The Emerging Threat of Drug-Resistant Tuberculosis in Southern Africa

Global and Local Challenges and Solutions

SUMMARY OF A JOINT WORKSHOP
by the Institute of Medicine and the Academy of Science of South Africa

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Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

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

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

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not endorse the final draft of the report before its release. The review of this report was overseen by **Melvin Worth.** Appointed by the Institute of Medicine, he was responsible for making

certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authors and the institution.

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Acronyms

ACME	Automated Classification of Medical Entities
ACR	adult clinical record
AIDS	acquired immune deficiency syndrome
AIR	Airborne Infection Research
ANRS	Agency for AIDS Research (France)
ARASA	AIDS and Rights Alliance for Southern Africa
ART	antiretroviral treatment
ARV	antiretroviral
ASADI	African Science Academy Development Initiative
ASSAf	Academy of Science of South Africa
BCG	Bacillus Calmette-Guérin vaccine
C-DOTS	Community-based Directly Observed Treatment Short Course
CAPRISA	Center for the AIDS Programme of Research in South Africa
CD4	Cluster of Differentiation 4
CDC	Centers for Disease Control and Prevention
CoSH	Church of Scotland Hospital
CSIR	Council for Scientific and Industrial Research
DNA	deoxyribonucleic acid
DOTS	Directly Observed Treatment Short Course
FIND	Foundation for Innovative New Diagnostics

GFP	green fluorescent proteins
GLC	Green Light Committee
GLI	Global Laboratory Initiative
GPS	global positioning system
HIV	human immunodeficiency virus
ICD-10	International Classification of Diseases, 10th revision
IFNg	interferon-gamma
IOM	Institute of Medicine
IRIS	immune reconstitution inflammatory syndrome
ISTC	International Standards for Tuberculosis Care
LAM	lipoarabinomannan
LIPHE	Laboratory Information for Public Health Excellence
LPA	line probe assay
LRP	luciferase reporter phage
M.tb.	*Mycobacterium tuberculosis*
MDR TB	multidrug-resistant tuberculosis
MGIT	mycobacteria growth indicator tube
MRC	Medical Research Council
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PCR	polymerase chain reaction
PETTS	Preserving Effective Tuberculosis Treatment with Second-line drugs study
QFT-GIT	QuantiFERON-TB Gold In-Tube test
RNA	ribonucleic acid
SAPiT	Starting Antiretroviral therapy at three Points in Tuberculosis therapy study
TB	tuberculosis
TCR	T cell receptor
TDR TB	totally drug-resistant tuberculosis
TF CARES	Tugela Ferry Care and Research Collaboration

UN	United Nations
UV	ultraviolet
WHO	World Health Organization
WP	work package
XDR TB	extensively drug-resistant tuberculosis

1

Introduction[1]

An estimated 2 billion people, one-third of the global population, are infected with *Mycobacterium tuberculosis (M.tb.)*, the bacterium that causes tuberculosis (TB) (Keshavjee and Seung, 2008). Spread through the air, this infectious disease kills 1.8 million people each year, or 4,500 each day (WHO, 2009a). TB is the leading killer of people with HIV, and it is also a disease of poverty—the vast majority of TB deaths occur in the developing world (WHO, 2009a). Exacerbating the devastation caused by TB is the growing threat of drug-resistant strains of the disease in many parts of the world. The development of drug resistance is a predictable, natural phenomenon that occurs when microbes adapt to survive in the presence of drug therapy (Nugent et al., 2010). Although antibiotics developed in the 1950s are effective against a large percentage of TB cases, resistance to these first-line therapies has developed over the years, resulting in the growing emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, and even totally drug-resistant (TDR) TB (see Box 1-1 for definitions).

In recognition of the grave threat posed worldwide by drug-resistant TB, in November 2008 the Institute of Medicine's (IOM's) Forum on Drug

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

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

Definitions

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

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

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

Pathways for Infection

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

Treatment

Treatment of MDR and XDR TB requires 2 years or more of daily, directly observed treatment with drugs that are less potent, more toxic, and much more expensive than those used to treat drug-susceptible TB. Despite the challenges, aggressive treatment with second-line drugs has produced successful outcomes in MDR and XDR TB patients. However, TDR TB is a growing threat. The spread of TDR TB is especially ominous as it would return the globe to the pre-antibiotic era with respect to this disease. Identifying and addressing barriers to effective and timely diagnosis and treatment of drug-resistant TB supports prevention of the further emergence of strains of TB with broad-spectrum resistance (Keshavjee and Seung, 2008).

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

Discovery, Development, and Translation held a workshop titled "Addressing the Threat of Drug-Resistant Tuberculosis: A Realistic Assessment of the Challenge," which brought together experts in drug-resistant TB and public health to speak frankly and openly about the problem.[2] That workshop led to plans for four additional workshops in countries with a high burden of drug-resistant TB. The first of these workshops, summarized in this volume, was held in Pretoria, South Africa, on March 3–4, 2010, with subsequent workshops being planned for Russia, China, and India. The workshop brought together about 65 disease experts, community leaders, policy makers, and patient advocates from South Africa, other countries in southern Africa, and the United States for 2 days of intensive discussions. The workshop was supported in part by the Doris Duke Foundation, by the Howard Hughes Medical Institute, and by the U.S. Department of State.

THE BURDEN OF DRUG-RESISTANT TB

Based on global drug resistance surveillance data, it is estimated that 3.6 percent of global TB cases, or a total of 440,000 cases, were MDR TB in 2008 (95 percent confidence interval, 390,000–510,000) (WHO, 2010a). However, a number of TB experts at this and prior workshops, noted that the available data on drug-resistant TB are inadequate and yield a gross underestimation of the true global burden of disease. Surveillance systems do not exist or are not capable of valid and reliable reporting in many developing countries where the MDR TB burden is likely to be substantial. Even the most recent global surveillance data on MDR TB do not include 79 countries—41 percent of all countries in the world (WHO, 2010a). According to the World Health Organization (WHO), although the estimate of 440,000 MDR TB cases for 2008 indicates a decrease relative to 2006 (best estimate of 489,000 cases), this change reflects the reporting of new data, changes in TB incidence, and the use of updated diagnostic methods and should not be considered reflective of a true decline in MDR TB cases (WHO, 2010a).

Data on the burden of XDR TB are even more limited because many countries lack the laboratory and infrastructure capacity necessary to test MDR TB patients routinely for susceptibility of their infecting organism to second-line drugs. (The relationship between the estimated incidence of drug-resistant TB and diagnostic tools is further discussed in Chapter 2.) Unfortunately, the drug susceptibility testing that many countries are ill-equipped to conduct is the basis for providing optimal patient care for

[2] The summary of that workshop (IOM, 2009) and the accompanying white paper (Keshavjee and Seung, 2008) provided background for and informed the development of and proceedings at the workshop summarized in this volume.

MDR and XDR TB patients. It is through such testing that physicians determine which drugs are likely to be effective against a particular drug resistance profile. A number of workshop participants noted that the vast majority of MDR and XDR TB cases are undetected and thus untreated with appropriate second-line drugs. Among the small proportion of patients who are being treated with second-line drugs, many are not taking the right drugs to effectively treat their drug resistance profile.

WORKSHOP OBJECTIVES

The objectives of the workshop were to learn from the experiences of the southern African public health community in its fight against drug-resistant TB, and to draw lessons regarding best practices and novel approaches that can be applied both within and beyond the region. The workshop was cohosted by the IOM and the Academy of Science of South Africa (ASSAf). As Roseanne Diab, executive officer of ASSAf, said in welcoming participants, the partnership between the IOM and ASSAf was particularly appropriate given ASSAf's close association with the National Academies over the past 5 years through the African Science Academy Development Initiative (ASADI). Enriqueta Bond, chair of the ASADI board, also participated in the workshop. As moderator of the closing session, Bond facilitated a discussion of the new scientific knowledge presented at the meeting and how this new evidence can inform future policy actions (see Chapter 8). Diab also assured the delegates that ASSAf would take the outcomes of the workshop forward for closer engagement with government.[3]

THE PROBLEM AND PRIORITIES

In her opening remarks, Gail Cassell, Forum co-chair, Eli Lilly and Company (retired), provided a summary of the problem and themes arising from the 2008 workshop. She noted that strains of *M.tb.* that are resistant to the drugs conventionally used to treat TB have become well established in many countries. Accurate estimates of the prevalence of MDR, XDR, and TDR TB are not possible because of a lack of laboratory capacity in many

[3] The National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health (NIH), held a meeting focused on TB research March 1–2, 2010, the 2 days prior to the IOM workshop. This meeting was co-sponsored by the Medical Research Council (MRC) of South Africa and the Howard Hughes Medical Institute and focused on TB research in drug discovery and development, diagnostics, vaccines, and biomarkers as well as the identification of opportunities for TB research collaboration in Africa. Topics and meeting participants overlapped between the NIAID and IOM meetings in South Africa, creating synergies and connections for future collaborations in the areas of TB research and policy. Appendix B of this report includes a summary of the NIAID meeting.

of these countries, but current estimates are sure to be grossly understated (see Chapter 2). Not all of the countries with the highest burden of TB participate in surveys by the WHO, the existing data are 2 to 3 years old, and many of the data are derived from modeling rather than surveillance. Thus the total number of cases of drug-resistant TB is certainly higher than the official WHO estimate (for MDR TB, 440,000 new cases in 2008 [WHO, 2010a]).

Furthermore, Cassell observed, the number of patients receiving appropriate treatment for drug-resistant TB is distressingly small. WHO estimates that worldwide only 7 percent of MDR TB patients are diagnosed (WHO, 2010a), and only about 1 percent of estimated MDR TB cases globally are enrolled in MDR TB treatment programs that use quality-assured drugs (programs approved by the Green Light Committee [GLC]). Thus even among those patients who are being treated, many are not receiving the drugs that address their drug resistance profile, which reduces the effectiveness of treatment.

Until recently, the perception was that resistant strains of TB were too weak to achieve high rates of transmission, and therefore that infection control was not the highest priority. However, new evidence indicates that human-to-human spread is more common than previously appreciated. Demonstrating infection in patients may take months, during which time they can spread the resistant organism within their households, to patients and health care workers, and to others in the community. Furthermore, the spread of TB has been greatly exacerbated by the HIV epidemic. The high prevalence of HIV threatens to make drug-resistant TB a more contagious, rapidly progressing, and highly lethal disease. Cassell suggested that, because the reality of drug-resistant TB is worse than the general perception, the urgent need for action will not be recognized until it is too late unless the perception changes to reflect the reality of the threat.

In Cassell's view, the presentations and discussions at the 2008 workshop yielded several themes:

- To address the problem of drug-resistant TB head-on, it will be important to recognize that TB strains resistant to all approved drugs are growing rapidly in number, although the number is currently unknown.
- Revolutionary and rapid changes are warranted to redress the current absence or limited availability of effective infection control strategies in health care and community settings in order to reduce the transmission of drug-resistant TB.
- The development and widespread deployment of accurate diagnostics and treatment based on drug susceptibility testing will help support the maximal effectiveness of existing drugs.

Cassell also noted that the 2008 workshop highlighted the tremendous challenge drug-resistant TB poses for drug developers. If patients with TDR TB are to be successfully treated, three to four new classes of antibiotics will be needed simultaneously. The drug discovery process has a 90 percent failure rate from target identification to regulatory approval; it has a 50 percent failure rate even in phase III trials. The average time for drug discovery and development from target identification to approval is 10 to 14 years, and probably considerably longer for TB drugs when the follow-up period is taken into account. The average cost to develop a single new drug, from discovery to approval, is more than $1.5 billion, and this does not include postlaunch surveillance for adverse events, manufacturing compliance, drug delivery, and so on. The technical and financial obstacles to the development of new drugs are so great that no one government, institution, or company has enough resources or expertise to succeed on its own. Only through the collaboration of all sectors can such challenges be overcome.

Cassell summed up by stating that the failure to acknowledge the new realities of drug-resistant TB and to act rapidly will be catastrophic for many countries. Furthermore, the volume of international travel and immigration, legal and otherwise, means that drug-resistant TB represents a grave threat to the public health of all countries, not just those in which TB is prevalent today. Members of the scientific and medical communities must communicate the realities of drug-resistant TB to the public and to policy makers, and they must translate data into policies commensurate with the magnitude of the problem. Cassell expressed the hope that this workshop summary, along with those of the three workshops to follow on this vitally important topic, will provide a base of information to help move such efforts forward.

ORGANIZATION OF THIS REPORT

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

- the incidence of drug-resistant TB in southern Africa, including the relationship between TB and HIV infection (Chapter 2);
- the molecular epidemiology of the epidemic and the challenges of monitoring and tracking the spread of drug-resistant TB (Chapter 3);

- growing understanding of the modes of transmission of drug-resistant TB and experience with infection control programs (Chapter 4);
- diagnosis of drug-resistant TB, as well as opportunities for the expansion of laboratory capacity and point-of-care diagnosis (Chapter 5);
- treatment of drug-resistant TB, including the capacity of current health systems to address the needs of TB patients, the limited numbers of patients receiving appropriate treatment, and the development of new drugs (Chapter 6);
- the devastating spread of drug-resistant TB among children and the unique challenges this group poses for prevention and treatment (Chapter 7); and
- the major viewpoints expressed at the workshop and next steps suggested by workshop participants (Chapter 8).

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

2

The Incidence of Drug-Resistant TB in Southern Africa

Key Messages

- The precise incidence of drug-resistant TB in southern Africa is currently unknown, but it has become a major health problem in the region.
- The increased incidence of MDR TB, XDR TB, and HIV infection places a tremendous burden on the region's health care systems.
- An outbreak of XDR TB in Tugela Ferry, KwaZulu-Natal Province, South Africa, reported in 2006, raised great concern about transmission in health care, community, and household settings.
- Since 2006, cases of XDR TB have occurred in all provinces of South Africa and in all surrounding countries.
- The HIV epidemic in southern Africa has exacerbated the spread and virulence of drug-resistant TB.

Gerald Friedland, Yale School of Medicine, reviewed recent data on the incidence of drug-resistant TB worldwide, stressing that these data are inadequate and underestimate the reality of the situation. Friedland noted that knowledge of the true extent of the MDR/XDR TB epidemic is hampered by a lack of in-country laboratory capacity and the inadequacies of the existing health system infrastructure.

According to the World Health Organization (WHO), the number of new TB cases globally was 9.4 million in 2008 (WHO, 2009a). The disease killed 1.8 million people in that year, or 4,500 per day. While the highest number of cases of MDR TB (estimated annual numbers of new cases) is in Asia, the greatest per capita rates are in Africa (WHO, 2010a). No accurate and up-to-date data concerning the prevalence of MDR and XDR TB are available for most African countries. However, WHO estimates that more than 75,000 new MDR TB cases will occur in Africa in 2010 (Figure 2-1). By WHO estimates, 440,000 global cases of MDR TB arose in 2008; about 5.4 percent of these cases were XDR TB. About 15 percent of all TB cases, or 1.4 million, are associated with HIV infection. The 450,000 deaths caused by HIV-associated TB represent 26 percent of TB deaths and 23 percent of HIV deaths.

After briefly examining the relationship between reported incidence rates and the diagnostic tools used, this chapter summarizes information presented at the workshop on the incidence and burden of drug-resistant TB in South Africa. It then summarizes presentations and discussions that looked more closely at the outbreak of MDR and XDR TB in KwaZulu-Natal Province and that addressed coinfection with HIV/AIDS in southern Africa.

RELATIONSHIP BETWEEN REPORTED INCIDENCE AND DIAGNOSTIC TOOLS[1]

There is evidence that differences in the reported incidence of drug-resistant TB could be attributable, at least in part, to the diagnostic tools used in particular areas. Sturm reported that since 2005, the Church of Scotland Hospital (CoSH) in Tugela Ferry has been the only health care facility in KwaZulu-Natal Province to use culture diagnostics for all possible TB cases. The Msinga subdistrict, in which CoSH is located, is also the region in the province with the highest reported number of cases of XDR TB. Yet the incidence of drug-resistant TB in the Msinga subdistrict would not be expected to differ from that in the province's other subdistricts and districts. The main difference appears to be that in the Msinga subdistrict, culture and drug susceptibility testing is done on all first contacts. Elsewhere, many patients die before a specimen is taken or the results of drug susceptibility testing become available.

Research also has found an association between the number of new cases of TB diagnosed by culture and the reported percentage of drug-resistant TB. In 2007, data on the presence of the F15/LAM4/KZN strain of

[1] This section is based on the presentation of Adriaan Willem Sturm, Nelson Mandela School of Medicine, University of KwaZulu-Natal.

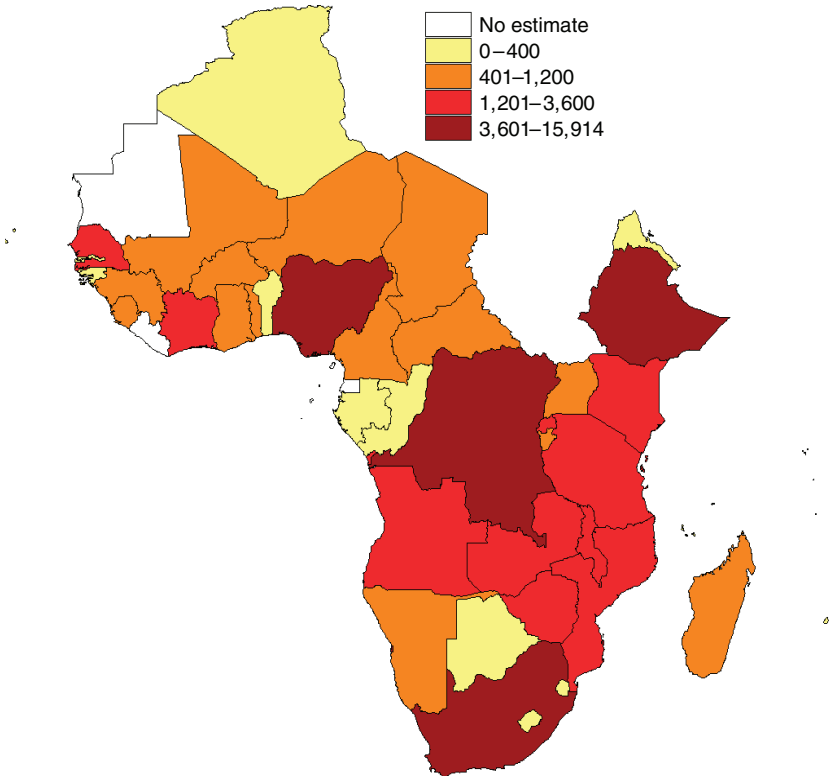

FIGURE 2-1 More than 75,000 new cases of MDR TB are estimated to have occurred in Africa in 2010.
SOURCE: Falzon et al., 2009.

M.tb. were published (Pillay and Sturm, 2007). This had been the dominant strain of MDR TB since 1994, and it had evolved into an XDR TB strain by 2001. The data suggest that the more new cases of TB are diagnosed by cultured specimens in a health district, the higher is the percentage of drug-resistant TB found in that district.[2] In addition, the districts with the highest rates of MDR and XDR TB are those that house or have a strong link with academic centers, which send greater numbers of specimens for culture relative to other facilities.

For every patient who is diagnosed with and treated for MDR TB in southern Africa, it is likely that several more are diagnosed and not treated.

[2] It was also noted that the impact of recently diagnosed cases on the proportion of drug resistance can be biased by nosocomial (health care facility-based) outbreaks.

Further, an even larger number of those infected with MDR TB are never diagnosed because diagnostic capabilities are inadequate or because these people die without ever having been seen and diagnosed through the health care system. The metaphor Friedland used—which became a theme for the workshop—is that the number of cases of drug-resistant TB seen in southern Africa represents the "ears of the hippo," a very small portion of a much larger entity that cannot be seen.

MDR AND XDR TB IN SOUTH AFRICA

According to several workshop presenters, drug-resistant TB imposes a tremendous health burden throughout southern Africa. Tomás Zimba of Mozambique's Maputo Central Hospital described efforts to control and treat MDR TB patients in the country. Zimba explained that challenges in dealing with the co-epidemics of HIV and TB in Mozambique are similar to challenges experienced throughout the southern Africa region (see Box 2-1). Most of the discussion at the workshop focused on the experience in South Africa, however, where the incidence of MDR TB now exceeds 25 cases per 100,000 people in certain areas, according to Neel Gandhi of Tugela Ferry Care and Research Collaboration (TF CARES) and Albert Einstein College of Medicine.

To illustrate the burden of drug-resistant TB in South Africa, Martie van der Walt, Medical Research Council of South Africa (MRC), described the experience of King George V Hospital, the referral center for drug-resistant TB in KwaZulu-Natal Province. From February to August 2006, 211 patients with a positive culture on admission for drug-resistant pulmonary TB began their first course of therapy for MDR TB. Most of these patients were very ill at baseline, weighing below 50 kg (110 pounds) at the start of treatment, and mortality was common. Among these 211 patients, 4 of 12 with XDR TB and 16 of 199 with MDR TB died during the first 6 months of treatment (Kvasnovsky et al., 2008).

Richard Chaisson, Center for Tuberculosis Research, The Johns Hopkins University, noted that one of the United Nations' Millennium Development Goals is to halve the amount of mortality and morbidity caused by infectious diseases relative to 1990 levels (UN, 2010). In large parts of Africa, this goal is becoming more distant for TB, according to Chaisson. In 1990, just 2 countries in Africa had a TB incidence greater than 300 per 100,000 population. This number had risen to 23 countries by 2005; in that same year, 6 countries had an incidence greater than 500 per 100,000 population, and 2 had an incidence greater than 1,000 per 100,000.

According to Chaisson, these figures translate into unmanageable numbers of patients presenting to the health care system. From 2005 to 2008,

BOX 2-1
Problems of Dealing with Drug-Resistant TB in Mozambique[a]

The experience of Mozambique illustrates the problems facing many areas of southern Africa in dealing with the epidemic of drug-resistant TB, according to Zimba. Almost constant warfare during the three decades from 1965 to 1994 created severe disruptions in the country's health care system, just as political instability elsewhere in southern Africa has hampered health care delivery. Only 45 percent of the population has access to health care. Of Mozambique's 22 million people, 12.5 percent of adults are estimated to be infected with HIV (UNAIDS, 2008) (see the discussion of TB and HIV coinfection later in this chapter).

Southern Africa has adopted the WHO guidelines for diagnosis and treatment of TB, using microscopy as the standard for diagnosis and follow-up of TB cases. In Mozambique, the national TB control program was launched in 1977. The country has seen some success in expanding Directly Observed Treatment Short course (DOTS) to the community (community-based DOTS [C-DOTS]) and improving access for people in underserved areas (USAID, 2009). However, drug resistance has proven to be a great problem in the country.

There are 255 laboratories in Mozambique that can diagnose TB using microscopy. But there is only one National Reference Laboratory that conducts culture and drug susceptibility testing for first-line anti-TB drugs. Samples for diagnosis from the district and provincial laboratories are transported to the National Reference Laboratory in the capital city of Maputo. Three months can pass before those laboratories receive feedback and the patient is informed of the diagnosis.

A 1998–1999 nationwide survey of 709 culture-positive TB cases in Mozambique found that 3.4 percent of new cases were MDR (Mac-Arthur Jr et al., 2001). Drug resistance was more common among those with a history of prior treatment. A 2002–2003 report from the Mozambique national TB program similarly indicated that 3 percent of new TB cases were MDR (Nunes et al., 2005). In 111 samples from HIV-infected patients, 9 percent were found to have MDR TB. About 6 percent of new TB cases in patients infected with HIV, as well as 16 percent of TB cases among previously treated patients, were MDR.

In 2009 there were an estimated 1,700 cases of MDR TB among notified pulmonary TB cases in Mozambique (WHO, Global Tuberculosis Control 2010; Annex 3). According to Zimba, however, it is known that the Mozambique national TB program has in the past seriously underestimated the numbers of new cases of MDR TB. The actual number of cases of primary MDR TB in Mozambique remains unknown.

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[a]This box is based on the presentation of Tomás Zimba, Maputo Central Hospital, Mozambique.

the largest hospital in South Africa, Chris Hani Baragwanath Hospital in Soweto, had between 6,500 and 6,800 new TB admissions per year. Inpatient mortality was 18 percent at 2 weeks, or about 1,200 deaths per year. Nine percent of those dying of TB had MDR TB, representing about 110 MDR TB deaths per year.

Estimating the contribution of TB to mortality in South Africa is difficult. This issue is addressed in Box 2-2.

Van der Walt presented data from the Preserving Effective TB Treatment with Second-line drugs (PETTS) study, which is a prospective cohort study of approximately 1,800 MDR TB patients in nine countries at 27 clinical sites and 17 laboratories. The objective of the study is to determine the frequency, timing, and risk factors for acquired resistance to second-line drugs in diverse MDR TB control programs. The study also is seeking to determine the effect of acquired second-line resistance on patient outcomes. Four provinces of South Africa, including KwaZulu-Natal, are participating in this study. A follow-up of the patients enrolled in the study has been performed every month to collect a culture and update a database used to monitor acquisition of resistance.

Van der Walt noted that cross-resistance[3] to second-line drugs is especially problematic in South Africa. MDR TB patients in South Africa are three times more likely than their counterparts from other PETTS sites/countries to have cross-resistance to all the injectable drugs for TB at baseline. The PETTS study has shown that XDR TB was present at baseline in 10.3 percent of cases in 2005 (Kvasnovsky et al., 2009), while a 2005–2006 analysis of the PETTS cohort found that 1 percent of drug-resistant TB cases were TDR.[4]

OUTBREAK OF MDR AND XDR TB IN KWAZULU-NATAL PROVINCE[5]

KwaZulu-Natal Province, which comprises 11 health districts divided into a number of subdistricts, has a population of about 9.6 million people. The province has an enormous TB burden, and MDR and XDR TB strains are present throughout.

[3] The development of resistance to first-line drugs can lead to resistance to second-line drugs because of the similar molecular basis of the first- and second-line drugs (Maus et al., 2005).

[4] The warning signs of TDR TB include low cure rates, high mortality rates, and a very slow rate of conversion that cannot be attributed to HIV alone. The management of XDR and TDR TB raises many ethical dilemmas, van der Walt observed. Complex questions include whether such patients should be subjected to particular kinds of infection control, up to permanent isolation.

[5] This section is based on the presentation of Neel Gandhi, Tugela Ferry Care and Research Collaboration (TF CARES) and Albert Einstein College of Medicine.

BOX 2-2
Estimating the Contribution of TB to Mortality in South Africa[a]

According to Tuoane-Nkhasi, information on the contribution of TB to mortality in South Africa can be obtained from the country's civil registration system based on registered deaths in the country. A medical practitioner must indicate the cause of death on the death notification form. Methods for analyzing cause-of-death data include the following:

- Cause of death is classified using the coding of the International Classification of Diseases, 10th revision (ICD-10). Causes of deaths classified as MDR TB and XDR TB have been included in the South African death notification system only since 2006.
- The underlying cause of death is derived automatically using the Automated Classification of Medical Entities (ACME). Causes that cannot be derived automatically are determined by experienced ICD-10 coders trained in deriving the underlying causes of death.
- The causes of death are ranked according to their frequency. In the ranking process, deaths due to symptoms, signs, and abnormal clinical findings not elsewhere classified are excluded since this group includes ill-defined conditions for which no classifiable diagnosis is recorded.

