis*).[58] Overall, using aggressive treatment regimens, direct-observation of therapy with incentives and enablers, and management of adverse events, the GLC pilot projects achieved cure-rates of 75 to 80 percent for new cases of MDR-TB and between 65 and 70 percent for previously treated

cases.[59,60,61,62,63,64] XDR-TB patients have been found to have cure rates of between 48 and 60 percent in program settings.[65,66]

Based on these results, as well as evidence that DOTS-Plus projects strengthen underlying TB control programs and reduce the reservoir of patients transmitting drug-resistant strains, the DOTS-Plus approach became the accepted management strategy for drug-resistant TB.[67] In 2006, the Stop TB Strategy incorporated DOTS-Plus into an integrated strategy for TB control.[68] Since 2000, the GLC has approved over 42,000 patients for treatment in 114 projects (see Figure 2).

Figure 2: GLC Projects and Patients as of August 2008



Alarmed over the surprising prevalence and growth of XDR-TB, policymakers from the WHO, key international partners, and affected countries met in the fall of 2006 to agree on a global strategy to combat MDR-TB and XDR-TB. They agreed on a two-year emergency plan— with a 2.15 billion USD budget—that called for aggressive revision of the 2015 targets to include "universal access" by 2015 (equating to nearly 1.6 million patients instead of the 800,000 patients covered in the original plan) and "universal access" by 2010.[69] In addition, the plan calls for the treatment of 134,000 individuals by the end of 2008. Thus, although the gains of the GLC are impressive, they neither meet the WHO targets for MDR-TB treatment that were established in 2005, nor subsequent targets.[70,71,72]

The gap between the goals set by the WHO and the ability of health-workers on the ground to achieve them continues to vex policymakers throughout the TB community. For one thing, the most obvious explanation—inadequate funding—appears to be a fairly minor factor thanks to support from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) and other funding sources. While

adequate financing is essential for successful implementation, evidence from the battle against other diseases (such as HIV, polio, and malaria) indicates that other issues must also be addressed by the global TB community.[15]

This White Paper, written for the Institute of Medicine (IOM), will attempt to delineate some of those other issues. The purpose of this document is not to provide an exhaustive inquiry into the complexities of MDR-TB care delivery. Rather, we aim to highlight and analyze the common difficulties that confront healthcare policymakers in resource-poor settings as they attempt to integrate MDR-TB treatment into their own national TB-control strategies and as they seek to expand treatment to all afflicted patients

2 A General Framework for Understanding Barriers to MDR-TB Scale-up

Care delivery consists of myriad inter-connected activities. The care-delivery value chain (CDVC) model allows researchers to assign a value to every activity that occurs during the care of a patient for a specific medical condition. It identifies the discrete activities that are required to deliver care, illustrates their sequence and organization, and assesses the results in order to maximize the benefit to patients. Value is measured as a product of the many interdependent activities that make up the cycle. The value of any discrete activity can only be understood by considering its relation to other activities within the CDVC.

The CDVC for MDR-TB can be divided into four categories: population risk-stratification, diagnosis, intervention, and management. Each of these is an essential element, and together they constitute successful MDR-TB care delivery. As thorough as it is in assessing care, at the local level, the CDVC does not take into account macro-level barriers, such as the quality of imported pharmaceuticals or the lack of a point-of-care test for MDR-TB. For example, if we were to look at the category of "intervention" and ask why a certain country is not using quality-assured second-line anti-TB drugs for their MDR-TB patients, the answer—linked to many political and economic factors— lies outside the CDVC.

To bring these external factors into the equation, we have expanded the CDVC concept into the "implementation value chain" (IVC). The IVC is concerned with global variables that affect whether MDR-TB treatment can be successfully delivered to patients. The *care cycle* for an MDR-TB patient begins at the moment of infection and lasts until cure or death. In a country where MDR-TB is present, the *implementation cycle* begins at the moment when MDR-TB is acknowledged as a public-health concern and lasts until the creation of a management program within that country. Given the complexity of MDR-TB care— which involves everything from identifying infected patients and negotiating the

purchase of antibiotics on the open market to providing continuous treatment over a two-year period—the CDVC is inextricably bound to the IVC. Although the focus of this paper will be on the IVC, the ultimate aim is to improve conditions at the level of the patient so that treatment can be delivered effectively.

It is with this framework in mind that we have approached the challenges of barriers to the implementation of appropriate MDR-TB care by dividing this discussion document into the following sections: (1) diagnosis of MDR-TB; (2) MDR-TB drug supply and access; and (3) strengthening the delivery of MDR-TB treatment. The authors believe that by focusing on these three areas healthcare providers and policymakers stand the best chance of attaining universal access to drug-resistant TB treatment and care for patients with MDR-TB.

SECTION II: DIAGNOSIS OF MDR-TB

1 INTRODUCTION

1.1 The inadequacies of sputum smear microscopy

Laboratory services for tuberculosis have traditionally emphasized smear microscopy for the diagnosis of active pulmonary TB.[73] Smear microscopy is a decentralized service conducted at or near the point of care (POC). The test, which is from the 19th century, has significant technical limitations (e.g. low sensitivity and problems with specificity in areas with a high prevalence of *Mycobacteria* other than TB),[74,75,76] Nevertheless, it remains an important part of TB control because it is widely available and because it targets patients with bacilli in their sputum (who are the most infectious).

Two important developments in the epidemiology of TB have called into question the over-reliance on sputum smear microscopy as the main modality for TB diagnosis. The first is the increasing incidence of HIV-TB co-infection, which although deadly, often manifests itself as paucibacillary and/or extra-pulmonary disease, which is often smear-negative. The second development is the rise of drug-resistant TB, including MDR-TB and XDR-TB. These strains of TB cannot be distinguished from drug-susceptible strains through microscopy alone, but must be subjected to drug-sensitivity testing (DST) either by mycobacterial culture or genetic analysis. Therefore, although sputum smear microscopy remains a vital service,[77] it does not provide the information required to reliably diagnose TB, identify drug-resistant cases, or monitor resistance in settings with high tuberculosis drug-resistance.

The success of the global response to drug-resistant tuberculosis hinges on the ability of the healthcare system to find and manage MDR- and XDR-TB cases. Mycobacterial culture and drug-

sensitivity testing are the foundations of current laboratory services for MDR/XDR-TB diagnosis and control, but they require more resources than smear microscopy does. Incubators, refrigeration, and biosafety hoods, in addition to laboratory consumables, are all needed for these techniques to be performed properly. In addition, the tests require improved biosafety containment facilities, which carry more intense design, engineering, construction, and maintenance costs. The turnaround time for culture-based DST, even for automated tests, is at least two to four weeks, and samples must contain viable TB bacilli.

New technologies to diagnose drug-resistance and/or smear negative TB are being developed that overcome some of the basic limitations of culture systems.[78,79] Some of these alternatives have recently been validated and their use is being expanded.[80] Even when new tests are implemented, they will still require the basic infrastructure of quality assured facilities, transport, and data management systems to make an impact. In the short term, culture and DST remains the mainstay of disease control and the infrastructure to support these techniques will assist in the roll out of future technologies.

1.2 Expanding Laboratory Capacity

Public health experts agree that controlling the MDR-TB epidemic and providing prompt curative services for those with TB disease is an essential public health function. As a result, significant attention has been drawn to the state of laboratory networks serving those missions. Observers have concluded that dramatic improvements in baseline capacity are necessary to meet anticipated surveillance and treatment targets.[81,82,83,84,85] In 2005, the World Health Assembly passed a resolution requesting the Director-General "to implement and strengthen strategies for the effective control of, and management of persons with, drug-resistant tuberculosis." The 2006 Global Plan to Stop TB stresses the importance of laboratory services, stating that "every country should have a well-resourced and fully functioning national reference laboratory."[86] The MDR-TB working group identified culture and DST services as indispensable components of the TB control effort."[87] The WHO Global Taskforce on XDR-TB echoed these recommendations in *The Global MDR-TB and XDR-TB Response Plan*. The plan called attention to three core priorities for TB laboratory infrastructure: accelerating access to laboratory services, improving infection control, and expanding surveillance.[88,89] Smear microscopy is still the foundation for TB control, but a broad consensus among public health officials now supports increased use of culture and DST services.[90,91]

To design an effective strategy to improve laboratory networks, policymakers must first have a clear understanding of the gap. The WHO's Global Tuberculosis Control report for 2007 (*Global Tuberculosis Control 2008: Surveillance, Planning, Financing*) succinctly summarizes the current state of laboratory services: "[National Tuberculosis Programs] in all WHO regions reported…too few laboratories, weak quality control, and limited facilities to carry out culture and drug susceptibility testing." The report concluded, "Facilities to diagnose and treat MDR-TB, including extensively drug-resistant TB (XDR-TB), are not yet widely available; the scale of the XDR-TB problem globally is not yet known."[92] To address this problem, the World Health Organization's Stop TB Department created the Global Laboratory Initiative (GLI), whose mandate is laboratory capacity development and coordination. According to material on the GLI website, in order to adequately diagnose MDR-TB in the general population, countries will need one culture facility per 5 million population and one DST facility per 10 million population. The GLI's calculations reflect the importance of tracking down difficult-to-diagnose categories of TB, including pediatric, extra-pulmonary, and sputum smear negative TB, as well as treatment failures and patients requiring retreatment for TB. Current global coverage is short of the GLI goals (see Table 1 on the next page).

The formation of the GLI is a major step forward. Recently the organization received funding to work with global partners, such as the Foundation for Innovative and New Diagnostics (FIND), to expand its well-regarded model of accelerated laboratory development in the Kingdom of Lesotho. FIND designed the model in conjunction with the Lesotho Ministry of Health and the international non-profit Partners In Health."[93] Despite achieving phenomenal gains, which will be discussed below, the GLI and its partnerships still face several important challenges, most notably in the development and deployment of true point-of-care testing for pulmonary and extra-pulmonary forms of TB—including drug-resistant TB.

Table 1: Coverage of laboratory services in select high-MDR-TB burden countries (2006)

		Population	National reference laboratory (NRL)	Access to diagnostic services					
				Sputum smear		Culture		DST	
		thousands		number of labs	per 100000 pop	number of labs	per 5 million pop	number of labs	per 10 million pop
1	India	1,151,751	Y	11,968	1.0	8	*0.03*	8	*0.07*
2	China	1,320,864	Y	3,010	0.2	360	*1.4*	90	*2.7*
3	Indonesia	228,864	N	4,855	2.1	41	*0.9*	11	*1.8*
4	South Africa	48,282	Y	143	0.3	13	1.3	8	2.7
5	Nigeria	144,720	N	694	0.5	0	*0.0*	0	*0.0*
6	Bangladesh	155,991	Y	687	0.4	3	*0.1*	0	*0.2*
7	Ethiopia	81,021	Y	713	0.9	1	0.1	1	0.1
8	Pakistan	160,943	N	982	0.6	3	*0.1*	1	*0.2*
9	Philippines	86,264	Y	2,374	2.8	3	*0.2*	3	*0.3*
10	DR Congo	60,644	Y	1,069	1.8	1	0.1	1	0.2
11	Russian Federation	143,221	N	4,953	3.5	978	*34*	302	*68*
12	Viet Nam	86,206	Y	874	1.0	18	1.0	2	2.1
13	Kenya	36,553	Y	770	2.1	2	0.3	2	0.5
14	UR Tanzania	39,459	Y	690	1.7	3	0.4	1	0.8
15	Uganda	29,899	Y	726	2.4	3	0.5	2	1.0
16	Brazil	189,323	Y	4,044	2.1	193	*5.1*	38	*10*
17	Mozambique	20,971	Y	250	1.2	1	0.2	1	0.5
18	Thailand	63,444	Y	937	1.5	65	5.1	18	10
19	Myanmar	48,379	Y	391	0.8	2	0.2	1	0.4
20	Zimbabwe	13,228	Y	180	1.4	1	0.4	1	0.8
21	Cambodia	14,197	Y	186	1.3	3	1.1	1	2.1
22	Afghanistan	26,088	N	500	1.9	1	0.2	1	0.4

Source: Global Laboratory Initiative, Stop TB Department, World Health Organization

2 THE ANATOMY OF A LABORATORY NETWORK

2.1 TB laboratory networks

A laboratory network coordinates the shipment of specimens from peripheral sites to central laboratories, and provides for the reporting of results. Though commonplace in the developed world, such networks are relatively new to developing nations, which in the past have relied on simpler, on-site testing. Performing culture-based diagnosis requires more advanced mycobacteriology laboratories than sputum smear microscopy. Therefore, such facilities are not likely to be universally available at the district level, let alone at health centers, due to the technical demands of building and operating culture laboratories. Expanding access to currently available TB diagnostics will require extending laboratory networks, including the referral and data management systems, in order to get samples to testing nodes.

The global TB laboratory network today is a four-tiered system, as described below. National public health officials determine the priorities of labs within their borders, as well as the volume, quality, and timeliness of services provided. Meanwhile, supra-national laboratories provide quality assurance, technical assistance, and research sites to develop improved techniques.

- Level IV Labs: There are 26 Level IV laboratories around the world. These labs, which maintain the highest standards and share responsibility for external quality control, together make up the Supra-national Reference Laboratories Network (SRLN).
- Level III Labs: These national reference laboratories provide services, such as culture and DST, which are appropriate for a referral facility. They are often located in the national capital, or in large provincial centers.
- Level II Labs: These regional facilities (sometimes called state or provincial labs) can often handle moderately sophisticated testing procedures—such as culture or DST—depending on such factors as geography and the size of the district.
- Level I labs: Clinic or district labs, located in towns and villages or in rural areas. These labs focus on such basic tasks as sputum smear microscopy.

Responsibility over the different levels varies by region and country. Some nations have dedicated national tuberculosis reference laboratories, while others maintain facilities that are shared among a number of disease-control units. Many Level II laboratories fall under the direct authority of national laboratories, but others are formally controlled by state or regional health departments and receive advice from national laboratories. Oversight of microscopy programs ranges from district laboratories to local health centers primarily operated by the National TB Program (NTP).

At the international level, Level III and Level IV laboratories interact with one another in a variety of ways. SRLNs engage in pioneering TB research, assist in capacity building, and support their national counterparts. The Level III laboratories operated by each individual nation handle the culture and DST needs of the domestic population. Level III and IV laboratories frequently collaborate on more ambitious projects, efforts that are normally funded by outside sources. Such collaborations are by their nature sporadic and are not available to all countries suffering from TB epidemics.

2.2 Third-party laboratories

Many nations have significant potential laboratory capacity located in for-profit facilities, universities, or within non-governmental organizations. It is not known how effectively this capacity has been tapped for diagnosing and treating TB. One report from India estimates that 60 to 88 percent of patients with "cough" were initially evaluated outside of the public sector, and up to 50 percent of TB cases were treated outside the NTP.[94] Whether dedicated to research or service provision, these third-party providers and laboratories represent an important source of in-country talent and capacity that could potentially be tapped. Currently, their impact on TB treatment is decidedly mixed. For example, Zambia has at least five organizations with advanced mycobacterial culture systems using liquid-media, and yet national drug resistance data is not universally available and there is no national MDR-TB treatment program or algorithm to access DST results. Private, third-party facilities frequently draw the best-qualified laboratory administrators and technicians from the less well-funded public and non-profit sectors, exacerbating already severe shortages in reliable talent. Even in those instances when privately owned facilities do provide services to TB patients, the quality of those services is difficult to gauge without a global accreditation system and sufficient monitoring by a member of the SNRL network.

In the United States, over 80 percent of mycobacterial sputum smear and culture tests and over 50 percent of DSTs are conducted by the private sector.[95] Tapping these types of private resources is not without difficulty. For example, researchers in developed countries have discovered persistent flaws in the coordination of services, ranging from transportation delays to inadequate adherence to testing protocols.[96] It is difficult to extrapolate those findings to resource-poor settings, but basic problems in service coordination are likely to be exacerbated. Furthermore, when NTP collaborate with third-party laboratory systems, there is considerable risk of parallelism and wasteful duplication of services. Any program that seeks to accredit and utilize third-party laboratories—as will soon be the case in the Philippines as the move toward universal access to MDR-TB treatment—will need to ensure quality levels, equitable access, and close coordination with the public network established by the country's National TB Reference Laboratory.

2.3 Drug resistance surveillance (DRS)

Close monitoring of drug resistance is key to the success of any country's TB-control strategy.[97,98,99] DRS data are used to create epidemiological profiles of countries and regions, to guide empiric treatment, and to respond to focal disease outbreaks and resistance trends. The WHO has completed four sequential surveys of global drug resistance.[100,101,102,103] Unfortunately, in many highly

burdened nations, capacity does not exist for continuous TB surveillance. As a result, there is widespread concern that the limited DRS coverage underestimates the global burden of drug-resistance.[104] Drug resistance surveillance gaps reflect the state of the global laboratory situation: just 11 of 22 high-burden countries have conducted recent DRS surveys, and 11 of 25 high-priority MDR-TB countries had conducted DRS as of 2006.[105] The global community still relies primarily on modeling and extrapolation to understand the true extent of the MDR/XDR-TB crisis.[106] In the past, these models have been dangerously wrong and have had a detrimental effect on global policy.[107]

It is considerably less burdensome to conduct periodic surveys of drug resistance than it is to sustain a national program of patient support. Surveillance data is usually based on representative samples, and in a significant number of cases, patients with active disease have not received treatment. In the future, this type of data collection needs to be linked with national TB treatment programs and local clinical teams.

Example: Global Polio Laboratory Network (GPLN)

The Global Polio Laboratory Network (GPLN) is a centrally coordinated laboratory system created to manage the diagnostic needs of the global eradication campaign. Seven supra-national reference laboratories, 15 regional laboratories, and 123 national laboratories operate the polio surveillance safety net. Under this structure, individual laboratories can serve the needs of multiple countries. Testing is conducted according to a hierarchy of technical sophistication: molecular biology, the most complex testing regimen, is reserved for supra-national laboratories; less complex testing is done at regional and national laboratories. The WHO coordinates an accreditation system for laboratories and works to assure the quality assurance mechanisms, standardized reagents, standardized methods, and testing algorithms.

Between 2004 and 2008, the network required $27.5 million in funding for laboratory operations and $12.5 million in staff costs, in addition to the contributions of national laboratories. The total cost was estimated by one source to reach $125 million annually.[108]

The GPLN laboratory network processes an estimated 80,000 samples annually—just a small fraction of the volume generated by the global TB community. The key features of the network include centralized standards and funding with strong coordination. Polio and measles laboratory facilities operate as regional centers of excellence: they are repositories of skills and they serve as training sites. They also provide additional capacity when other labs in the network become overwhelmed. There are clear service level benchmarks; measles laboratories are required to report results within 7 days of receiving a sample, and test results and data are documented on a central database.[109] The outcome is a network which can

manage the collection, processing, and reporting for a disease with relatively low-incidence requiring rapid laboratory responses.

With its high incidence, prevalence and its need for sustained local service provision, the nature of global TB calls for a different, more decentralized laboratory structure. Nevertheless, the general systems developed to monitor polio—including the establishment of laboratories as centers of excellence, the sharing of capacity and funding, and the coordination of activities—can certainly inform the development of MDR-TB laboratory services at the local, regional and global levels.

2.4 Capacity gap

One proxy for laboratory capacity is total laboratory volume reported compared against total estimated need. Culture capacity is believed to be significantly more developed than DST. In 2005, 12 million requests for mycobacterial culture were issued in developing nations, 8.6 million of those from high-burden countries. Russia, South Africa and India accounted for 92 percent of the high-burden requests; Russia alone had 6.6 million requests. An estimated 1.5 million liquid culture requests were performed in developing countries, although the number for high-burden countries is not known. While this figure seems impressive, based on epidemiological modeling the Stop TB Partnership's Sub-group on Laboratory Capacity Strengthening (SLCS) estimates that 60 million annual cultures will be needed by 2015 to meet targets. While there has been some growth in access to mycobacterial cultures,[110] the gap between need and capacity is quite considerable.

With respect to drug sensitivity testing (DST), the situation is even more worrisome. In 2006 developing countries ran approximately 630,000 DSTs as reported by FIND,[111] of which an estimated 512,000 occurred in high burden countries. The WHO reported that 100,000 MDR-TB cases received DST support during that same year. Mathematical modeling conducted by FIND and the SLCS projects that 5 million annual DSTs will be required to meet basic treatment goals. This is a shortfall of almost 4.5 million DSTs compared to current capacity.

In 2005 18,000 new, laboratory-confirmed cases of MDR-TB were reported, at a time when epidemiological models predicted approximately 424,000 new cases of MDR-TB per year. Thus, only 4.3 percent of the disease burden was captured by the laboratory system. If we look only at high-burden countries, the numbers improve slightly, but the result is still well below what was predicted: 6.1 percent of predicted cases were captured by official reporting. These statistics are aggregate and difficult to

interpret, particularly in settings like China and India where significant private treatment alternatives exist. However, the size of the gap demonstrates the fundamental challenge facing the laboratory network.

Poor distribution of global laboratory resources may indicate that the shortage of testing capacity in high-burden countries is even more severe than at first glance. The recommended density of culture and DST laboratories globally is 1 culture lab per 5 million population and one DST lab per 10 million population. Actual global ratios are 1 per 1.2 million and 1 per 4.95 million, respectively, figures that may be skewed by the heavy concentration of such resources in developed countries. Sub-set analysis shows significant inequalities in distribution. Among high priority nations, the ratios are 1 culture laboratory per 7.8 million people and 1 DST laboratory per 14.2 million people. This means that laboratory services are hardest to find in precisely those settings that need them the most.

Measuring the strength of laboratory networks is a sufficiently complex task that different agencies have come up with widely divergent estimates of capacity. For example, FIND came up with a culture-laboratory density figure three times higher than the one arrived at by WHO's 2007 report (*Global Tuberculosis Control 2008: Surveillance, Planning, Financing*), and twice as high for DST facility density. FIND included private facilities in key countries, a decision that accounts for part of this discrepancy. Regardless of methodology, both reports confirm that current laboratory infrastructure does not meet basic density requirements in high-priority or high-burden countries. Significant work remains to be done to determine if integrating private sector capacity with public programs is realistic in resource-poor settings. What is also abundantly clear is that excess capacity in developed nations is clearly not being utilized sufficiently. According to Dr. Alex Sloutsky of the Massachusetts State Laboratory Institute (MSLI), a supra-national reference laboratory, facilities in developed countries could use their excess capacity to help diagnose MDR-TB for programs where infrastructure is currently inadequate (and is being developed), or in places where disease and population dynamics would likely never warrant the creation of a dedicated laboratory.

2.5 Financing gap

In 2006, researchers drafting the *Stop TB Strategy* projected an enormous shortfall in the financing of efforts to combat the MDR-TB.[112] Between 2006 and 2015, the authors warned, funding would lag behind target amounts by $31 billion. The SLCS estimated the gap in laboratory funding to be at least $2.5 billion between 2007 and 2015. By 2015 the infrastructure and capital expenditures for

laboratory expansion are estimated to require $700 million in funding and 800 new facilities.[113]

3 LABORATORY CAPACITY BUILDING

Country Example: Peru

In the early 1990s, Peru's culture and DST laboratory system had key deficiencies in policy, physical and biosafety infrastructure, and data management. Since Peru lacked a national policy for when to perform drug sensitivity testing (DST), local physicians requested testing on a case-by-case basis. Some physicians waited until a patient's disease was quite advanced and others never requested DST at all. Technicians had inadequate equipment and training that endangered the integrity of the results, as well as their own safety. Mycobacterial cell culture occurred at the district level labs, and positive samples were sent to the National Reference Laboratory (NRL) for DST. DST results typically took almost six months to reach health centers, delaying treatment significantly.

In 1996, an international research team[1] began looking into ways to help Peru's National TB Program improve access to culture and DST. In 2000, through the support of the Bill & Melinda Gates Foundation, the coalition expanded, and the goal became to expand laboratory capacity to support MDR-TB treatment throughout Peru.

The Laboratory Improvement Project set the following goals: improving infection control and biosafety, setting national standards for ordering culture and DST, establishing systems for specimen transport and data management, streamlining culture and DST testing through conventional and rapid methods, and guaranteeing quality assurance through external monitoring and assistance.

To establish biosafety and sound laboratory infrastructure, the project team had to make structural modifications and import equipment. Initially, the team could not find local experts with crucial technical skills in airflow engineering required for the construction of new facilities, and the lack of inspectors complicated routine maintenance. To solve these problems, project personnel sought funding from external grant and training programs to develop in-country capacity. They then formed teams of engineers and architects to improve individual laboratories.

[1] The international team originally consisted of the Massachusetts State Laboratory Institute, Partners In Health, the Peruvian National Tuberculosis Program, the Peruvian National Reference Laboratory (NRL), and Socios En Salud. In 2000, the Centers for Diseases Prevention and Control, the World Health Organization, and the Task Force for Child Survival joined the original team under the auspices of the PARTNERS Laboratory Improvement Project.

Project participants collaborated closely with the NTP to agree upon programmatic standards for laboratory utilization. On-site trainings allowed staff to tailor these norms to meet specific program conditions. Through an iterative process and facilitation of a close working relationship between laboratory personnel and the clinical teams, efforts to improve diagnostic standards throughout Peru were improved.

Additionally, because efficient data collection and management are essential aspects of a strong laboratory network and good clinical care, the team devoted considerable effort and funding to improving these capacities. For example, in the city of Lima, which has a high density of MDR-TB, the program purchased two trucks that were used exclusively to transport specimens to laboratories. The team also analyzed every aspect of the system, from the collection of patient data to the reporting of lab results, to identify and improve areas where delays could be reduced and to monitor process improvement. Adequate funding was given to clinics and labs to ensure that they did not try to charge patients for lab or transport fees, deterring use. A real-time, web-based system was set up to simplify data management and provide access to staff members at all levels.

Team members made a strategic decision to expand the capacity of district laboratories in areas with high MDR-TB rates, rather than expect these localities to rely on the national laboratory in Lima. The national lab was tasked with assisting local and regional facilities in monitoring quality control, upgrading data-management systems to facilitate the sharing of data, and other forms of problem-solving.

While approximately 48,000 cultures and 1,000 DSTs were performed in Peru in 1996, a decade after the program's launch, these figures had increased to approximately 101,000 cultures and 8,300 DSTs annually. Preliminary data from the first district indicates 96.4 percent concordance (used to assess testing accuracy) for rifampicin DST and 99.5 percent concordance for low-level INH resistance, with a median turn-around-time of 28 days to receive these results. The 28-day response time fulfills U.S. standards established in 1993, which suggest that initial DST results be reported within 30 days.

Thanks to a collaborative approach, external technical assistance and funding, from 1996 to 2007, the NRL expanded laboratory capacity and quality in culture, first-line DST (by BACTEC 460), first-line conventional testing, first-line rapid DST in two districts, and second-line DST.

3.1 Fragmented organization and a poorly defined role in TB control

Despite their critical role in TB control, laboratories have a poorly defined role in the overall strategy and mission of TB control in countries. The NTP—responsible for TB treatment, establishing norms and standards, writing large grants to multilateral institutions, and providing myriad other essential functions—is often managed separately from the laboratories on which they rely for essential and timely diagnostics. Central or national laboratories are often distinct from district laboratories, despite operating in a common network. Further, the degree of collaboration between laboratories and treatment providers is highly variable.[114,115] Because resources and planning frequently flow through the NTP, laboratory integration is critically important, but often lacking.[116] TB laboratory directors need to have formal input in the design and management of TB strategy to ensure that the laboratory component is developed along with rest of the treatment strategy. Most importantly, they need partners at the level of clinical implementation to ensure the overall network functions smoothly, and that samples and ultimately, results, are transferred without problems. Greater collaboration is a basic requirement to establish service levels, drive appropriate utilization, and improve laboratory and clinical information systems.[117]

The complexity of MDR-TB treatment requires an additional level of integration of laboratory services since the management of the disease requires hematologic and biochemical monitoring of patients. This requires integration of laboratory services that goes beyond mycobacteriology, and in many settings, requires substantial strengthening of health systems.

3.2 Laboratory technical assistance

Increasing laboratory capacity rapidly requires the input of experienced (senior) laboratory personnel, the allocation of appropriate human and financial resources by laboratory leadership, and the mentoring and training of local laboratory staff. Discussions with individuals involved in the laboratory capacity-building efforts in Lesotho, Peru, and Uganda noted that the ability to scale up laboratory efforts was directly related to the skill and experience of their supervising director, the mentorship provided by those providing technical assistance, and financial, technical, and logistical assistance from a reliable non-governmental partner. Technical assistance needs to be provided by personnel (national or international) who have the capacity to establish routines, maintain quality assurance, train technicians, and control the supply chain, while working within the framework of the national laboratory. This individual must also

liaise with the rest of the tuberculosis control infrastructure including the NTP and the primary treatment teams.

Through our discussions with those who have participated in successful laboratory capacity-building endeavors we have identified some definable characteristics of effective technical assistance:

1. The technical assistance is on-site, in-country, and conducted by a person or team with a skill set that includes an understanding of both the scientific functions of the laboratory and laboratory management.

2. The technical assistance is long-term (not just one or two short visits), and can range from one or two months to an entire year, depending on the needs of the laboratory.

3. Laboratory staff members have dedicated time to interact and work with the technical assistance provider.

4. The technical assistance is closely tied to a capacity building plan for sustainable local leadership.

5. The technical assistance provider must have the authority and channels to work closely with partners in the clinical system, and must have a clear mandate with resources to execute their tasks.

How such a system is orchestrated is critical to its success. Possible structures range from a centrally administered program at a multilateral institution to a completely decentralized system based at regional supra-national reference laboratories or at regional MDR-TB technical assistance centers. Other alternatives include the establishment of fellowship programs modeled on the US Center for Disease Control and Prevention's Epidemic Intelligence Service in which developing professionals are engaged with an extensive network of peers and mentors.

Laboratory functions are a specialized domain of knowledge and mobilizing the right people with the right competencies to address the problem will likely require a unique solution. As new rounds of funding from multilateral and bilateral initiatives expand access to technical assistance funds for countries, the laboratory community must be able to meet demand with qualified professionals. Locating the appropriate supply will be a key challenge.

3.3 Human resources

There has been significant global attention paid to human resources and health, both within TB control and more broadly. [118,119,120,121] Universal themes of inadequate pre-service and in-service training programs, poor skill distribution, poor compensation, low motivation, and insufficient resources are consistent problems. Critical human resources for laboratory scale-up fall into three basic categories: laboratory management, laboratory technicians, and biosafety support staff.

3.3.1 Laboratory Management

Laboratories require management teams capable of logistics and forecasting, planning for staff turnover and sustaining quality. Updating standard operating procedures, ensuring that protocols are adhered to, and adapting program guidelines to changing conditions requires more advanced training and there is an acute shortage of staff with the required competencies. Laboratory directors in Uganda, Peru, Lesotho, Botswana, and Zambia all indicated that training staff in the technical aspects of mycobacteriological control may be relatively easy, but the crucial role of laboratory leadership faces challenging shortages because the training to acquire the necessary management skills is resource and time intensive.

Discussions with the 10-year laboratory capacity building project in Peru noted that the greatest impediment to improving the speed of laboratory improvements was the lack of a dedicated, on-site, external (to the laboratory), experienced, technical assistance provider that could work with laboratory management (e.g. laboratory director) to build laboratory leadership capacity. This theme is not unique to Peru: for example, a laboratory in Zambia recently purchased MGIT technology and found that implementation was slower than desired. Ultimately, a consultant from the United States was required and an experienced MDR-TB laboratory director from Eastern Europe was hired to lead the project. Program administrators from Lesotho identified strong laboratory technical assistance provided by an individual based in-country and working closely with the TB laboratory director and leadership as a key driver to their rapid expansion. Anecdotal experiences from case studies reflect the broader evidence base for improving quality and capacity in health systems: appropriate technical knowledge and supervision with feedback is the most validated technique for expanding quality services. Country experiences also noted that common problems with laboratory capacity building included technical assistance provided during brief visits without hands-on interactions with all staff, supervisors who had insufficient time in their job descriptions to provide daily support, staff absences (due to salary supplementation by per diems, hence the desire to travel for work), and poor accountability structures due to insufficient resources.

3.3.2 Technicians

The requirements for mycobacteriology necessitate rigorous laboratory technique, attention to detail, and quality assurance protocols for laboratory technicians. Significant debate exists about the formal educational requirements for staff in these roles,[122] but emerging experience suggests that with strong leadership, secondary-school graduates with appropriate and sufficient training can work as basic laboratory technicians. The individual competencies to provide services are not exceedingly complex and training does not require exorbitant capital expenditures. Critical to success are clear standardized operating procedures and their consistent application under supervision with feedback. Significant debate still exists about what level of accreditation and pre-service training is adequate for laboratory operations and how government hiring regulations should be adapted[123]

3.3.3 Biosafety personnel

Another critical barrier to expanding laboratory capacity is the physical plant to support culture and DST services in the setting of an airborne infectious disease with high mortality. Rehabilitation or construction of new facilities demands scarce resources beyond mere financing, including advanced engineering and construction skills. The physical requirements for mycobacterial culture include biosafety hoods, the preparation of media and reagent supply, proficiency in sterile laboratory technique, incubators, refrigeration and machine service contracts if automated systems are utilized. Successful facilities have negative air flow systems which also require appropriate maintenance support. The equipment can be purchased and imported easily; the staff required to design the facility, the biosafety protocols, and to maintain standards are more difficult to access.

Laboratory officials in Southern Africa speculated that South Africa is the only regional country with sufficient supply of biosafety personnel capable of designing facilities and developing the necessary protocols. Neighboring nations reported having to import experts for elements ranging from design to construction to maintenance. Estimates vary, but design and approval processes can take up to six times as long as construction, frequently due to insufficient local resources. Further, key stakeholder interviews revealed that shortages in infection control personnel are also prevalent in multilateral institutions. Yet, this gap was unrecognized in the most recent Global Plan to Stop TB and the GLC process still has no formal guidelines for infection control planning.

3.4 The referral network

A study of laboratory function in Peru documented that over 50 percent of the total turnaround time is occupied by factors related to the referral and data management components of laboratory operations,[124] highlighting the critical role these areas play in laboratory service provision. Improvements in referral network operations and data management that previously required less attention due to local services are now critical as samples and data routinely flow from institution to institution. For wide-spread access, caregivers need to know when culture or DST is indicated, how to get the sample, where to send it, and when they expect a quality assured result to inform clinical decision making. Each of these steps are relatively simple, but taken together it creates a system with multiple parts that must function together. To be successful, laboratory business plans focusing on maximizing network function need to be financed and encouraged.