About 85 percent of all deaths in the country are registered. The levels and trends of registered deaths from 1997 to 2007 in South Africa show that about 10 percent of deaths were among children aged 0–4. The majority of these deaths occurred during the first year in the postneonatal period. The annual number of child deaths increased consistently from 1997 to 2006, with a slight decrease in 2007. There were more male than female deaths among children, and more infant deaths occurred in KwaZulu-Natal and Gauteng than in the other provinces. In 2007, 11 death notification forms indicated that MDR or XDR TB was the underlying cause of death among children aged 0–4. Of the 10 leading underlying causes of death in that age group, TB was ranked sixth, accounting for 2.5 percent of deaths. Respiratory and cardiovascular disorders specific to the perinatal period were indicated as the leading cause of death.

For both males and females aged 15–64, TB has been the leading underlying cause of death in South Africa since 1997. Since 2002, about 12 percent of all deaths in the country have been caused by respiratory TB, but the death notification forms usually do not specify whether this diagnosis was confirmed either bacteriologically or histologically. In 2006,

continued

BOX 2-2 Continued

the underlying cause of death among 607 people was identified as MDR TB; in 2007, this number decreased slightly to 597.

There are a number of sources of uncertainty in these statistics:

- underregistration of deaths, particularly among children and in rural areas;
- late registration of deaths;
- content errors and omissions;
- misreporting and insufficient reporting of causes of death on death notification forms;
- the time lag between the actual event, registration, and the publication of statistics; and
- limited information for in-depth analysis of mortality.

Information from South Africa's civil registration system is useful in providing numbers of deaths and their causes each year, but the statistics produced depend on the quality of the data input to the system. According to Tuoane-Nkhasi, concerted efforts of the public, the Department of Home Affairs, the Department of Health, and Statistics South Africa are required to improve these data.

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[a]This box is based on the presentation of Maletela Tuoane-Nkhasi, Statistics South Africa.

In 2006, a group led by Gandhi reported on 53 cases of XDR TB in Tugela Ferry in the Msinga subdistrict, which has a population of about 200,000 traditional Zulu people living largely in poverty (Gandhi et al., 2006). In June 2005, within a few months of the discovery of the first XDR TB case in Tugela Ferry, 5 other facilities in KwaZulu-Natal had cases. By December 2005, a further 18 facilities had reported cases; by June 2006, the total was 32 facilities; by December 2006, the total was 39; and by March 2007, it was 42. The latest estimates are that more than 60 facilities in KwaZulu-Natal have reported at least one case of XDR TB. In addition, every province in South Africa and all neighboring countries have reported cases of XDR TB.

MDR TB has undergone a similarly dramatic increase in KwaZulu-Natal Province. Gandhi noted that there were 2,654 cases of MDR TB in 2007 alone, representing a prevalence of 26 cases per 100,000 population.

According to Friedland, given the widespread distribution and continuing appearance of new cases of both MDR and XDR TB as of 2010, the situation is more appropriately defined as an epidemic than as a series of outbreaks.

The rapid increase in drug-resistant TB in KwaZulu-Natal Province was not consistent with the relatively small numbers of MDR TB cases among patients who had no prior history of treatment according to a 2001–2002 survey of drug-resistant TB in South Africa, the last survey conducted in the province prior to the outbreak of drug-resistant TB in 2006 (Weyer et al., 2004). That survey found, for example, that just 1.7 percent of patients with no history of prior TB treatment in KwaZulu-Natal Province had MDR TB. The outbreak of XDR TB in the province therefore raised the question of whether the 2001–2002 data underrepresented the extent of MDR TB infection.

The study reported by Gandhi, which received international attention, found that XDR TB in that population was highly fatal. All but one of the patients died (98 percent mortality), with a median survival of just 16 days from sputum collection.[6] The study revealed high clustering rates, with 85 percent having genetically similar TB strains. The study also found that half of the patients had never been previously treated for TB, and more than 95 percent of patients with XDR TB had never been treated for MDR TB. Thus, these patients had not had the long-term exposure to second-line drugs that would be expected to lead to resistance. The study authors concluded that the transmission of XDR TB strains from person to person was likely.[7]

More recently, high levels of mortality have been confirmed in a much larger group of patients from Tugela Ferry with coinfection rates of HIV with MDR and XDR TB of 90 and 98 percent, respectively (Gandhi et al., 2010). MDR TB 1-year mortality was 71 percent, with a median survival of 60 days; XDR TB 1-year mortality was 83 percent, with a median survival of 28.5 days. Mortality was highest in the 30 days after sputum collection—prior to diagnosis of drug-resistant TB by conventional culture and drug susceptibility testing methods (Gandhi et al., 2010). Because these methods typically take 6–8 weeks to yield a result, the majority of drug-resistant TB patients in this high HIV-prevalence setting die before they are diagnosed

[6] This severe mortality may be partially explained by the fact that all the patients whose HIV status was known were HIV-positive.

[7] Transmission of drug-resistant strains has been seen in the past, when numerous outbreaks of MDR TB occurred in congregate settings in the early 1990s. As in more recent outbreaks, HIV coinfection was extremely high in the outbreaks of the 1990s (Wells et al., 2007). The prior outbreaks, too, had a very high mortality rate, ranging from 72 to 98 percent, with most deaths occurring within 4 to 8 weeks of collection of sputum culture.

and treated.[8] Gandhi suggested that a comprehensive response to the high mortality seen in MDR and XDR TB patients should include

- prevention of the development of drug resistance through the expansion of DOTS and infection control strategies;
- implementation of rapid diagnostics to reduce the time to diagnosis from 6–8 weeks to 1–10 days and use of intensified case finding to locate patients at earlier stages of disease; and
- empiric use of second-line drugs in HIV-infected patients suspected of MDR or XDR TB, as well as integration of antiretroviral therapy into MDR and XDR TB treatment programs to facilitate early and widespread use.

Recent studies have demonstrated that survival decreases with an increasing degree of drug resistance. MDR TB patients with resistance to only isoniazid and rifampicin do better than those with additional first-line drug resistance. Likewise, XDR TB patients with resistance to only four or five drugs do better than those with resistance to all six drugs tested. Furthermore, resistance is increasing. At Tugela Ferry, the proportion of XDR TB isolates with resistance to six drugs increased steadily and consistently over a 2-year period, with a six-drug pattern being identified among more than 95 percent of patients by 2007 (Moll et al., 2007). When data from a different study performed in 2008–2009 are added, the six-drug phenotype constitutes 100 percent of the XDR TB strains. When the 2008–2009 group was tested for additional resistance to ethionamide and capreomycin, the vast majority of these XDR TB strains were found to be resistant not only to the six drugs previously identified but to all eight drugs tested. Further studies are required to understand the correlates of survival among those patients whose infection is resistant to eight drugs.

Other investigators have found high levels of resistance in the XDR TB seen in KwaZulu-Natal Province (Pillay and Sturm, 2007). Of 52 isolates of the F15/LAM4/KZN XDR TB strains, 100 percent were found to have mutations in the *rss* gene conferring resistance to streptomycin, kanamycin, amikacin, and capreomycin. In addition, 69 percent were found to have mutations in the *pcnA* gene conferring resistance to pyrazinamide. Most of the isolates were resistant to isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, kanamycin, amikacin, capreomycin, ofloxacin, and ethionamide. That level of resistance leaves very few antibiotics that can be used to treat the disease.

[8] WHO and International Standards for Tuberculosis Care (ISTC) guidelines recommend that an empiric regimen of second-line drugs should be used in suspected MDR TB patients (TBCTA, 2009).

TB AND HIV COINFECTION IN SOUTHERN AFRICA[9]

TB has become epidemic in the setting of a generalized HIV epidemic in southern Africa, and HIV infection has had a strong influence on the increased numbers of drug-resistant TB cases in the region. As several workshop participants emphasized, where there are high rates of HIV coinfection, the potential exists for the explosive spread of drug-resistant TB. Thus a theme of the workshop presentations and discussions was that understanding the dynamics of the TB epidemic in southern Africa requires knowledge of the ongoing HIV epidemic. Chaisson offered the following metaphor to illustrate the relationship between TB and HIV: if the TB cases seen in hospitals are the tip of an iceberg of TB infection, then the iceberg is floating in an ocean of HIV.

Drug-resistant TB in the context of southern Africa's HIV epidemic raises many important clinical issues, including

- the lack of diagnostic capacity to detect TB and perform drug susceptibility testing, with many patients dying before the extent of their drug resistance can be assessed;
- infection control;
- TB infections that test negative on sputum smears and extrapulmonary TB;
- the availability of treatments, including second-line drugs;
- drug toxicity;
- treatment with antiretrovirals and the challenges of managing multiple medications and their interactions; and
- immune reconstitution inflammatory syndrome (IRIS).[10]

Chaisson noted that default rates (the rate at which patients cease to continue prescribed treatments) in South Africa have been up to 20 percent of patients on second-line anti-TB treatment, with no difference between HIV-positive and HIV-negative groups. A retrospective study of 2,070 patients on standardized MDR TB treatment in nine provinces of South Africa between 2000 and 2004 revealed that patients coinfected with HIV were three times more likely to die than patients without HIV (van der Walt et al., 2007). According to Chaisson, it is not known whether the deaths were due to poor treatment outcomes, including the development of XDR TB, or the failure to receive appropriate therapy.

[9] This section is based on the presentation of Chaisson.

[10] IRIS is an inflammatory response in HIV-infected patients that is triggered by the initiation or reinitiation of antiretroviral therapy or a change to a more active antiretroviral therapy regimen.

Looking at South Africa in particular, Chaisson noted that it has made remarkable progress in extending antiretroviral therapy among its population. The current challenge is to meet the global standard of care for providing antiretroviral therapy to TB patients coinfected with HIV, as it has been shown that survival is dramatically improved when antiretrovirals are given during rather than after TB therapy (Abdool Karim et al., 2010).

3

Surveillance and Tracking of Drug-Resistant TB

Key Messages

- Improved case finding requires regular, comprehensive global surveillance for drug-resistant TB, as well as improved planning and evaluation.
- A comprehensive HIV clinical record integrated with a simple TB screening questionnaire and routine HIV care elements can lead to improved tracking and be beneficial for quality and continuity of care.
- A strengthened information infrastructure for TB laboratories could support both the detection and treatment of drug-resistant TB.

Systematic surveillance and tracking of drug-resistant TB helps in understanding the overall burden of the disease and can inform research and practice in diagnosis, treatment, and infection control. Speakers at the workshop described various approaches being taken to advance the tracking of drug-resistant TB in South Africa. This chapter summarizes those presentations. The first section reviews the use of genetic fingerprinting methodologies to understand the genotype and physiology of the various drug-resistant TB strains found in South Africa. The second section describes a clinical screening tool that has been developed to intensify TB case finding. The final section addresses the need for information systems to increase laboratory capacity.

GENETIC ANALYSIS OF DRUG-RESISTANT STRAINS[1]

Emergence of Beijing Strain

In South Africa and most of the world, three standardized methods are being adopted to classify TB strains by genotype. Warren and his colleagues have been applying these methods in numerous settings throughout South Africa to elucidate the mechanisms driving the drug-resistant TB epidemic in different regions.

An early study revealed a complex population structure of drug-resistant strains in the Western Cape Province of South Africa, with some strain genotypes being highly dominant (i.e., Beijing, LAM, and Low Copy Clade) (Streicher et al., 2001). A more detailed examination of this data set demonstrated the evolutionary history of an outbreak strain (DRF 150) (Victor et al., 2007). The study found that isoniazid resistance occurred first, followed by streptomycin resistance. With the subsequent introduction of rifampicin, many of these strains acquired rifampicin resistance on different occasions. Most important, the strains that had acquired additional mutations conferring resistance to ethambutol and pyrazinamide were the most dominant.

At about the same time, a preliminary study found that the Beijing/R220 strain was widespread in the Western Cape (Johnson et al., 2006). Warren and his colleagues conducted a follow-up study of the drug-resistant strains in the Western Cape to determine whether there had been a change in the drug-resistant TB epidemic from 2002–2003 to 2005–2006 (Johnson et al., 2010). The number of identified cases was found to be doubling approximately every 8 years. Of significant concern was their observation that 90 percent of all drug-resistant cases tested were smear positive and thus indicative of being highly infectious, leading to extensive transmission. Stratification of the data by drug resistance pattern showed that the observed increase was strongly driven by MDR TB. The Beijing/R220 strain contributed to 42 percent of this increase, with a doubling time of 2.4 years (Johnson et al., 2010).

A third outbreak strain was identified in an urban setting in Cape Town, South Africa (van Rie et al., 1999). This strain (strain U) is a member of the Beijing genotype and showed a doubling time of approximately 5 years. Thus, as in KwaZulu-Natal (see Chapter 2), the increase in drug-resistant TB in the Western Cape Province was driven by a small number of specific strains. The implication is that the current TB control program is unable to prevent ongoing transmission of these highly resistant strains.

Studies from the Eastern Cape are limited. An initial study showed the spread of an atypical Beijing strain (Strauss et al., 2008). This finding was

[1] This section is based on the presentation of Rob Warren, Stellenbosch University.

surprising, since it had been assumed that the strain was not spreading (as was observed in the Western Cape). According to Warren, the collation of genotyping data supports the notion that the population structure of drug-resistant strains differs among the provinces of South Africa. However, insufficient data are available from the Northern Cape and Limpopo Provinces, as well as Namibia and Botswana, with which to make accurate assessments of the population structure of drug-resistant TB in southern Africa.

Genetic Analysis of XDR TB

Since the outbreak at Tugela Ferry was disclosed, XDR TB has been identified in all the provinces of South Africa, particularly in the Western Cape, which has a very high incidence of drug-resistant TB. DNA fingerprinting of MDR and XDR TB strains has shown that the main outbreak strains seen in the Western Cape (discussed above) are those that evolve into the pre-XDR and XDR group. At first glance, the DNA fingerprinting data suggest ongoing transmission of pre-XDR[2] and XDR TB—a situation analogous to the Tugela Ferry outbreak. Warren pointed out, however, that genetic fingerprinting has certain limitations, and not all interpretations are necessarily correct. The discriminatory power of the DNA fingerprinting method can be improved by sequencing of the target genes conferring drug resistance. Using this approach, Warren and his colleagues showed that MDR TB strains with associated pyrazinamide and ethambutol resistance are spreading and that most XDR TB is acquired. According to Warren, these findings clearly indicate that patients with MDR TB are not being managed aggressively enough. This conclusion contrasts with the case of the Tugela Ferry outbreak, for which ongoing transmission due to poor infection control (hospital and community) was identified.

Strains with isoniazid resistance and associated cross-resistance to ethionamide have become the dominant population in the XDR TB group. This may be explained by the fact that patients with MDR TB received a standardized treatment regimen that included ethambutol, pyrazinamide, ethionamide, ofloxacin, and amikacin or kanamycin. Only two of these drugs would have been active, given that MDR TB was found to be strongly associated with resistance to ethambutol and pyrazinamide and that cross-resistance to ethionamide was common in the Western and Eastern Cape Provinces. Warren suggested that cross-resistance between isoniazid and

[2] Pre-XDR TB refers to MDR TB plus one-half of the resistance equation for XDR TB. As defined in Chapter 1 (Box 1-1), XDR TB is resistant to the same drugs as MDR TB (isoniazid and rifampicin), as well as any fluoroquinolone (levofloxacin, moxifloxacin, or ofloxacin) and at least one second-line injectable drug (kanamycin, amikacin, or capreomycin). Pre-XDR TB is MDR TB that displays resistance to one of the fluoroquinolones or a second-line injectable drug.

ethionamide would be easily identified using the line probe assay (LPA) diagnostic test and that this information (which already exists) should be made available to expert MDR TB clinicians.

Warren concluded by noting that XDR TB is a major component of the drug-resistant TB epidemic in the Eastern Cape Province. In the MDR TB group, the atypical Beijing strain is seen in only 26 percent of the population, and is strongly selected in the pre-XDR and XDR TB population (accounting for approximately 90 percent of cases). This selection is driven by isoniazid/ethionamide cross-resistance and the associated standardized treatment regimen (see above). Of further concern is the significant association between the atypical Beijing strain and aminoglycocide resistance in pre-XDR and XDR TB strains in the Eastern Cape. In these strains, aminoglycoside resistance occurs through a mutation in the *rrs* gene. This mutation also leads to capreomycin resistance, thereby potentially compromising the XDR TB treatment regimen. Finally, Warren showed that pre-XDR and XDR TB strains are moving between provinces, emphasizing the need for rigorous TB control in both the Eastern and Western Capes.

INTENSIFIED TB CASE FINDING[3]

According to Verkuijl, the South African national guidelines recommend a three-tiered approach to establishing collaborative TB–HIV activities. First is to establish coordinating bodies to organize surveillance, planning, monitoring, and evaluation. Second is to decrease the burden of TB in people living with HIV/AIDS through the internationally recommended "three I's" strategy: intensified TB case finding, isoniazid preventive therapy, and infection control. Third is to decrease the burden of HIV in TB patients through HIV counseling and testing for TB patients, HIV prevention, cotrimoxazole preventive therapy, enrollment of coinfected patients into HIV care and support, and access to antiretroviral therapy for coinfected patients.

Verkuijl's presentation focused on the first of the "three I's": intensified TB case finding through a method of TB symptom screening that was developed in the Eastern Cape. The identified need to shift from an acute to a continuing care model led to the development of a comprehensive HIV adult clinical record (ACR) through a partnership between the Department of Health and several nongovernmental organizations. The objective was to achieve uniformity in recording patient data and to help site staff track patients' clinical progress and social support needs. A four-page version was piloted, and a revised eight-page record is now being implemented. Staff are being trained and mentored regularly to ensure the correct use of the

[3] This section is based on the presentation of Sabine Verkuijl, International Center for AIDS Care and Treatment Programs, Mailman School of Public Health, Columbia University.

ACR. A six-question TB screening questionnaire is integrated into the ACR in such a way that clinicians can record information on TB symptoms at every visit. The six questions concern

- weight loss (unintended),
- cough for more than 2 weeks (including haemoptysis),
- night sweats for more than 2 weeks,
- fever for more than 2 weeks,
- swollen lymph nodes, and
- respiratory symptoms and/or chest pains.

These questions should be asked at each visit, and if the conditions are present, boxes in the ACR should be ticked accordingly. Patients presenting with any of the TB symptoms should be further investigated to confirm or rule out active pulmonary or extrapulmonary TB. Patients without symptoms are eligible for isoniazid preventive therapy. The ACR also includes room for findings from the physical examination and sputum results (two smears and one culture), as well as other results, including those of x-rays, needle aspirate biopsies, and drug susceptibility testing.

Currently, the ACR is being revised to accommodate the new guidelines for antiretroviral therapy. The record complements existing monitoring and evaluation systems; in addition, an electronic database, mirroring the ACR, is currently being piloted in East London. This database will provide a link with the District Health Information System, the national monitoring and evaluation system.

The ACR addresses all the steps that need to be taken during the TB screening process, from symptom screening to management of patients with TB. If a patient has positive symptoms upon screening, the ACR indicates that investigations need to be done. If TB is diagnosed, the ACR indicates that TB treatment and cotrimoxazole prophylactic treatment need to be started.

The ACR captures information from each clinical visit. For example, it includes entries for the clinician to mark if a patient is on TB treatment at the time of that visit. This feature helps prompt the clinician to monitor the clinical response to TB treatment and can assist in identifying patients not responding to first-line treatment. This integrated screening tool provides for quality and continuity of care through

- screening for active TB at every visit for patients enrolled in HIV care (who are not yet eligible for antiretroviral therapy) and for patients on antiretroviral therapy,
- early diagnosis and treatment of active TB,
- identification of TB-associated IRIS,

- monitoring of TB investigation results and TB treatment progress and outcomes,
- improved practical integration of HIV and TB programs, and
- identification of patients eligible for isoniazid preventive therapy.

In addition, the tool benefits prevention and early diagnosis of drug-resistant TB by monitoring the clinical progress of patients on first-line TB treatment, assisting with the identification of TB patients with suspected drug resistance, and monitoring breakthrough TB disease in patients on isoniazid preventive therapy. It allows for the monitoring and evaluation of the entire TB screening process using standard pre-antiretroviral therapy and antiretroviral therapy registers. The indicators that can be collected from the ACR include, for example:

- proportion of patients screened (among those enrolled in HIV or antiretroviral therapy care),
- proportion of patients who screened positive (among those screened),
- proportion of patients with investigations performed (among those screening positive),
- proportion of patients diagnosed with active TB (among those screening positive),
- proportion of patients starting on TB treatment (among those diagnosed with active TB), and
- proportion of patients starting on cotrimoxazole (among those diagnosed with active TB).

To illustrate the effectiveness of the tool, the proportion of patients in the Qaukeni Local Service Area (O.R. Tambo District) who were screened improved from less than 50 percent to more than 76 percent after use of the tool began. The proportion of new TB cases diagnosed among patients newly enrolling in HIV care gradually increased from 1.6 to 5.8 percent. Similarly, the proportion of patients with TB among the cohorts of patients starting HIV care, which includes patients already on TB treatment upon enrollment in HIV care, steadily increased from 4.5 to just over 20 percent.

According to Verkuijl, lessons learned include the following:

- A TB screening questionnaire integrated into a comprehensive HIV clinical record reminds clinicians to "think TB" at all times.
- The ACR facilitates effective monitoring of TB screening among HIV patients at enrollment and subsequent visits.
- The ACR facilitates proactive TB screening, leading to increased TB case finding.

- The TB screening questionnaire can be used to monitor the clinical progress of TB patients on first-line regimens and identify patients with suspected drug-resistant TB.
- Routine TB screening is critical in identifying breakthrough TB disease in patients on isoniazid preventive therapy.
- The ACR can be linked with the District Health Information System through an electronic database.

Verkuijl offered the following recommendations:

- TB and HIV should be managed by a comprehensively trained health care provider ("under one ceiling").
- TB and HIV clinical records should be kept together for improved clinical management.
- The electronic ACR database should be finalized based on the results of the current pilots for adoption in the Eastern Cape to ensure that the link with the District Health Information System is available in all facilities.

INFORMATION SYSTEMS TO ENHANCE LABORATORY CAPACITY[4]

The World Health Organization (WHO) Global Laboratory Initiative (GLI) has identified the need for an "urgent and massive scale-up of laboratory services" (WHO, 2010b). More specifically, it has stated that "the critical lack of TB laboratory capacity constitutes a global crisis, requiring a paradigm shift in providing laboratory policy guidance, quality assurance, and knowledge creation within a global and integrated laboratory network."

Nordenberg identified some of the issues related to the urgent information needs of TB laboratories:

- Laboratory capacity is desperately insufficient.
- Laboratory capacity building efforts rarely take into account the development of data and information management capabilities.
- Laboratory services are microbe- or specimen-focused, in contrast to clinical and population health programs.
- The sensitivity and specificity profiles of emerging diagnostics may differ from those of existing diagnostics, rendering surveillance trend estimates difficult to interpret.

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

- There is a critical need to integrate laboratory information systems with those of clinical and population health programs.
- There is a critical need as well for information systems to track operational activities focused on drug-susceptible and drug-resistant TB, such as infection control programs and drug supply chains, as well as to support performance improvement programs.
- Information services and products must be thought of as a supply chain that moves information in a highly structured way. Building information supply chains is work-intensive, but their public health impact could be enormous.

These issues represent a large-scale problem that requires a large-scale solution. Unfortunately, according to Nordenberg, solutions that support capacity building for laboratory information management across many countries and thousands of laboratories have not been available.

The GLI addresses data and information needs in terms of TB diagnostics (WHO, 2010b). Information derived from diagnostics needs to be delivered to the right places at the right times. Nordenberg noted that, although WHO's New Diagnostics Working Group of the Stop TB Partnership has developed an effective workflow model for the development of new diagnostic tests to support TB control programs globally, this model lacks reference to the necessary data and information supply chains that are critical to optimize the public health impact of emerging TB diagnostics (WHO, 2009b). This omission represents a major information chasm that requires urgent attention, according to Nordenberg.

Several years ago, the Association of Public Health Laboratories and the Public Health Informatics Institute identified 16 essential business processes for U.S. public health laboratories (Association of Public Health Laboratories and Public Health Informatics Institute, 2003). These unique functions highlight the different workflows that exist in the laboratory as opposed to the clinic or public health program office. Therefore, laboratory information systems that support these unique workflows will be most effective in supporting the laboratory's public health mission. Given that the laboratory is the source for much of the information used to control TB and MDR and XDR TB, as well as other diseases, laboratory information management systems are central to any health care system. Regardless of what scientific or diagnostic work is being done in laboratories, the data and information they produce must be linked to clinical and public health programs.

Laboratories need to manage data and information more systematically, said Nordenberg. Public health programs require at least three critical supply chains to be successful: people, products, and information. The

information supply chain is complex. Information must be viewed as an intervention, not a technology, as it drives the right therapy to the right patient, prevents the emergence of drug-resistant strains, enables patients to be treated more cost-effectively, and improves operations. A disciplined approach to data and information provisioning will facilitate measurement of the quality and impact of the data and information. Such an approach will also enable performance improvement of the information supply chain to optimize public health impact.

Analyzing information gaps can be a means to achieve several important objectives:

- designing the model information supply chain for control of TB/drug-resistant TB;
- assessing gaps within one or more communities;
- quantifying the impact of the gaps in terms of treatment timeliness, treatment appropriateness, the drug supply chain, and so on;
- calculating the cost of the gaps in terms of the spread of disease, the emergence of resistance, morbidity and mortality, and other negative outcomes; and
- developing information supply chains for drug-sensitive and drug-resistant TB at the community, district, provincial, and national levels.

The building of laboratory information management capacity globally is being undertaken through participation in public–private partnerships. An example is the Laboratory Information for Public Health Excellence (LIPHE) program based at the CDC Foundation. This program is a growing collaboration that includes the Centers for Disease Control and Prevention (CDC), Eli Lilly, Fondation Merieux, the GLI, and WHO. LIPHE has created a set of processes and a framework designed to enable laboratories to work together to define best practices. The platform may vary, but standardization of the information is encouraged to facilitate sharing across communities, regions, and countries. Currently, however, no efforts are under way to develop an information supply chain model for TB.

According to Nordenberg, all the components needed to develop a robust model for information flow in TB control programs are available. Information products can be identified based on the questions that need to be answered to support TB control programs. Information supply chains can then be designed to deliver these information products. Once TB information supply chains have been designed and implemented, it will be possible to develop models that can quantify the public health impact of suboptimal information supply chains (e.g., data on missed diagnoses,

delayed treatments, propagation of drug-resistant TB, increased hospitalizations, increased cost of drugs, and increased mortality). These data should help make the development of effective TB information supply chains a priority along with the development of new therapeutics, new diagnostics, improved infection control practices, and other critical components of an effective TB control program.

4

Transmission and Infection Control

Key Messages

- Experiments have demonstrated that MDR TB is transmitted through the air from individual to individual.
- The outbreak of XDR TB in Tugela Ferry demonstrated the potential for XDR TB to be transmitted in a health care setting.
- The infection control program in Tugela Ferry has demonstrated that transmission can be substantially reduced through administrative, environmental, and personal protection controls.
- By improving cure rates and decreasing default rates, community-based care and treatment in Tugela Ferry has likely reduced the transmission of drug-susceptible and drug-resistant TB.
- Health care workers are at particular risk for contracting TB and need much higher levels of education and environmental protection than they currently receive.
- Household contacts of active TB cases, vulnerable populations in poorly ventilated congregate settings (such as prisons and drug treatment programs), and certain vocational workers, particularly migrant workers and miners, also are at a high risk of contracting TB. Special efforts are warranted to reach and protect such groups.