Laboratory services start at the point-of-care where a treatment team decides to request services, guided by indications for testing. Patient information is then collected. A sample must be procured containing live bacilli. That sample must then be stored securely and transported to the appropriate culture facility. Indications for testing and transport logistics are critical barriers to expanding services. Solutions to sample transport are readily available but take time and money to implement in a considered fashion. Some countries, like Botswana, have invested in contracts with commercial carriers such as DHL. The United States has provided block grants to states to hire couriers, and a variant of that system was used in Georgia via a central dispatch mechanism. Papua New Guinea has experimented with international courier service to Australia for sample processing. Uganda and Malawi have experimented with utilizing local bus companies,[125] while Peru bought trucks and hired drivers. Many countries reported that currently the indications for testing, the collection and storage systems, and transport are often ad hoc events. Samples frequently travel with whatever form of transport is available and testing is often initiated through informal requests and peer networks. What is important is that for any system to be successful for TB patients, the majority of whom tend to be poor, the system of sample-transportation has to fall squarely under the aegis of the NTP and laboratory system, so that the burden (and cost) does not fall upon the patient. Secondly, once samples actually reach the laboratory, systems of internal transportation (within the laboratory itself and between laboratories) has to be highly organized so as not to result in samples piling up unanalyzed, or samples waiting for transfer to another laboratory within the system.

Making referral networks operational will require highly individualized solutions depending on local conditions; it is unlikely that any single solution exists. The key component to overcoming the barrier is

dedicated resources to support expanded services and a requirement to invest and develop timely, sustained referral networks with clear operating procedures supported by the lab and the clinical providers.

3.5 Data management

Accurate information about the sample type, patient demographics, and TB history must be accurately transmitted to the laboratory for drug resistance surveillance, while routine management requires more basic patient identifiers. The laboratory must perform the tests and document results. Results then must go to national registry and to the treatment team. Historically, laboratory systems in developing countries relied on on-site testing and paper documentation. Because the monitoring regimen for MDR-TB requires multiple follow-up tests, the volume of information for each patient is large. As laboratories expand to networks and samples and data move geographically the complexity expands.

Many commercial culture systems and DST allow for easy digital documentation, but getting electronic results to the local clinical information systems and central data repositories at the national reference lab is significantly challenged by highly variable resource levels. Direct web-access has facilitated clinical information access in Peru,[126,127] but other sites have limited access to the web-based resources. Automated or manual faxes have been utilized but maintenance of peripheral machines (paper and ink shortages) complicates sustainability, though the basic infrastructure of telephone lines may be available. Final solutions maybe as simple as dedicated manual systems based on paper hard-copies and clear protocols. While there is no single recommendation for all nations, solutions to these problems are readily available. What is needed are country-level resources, dedicated planning to account for crucial systems components, and teams to design and implement them.

3.6 Quality assurance

Multiple strategies exist for quality assurance, but the ability to produce consistently accurate results regularly supported by quality control is fundamental to laboratory operations. Quality initiatives generate confidence among the treatment community to expand reliance on services. Quality also establishes a platform or foundation for the expansion of services and integration of new, more advanced testing. Those involved in laboratory scale up in Uganda, Botswana, Peru, and Lesotho all noted that sustaining initial laboratory quality was a significant challenge. The reasons for this are that many laboratories in resource-limited settings have limited human and financial resources to devote to quality assurance, and many laboratory directors have neither the time nor training to guide the process appropriately. Furthermore, in order to maintain quality standard of operations laboratories must have

managers who can anticipate stock needs and supply reagents and supplies regularly, service for machinery to keep the system working, reliable access to engineers who can address air-flow needs, coordination with treatment sites to predict volume and deliver at mutually determined service levels. Finding and supporting these systems over time is an issue of training, financing and political will.

Our case study of Peru showed that while making quality assurance a routine component of good laboratory practice was critical, the program faced two important challenges: (1) having sufficient preparatory training prior to laboratory expansion; and (2) sustaining quality over time. Quality assurance activities for culture systems create the need for global operations; samples or staff must flow from national reference laboratories to supra-national reference laboratories for proficiency checking, while foreign talent is often necessary to provide initial guidance on facility maintenance and to build sufficient local capacity. For instance, laboratories in Botswana had little trouble accessing talent from South Africa to build their reference laboratories but had more trouble maintaining the facility—both getting the right people and ensuring the political support to fund the activities.

As a result of these difficulties, it is no surprise that the availability of external quality assurance among high burden/high priority countries is still quite variable. Most countries had laboratory supervision plans in place (a key measure in quality control of smear-microscopy), but only 50 percent of these plans were implemented. The Global Tuberculosis Control Report 2007 concludes that: "Most countries had neither national policies to expand culture and DST services nor the technical capacity to implement and support such services."[128] The culprits identified include problems with infrastructure, transport, human resources, and funding. Despite the significant improvements many countries still do not have the foundation of successful quality assurance programs.

The case of rapid laboratory capacity building in Lesotho

A laboratory improvement initiative in Lesotho was initiated following the outcome of a WHO Laboratory Assessment mission in November 2006. Key partners from the Ministry of Health, Partners In Health (PIH), the Foundation for Innovative New Diagnostics (FIND) and WHO, determined that laboratory capacity improvement was a necessary component of Lesotho's MDR-TB control strategy. Coalition partners felt that technical consultants operating on periodic assessments would be insufficient to drive the process at the required rate. PIH was delegated responsibility for logistics and coordinating the referral network, WHO contributed the needs assessment, FIND seconded experienced laboratory consultants to provide on-site long-term technical assistance, and the Government of Lesotho committed sustained resources.

A technical consultant with advanced laboratory training was on-site by May 2007. The early stages were characterized by improvisation; at one point, offices were based out of trailers to ensure adequate space for laboratory renovations. Because of the rural/urban mix, Lesotho focused on building centralized capacity at the National TB Reference Laboratory. Engineering controls, such as a continuous negative air pressure system with a HEPA filtered air source to supply more than 10 air exchanges per hour, and an on-site sterilization system were established. The process was complete by July 2007 – less than 1 year after the initial assessment – and supported by funding from PIH, the Open Society Institute, FIND, and GFATM.

Prior to the initiation of this collaboration, the National TB Reference Laboratory was able to process 150 cultures and 30 DST to 1st-line anti-TB agents per year. Clinicians referred samples for testing through informal channels with no systematic indications for testing. When the initiative began, set indications for referral were established as well as systems to get samples to the laboratory in timely fashion. SOP and quality assurance mechanisms were firmly embedded as staff training continued. The South African Medical Research Council (SAMRC) became an integral partner in establishing proficiency testing and technical assistance. Initial procedures focused on the use of solid culture via solid medium. Capacity was improved to 160 specimens per week and 20 DSTs per week. By August 2007 the first cultures were processed and proficiency testing began. This was later expanded to a more rapid, automated liquid-medium (MGIT) culture system.

In collaboration with the MSLI, a rapid survey was done to establish baseline epidemic knowledge in the Kingdom of Lesotho. A nationwide DRS is now in process. Long-term challenges will be transitioning leadership from technical advisors to local leadership, supporting the MDR-TB treatment program, and rolling out rapid screening of isoniazid and rifampin resistance with molecular diagnostic techniques.

Critical challenges for Lesotho include sustaining initial quality. The rapid improvements were credited to on-site leadership by a strong technical assistance provider with experience in developing countries, complete government support, and access to resources for appropriate staffing. Training local talent in laboratory procedures was easy to accomplish but required strong commitment from technical partners, the laboratory system and the Government of Lesotho.

3.7 Lessons learned from the experiences of Peru and Lesotho

Despite different population sizes, resource levels, and disease dynamics there were six important themes to be taken from the work in Lesotho and Peru, themes that have resonated strongly with laboratory leaders in multiple settings.

1. Political Will: Collaborative leadership across multiple groups. Both Peru and Lesotho had strong relationships with local NTPs and SNRLs to guide optimal program decision making and link laboratory and clinical systems. Both programs also noted that initially, those relationships were not robust and significant work was done to strengthen and develop communication.

2. Technical leadership: Lesotho succeeded in less than one year because of on-site technical assistance. The number one barrier to improved speed in the Peruvian initiative was lack of a full time technical expert on-site in Lima to oversee the project.

3. Physical Plant: Both projects required expatriate teams for engineering, architectural, construction, and maintenance needs. Finding and utilizing these teams were significant barriers, ultimately taking more time than construction and training.

4. Quality Assurance: Lesotho credited strong quality assurance protocols at the initial training as a key success factor in rapid capacity development. Peruvian leaders noted that a more rigorous focus on quality assurance would have delayed initial capacity but would have ultimately led to faster, more robust service. Both sites emphasized that sustained political commitment to quality was essential to success, and a significant future challenge.

5. Referral and Data Management: Lesotho has yet to scale up primary treatment nationally, however solving transport and programmatic concerns surrounding indications for testing, results reporting, data management, and service levels were critical to success in Peru.

6. Local conditions create vastly different solutions – flexibility is paramount: In Lesotho centralized laboratory services was the preferred approach because of the geographic considerations and estimated volumes. In Peru, a centralized solution would quickly have been insufficient and decentralized strategies were required. Lesotho has insufficient resources and a stronger rural service network while Peru has concentrated levels of MDR-TB in major cities. For Peru, purchasing laboratory-based trucks for

transport made sense while in Lesotho new solutions will be needed. Both countries had shortages in technical capabilities – in Peru training local experts in new competencies was the solution for long-term sustainability, while Lesotho can likely use its proximity to South Africa and relationship with the South African Medical Research Council (MRC) to provide for maintenance and structural needs.

It is clear that the provision of sufficient on-going technical assistance has a bearing on the ability of the laboratory to build capacity rapidly. This is not the only requirement—others, as discussed above, include sufficient staffing, funding, and infrastructure—but it is one that has repeatedly emerged from our discussions with sites that have undertaken capacity building. In order to facilitate long-term sustainability, any technical assistance has to involve laboratory management, training-of-trainers, and partnership with national TB programs.

4 New TB Technologies and the Need for Point-of-Care Testing

In analyzing risk factors for delay in the diagnosis of pulmonary tuberculosis, a study from Thailand in 2006 divided delays into patient factors and physician factors.[129] Interestingly, they found that having health insurance was not associated with shorter patient delay (in fact, it was associated with an increase in delays). Rather, some TB suspects reported not seeking treatment because they had to pay for different tests, including x-rays, and could not afford them. Others, who did not have to pay for tests, reported inconvenience of transportation, lengthy queues, and lack of confidence in the quality of the public health care system as their reason for not coming in quickly. Even when a qualified provider was consulted, TB suspects had to make an average of 3.3 visits before they were given a final diagnosis. Only 8.4 percent of patients were diagnosed at the first visit; only 36.6 percent were treated within one week after seeing a qualified provider. Similar findings have been seen elsewhere.[130, 131, 132, 133]

It is startling to see these delays in patients who have no obvious risk factors for paucibacillary disease or extra-pulmonary tuberculosis. In a recent study from Rwanda (where the rate of TB-HIV co-infection was 62 percent), smear-negative pulmonary tuberculosis, extra-pulmonary tuberculosis, and the use of an antibiotic trial (in the absence of a TB diagnosis; recommended by WHO) was associated with significant delays in the initiation of therapy.[134] When analyzing the distribution of time delays before initiation of TB treatment, the study found that patient delays constituted 44 percent of the delay; 56 percent was due to health service delays and treatment delays. In the end, only 18 percent of patients were started on TB therapy within one month; only 56 percent were started on therapy within two months. Although the

authors of the study cited rural residence as a risk factor to later initiation of therapy, they attribute the bulk of the health care system to difficulty of diagnosis.

Both of these studies underscore the difficulty patients face getting to health facilities, and once they are there, having their TB disease properly and rapidly diagnosed and treatment initiated. For patients with drug-resistant tuberculosis disease, the problem is exacerbated by the fact that simply diagnosing tuberculosis is not enough; the drug-resistant phenotype has to also be identified. It is toward addressing this problem that the GLI and FIND have been working to scale-up the ability for countries to rapidly test for drug resistance using rapid molecular tests (e.g. one produced by Hain Lifesciences). Such tests identify *Mycobacteria tuberculosis* (versus other mycobacteria) as well as probe for resistance to isoniazid and rifampin resistance and provide results within 48 hours. This allows for more rapid initiation of appropriate therapy, of paramount importance in high HIV settings where TB mortality is rapid and high.

While these steps are significant, they do not address the problems described by the Thai and Rwandan studies discussed above, where part of the problem was that patients had to repeatedly return to the physician in order to get a diagnosis. If their TB was not pulmonary or not captured from their sputum, they had an even longer wait before therapy would begin. In order to address this problem, Treatment Action Group (TAG) and the AIDS and Rights Alliance for Southern Africa (ARASA) organized a meeting in Cambridge, United Kingdom, to develop an agenda for expediting research and development of point-of-care assays for diagnosing active TB in resource poor settings through an analysis of the gaps in current efforts, challenges to test development and unanswered scientific questions. The meeting brought together research and technical partners, many of whom had been involved in the development of a dip-stick test for HIV. The meeting concluded that such a test is possible for TB (using sputum, urine, and/or blood), and is actually within reach, but will require significant resources and political commitment.

5 RECOMMENDATIONS

5.1 Sustainable funding from bilateral and multilateral donors must be increased to support construction of in-country drug-sensitivity testing/rapid-testing laboratories and ongoing external quality assessments by supranational reference laboratories. Construction of laboratories capable of performing reliable mycobacterial culture and drug-sensitivity testing to important first- and second-line anti-TB drugs is the cornerstone of the current diagnostic strategy for drug-resistant TB. These laboratories will require external quality control by SNRLs. Laboratories also need protected staff, salaries, budgets, and time to execute quality assurance responsibilities.

5.2. Creation of a system of long-term on-site technical assistance would help countries build and/or rapidly expand their capacity to perform mycobacterial culture, DST, and rapid molecular genetic tests for drug-resistant tuberculosis. Building TB laboratory capacity requires sustained technical assistance by experienced individuals with experience in laboratory management and high technical proficiency. Case studies of laboratory scale up and literature reviews support the hypothesis that on-site, long-term technical assistance with strong feedback is one of the strongest mechanisms to improve system performance. Systems are needed to develop, fund, and allocate scarce technical assistance talent to accelerate laboratory scale up.

5.3. In-country laboratory networks for: specimen transport, data management, and certification and coordination of private laboratories need improvement. Ad hoc indications for testing, transport of specimens to central laboratories, and poor data management have been longstanding barriers to successful treatment programs. Country level resources and action plans targeting referral networks and data management, the processes of getting samples in and data out, are essential to expanding laboratory capacity. Because many countries have private laboratories with mycobacterial culture and DST capabilities, attention needs to be given to helping these countries certify and coordinate the work of these laboratories so that they can make better use of this capacity.

5.4 Use of excess laboratory capacity for mycobacterium culture and drug-susceptibility testing in wealthy nations should be encouraged while laboratories are being built in poorer regions. Data from the GLI show that rich-nation mycobacterial laboratories possess unused capacity to perform mycobacterial culture and DST. While capacity is being built up in countries lacking laboratories, a consortium of laboratories with excess capacity should be developed and utilized so that patients can begin drug-resistant TB treatment regardless of their country's current laboratory capabilities.

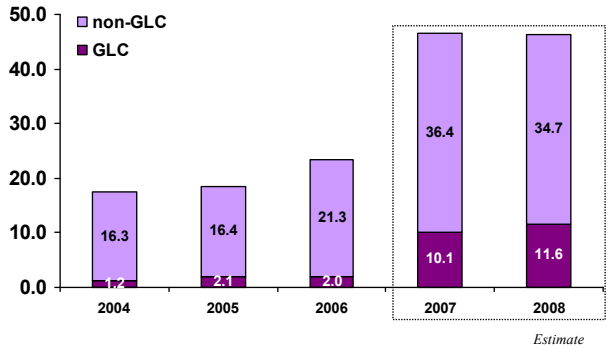
5.5. Priority must be given to research on—and funding for—the immediate development and rapid deployment of point-of-care testing for drug-susceptible and drug-resistant tuberculosis. Current approaches to laboratory capacity-building are aimed at ensuring that existing diagnostics are available to countries. Efforts need to be expanded on the development of rapid point-of-care testing for TB as a means of ensuring timely and accurate diagnosis of TB and drug-resistant TB. This is critical for high-HIV settings, for pediatric tuberculosis, and for patients with extra-pulmonary drug-resistant TB.

SECTION III: MDR-TB DRUG SUPPLY

1 INTRODUCTION

The World Health Organization (WHO) estimated in 2008 that approximately 490,000 new cases of MDR-TB emerged in 2006.[135] However, less then 10 percent of these patients will receive any care (with drugs of unknown quality and under varying programmatic conditions) and approximately 2 percent will receive care using quality-assured second-line anti-TB drugs in programs complying with WHO's *Guidelines for the programmatic management of drug-resistant tuberculosis* (see Figure 3).

Figure 3: MDR-TB patients scheduled to receive treatment in WHO/GLC-approved projects and non-GLC projects (1000s of patients; 2004 to 2008; Source: WHO 2008)



MDR-TB treatment projects currently have two options for procurement of second-line drugs:

- Procuring quality-assured drugs from the Global Drug Facility (GDF) under the auspices of WHO's Green Light Committee (GLC initiative), often at concessionary prices; this is the required option for projects with financing from the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) or UNITAID.
- Procuring drugs of unknown quality through state procurement mechanisms and/or the open market.

The Stop TB Partnership's MDR-TB Working Group met in Tbilisi, Georgia in September 2007 to assess the state of MDR-TB management internationally, measured against the standards of the World Health Organization Global Plan to Stop TB (2006-2015) and the Global MDR/XDR-TB Response plan (2007-2008). [136,137] Worldwide shortages of quality-assured second-line drugs (most notably shortages of PAS in 2006 and Capreomycin in 2007) and delays in delivery of quality-assured drugs by the GDF to GLC-approved projects were topics of urgent concern.

In light of the increased numbers of programs applying to the GLC and the projected increase in patients to be enrolled for MDR-TB treatment in GLC-approved projects, it was clear to participants in Tbilisi that failure to resolve these shortages and delays would result in many treatment projects' circumventing the GLC/GDF mechanisms and would thereby undermine efforts to ensure the increasing use of quality-assured drugs. There was even evidence to suggest that the shortages and delays would encourage some large high-MDR-burden countries to seek exemption from the GFATM to the requirement for GLC-approval of the MDR-TB component of GFATM-supported projects.

In response, the MDR-TB Working Group of the Stop TB Partnership formed a Drug Management Sub-group (DMSG) to address the XDR-TB emergency and to foster effective communication with all relevant institutions and organizations.

2 THE GLC INITIATIVE: ACTORS AND RESPONSIBILITIES

2.1 The Green Light Committee (GLC)

The mandate of the GLC is: (1) to mobilize an effective response to inaccessibly high prices and questionable quality of second-line drugs on the international market; (2) to prevent development of resistance through monitoring and evaluation of GLC-approved MDR-TB pilot projects; and (3) to act as

an advisory body to WHO on MDR-TB policy. Since the GLC's launch in 2000, the GLC has approved over 40,000 patients for MDR-TB/XDR-TB treatment in 114 projects. Evidence has demonstrated that the integration of MDR-TB treatment into national TB control strategies is both clinically appropriate and cost-effective; as a result, the committee's responsibilities have expanded beyond small, "pilot" projects, and include programs of increasing size and complexity.[138]

The system of affiliated institutions that has collectively accepted responsibility for the practical implementation of this growing mandate is now known as the GLC initiative, with the GLC itself assuming specific duties within that group. Accordingly, the GLC is responsible for MDR-TB project approval, which allows the release of GFATM or UNITAID monies to a project on condition of continuing compliance with programmatic standards and provides access to concessionary-priced quality-assured second-line anti-TB drugs. The GLC mechanism provides technical assistance to projects through WHO's Stop TB Department (TB/HIV and Drug Resistance, THD) to facilitate effective program management (see Figure 4). This includes pre-application planning and, if necessary, pre-application site visits.

Figure 4: Areas of Practical Responsibility for the GLC Initiative

Institutions currently represented on the GLC are the United States Centers for Disease Control (Atlanta, USA), Hospital Muniz (Buenos Aires, Argentina), International Union Against Tuberculosis and Lung Disease (Paris, France), KNCV Tuberculosis Foundation (Den Haag, Netherlands), Médecins Sans Frontières (Paris, France), Partners In Health/Harvard Medical School (Boston, USA), National TB

Program (Riga, Latvia), the World Health Organization (Geneva, Switzerland), and the World Care Council.

Programs apply to the GLC using a standard application form available on the GLC website. Often the number of patients approved by the GLC for treatment can be modified from the project's original request; GLC members' institutional experience informs this modification based on perceived project capacity. Regular missions carried out by a trained cadre of GLC consultants evaluate project performance and attempt to catalyze program scale-up (to achieve universal access) as appropriate.

It is important to note that the GLC itself is not responsible for drug procurement. The GLC is responsible for ensuring that GLC-approved projects use only quality-assured drugs and deliver these drugs under optimal program conditions as described in WHO's *Guidelines for the programmatic management of drug-resistant tuberculosis*. The procurement of these drugs is the responsibility of the GDF and its contracted procurement agent—currently the International Dispensary Association (IDA).

2.2 The Global Drug Facility (GDF)

Founded in 2001 under the Stop TB Partnership and hosted by the WHO, the Global Drug Facility (GDF) originally was mandated to oversee procurement of first-line TB medications. In May 2007, the GDF announced that it had provided anti-TB drug treatments for 10 million people to 78 countries since its inception.[139]

In 2006, the Stop TB Partnership Coordinating Board, the Stop TB Department of WHO, and the Working Group on DOTS-Plus for MDR-TB assigned to the GDF responsibilities for procurement of second-line anti-TB drugs for GLC projects. The GDF gradually assumed these responsibilities, taking them up fully in 2007. The GDF has contracted with its procurement agent, IDA, to supply drugs to all GLC projects. Some projects place orders through the GDF, which then forwards the orders to IDA. Other projects place their orders directly with IDA. The GDF tracks orders, monitors the performance of the procurement agent, compiles forecasts of future drug needs, and negotiates with suppliers interested in being added to the GDF's approved suppliers list.

In November 2007, the GDF began purchasing a buffer stock of second-line drugs for up to 800 patients. When this buffer stock is in place, it will ensure that a ready supply of MDR-TB drugs is available for projects needing immediate assistance. They have recently received additional funding from UNITAID to expand the buffer stock to include enough drugs for 5000 patients. When the buffer stock is eventually built—and this has been difficult because of global shortages of quality-assured second-line drugs—drugs

from this stockpile will be used to avoid stock-outs with existing projects and to expedite the launch of new sites.[140]

2.3 Procurement agent

The procurement agent's contract is currently negotiated with the GDF for a period of 24 months, with the option of a further extension of 12 months.[141] At the time of the GLC's inception in 2000, the procurement agent was the Belgium-based logistic and supply division of the international non-governmental organization Médecins Sans Frontières (MSF), Transfer (now called MSF Supply). Since 2001, the role of procurement agent has been filled by the International Dispensary Association (IDA) of the Netherlands. Upon transfer of the procurement responsibilities from the GLC Secretariat to the GDF, IDA won a competitive tender for contract as procurement agent in 2007; its current contract is in place through 2009.

The procurement agent is responsible for overseeing second-line drug purchases, identifying potential suppliers for each medication, and soliciting agreements with the manufacturers for reduced prices for GLC-approved projects. Such agreements may include the establishment of a maximum quantity or volume of reduced-price drugs. The agent communicates directly with suppliers to inform them of the expected need for a particular drug, and then arranges delivery to its facility (currently in Amsterdam). Following this, the agent allocates those drugs to GLC treatment sites per the orders received from the respective projects. Before placing an order with IDA, all GLC-approved projects must submit the total expected drug needs for a full 2-year course of treatment for their patient cohort. These quantities are approved by the GLC and shared with the GDF, which procures the second-line drugs for approved projects by working in partnership with the procurement agent. The GDF sends an authorization letter to IDA indicating the drug needs for the project in question. Once IDA has received the letter of authorization from the GDF they are able to sell the project the drugs required, up to the approved quantity.

The agent receives the quotation request from a project site and responds with pricing information and expected delivery dates. Once an order is confirmed by a project site and full payment for the drugs made to IDA, the agent communicates with the manufacturers and production begins. The project site is kept informed of delivery status and any expected delays. The procurement agent contacts the project site when delivery is arranged, and at that time provides the project with the shipping date and relevant paperwork.

2.4 The WHO Essential Drugs Monitoring (EDM) Prequalification Program

The GLC requires that all manufacturers of second-line drugs wishing to participate in the GLC initiative be approved by the WHO's Essential Drugs Monitoring Prequalification Program. The program was launched in 2001 to facilitate approval of high-quality medicines for HIV/AIDS, malaria, and tuberculosis and has already approved a number of fixed-dose combination antiretroviral medicines. It is operated in close cooperation with UNAIDS and UNICEF, and draws its financial support from the World Bank, GFATM, UNITAID, the Gates Foundation, and contributions from several national governments. The program's focus initially targeted medicines to treat HIV/AIDS. A system for assessing and increasing access to pharmaceutical products for the treatment of tuberculosis was adopted by the program in 2002.

The prequalification program's two priorities are: (1) to evaluate the compliance of pharmaceutical products with WHO standards for generic products; and (2) to certify that these products are manufactured according to good manufacturing practices (GMP). Although the WHO Prequalification Program has approved a large number of drugs for HIV/AIDS, it has approved many fewer anti-TB medications and only two second-line anti-TB drugs (cycloserine and ethionamide, both from Macleods Pharmaceuticals Ltd of India). The GDF also accepts as quality-assured those second-line anti-TB drugs that have documented approval from a "stringent national drug regulatory authority" (SNRA), such as the US Food and Drug Administration (FDA) or European Medicines Agency (EMEA). However, even with this waiver of WHO Prequalification, the GDF offers access to only one quality-assured supplier for most second-line drugs. The reliance on single sources of supply offers little leverage for reducing prices of the drugs. It also subjects orders to logistical delays and supply disruptions that delay patient treatment and enrollment in existing projects and could significantly impede the launch of newly-approved projects in the next 12 to 18 months, if there are no newly-approved quality-assured suppliers.

2.5 UNITAID

UNITAID is a new source of funding for second-line anti- TB drugs. Officially launched in September 2006, UNITAID is a consortium of five countries (France, Brazil, Chile, Norway and the United Kingdom) that has created an international drug purchase facility. The goal of UNITAID is "to provide long-term, sustainable and predictable funding to increase access and reduce prices of quality drugs and diagnostics for the treatment of HIV/AIDS, malaria and tuberculosis in developing countries."[142] Funding for UNITAID is raised by levying a tax on airline tickets in its participating countries.

UNITAID is funding the purchase of second-line anti-TB drugs for seventeen low-income countries over a 5-year period.[143] Recipient countries will transmit all orders through the GDF and UNITAID will

prepay the procurement agent (IDA) for drug orders. UNITAID and the GFATM have recently reached an agreement that all GFATM-grantees will have their second-line anti-TB drug orders paid for by UNITAID through this mechanism.[144]

The procurement experience of the Philippines[145]

The Tropical Disease Foundation (TDF) started treating MDR-TB at the Makati Medical Center in Manila in 2003. They found early on that they were unable to budget properly for medications because the prices offered through the GLC mechanism varied by year for each individual drug, especially ofloxacin, cycloserine, and capreomycin (see Figure 5 and Figure 6).

Figure 5: Price variation for ofloxacin, prothionamide, kanamycin, and cycloserine (2003-2007)

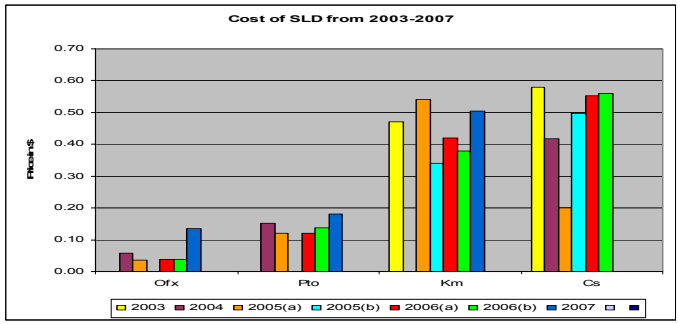
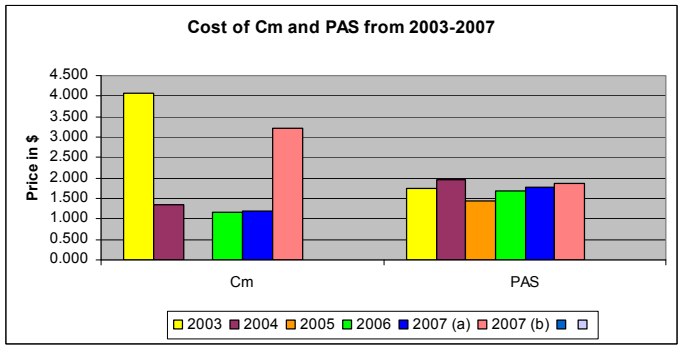
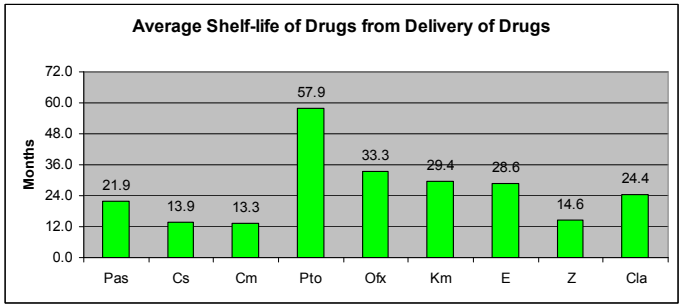


Figure 6: Price variation for capreomycin and PAS (2003-2007)



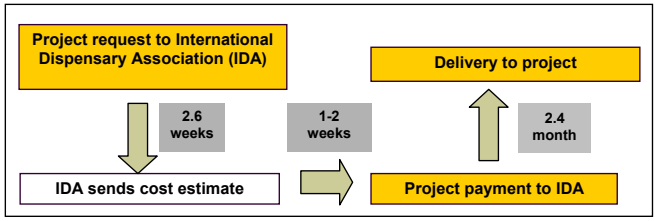
They also found that the average shelf-lives of drugs from time of receipt in-country varied. For example, as shown in the graph below, capreomycin, cycloserine, pyrazinamide and para-aminosalicylic acid (PAS) were received by the project with expiry dates within less than 2 years (See Figure 7). Some of this was due to the shelf-lives of the drugs themselves, others were due to the delivery of short-life stock. In any case, the natural time constraints inherent in these drugs are exacerbated by late delivery times, to the detriment of the recipient programs and their patients.

Figure 7: Average shelf-life of drugs from date of delivery, TDF, Manila, Philippines



For various technical reasons, TDF initially used an ordering system that involved the local WHO office. In 2007, they began ordering second-line medications directly from the GDF's procurement agent, IDA. They calculated the average time between placing an order directly with IDA and receiving the drugs in the country (see Figure 8).

Figure 8: Average time to delivery for second-line medications ordered directly through IDA (2007; Philippines)



They found that the mean time required to receive second-line medications was 3.6 months. Despite this mean, they have had situations in which they have not received certain essential second-line drugs (e.g. kanamycin) for more than 6 months.

3 THE GLC INITIATIVE: INSTITUTIONAL BARRIERS

The GLC initiative has approved life-saving therapy for more than 40,000 patients since its establishment in 2000. More than 10,000 patients per year are now being approved for treatment and that number is expected to grow. It is clear that the GLC "pilot program" phase—a phase characterized by the small projects that helped establish the GLC protocols and helped lay the foundation for the creation of a functional mechanism to assure that patients were receiving quality-assured drugs under sound programmatic conditions—is now over. Given the large burden of MDR-TB in many settings, MDR-TB treatment has to become standard of care in all TB programs. If treatment projects around the world are to be initiated and expanded using quality-assured drugs under WHO program protocols, countries will need access to an expanded supply of second-line drugs. If there are not adequate supplies and smooth, effective mechanisms to procure them, there will be little incentive for projects to seek GLC endorsement. At the moment, there is only one quality-assured supplier available for most second-line anti-TB drugs purchased through the GLC mechanism. Projects are experiencing delays due to inadequate drug supplies and logistical problems, resulting in significant complaints about the GLC initiative and significant pressure from large MDR-TB-burdened countries to circumvent the GLC. If the GLC is to play a meaningful role in the next decade of MDR-TB expansion, it will certainly have to improve the procurement mechanism and the availability of quality-assured second-line drugs.

3.1 Single procurement agent, the GDF, and transparency

At the moment, the GDF has a single procurement agent—currently IDA—for all the second-line anti-TB drugs it offers. It holds a monopoly on all GLC procurement, which interferes with legal requirements in some countries that all purchasing be open to transparent tender. As there are increasingly more GLC projects and patients, the GLC and the GDF are likely to find it increasingly difficult to maintain their insistence on a single procurement agent for projects around the world.