Drug resistance arises through either acquired resistance or transmission. As discussed in Chapter 3, there is evidence that transmission plays an important role in the development of MDR TB. Of the 511,000 individuals estimated by the World Health Organization (WHO) to have MDR TB in 2007, 57 percent had never previously been treated for TB and thus could not have acquired resistance from prior treatment. The remaining 43 percent were retreatment cases; however, it is known that reinfection through transmission also occurs in this population. This chapter reviews what is known about the transmissibility of TB from person to person, as well as experience with infection control programs to reduce or eliminate transmission. Overall, many presenters emphasized that a number of fundamental questions about transmission remain unanswered and that, if infection control is to be successful, much more research and evaluation of these issues will be necessary.

TRANSMISSIBILITY OF TB[1]

According to Mphahlele, experiments done for more than half a century have demonstrated great variability in the infectivity of patients with TB. Guinea pigs have often been used in these studies because they are highly susceptible to infection by human *M.tb.*, more so than mice and rabbits and perhaps as much as AIDS patients; in addition, their immunological response is similar to that of humans.

Beginning in the 1950s, Riley and colleagues exposed guinea pigs to untreated TB patients to measure the infectiousness of *M.tb*. Of the 156 guinea pigs, 71 were found to be infected at the end of the 2-year study, demonstrating the ease of transmission in the absence of direct contact (Riley et al., 1959). Recent studies conducted at the Airborne Infection Research (AIR) facility in Witbank, Mpumalanga Province, South Africa, examined both the infectivity of MDR TB and the question of whether transmission can be interrupted. The infectivity experiment, which involved 360 guinea pigs exposed to 26 MDR TB patients, revealed that some infecting MDR and XDR TB strains may be immunogenic but not sufficiently virulent to cause progressive disease in guinea pigs and that guinea pigs may be clearing TB infection. In that study, 75 percent of the guinea pigs became infected, and of those strains recovered from the guinea pigs, only two matched the strains of patients. Despite large positive skin test results, however, many of the guinea pigs showed no histological evidence of residual TB infection, and the burden of TB infection was higher among recent large skin test converters than among more remote converters. Many of the guinea pigs

[1] This section is based on the presentation by Matsie Mphahlele, Medical Research Council of South Africa.

appeared to have had "transient" TB infection, which is consistent with the results of skin test and interferon-gamma release assay conversions reported in the older literature.[2]

Other studies have demonstrated some of the factors associated with the transmission of *M.tb*. among individuals, finding, for example, that transmission in a hospital setting can be widespread within a brief period of time (Haley et al., 1989). Another study that looked at TB transmission on airplanes revealed that duration of exposure and proximity to the index case have an effect on transmission (Kenyon et al., 2009).

The infection control experiment done at the AIR facility assessed the efficacy of an infection control intervention. In a two-phased study, ultraviolet (UV) radiation was switched on and off on alternate days in two animal rooms. When the UV radiation was switched on, air was transmitted to the intervention group of guinea pigs; when the UV radiation was off, air was transmitted to the control group of guinea pigs. In the first phase of the study, after 4 months of exposure, 9 guinea pigs in the control group were infected and none in the intervention group, showing 100 percent protection. In the second phase, after 3 months of exposure, 48 guinea pigs were infected in the control group and 15 in the intervention group, showing 85 percent protection.

Mphahlele observed that the findings of the AIR studies indicate a global need to better understand transmission of MDR and XDR TB through basic research. She noted that future studies planned for the AIR facility will address the efficacy of surgical masks for patients; novel interventions, such as inhaled antibiotics; transient TB infection, strain variation, and XDR TB transmission; and determination of when MDR and XDR TB patients become noninfectious.

INFECTION CONTROL IN HOSPITAL AND OTHER HEALTH CARE SETTINGS

The 2006 study of 53 patients with XDR TB in Tugela Ferry described in Chapter 2 provided evidence for nosocomial[3] transmission (Gandhi et al., 2006). Evidence supporting the suggestion that infections had been acquired largely in the health care setting included four findings: (1) most patients had been admitted to the hospital during the preceding 2 years, (2) initial community contact tracing uncovered few additional cases,

[2] Riley and colleagues also observed small, nonprogressive reactions not consistently associated with disease on autopsy. Reversion of skin test results is known to occur in humans after prompt treatment for latent TB infection and among the elderly. Also, with interferon-gamma release assays, reversions have been observed with and without treatment.

[3] Nosocomial infections are infections that are a result of treatment in a hospital or a health care service unit.

(3) health care workers were among those who died from XDR TB, and (4) genotyping showed a similar strain in 83 percent of patients. According to Friedland, since that time, a number of other studies have confirmed transmission within the hospital setting from patients identified as having had XDR TB. TB infection is transmitted not only from patient to patient but also from patient to health care worker and from health care worker to patient. WHO and the Centers for Disease Control and Prevention (CDC) have formulated procedures for reducing nosocomial transmission through infection control measures. Infection control protocols are divided into three categories: administrative, environmental, and personal protection.

Infection Control Practices Reported by Health Care Workers in Five Primary Care Sites[4]

Shean reported on the preliminary results of an ongoing study of latent and active TB in 267 health care workers at five primary care sites, conducted by Dr. Shahieda Adams. Information had been collected on occupational and environmental determinants of TB infection, including infection control practices at work sites (Adams et al., 2010). In the studied population, the majority were female (78 percent), and all worked at community health centers or primary care clinics. The majority reported having had a BCG vaccination,[5] 6 percent were diabetic, 15 percent were current smokers, and 27 percent reported using alcohol. A questionnaire on infection control practices was administered. HIV status could be disclosed to researchers, but participants were also encouraged to be tested; 72 percent of the respondents were willing to be tested for HIV at the time of the questionnaire. Those who had received previous TB treatment made up 18 percent of the group, and 31 percent had at least one current TB symptom. The majority of health care workers reported having daily contact with TB patients (89 percent), and 32 percent had some level of health qualification. Table 4-1 shows the percentage of the health care workers who reported that various infection control measures were in place in the facilities in which they worked.

Tests done on the health care workers showed that

- 31 percent were positive on a screen of symptoms,
- 19 percent were HIV-positive (either reported as or tested positive),

[4] This section is based on the presentation of Karen Shean, Lung Infection and Immunity Unit, University of Cape Town (UCT) Department of Medicine.

[5] Bacillus Calmette-Guérin (or Bacille Calmette-Guérin, BCG) is a vaccine against TB that is prepared from a strain of the attenuated live bovine TB bacillus, *Mycobacterium bovis*, which has lost its virulence in humans by being specially cultured in an artificial medium for years.

TABLE 4-1 Percentage of Health Care Workers Reporting Various Infection Control Measures

Measure	Percent Reporting
Infection control policy	66
Ventilation measures (natural/mechanical)	93
UV lights in facility	12
Cough etiquette	81
Early triage	57
Separation of TB patients	71
Onsite diagnostic services	85
Disposable surgical masks	94
N-95 respirators[a]	89

[a]A workshop participant noted that it is essential for introduction of N-95 respirators into any infection control program to be accompanied by fit testing to ensure that the respirators can be used most effectively.
SOURCE: Shean, 2010.

- 10 percent were positive on a chest x-ray,
- 84 percent were skin test positive,
- 66 percent were positive on the QuantiFERON-TB Gold In-Tube (QFT-GIT) test, and
- 57 percent were positive on the T-SPOT.TB test.[6]

Shean reported that active TB was found in five of the health care workers.

Infection Control Practices at Church of Scotland Hospital[7]

Friedland spoke about important work on transmission performed at the Church of Scotland Hospital (CoSH) in Tugela Ferry. CoSH is a rural district hospital with 350 beds, including male and female medical and TB wards of about 40 beds each. Both inpatient and outpatient facilities are overcrowded in a congregate area conducive to airborne transmission of TB. The local community has a 17.5 percent prevalence of HIV-positive adults and a TB–HIV coinfection rate of more than 90 percent. The TB case rate is 1,100 per 100,000 population per year.

CoSH has implemented infection control measures in each of the three WHO/CDC categories (administrative, environmental, and personal protection) as part of its infection control program:

[6] The QFT-GIT and T-SPOT.TB tests are two diagnostic methods that use interferon-gamma release assays to detect both latent and active *M.tb.* in a patient's blood sample (Mazurek et al., 2010).

[7] This section is based on the presentation of Gerald Friedland, Yale School of Medicine.

- Administrative
  - A dedicated infection control officer was appointed.
  - Cough officers were placed in all ambulatory care areas to separate out suspected TB cases.
  - A TB infection control policy was ratified.
  - Reductions in admissions and lengths of stay were accomplished.
- Environmental
  - Isolation wards were created for male and female MDR TB patients.
  - Extractor fans were installed.
  - Natural ventilation was assessed, and an open-window policy was implemented.
  - The DOTS office was moved to the periphery of the hospital, and all patients were offered voluntary counseling and testing.
  - A well-ventilated antiretroviral therapy clinic was relocated to the periphery of the hospital, and all patients were screened by a cough officer.
  - Remediable environmental flaws were evaluated.
- Personal protection
  - Staff surveys were conducted regarding infection control knowledge, attitudes, and practices.
  - TB education sessions were held.
  - Regular staff screenings were performed by the occupational health officer.
  - The use of N95 respirators was introduced, along with fit testing and staff education regarding fit checks.
  - Voluntary counseling and testing was promoted for staff and inpatients, with provision for antiretroviral therapy and the option for health care workers to transfer discreetly to lower-risk areas.

In addition, a series of simple and inexpensive evaluations was performed, including

- assessment of lengths of stay and admissions by review of TB ward/hospital registers,
- cough officer program results,
- unannounced audits of ventilation and open windows,
- unannounced audits of N95 respirator use by health care workers,
- voluntary counseling and testing of staff and patients, and
- screening of health care workers for TB.

Outcome measures in inpatient TB wards showed dramatic results. In 2005, 88 percent of patients screened were culture positive, and 64 percent of the patients screened (16 of 25 patients) had MDR or XDR TB. In 2009 in the same wards, 59.3 percent of patients screened were culture positive, and only 7.4 percent of the patients screened (2 of 27 patients) had MDR or XDR TB. Thus, the effective implementation of administrative, environmental, and personal protection infection control measures created a hospital environment in which a decline in drug-resistant TB cases was possible and ultimately became reality.

A mathematical model was used to evaluate the infection control program by estimating the number of XDR TB cases that could be averted by the implementation of different combinations of infection control strategies (Basu et al., 2007). The model showed that using combinations of the available infection control measures over the period from 2007 to 2012 could result in preventing 48 percent of new cases. The model also showed that of the estimated 1,300 new cases of XDR TB, 3 percent would be among health care workers, and that 75 percent of those new cases among health care workers could be prevented through the use of natural ventilation; the use of N95 respirators; and voluntary counseling and testing for HIV, with redeployment of HIV-positive staff. The model showed further that the provision of antiretrovirals to eligible HIV-positive individuals would avert 24 percent of new XDR TB cases. Of note, involuntary confinement would increase transmission by 3 percent by bringing together individuals with strains of differing resistance.

Discussion

In the workshop discussions of the implementation of infection control protocols, it was noted that available transmission control strategies and technologies, such as early diagnosis, triage and separation, natural ventilation, UV masks on patients, and treatment, need to be implemented. Once implemented, those interventions need to be evaluated to determine their efficacy. Monitoring and further direction by infection control practitioners will be required in areas where the interventions have not been successful to improve the measures and reinforce the importance of infection control. In addition, it will be necessary to develop novel effective transmission control interventions.

Another theme of the discussion was related to behavior change and best practices for health care workers. It was noted that infection control training for nurses is lacking, as is systemic training capacity. Large-scale, long-term training in infection control is required for the South African context. Other interventions that have shown some success include such simple measures as using checklists and having an infection control practi-

tioner. Finally, discussants suggested that there needs to be a general shift away from the concept of centralized infection control and toward a model in which each person in a health care unit is considered to be individually responsible for infection control.

CONTACT TRACING AND COMMUNITY-BASED INFECTION CONTROL PRACTICES[8]

In his presentation, Marra suggested that, although addressing the issue of transmission in the hospital is of critical importance, community-based interventions to combat the transmission of MDR and XDR TB are needed as well. According to Marra, contact tracing, which includes education in and awareness of infection control, should be part of the normal TB control program, and infection control should be part of every intervention. In Tugela Ferry, for example, health care workers have been visiting the households of MDR and XDR TB index cases to offer TB screening and education about the disease and its prevention, demonstrating the feasibility of household contact investigation.[9] The household contact investigation and infection control strategy applied in Tugela Ferry, which started in 2006, involves

- visiting the homes of all index MDR and XDR TB patients;
- taking the global positioning system (GPS) coordinates of each home; and
- screening all household contacts by obtaining a TB symptom history, collecting sputum from all sputum producers, bringing all suspected TB cases to CoSH for evaluation by a medical doctor,

[8] This section is based on the presentation of Claudio Marra, Tugela Ferry Care and Research Collaboration (TF CARES).

[9] The characteristics of the 508 MDR and XDR TB index cases showed that 51 percent were female, the median age was 34, 64 percent had smear-positive sputum, and 50 percent of the households had a previous history of treatment. During the period of observation, 81 percent of cases died. A total of 1,766 household contacts of the MDR and XDR TB index cases were evaluated at baseline, 66 percent of whom were female and most of whom were between the ages of 13 and 24. The results of the culture and drug sensitivity tests showed a transmission rate of 3.7 percent in a family. However, only 44 percent of MDR and 59 percent of XDR index cases were concordant with the type of drug resistance that was discovered. This means the household transmission figure of 3.7 percent could be lower, with transmission also occurring outside the household. Among the households to which the 508 index cases belonged, 89 percent had no cases of TB, while 11 percent had one or more cases. However, since this study identified only active TB cases, many more household contacts could have been infected with TB. A workshop participant also noted that there is a large amount of discordance in *M.tb.* isolates between coprevalent cases in the household. This discordance could have implications for preventive therapy in households.

and having a chest x-ray taken (currently, 4,000 contacts are in a central database).

Most of the MDR and XDR TB cases were situated in Msinga, the subdistrict in which Tugela Ferry is located, in close proximity to the hospital, while fewer cases were found in the surrounding subdistricts. The greatest number of cases was found in 2007. The study evaluated but did not find associations with the terrain, access to health care, and the number of people sharing a home.

According to Marra, the infection control program in Tugela Ferry, the household contact investigation of MDR and XDR TB families, and the strengthening of the normal TB program have met with considerable success. The cure rate has risen from 70 to 82 percent, and a default rate that had been around 20 percent is now close to zero. No patients have been lost to follow-up. Marra stressed that the introduction of rapid diagnostic tests to reduce the infectious period is essential, and community spread of MDR and XDR TB needs to be further investigated.

In the discussion following Marra's presentation, Jason Farley, Johns Hopkins University School of Nursing and Johns Hopkins AIDS Service, noted that infection control in the community requires a tremendous investment of resources and research. Moreover, it depends not only on the health care infrastructure but also on the infrastructure of individual households. To prepare patients for discharge from the hospital, this household infrastructure must be assessed and appropriate education ensured. Shean said that in the Western Cape, such cases are dealt with by a review board that makes decisions based on assessments of the home and the community by social workers, with the involvement of families to ensure treatment literacy. UV lights and mechanical ventilation are sometimes installed in homes. Friedland suggested that various practical approaches can be applied, such as keeping patients outdoors as much as possible, separating TB patient sleeping quarters, and implementing cough etiquette.

PARTICULAR CHALLENGES FOR HEALTH CARE WORKERS[10]

In her presentation, Shean observed that sub-Saharan Africa has 11 percent of the world's population, 25 percent of the global burden of disease, and just 3 percent of the world's health care workers. This limited number of health care workers presents one of the greatest challenges to health care systems in the region. Furthermore, the situation is becoming worse. The ratio of registered nurses to patients in South Africa decreased from 120 per 100,000 population in 2000 to 109 per 100,000 in 2005.

[10] This section is based on the presentation of Shean.

The HIV crisis is rapidly depleting current health care workforces, with an average of 15.7 percent of nurses in four provinces of South Africa being HIV-positive (Shisana et al., 2003). Moreover, drug-resistant TB has placed a significant additional strain on the overwhelmed TB control programs in high-burden areas. And according to Shean, the national policy of admitting all XDR TB patients to the hospital until they are smear negative has added to the challenge of providing access to affordable and appropriate infection control in health care facilities.

Very few data are available on the incidence and treatment-related outcomes of XDR TB in health care workers. A retrospective review of case records of passively detected XDR TB cases diagnosed between 1992 and 2008 from three provinces in South Africa found 36 health care workers who were sputum culture positive for XDR TB (Jarand et al., 2010). One case was diagnosed in 1996, with an incremental increase until 2008, when 14 cases were diagnosed, 80 percent of whom were on antiretrovirals. Ten of the health care workers had bilateral disease, and the mean number of drugs in the XDR TB treatment to which resistance was found was six. The majority of the health care workers worked in district hospitals. Thirty-four percent of the health care workers died, with a median of 3.7 months from diagnosis to death. These numbers reveal that XDR TB is an important risk for health care workers globally, particularly those who work in high-burden areas. Factors contributing to the risk of infection include

- the concentration of organisms in the source case (associated with severity of disease);
- the duration of exposure to air contaminated with tubercle bacilli;
- the type of health care facility; and
- comorbid diseases, such as HIV/AIDS, diabetes, or cancer.

A personal challenge facing health care workers is the fear of being diagnosed with TB or HIV infection, which would lead to marginalization by colleagues and the possible loss of one's job. Notwithstanding this challenge, drug-resistant TB should be considered in any health care worker suspected of TB, irrespective of HIV status, and implementation of infection control measures and rapid diagnostic testing for all health care workers suspected of TB are necessary. At the same time, health care institutions must support and protect health care workers by helping them cope with stressful situations and by acknowledging their sometimes dangerous and difficult work conditions, said Shean. Workable plans for emergency situations need to be in place. Employers are responsible for providing a safe working environment, which includes necessary and sufficient information, human resources, protective equipment, and supplies.

TRANSMISSION AND INFECTION CONTROL AMONG MINERS AND MIGRANT WORKERS IN LESOTHO[11]

Lesotho is a land-locked mountainous country surrounded by South Africa. Its population is 1.8 million, with an HIV prevalence rate of 23.2 percent and a TB incidence rate of 544 per 100,000 population. The number of people living with HIV is 270,000; 22,000 are on antiretroviral therapy, and 81,000 still need it. The TB–HIV coinfection rate is about 64 percent, and the number of TB deaths is 107 per 100,000 population per year. The unemployment rate is 45 percent, and 56 percent of the population lives on less than $2 per day. In 2007 the textile and apparel industry employed about 46,000 workers in three districts of the country. In addition, Lesotho contributes more than 50,000 migrant workers to the South African mining industry, and thousands of migrant workers stay and work illegally in South Africa.

Thotolo stressed that in fighting TB, it is necessary to address the cross-border movement of migrant workers. At times, these workers visit their families in Lesotho without informing their clinics or doctors, thereby putting family members at risk. Illegal workers generally do not present at clinics upon realizing they are ill; instead, they treat themselves with traditional remedies and return to their homes when the illness is at an advanced stage. Some patients claim that they are refused TB treatment in South Africa because they are unable to present the necessary identity documents. Factors that contribute to the spread of drug-resistant TB in these workers include the following:

- Unauthorized home visits by patients sometimes interrupt and undermine treatment.
- Houses are overcrowded and have poor ventilation.
- Infection control is inadequate, particularly in relation to cough etiquette in public transport and crowded public places.
- Medical TB treatment is combined with remedies offered by traditional healers.
- Loss of income leads to poverty and malnutrition among the entire household.

According to Thotolo, transborder control of drug-resistant TB can be improved by

- establishing better systems for the prevention, diagnosis, and treatment of TB and HIV for mine workers, ex-miners, and their families in Lesotho and South Africa;

[11] This section is based on the presentation of Maketekete Alfred Thotolo, Adventist Development and Relief Agency.

- establishing linkages between TB and HIV programs in and between Lesotho and South Africa, as well as between the public and private sectors, including traditional healers;
- building capacity among individuals and communities affected by the cross-border TB/HIV epidemic, including treatment literacy training; and
- addressing the legal, human rights, and socioeconomic issues affecting TB and HIV control among mine workers, ex-miners, and their families through an advocacy program.

The Department of Health's *Tuberculosis Strategic Plan for South Africa, 2007–2011* states that the South African gold mining industry probably has the highest incidence of TB in the world—between 3,000 and 7,000 per 100,000 population per year (DoH, 2007). The mining companies need to take the burden of TB in mine workers seriously and invest in the fight against the disease. In particular, the "three I's"—intensified TB case finding, isoniazid preventive therapy, and infection control (see Chapter 3)—need to be advocated on behalf of migrant populations.

In May 2008, the AIDS and Rights Alliance for Southern Africa (ARASA) convened a meeting in Johannesburg together with mining companies, trade unions, the ministries of health of both countries, and activist groups to discuss the prevention and treatment of TB. An outcome of the meeting was a recommendation for collaboration between the ministry of health in Lesotho and the mining companies in South Africa so that when patients are referred to TB facilities in Lesotho, proper documentation concerning previous treatment will be made available and special procedures followed.

Warren observed that in South Africa, the mines have a far more efficient TB control policy than do communities. Among miners, all patients are diagnosed, hospitalized, and treated, and DOTS management is exceptionally good. Despite this infrastructure, and even though a high proportion of patients are cured, outbreaks of drug-resistant TB are still observed. These data have been interpreted to imply that the treatment of patients with standardized regimens for MDR TB inadvertently leads to the emergence of XDR TB. It could not, however, be discerned whether transmission occurred in the household, in the compounds where the miners lived, in the hospitals, or in the mines.

5

Diagnosis of Drug-Resistant TB

Key Messages

- An inability to diagnose drug-resistant TB rapidly and accurately is contributing to the severity of the TB epidemic.
- The ideal diagnostic test will produce a result in less than 24 hours, be inexpensive, distinguish the drug susceptibility of TB strains, and be accurate and easy to perform.
- A strengthened health care infrastructure in South Africa would support detection and treatment of drug-resistant TB.

TB patients progress from exposure to cure in discrete steps: infection, symptoms, clinic visit, diagnosis, treatment onset, conversion from an active infection to a noncontagious state, and cure. To decrease transmission, the time between each of these stages needs to be reduced. The workshop addressed challenges in the capacity of the health care system in a high-burden country such as South Africa to meet the need for rapid and effective diagnosis of TB. Diagnostics not only can help reduce the interval between presenting at a clinic and diagnosis, but also can be used within a comprehensive program to address and perhaps reduce the earlier and some of the later intervals in the progression of TB. Thus diagnostics can play a key role in curbing the epidemic if they are dramatically improved and

used proactively. This chapter summarizes the workshop presentations and discussions addressing the need for rapid diagnostics, progress on point-of-care diagnostics, the challenges of laboratory capacity in South Africa, and the use of biomarkers to diagnose TB.

NEED FOR RAPID DIAGNOSTICS[1]

Although some have suggested that greater than 70 percent detection and cure rates for TB will constitute success, van Helden suggested that in fact, this will not be enough. If only 70 percent of infected individuals are detected and only 70 percent of that group is cured, the overall cure rate will be the product of those two numbers, or 49 percent. Furthermore, even infected people whose disease resolves will spread the organism before they are diagnosed. A mathematical model suggests that if diagnosis takes 40 days, a rising epidemic will continue, whereas diagnosis within 6 days or less will result in the epidemic's decreasing.

The need for patients to return to the clinic is a factor. Studies of the current system for diagnosis indicate that 20 percent of patients fail to return after their first visit to a clinic and thus are lost to follow-up. A point-of-care diagnostic device (see the discussion below) could prevent those patients from being lost to follow-up at that early stage of diagnosis and treatment of their TB. The algorithm used suggests that typically when patients present to a clinic or TB facility, a point-of-care test that may be 40–50 percent sensitive is administered. Positive patients are absorbed into therapy, and it may not be necessary that they provide another sputum sample. Negative patients that are highly clinically suspicious should be managed according to the normal National Health Laboratory Service algorithm for that country, suggested van Helden.

Considerations and Trade-Offs in Developing and Adopting Diagnostics

In considering what types of diagnostic tests should be developed and adopted within a high-burden country, a number of criteria come into play. An ideal needs assessment may have to be evaluated and judged against what is realistic.

To illustrate this point, van Helden used the example of the Ziehl-Neelsen stain test,[2] which is used to evaluate sputum. Many argue that this test is appropriate because it is effective, relatively quick, and inexpensive. Others argue that it is insufficient, and a test that is better on all criteria

[1] This section is based on the presentation of Paul van Helden, Stellenbosch University.

[2] The Ziehl-Neelsen stain, also known as the acid-fast stain, is a special bacteriological stain used to identify acid-fast organisms, mainly mycobacteria.

(more effective, simpler, and even less expensive) should be adopted. Still others argue that a test that is more effective and more rapid than Ziehl-Neelsen should be adopted even if it is more expensive. And, as discussed in this chapter, there are strong arguments that anything less than the ability to make a point-of-care diagnosis of drug-resistant TB ultimately will not succeed against the disease.

A variety of criteria can be applied in considering the desirability of a diagnostic test. Speed, cost, sensitivity, and specificity are among the most important; one issue is whether speed, sensitivity, or specificity should be paramount. Current tests generally are 50 percent sensitive and usually are not performed at the point of care. On the other hand, rapid point-of-care diagnosis could result in very few TB cases in 5 years' time; ultimately, such lowering of case burden would cost less overall. Indeed, the development of new diagnostics will be essential to stem the TB epidemic; saving money on cheap, ineffective diagnostics will result in the epidemic's continuing. In considering implementation and efficacy, issues include number of manipulations; repeats (including client returns); invasiveness of sample taking; skills, instruments, and personnel required; and central versus decentralized laboratory capacity and logistics.

Problems with Current Diagnostics

The problem with many diagnostic methods currently in use is that the answer they provide can be both yes and no, said van Helden (Box 5-1 describes some of these methods). For example, genotype information can reveal that an inhA mutation is present, but in this case isoniazid should not be excluded and is still a potentially usable drug. However, when a KatG mutation is present, treatment with isoniazid is not recommended. Genotyping and phenotyping will give different results, and even phenotypes are not yet fully understood.

Results from testing in miners reveal some of the negative consequences of reliance on simple diagnostics. The diagnoses were unreliable, and regimens were implemented in a formulaic way, resulting in the development of MDR and XDR TB. The epidemic was amplified by transmission of MDR TB, after which some individuals progressed to XDR TB.

Need for Research into New Diagnostic Methods

Other methods need to be considered to yield informative diagnostics. Some of the antibody tests used in the 1990s had a sensitivity of 30 to 70 percent and were simple to use. The sensitivity of lateral flow devices may be 77 percent, with a specificity of 93 percent. According to van Helden,

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

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

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

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

SOURCE: van Helden, 2010.

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

more time and effort should have been invested in testing and developing these methods, which now need to be reconsidered.

The presence of antibodies implies the presence of antigens and could be useful in detecting infection. The Foundation for Innovative New Diagnostics (FIND), together with a number of researchers, is investing in the advancement of lipoarabinomannan (LAM) tests. Lipids and mycolic acids also are potentially interesting antigens because they drop very quickly as

the bacterial load disappears. Studies of urine-based tests for LAM show that sensitivity is lower in smear-negative patients but increases as CD4 count decreases,[3] making these tests potentially highly useful in the South African context.