Equity and transparency in the allocation of concessionary-price drugs are additional challenges for the GDF/IDA as they respond to increasing numbers of projects and orders for drugs. The allocation of scarce, reliable supply presents obvious budgetary and scheduling challenges as projects often cannot predict which product they will be allocated, at what price, and when they will ultimately receive delivery. For example, Eli Lilly offers the GDF a fixed annual quantity of capreomycin at a reduced price of roughly $1 per vial and a larger quantity of the product at around $3 per vial. Once these quantities are consumed, subsequent orders are filled by the GDF/IDA at higher prices Projects paying higher costs struggle to understand the basis on which the lower-cost supplies of capreomycin are distributed. For

example, some projects question whether priority is given to large projects over small projects or to existing patients over new (or expansion) cohorts. A similar situation exists with cycloserine: a fixed quantity from Eli Lilly is available at a discounted cost of $0.14 per capsule; once consumed, the remaining supply is sourced from MacLeods Pharmaceuticals at a cost of $0.50 per capsule. This dramatic price variance, coupled with the inability to predict which supplier's product they will receive, can cause a project site to face a severe budget shortfall. Information gathered from multiple projects indicates that it is not unusual to submit a request to IDA assuming that the Lilly cycloserine will be available, only to receive a quotation that includes MacLeod's cycloserine and is significantly costlier than anticipated; in the case of larger projects the difference can range in the hundreds of thousands of dollars for sizable shipments. Projects routinely submit large annual orders to IDA along with a proposed delivery schedule; however, product availability, quality-assurance procedures, national registration and customs issues (discussed further below), packing, and document preparation often result in delivery delays. Projects routinely operate with minimal supplies and are often forced to alter or suspend patient enrollment to correspond to the available supply of drugs.[146]

3.2 Prequalification of second-line anti-TB drugs has been slow at WHO

There are only two second-line anti-TB drugs that are prequalified by the WHO Prequalification Program and only 17 products for TB in total. In contrast, there are 62 antiretroviral agents and 33 medicines pre-qualified for HIV/AIDS-related diseases.[147] This discrepancy likely results from the attractiveness of the high-volume HIV/AIDS-drug market to suppliers. In addition, the international commitment to funding for HIV treatment in developing countries has been more robust than that for TB, at least until recently. More recently, the Prequalification Program has reported having made an effort to prequalify second-line anti-TB drugs, but the response from both EDM and potential suppliers has been disappointing, for reasons that are somewhat unclear. Some suppliers complain that the prequalification program is slow and bureaucratic, and that it does not effectively engage with manufacturers on the level required to encourage improvement of production standards to international levels. There may be evidence to support this complaint. All GDF-approved second-line drugs have been approved by other Stringent National Regulatory Authorities, such as the FDA, yet only two of these products are WHO-prequalified. With financial support from The Bill & Melinda Gates Foundation, the Prequalification Program has recently added professional staff, but it will be a challenge for this approval process to keep up with the rapidly increasing demand for second-line drugs in projects approved by the GLC.

Second-line drugs are widely available in MDR-TB-priority countries and only a small proportion of these drugs are quality-assured. A Russian case study provided by the authors of *Pathways to Patients*, a

2007 publication from the TB Alliance, estimates the value of the second-line drug market in Russia to be $56 million. Only $6 million of this was to be financed through Global Fund grants and purchased through the GDF. The remainder was to be financed by the federal budget in Russia and likely sourced from domestic Russian pharmaceutical firms, none of which are prequalified by the WHO. *Pathways to Patients* places a rough estimate of the size of the second-line drug market in China at $25 million. Although the authors stress the difficulty of accurately estimating second-line drug sales in Russia and China, the combined total for these two countries of more than $75 million represents roughly 8 to 10 times the value of quality-assured drugs sold to GLC projects in 2007. It will take a concerted effort by international partners and national regulatory authorities in large, high-MDR-TB-burden countries to facilitate and increasingly insist upon quality-assured products. These products typically will be more expensive[2] and their introduction will threaten vested economic interests of local non-quality-assured producers, but the patient outcomes will surely be improved.

Figure 9: WHO's twenty-five priority MDR-TB and XDR-TB countries[148]

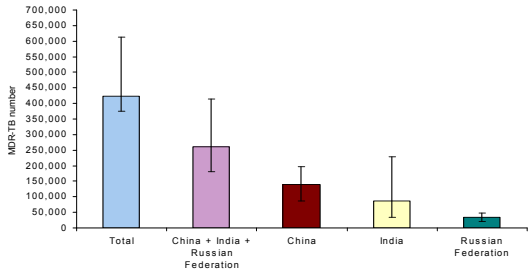
WHO region	Country	Estimated total number of MDR-TB cases	Estimated proportion of MDR-TB among combined* cases (%)
WPR	China	139 894	6.9
SEAR	India	87 413	4.1
EEUR	Russian Federation	34 055	16.8
AFR	South Africa	10 348	2.6
SEAR	Indonesia	10 024	1.8
EMR	Pakistan	9 306	3.2
AFR	Nigeria	7 969	2.0
EEUR	Ukraine	7 854	13.6
SEAR	Bangladesh	7 216	2.2
EEUR	Uzbekistan	7 043	18.5
EEUR	Kazakhstan	6 718	23.4
AFR	Ethiopia	5 102	1.9
WPR	Viet Nam	5 033	3.2
AFR	Democratic Republic of the Congo	4 641	2.3
SEAR	Myanmar	4 756	5.2
WPR	Philippines	4 469	1.8
EEUR	Azerbaijan	1 579	18.8
EEUR	Republic of Moldova	1 459	18.9
EEUR	Tajikistan	1 394	10.9
EEUR	Georgia	980	19.5
EEUR	Kyrgyzstan	766	10.6
EEUR	Belarus	707	10.4
EEUR	Lithuania	422	16.4
EEUR	Latvia	208	11.5
EEUR	Estonia	147	20.1
TOTAL		359 802	5.1

[2] The costs of quality-assured drugs may not always be more expensive, but international competition will surely threaten profit margins for domestic producers. By way of example, the Russian Case Study for *Pathway to Patients* notes that the cost of a second-line anti-TB drug regimen in the Tomsk project prior to GLC approval ranged from $7,500 to $15,000 as compared to a cost of $3,500 for the regimens later purchased through the GLC.

National regulatory and legal barriers to procurement: the Case of Russia

As of 2003, the WHO determined that 62 percent of MDR-TB patients resided in three countries: Russia, India, and China (see Figure 10).[149] This reality necessitates that the international TB community institutionalize effective cooperation and compliance practices with national customs services of recipient countries. The case of Russia is emblematic of the problems faced in importing quality-assured second-line anti-TB drugs into individual national markets and warrants an in-depth analysis.

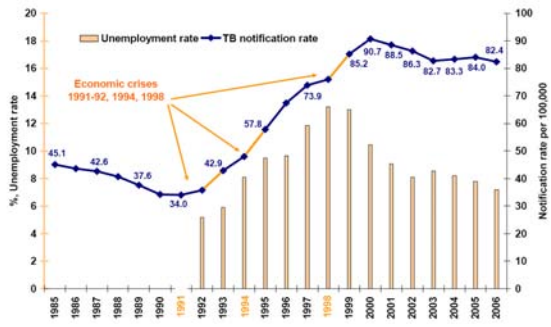
Figure 10: MDR-TB infections by Country, WHO Estimate (with confidence interval)



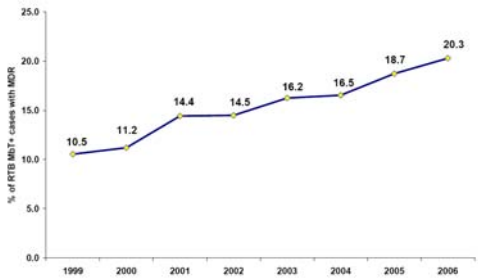
Source: WHO 2003

Significant improvements in the economy of the Russian Federation in recent years have resulted in its reassignment as an upper-middle-income country by the World Bank. This designation preceded the announcement by World Bank president Robert Zoellick in October 2007 that Russia had changed its World Bank status from that of borrower to donor, effective immediately. Despite the upward trajectory of the Russian economy and increasing political willingness to contribute to, rather than receive money from, international aid institutions, public health systems throughout the country continue to be deeply flawed and underfunded. Of particular concern in Russia is the rise of TB in the post-Soviet period (closely associated with economic crises and poverty) and the increase in incidence of MDR-TB (see Figure 11 and Figure 12).

Figure 11: TB notification rate and unemployment rate, Russian Federation, 1985-2006 (all jurisdictional entities)[150]



In 2004, the province of Tomsk, located in western Siberia, began a five-year, USD 10.8 million GFATM grant for management of TB and MDR-TB. One year later, the Russian Health Care Foundation (RHCF) began its primary phase as principal recipient of a $88.1 million GFATM grant for the treatment of MDR-TB in 20 provinces/territories. GLC approval was required for the disbursement of both grants, as mandated by the GFATM grant agreements.



In 2006, the Russian Federation changed the requirements for the importation of pharmaceutical products, primarily in the sphere of registration procedures. Along with submission of additional documentation, all manufacturing companies were required to have a physical representative office in the Russian Federation. Despite the compliance of providers within required timelines, several factors turned these procedural changes into life-threatening crises for hundreds of patients. Of particular concern was the cessation of importation of quality-assured PAS sodium and PASER® (a gradual release formulation of

para-aminosalicylic acid) for GLC-approved projects. This resulted in the interruption of treatment regimens for hundreds of TB patients throughout the Russian Federation.

One factor contributing to this crisis was the lack of effective, timely communication between the federal government, regional TB services, and international/national institutions. Earlier announcement of the change in registration procedures (e.g. six months in advance), as well as higher drug ceilings for importation as permitted by the Russian Federation's Humanitarian commission, could have allowed for projects to establish buffer stocks at their projects to prepare for potential cases of prolonged procedural or legal obstacles to the importation of GLC-approved second-line drugs. Because the government of the Russian Federation has not designated the MDR-TB crisis as an "emergency situation," fast-track importation of second-line medications has not been possible.

Another challenge faced in the Russian Federation is the importation quota established by the country's Humanitarian Commission (a semi-governmental organization, which must determine which organizations seeking tax exemptions for importation qualify as "humanitarian" versus "technical"). The quantities of drugs allowed to be imported are limited and must be determined at the start of each year, when a project submits a dossier that is approved by the Humanitarian Commission. This prevents projects from establishing a substantial buffer stock. More importantly, it also limits flexibility in response to occasional donations or accelerated delivery dates. Russian projects have had to decline offers of short-dated capreomycin because of quota limitations.

Although Russia has many second-line anti-TB drug suppliers (there are 10 suppliers of amikacin, eight of kanamycin, five of capreomycin, 24 of ofloxacin, six of levofloxacin, one of moxifloxacin, 12 of prothionamide, four of ethionamide, and four of cycloserine), none are prequalified by WHO.[152] Russian registration and importation regulations are strict, and consequently it is difficult to find suppliers that are both approved by the GDF and registered in Russia. This often limits Russian procurement to a single supplier and in some cases, a single production facility. For example, Eli Lilly's capreomycin is registered in Russia, but only the product produced at the company's German facility is approved; capreomycin produced by Eli Lilly in the United States or Hungary cannot be imported into Russia. Matters are often further complicated by the fact that drug importations by organizations not designated as "humanitarian" (e.g. the Russian Health Care Foundation) face even stricter rules and are often not able to import non-Russian-labeled or short-dated drug stocks. Shipments from IDA have been returned for these reasons and other paper-work issues.

The lesson drawn from the experience in Russia is that some of the larger nations have well-developed regulatory institutions that govern the importation of medicines and the use of medicines within their borders. It is crucial that the GDF and the procurement agent are extremely well-informed regarding customs documentation and shipment preparation requirements for each country. Since the role of both entities is to ensure that drugs are successfully imported by TB programs, mechanisms must be created so that predictable delays and complications in the customs service are avoided, and that changes to national policies are monitored and anticipated. Also, sustained political action will be required to encourage Russia-based producers to enter the WHO/EDM prequalification system and thereby ensure a long-term in-country supply of quality-assured second-line drugs.

4 Drug Supply and Engagement of Drug Manufacturers in MDR-TB Response

4.1 MDR-TB projects working outside the GLC initiative

As described above, a large global proportion of patients receiving MDR-TB treatment do so outside of the GLC mechanism. Countries reported to the WHO that they treated an estimated 36.4 thousand patients outside of the GLC system in 2007 and that they will similarly treat 34.7 thousand patients in 2008. Countries like Brazil and South Africa have treatment policies that differ from WHO guidelines and strict policies about second-line anti-TB drug purchasing that require them to use local manufacturers. The case of Brazil is illustrative of the drugs-related issues faced in these countries.

Country Profile: Brazil

The Brazilian National TB program has no formal ties to the GLC initiative for procurement. Rather, Brazil has implemented a largely self-contained system of drug production, allocation, and tracking for second-line drugs. The program currently receives institutional support and financing from the Brazilian government and USAID.

A network of public research and production facilities produces a majority of drugs, though on occasion public labs have experienced delays up to 6 months in providing product to the system. Private Brazilian anti-MDR-TB drug manufacturers often provide quicker emergency responses to drug shortages, as they are largely unencumbered by procedural government restrictions.

By law, the Brazilian TB system maintains a buffer stock of 25 percent of total anti-TB drugs in circulation at the central Helio Fraga facilities, which are solely responsible for second-line drug storage.

Strict purchasing regulations apply in Brazil, resulting in a TB system that only utilizes the international drug market as a last resort, after all public and private domestic options have been exhausted.

In 2007, the Brazilian TB community commissioned quality screening for dozens of samples of state-produced anti-MDR-TB medications. According to data from this evaluation, 36 samples representing 14 different products, 10 different active ingredients, and 11 different producers were collected during the first phase of the National Program for Quality Testing of Essential Medicines (Proveme). In total, 35 samples were analyzed, of which 22 were approved (63 percent) and 13 were considered non-satisfactory (37 percent). Of these 13 samples, seven were found with labeling non-conformities (20 percent) and six did not meet product quality standards (17 percent).[153]

This investigation suggests that quality control is an crucial issue, even in a highly-developed, largely self-sufficent national MDR-TB program. The fact that Brazil is actively investigating the quality of the medications in its system is an encouraging sign, though other national programs may not be so transparent.

4.2 Available drug supply through GLC initiative

All second-line anti-TB drugs approved for use at GLC sites are currently off patent.[3] The following chart displays prices for available second-line drugs through the Global Drug Facility (GDF), available to GLC-approved projects:

Table 2: Second-line anti-TB drug (with pricing) available through the GLC mechanism (2007)

Product	Description	Pills/ Vials/Kits	Unit Price (US$)	Avg. cost per Pill/Vial/Kit	GDF-approved manufacturers	WHO Prequal.[4]
Amikacin	500 mg / 2 mL injectable vial	10	$15.10	$1.51	Medochimie Pharmaceuticals	NO
Capreomycin (A)	Powder for injection - 1 gram vial	1	$3.21	$3.21	Eli Lilly	NO
Capreomycin (B)	Powder for injection - 1 gram vial	1	$1.07	$1.07	Eli Lilly	NO
Cycloserine (A)	250 mg capsule	100	$50.96	$0.51	MacLeods Pharmaceuticals Ltd.	YES
Cycloserine (B)	250 mg capsule	100	$14.12	$0.14	Eli Lilly	NO
Ethionamide	250 mg tablet	100	$10.21	$0.10	MacLeods Pharmaceuticals Ltd.	YES
Kanamycin	Powder for injection - 1 gram vial	50	$26.50	$0.53	Panpharma	NO
Levofloxacin 250	250 mg tablet	100	$4.00	$0.05	MacLeods Pharmaceuticals Ltd.	NO
Levofloxacin 500	500 mg tablet	100	$6.98	$0.07	MacLeods Pharmaceuticals Ltd.	NO
Ofloxacin	200 mg tablet	100	$3.49	$0.03	MacLeods Pharmaceuticals Ltd.	NO
PASER	4 gram granules sachet	30	$59.10	$1.97	Jacobus Pharma Company Ltd.	NO
Prothionamide	250 mg tablet	100	$16.00	$0.16	Fatol Arzneimitel	NO
Moxifloxacin[154]	400 mg tablet	1	$5.93	$5.93	Bayer Pharmaceuticals	NO

Source: Stop TB[155]

[3] Moxifloxacin, which has been recommended in the 2008 version of the *WHO guidelines for the programmatic management of drug-resistant tuberculosis* as a newer-generation fluoroquinolone for use in certain groups of patients, is still protected by patent in some countries until 2011.

[4] Although these drugs have not completed the process for prequalification through the WHO, they are approved by stringent drug authorities, and can therefore be offered for sale by the GDF.

4.3 Incentives and disincentives for entry into the second-line anti-TB drug market

Shortly after the GLC's launch in 2001, authors Gupta, Kim, Raviglione, et al. argued in *Science* that there were four distinct advantages for manufacturers who would enter the pooled GLC procurement system:[156]

1. Involvement with the GLC process represented a chance for a manufacturer to display commitment to increasing access to critical therapies in developing countries. It also can build a unique, high-profile international relationship for smaller manufacturers.
2. Participation in the GLC initiative would assure proper use of a manufacturer's drugs and would not result in the creation of significant further resistance.
3. The GLC and the GDF would provide institutional support for the registration and importation of drugs; since they would be provided through a WHO mechanism, it would not require the payment of national tariffs and duties.
4. Industry benefits from single-source demand, which allows for manufacturers to adjust facilities and production capacity for scheduled long-term production, rather than responding to irregular orders from particular projects.

Advantages (1) and (2) are difficult to measure (and therefore difficult to dispute) though they appear self-evident. Advantage (3) has generally proven true with regards to tariffs and duties, although some programs have experienced difficulties with tariffs and duties and there have been problems that persist on the part of the procurement agent, the GDF, and national governments in coordinating timely preparation of required documentation. Advantage (4), which predicts stable, reliable forecasting for manufacturers through the GLC initiative, proves to be the least true of the four advantages over the past seven years; only now are more sophisticated forecasting systems being designed at the GDF to strengthen the existing ad hoc ordering system inherited from the early days of the GLC initiative.[157]

Many manufacturers of anti-MDR-TB drugs based outside of North America and Western Europe have not been overly eager to participate in the GLC Initiative, as they have existing, often lucrative contracts with their national TB programs. It is fair to assume that some of these manufacturers are not subject to quality control or quality assurance at the level required for prequalification by the WHO. The issue is exacerbated by the fact that with the small number of patients being treated under the GLC initiative, there is little financial incentive for manufacturers to undergo the arduous task of WHO Prequalification. Currently, due to high production costs, inaccurate forecasting, and concessional pricing, even companies

who are already providing drugs to the GLC Initiative report having limited motivation to stay involved purely for the purposes of profit generation. The companies involved further report that regardless of a second-line anti-TB drug's profitability (which if it exists, is often modest, according to industry interviews),[158] use of company facilities for second-line drug production typically does not maximize profit generation. Furthermore, no entity exists to assume risk and absorb financial losses from incorrect projections. For this reason, expansion of the number of patients treated under the aegis of the GLC initiative and expansion of the GDF buffer stock to 5000 patients are particularly important to convince manufacturers to stay in the market.

As discussed earlier, another disincentive to participating in the GLC Imitative and WHO Prequalification is that some countries (e.g. Brazil, China, Korea, India, Russia, and South Africa) have local pharmaceutical industries and robust national markets for second-line drugs. Private market sales of second-line drugs are significant in most countries and have increased substantially in the last three years. For example, preliminary survey data on private-sector sales in MDR-TB priority countries show that sales of second-line drugs used solely for TB, such as prothionamide, rose dramatically in China (up 73 percent) and Russia (up 338 percent).[159] In China, seven different suppliers, none of whom were quality-assured, accounted for these private-market sales of prothionamide; 12 separate suppliers sold the drug in Russia, one of whom sold quality-assured product but accounted for only two percent of total volume. Quantities of second-line drugs sold in the private sector were sufficient to treat many more MDR-TB patients than the countries had enrolled in GLC projects, by significant factors: sales of prothionamide in China were adequate for more than 3,500 MDR-TB patients and the country has a GLC project that is projected to enroll 354 patients; sales of the drug in India would have treated more than 1,800 patients, nine times more than the 200 patient in India's GLC project. Data on sales of second-line drugs used for indications other than TB are still more impressive. Private-sector sales of ofloxacin in India, for example, would have treated more than a million MDR-TB patients last year; there were more than 100 suppliers selling the drug, few of whom are quality-assured. So there are substantial and efficient markets throughout the world for second-line drugs, but the market for quality-assured second-line anti-TB drugs appears not to be one of them.

If a majority of the manufacturers of second-line anti-TB medications in key high-burden MDR-TB countries could be brought in to the prequalification program, the shortfall of drugs for GLC projects could be addressed while simultaneously guaranteeing that the drugs supplied to NTP in high-burden countries would be of demonstrably superior quality. Pharmaceutical company executives and governmental health authorities are both positioned to make decisions regarding this possibility.

The dynamics of the second-line anti-TB drug market could change in coming years. From all indications, the sales of second-line drugs—quality-assured or not—will continue to grow considerably. Evidence from GLC applications and reports to WHO of patients already on treatment indicate that public market purchases of second-line drugs will continue to increase rapidly and it is likely that private market demand will as well. Demand for second-line drugs will expand with the increasing availability of international financing for poorer countries that have significant MDR-TB burdens (e.g. through GFATM, UNITAID, and possibly PEPFAR). Very recently, demand was also bolstered by UNITAID financing for a buffer stock of second-line drugs for up to 5,000 patients, to be purchased by the GDF. This last development is particularly significant in the short term, in that it creates well-characterized, firm, and immediate demand for quality-assured second-line drugs (for more than half as many patient regimens than the market supplied all of last year), subject to none of the delays and uncertainties that have always characterized this small, peculiar, and idiosyncratic market in the past.

These changes in the market for quality-assured drugs will take some time to be understood by national and international market participants because up until now, the market for these drugs has been so small, so strictly controlled, and limited to such a small number of approved suppliers. The sooner suppliers of second-line drugs understand the changing dynamics of the market, the more inclined they will be to incur the upfront expense of having their products quality-assured. The more readily national governments and other purchasers of second-line drugs are able to access quality-assured drugs, the more likely they will be to insist upon them for their patients. WHO, GLC, and the GDF could take some steps to facilitate mechanisms and improve incentives for suppliers and purchasers of second-line drugs. In so doing, they could catalyze a virtuous cycle wherein the supply and the demand for quality-assured drugs both increase as the overall market continues to expand.

4.4 New therapies for MDR-TB

Given the market realities surrounding the second-line anti-TB drug market, it should come as no surprise that the emergence of drug-resistant disease as a public health concern has not resulted in a proportional response from pharmaceutical companies in research and development. No new treatment breakthroughs have been made available to patients in decades, despite progress in the laboratory. According to the Treatment Action Group, $120 million was spent for anti-TB (including MDR-TB) drug development in 2005 worldwide yet the total invested in clinical trials was no more than $20 to $30 million.[160] If successful, human trials currently underway which aim to shorten the duration of first-line therapy could eventually decrease incidence of drug-resistant disease, though the likelihood of any of these compounds reaching the market by 2010 has been estimated at less than 5%.[161]

Compared to first-line drugs, the development of second-line therapies offer comparative advantages and disadvantages. As Glickman et al. assert in *Seminars in Respiratory and Critical Care Medicine*, "for MDR- and XDR-TB, the target product profile might pose a somewhat lower 'bar' because the currently available drugs are less effective, have more associated adverse effects, and are significantly more expensive."[162] While this is promising for patients with MDR-TB, various factors including the extremely long treatment period for MDR-TB patients, the multi-year follow-up that is required, and the concurrent medications given in the current standard of care that can obscure the effect of new therapies all make testing new drugs on MDR-TB patients less attractive.[163]

However, the relatively large number of MDR-TB patients being treated by GLC-approved projects creates a new possibility for clinical trials where none existed previously. As Mitnick et al. points out, "for the first time in 30 years, several new drug classes that hold promise for MDR-TB treatment are under development," and "the expansion of MDR-TB treatment programs provides the settings in which trials can be implemented… Four elements are needed to make MDR-TB treatment trials a reality: money; additional work on the drug pipeline; rigorous, interdisciplinary preclinical work on individual agents and regimens; and an understanding that TB clinical trials need not be a zero–sum endeavor."[164]

Aside from the availability of sites for clinical trials, a debate is currently underway regarding the cost and likelihood of development of major new TB therapies. Glickman et al. assert that "achieving 95% confidence of at least one new tuberculosis drug will take 12 years and costs will approach $400 million."[165] Andrew Farlow of Oxford University challenged this claim, putting the figure (using Glickman's transition probabilities) at $136.75 million.[166] Regardless, the outlook for new therapies is a complicated picture which demands continuing commitment from policy-makers, researchers, research funding agencies, and the pharmaceutical industry.

Recently there has been some consensus among stakeholders to marshal resources and political will to provide capacity for clinical trials of new MDR-TB therapies. In June 2008, representatives from NGOs, governments, donors, the pharmaceutical industry, and academia met in Cambridge, Massachusetts[167] and declared the formation of a new initiative called RESIST-TB, whose aims are: to conduct priority clinical trials that test strategies in adults and children to prevent drug-resistant TB; to shorten and improve treatment for drug-resistant TB; to mobilize the resources needed for these trials; to build the capacity of trial sites; and to ensure that these efforts complement those of other groups.

4.5 Governmental health authorities and high quality second-line drugs

As of summer 2008, the majority of high-burden countries are working outside the GLC initiative to provide most or all MDR-TB treatment to their citizens. The spectrum of engagement varies from very limited involvement (e.g. South Africa), to some involvement (e.g. China and India), to significant involvement (e.g. Russia). Regardless of the level of involvement, drugs of unverifiable quality produced by local industries should surely be a major focus of concern as MDR-TB continues to spread apace in those nations. The financial benefit of buying drugs of questionable quality will be outweighed by the problems associated with a growing population of MDR-TB patients and of those with higher-spectrum resistance (e.g. XDR-TB). This could result in governmental health authorities urging or financing their national manufacturers to go through WHO Prequalification for the sake of its citizens' health, or initiating the process to have its own regulatory authority deemed stringent (as has been done in South Africa-MCC). The outcome in either case would be higher-quality drugs manufactured in high-burden areas. The GLC initiative/GDF and WHO Prequalification could assure that its capacity to provide second-line anti-TB drugs to participating projects are increased by assisting manufacturers through the process early on in return for agreements of supply at a reduced price for some period of time after approval.

4.6 Manufacturers in high-burden countries

There are reasons to expect that manufacturers of second-line drugs in high-burden countries may become more amenable to GLC involvement in the future. Producers in these countries operate in fundamentally different business environments than their North American and Western European counterparts, but significant state intervention in the pharmaceutical industry does not necessarily result in security for these companies; often the opposite is true. Profit-margin regulations and price caps in countries like China and India change regularly, and as a result many of their companies have expressed interest in selling their products internationally to diversify their revenue streams.[168,169] Indeed, China and India are presently working together to streamline the production of raw materials for ailing pharmaceutical companies in India that are languishing under the price-control regime.[170]

Public-Public Partnership: Eli Lilly Technology Transfer for Capreomycin and Cycloserine

American pharmaceutical company Eli Lilly and Co. developed capreomycin (Capastat®) and cycloserine (Seromycin®) in the 1950s and early 1960s, and has been the leading global producer of these drugs. Since the inception of the GLC in 2000, Eli Lilly has undertaken a philanthropic effort to provide concessionary-priced second-line drugs to GLC-approved programs. In 2006 alone, 1.2 million capsules of cycloserine and 280,000 vials of capreomycin were provided (a large proportion at a discount) to the GLC initiative.[171] Additionally, Lilly introduced another innovative philanthropic initiative in the form of production technology transfer to high-burden countries.[172] This was done in the context of Lilly's desire to eventually withdraw from the MDR-TB market.[173] At the time of transfer, capreomycin was a non-patented monopoly drug. Cycloserine had been approved by the WHO Prequalification Program for production by Macleod's of India, though it is sold at a significantly higher price by that producer.

The transfer provided manufacturers with the necessary knowledge and manufacturing technology required to produce the active pharmaceutical ingredients (APIs) and final products. Lilly committed to purchase equipment, upgrade facilities, and provide training in business management and Good Manufacturing Practices (GMP) for selected partners. A pharmaceutical company in each of the four highest-burdened countries was selected based primarily on its willingness to supply the drugs to the GLC at a negotiated rate. SIA International (Russia), Aspen Pharmaceutical (South Africa), Hisun Pharmaceutical (China), and Shasun Chemicals and Drugs (India) were selected to take part in the process. All partners contributed financially to the initiative and agreed to supply the drugs to the GLC with a maximum of 20 percent profit margin.[174]

Aspen sold its first batch of cycloserine to Botswana in 2005, while the new facility was under construction. Currently, the factory is at full capacity (it is designed to manufacture 4 billion capsules annually) and is assuming Lilly's share of cycloserine production for the GLC initiative. Its production of cycloserine had been approved by South Africa's regulatory body, Medicines Control Council (MCC), now considered a stringent drug authority (though it is not a retroactive consideration and Aspen must still complete its WHO Prequalification application). It has additionally received GMP certification from the WHO and all associated parties predict that full-scale production of capreomycin by Aspen should be possible by the second quarter of 2009.[175]

According to Lilly representatives, the difficulties arising from the complex production of cycloserine and capreomycin were exacerbated by poor forecasting of need, both by the WHO at the partnership's inception in 2003 and by the GLC initiative in the years following.[176]

5 REDEFINING THE PARADIGM OF THE GLC MECHANISM

Although the GLC "pilot project" era officially ended with the change in WHO treatment guidelines for MDR-TB patients in 2006, the GLC initiative is still functioning with "pilot project" procurement mechanisms and policies. Changes in both operating procedure and logistics could significantly enhance the supply and demand of quality-assured second-line drugs.

In the pilot project era of the GLC, the demand for quality-assured drugs was small; this is clearly no longer the case. Drugs could only be accessed through a single procurement agent, which is still the case: projects purchasing second-line drugs with financing from GFATM or UNITAID are required, by the terms of the grant, to have GLC approval and to use only the GDF and its procurement agent. As the market has expanded rapidly, it has outgrown the capacity of a single procurement agent and for many second-line anti-TB drugs, a single quality-approved manufacturer. Experience has shown that it is no longer practical to require all GLC projects to purchase second-line drugs only through one procurement agent and indeed some countries are prohibited by law from purchasing from a sole, pre-determined source. The GFATM and UNITAID will certainly continue to insist that their grant funds be used only for the purchase of second-line drugs that are quality-assured, but they are not likely to long maintain their requirement that recipients use a single procurement agent, especially if the procurement agent is unable to procure and deliver the second-line drugs in a timely and consistent manner over an extended period of time.

Through some modification in the way it operates, the GDF could strive to become the most attractive supplier of second-line drugs in the market—on pricing and supply logistics—becoming the option that GLC projects want to use. A first step would be for the GDF to move as expeditiously as possible to retain more than one procurement agent to act on its behalf. This would provide the GDF with a choice of procurement agents; it could award contracts based on the ability of agents to fill orders most expeditiously and to take advantage of regional capabilities and relationships. Through this approach, another major advantage will have been secured: the GDF will become the largest and most consistent purchaser of second-line drugs. If it can maintain a buffer stock of second-line drugs for up to 5,000

patients, the procurement of those drugs will give it pooled procurement advantages and market pricing power over and above discounted prices it obtains through its role as the GLC-procurement mechanism.

In order to open the market to alternative procurement strategies, the GLC could take the additional step of separating GLC approval from the requirement to purchase only through the GDF and its procurement agent; instead, it could require that all GLC-approved projects purchase quality-assured drugs. This would open the door for GDF and other international partners to create criteria for "quality-assurance" (drawing from WHO Prequalification requirements as well as those of Stringent National Regulatory Authorities and agreements governing their operations) that could be used by countries who choose to open drug purchases to tender.

By both expanding the number of its own procurement agents and expanding the ability of countries to purchase quality-assured second-line drugs on their own, the GDF would strengthen the following areas:

1. **Logistics.** The GLC/GDF will have responded to the logistical problems, which now cause so much concern, by establishing a limited number of procurement agents to operate in various regions of the world and who will likely respond more efficiently to increasing demand and be better equipped to resolve the types of registration and customs obstacles which delay the delivery of second-line drugs.

2. **Pooled Procurement**. The GDF will retain access to information on all purchases of second-line drugs for GLC projects, can assist regional procurement agents in pooling purchases, and can increase the size of orders for projects as it fills its own UNITAID-funded buffer stock.

3. **Negotiations with quality-assured suppliers for preferred pricing**. The GDF can keep the responsibility of negotiating standard, preferred pricing for all regional GDF procurement agents, while allowing the procurement agents to purchase quality-assured second-line drugs on better terms if available.

4. **Preferred pricing**. If the GDF is the major high-volume purchaser of quality-assured second-line drugs (through its procurement agents) it would be unlikely that many countries (except perhaps the largest) would garner better terms from manufacturers. For countries that require multiple bid-procurement processes, GDF's regional agent could submit a bid as one of many potential suppliers to the country. It is likely, backed-up by access to the GDF buffer stock and pre-negotiated GLC prices, that the GDF agent would win the majority of contracts.

6 RECOMMENDATIONS

6.1 The WHO and international partners should take immediate and rapid steps to increase the number of manufacturers of quality-assured second-line anti-TB drugs. A mechanism needs to be developed to make these drugs available at pre-negotiated prices to programs purchasing via the GDF *and* through direct-purchase by countries. Specifically, this means having the GLC uncouple the important emphasis on quality-assured drugs from the mode of purchase. Countries should be able to purchase second-line drugs however they choose, as long as they use quality-assured products as specified on a list of GDF-approved suppliers. In order to remain competitive and address some of the shortfalls in the current system, the GDF should increase the number of procurement agents available to countries participating in the GLC initiative. This would allow the system to take advantage of regional competencies such as knowledge of local manufacturers and understanding of national customs/regulatory rules. Lastly, WHO should define their quality-assurance criteria along the lines likely to be adopted next month by the GFATM and create a system to monitor that the criteria are being followed.

6.2 The GDF should create a tiered system of approval for manufacturers of second-line drugs who are in the WHO Prequalification Program. Large countries operating within the GLC initative should be allowed to purchase second-line anti-TB drugs from domestic manufacturers who have entered the WHO Prequalification process. In the current system, manufacturers are unable to sell their products unless they are prequalified by WHO or have prequalification from a Stringent Regulatory Authority. Manufacturers who are in the process of WHO Prequalification are unable to sell their products even though they may be very close to full approval. A tiered purchasing approach—where manufacturers who commit to completing the WHO process can sell their products under certain circumstances and with stringent batch testing—would act as an incentive to manufacturers to enter the WHO process, increase the number of qualified manufacturers who can sell drugs through the GLC initative, and alleviate the global shortages experienced with some second-line drugs. This would increase competition and lower price (as mandated by UNITAID funding). Criteria for participation in such a system would have to be developed along the lines of the tiered system that already exists for first-line TB drugs.