PROGRESS ON POINT-OF-CARE DIAGNOSTICS[4]

According to Jacobs, intensified case finding (see Chapter 3) is essential in South Africa to reach MDR TB cases that are not yet being treated. Such case finding would be dramatically enhanced by tools enabling point-of-care diagnoses, but important questions about such tools remain unanswered.

Jacobs remarked that the ideal point-of-care diagnostic test will produce a diagnosis in 1 to 24 hours, be inexpensive, distinguish drug-susceptible TB from MDR and XDR TB, be accurate and easy to perform, and give fractional drug resistance. One simple approach for a drug susceptibility assay relies on the luciferase reporter phage (LRP), also called the "turn on the light" assay. A TB sample is divided into five tubes, and different drugs are added to four of the tubes, with the fifth serving as a control. If a drug works, it kills the cell and the light does not come on; if the cell is drug resistant, the light comes on. Despite skepticism from reviewers, this has proven to be a simple and inexpensive test. Important questions for this assay, according to Jacobs, are

- What are the accuracy and speed of reporter phages for susceptibility testing of clinical *M.tb.* isolates?
- What is the feasibility of performing a phage-based susceptibility assay in developing countries?

One evaluation of the use of LRPs in Mexico and South Africa found that they provided susceptibility results with an overall accuracy of 99 percent and had a median turnaround time of 3 days, making them the fastest phenotypic method available. The future direction of LRPs is toward a 1-hour test, extended for XDR TB, as well as the development of reporter phage assays for susceptibility testing with second-line drugs.

Recently, a reporter phage test based on green fluorescent proteins (GFPs) was developed by Jacobs and his collaborator Graham Hatfull from

[3] CD4 (Cluster of Differentiation 4) is a glycoprotein expressed on the surface of T helper cells, regulatory T cells, monocytes, macrophages, and dendritic cells. CD4 is a coreceptor that assists the T cell receptor (TCR) to activate its T cell following an interaction with an antigen-presenting cell.

[4] This section is based on the presentation of William R. Jacobs, Howard Hughes Medical Institute, Albert Einstein School of Medicine.

the University of Pittsburgh. This test has been shown to have a number of potential advantages, including

- expected low cost,
- monitoring of individual cells for drug resistance,
- fixation of cells for enhanced safety,
- analysis of mixed cultures,
- potential multicolor internal controls, and
- alternative detection systems.

The initial GFP test took about 24 hours to provide a response. It could be used to assess drug susceptibility and detect rifampicin and streptomycin resistance. Further work is needed to develop assays that can produce results in cells in 1 hour. Jacobs stated that GFP tests using fluoromycobacteriophages have considerable potential. They can provide a simple, inexpensive, quick, and reliable method for drug susceptibility testing and offer multiple platforms for detection. Efficient recovery of *M.tb.* from sputum is needed, as are second-generation phages with enhanced fluorescence and specificity. Current studies evaluating the efficacy of these tests are under way in Durban, South Africa.

CHALLENGES OF LABORATORY CAPACITY[5]

Coetzee observed that South Africa's response to MDR TB has been limited by the unsatisfactory performance of its laboratory services and inadequate human resources. In 2009 nearly 1 million cultures were performed in South Africa, most of which were followed up with drug susceptibility testing, and these tests identified 9,000 new MDR TB cases. Yet many communities still are not receiving adequate laboratory services. The National Health Laboratory Service now has well over 100 MGIT (mycobacteria growth indicator tube) machines, but little progress is being made in identifying all MDR TB cases.

In 2008, the World Health Organization (WHO) endorsed the use of line probe assays (LPAs) capable of detecting resistance to rifampicin and isoniazid (MDR TB is defined by resistance to both of these drugs). The new WHO TB guidelines, which became operational on April 1, 2010, have led to a doubling of laboratory investigations. The roll-out of this test in South Africa is currently being organized. As of the middle of 2009, 5 laboratories were able to conduct a substantial volume of LPA tests. It was decided that by the end of 2010, 20 more secondary (not academic)

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

laboratories would be rolled out; 11 of these are already functioning. The objectives of the roll-out include

- achieving rapid diagnosis of MDR TB;
- providing effective treatment to patients at the appropriate time;
- preventing further resistance to anti-TB drugs;
- preventing further TB transmission;
- decreasing the cost of treating TB by reducing unnecessary transmission through earlier diagnosis, as well as by preventing the development of drug resistance, which is more expensive to treat; and
- realizing financial savings by eliminating drug susceptibility tests from the diagnostic process (it is expected that these savings will fund the implementation of LPAs).

A procedure was developed for the early detection of MDR TB. Every new smear-positive patient in South Africa will receive an LPA test to rule out MDR TB. A 7-day sputum will be taken at the facility, and an MGIT culture will be performed on patients who are still symptomatic. Positive patients will again receive an LPA test.

Because the existing infrastructure could not accommodate new laboratory space, modular park home units were specially designed to be suitable for use as laboratories, and specifically for polymerase chain reaction (PCR) testing. Staffing these facilities has presented the biggest obstacle to rolling out the 20 additional laboratories. A new category of laboratory staff called "TB technician" has been approved, and a 2-year training program for these staff is due to commence. Sixty new laboratory staff were employed during 2009, and a further 60 will join the National Health Laboratory Service during 2010.

One of the concerns with regard to the roll-out of additional laboratories is quality control. Currently, no international quality assurance program is in place for LPAs, and only interim measures have been taken to accommodate quality control in laboratories. The biggest technical problem has been the variability of LPAs; to address this problem, a scanner was developed that automatically reads and quantifies the results and actual mutations.

One workshop participant cited another concern with the implementation of the LPA test: to the extent that many more undiagnosed cases of MDR TB will be diagnosed through use of this test, it will be necessary to consider how the health care system will treat those additional cases.[6]

[6] In December 2010, WHO released a guidance document providing recommendations for governments on how to address difficult ethical issues that arise in efforts to combat the TB (both drug-susceptible and drug-resistant) epidemic (WHO, 2010e).

Community-based care beyond present practice may be a potential solution (see Chapter 6). Current policy is that all MDR TB cases must be admitted until culture conversion is seen. In KwaZulu-Natal Province and the Western Cape, however, pilot studies are under way on community-based care that will be decentralized by strengthening existing hospitals and other TB facilities and by creating satellite centers in communities, with teams that travel throughout an area. Integration of MDR TB and HIV care will take place at the primary care level.

USE OF BIOMARKERS TO DIAGNOSE TB[7]

Parida reported that sub-Saharan Africa experiences 12 times more deaths from TB every hour than Europe. More needs to be known about the outcomes associated with exposure to *M.tb.* to devise interventions, he suggested, and one way to learn more is to reduce the gap between the research laboratories and clinics. There are important differences in immune response between individuals who are exposed to TB and protected from the disease and those who develop active disease. Particularly for people coinfected with *M.tb.* and HIV, the design and testing of new TB vaccines, drugs, and diagnostics will be critical.

The project Biomarkers of Protective Immunity against TB in the Context of HIV/AIDS in Africa, which involves 15 partner institutions from Africa, Europe, and the United States, has been seeking to identify correlates of protective immunity and host biomarkers of TB that have prognostic potential for delineating disease susceptibility and protection.[8] The project's objectives are to

- investigate differences in immune response between individuals who are exposed to TB and protected from the disease and those who develop active disease; and
- coordinate to promote the design and testing of new TB vaccines, drugs, and diagnostics, especially in areas with high HIV infection rates.

Particular attention is being paid to people coinfected with both *M.tb.* and HIV, whether or not they are receiving antiretroviral therapy.

[7] This section is based on the presentation of Shreemanta K. Parida, TB Research Specialist, Berlin, Germany.

[8] More information on the Biomarkers of Protective Immunity against TB project can be found at: http://www.grandchallenges.org/NewVaccines/Challenges/LearnaboutImmunologicalResponses/Pages/Biomarkers.aspx (accessed February 22, 2011).

The different platforms for biomarkers are immunologic, transcriptomic, proteomic, and metabolomic. Most likely, a combination of these markers will prove to be useful. Specific biomarker needs in the context of TB are

- surrogate markers of immune protection for assessing potential vaccine candidates,
- a surrogate marker of bacterial clearance (the clinical end point) for assessing potential drug candidates,
- markers of relapse,
- markers of treatment failure (drug resistance),
- diagnostic markers,
- markers for infection, and
- prognostic markers for reactivation of disease.

The project has been structured around five different cohorts, or work packages (WPs). WP1 is focused on pathogens; WP2 is focused on host responses to infection; and WPs 3, 4, and 5 are prospective cohorts in African field sites used to study the natural history of TB. WP1 and WP2 are based on cross-cutting methods carried out in the northern laboratories in collaboration with the field sites to narrow down the biomarkers to 25–50. As noted, the focus is on pathogen and host, respectively, which then can be assessed in longitudinal prospective studies in the field sites. WP5 is being used to assess the immune responses to BCG vaccination and the effects on disease progression. About 17,000 individuals from different age groups with a varied spectrum of TB with or without HIV in five African countries are being followed. The group characteristics are as follows:

- 898 HIV-negative TB index patients,
- 3,935 HIV-negative subjects with latent TB infection free of any disease symptoms and signs,
- 6,363 adolescents with latent TB infection free of any disease symptoms and signs,
- 894 HIV-positive subjects with latent TB infection and 304 HIV-positive and TB-positive patients, and
- 5,663 neonates plus 200 children following BCG vaccination.

At the start of the project, the hypothesis was that different clinical strains of *M.tb.* would show differences in gene expression levels. At that time, this hypothesis faced considerable skepticism. After a series of discussions with experts, two of the most divergent strains in the phylogeny—one from Gambia (a strain of *M. africanum* that is prevalent in West Africa) and the other from Uganda (an *M.tb.* strain of the same phylogeny of Euro-American lineage to which the laboratory strain H37Rv and clinical

strains such as CDC1551 belong)—were compared with the H37Rv reference strain. The analysis found striking geographic variations among the clinical strains, with the implication that effective universal vaccines and diagnostics cannot be produced. Rather, the uniqueness of the strains must be considered in the development of vaccines and must be reflected in the treatment of drug-resistant TB.

The project addressed about 100 genes, focusing on latency and reactivation, and made 86 novel antigens that were studied in five sites. The antigens were initially screened in a 7-day whole-blood stimulated assay, with interferon-gamma (IFNg) as readout in the antigen-stimulated supernatants. Then the antigens were subjected to 42 cytokines in an effort to uncover combinations that would result in biomarkers. It was speculated that a combination of antigens and cytokines might lead to a possible biomarker profile. Host biomarkers in disease and protection were assessed using microarray analysis of total ribonucleic acid (RNA) from whole blood from TB patients, tuberculin skin test–positive (latently infected) subjects, and tuberculin skin test–negative (noninfected) subjects. An earlier study with Caucasian subjects had identified three host biomarkers—CD64, LTF, and Rab33A—that could differentiate between TB patients and healthy contacts.

The TB contact study (cohorts WP3 and 4) followed the subjects over a 2-year period, with a focus on those both infected and clinically healthy. These subjects were followed up clinically over the 2 years, with blood samples being taken at three time points—0, 6, and 18 months. The objective was to assess immune responses over time using all the platforms described earlier and to identify biomarkers of disease susceptibility and protection, comparing subjects who contracted disease during the course of this follow-up period with those who remained healthy without succumbing to disease progression. Based on studies performed earlier, it was expected that 5 to 10 percent of subjects would develop TB during the 2-year period. The current follow-up status shows only 63 secondary cases from among almost 4,000 subjects in the HIV-negative cohort. However, the reactivation rate is about 2 percent rather than the 5 to 10 percent expected (which, according to Parida, has been a convention in the field that has never been verified). The ramifications of the TB contact study are complex and time and resource intensive, involving multiple teams working in tandem. There currently are 22 (about 2.5 percent) secondary TB cases based on progressors in WP4 (the HIV-positive cohort).

The current status of the project is as follows. Recruitment of the cohorts has been completed, and follow-up will be concluded in October 2010 (Parida and Kaufmann, 2010). Additional recruitment has been initiated and is ongoing to obtain more secondary cases, assay qualification is being completed at all sites, and large-scale production of antigens has been achieved. There are plans to perform analysis centrally on all second-

ary cases and matched controls at the end of the follow-up period and to validate patterns showing an association with protection. A complementary analysis using longer-term assays to delineate soluble cytokine expression patterns associated with protection also is planned.

This biomarker study for drugs and treatment outcomes has looked at the normal patient therapy seen in clinics. The aim of the study has been to make it possible to differentiate among patients at the time they seek medical help so they can be assigned directly to the correct regimen. According to Parida, the objectives include

- bringing together basic scientists from the laboratories and clinicians from clinics in the communities and hospitals through effective communication and interaction;
- achieving a holistic understanding of resistance, susceptibility, and protective immunity, taking an open-minded, global approach;
- coordinating initiatives and finding synergies within the scientific community, including interdisciplinary approaches and cross-fertilization of ideas;
- establishing global, shared, and comprehensive biorepositories;
- aligning vaccine trials and intervention studies;
- creating an open access policy and enforcing it through the buy-in of all stakeholders;
- generating public–private–philanthropic partnerships; and
- enhancing functional collateral/symbiotic interactions between basic science and real lives in clinics to translate research knowledge into products of public health importance.

The following issues require further consideration:

- the natural history of infection in the context of drug-resistant TB and immune responses; and
- differential gene expression patterns of MDR and XDR TB strains, with virulence depending on the host environment.

Parida also noted that a number of conventionally accepted "dogmas" in the field have not been systematically questioned. According to Parida, evidence-based studies are needed in areas that include microbial persistence, immune evasion mechanisms, strain diversity, limitations of animal models, extrapolations of experimental results, ways to bridge the experimental results with clinical observations, and integration of multiple observations rather than a reductionist approach. Ultimately, lessons learned in the clinical setting need to be brought back to the laboratory to close links and fill the gaps.

6

Treatment of Drug-Resistant TB

Key Messages

- Existing treatment programs in South Africa have been insufficient to prevent the spread of drug-resistant TB and extensive mortality.
- Financial support for treatment in locations such as Tugela Ferry has greatly improved the rate and outcomes of treatment.
- The success of community-based care for drug-resistant TB in South Africa has led to greater support for decentralized treatment programs.
- Antiretroviral therapy has a substantial protective effect for TB.

The workshop presentations and discussions highlighted a number of challenges and open questions for consideration in efforts to improve the treatment of drug-resistant TB. First, as a precursor to successful treatment, early diagnosis of drug-resistant TB is essential; otherwise, delays in treatment lead to higher mortality (see Chapter 5). Second, emerging information from a study of patient-specific resistance profiles and appropriate treatment regimens was presented (Keshavjee and Seung, 2008). Successful treatment outcomes for both MDR and XDR TB have been observed in low- and middle-income countries with a low prevalence of HIV infection, but this observation may not be applicable in a setting such as South Africa where HIV prevalence is high. With HIV coinfection, drug-resistant TB

appears to take a different and more aggressive course. Most patients with HIV-associated MDR and XDR TB die within 6 to 8 weeks, which is also the time typically required to make the diagnosis by conventional culture and drug sensitivity testing. Thus, the majority of patients die before their diagnosis can be documented and before second-line drug treatment can be initiated.[1] A third issue concerns the locus of treatment. On the one hand, it was noted that XDR TB treatment, especially in the earliest stages, should take place in a hospital to ensure management of side effects, treatment literacy in patients, nutritional support, and infection control. On the other hand, it was argued that a move toward a decentralized model of care is necessary for prevention of transmission. For example, as the number of patients on antiretroviral therapy increases, antiretroviral therapy facilities will become more crowded with patients, many of whom are highly susceptible to TB. It is important to recognize that combining HIV and TB programs could result in spreading TB among HIV-infected people. A final set of challenges relates to limitations of health care systems and cost issues.

TREATMENT OF DRUG-RESISTANT TB

General Principles

Presenters offered general principles for the treatment of drug-resistant TB, including the need for a comprehensive approach that includes intensified case finding, preventive therapy, improved treatment literacy, and good infection control. In addition, presenters suggested that patients should have increased access to anti-TB drugs as well as other treatment modalities, including thoracic surgery and immune modulators.

Nesri Padayatchi, University of KwaZulu-Natal, elaborated on the objectives of MDR TB management in KwaZulu-Natal Province:

- to make the diagnosis of MDR TB in patients,
- to ensure that the best possible treatment is available,
- to provide support for each patient to ensure access to treatment,
- to facilitate the continuation of care for each patient,
- to factor the management of HIV into the treatment of TB, and
- to explore other options for treatment.

Gandhi described the program that has been instituted in Tugela Ferry, which has three main components:

[1] As noted in Chapter 2, World Health Organization (WHO) and International Standards for Tuberculosis Care (ISTC) guidelines promote the use of an empiric regimen of second-line drugs in suspected MDR TB patients (TBCTA, 2009).

- *Prevention*—Preventing the development of drug resistance by strengthening the DOTS program to curb the creation of drug-resistant strains and by implementing an infection control program to prevent the transmission of such strains.
- *Diagnosis*—Facilitating early diagnosis by testing and implementing rapid diagnostic assays, which may reduce the time required for diagnosis of drug resistance from 6–8 weeks to 1–10 days.
- *Treatment*—Decentralizing access to second-line TB therapy to reduce delays in referral, increase capacity, and improve treatment completion rates. When necessary, second-line drugs have been initiated for HIV-infected patients suspected of MDR or XDR TB, and antiretroviral therapy has been integrated into the drug-resistant TB treatment program.

Finally, Padayatchi described some of the common concerns about treatment default rates. The extent to which the current data may underestimate the default rate is unclear. Loss to follow-up is often due to the toxicity of drugs and the duration of treatment for drug-resistant TB, as well as the patient's distance from the place of treatment. With respect to adverse drug effects, sudden deaths from hypokalemia have been found to be caused by capreomycin; however, renal failure may be related to the presence of a renal condition. More intensive monitoring may decrease deaths related to the drug.

Treatment of Drug-Resistant TB in South Africa

Presenters summarized the findings from studies conducted to characterize TB patients in South Africa and to evaluate the effectiveness of treatment regimens that have been used in those with drug-resistant TB.

King George V Hospital

Padayatchi presented findings of a study conducted at King George V Hospital. She noted that historically, the outcomes of MDR TB in South Africa have been documented to a limited extent. One of the first outcome studies, by Simon Schaaf in the late 1980s, showed a 33 percent cure rate for MDR TB, with 48 percent of patients dying (Schaaf et al., 1996). In the late 1990s, a national study of outcomes showed that after 6 months of MDR TB treatment, more than 70 percent of patients discontinued the treatment. This remains a huge public health problem in South Africa and particularly in KwaZulu-Natal, where the cure rates are below 50 percent. Figures from 2005 to 2007 in Tugela Ferry show that by 30 days from sputum collection, the mortality rates in MDR and XDR TB patients were

already 40 percent and 53 percent, respectively (Gandhi et al., 2010). Most of the deaths occurred within 2 months, accentuating the need to diagnose MDR and XDR TB earlier.

At King George V Hospital, MDR TB cases increased exponentially from 1994 to 2008. Padayatchi's team evaluated more than 1,200 patients at the hospital between 2000 and 2003 (Brust et al., 2010). The cure and completion rate was about 44 percent, 21 percent of patients defaulted, 18 percent died, and 17 percent failed treatment.

The 12-month outcomes for patients with XDR TB at King George V Hospital showed that antiretroviral therapy increases survival. Mortality was highest in the first 2 months after XDR TB treatment. Among those who survived 2 months on second-line drugs, survival rates were higher for those on antiretroviral therapy and those with CD4 cell counts above 200. Decentralized management will allow earlier access to care and initiation of treatment of MDR and XDR TB, as well as HIV coinfection, at decentralized sites (O'Donnell et al., 2009).

Padayatchi noted that several new and existing drugs are undergoing randomized controlled trials in South Africa, including TMC207, linezolid, and fluoroquinolones (e.g., moxifloxacin). The outcomes of the TMC207 study were published in the *New England Journal of Medicine* toward the end of 2009 (Diacon et al., 2009). Clearly this is a drug with potential, Padayatchi said. Linezolid has been known to have in vitro and in vivo activity against *M.tb.* and increasingly has been used in drug-resistant TB patients. Adverse side effects include anemia and peripheral and optic neuropathies related to mitochondrial toxicity. These neuropathies tend to occur after about 4 months of therapy and may not be resolved with the discontinuation of linezolid.

Several studies have examined the sensitivity of various strains of *M.tb.* to fluoroquinolones, and independent studies have confirmed that moxifloxacin is among the most active of the drugs tested. Use of this effective group of drugs needs to be continued, despite the levels of resistance that have been indicated, Padayatchi said. Except for linezolid and TMC207, other new classes of drugs have not yet been studied in randomized controlled trials for drug-resistant TB.

Padayatchi referenced a study in Europe evaluating 425 patients with fluoroquinolone-resistant versus fluoroquinolone-susceptible MDR TB. Study data reveal that a higher proportion of deaths and treatment failures occurred in the fluoroquinolone-resistant patient group (Migliori et al., 2008). According to Padayatchi, the judicious use of fluoroquinolones needs to be encouraged.

Eastern Cape Province

Charlotte Kvasnovsky of the South African Medical Research Council (MRC) reported findings from a 2008 MRC retrospective analysis of patients diagnosed between October 2006 and January 2008 in South Africa's Eastern Cape Province, where MDR TB cases have been diagnosed and treated with a standardized regimen since 2000 (Kvasnovsky et al., 2010). The study looked at data collected during site visits to two TB hospitals in June 2008 and January 2009, with the data being censored (cessation of data collection) at 12 months of treatment or upon the death of a patient. The objectives of the study were

- to describe the characteristics of HIV-negative and HIV-positive patients with XDR TB in the Eastern Cape,
- to determine patient mortality after 12 months on XDR TB treatment,
- to elucidate risk factors for early mortality,
- to ascertain the role of HIV in mortality due to XDR TB, and
- to consider the effect of treatment regimens on patients with XDR TB.

Over the 15 months, 274 patients were diagnosed with XDR TB; 65 of those patients, or 23.7 percent, died before starting XDR TB treatment. Of the 206 patients in whom treatment was initiated, the HIV status of 195 was known: 108 patients, or 55 percent, were HIV-positive, and 87 patients, or 45 percent, were HIV-negative. Patients were treated with individualized regimens composed of the six first-line and second-line anti-TB drugs available in the province at the time, which were capreomycin, p-aminosalicylic acid, ethionamide, terizidone, ethambutol, and pyrazinamide. Capreomycin and p-aminosalicylic acid, which were available for treatment of XDR TB beginning in October 2006, formed the backbone of the regimen. The effectiveness of each drug was assessed, and drug resistance was tested. Most patients had undergone at least 7 months of previous MDR TB treatment and were dealing with a large burden of TB disease when the XDR TB treatment began.

Among the 206 patients, there were 95 deaths in the first year of treatment. Overall, 36 percent of HIV-negative patients died, as compared with 51 percent of HIV-positive patients. Most of the HIV-positive patients who died were not on antiretrovirals. HIV-positive patients not on antiretrovirals had 2.5 greater odds of death at 12 months compared with known HIV-negative patients. More than 90 percent of HIV-positive patients were diagnosed with HIV prior to admission for XDR TB treatment, and 55 percent of the HIV-positive patients were on antiretrovirals

at the time XDR TB treatment was initiated. As in the model including all patients, patients aged 25–42 or smear positive at the start of treatment had poorer 12-month survival. In assessing the effectiveness of the treatment regimens, a drug was considered effective if (1) it is recognized as an agent for the treatment of TB by the World Health Organization (WHO), (2) the patient had either never received it or received it for less than 3 months prior to XDR TB treatment, and (3) patient isolates were not found to be resistant to the drug by drug susceptibility testing.

Patients were treated with an average of 5.2 different drugs. Of those total drugs, patients received an average of 1.7 drugs that were considered effective. WHO recommends the use of at least four drugs to which the patient's TB is considered susceptible. It was suggested that, in light of the overall poor outcomes for XDR TB, even the WHO recommendation may not be sufficient to cure patients with XDR TB, at least using those drugs available in the Eastern Cape at the time of the study.

Serious adverse effects were noted when a provider withheld a drug because of side effects or when a patient refused to continue with a drug. Overall, 36 patients (18 percent) experienced a severe adverse reaction to at least one anti-TB medication. HIV-negative patients experienced severe adverse effects at three times the rate of HIV-positive patients—31 percent compared with 9.3 percent. It was found that the use of antiretrovirals made no difference in the rate of adverse effects among HIV-positive individuals.

Of the 195 patients, 190 were culture positive at the start of treatment. Sixteen patients (8.4 percent) achieved sputum culture conversion in a median of 143 days, demonstrating the possibility that XDR TB can be cured. There was no difference in the frequency of culture conversion between HIV-positive (10/108, 9.2 percent) and HIV-negative (6/87, 6.9 percent) patients. In the year since these data were collected, four patients have been cured of XDR TB, and follow-up data continue to be gathered.

Kvasnovsky stated that this research confirmed the benefit of using antiretrovirals in HIV-positive XDR TB cases. Therefore, although the current protocol in South Africa is to start antiretroviral therapy when the CD4 count is under 200 and after the first month of XDR TB treatment, Kvasnovsky recommended the early initiation of antiretroviral therapy in all HIV-positive patients irrespective of CD4 count.[2]

[2] South Africa updated its guidelines for antiretroviral therapy to give priority to treatment of individuals coinfected with TB and HIV. Taking effect in April 2010, the national eligibility criteria for adults and adolescents to start antiretroviral therapy regimens include HIV–drug-susceptible TB patients with a CD4 count below 350, as well as all MDR and XDR TB patients coinfected with HIV, regardless of CD4 count. In addition, MDR and XDR TB patients are required to start antiretroviral therapy on a fast track (within 2 weeks of being eligible [i.e., diagnosed with MDR or XDR TB]).

Treatment of Drug-Resistant TB in Other Countries

For purposes of comparison, speakers described treatment of drug-resistant TB in two other countries—Ethiopia and South Korea.

Ethiopia

Anne Goldfeld, Harvard University, described treatment of drug-resistant TB in Ethiopia. Ethiopia has the second-largest population in sub-Saharan Africa, with approximately 80 million people. WHO estimates that there are 129,000 new TB cases per year in the country and ranks Ethiopia seventh among the 22 countries with the highest TB burden worldwide. Based on a survey conducted in 2003–2006, 1.6 percent of these cases are MDR TB, and WHO estimates that there are at least 6,000 new cases of MDR TB each year. According to Goldfeld, the backlog of MDR TB cases needing treatment in Ethiopia is significant, and diagnosis remains a challenge.

In 2008, 221 MDR TB cases had been documented at the Ethiopian National Reference Laboratory in Addis Ababa. The Ethiopian Federal Ministry of Health submitted a funding application to the Green Light Committee (GLC) and received approval for treating a cohort of 45 patients in August 2008, with arrival of drugs anticipated in October 2008.

The Cambodian Health Committee conducted the first MDR TB training for doctors, nurses, health workers, and pharmacists in Addis Ababa in October 2008. As follow-up, the Ethiopian MDR TB team attended MDR TB training in Cambodia led by the Cambodian Health Committee. This program involved both didactic and hands-on training in the Cambodian Health Committee's hospital-, community-, and home-based MDR TB care program. Along with a donation of capreomycin from Eli Lilly, other drugs were acquired with support from the Jolie-Pitt Foundation to begin treating the first cohort of Ethiopian MDR TB patients.