6.3 The GLC initiative and the GDF should institute a reliable and transparent system for quantification of demand for second-line drugs. The GDF should expedite its ongoing efforts to develop a comprehensive system of needs projection that takes into account projects' patient enrollment, capacity, and GFATM grant disbursements. The expertise needed for this effort is available; private industry experts, logistics consulting firms and non-governmental organizations (e.g. Management Sciences for Health) are qualified to assist in needs projection and in creating systems to track medications from the point of production to the point of consumption by the patient. This will not only help countries know when they are going to receive their drug orders, but will allow manufacturers to estimate the future market.

6.4 The GDF should maintain a second-line anti-TB drug buffer stock (at minimum, enough to treat 5,000 patients) in order to facilitate rapid delivery of drugs to programs (less than one month). The GDF has recently received funding from UNITAID for a 5,000-patient buffer stock of second-line drugs. Orders for this stock should be placed independent of orders from projects and should be specifically targeted at encouraging new manufacturers to enter the market. The presence of a buffer stock will also reduce waiting time for drugs to less than two weeks rather than the current three to six months.

6.5 There should be a global effort to increase the options available for treating MDR-TB and XDR-TB, by optimizing current regimens and by developing at least three new anti-TB drugs. Increased TB clinical trial capacity needs to be created, and mechanisms developed to fast-track new anti-TB drugs through the regulatory process. Current therapies for MDR-TB and XDR-TB are woefully inadequate: the treatment takes two years, throughout which patients face numerous medication-related adverse events. These regimens need to be optimized so that adverse events are minimized. New therapies targeted specifically to *M. tuberculosis* need to be developed and mechanisms for fast-tracking regulatory approval of promising agents need to be worked out with regulatory agencies. Increased clinical trials capacity for novel TB treatments must be developed simultaneously.

SECTION IV: MDR-TB TREATMENT DELIVERY

1 INTRODUCTION

According to the recent WHO/IUATLD survey of global drug resistance, the global burden of drug-resistant TB is significant and growing very quickly. Although early intervention with appropriate and aggressive second-line drug regimens can result in cure rates over 75 percent, MDR-TB diagnosis and treatment programs have not even begun to keep pace with the epidemic.[177,178,179,180]

At the country level, the growing problem of drug-resistance is unwelcome by most NTPs, many of which are still struggling to control drug-sensitive TB. Spurred by the rapid increase in MDR-TB and XDR-TB observed globally, programs are trying to come to terms with their drug-resistant TB epidemics. Treatment of drug-resistant TB, however, is expensive and complex: patients require 18 to 24 months of therapy with four to eight medications, including daily injections for at least six months; treatment is fraught with numerous adverse events which require additional management. Most national TB programs are ill-equipped to provide the necessary services for management of MDR-TB/XDR-TB.[181] In some cases, the required clinical and laboratory expertise may not even exist within the public sector; in many countries, human resources for the actual delivery of care and systems of care delivery themselves are lacking. All of this is exacerbated by weak health systems in many settings[182,183,184,185] and by the challenges of delivering treatment to poor and marginalized patients who often face many social and economic barriers to receiving adequate care.[186,187,188,189,190,191,192]

The area of treatment delivery is complex and broad, and this paper does not fully address all relevant aspects of care delivery. Rather, the purpose of what follows is to highlight important factors that may have an effect on the rate and nature of MDR-TB treatment scale-up, and to offer some targeted solutions.

2 Shifting the Paradigm From "Pilot" Projects to an Integrated Strategy

When drug-resistance was identified as a major global problem in the mid- to late-1990s, it was initially considered an additional intervention that countries could choose to implement, if needed, in their TB-control strategies. Because of the belief that drug-resistant TB would disappear as DOTS programs improved and the worry that MDR-TB treatment (at that time called "DOTS-Plus") would draw important financial and human resources away from DOTS programs, a false dichotomy emerged between the programmatic management of drug-susceptible and drug-resistant TB. For a long time, countries were advised by the WHO and other international partners to focus primarily on drug-susceptible TB. This resulted in a lack of integration of drug-resistant TB treatment into national programs and, as evidenced by findings from the recent WHO/IUATLD global drug-resistance survey, had profound effects on the epidemiology of TB.[193] In 2006, the Stop TB framework called for the integration of drug-resistant TB treatment as part of national TB-control strategies.

As discussed previously, the GLC initiative was formed in 2000 with the aim of providing concessionary-priced quality-assured second-line drugs to MDR-TB treatment pilot projects.[194] The idea was to maintain a high standard of programmatic vigilance in order to prevent the emergence of super-drug-resistant strains of TB. Initial pilot projects in Estonia, Latvia, Peru, the Philippines, and Tomsk (Russian Federation) were quite successful and yielded cure rates of 77 percent among new cases of MDR-TB and 69 percent among previously treated cases of MDR-TB patients.[195,196,197,198] Recent data suggest that the MDR-TB epidemics in Estonia and Latvia—both of whose pilot projects offered universal access to MDR-TB treatment—might in fact be leveling off.[199]

The WHO's Global Plan to Stop TB: 2006-2015 established a set of treatment targets for 2015, including the treatment of 800,000 patients with MDR-TB.[200] With the XDR-TB outbreak in the Republic of South Africa in 2006, a two-year emergency plan called for an aggressive revision of the 2015 targets to include "universal access" by 2015 (equating to nearly 1.6 million patients) and for the treatment of 134,000 individuals by the end of 2008. However, because just over 40,000 patients have been approved for treatment in GLC projects to date and a smaller number have actually received treatment, it is unlikely that this goal will be met.

One of the main problems has been the integration of MDR-TB care into national TB-control strategies. The dichotomy between drug-susceptible and drug-resistant TB created by early policies, coupled with the current approach to drug-susceptible TB—using Category I then Category II, etc.—has resulted in lukewarm commitment on the part of some global partners to MDR-TB scale-up and mixed messages reaching programs, leaving some countries confused as to how to proceed. The XDR-TB outbreak changed some of these dynamics, but still many countries report being advised not to include MDR-TB treatment until they have a fully functioning DOTS program. Because the disease is airborne, this approach has resulted in a growth of MDR-TB in many settings and the unnecessary deaths of countless patients.

Since the GLC is the gatekeeper both to concessionally-priced second-line drugs and to the release of GFATM and/or UNITAID funding, programs are required to use the mechanism. Although the GLC is not charged with the task of global scale-up of MDR-TB treatment, many observers perceive the GLC as part of the scale-up bottleneck; in some countries, it is referred to as the "red-light committee." This, however, is not the case: projects are rarely rejected as the process is designed to assist any interested project in improving its program to the point of GLC approval. Because of the iterative process that the GLC undertakes with each application, approval time (from time of submission to full approval) can take months even for a few patients. Eventually a small cohort of patients is permitted to begin treatment while the TB program increases its capacity for program expansion. GLC consultants visit programs regularly for monitoring, evaluation, and the provision of technical assistance. It is during these visits, often conducted yearly, that further program expansion can be recommended. Therefore, the "bottleneck" lies in the very process of ensuring the integrity of projects and their ability to safely deliver MDR-TB treatment.

Because many countries lack the necessary infrastructure for MDR-TB treatment, nearly all projects are approved as part of a limited effort in a country—a "GLC pilot project." The justification for pilot projects is that they allow clinical and programmatic experience to be gained and epidemiological data to be collected in preparation for scale-up of a larger, national program. While the reason for the pilot project approach is obvious—to prevent the emergence of broad-spectrum anti-TB drug resistance resulting from poorly delivered MDR-TB care—its most serious flaw is that it does not address the epidemiological reality of a rapidly spreading, airborne illness. Early diagnosis and effective treatment of MDR-TB patients is not just good clinical care—it is also a public health intervention that prevents many new cases. As the recent global MDR-TB surveillance report has shown, treating a small fraction of known MDR-TB cases does nothing but ensure that the number of MDR-TB cases will continue to increase. Sadly, only five GLC projects—Estonia, Latvia, Lesotho, Nepal, and Peru—currently offer

universal access to MDR-TB treatment, a far cry from what one would expect given the current Stop TB recommendations.

One of the reasons that WHO's DOTS strategy for the treatment of drug-susceptible TB has been so successful is that countries were encouraged to rapidly scale-up implementation and were given ample assistance to do so. Despite the extra staffing requirements for the direct observation of therapy, the need for quality-assured smear microscopy, and the management required for maintaining drugs stocks, the project has been a resounding success. The same needs to be accomplished for MDR-TB. In order to do so, the approach of the GLC toward projects has to shift from a "pilot project" mentality to one where full integration of MDR-TB treatment in national TB-control strategies is the immediate and desired outcome. At a time when GFATM money is available to countries facing MDR-TB/XDR-TB epidemics, waiting for countries to have perfect DOTS programs before they can expand MDR-TB treatment risks losing an important opportunity for program strengthening. MDR-TB treatment integration can bring additional resources into cash-strapped NTPs, encourage renewed political commitment, and strengthen the capacity of diagnostic services, clinical management, and case management.[201] With the current funding streams, NTPs are now in a position to innovate beyond their current models of care, specifically addressing barriers such as poor nutrition, lack of transportation, adverse event management, and social isolation, all of which can have a bearing on improved management of both drug-susceptible and drug-resistant TB disease.

In order to achieve the goal of full integration and universal access to MDR-TB care, the role of the GLC initiative as a whole needs to shift away from a "pilot project" approach to one which encourages projects to scale-up MDR-TB treatment as rapidly as possible, by facilitating solutions to implementation barriers. This will require both a concerted effort on the part of the entire GLC initiative, the WHO, and international partners, innovative approaches to the provision of technical and material assistance, and in some cases, long-term on-site teams that can aid ministries of health with actual program implementation.

3 ADDRESSING THE MDR-TB TREATMENT IMPLEMENTATION GAP

Countries as diverse as Azerbaijan, Peru, Latvia, and Lesotho all emphasize the important role that technical assistance played in the initial stages of their MDR-TB programs. They also note problems with the technical assistance that they received, and report that the most useful assistance tended to be on-site and long-term.

International consultants often spend limited time in each country, leaving a list of recommendations specific to their narrow areas of expertise. Despite plenty of resources and trained field workers, some

programs are unable to move forward: organizations disagree on how to collaborate or share facilities; people disagree on who gets what role; groups disagree about how to divide the territory. These are issues that consultants are not always prepared to mediate; even for those who are willing to mediate, it is almost impossible to do so from outside the country after a technical assistance mission is completed.

The case of Lesotho, described below (p. 73), is illustrative. Because of local will and sufficient on-site expert assistance, Lesotho was able to rapidly launch an MDR-TB treatment program that included a safe, well-though-out plan to care for very ill patients in a hospital facility. Without the guidance and hands-on interaction of technical partners, it is likely this would not have happened so rapidly. Similar experiences were described in interviews with programs in Azerbaijan, Latvia, Tomsk, the Philippines, and Peru. The major lesson from all these examples is that having intensive technical assistance— a very hands-on form of technical assistance that we could perhaps call *technical accompaniment*—helps countries achieve integration of drug-resistant TB management into their national TB-control strategies and programs.

While the GLC initiative has done its utmost to provide technical assistance to projects before and during MDR-TB treatment implementation, there is limited capacity to engage with projects with the depth of commitment required to fuel rapid scale-up. The GLC's mandate is to approve projects based on their applications and to provide guidance as to how they may improve their projects if needed. In many poor countries, projects need ongoing training, help with their GLC application, help with their GFATM application (to fund the project), help with program implementation, and ultimately, help in program operations. Yearly visits from the GLC and other international advisory/monitoring boards have not appeared to be enough to help countries expand programs and integrate MDR-TB treatment into their TB-control strategies.

Given the profound gap in the estimated number of patients with MDR-TB and those who receive any treatment—it is estimated that less than 50,000 of the almost half a million new annual cases receive any treatment—solutions are urgently needed (see Figure 12). What is required is a mechanism for the delivery of technical assistance and technical accompaniment based on a country's need. An example of this is a global health initiative similar to PEPFAR. Since 2004, PEPFAR has provided treatment to over 1.6 million patients in 15 focus countries, including 367,000 patients co-infected with HIV and TB (see Figure 13). The example of PEPFAR suggests that appropriate diagnostic technology and access to quality assured medications is not enough to ensure project implementation; rather, in order for a complex health intervention to be successful in a short period of time, it requires: (1) sufficient resources; (2) an implementation strategy; and (3) an on-site implementation mechanism.

Figure 12: MDR-TB patients scheduled to receive treatment in WHO/GLC-approved projects and non-GLC projects compared to the estimated number of patients who require treatment (1000s of patients; 2004 to 2006; Source: WHO 2008)

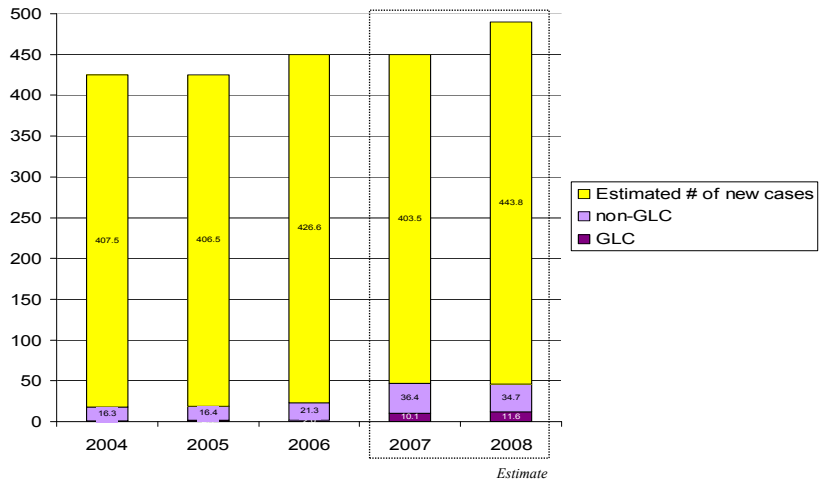
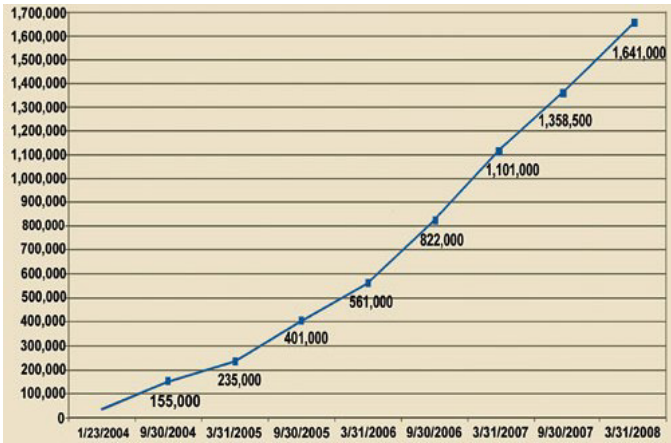


Figure 13: The number of individuals receiving antiretroviral treatment in PEPFAR's 15 focus-countries[202]



Countries included: Botswana, Cote d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam (added in 2004), Zambia

Addressing the MDR-TB program implementation gap is a complex problem because it requires health system strengthening and the integration of often-vertical TB programs into broader health services. Much knowledge on how to achieve this goal exists in some of the earlier GLC pilot sites, many of which are now national programs. Achieving universal access to MDR-TB treatment will require a considerable increase in the pace of patient enrollment in high-burden MDR-TB settings; in order to achieve this, the TB community will need to look at its own achievements (e.g. GLC programs that have achieved nation-wide expansion), as well as draw from the experience of other global health initiatives (e.g. PEPFAR, Guinea Worm eradication, etc.). At the very minimum, the following are needed: (1) a mechanism for using the lessons learned at the early GLC pilot sites and drawing on regional expertise to assist programs/countries in rapid MDR-TB treatment expansion; (2) a system to provide long-term on-site laboratory, programmatic, and clinical assistance and mentorship to national TB-control programs through implementation agencies; (3) the participation of global health initiatives, such as PEPFAR, in MDR-TB treatment expansion; and (4) the prioritization of MDR-TB treatment delivery (program implementation) by large bilateral donors—such as the Canadian International Development Agency (CIDA) and the United Kingdom Department for International Development (DFID)—and large global health foundations such as the Bill & Melinda Gates Foundation.

4 EXPANDING MODELS OF CARE

4.1 Community-based models for MDR-TB treatment

There are significant differences in the way that countries treat patients with MDR-TB. One of the most important differences is varying use of inpatient care.

When designing MDR-TB treatment programs, countries often turn to inpatient care for two reasons. Firstly, many chest specialists are more comfortable with treating MDR-TB patients in the hospital, where complicated regimens can be monitored closely for adverse events. This is particularly true in countries of the former Soviet Union, which have a history of hospitalizing even drug-sensitive TB patients, but also in many other countries, such as South Africa (which uses an ambulatory model for patients in treatment for drug-sensitive TB but not MDR-TB). Secondly, as discussed above, many countries lack sufficient ambulatory infrastructure—human and physical—to provide the complex treatment required for MDR-TB, and therefore find it easier to launch hospital-based programs.

In countries with a rapidly increasing numbers of drug-resistant TB patients, an emphasis on hospitalization can become a serious bottleneck to scale-up. As hospital beds run out, clinicians create waiting lists of patients who are already diagnosed with MDR-TB but cannot start treatment. While waiting for a hospital bed, infected patients can transmit their disease to others and by the time they are finally admitted, they may be seriously ill and at higher risk for treatment failure and death. Furthermore, hospitalization at the beginning of treatment does not guarantee adherence until the end of treatment. Patients who are discharged from the hospital may immediately default if adherence support is not provided.