A cohort of 8 patients was started on treatment in February 2009, a second cohort of 12 patients was started in June 2009, a third cohort of 16 patients was started in August 2009, and a fourth cohort of 14 patients was started in October 2009. Treatment of these cohorts was initiated prior to the arrival of the GLC drugs later in 2009, a year after they were expected. When those 45 courses of drugs eventually arrived in Ethiopia, patients were rapidly initiated on them. The 92 patients started on therapy by March 2010 had received an average of three prior treatments for drug-sensitive TB, which had been given because no second-line drugs were available. Fifty patients completed the intensive phase of treatment and have been placed in the continuation phase at home using a community-based approach pioneered by the Cambodian Health Committee in collaboration

with the Ethiopian Federal Ministry of Health, with no defaulters. Approximately 25 percent of the 92 patients were HIV-positive. Three patients died in therapy, two of whom were HIV-positive.

Of the 221 patients who had been diagnosed with MDR TB as of August 2008, all eligible backlog patients who could be traced were started on therapy. Unfortunately, a house-to-house search for these patients revealed that 20 percent were confirmed dead and 50 percent could not be found, some of whom presumably had also died while awaiting therapy.

Goldfeld noted that many of the issues involving TB and MDR TB care in Ethiopia have previously been addressed in Cambodia. One of the first effective programs using short-course chemotherapy with directly observed treatment was begun on the Thai–Cambodian border in a refugee camp in an open war zone in 1980. Subsequently in Cambodia, beginning in 1994, the Cambodian Health Committee began to develop a community-based care approach, "community DOTS," that has been scaled up to the entire country in recent years. A home-based care approach also has been developed and has been highly successful. In addition, the Cambodian Health Committee initiated integrated TB and HIV care in a provincial TB program and in the TB ward of the largest public hospital in Cambodia. Clinical research performed by the Cambodian Health Committee, supported by the National Institutes of Health (NIH) and the French National Agency for AIDS Research (ANRS), has addressed the question of the optimal timing for the introduction of antiretrovirals in immunosuppressed AIDS patients with TB. This research provided an opportunity for the country to obtain first-line AIDS drugs and then drugs for MDR TB cases. The Cambodian Health Committee subsequently obtained second-line drugs for MDR TB through the GLC process and initiated treatment for 136 patients throughout the country by March 2010. Twenty percent of these patients were initiated on MDR TB therapy at home in accordance with the community- and home-based models. An extensive community network of patient supporters administers the drugs with the help of health workers and local health centers. Goldfeld suggested that these approaches are eminently suitable for application in Ethiopia and that this South-to-South transfer of knowledge can serve as a model for expansion.

South Korea

In southern Africa, there is little doubt that HIV infection is accelerating the development of resistance to TB drugs, said Clifton Barry III, NIH. However, resistance is also a natural consequence of treatment with drugs, as is demonstrated by the fact that the same phenomenon is taking place in regions where HIV infection is not common.

Barry described the experience of South Korea, where HIV infection is rare. The National Masan Tuberculosis Hospital is the largest TB referral hospital in the country. It treats about 800 newly admitted patients every year and has about 350 outpatient visits per day. Patients are staying for an increasingly long time, with the mean average duration of admission currently being about 130 days.

Closely tied to the work of the National Masan Tuberculosis Hospital is that of the International Tuberculosis Research Center, which was established in 2005 in South Korea with the aim of improving the diagnosis and treatment of drug-resistant TB and the methodology used for clinical trials of new drugs, as well as understanding the virulence of drug-resistant TB. About 800 patients are currently on four open protocols, the first of which started in 2005. A natural history collection is used to benchmark every patient who comes to the hospital, and the treatment duration is 2 years. In South Korea, a diagnosis of TB requires a mandatory report to the ministry of health, which results in perfect recall for patients who relapse.

Barry reported on a study begun in 2005 at the center, which involves collecting all the strains from patients infected with MDR TB, determining host genetic information, and characterizing different responses to therapy in a large cohort of infected patients. An extensive database of information has been collected by following patients essentially for life. Cohort A includes patients who have never before been treated for TB. Cohort B includes patients for whom retreatment is documented. The cure rate is approximately 58 percent. About 10 percent withdraw from the study for various reasons: 11 percent die; 18 percent default; and 3 percent are chronic cases, almost all of whom have TDR TB (where total drug resistance is defined operationally). Most of the strains are either MDR or XDR TB.

Genotyping and clustering were performed in the cohort enrolled from May 2005 to December 2006, which included 208 culture-positive patients. Even though the rate of clustering was not insignificant, it could be concluded that the XDR TB was not spreading effectively. However, the strains responsible for the individual branches of the epidemic were definitely expanding. In northern parts of South Korea, one subset of the Beijing strain was expanding; in the southern region, a different subset was found.

To date about 1,400 bacterial isolates have been collected. Patients who are on therapy can be followed individually, and drug susceptibility tests can be compared. The injectable drugs used to treat drug-resistant TB are associated with very different rates of adverse reactions, which constitute a significant and underappreciated problem for the management of these patients. Individualized regimens are used wherever possible and are adjusted for adverse reactions. The major predictor of adverse reactions is previous treatment history.

Researchers have compared the results of drug sensitivity testing with clinical outcomes and have found groups of organisms with discrete resistance patterns. They also have detected the major mutations associated with each strain. Four major allele changes are associated with injectable drug resistance, some of which confer cross-resistance. Streptomycin and capreomycin resistance involves discrete genotypic changes. Prior acquisition of kanamycin resistance confers capreomycin cross-resistance, but prior acquisition of capreomycin resistance does not confer kanamycin cross-resistance. Kanamycin and amikacin have particularly high levels of cross-resistance and therefore should be reserved for last use. This approach would require a change in policy guidelines, but it would bring some order to the way these drugs are used clinically and improve outcomes.

Barry stated that within a year or two, resistance will be determined using genotypic resistance determinations. Genotypic drug susceptibility testing has performed well in predicting clinical outcomes, as measured by 6-month sputum conversion.

Treatment and Management of HIV-Associated MDR TB

Padayatchi discussed the recently published SAPiT (Starting Antiretroviral therapy at three Points in Tuberculosis therapy) study, the first randomized controlled trial that corroborated previous evidence on the need to integrate TB care and antiretroviral therapy (Abdool Karim et al., 2010). The study showed that mortality was 56 percent lower in patients who began antiretroviral therapy as soon as possible compared with those who waited until TB treatment had been completed. There have been concerns about potential overlapping toxicities in drugs for MDR TB and HIV; some of the common concerns are peripheral neuropathy, psychiatric symptoms, and hepatitis. However, there are many ways in which these and other potential toxicities can be managed.

Of South Africa's approximately 500,000 TB cases per year, 73 percent are associated with HIV infection, compared with about 12,000 such cases in the United States. It is impossible to "treat our way out of the epidemic," said Stephen Lawn, University of Cape Town. Prevention strategies are essential.

Lawn cited recent data on nine cohorts around the world from both high- and low-prevalence countries showing that antiretroviral therapy substantially reduces TB rates in HIV-positive people, with a range of 54 to 92 percent protection (Lawn et al., 2009) and a pooled estimate of 67 percent (95 percent confidence interval [CI], 61–73 percent) (Lawn et al., 2010). The data demonstrate that there is a time-dependent reduction in TB rates, but the maximum benefit is probably acquired within the first 2 years of treatment. This represents a major advance in preventing TB across different settings, in patients with both moderate and advanced

immunodeficiency, and in both skin test–positive and skin test–negative patients. It is likely that this observation applies to both drug-sensitive and MDR TB, said Lawn.

Patients referred into the antiretroviral therapy program in Gugulethu in the Western Cape, where the burden of TB is high, undergo a 1-month period of screening and investigation for TB before starting antiretroviral therapy. This period is one of great risk for nosocomial TB transmission. More than half of patients referred to the antiretroviral therapy program have already undergone one or more courses of completed TB treatment in the past, a quarter have prevalent disease at baseline, and 11 percent develop TB during the first year of antiretroviral therapy (Lawn et al., 2006). Forty percent of patients are newly diagnosed with TB and commencing treatment for TB at the time they begin antiretroviral therapy, showing that presenting for antiretroviral therapy is unmasking cases of TB that would otherwise go undiagnosed. If these patients were rigorously screened for TB using active microbiological screening prior to starting antiretroviral therapy, the risk of nosocomial TB and MDR TB transmission could be decreased.

Observations made in Tugela Ferry from 2005 to 2007 provided valuable data concerning drug-resistant TB. Virtually all the cases of MDR and XDR TB were associated with HIV and occurred in patients with very low CD4 cell counts (see Box 6-1 for a discussion of CD4 count as a predictor of mortality among MDR and XDR TB patients).[3] The proportion of patients who were on antiretroviral therapy upon diagnosis of MDR and XDR TB was 15 percent and 22 percent, respectively (Gandhi et al., 2010). Almost two-thirds of patients had received a previous diagnosis, most within the previous year and most of drug-susceptible TB. Thus, many of these patients had been under the care of the health care system for some time prior to acquiring MDR TB, and an opportunity to prevent these infections using antiretroviral therapy was missed.

Because many MDR TB outbreaks are driven by HIV-positive patients with very low CD4 cell counts, antiretroviral therapy has a potent preventive effect. The development of new drugs to treat MDR and XDR TB patients effectively will be extremely costly and will take a very long time. By contrast, more than 20 antiretroviral drugs are currently available, and the potential to use them more effectively to prevent HIV-associated TB and MDR TB is currently being squandered. An aggressive scale-up of antiretroviral therapy at the earliest opportunity is warranted, said Lawn.

[3] In October 2006, the National Health Laboratory Service began second-line drug susceptibility testing for amikacin and ofloxacin, allowing for the diagnosis of XDR TB in the Eastern Cape. From October 2006 to June 2007, second-line drug susceptibility testing was available only for patients on MDR TB treatment. After July 2007, isolates from all newly diagnosed MDR TB patients received such testing as well.

BOX 6-1
CD4 Count as a Predictor of Mortality Among MDR and XDR TB Patients

Preliminary data from a case control study conducted in Tugela Ferry to determine risk factors for death among MDR and XDR TB patients show that the CD4 count at TB diagnosis appears to be the best predictor of mortality. Those patients with the lowest CD4 counts are at the highest risk (Lawn et al., 2009). The CD4 count rises during antiretroviral therapy, and the TB incidence falls dramatically. Patients are safest when their CD4 count has passed the threshold of 500, and this should be the goal, according to Lawn. The cumulative lifetime HIV–TB risk depends on the total time spent in different CD4 strata, both before and during antiretroviral therapy. The recently revised WHO guidelines recommend that antiretroviral therapy be started for all people living with HIV at a CD4 count of 350 or less, which will decrease the risk of acquiring TB (WHO, 2010c).

Salim Abdool Karim, University of KwaZulu-Natal, Center for the AIDS Programme of Research in South Africa (CAPRISA), pointed out that the average CD4 count at the initiation of antiretroviral therapy is around 100 because the bulk of these patients have come to the service with an opportunistic infection. If people were put on treatment at a CD4 count of 350 instead of 200, the result would be a roughly 30 percent increase in the number of patients, as it is impossible to test millions of people who look healthy to identify those who are infected. Furthermore, if testing were extended in this way, not enough health services would exist to treat the number of patients. The shift from 200 to 350 would have a greater effect on mortality than on the prevention of HIV or TB, Abdool Karim said. Patients identified with a CD4 count of 350 could receive antiretroviral therapy, but this is not the miracle people are seeking.

It is important that antiretroviral therapy be initiated as soon as possible, with patients receiving treatment immediately upon presenting to the health care system. Lawn noted that current WHO guidelines recommend that antiretroviral therapy be initiated in all HIV-infected individuals with active TB as soon as practicable after the start of TB treatment, irrespective of CD4 cell count (WHO, 2010c).[4]

[4] South Africa's national guidelines for antiretroviral (ARV), which took effect in April 2010, provide that antiretroviral treatment (ART) regimens should be commenced in HIV/drug susceptible TB patients with a CD4 count less than 350, and in all HIV/MDR or XDR TB patients, regardless of CD4 count. MDR and XDR TB patients are required to start ART on a fast-track (within 2 weeks of being eligible [i.e., diagnosed with MDR or XDR TB]).

Several workshop participants noted that physicians can inadvertently increase the non-TB patient population's exposure to important anti-TB drugs. For example, common infections, such as urinary tract infections, often are treated with fluoroquinolones (which are also used to treat MDR TB), a practice that can increase an individual's resistance to this important category of antibiotics. Doctors may need an intensified education program concerning the management of TB and the importance of accurate diagnoses, suggested one participant.

In addition to the cotoxicities of antiretrovirals and second-line TB drugs, the risk of immune reconstitution inflammatory syndrome (IRIS) is greater when the interval between the start of TB treatment and the start of antiretroviral therapy is shorter. Patients thus need to be monitored for cotoxicities and IRIS, said Lawn. An early start on antiretroviral therapy can lead to toxicity problems, but given the positive effect of antiretroviral therapy on lowering mortality and morbidity rates, an option to be treated early is necessary. At the same time, Lawn suggested, research is needed to assess the relationship between the early initiation and the toxicity of antiretroviral therapy, and ways must be found to make early antiretroviral therapy sustainable. Moreover, Lawn noted, the recent revision of the WHO guidelines has promoted a phasing in of less toxic antiretroviral regimens (WHO, 2010c). According to the WHO guidelines, initial antiretroviral therapy should include a non-nucleoside reverse transcriptase inhibitor plus two nucleoside reverse transcriptase inhibitors, one of which should be zidovudine or tenofovir. WHO also recommends that countries begin to phase out the use of stavudine (d4T) in first-line antiretroviral regimens because of its toxicities.

Research Needs

Chaisson suggested that much more clinical research on the treatment of MDR TB is needed. For example, more research is needed on existing drugs and their effectiveness against particular TB strains.

Jacobs emphasized the potential of research on preventing the emergence of drug resistance with simple compounds available in the diet. He explored the possibility that particular compounds can block the mutations that lead to resistance. When excess cysteine was added to a culture undergoing selection for isoniazid resistance, it sterilized the culture. In other words, mutants were unable to arise from the persistent cell population when cysteine was present. The effect is dose- and time-dependent, and the thiol group of cysteine is essential for activity. Jacobs suggested that this idea should be examined in the search for compounds that can prevent the emergence of drug resistance.

Sturm noted that the variation among strains in southern Africa is

much greater than is suggested by the broad categories of MDR and XDR TB. Standardized treatment regimens for these categories are therefore inadequate and will lead to greater resistance; however, the region is not yet at the point at which individualized treatments can be instituted, according to Sturm. Much more needs to be known about resistance patterns for TB strains throughout southern Africa to support the development of individualized treatment regimens, he noted. Barry pointed out that XDR TB is not a biological descriptor of the strain; the question that should be asked is how the structure has changed and what is seen in the patient.

COMMUNITY-BASED CARE[5]

Wallengren explained that the experience in KwaZulu-Natal demonstrates some of the challenges and opportunities of community-based care. As MDR TB cases have increased, there has been an increase in admission of MDR TB patients to King George V Hospital in Durban, South Africa, which has only 320 beds. It takes approximately 16 weeks to initiate treatment once a sputum culture has been taken and the patient has been admitted to the hospital. To accommodate the dramatic increase in admissions, it has become necessary to discharge patients, many of whom are not yet healthy and are still infectious. The average length of stay in the hospital has decreased from 6 months to 2 months. In 2006, more than 30 percent of patients were culture positive, and more than 15 percent were smear positive when they left the hospital. These patients went home to households that were unprepared to manage side effects or practice infection control. Patients had to return to King George V Hospital once a month for follow-up visits, sometimes traveling distances of up to 500 km. A lack of infrastructure support for patients has resulted in poor treatment outcomes and a cure rate of just 40 percent over the last few years at the hospital.

Today hospitalization is not feasible because of the high numbers of MDR TB patients. In KwaZulu-Natal Province, alternative treatment is already taking place, with many patients returning to their households and communities, where treatment is continued. The challenge is to provide these patients with the support they need.

To this end, decentralized MDR TB treatment is being piloted at four sites situated in four districts of KwaZulu-Natal; patients began treatment in the decentralized system in 2008. King George V Hospital has a supervisory role and provides technical support to the decentralized sites. Complicated cases are admitted to the hospital. Eligible patients are started on the intensive phase of treatment. They receive appropriate education

[5] This section is based on the presentation of Kristina Wallengren, South African Medical Research Council.

about their disease, their homes are assessed with respect to decentralized care, and a plan for continued care is issued. When patients are discharged from the hospital, they are assigned to teams within the decentralized unit. The teams administer injections, monitor side effects, support treatment, refer complications to the unit, and continue patient and family education in TB and infection control. The teams are assisted by DOTS supporters or family members who are trained as treatment supporters. Family members are involved in both the intensive phase and the continuation phase of treatment. Patients return to the decentralized clinics for a monthly visit, where treatment is assessed and side effects are addressed. The teams transport drugs in cooler boxes and use a GPS unit to locate patients. When roads are impassable, team members sometimes have to walk considerable distances to get to patients. The selection criteria for decentralized care are as follows:

- Patients must have noncomplicated MDR TB.
- The decision to place a patient under community care is made by a multidisciplinary group consisting of a medical doctor, a nurse, an MDR TB coordinator, and a social worker.
- The patient should be smear negative and have stable accommodations and nutritional support.
- The patient and family must have received adequate education and be able to follow the plan for the administration of drugs.

Since July 2008, 420 patients have been placed in decentralized care, and their progress has been compared with that of patients in centralized care at King George V Hospital. Some early results are as follows:

- Most patients are tested for HIV, and the HIV-positive rate is 74 to 78 percent.
- Decentralized sites have been effective in ensuring that HIV-positive patients receive antiretroviral therapy.
- Integration of antiretroviral therapy into the MDR TB treatment program has been problematic. A lack of communication among vertical programs is a notable challenge. Moreover, it seems that the TB/HIV integration itself has become a vertical program. Wallengren noted that the challenge for both TB and HIV treatment lies in the clinics delivering the care, rather than in the patients not complying with treatment.
- Mean TB smear positivity at diagnosis is 73 percent in the decentralized sites and 57 percent in the centralized hospital.
- The treatment delay is shorter at the decentralized sites, with an average of 90 days from diagnosis to treatment, compared with 108 days at King George V Hospital.

- TB culture conversion is 66 percent in the decentralized sites.
- With respect to early treatment outcomes, 14 percent died, 3 percent failed, and 2 percent defaulted.

According to Wallengren, the challenges faced by the decentralized program include high staff turnover, inadequate staff training, inadequate support for nurses (clinically, monetarily, and administratively), drug shortages (due to either reduced orders at the district level or problems with procurement and distribution at the provincial level), and integration of antiretroviral therapy.

LIMITATIONS OF HEALTH CARE SYSTEMS AND COST ISSUES

The current TB epidemic is reminiscent in some ways of the HIV epidemic in the late 1980s and early 1990s, said Robin Wood, University of Cape Town. The numbers of patients were so great that the capacity of existing health care facilities was inadequate. There was great fear among health professionals, some of whom shunned infected patients. A major difference, however, is that the HIV epidemic was more linked with human rights issues, and patient and activist groups served as advocates for change.

Because sufficient beds are not available, drug-resistant TB patients diagnosed in the general ward of a hospital generally remain there while they wait for a bed to become available at a referral hospital. These patients are being cared for by people who are insufficiently trained and unaware of both the needs of the patients and infection control. Building more capacity requires money and time. A short-term solution, said Wood, is to modify existing health care facilities, improve infection control, and incorporate community-based management of TB. Wood emphasized that concern for the human rights of patients should underpin any strategy used to manage TB. Of equal concern is the health of health care workers.

Padayatchi called for simultaneous advances on several fronts. She cited the need for (1) rapid diagnostics and new TB agents; (2) health systems research to analyze such options as decentralized treatment and integrated management of HIV, MDR TB, and XDR TB; (3) better referral and outreach systems to minimize the default rate; (4) advocacy; (5) improved surveillance; (6) an appropriate prophylactic for contacts (for both adults and children); and (7) further exploration of empiric treatment, which is already being started in Tugela Ferry.

Lerole David Mametja, Department of Health, South Africa, stressed the need for financial support. When WHO reviewed South Africa's TB control program in July 2009, it estimated that 1 percent of the population or approximately 490,000 South Africans had TB in 2008 and that 2 percent of the TB cases were MDR. Data from the National Health Laboratory

Service showed that about 6,200 cases of MDR TB were diagnosed in 2008, but only 4,600 became part of the treatment program. Thus a large number of MDR TB cases are disappearing from the system.

WHO has estimated that successful TB control and management in South Africa would require R5.2 billion. Mametja stated that not enough funding is available to produce the required response to TB in the country. Challenges involving the interactions between national and provincial governments have resulted in the inability of the national TB program to access all the funds assigned to it. These challenges have impeded the reversal of the spread of TB and drug-resistant TB.

According to government policy, all drug-resistant TB cases must be hospitalized, but only 2,000 beds are available for this purpose. Thus the policy is unworkable, said Mametja. Although South African governments have tried to expand the bed capacity, funding this expansion has been difficult. Moreover, the solution will have to go beyond creating more beds; it may require returning to the basics of TB control and management so as to preempt the onset of MDR and XDR TB. One workshop participant added that the cost of drugs is an issue as well, with a course of moxifloxacin and capreomycin, for example, costing thousands of U.S. dollars. Barry said that the choice is either to add to the problem by using suboptimal drugs or to design a regimen that contains the epidemic. Pressure must be applied to bring the price of drugs down, said a participant.

Cassell noted that a good DOTS program will not necessarily prevent the spread of MDR TB, which has continued to increase even in areas with such programs. However, a major requirement for accessing global funds is to have a good DOTS program in place. In fact, patients are spreading resistant strains for almost 2 years until drugs arrive.

Gandhi observed that since 2007, Tugela Ferry has seen a major influx of resources, primarily financial, that have allowed staffing for the TB treatment program to be increased. From two nurses in 2004, the TF CARES facility now has more than 30 staff members working in the program. As a result, treatment for drug-susceptible TB has improved from a little more than 60 percent to more than 83 percent at present, and the default rate for 2 consecutive years has been zero.

7

Drug-Resistant TB in Children

Key Messages

- An increasing number of children in southern Africa are contracting drug-resistant TB, mainly through transmission.
- Diagnosis of drug-resistant TB and assessment of side effects are often more difficult in children than in adults.
- The optimal duration of treatment in children is unknown but is likely shorter than in adults.
- Better data on mortality and causes of death would clarify the extent of the epidemic among children.

An increasing number of children in southern Africa are contracting drug-resistant TB. Simon Schaaf, Department of Paediatrics and Child Health, University of Stellenbosch, reviewed special issues in the diagnosis and management of pediatric MDR TB, illustrated by the family case study in Box 7-1.

EPIDEMIOLOGY OF PEDIATRIC DRUG-RESISTANT TB[1]

Drug susceptibility testing and DNA fingerprinting have demonstrated that MDR TB in children results mainly from transmitted drug resistance.

[1] The remainder of this chapter is based on the presentation of Schaaf.

BOX 7-1[a]
A Family Case Study Illustrating Issues in Pediatric MDR TB

MDR TB and drug-susceptible TB cases commonly live in the same household in South Africa. In one family, the maternal grandmother had her fourth episode of TB in 2007 and had previously been identified as an MDR TB case. The grandfather died of MDR TB before 2004. An uncle had drug-susceptible TB during that same period and has since been treated and cured.

When the uncle left the household, the mother and a child aged 10 months remained. At the time, the child was asymptomatic and had a negative Tine tuberculin skin test;[b] it was unknown whether a chest xray had been taken. He was started on a regimen of isoniazid prophylaxis. The child presented 4 months later when the grandmother was again admitted for confirmed MDR TB. The child had had a cough for a week; his weight was in the 75th percentile; he was clinically well, but his Mantoux test[c] converted to positive at 30 mm and was ulcerating; his chest x-ray showed some nodes and opacification; and he was HIV-negative.

The child was started on a treatment regimen of isoniazid, pyrazinamide, ethambutol, ethionamide, ofloxacin, and amikacin. Gastric aspirates were taken, two of which were culture positive, resistant to isoniazid and rifampicin, and susceptible to ethambutol. The grandmother's second-line drug resistance returned a few months later—this time not only to isoniazid and rifampicin but also to amikacin. The child's treatment was changed from amikacin to capreomycin, and terizidone was added.

During the child's follow-up, hearing tests could not be administered because the child was too young, but renal function was normal. Each of the six monthly follow-up cultures was negative. The child was treated for 18 months after the first negative culture. The capreomycin was stopped after 4 months, for a total of 6 months of injectable drug treatment. The child was discharged in April 2008. The grandmother was diagnosed with pre-XDR TB[d] and died in March 2008.

The mother was pregnant and moved to live with the paternal grandmother in a nearby town. She was diagnosed with TB in August 2008, 4 months after the child was discharged, and did not disclose that the paternal grandmother had MDR TB. The child was still on MDR TB treatment. The mother started treatment but defaulted and, not surprisingly, did not respond to the treatment. She was smear positive at 2 months, when her baby was born, and MDR TB was confirmed in December 2008. She died of MDR TB 3 months later. It was confirmed 3 months after her death that her TB had been susceptible to second-line drugs.

The baby was not given a BCG vaccine at birth and was started on a low dose of isoniazid treatment a few weeks after birth (as prophylaxis because the mother had TB). The local doctor interpreted a chest x-ray as normal. The baby's treatment was changed to isoniazid (high dose), ethambutol, and ofloxacin, with questionable compliance, as prophylaxis against MDR TB (when the mother was confirmed to have MDR TB). The baby's first visit to the local clinic was in March 2009. He was a healthy-looking baby who had good weight gain, a 1-week fever, and no other symptoms. The prophylactic treatment was defaulted for only 2 weeks during the mother's funeral. The baby was HIV-negative, and his Mantoux test was 10 mm. A chest x-ray showed progression of the disease despite the prophylaxis, and the regimen was changed to isoniazid, pyrazinamide, ethambutol, ethionamide, ofloxacin, terizidone, para-aminosalycilic acid, and capreomycin. Baseline renal function and liver function tests were normal, and the baby was progressing well on the treatment. However, the culture results and drug susceptibility tests showed that his TB was resistant to isoniazid, rifampicin, and ofloxacin. The paternal grandmother took over the care of both children once the injectable drug regimen had been completed, and both are doing well.

According to Schaaf, lessons learned from this case study include the following:

- It is critical to take a full history of all adult TB cases, and it is important to know when to screen for MDR TB.
- Screening for TB is important in child contacts. If there is no disease, children need the appropriate prophylaxis, and they must be put on the correct regimen at the right time. Follow-up must be done to ensure that they are well.
- Screening with chest x-rays is necessary for children, but the x-rays must be interpreted correctly.
- TB in children should be treated according to the drug susceptibility tests of the adult source case until the results of the child's own culture and drug susceptibility tests are available.
- Good weight gain is not always a sign of a good clinical response.
- Management of MDR TB in pregnancy needs to be studied and discussed further.
- MDR TB and pre-XDR TB are curable diseases.

[a]This box is based on the presentation of Simon Schaaf, University of Stellenbosch.

[b]The Tine test is a multiple-puncture tuberculin skin test used to aid in the medical diagnosis of TB. It uses a small "button" that has four short needles coated with TB antigens (tuber-

continued

BOX 7-1 Continued

culin). The needles are pressed into the skin (usually on the inner side of the forearm), forcing the antigens into the skin. The test is read by measuring the size of the largest papule that emerges. A negative result is the presence of no papules.