The advantages of an ambulatory model of care for MDR-TB are much the same as for drug-sensitive TB. Ambulatory care allows patients to integrate themselves into community and family life and rejoin the workforce. Many GLC-approved MDR-TB treatment programs have a strong ambulatory care component using trained community-based workers, and some of the most successful have initiated MDR-TB treatment on an outpatient basis in all but the most severely ill patients. Outpatient models of care also decrease the problem of nosocomial transmission to other patients and staff within overcrowded, poorly ventilated hospital wards.

At the Stop-TB Partnership's MDR-TB Working Group meeting in Tbilisi, Georgia, in September 2007, members endorsed a community-based approach for MDR-TB management as a way forward for NTPs. As the next case illustrates, the challenges to achieving this goal are great and much needs to be done to help countries make the important transition from inpatient to outpatient MDR-TB care.

Country Profile: Azerbaijan

Many countries are faced with difficulties in changing their models of care to allow for universal access to MDR-TB management. Azerbaijan is an interesting example of a country primed for MDR-TB treatment expansion, but which has faced many challenges along the way. In 1995, it was estimated that drug-resistance among new and retreatment patients was not a significant problem; by the time the 2008 WHO Drug Resistance Survey data was published, Azerbaijan was found to have 22.3 percent MDR-TB among new patients and 55.8 percent among retreatment patients.

Azerbaijan is an oil-rich country located in Southwestern Asia, bordering the Caspian Sea on its east and sandwiched between Iran and Russia with European borders. It is home to 8.4 million people, evenly divided between rural and urban areas. The country gained independence from the Soviet Union in 1991, but it has been struggling with territorial conflicts, displaced people, and corruption since that time, with

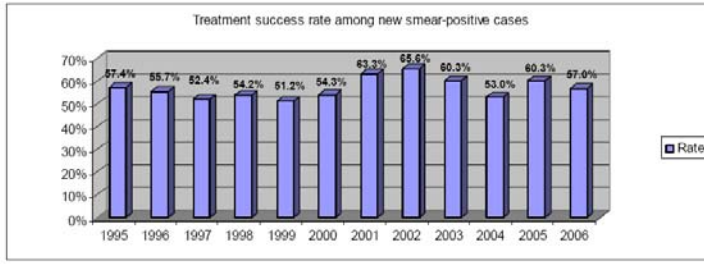
accusations of authoritarian rule. Gross Domestic Product is USD 6,476 (PPP) per capita and literacy rates are almost at 100 percent. The most recent prevalence of HIV/AIDS is 0.1 percent and prevalence of TB is 85 per 100,000 population per year, as of a 2005 estimate.[203]

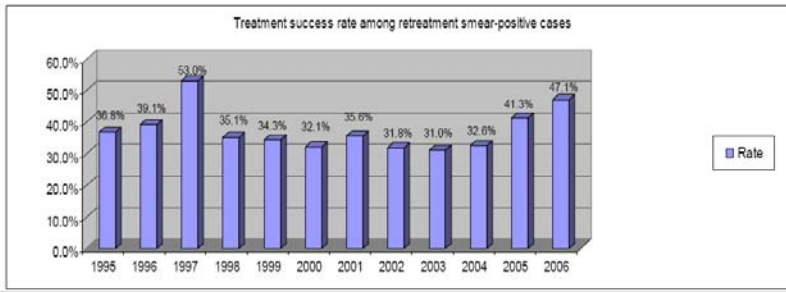
After the fall of the Soviet Union, the health care system remained a function of the state, but some private institutions and providers emerged. Pharmaceuticals became privatized and unregulated, with 70 percent of the drugs on the market today being imported and only 5 to 10 percent is free of charge. In 1998 fee-for-service and informal payments began, accounting for 57 percent of healthcare costs. The new payment schemes created a barrier to care for many. A 2001 survey found one third of households could not access necessary health care services.[204]

In 1991, Azerbaijan faced a recurrence of TB. At the time, the country also faced a shortage of TB medications, did not have a national reference laboratory, had limited managerial capacity, and no longer offered tuberculosis-treatment training previously mandated by the former Soviet Union. In 1994 TB prevalence in the prisons was almost 50 times the national rate and 24 percent of cases died. There were about 25,000 people in prisons, where overcrowding, poor health, and other risk factors contributed to the rapid spread and the high prevalence. In the civilian population, treatment was mostly provided by private practitioners, many of whom were paid by pharmaceutical companies for each second-line drug prescription they wrote.[205] During this time, patients turned to self-treatment with intermittent supplies of first- and second-line drugs from family members or other outside sources when possible.

The International Committee of the Red Cross (ICRC) helped set up the first DOTS program in the prison system in 1995, treating over 300 patients in the central prison hospital. Despite strict compliance and 100 percent DOTS coverage in the penitentiary sector by 1998, many patients were found to be failing treatment.[206] Studies later revealed that these patients were suffering from drug-resistant disease.[207,208] DOTS was adopted as the national strategy by the Ministry of Health in 2005, after which the country reported 100 percent coverage. Despite this coverage, treatment success rates among DOTS patients were quite low because of increasing drug resistance.

Figure 14: Treatment success among new and retreatment sputum-smear positive patients in Azerbaijan (1995-2006)





It is likely that MDR-TB spread in Azerbaijan for a number of reasons: intermittent supply of first- and second-line medication given in non-standard regimens, a weakened health system unable to deliver TB medications under DOT, continued use of short-course chemotherapy in patients with drug-resistant disease, and transmission in congregate settings and the community.

In 2004 the ICRC assisted the Azerbaijani authorities in submitting an application to the Green Light Committee to launch a pilot project to provide MDR-TB treatment in the prisons. The following year Azerbaijan applied to the Global Fund for AIDS, Tuberculosis and Malaria (GFATM) for funding to provide MDR-TB treatment nationally, building on the DOTS program. The first patients started the two-year course of MDR-TB treatment in the prison system in April of 2007, close to the time a national reference laboratory was created. Because of lack of safe hospital facilities and an underdeveloped ambulatory care system, to date less than 15 patients (out of hundreds who have been identified) are receiving treatment in the civilian sector.

4.2 Participation of the private sector

In many countries (e.g. India and the Philippines) the private sector plays a significant and important role in the diagnosis and treatment of TB.[209,210,211,212,213] While the private sector does offer the opportunity for treatment to many patients, the impact on TB control is mixed for a number of reasons: (1) private practitioners may deviate from international standards and use non-standard treatment regimens, which may contribute to treatment failure (with possible amplification of drug resistance) and death; (2) private practitioners often do not have the resources to provide adherence support (incentives and enablers) between clinic visits; and (3) patients often have to pay for follow-up sputum examinations and clinic visits, which is a disincentive to completing the entire treatment (6 months for drug-susceptible TB and 18 to 24 months for drug-resistant TB).

The relative proportion of MDR-TB treated by the private sector is not known because it often takes place outside of the reporting structures of NTPs. It is likely, however, to be quite substantial, simply because the capacity to diagnose and treat MDR-TB does not exist within the public sector in many countries. However, as in the treatment of drug-sensitive TB, the epidemiological impact of treatment in the private sector can be mixed. Even in middle-income countries where pulmonologists and chest specialists exist, they may not have expertise or experience with MDR-TB. The high cost of MDR-TB treatment is generally passed on to the patients, who cannot possibly afford to complete a full course of treatment (not to mention the ancillary care required to manage adverse events). MDR-TB treatment in the private sector is notoriously irregular; high default and failures rates are likely to be quite common and have been blamed in some settings for the creation of XDR-TB strains.

While technical assistance for the programmatic management of MDR-TB has been largely focused on NTPs, there are important potential lessons in the experience of PPM-DOTS (public-private mix DOTS). PPM-DOTS has been successful in several countries by pioneering collaboration between the NTP and private practitioners. In Manila, Philippines, the Tropical Disease Foundation and the Philippines National Tuberculosis Program are working to provide private practitioners with training about MDR-TB and current treatment guidelines, are providing assistance with the provision of DOT and patient supports, and are registering and following patients who initiate therapy outside of the national system. They have also begun to enlist private laboratories in MDR-TB-treatment expansion through training and supervision and the provision of external quality assurance.

Given that few countries have treatment programs that are run solely by NTPs, it is clear that engaging with the private sector is integral to ensuring proper treatment for both drug-susceptible and drug-resistant TB.

4.3 Transmission control

A major factor behind the growth of MDR-TB globally is transmission, much of which is occurring in congregate settings. The classic example in recent years is that of Russia, where the role of the prison system in fueling the TB epidemic is clear. In 1997 notification rates among the 1.1 million incarcerated people were 4000 per 100,000 population and among civilians 81.3 per 100,000 people. The 300,000 incarcerated people who are released each year move through the vast prison system relatively quickly, spending anywhere from three months to three years in various sectors. Among patients in the civilian sector, about 25 to 30 percent of new cases report a history of prior incarceration. Prisons have served as an "epidemiological pump" for transmitting resistant strains of TB.[214] A similar phenomenon may be taking place in hospitals and clinics throughout the world, which are commonly crowded, poorly ventilated, and filled with highly-infectious TB patients. In one study performed at a large public hospital in Lima, Peru, 13 percent of the 250 patients admitted to the general medical ward had TB and 20 percent of those with TB had multi-drug resistance; 75 percent of MDR-TB patients had not been suspected of having TB at all when they entered the hospital.[215] In a study of DOTS patients in Tomsk, Russia, hospitalization was found to be the greatest risk factor for the acquisition of MDR-TB.[216] Similar findings have been noted elsewhere.[217] The situation is exacerbated by the HIV epidemic in many countries and the increased risk of nosocomial transmission in health facilities.[218] The XDR-TB epidemic in KwaZulu Natal, South Africa took place largely among HIV-infected patients who had been in congregate settings.[219]

Transmission control is possible in poor settings: an example from Lesotho[220]

Lesotho is a mountainous country located entirely within the borders of South Africa, with a population of approximately two million people. It has one of the highest reported rates of TB incidence in the world: 602 per 100,000 population in 2005, translating to over 10,000 reported cases per year.[221] Approximately 10 percent of these patients are believed to have MDR-TB and a further 20 percent mono- and poly-drug-resistant TB. At least 25 percent of the population is already infected with HIV,[222] with a TB-HIV co-infection rate estimated at between 76 and 92 percent.[223] In 2006, after the XDR-TB outbreak in the Republic of South Africa (where an estimated 70 percent of working-age men migrate for employment), the Government of Lesotho formed a partnership with Partners In Health (PIH), the

Foundation for Innovative New Diagnostics (FIND), and the WHO to create a national MDR-TB-treatment program.

Although this new MDR-TB-treatment program was envisioned as primarily outpatient, it became clear very early in the planning process that, given the high level of HIV co-infection, malnutrition, and advanced TB disease, some patients will require hospital-level care. Once this need was identified, the Ministry of Health and Social Welfare (MoHSW) approved as part of this initiative the refurbishment of an unused leprosy hospital at Bostabelo, Maseru (the capital city). Guidance for renovation was obtained from an international infection control and engineering consultant working in South Africa. PIH staff were on-site and worked closely with the MoHSW, the Ministry of Planning, contractors and the engineering consultant to create an appropriate renovation plan and see it to completion.

Prior to renovation, the facility was in reasonable physical shape, but had no adequate infection control mechanisms in place. Additionally, it lacked appropriate toilet and shower facilities, family or visiting areas, and a functional nurses' station. A sophisticated ventilation system that meets international standards was installed at Botsabelo MDR-TB hospital to minimize the risk of infection transmission and cross-infection among the medical staff and patients. The refurbishment also included the creation of a family room for patients, separation of the TB Unit from a nearby HIV Unit on the same hospital grounds, updated toilet and shower facilities, and creation of a pleasant and humane environment, including an outdoor veranda and sitting area, for patients undergoing long-term treatment. A multi-year maintenance contract was established with the company that installed the equipment.

Patients are stabilized at Botsabelo Hospital before being discharged to community-level care. This care is delivered by paid and carefully-trained treatment supporters who visit patients in their homes twice a day. These workers are provided with respirators. Patients with very advanced disease, those who are living long distances from health centers, or those who live in very crowded conditions are provided with furnished temporary accommodations near a public health center.

Transmission control should not only be limited to facilities. Where possible, patients should be treated outside of congregate settings; this way, more patients can be treated with less risk of cross-transmission. Health workers delivering care to peoples' homes, and even family members, need to be protected with properly designed and fitted respirators. Families should receive necessary assistance to ensure that patients are not living in overcrowded rooms with insufficient ventilation.

The case of Lesotho demonstrates that even in very poor countries, it is possible to have appropriate infection control. In order for this to happen, infection control needs to be a priority and assistance should be given to countries to facilitate this. The Lesotho example entailed outside resources and a fairly technologically sophisticated solution which may not be possible is many high-risk settings. However, every congregate setting where both TB and HIV are prevalent should employ a sound triage strategy coupled with the use of thoughtfully designed or renovated buildings. One such triage strategy, in use for a decade in Haiti, is described below.

Administrative and simple engineering controls make a difference: an example from Haiti

In the Partners In Health site in Cange, Haiti, most TB is treated in the community. However, when hospitalization is required, patients can be separated into one of three settings based on the status of two readily obtained tests: the AFB smear and the HIV serology. Patients who are AFB-smear negative can be hospitalized on the general medical ward regardless of HIV status. The rationale is that the TB risk for HIV patients will be low if all AFB-smear positive patients are carefully excluded. Patients who are AFB-smear positive but HIV-negative are hospitalized on an especially well-ventilated TB ward equipped with upper room ultraviolet germicidal air disinfection. Finally, patients who are both AFB-positive and HIV-positive, who cannot be reasonably hospitalized on either the general medical ward or the TB ward, are assigned to one of the few simple isolation rooms, equipped with an exhaust fan and upper room ultraviolet germicidal air disinfection. More of these simple isolation rooms provide greater flexibility and can accommodate MDR or XDR cases, but the Cange Hospital in Haiti has functioned well with just 6 isolation rooms.

This is not an ideal transmission control program, since smear-negative TB patients are known to transmit and undiagnosed TB cases may be on the general medical ward, but it is a vast improvement over the chaotic conditions of hospitalization commonplace in many parts of the world. Implementation of such a program is not resource intensive and should be considered a minimum standard for transmission control in hospitals without the resources or expertise to do what Lesotho was able to do. However, some expertise is still required in the design of general medical wards, TB wards, and simple isolation rooms to ensure that conditions are as safe for patients as staff and resources allow. As additional resources become available, programs can aspire to solutions like that implemented in Lesotho.

5 RECOMMENDATIONS

5.1 Universal treatment for drug-resistant TB within national TB control strategies—side by side with drug-susceptible disease—has to be clearly and actively promoted by multilateral and bilateral agencies, non-governmental organizations, and within countries. Universal TB treatment also must be well integrated with current HIV treatment initiatives. This will entail being more pro-active in providing technical assistance and advising countries to rapidly build capacity for MDR-TB treatment and management. The successful example of DOTS scale-up can provide guidance for this approach. Because of the high risk of TB infection in patients with HIV, TB control strategies have to be integrated with HIV treatment initiatives.

5.2 The system of international technical assistance provision is currently inadequate. It must be transformed in order to better draw on the experience of successful regional MDR-TB-treatment programs, to include the provision of on-site, long-term technical assistance, and where necessary, to involve on-site implementation teams. With appropriate funding, such an approach will ensure that countries receive timely and appropriate technical assistance that can have a direct bearing on their scale-up plans. The regional Technical Assistance Center (TAC) Consortium being developed by the Core Group of the Stop TB Partnership's MDR-TB Working Group is an important initial step to addressing this problem, but will not be sufficient on its own.

5.3 The Community/Ambulatory-based MDR-TB treatment, and where appropriate, active collaboration with private-sector laboratories and tuberculosis treatment providers, should be actively promoted as a safe means of rapidly treating the largest number of patients. Delivery systems that support this will need to be strengthened and/or built. There has to be a greater overt push for sound approaches to ambulatory care so that more patients can receive treatment at home and avoid spending extended periods of time in congregate settings. Additionally, the private sector should be engaged in all aspects of diagnosis and treatment in order to leverage national resources and optimize patient care.

5.4 Infection control to prevent transmission of TB strains has to be integrated fully into national TB-control strategies, with appropriate resources, training, implementation strategies, and monitoring. This means programmatic integration of engineering and administrative strategies to reduce of transmission; developing active triage and separation strategies for all settings; and an emphasis on protecting health workers from infection. The WHO, other multi-lateral and bilateral agencies, and international partners must increase the provision of technical assistance to strengthen transmission control, and ensure that it is a part of all funded projects.

5.5 Large global health initiatives—such as PEPFAR—and bilateral and institutional donors for global health should make improving the capacity to deliver MDR-TB treatment an important priority. The GFATM and UNITAID have done so, and others should follow this lead with their influence and resources. Programs such as PEPFAR have been phenomenally successful in delivering treatment to large numbers of patients infected with HIV. In areas with high TB-HIV co-infection, MDR-TB treatment needs to be better integrated into existing programs. Similarly, large donors should include active MDR-TB treatment delivery as a program priority.

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