[c]The Mantoux test (also known as the Mantoux screening test, Tuberculin Sensitivity Test, Pirquet test, or PPD test [for purified protein derivative]) uses a glycerol extract of the tubercle bacillus. PPD tuberculin is a precipitate of non-species-specific molecules obtained from filtrates of sterilized, concentrated cultures. A standard dose of 5 tuberculin units (0.1 mL) is injected intradermally and read 48 to 72 hours later. A person who has been exposed to the bacteria is expected to mount an immune response in the skin containing the bacterial proteins.

[d]Pre-XDR TB refers to MDR TB plus one-half of the resistance equation for XDR TB. As defined in Chapter 1 (Box 1-1), XDR TB is resistant to the same drugs as MDR TB (isoniazid and rifampicin), as well as any fluoroquinolone (levofloxacin, moxifloxacin, or ofloxacin) and at least one second-line injectable drug (kanamycin, amikacin, or capreomycin). Pre-XDR TB is MDR TB that displays resistance to one of the fluoroquinolones or a second-line injectable drug.

Acquisition of MDR TB is more difficult because of the paucibacillary nature of the primary disease, but it is possible with cavitary pulmonary disease. Disease in children usually develops within 12 months of infection.

Epidemiological surveillance undertaken at the Tygerberg Children's Hospital in the Western Cape between 1994 and 2009 produced several important findings related to the epidemiology of drug-resistant TB in children:

- There is a high prevalence of drug-resistant TB in the Western Cape.
- Despite previous treatment, more than 90 percent of all drug-resistant TB in children was most likely due to transmitted resistance.
- Hospital-based surveys are potentially biased because sicker children or children with complications usually are referred to a hospital. However, no significant difference was found in drug-resistant TB in children in a community-based versus a hospital-based survey.
- Drug resistance is not significantly different between HIV-infected and HIV-uninfected cases.
- A lack of drug susceptibility tests in adult source cases hampers effective management of child TB contacts.

PROPHYLAXIS AND DIAGNOSIS OF PEDIATRIC DRUG-RESISTANT TB

Contact tracing and follow-up of children exposed to MDR and XDR TB should receive high priority so prophylactic treatment can be initiated, suggested Schaaf. When adults present with TB, the entire household should be screened. A 2002 study showed that giving a child two drugs to which the adult case is susceptible can prevent MDR TB cases. A combination of high-dose isoniazid plus ethambutol or ethionamide plus ofloxacin for 6 months has been used in the Western Cape, but studies are needed to determine whether a single drug could be used. Failure of isoniazid or isoniazid plus rifampicin to prevent MDR TB has been reported in many cases. The solution to isoniazid monoresistance is to give rifampicin for 4 months. Rifampicin monoresistance is treated with isoniazid for 6 months. Pre-XDR or XDR TB cases can be given only a high dose of isoniazid (15–20 mg/kg). In both MDR and XDR TB cases, regular follow-up for a minimum of 12 months is essential.

In general, the prophylactic treatment of children in South Africa is not optimal, said Schaaf, although there is a policy that children under age 5 and all HIV-infected children should be screened for TB and if there is no disease, should be placed on prophylactics. Schaaf's policy is to start children with HIV infection, who constitute about 30 percent of his pediatric patients, on antiretrovirals as soon as possible. He has experienced very few problems with antiretrovirals and second-line TB drugs.

Diagnosis of MDR and XDR TB in children requires a microbiological diagnosis, which is often difficult because of paucibacillary TB. The use of line probe assays for diagnosis of children may mean that about 10 percent of MDR TB cases are misdiagnosed as rifampicin-monoresistant TB. Drug-resistant TB is probable, however, if a child has had known contact with an adult drug-resistant pulmonary TB case. Drug-resistant TB should further be suspected if a child is adhering to treatment and fails therapy or if an adult source case with an unknown drug susceptibility test result is a treatment failure, is a retreatment case, or has died of TB during adherent treatment.

DRUG TREATMENT REGIMENS FOR PEDIATRIC DRUG-RESISTANT TB

According to the 2008 updated WHO guidelines on drug-resistant TB, the drugs used to treat MDR TB in children fall into five groups:

- *Group 1*—Remaining first-line drugs: a combination of a high dose of isoniazid and ethionamide can create one effective drug.

Although ethambutol and pyrazinamide are used, they are not regarded as reliable, and 50 percent of cases of MDR TB in children are resistant to ethambutol.[2]

- *Group 2*—Second-line injectables: kanamycin, amikacin, and capreomycin. The reason for using amikacin is that it causes fewer side effects in children, and the doses are relatively easy to administer.
- *Group 3*—Fluoroquinolones: although said not to be suitable for children, maximum doses are used. These are very important drugs in MDR TB therapy.
- *Group 4*—Second-line oral bacteriostatic drugs: split into two doses per day initially to alleviate any adverse effects.
- *Group 5*—Drugs that have an unclear role in the treatment of drug-resistant TB. Linezolid and clarithromycin are sometimes used, although they are very expensive and difficult to obtain.

Schaaf emphasized the importance of documenting and trying to prevent adverse effects associated with these drugs. About 30 percent of children have experienced hearing loss, and a high percentage have developed hypothyroidism. Other common adverse effects in adults are not common in children.

The optimal duration of treatment in children is still unknown. Cavitary or extensive pulmonary TB needs to be treated as for adults. Primary, non-cavitary MDR TB is often culture negative, and treatment for 12 to 15 months should suffice. Treatment in the intensive phase includes a second-line injectable drug, which is usually discontinued in the continuation phase.

Schaaf said health care providers have become more aware of potential adverse effects of drug treatment in children and need to monitor patients carefully to detect such effects and determine when the drugs must be stopped. The World Health Organization (WHO) calls for the administration of drugs for 2 years, but Schaaf believes children can be treated for shorter times, particularly for early, paucibacillary disease. He has treated many patients for 12 months and has seen no relapses, but the length of treatment for each child needs to be evaluated individually. In addition, new drugs should be tested on children as well as adults, said Schaaf. Not enough is known about the pharmacokinetics and adverse effects of

[2] During the discussion period, Schaaf was asked whether he has noticed problems with vision in children caused by ethambutol. He responded that it is difficult to test vision in younger children, and only color charts are used. Studies have shown that as long as the dose of the drug is lower than 25 mg/kg, the chances of developing such problems are small, and none of Schaaf's patients have had adverse reactions related to vision. Ethambutol is used in drug-resistant as well as drug-susceptible cases since isoniazid resistance is very high in the Western Cape.

drugs in children, including their interactions with antiretrovirals. Finally, management of children and adolescents to ensure compliance with drug regimens is necessary.

MANAGEMENT OF PEDIATRIC DRUG-RESISTANT TB

The management of MDR TB in children should be carried out as follows, according to Schaaf:

- Confirm MDR TB if at all possible.
- If MDR TB is confirmed, also do drug susceptibility testing for second-line drugs.
- Manage cases at a specialized MDR TB clinic.
- Use first-line drugs to which the isolate is susceptible plus second-line drugs, taking into account that 50 percent of cases of MDR TB in children are resistant to ethambutol.
- Be aware of different drug groups and cross-resistance.
- Recognize that second-line drugs are generally more toxic than first-line drugs.
- Recognize that adverse events can be more difficult to assess in children than in adults.
- Be mindful of the difficulty of preserving the correct dosage when breaking tablets up to make them easier for the child to swallow.
- Isolate children who are infected with TB. In practice, this can be difficult since the adults accompanying children are often infected with MDR or XDR TB but not diagnosed.

Schaaf outlined the following principles of childhood MDR TB treatment:

- Directly observed therapy with daily treatment is essential.
- Three, four, or more drugs to which the patient's isolate is susceptible and/or naïve should be administered, depending on the extent of the disease.
- If a treatment regimen is failing, a single drug should not be added (combination therapy should be used).
- The drug susceptibility test pattern of the adult index case's isolate should be used if no isolate from the child is available.
- Patients, parents, and family members should be counseled at every visit with respect to adverse events and the importance of adherence to treatment, as well as to offer support.
- It is essential to ensure that follow-up occurs, including clinical and radiological follow-up, as well as cultures.

OUTCOMES OF PEDIATRIC DRUG-RESISTANT TB

Very few studies have reported on the outcomes of drug-resistant TB in children. One such study is from Peru, where 36 of 38 MDR TB cases were cured (Drobac et al., 2006). Another, conducted in South Africa in 2003, showed that of 39 confirmed MDR TB cases, the majority were clinically cured (Schaaf et al., 2003). More data on morbidity and long-term mortality in children, as well as on HIV-infected and HIV-uninfected children, are needed, said Schaaf.

Asked about the mortality figures for children with MDR and XDR TB, Schaaf replied that data since 2003 show 150 culture-confirmed cases of MDR TB, with a mortality rate of about 10 percent. There are currently 6 confirmed XDR TB cases, 3 with culture confirmation and 3 having had contact with adults with XDR TB. Schaaf said he has not had a child die from XDR TB.

Schaaf emphasized that if children are treated incorrectly when there is a known adult index case with MDR TB in the household, much lung damage can be done, leading to chronic lung disease. He suggested that mortality and morbidity should both be examined in looking at the outcomes of pediatric patients with MDR TB.

8

Convergence of Science and Policy to Create a Blueprint for Action

In the final session of the workshop, Enriqueta Bond and Salim Abdool Karim summarized the major conclusions and recommendations offered by the speakers. A panel consisting of Gail Cassell; Norbert Ndjeka, Department of Health, South Africa; Sidney Parsons,[1] Council for Scientific and Industrial Research (CSIR); Janet Tobias, Ikana Media; and Martie van der Walt, then raised additional issues and responded to questions from workshop participants. This chapter synthesizes the points made, as well as a number of individual suggestions for actions to address urgent needs related to drug-resistant TB, in the areas of epidemiology, infection control, diagnostics, treatment, pediatric TB, research needs, and the need for partnerships. It should be noted that this synthesis is offered as part of the factual summary of the workshop, and should not be construed as reflecting consensus or endorsement by the workshop, the Drug Forum, or the National Academies.

EPIDEMIOLOGY

Bond stated that the alarming epidemiology of MDR and XDR TB creates a new urgency for action. Drug-resistant TB is a difficult-to-treat disease that is spreading in the community and is exacerbated by HIV infection. Growing evidence that drug-resistant TB is being transmitted from person to person supports the conclusion that the number of cases seen in southern Africa are only the visible portion of a much larger phenomenon.

[1] Deceased.

Abdool Karim remarked that, as Friedland's presentation highlighted, when patients are placed on antibiotics, pressure to select resistance grows. The experience in Tugela Ferry (Chapter 2) illustrates the person-to-person spread of drug-resistant TB and the fact that fatalities can occur quickly following infection with XDR TB, particularly among patients with HIV coinfection. Abdool Karim added that a steady increase in resistance eventually will make TDR TB a serious and common problem. Cassell commented that another disturbing observation is the 60 percent rise in XDR TB incidence rates in the Eastern Cape.

As Chaisson noted, a good definition of TDR TB in terms of either the molecular detection of resistant genes or clinical failures does not yet exist. According to Abdool Karim, given the variability in drug susceptibility testing among patients in the region, susceptibility testing on second-line drugs is not necessarily a good way to define TDR TB. Instead, the definition of TDR TB could be based on a clinical diagnosis after failure of treatment for MDR/XDR TB. A workshop participant stressed the importance of accurately measuring the magnitude and distribution of the spread of TDR TB as part of efforts to confront and reverse the epidemic.

INFECTION CONTROL

Improved infection control and contact tracing could lower morbidity and mortality from drug-resistant TB and lead to the treatment of many more cases. In addition, the creation of a culture of safety through infection control policies could provide greatly increased protection for patients and health care workers. Abdool Karim stated that infection control should be a part of every TB intervention and needs to begin when a patient is identified, diagnosed, and hospitalized. To support infection control, there is a need for further investigation of the mechanisms and sites of the spread of TB within communities, said Abdool Karim, and once infection control measures have been implemented, it will be important to evaluate their effectiveness and make them more broadly available. Improvement in the safety of existing health care facilities is warranted, as is incorporation of infection control in the design and construction of new health care facilities.

An important problem is the lack of district nurses to visit schools and homes. Part of the solution, Cassell suggested, could be to train community workers to become specialists in infection control, with a certificate program that could offer practical training and raise the profile of the role of the community worker. When community health workers are paid, trained, and qualified, they can help ensure that everyone becomes an active participant in health care. Abdool Karim highlighted Lawn's remarks that contact tracing should be part of all TB programs and should include TB education as a component of the intervention.

Abdool Karim added that, as noted in Thotolo's presentation, better systems are also needed for the prevention, diagnosis, and treatment of TB and HIV for special populations, including mine workers, ex-miners, and their families; incarcerated populations; and others in difficult-to-reach congregate settings. In addition to health care interventions, it is essential to address the legal, human rights, and socioeconomic issues affecting TB and HIV control among these populations.

DIAGNOSTICS

Abdool Karim noted that, in the discussions about diagnostics, it became clear that additional screening mechanisms and new assays, including point-of-care TB diagnostics, could transform the ability to deal with drug-resistant TB. Developing these tools will require a greatly expanded research effort. At the same time, current diagnostic approaches require safe laboratory infrastructure to protect against drug-resistant TB. Bond added that meeting the pressing need for laboratory and health care infrastructure will require ongoing, long-term capacity building.

Parsons added that unsuspected cases are a danger. These cases are causing great concern and putting health care workers, communities, and households at risk. Parsons suggested that a process for making interim diagnoses while awaiting the results of more detailed yet time-consuming diagnostics is needed to identify potential TB cases and the strains involved so health care workers can assist with managing patients in the community.

TREATMENT

Although the cure rate of MDR TB in South Africa and surrounding countries remains uncertain, drug-resistant TB clearly is not being managed well enough, suggested Ndjeka. Abdool Karim highlighted the growing prevalence of resistance to multiple agents and the especially dire observation that increasing numbers of isolates are resistant to ten key anti-TB drugs. A workshop participant noted that the field of therapeutics for drug-resistant TB has been neglected, and there is a lack of adequate evidence to guide best practices in treatment. Thus, there is a critical need for basic, translational, clinical, and operational research in this area. As Barry suggested, the available evidence must be carefully weighed to determine the sequence in which various antibiotics should be used to avoid resistance while taking into account that cost is also an issue in the choice of drugs. In addition, Abdool Karim remarked, Friedland's presentation highlighted that the default rate must be addressed if a reasonably high cure rate is to be achieved. Good adherence to treatment and prevention of person-to-person spread of drug-resistant TB are essential to controlling the disease.

Cassell remarked that existing drugs need to be used to maximum effect through the application of available evidence and the results of microbiological and pharmacokinetic studies. In the discussion of Schaaf's experience in treating children with TB (Chapter 7), it was suggested that pediatric MDR and XDR TB cases should be treated for 12 months, not 24 months as stipulated by the World Health Organization (WHO). A participant observed that, given the adverse effects of second-line drugs, this is an important suggestion, but it needs to be confirmed by rigorous studies. Another suggestion was that drugs used for cross-resistance be reserved for later in treatment regimens. One workshop participant recommended that a group of experts be convened in South Africa to study side effects and cross-resistance.

Van der Walt noted that individualized regimens based on drug sensitivity testing and drug toxicity have become necessary, but in reality, management of MDR TB must be both simplified and decentralized to clinics and other sites, and treatments for TB and HIV need to be integrated. This is a challenge for clinics, one that requires translating policies into practice and applying research evidence in the field. Health care workers will also need training in the diagnosis and treatment of coinfection with HIV, according to van der Walt.

Parsons remarked that funding of $13–$15 million was recently received to increase bed capacity in South Africa. Models are being developed for treatment facilities, most of which will be built to have seven units, each with 40 beds. A minimum of 280 additional beds will be available by December 2010. These beds should be used specifically for intensive-phase treatment and for initial management of patients. However, even these new facilities will not be adequate for the hospitalization of MDR and XDR TB patients, according to Parsons. Van der Walt added that, according to South Africa's current policy, MDR TB patients must be hospitalized until culture conversion. Hospitalization provides the patient and the family with treatment management and aids their well-being, and the additional beds will be extremely beneficial. With the increasing numbers of MDR TB cases, however, there will continue to be a shortage of beds.

A related problem is that the success rate of MDR TB treatment within 6 months at a facility is extremely low. Gandhi commented that documenting a negative culture means that 10 weeks must pass before results are returned, which doubles the duration of a typical hospital stay. Defaulters are often stigmatized, but in reality the structure makes it very difficult for them to adhere to treatment.

Parsons added that being a patient in a typical facility for 10 months or more is difficult to imagine. While the treatment is good, the hospital environment is not the best place for healing the patient. The process

needs to be humanized, with attention to patients' dignity and comfort, good meals, and the like, and for most patients, particularly from rural areas, closer proximity to their families and loved ones. A comprehensive approach, including outpatient and community-based treatment and care management, is warranted.

Coetzee commented that patients can be treated effectively and humanely within the community. However, discharging TB patients into the community poses a risk. Patients should not be discharged until appropriate structures are in place to provide adequate treatment and care, especially since DOTS supporters are already overburdened. Gandhi stated that parts of KwaZulu-Natal Province have made the necessary transition to community-based care over the last few years. In 2007, as a result of the overwhelming burden of MDR TB, many people were receiving outpatient treatment in an informal way. Since then, care has been decentralized to centers, to communities, and to homes. When this is done in a structured way, as has been the case in Tugela Ferry, outcomes are very good. In Tugela Ferry, an intensive monitoring system is in place, with teams that visit patients' homes. Community health workers who are doing the monitoring are paid, which has made a difference.

Parsons noted that one problem with community-based care is that many different types of communities exist in southern Africa. For example, although more study is warranted, community-based care programs appear more likely to succeed in rural communities than in informal settlements. As another example, work in the Eastern Cape to understand the dynamics of rural communities has uncovered a network of traditional leaders and healers who will need to be included in community- and home-based care. Because of the diversity of communities, Parsons said, a multidisciplinary, community-appropriate approach is needed to combat the disease.

Ndjeka remarked that the first draft of a policy to decentralize MDR TB treatment in South Africa has been circulated, but more input and consultation are needed. Because of the diversity of South Africa, each province will have different needs in implementing the policy, with a standard package of requirements being made available across all programs. More generally, said Ndjeka, the actions necessary to control the epidemic need to be clearly articulated, and a plan for moving forward, including costs, needs to be formulated at the highest levels of government.

XDR TB cases will continue to pose great therapeutic challenges. The burden of untreatable cases needs to be assessed based on the available scientific and medical evidence, as do the reasons for these cases being potentially untreatable. Van der Walt noted that new policies could raise human rights concerns and foster public panic; nevertheless, the extent of the problem needs to be communicated, and policy makers will need assistance with the ethical issues associated with untreatable cases.

Abdool Karim noted that the presentations highlighted the challenge of managing TB–HIV coinfection. He suggested that both diseases should be treated concomitantly, and systems of care for each should be better integrated. Separation of TB and HIV treatment reduces the likelihood of therapeutic success and survival of patients. As Lawn suggested, antiretroviral therapy should be initiated immediately in all HIV-positive individuals irrespective of CD4 count to lessen vulnerability to TB infection. Studies are under way to test this hypothesis.

Finally, Ndjeka noted that WHO's review of the South Africa TB program in 2009 found that the management of MDR TB in the country does not comply with WHO guidelines. Indeed, it does not comply with the guidelines of the country's own Department of Health. Monitoring and evaluation are not being performed efficiently, the time required for injectable drug treatments contributes to defaulting, and patients and communities need more information about MDR TB.

PEDIATRIC TB

According to Bond, a key problem identified during the workshop was that an increasing number of children in southern Africa are contracting drug-resistant TB, mainly through transmission. Children serve as sentinels of the burden of disease, but knowledge of the sources of transmission and of what drug regimens are best for children, as well as pregnant women, is still lacking. Policies and strategies need to accommodate specific situations and scenarios, suggested Bond.

Abdool Karim remarked that as treatment is decentralized not just into district-level facilities but into community-based care, special populations such as children and pregnant women may be easier to reach. One way to improve identification of TB in children is to take a full history of all adult TB cases, including screening for TB in child contacts. Counseling of patients, parents, and family members at every visit would provide support and information about adverse events and the importance of adherence to treatment and follow-up. TB in children could be treated according to the results of drug susceptibility tests of the adult source case until the results of the child's own culture and drug susceptibility tests were available. Improved pediatric diagnosis is a priority, as most cases are treated empirically without microbiological confirmation and thereby go unrecognized.

RESEARCH NEEDS[2]

Over the course of the workshop, individual participants suggested a number of research questions that, in their judgment, need to be pursued, such as the following:

- How many cases of drug-resistant TB are occurring in southern Africa that are not being diagnosed? How can diagnosis be improved?
- What is the current extent of MDR, XDR, and TDR TB? How can cases be identified more rapidly?
- What is the benefit of intensive case finding in health care facilities and community settings in terms of earlier detection, improved outcomes, and reduced transmission of drug-resistant TB?
- How should information systems be developed and implemented for the management of laboratory and surveillance data?
- What are the best available and future treatment regimens? How can clinical trials be designed and executed to test existing drugs, new drugs, and drug combinations to optimize treatment of MDR and XDR TB?
- How can TB programs be strengthened and suboptimal adherence to treatment regimens be addressed?
- What are the cure rates for MDR and XDR TB?
- What proportion of cases can be attributed to health care facilities, transmission in the community, or evolution of the organism?
- How can preventive, diagnostic, and therapeutic operations in health care facilities, including infection control, be changed and improved? How can steps to that end be taken in lower-level hospitals, and how can households be reached?
- How can the protection of health care workers be enhanced?

THE NEED FOR PARTNERSHIPS

Bond and Abdool Karim offered closing remarks addressing the need for partnerships and multidisciplinary approaches to the problem of drug-resistant TB. Bond stated that TB is not just a medical problem. Many of the challenges involve social issues such as poverty, migrant labor, overcrowding, poor nutrition, and inadequate ventilation. Solutions entail not just new diagnostics, vaccines, and treatments but also behaviors of patients

[2] The workshop held by the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, in Pretoria, South Africa, 2 days prior to the Drug Forum's South Africa workshop reviewed the latest TB research and highlighted areas for further research. A summary of this meeting can be found in Appendix C.

and health care workers, health systems, political commitments, and social mobilization. Ultimately, as has been the case in developed nations, addressing issues of health disparities and social inequities that lie at the root of TB, drug-resistant TB, and HIV will be necessary to combat these convergent epidemics successfully. Actions taken today can help prevent the crisis from worsening. A sense of urgency needs to be communicated to the public and policy makers to mobilize efforts against MDR and XDR TB, said Bond. Central to fostering this agenda is the creation of a strong patient advocacy culture to champion the need for increased resources, help educate the public and policy makers, and raise awareness of human rights issues.

Abdool Karim remarked that the patient, the community, and the family must be regarded as partners if information about TB is to be communicated successfully. This information often needs to be provided proactively, with the proper balance of fear and awareness. Different advocacy partners are needed at different levels. Members of the scientific and medical communities must communicate the realities of drug-resistant TB to the public and to policy makers, and they must translate data into policies commensurate with the magnitude of the problem, said Abdool Karim.

Bond concluded that the collaboration of the IOM and ASSAf at this workshop demonstrates the need for as well as the potential benefit of engaging neutral bodies to assess the evidence; build and share expertise; and prepare medical and educational institutions to play roles in prevention, diagnosis, treatment, training, and research. Bond noted that ASSAf is in an excellent position to continue to convene groups to address the issues surrounding MDR and XDR TB and to solicit the input of a broad array of groups that include patients; health care workers; public health officials; policy makers; the academic community; and groups from the sectors of industry, government, academia, and advocacy.

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Appendix A

Agenda

With the development of antibiotics in the twentieth century, tuberculosis gradually lost its central position as a global health concern—it was considered a disease of the past or one that was only associated with the extreme poverty of the developing world. However, this view of tuberculosis is out of date.

Tuberculosis is today one of the leading causes of death in the world—4,500 people die daily from the disease. Although many cases of TB can be cured by available antibiotics, multidrug-resistant TB (MDR TB) is a major and growing threat worldwide. Strains of TB resistant to even the second-line therapies (XDR TB) are documented in over 50 countries, including the United States, and we are seeing the emergence of strains that are fully resistant to treatment. And while the epidemic of TB is still primarily centered in the developing world, the reach of MDR extends to every continent, including both rich and poor countries. The global battle against TB, once thought won, is today very real.

The Institute of Medicine (IOM) Forum on Drug Discovery, Development, and Translation is conducting a series of workshops in the United States and in high-burden countries—including South Africa, Russia, China, and India. The first workshop, held in November 2008, included experts from around the world, and was framed by a commissioned paper developed by Partners in Health that provided new data on the nature and spread of MDR TB. In addition, in February 2009, the Forum held a public briefing on MDR TB for Congressional staff in Washington, DC. Details of both meetings, including the agendas and speaker presentations, are available on the Forum's website (www.iom.edu/drug).

IOM is partnering with the Academy of Science of South Africa (ASSAf) to convene a 2-day workshop on MDR TB. The workshop will bring together disease experts, community leaders, policy makers, and patient advocates to examine the state of MDR TB in the South Africa region, to learn from the experiences of the South African public health community in its fight against MDR TB, and to draw lessons regarding best practices and novel approaches that can be applied both within and beyond the region. Proceedings of the workshop will be published and disseminated globally.

The South Africa meeting will focus on various aspects of MDR TB:

1. **Epidemiology.** The latest information on the spread of MDR/XDR TB in Africa and globally, including the nature of the coinfection with HIV, will be presented and discussed.
2. **Diagnostics and Preventive Therapies.** The challenges associated with rapid diagnosis of TB and resistance testing in resource-constrained environments will be explored, as well as opportunities for expansion of laboratory capacity and point-of-care diagnosis.
3. **Treatment.** The limitations of current treatment, including the capacity of current health systems to address the needs of TB patients, the limited numbers of patients receiving appropriate treatment, and challenges in treating migrant workers, will be examined.
4. **Transmission and Infection Control.** The meeting will explore our growing understanding of the modes of transmission of MDR TB, and the strategies needed to address them.
5. **Pediatric TB.** The devastating spread of MDR TB among children and the unique challenges they pose for prevention and treatment will be explored.
6. **Policy.** The workshop will analyze the effects of MDR TB beyond patients in order to highlight areas for improved policy and next steps.

The Emerging Threat of Multidrug-Resistant Tuberculosis: Global and Local Challenges and Solutions
Pretoria, South Africa

Day 1
March 3, 2010

8h30-9h00 **Registration**

Breakfast and coffee will be served at this time.

9h00-9h30 **Welcome and Opening Remarks**

Roseanne Diab, ASSAf

Lerole David Mametja, Ministry of Health, South Africa

9h30-9h45 **Perceptions vs. Realities: Summary of 2008 MDR TB Workshop in Washington, DC**

Gail Cassell, Eli Lilly and Company

9h45-11h45 **Session 1: A Realistic Assessment of the Spread of MDR/XDR TB in Sub-Saharan Africa with an Emphasis on South Africa**

Moderator: Gerald Friedland, Yale School of Medicine

Capacity for Health Care Across Southern Africa and MDR/XDR TB
Tomas Zimba, Maputo Central Hospital, Mozambique

Evolution of XDR TB in KwaZulu-Natal
Willem Sturm, Nelson Mandela School of Medicine, University of KwaZulu-Natal

Prevalence of Drug Resistance at the Initiation of Second-Line Drugs and Existence of Totally Drug-Resistant TB
Martie van der Walt, Medical Research Council of South Africa

Putting Resistance in Perspective: The Korean Experience and Polymorphisms Associated with Resistance and Cross Resistance
Clifton Barry, National Institutes of Health

11h30-11h45 **Discussion with Audience**

11h45-12h45 **LUNCH**

12h45-13h45 **Keynote Address**

Moderator: Janet Tobias, Ikana Media

Epidemiology and Management of MDR TB in Children
Simon Schaaf, Department of Paediatrics and Child Health, Stellenbosch University

13h30-13h45 **Discussion with Audience**

13h45-15h15 **Session 2: Coinfection with HIV/AIDS: Clinical Outcomes and Consequences**

Moderator: Richard Chaisson, Center for Tuberculosis Research, Johns Hopkins University

Tugela Ferry Experience in a Community Hospital
Neel Gandhi, Tugela Ferry Care and Research Collaboration (TF CARES)
Albert Einstein College of Medicine

Outcomes from TB Referral Hospitals, KwaZulu-Natal
Nesri Padayatchi, University of KwaZulu-Natal

Outcomes from the Eastern Cape
Charlotte Kvasnovsky, Medical Research Council

Mortality and Causes of Death in South Africa
Maletela Tuoane-Nkhasi, Statistics South Africa

15h00-15h15 **Discussion with Audience**

15h15-15h30 **BREAK**

15h30-17h00 **Session 3: Alternative Strategies**

Moderator: Robin Wood, University of Cape Town

Community-Based Care
Kristina Wallengren, Medical Research Council

ART for the Prevention and Treatment of MDR TB
Stephen Lawn, University of Cape Town

Intensified TB Case Finding Among HIV-Infected Patients
Sabine Verkuijl, International Center for AIDS Care and Treatment Programs (ICAP-SA), Mailman School of Public Health, Columbia University

South-to-South Assistance to Initiate MDR TB Care in Ethiopia (Note: via phone)
Anne Goldfeld, Harvard University

16h45-17h00 **Discussion with Audience**

17h00 **ADJOURN**

18h00 **Group Dinner for Speakers**

Day 2
March 4, 2010

8h00-10h00 **Session 4: Transmission and Strategies for Infection Control**

Moderator: Neel Gandhi, Tugela Ferry Care and Research Collaboration (TF CARES)

Proof of Principle: Transmission of MDR TB in the AIR Facilities
Matsie Mphahlele, Medical Research Council

Epidemic in Tugela Ferry: Transmission and Impact of Infection Control
Gerald Friedland, Yale School of Medicine (in place of Anthony Moll, Church of Scotland Hospital)

Household Contacts
Claudio Marra, Church of Scotland Hospital

Careworkers
Karen Shean, University of Cape Town

Migrant Workers in Lesotho
Maketekete Thotolo, Adventist Development and Relief Agency

An Evaluation of Infection Control Infrastructure and Health Worker KAP in MDR/XDR TB Care Settings
Jason E. Farley, Johns Hopkins University

9h45-10h00 **Discussion with Audience**

10h00-10h30 **BREAK**

10h30-12h15 **Session 5: Application of Molecular Biology to Shape Policy**

Moderator: Elaine Gallin, Doris Duke Charitable Foundation

Drug-Resistant Genotypes: Implication for Point-of-Care Detection of Resistance in Different Geographies
Paul van Helden, Stellenbosch University

Genetic Analysis of Drug-Resistant Strains in South Africa
Robin Warren, Stellenbosch University

Bench to Bush in Biomarker Studies in Africa: Implications for MDR TB Treatment and Drug Development
Shreemanta Parida, Max Planck Institute for Infection Biology, Berlin, Germany

12h00-12h15 **Discussion with Audience**

12h15-13h00 **LUNCH**

13h00-14h15 **Session 6: How Close Are We?**

Moderator: Martie van der Walt, Medical Research Council of South Africa

Current Status of Diagnostics Globally for the Detection of Drug Resistance with Emphasis on Point of Care
William Jacobs, Einstein School of Medicine

Challenges in Laboratory Capacity in Diagnosing Drug-Resistant TB in South Africa
Gerrit Coetzee, National Health Laboratory Services, South Africa

Information Solutions to Enhance Laboratory Capacity in Evaluation of New Diagnostics and Therapies
Dale Nordenberg, Novasano Health and Science

14h00-14h15 **Discussion with Audience**

14h15-15h15 **Session 7: Research Gaps, Priorities, and Opportunities—Report from NIH Workshop**

Valerie Mizrahi, National Health Laboratory Service

Barbara Laughon, National Institutes of Health

15h00-15h15 **Discussion with Audience**

15h15-15h30 **BREAK**

15h30-16h45 **Session 8: Convergence of Science and Policy to Create a Blueprint for Action**

Moderator: Queta Bond, Burroughs Wellcome Fund (retired)

Where Are We and Where Do We Go from Here?
Salim Abdool Karim, University of KwaZulu-Natal

Panelist Response:
Gail Cassell, Eli Lilly and Company
Norbert Ndjeka, Department of Health, South Africa
Sidney Parsons, Council for Scientific and Industrial Research

16h30-16h45 **Discussion with Audience**

17h00 **ADJOURN**

Appendix B[1]

Report from the National Institute of Allergy and Infectious Diseases (NIAID) Workshop

On March 1 and 2, 2010, during the 2 days before the workshop summarized in this volume, NIAID held the United States–Southern Africa Joint Research Forum on Tuberculosis in Pretoria, South Africa. The purpose of the workshop was to discuss research on TB that is taking place in southern Africa, to identify opportunities for collaboration within both South Africa and its neighboring countries, and to explore opportunities for collaboration between southern African countries and the United States. The highlights of that workshop were presented during the proceedings of the Institute of Medicine (IOM)–Academy of Science of South Africa (ASSAf) workshop by Valerie Mizrahi of the National Health Laboratory Service and University of Witwatersrand and Barbara Laughon of the National Institutes of Health, and are summarized below.

THE INCIDENCE OF DRUG-RESISTANT TB

- HIV is a key driver of the TB epidemic in southern Africa, bringing about a six-fold increase in incidence in South Africa, Lesotho, and Swaziland.
- There is a large burden of undiagnosed TB in the community.
- The same epidemiological model cannot be used for TB and HIV epidemics in different countries.

[1] This Appendix B summarizes the presentation made by Valerie Mizrahi of the National Health Laboratory Service and University of Witwatersrand and Barbara Laughon of the National Institutes of Health.

THE TRANSMISSION OF DRUG-RESISTANT TB AND INFECTION CONTROL

- Most TB disease, both drug-sensitive and drug-resistant, is recently transmitted via social interactions away from the household. Thus, there is a need to understand the adult and childhood social networks in South African townships that contribute to TB transmission.
- Surrogate biomarkers are essential for public health interventions.
- Transmission and infection need to be studied intensively.
- A TB control program must be able to rapidly identify cases and commence therapy.
- Operational research and implementation science are needed to enhance feasible and available infection control strategies and support the development and testing of new approaches.

THE MOLECULAR EPIDEMIOLOGY OF DRUG-RESISTANT TB

- Strains of TB are more diverse than previously appreciated.
- The immense amount of variation occurring between strains suggests that purifying selection is reduced in *Mycobacterium tuberculosis (M.tb.)*.
- Strain variation is extensive within individual study sites and across regions, with the University of Stellenbosch group reporting more than 150 strains per square kilometer in the study areas.
- The population structure of *M.tb.* is highly variable, with a dominance of Beijing genotype (both typical and atypical) being uncovered in some study areas and playing a major role in driving drug resistance in South Africa. Intriguingly, Beijing strain has not (yet) been observed in Zambia, and the KZN strain predominates in XDR TB cases in that area.
- DNA sequence data are highly informative and will soon be the standard for molecular epidemiology.
- Although genetic and molecular epidemiology is powerful, it has been studied only in some areas of the region.

DIAGNOSING DRUG-RESISTANT TB

- While new diagnostics could detect 400,000 cases each year, the realities of using new versus current diagnostics need to be taken into account.

- Novel diagnostics being evaluated in Africa, all of which have various advantages and disadvantages, include
  - Light emitting diode (LED) microscopy
  - GeneXpert
  - Line probe assay (LPA)
  - Urine lipoarabinomannan (LPA) immunochromatographic (ICT) strip test
  - Interferon-gamma release assay (IGRA)
  - Microscopic observation drug susceptibility (MODS)
- Key questions beyond the performance characteristics of a new diagnostic involve delivery, roll-out, and scale-up, as well as the impact on patient outcomes, program performance, the burden of disease, and global TB control.
- The experience of the National Health Laboratory Service in moving from validation of new technology to roll-out of the LPA was illuminating. Fitting the LPA into an algorithm for TB diagnosis and the development of an algorithm for early detection of MDR TB involved several challenges:
  - the plan to roll out the LPA to an additional 20 laboratories by December 2010;
  - requirements for laboratory space, equipment, staff recruitment training, the implementation of the assay, and review of its success;
  - preparation for the roll-out of GeneXpert to four additional laboratories later in 2010; and
  - human resource limitations particular to South Africa, some of which relate to policy.
- the GeneXpert *M.tb.*/Rifampicin test is being evaluated in five countries with differing HIV and MDR TB status.
- The search for TB antigens is under way for a proof-of-concept test.
- The Foundation for Innovative New Diagnostics has 20 trial sites for TB diagnostics in Africa.
- The establishment of more laboratories and the development of proof-of-concept tests should not be viewed as mutually exclusive.
- Molecular diagnostic technology is moving toward being less complex and more robust, with the potential for a proof-of-concept diagnostic in 2015.

THE TREATMENT OF DRUG-RESISTANT TB

- Many drug-resistant TB cases are untreatable with existing or available antibiotics.
- New drug regimens are needed now to treat drug-resistant TB. In particular, combination therapy is needed with new classes of drugs and novel mechanisms of action.
- Better tolerability, less toxicity, and shorter treatment courses are needed.
- Three to four new drugs need to be developed against which resistance is not established.
- The number of new drugs that have novel targets and mechanisms of action is not adequate. More basic research is needed to increase the number of compounds entering the pipeline. In particular, there are gaps in candidates with preclinical safety.
- Going from discovery to the launch of a successful drug takes 10 to 15 years. Five to 10 new entities generally need to enter human trials to yield one drug that will be safe, sufficiently effective, and affordable to be used for TB treatment. The estimated cost of a new entity is $1–$1.5 billion. Most of the drugs are being developed by public–private partnerships and by philanthropic organizations.
- There is a huge R&D funding gap. More funds are needed to facilitate preclinical development, to build capacity at trial sites, to perform clinical trials, and to provide enabling infrastructure.
- In terms of pharmacology and pharmacokinetics, there is a need to optimize dosing in neglected subpopulations, such as children and pregnant women. This goal can be facilitated by new technology.
- Surrogate markers to monitor response to therapy quantitatively are critically needed. Large cohorts are required to validate biomarker studies of treatment efficacy, relapse, and latent TB infection and should be built into drug trials.
- The pulmonary route of delivery is underexplored. Preliminary work suggests that the formulation of TB drugs and vaccines as spray-dried powders using large porous particles for inhaled delivery holds promise in the future.
- Directly Observed Treatment Short Course (DOTS) coverage is reasonably good in the African region but is clearly inadequate to curb the epidemic.
- The Malawi Public Health system offers lessons in best practice.
- Botswana has close-to-universal access to antiretrovirals and IPTG (isopropyl-β-D-thio-galactoside), which may be a reason for the slight reduction in the case rate there. An important message from

the latest Botswana study is that there is no evidence for isoniazid preventive therapy fueling isoniazid resistance.

- An African regional collaboration is essential in order to:
  - — establish a clinical trials network for TB treatment and prevention regimens,
  - — establish more registration-qualified clinical sites with adequate laboratories for future Phase III efficacy trials, and
  - — establish regulatory agencies to harmonize and improve approval processes so that studies can be started more quickly.
- Regional collaboration also could make possible a "20 communities study" of regional epidemiology, including molecular epidemiology.
- A working group on new drugs is making information available on the website www.newtbdrugs.org.

VACCINES FOR TB

- The goal is for a new vaccine to be developed by 2016, with 20 candidates in Phase 1 by 2015 and 9 in Phase II by 2018. These are ambitious targets.
- Highlights of the work done on immune responses induced by new vaccines include
  - — Novel boost vaccines induce T cells in distinct patterns.
  - — Differences in response may reflect an interaction with the innate immune system.
  - — Candidates differ in terms of local and systemic side effects.
  - — Patterns of immune activation may differ in infants and adults.
- Some points concerning biomarkers of protection were:
  - — Cytokine expression does not correlate with protection.
  - — Soluble IFNg levels do not correlate with protection.
  - — T cell expression of cytotoxic markers may delineate protection.
  - — Models based on combinations of markers may have value as biomarkers in the future.
  - — Unbiased approaches to biomarker discovery (such as gene expression profiles) need to be pursued.
- In terms of clinical preparedness for new vaccines, challenges include
  - — costs, site development, a lack of immunological correlates of protection, TB diagnoses in children, and the need for clinical end points for determining efficacy; and
  - — key issues regarding the regulatory environment.
- Important issues involving efficacy trials in HIV-infected and -exposed adults against TB include
  - — whether vaccines are safe and immunogenic, and
  - — the size of the sample required to achieve an efficacy outcome.

- Sustained commitment and extensive collaboration are required within and between developed and developing countries.

DRUG-RESISTANT TB IN CHILDREN

- TB in children has been neglected; it is underreported and extremely difficult to diagnose, and has a limited evidence base on which to base treatment decisions.
- Diagnostics need to be child friendly, cost-effective, and operationally feasible. Application in pediatric TB should be considered in the development of any new diagnostics as early as possible.
- New tools for clinical management, epidemiology, and surveillance are urgently needed, as is an end point for Phase III trials.
- Extra-short-course therapy is needed for less severe forms of TB in children, but needs confirmation.
- The value of targeted screening in high-risk populations needs to be explored.
- The degree of exposure needs to be assessed as a possible predictor of infection, persistent infection, or disease.
- Additional pharmacokinetic studies are needed in children.
- An Extrapulmonary TB Trials Consortium needs to be created.

CONCLUSIONS AND POLICY DISCUSSION

- Rapid and accurate drug sensitivity testing should be a prerequisite for the commencement of therapy, given the amplifying role of drugs in the evolution of resistant strains.
- The South African government should collaborate in the development of capacity and infrastructure. There is only one supranational TB reference laboratory in the region, and there is insufficient capacity to cope in the regional laboratories. In addition, the capacity to conduct clinical trials is very limited.
- Lessons can be learned from the HIV field, where major National Institutes of Health (NIH) grants for research have been linked with development and capacity development grants. Synergy between research grants and capacity development is necessary.

Appendix C

Participant Biographies

Salim S. Abdool Karim, MBchB, Ph.D., is pro vice-chancellor for research at the University of KwaZulu-Natal in Durban, South Africa. He is also director of the Centre for the AIDS Programme of Research in South Africa (CAPRISA), a professor at Columbia University, and an adjunct professor at Cornell University. A clinical infectious disease epidemiologist, Dr. Abdool Karim performed research on TB and HIV treatment that shaped the current therapeutic approach to treating coinfected patients. He is coinventor of part of South Africa's first HIV subtype C vaccine and subsequently led the first HIV vaccine trial in South Africa. His recent research on microbicides showed that an antimicrobial gel may prevent HIV infection in women. Dr. Abdool Karim is chair of the World Health Organization (WHO) Scientific Advisory Group for Reproductive Health and is a member of the WHO Expert Advisory Panel on Sexually Transmitted Infections and HIV.

Clifton E. Barry, III, Ph.D., received his Ph.D. in organic and bioorganic chemistry in 1989 from Cornell University, designing and synthesizing inhibitors to study the mechanism of a complex enzyme involved in actinomycin D biosynthesis. He then spent 2 years doing postdoctoral research at The Johns Hopkins University in one of the leading laboratories involved in beta-lactam synthesis before joining the Intramural Research Laboratories of the National Institute of Allergy and Infectious Diseases in Hamilton, Montana, to study bacterial pathogens. After studying the pathogenesis of *Chlamydia trachomatis*, the leading cause of blindness in the developing world, he was given the opportunity in 1993 to start his own laboratory on

the pathogen of his choice—*Mycobacterium tuberculosis (M.tb.)*. TB was a natural choice given the reemerging epidemic that was gaining public attention in the early 1990s and Dr. Barry's increasing interest in global health. Over the next 5 years, his laboratory focused on understanding some of the basic biochemistry of the cell wall of TB, a rich source of potential drug targets. In 1998, Dr. Barry was tenured as chief of the Tuberculosis Research Section (TBRS) and relocated his laboratory to the main campus of the National Institutes of Health (NIH) in Maryland. In addition to his research group at NIH, with more than 30 members focusing on drug and diagnostic development, he has developed an active clinical research program in South Korea, where he has five ongoing trials with more than 700 participants. Dr. Barry's group contributed to the development of PA-824, a new drug for TB now in Phase II clinical trials, and developed SQ109, another new TB drug now in Phase Ib trials. Dr. Barry is a member of several editorial boards and has authored more than 130 research publications on TB since entering the field. In 2009 he was named by ScienceWatch as the most highly cited researcher working in the field of TB.

Enriqueta C. Bond, Ph.D., retired in August 2008 as President of the Burroughs Wellcome Fund (BWF), a private foundation whose mission is to advance the medical sciences through the support of research and education. Dr. Bond is a founding partner of QE Philanthropic Advisors and now consults with philanthropic and nonprofit organizations on program development and governance. Previously Dr. Bond served for nearly 20 years as staff officer and division director at the Institute of Medicine, National Academy of Sciences, serving as executive officer from 1989–1994. She serves on numerous board and advisory groups such as the Scientific Advisory Committee on Stewardship for Research on Infectious Diseases of Poverty at WHO's Program for Research and Training in Tropical Diseases, the NIH Council of Councils, the board and executive committee of the Hamner Institute for Health Sciences, the board of the Health Effects Institute and the James B. Hunt Jr. Institute for Educational Leadership. She currently chairs a National Academies Board on Developing the Capacity of African Academies of Science, is a member of the National Research Council (NRC) Committee on Research Universities, a member of a Task Force on the Organization of the National Academies, and serves as a frequent reviewer of Academy Reports. Dr. Bond previously chaired the Institute of Medicine Clinical Research Roundtable and was a member of the Council of the Eunice Shriver National Institute of Child Health and Human Development. Dr. Bond is a member of the Institute of Medicine and is a fellow of the Association for the Advancement of Science. She was educated at Wellesley College (A.B.), the University of Virginia (M.A.), and Georgetown University (Ph.D.) in genetics and molecular biology.

Gail Cassell, Ph.D., is a Visiting Professor in the Department of Social Medicine, Harvard Medical School, and Vice President of TB Drug Discovery of the not-for-profit Infectious Disease Research Institute in Seattle. Dr. Cassell has recently retired as Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company in Indianapolis, Indiana. In this capacity among other things, she was responsible for initiating and leading the not-for-profit Lilly TB Drug Discovery Initiative launched in 2007. In 2003, she was one of two individuals at Lilly who initiated and developed the Lilly Multidrug Resistant Tuberculosis (MDRTB) Partnership. The partnership has resulted in company support to date of $135 million dollars and is the largest philanthropic effort in Lilly's 125-year history. The partnership now involves over 20 partners, including WHO and CDC. She is the former Vice President of Infectious Diseases Drug Discovery and Clinical Development of Eli Lilly where she led the program of a hepatitis C protease inhibitor from the discovery phase to clinical candidate. The compound is now in phase III clinical trials under the direction of Vertex. Prior to moving to Lilly in 1997, Dr. Cassell was the former Charles H. McCauley Professor and Chair of the Department of Microbiology at the University of Alabama Schools of Medicine and Dentistry at Birmingham, a department which ranked first in research funding from the National Institutes of Health during the decade of her leadership. She obtained her B.S. from the University of Alabama in Tuscaloosa and in 1993 was selected by that institution as one of the top 31 female graduates of the 20th century. She obtained her Ph.D. in Microbiology from the University of Alabama at Birmingham and was selected as its 2003 Distinguished Alumnus. She is a past President of the American Society for Microbiology (the oldest and single largest life sciences organization with a membership of over 42,000). She was named to the original Board of Scientific Counselors of the Center for Infectious Diseases, Centers for Disease Control and served as Chair of the Board. She has served on the Advisory Board of the Director of National Institutes of Health, the Director of the Centers for Disease Control, and the Secretary of Health and Human Services Advisory Council of Public Health Preparedness, the FDA Science Board: Advisory to the Commissioner. Currently she is a member of the NIH Science Management Board, the newly appointed "NIH Board of Trustees" and the Advisory Council of the Fogarty International Center of NIH. Since 1996 she has been a member of the U.S.–Japan Cooperative Medical Science Program responsible for advising the respective governments on joint research agendas, (U.S. State Department/Japan Ministry of Foreign Affairs). She has served on several editorial boards of scientific journals and has authored over 350 articles and book chapters. Dr. Cassell has received national and international awards and two honorary degrees for her research in infectious diseases, including the CDC Honor Award in

Public Health for exceptional leadership and contributions in the development and implementation of CDC's Emerging Infectious Disease Plan 1997 and a Citation from the FDA Commissioner for her role as chair of the review of science and technology at the FDA and the Report FDA: Science and Mission at Risk 2008 and the Emmy Klineberger-Nobel Award in 2008 by the International Organization for Mycoplasmology for outstanding and sustained research contributions to the field of mycoplasmology. She is a member of the Institute of Medicine (IOM) of the National Academies and has recently completed a second 3-year term on the IOM Council, the governing board. Dr. Cassell has been intimately involved in establishment of science policy and legislation related to biomedical research and public health. For nine years she was chairman of the Public and Scientific Affairs Board of the American Society for Microbiology; 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 LCME, the accrediting body for U.S. medical schools as well as other national committees involved in establishing policies in training in the biomedical sciences. She is an Emeritus Member of the Board of Research!America and a former member and Chair of the Board of Directors of the Burroughs Wellcome Fund. She has completed a term on the Leadership Council of the School of Public Health of Harvard University. Currently she is a member of the Morehouse School of Medicine Board of Trustees, Executive Committee of the Board of Visitors of Columbia University School of Medicine, the Advisory Council of the School of Nursing of Johns Hopkins, and the Advisory Council of the University of North Carolina Gillings School of Global Public Health.

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 in Baltimore. His research focuses on TB and HIV infection, including global epidemiology, prevention, treatment, and public health interventions. He is 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 2006 American Thoracic Society World Lung Health Award for his contributions to global control of pulmonary infections.

Gerrit Coetzee is a pathologist currently living in Johannesburg, South Africa. He is the head of the National Tuberculosis Laboratory (NTBRL)

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

Roseanne Diab, Ph.D., is executive officer of the Academy of Science of South Africa (ASSAf) and a senior professor at the University of KwaZulu-Natal in Durban. Her research interests are broadly based in the atmospheric sciences, with a particular focus on air pollution and air quality management and climate change. Dr. Diab serves on the editorial board of the *South African Journal of Science*, the *Clean Air Journal*, the *South African Geographic Journal*, and *Atmospheric Environment*. She has served on a number of international commissions, including the Commission on Atmospheric Chemistry and Global Pollution and the International Ozone Commission. Dr. Diab is a fellow of the South African Geographical Society and of the University of Natal. She holds a Ph.D. in environmental sciences from the University of Virginia.

Jason E. Farley, Ph.D., M.P.H., CRNP, is an assistant professor at The Johns Hopkins University School of Nursing and a nurse practitioner in the Division of Infectious Diseases within The Johns Hopkins AIDS Service. He also holds an adjunct faculty appointment at Stellenbosch University in Cape Town, South Africa. Dr. Farley has been working in the arena of infection control for the past 10 years and is member of the Association of Professionals in Infection Control, as well as the Infectious Disease Society of America. He is presently on the editorial board of the *American Journal of Infection Control*. Dr. Farley's current research is assessing the epidemiologic interactions of patients with HIV and drug-resistant infections in both domestic (U.S.) and international settings. His research projects include an evaluation of treatment outcomes in patients with multidrug-resistant (MDR) TB in the context of a high HIV/AIDS prevalence in South Africa in collaboration with the South African Medical Research Council (MRC). Further, his team recently completed a countrywide assessment of knowledge, attitudes, and practices related to infection control in MDR/extensively drug-resistant (XDR) TB hospitals in South Africa. This project successfully enrolled 24 of these hospitals, 100 percent of such hospitals across all nine provinces of the country. In addition, his team enrolled 499 health care workers across these sites. In the United States, Dr. Farley is working to assess methicillin-resistant *Staphylococcus aureas* (MRSA) colo-

nization and infection among patients with HIV/AIDS in Maryland. He is also the principal investigator on a grant addressing adherence to guidelines for cardiovascular disease among providers of HIV care within The Johns Hopkins AIDS Service.

Gerald Friedland, M.D., is professor of medicine and epidemiology and public health at Yale School of Medicine and adjunct professor at the Mailman School of Public Health, Columbia University. He is a former member of the Governing Council of the International AIDS Society, National Advisory Council, Office of AIDS Research, and currently serves on the WHO HIV/TB Working Group, the NIH/NIAID–Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents, and the NIH International HIV Research Planning Group. He also serves as chairman of the board of directors of the Aaron Diamond AIDS Research Center in New York City. Dr. Friedland is actively involved in international research on HIV/AIDS and TB, with a major focus on the integration of care and treatment in coinfected patients and the aim of improving diagnosis, treatment, and outcomes for both diseases. This work has led to the uncovering of XDR TB as a major cause of death among HIV/TB coinfected patients in South Africa. With U.S. and South African colleagues, Dr. Friedland formed Tugela Ferry Care and Research (TF CARES), a clinical and research collaboration in rural KwaZulu-Natal. The work of TF CARES currently focuses on defining the epidemiology, reducing the transmission, and decreasing the morbidity and mortality from MDR and XDR TB.

Elaine K. Gallin, Ph.D., is currently a senior advisor at the Doris Duke Charitable Foundation (DDCF). From 1999 through February 2010, she served as DDCF's first program director for medical research, leading the creation and management of a portfolio of grant programs that has committed approximately $185 million to supporting clinical research. Dr. Gallin also designed and led the foundation's $60 million African Health Initiative. Launched in September 2007, this initiative is supporting large-scale health service delivery projects in sub-Saharan Africa that are linked to rigorous operations and implementation research. Before joining the foundation, Dr. Gallin spent two decades, first as a research physiologist and then as a research administrator, with the U.S. government, last serving as deputy director of the Office of International Health Programs in the U.S. Department of Energy. She has participated on numerous professional committees and review panels. Currently, she is member of the board of directors of the Health Research Alliance (an alliance of nongovernmental research funders); the IOM's Forum on Drug Discovery, Development and Translation; and the Sickle Cell Disease Advisory Committee at the

National Heart, Lung and Blood Institute. Dr. Gallin received her Ph.D. from the City University of New York and completed postdoctoral fellowships at The Johns Hopkins University Medical School and Columbia University Medical School.

Neel Gandhi, M.D., is an assistant professor of medicine and epidemiology at Albert Einstein College of Medicine and Montefiore Medical Center and a principal investigator in TF CARES. He has been engaged in clinical research on TB/HIV coinfection since 1998. In November 2006, he was the lead author for a study describing high rates of mortality in patients with XDR TB and HIV coinfection. This study has been credited for uncovering a rapidly expanding MDR and XDR TB epidemic in South Africa. Dr. Gandhi continues to focus on the converging epidemics of drug-resistant TB and HIV in South Africa. A particular emphasis of his work is on elucidating the role of primary transmission in the expansion of this epidemic and on developing optimal treatment strategies for MDR TB/HIV coinfected patients. Dr. Gandhi is currently funded through a Clinical Scientist Development award and an Operations Research on AIDS Care and Treatment in Africa award from DDCF. These grants provide support to elucidate risk factors for developing MDR and XDR TB, to test the microscopic-observation drug-susceptibility (MODS) assay (a rapid TB drug resistance assay) in a high HIV prevalence setting, to create a community-based treatment 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 coinvestigator on grants to expand TB/HIV integration efforts in rural South Africa (President's Emergency Plan for AIDS Relief [PEPFAR], U.S. 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).

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

a senior investigator at Uganda's Infectious Diseases Institute (IDI), a professor of medicine at Harvard Medical School, and a physician in medicine in the Division of Infectious Disease at Brigham and Women's Hospital.

William R. Jacobs, Ph.D., is a professor of microbiology and immunology and a professor of molecular genetics at the Albert Einstein College of Medicine, and a Howard Hughes Medical Institute (HHMI) investigator. He is an expert in TB and other diseases in the mycobacteria family. His research uses bacterial viruses—called phage—to introduce foreign DNA into the bacteria that cause TB, *(M.tb.)*. That work has revolutionized scientists' understanding of TB bacteria. Prior to Jacobs' development of gene transfer mechanisms, little was known about the genetics behind *M.tb.*, including which genes were related to virulence and drug resistance. Jacobs and former Einstein colleague and HHMI investigator Barry Bloom collaborated on a series of experiments that led to the first genetic manipulation of *M.tb*. Dr. Jacobs, who wrote his doctoral dissertation on leprosy, is currently developing a multipurpose vaccine that could attack malaria, HIV, and TB.

Charlotte Kvasnovsky, M.D., M.P.H., is a guest researcher with the Division of TB Elimination at CDC, where she has served since 2007 on the Global Preserving Effective TB Treatment with Second-line drugs (PETTS) Coordinating Team and as coordinator for South Africa. She conducts research with the MRC on XDR TB. Dr. Kvasnovsky received her medical degree from Emory University in May 2010, as well as an M.P.H. in epidemiology from the Rollins School of Public Health. She is a resident in general surgery at the University of Maryland.

Barbara Laughon, Ph.D., is senior scientist for TB Drug Development Partnerships at NIAID. She is the primary NIH liaison with the Lilly TB Drug Discovery Initiative. She also serves as chair of the Scientific Advisory Committee of the TB Alliance and was one of the original founding stakeholders of this public–private partnership. Dr. Laughon is an active participant in the Stop TB Partnership, serving on working groups on new drugs and TB/HIV coinfection; she will be serving as executive secretary of the board of advisors.

Stephen Lawn, M.D., is an associate professor of infectious diseases at the University of Cape Town, South Africa, and a reader in infectious diseases and tropical medicine at the London School of Hygiene and Tropical Medicine. He trained in infectious diseases in London and has also worked in Ghana, west Africa, and at CDC in the United States. Dr. Lawn has been based in Cape Town since 2005, funded by the Wellcome Trust. His princi-

pal research focus has been on HIV-associated TB in the context of scale-up of antiretroviral therapy (ART).

Lerole David Mametja, M.P.H., is currently the Chief Director for TB Control and Management in the National Department of Health. He has more than 15 years of experience in the social sector, in particular, public health. As Executive Director of the Health Systems Trust (HST) he gained experience in setting up processes needed to facilitate implementation of organizational policies and decisions and managing an annual budget of between R60 and R200 million. He has managed senior employees, and has interacted with both governmental (including ministerial levels), and non-governmental institutions. He was also Regional Health Sector Manager for RTI International, overseeing its health program operating in the Southern African Development Community (SADC). In this capacity, he was responsible for the identification of opportunities for research and development projects, negotiating partnerships, project proposal design, management and monitoring of projects, particularly in Mozambique, Lesotho, Swaziland and Namibia. He was also the Chief Executive Officer of the Health and Welfare Sector Education Training Authority (HWSETA), an entity that focuses on providing training and skills development opportunities for South Africans. He holds a master's degree in public health (M.P.H.) in Health Policy and Management from Columbia University, New York. While working on his M.P.H. he served as an Assistant to the Deputy Chief Medical Officer and Vice President, Health and Hospital Corporation, City Health Department, New York City, where he was responsible for reviewing and evaluating hospital quality care systems.

Claudio Marra, M.D., graduated from the Università La Sapienza in Rome in 1978, and specialized in internal medicine in 1983. For the past 15 years he has been working in public health in both development and emergency settings in Kenya, Somalia, Mozambique, Malawi, and South Africa with international nongovernmental organizations (NGOs), the Italian Development Cooperation, the Italian National Institute of Health, and United Nations agencies. In all these countries he has worked in close partnership with the respective local health authorities and other stakeholders. His focus has been on health system development, in particular on development of district health systems; prevention and control of communicable diseases, including coinfection with TB and HIV/AIDS; prevention, care, and treatment of HIV/AIDS and malaria; maternal health; and emergency preparedness and response in the area of health. Since 2005 Dr. Marra has been providing technical assistance to the KwaZulu-Natal (KZN) provincial Department of Health in understanding and addressing the complexity of MDR and XDR TB, as well as the challenges posed by coinfection with

TB and HIV/AIDS. In the Umzinyathi district of KZN, the district with the largest number of cases of MDR and XDR TB in South Africa, he developed an innovative household surveillance and community-based tracing system using GPS mapping software. The report documenting the experience in Umzinyathi district is available online on the KZN Department of Health website at www.kznhealth.gov.za.

Valerie Mizrahi, Ph.D., was born and raised in Zimbabwe. She obtained her Ph.D. in chemistry from the University of Cape Town in 1983. She completed a postdoctoral fellowship at the Pennsylvania State University, and worked at SmithKline and French Research and Development in King of Prussia, Pennsylvania, before returning to South Africa in 1989 to establish a research unit at the South African Institute for Medical Research in Johannesburg. Currently, she is director of the MRC/National Health Laboratory Service (NHLS)/University of Witwatersrand (WITS) Molecular Mycobacteriology Research Unit at NHLS and research professor at the University of the Witwatersrand. She is also codirector of the Department of Science and Technology (DST)/National Research Foundation (NRF) of South Africa Centre of Excellence for Biomedical TB Research, which she leads together with Professor Paul van Helden from the University of Stellenbosch. Dr. Mizrahi is the two-time recipient of an International Research Scholar's grant from the Howard Hughes Medical Institute in the United States (2000 and 2005). She has received numerous awards and honors in South Africa, and in 2009 was elected a fellow of the American Academy of Microbiology. Dr. Mizrahi has published 80 articles and book chapters in the fields of organic chemistry, enzymology, and mycobacteriology. In 2002, she shifted the focus of her research to the field of TB. Her research team played an instrumental role in developing genetic tools for validating new drug targets and vaccine candidates for TB and is internationally recognized for its work on molecular mechanisms of DNA metabolism, stress responses, resuscitation, and drug action in mycobacteria. Dr. Mizrahi is an active member of the TB research community. She chaired the Gordon Research Conference on Tuberculosis Drug Development in Oxford in August 2007 and organized the Keystone Symposium on Pathogenesis and Control of Emerging Infections and Drug Resistant Organisms in Bangkok in 2008. She chairs the International Scientific Advisory Committee of the Institute of Infectious Disease and Molecular Medicine (University of Cape Town) and serves on the scientific advisory boards of numerous local and international research programs and institutes. She has served on the editorial advisory boards of four international journals and on the Department of Science and Technology's South Africa Reference Group for Women in Science.

Matsie Mphahlele, M.Phil., is a senior scientist at the MRC's TB Epidemiology and Intervention Research Unit, which she joined in 1997. She has worked as a laboratory manager in the unit, responsible for overseeing Supranational Reference Laboratory (SRL) activities including rapid surveys, laboratory support, and capacity strengthening for South African Development Community (SADC) countries. She is responsible for the clinical, laboratory, and experimental work undertaken at the MRC Airborne Research Facility in Witbank, which is currently investigating the transmission dynamics of MDR TB and the efficacy of various environmental infection control interventions in reducing the transmission of TB. Ms. Mphahlele holds an M.Phil. degree in international health from the University of Bergen in Norway and an M.Sc. degree in microbiology from the University of Pretoria.

Norbert Ndjeka, M.D., is a specialist family physician with an interest in TB and HIV. He is employed as director, drug-resistant TB, TB and HIV under the TB Cluster, Department of Health, Republic of South Africa. He has extensive clinical and programmatic experience in the management of TB and HIV. Dr. Ndjeka also serves as WHO temporary MDR TB advisor and is a member of the TB TEAM Experts Roster, serving as an experienced expert in M/XDR-TB under the Stop TB Department of WHO. Previously, he worked as medical officer at Kgapane Hospital and Botlokwa Hospital in Limpopo, South Africa. He was also senior medical superintendent at St. Rita's Hospital and Warmbaths Hospital in Limpopo and clinical head of Limpopo's MDR TB unit. Previously, he was a senior specialist and senior lecturer in family medicine at the University of Limpopo. Dr. Ndejka was also an MDR TB and infection control advisor with the University Research Corporation, LLC. He holds a medical degree from the University of Kinshasa, Democratic Republic of the Congo; a postgraduate diploma in health services management from Witwatersrand University, Johannesburg, South Africa; a diploma in HIV medicine from the College of Medicine of South Africa; and a master's degree in family medicine from the University of Limpopo, Medunsa.

Dale Nordenberg, M.D., is a principal with Novasano Health and Science. He is a physician executive who leverages his experience as a pediatrician, medical epidemiologist, and informatician to deliver strategic, operational, and scientific services to domestic and international clients in the health care and health information technology arenas. Recent projects include the development of a public–private partnership to build laboratory capacity for MDR TB across diverse international settings, which he is currently leading; development of governance structures for the National Biosurveillance System for Human Health; development of a multi-institutional collaboration

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

Nesri Padayatchi, M.D., is the CDC Durban site manager for the Starting Tuberculosis and Anti-Retroviral Therapy (START) project of Centre for the AIDS Programme of Research in South Africa (CAPRISA). She has 18 years of clinical and research experience in the management of TB and related problems. She was manager of the Provincial Tuberculosis Referral Hospital for 14 years. She was also acting director of the MRC's Tuberculosis Lead Program from 1999 to 2003. Dr. Padayatchi has received the Columbia University–South Africa Fogarty AIDS International Training and Research Program (AIRTP) fellowship and completed her M.S. in epidemiology from Columbia University. The focus of her M.S. was on temporal trends in drug-resistant TB (1998–2001). She has extensive experience participating in multicenter clinical trials from 1996 to the present.

Shreemanta K. Parida, M.D., Ph.D., is a physician scientist from India working in the field of infectious diseases, with a particular focus on

mycobacterial diseases over the last 23 years. His expertise encompasses clinical, field, and laboratory settings; clinical trials of vaccines; immunopathology; molecular pathogenesis; molecular immunology; epidemiology; and vaccinology. Dr. Parida obtained his Ph.D. from the National Institute of Immunology (NII) in India. Since 1990, he has worked in several institutions in Europe, including the WHO Immunology Research and Training Center (IRTC) in Geneva, the University of Giessen in Germany, the Pasteur Institute of Brussels, and Oxford University. From 2003 to early 2006, he worked in Africa at Armauer Hansen Research Institute in Addis Ababa, Ethiopia, and thereafter at the Max-Planck-Institute für Infektionsbiologie (MPIIB) in Berlin. He also received an advanced diploma in vaccinology from Foundation Merieux, France, in 2003. Dr. Parida started his research career with Phase II and III clinical trials of a leprosy vaccine based on an atypical mycobacterium—*M.w* (*M. indicus pranii*)—at NII. The vaccine has been licensed as an immunotherapeutic agent for leprosy. Dr. Parida was an early proponent of postexposure T cell boosting vaccine for nonreplicating persistent TB and received a vaccine innovation grant from Sequella and WHO/Special Programme for Research and Training in Tropical Disease (TDR) in 2000–2002. In his current position, he has been instrumental in building a cohesive and functional team focused on the quest for TB biomarkers; the team includes 15 partners from Africa, Europe, and the United States. Dr. Parida is committed to translating research from the bench to the clinic to combat the TB emergency in the developing world. He is passionate about science and translational research in the pursuit of solutions to public health problems, and has particular skills in networking, initiating collaborations, and coordinating multicenter studies.

Sidney Parsons, Ph.D.,[1] is an international expert in energy management of buildings. His expertise and research also include indoor air quality and environmental control for building-related illnesses, in particular the spread of hazardous biological agents such *M.tb.,* as well as commissioning processes for buildings, particularly within the health care sector. Dr. Parsons is a professional engineer registered with the Engineering Council of South Africa and with the International Society for Professional Engineers. His research interests are in the fields of indoor air quality, building-related illnesses, and infection control. Dr. Parsons has worked as a consulting engineer for more than 28 years. While in private practice, he undertook a broad spectrum of work for the public and private sectors in the areas of university campus utility planning; health care, research, and pharmaceutical facilities (clean room applications); commercial developments; and mechanical installations for industrial applications. During 2002 and

[1] Deceased.

2003, he took a sabbatical from his practice and was contracted to Arup Consulting Engineers to provide support in developing its health care portfolio. He also conducted a course in air-conditioning and refrigeration at the University of KwaZulu-Natal. Dr. Parsons has coauthored a number of publications and presented peer-reviewed papers and presentations at international conferences and seminars. He has also been an invited copresenter in professional development programs, focusing on indoor air quality and occupational safety influences, including energy management and efficiency strategies. Over the past 8 years, he has worked with the MRC, CDC, and the Harvard School of Public Health on investigations into the efficacy of electro/mechanical building service systems for the protection of health care workers against airborne infectious diseases such as TB.

Simon Schaaf, MBChB, DCM(SA), MMed(PAED), is a pediatrician with a subspeciality in infectious diseases in the Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, and Tygerberg Children's Hospital. He has focused most of his clinical and research efforts on TB, especially drug-resistant TB in childhood. His doctoral studies were on drug-resistant TB in children and included a pharmacokinetic study on isoniazid and its possible role in low-level isoniazid-resistant TB cases. Currently he is involved in ongoing drug resistance surveillance in children in the Western Cape of South Africa, as well as in several studies on children as contacts of MDR TB cases and children with drug-resistant TB. His other area of interest is the pharmacokinetics of anti-TB drugs in children. Professor Schaaf completed both pre- and postgraduate studies at Stellenbosch University. He has authored or coauthored many articles, most on childhood TB, and is, together with Ali Zumla, coeditor of the book *Tuberculosis: A Comprehensive Clinical Reference,* published by Saunders Elsevier in 2009.

Karen Shean, PN, is a professional nurse and has been a member of the Lung Infection and Immunity Unit (LIIU) at the University of Cape Town (UCT) for the past 2 years. Enrolled at UCT, she is presently completing her MscMed and operates as MDR TB study coordinator. She has a vast wealth of experience in TB, specifically drug-resistant TB. Prior to joining the LIIU, Ms. Shean had worked in the provincial TB program since 1990, eventually attaining the position of TB advisor and provincial TB hospital MDR/XDR TB coordinator. She has presented at many conferences internationally, nationally, and locally on MDR TB, XDR TB, infection control, and health care worker issues. In 2007 she was the provincial nominee for the International Council of Nurses (ICN)/Lilly Award for Nursing Excellence in TB Care. In 2009 she received the Investigator Award on Multidrug-Resistant Tuberculosis for the best abstract submitted to the European Respiratory Society in that category.

Adriaan Willem Sturm, M.D., Ph.D., is dean of the Nelson R. Mandela School of Medicine at the University of KwaZulu-Natal in Durban, South Africa. He is also interim director of the new KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH). During his career as a medical microbiologist, Dr. Sturm has studied TB, HIV, and sexually transmitted diseases. He was a leading scientist investigating the first outbreak of XDR TB in KwaZulu-Natal Province and a principal investigator on the project that sequenced the genetic code of that pathogen. Dr. Sturm began his research career in the Netherlands and became chair of the microbiology department at Aga Khan University in Pakistan in 1990. He came to the University of KwaZulu-Natal in 1993 and has served as a professor, head of the medical microbiology department, and dean. He is also director of the MRC's genital ulcer disease research unit at the university.

Maketekete Alfred Thotolo has worked for the Adventist Development and Relief Agency (ADRA) in Lesotho as a treatment literacy and advocacy coordinator since April 2008. Previously he served as director of that same organization from July 2007 to March 2008. From January 2006 to June 2007, Mr. Thotolo worked as national HIV/AIDS coordinator for the Seventh-Day Adventist Church in Lesotho. He holds a diploma in science education from the National University of Lesotho. He taught mathematics and science in a number of high schools in Lesotho from 1986 to 2005, when he started working full time in the field of HIV/AIDS. From July 1997 to March 2001, Mr. Thotolo worked in South Africa for the Professional Assignment Group (PAG) as a payroll officer; he also worked as a payroll helpdesk officer and an HIV/AIDS coordinator. Mr. Thotolo took an active part in the formation of the Lesotho Teachers' Trade Union in 1990, where he served for a number of years as Leribe District chairperson. He also served as chairperson for the Leribe District Math Teachers coalition, and was instrumental in the formation of community support groups in various districts of Lesotho.

Janet Tobias is a media/technology executive and an Emmy award–winning director/producer with 20 years of experience working for three American networks—PBS, Discovery, and MSNBC. Ms. Tobias started her career with 60 Minutes as Diane Sawyer's associate producer, where she distinguished herself working on a wide range of domestic and international stories. Ms. Tobias then moved with Ms. Sawyer to ABC News to launch Prime Time Live, where she produced/directed both domestic and international stories. Subsequently, she served as a national producer for Dateline NBC and also continued to produce and direct her own stories. Moving to VNI (which became New York Times Television) as an executive producer, she supervised the production of a foreign news show and reporting on a

variety of foreign stories. Ms. Tobias then returned to ABC News to head editorial activities at its newly created Law and Justice Unit. In 1998, she began working as an executive with PBS, where she developed and produced programming not only for PBS but also for joint projects with ABC and Discovery. She continued her directing and writing career, winning two American Bar Association silver gavels. In 2001, she launched LIFE 360, a weekly PBS series. In 2002, Ms. Tobias joined Sawyer Media Systems, a creator of video technology for the web, where she served as vice president of production and a member of the executive committee. She also continued to be involved in documentary production through her own company, Sierra/Tango Productions. In 2004, she was a founding partner of Ikana Media, a digital strategy and production company whose primary focus is on health care information. Over the last 5 years she has worked with a variety of clients in the health care arena on subjects ranging from broad-based delivery of health care information to communications efforts around obesity and HIV/AIDS. Ms. Tobias has received a number of additional awards, including two Cine Golden Eagles, two Casey medals for meritorious journalism, a National Headliner award, a Sigma Delta Chi award, and honorable mention Robert F. Kennedy Journalism and Overseas Press awards. She is a member of the Writers Guild of America and a graduate of Yale University. She serves on the boards of Healthright International, Mindset Media Society, Rwanda Works, and SochiReporter. She served from January to September 2009 as a senior fellow at the University of British Columbia, Sauder School of Business Centre for Sustainability and Social Innovation.

Maletela Tuoane-Nkhasi, Ph.D., holds her Ph.D. in social statistics from the University of Southampton, a master's degree in population studies from the University of Ghana, and a bachelor's degree in statistics and demography from the National University of Lesotho. She has worked as a lecturer and senior lecturer in demography at the National University of Lesotho and as research project manager at the Department of Social Development in South Africa. Dr. Tuoane-Nkhasi is currently a manager in the Births and Deaths component of the Health and Vital Statistics Division at Statistics South Africa. She is responsible for management of data processing for information on mortality and causes of death from civil registration systems, and for the production of statistical reports on mortality and causes of death and recorded live births.

Martie van der Walt, MScAgric, M.B.A., Ph.D., is interim director for the TB Epidemiology and Intervention Research Unit and joined TB research at the MRC in 1998. She has more than 9 years of experience in research on drug-resistant TB, operations research, diagnostics evaluation, and TB

infection control. 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 the uptake of new diagnostics. Dr. van der Walt has been responsible for the large-scale rapid MDR TB diagnosis project, which is providing evidence to WHO for evaluating rapid assays for routine use in developing countries. She has also been overseeing the 5-year cooperative agreement between CDC and the Unit, which has included managing subpartners (for example, the THAT'S IT program). She is also responsible for the Unit's operational research program and for projects covering such areas as program implementation, Directly Observed Treatment Short course (DOTS) evaluation, and drug-resistant TB and epidemiology. Through the Unit's operations research activities, Dr. van der Walt has a network encompassing TB control programs on both the national and provincial levels. 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, and served on the Green Light Committee from 2005 to 2007 as the MRC alternate. She received her basic training in microbiology (MScAgric) from the University of Pretoria, a master's degree in business administration from the University of Pretoria, and a Ph.D. in biotechnology from the University of Pretoria.

Paul van Helden, Ph.D., obtained his doctorate in biochemistry in 1978 and has served on the Faculty of Health Sciences at Stellenbosch University, Cape Town, since January 1979. He is professor and head of the Division of Molecular Biology and Human Genetics and also director of the MRC Centre for Molecular and Cellular Biology, as well as codirector of the Department of Science and Technology/National Research Foundation (DST/NRF) Centre of Excellence for Biomedical TB Research. He has been associated with the MRC since 1979 and employed by the Council since 1990. He has been awarded the Vice-Chancellors' Award for Excellence in Research (University of Stellenbosch, 2000); the Gold Medal Award, South African Society for Biochemistry and Molecular Biology (2001); the MRC Silver Medal for Research (2004); and the National Science and Technology Forum (NSTF) Award for Outstanding Contribution to Science and Technology in the Republic of South Africa (RSA) over 5 years (2005). Dr. van Helden's interest in TB began in 1989. This interest has grown and is now a major focus of the Division and faculty. The Division operates across diverse areas of TB research, from diagnostics, to immunology and genetics, to clinical trials and veterinary TB. Dr. van Helden has published more than 220 research publications, and his team has extensive global networks. He describes their efforts as attempting to develop a continuum of activities to span the divide between basic research and clinical practice in hospitals, clinics, and community settings. A disease such as TB not only

has scientific components, but also is intimately linked to culture, society, poverty, and local and international norms and activities, which cannot be ignored.

Sabine Verkuijl, M.D., has worked in South Africa since 1998. She holds a DTM&H from the Royal Tropical Institute in Amsterdam (The Netherlands) and an MMed (FamMed) degree from UNITRA (South Africa). From 1998 to 2002, Dr. Verkuijl was employed as a senior/principal medical officer in Bambisana Hospital, a rural district hospital in the former Transkei (O.R. Tambo District, Eastern Cape). With funding from the Netherlands, she initiated and supervised a community-based DOTS project in primary health care facilities under Bambisana. Between 2002 and 2006, Dr. Verkuijl worked with the Health Systems Trust, first as a facilitator for the Initiative for Sub-District Support (ISDS) around district health systems development in the OR Tambo District, and later as Eastern Cape provincial coordinator for the Technical Assistance Service Contract for Tuberculosis (TASC-TB) program, in collaboration with University Research Corporation (URC) and Management Sciences for Health (MSH). From 2006 to 2007, she was a part-time HIV and TB/HIV clinician in primary health care facilities and a TB Hospital in East London. Since 2006 she has been employed by the International Center for AIDS Care and Treatment Programs (ICAP), under Columbia University, as a technical advisor for TB/HIV integration, supporting selected districts in the Eastern Cape, KwaZulu-Natal, Free State, and Northern Cape Provinces to improve TB/HIV collaborative activities.

Kristina Wallengren, Ph.D., technical advisor to the Provincial TB Control Programme, Department of Health, KwaZulu-Natal (KZN), since 2007, is presently evaluating piloting of decentralized MDR TB treatment in KZN with support from IZUMI Foundation. Supported by WHO, Dr. Wallengren conducted a situational analysis of MDR and XDR TB in KZN following the XDR TB outbreak reported by Church of Scotland Hospital (CoSH). Dr. Wallengren has worked as TB and HIV research investigator with Harvard University in KZN since 2005, and has also undertaken an HIV seroprevalance and knowledge, attitudes, and practice (KAP) survey in the apparel industry in Lesotho. Currently, Dr. Wallengren is the Acting Clinical Core Manager at KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH). She holds an MPH in international health from Harvard School of Public Health and a PhD in molecular biology and virology from Karolinska Institute in Sweden.

Rob Warren, Ph.D., obtained his doctorate in biochemistry from the University of Cape Town in 1995 and subsequently joined the Department of

Medical Biochemistry, Stellenbosch University. He was appointed associate professor in the department in 2004. Under his guidance, the study of the molecular epidemiology of *M.tb.* in a high-incidence setting (Cape Town, South Africa) has been brought to the forefront of international TB research. This study now represents the largest molecular epidemiological data set in the developing world and has been referred to as a national heritage. Much of this work has provided new understanding that has allowed long-standing dogmas to be challenged. Dr. Warren has published more than 110 papers in international peer-reviewed journals in the fields of molecular epidemiology, drug resistance, and bacterial evolution since 1996. From this work, five patents have been registered, which hold promise for the development of novel vaccines, new diagnostics, and genetic manipulation of *M.tb*. Dr. Warren's current research focuses on (1) the disease dynamics of drug-sensitive and MDR/XDR TB in the Western Cape, (2) the development of novel diagnostics that are applicable to the developing world, (3) discovery of the mechanisms whereby drug resistance develops, (4) speciation of mycobacteria causing disease in humans and animals, (5) application of novel methods to improve the speed of diagnosing smear-positive disease, (6) host–pathogen compatibility, (7) identification of highly pathogenic strains of *M.tb.*, (8) pathogen evolution, and (9) mycobacterial epigenetics.

Robin Wood, M.D., is director of the Desmond Tutu HIV Research Centre and Professor of Medicine at the University of Cape Town, visiting scientist at Harvard University Medical School, and a member of the governing council of the International AIDS Society. He received his undergraduate training at London University and his medical degree from Oxford University. His internist specialization was at the University of Cape Town, and he completed an Infectious Disease Fellowship at Stanford University. Dr. Wood's research interests include treatment of HIV infection and interactions between HIV and TB; he has published more than 200 scientific articles. He has acted as a consultant on HIV and TB issues to international pharmaceutical industries, the South African mining industry, and WHO.

Tomás Zimba, M.D., MMed, is director of the Clinical Laboratories at Hospital Central de Maputo in Maputo, Mozambique, and a lecturer in virology at at Instituto Superior de Ciências e Tecnologia de Moçambique. From 2007 to 2009, Dr. Zimba served as director of the laboratory course in Instituto Superior de Ciências de Saúde. From 1999 to 2000, he served as a general practitioner at Provincial Hospital of Tete, clinical director of the Department of Medicine and Provincial Laboratory, clinical counselor at the provincial level of the National Program against Tuberculosis, and

clinical counselor at the provincial level of the Essential Drugs Program at Provincial Hospital of Tete. Dr. Zimba received his M.D. from the First Medical University of St. Petersburg, Russia, and holds an MMed in medical microbiology from the Nelson Mandela School of Medicine of the University of KwaZulu-Natal in South Africa.