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## **Plan to Combat Extensively Drug-Resistant Tuberculosis**

**Recommendations of the  
Federal Tuberculosis Task Force**



**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
CENTERS FOR DISEASE CONTROL AND PREVENTION**

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# Plan to Combat Extensively Drug-Resistant Tuberculosis

## Recommendations of the Federal Tuberculosis Task Force

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### Summary

*An estimated one third of the world's population is infected with Mycobacterium tuberculosis, and nearly 9 million persons develop disease caused by M. tuberculosis each year. Although tuberculosis (TB) occurs predominantly in resource-limited countries, it also occurs in the United States.*

*During 1985–1992, the United States was confronted with an unprecedented TB resurgence. This resurgence was accompanied by a rise in multidrug-resistant TB (MDR TB), which is defined as TB that is resistant to the two most effective first-line therapeutic drugs, isoniazid and rifampin. In addition, virtually untreatable strains of M. tuberculosis are emerging globally. Extensively drug-resistant (XDR) TB is defined as MDR TB that also is resistant to the most effective second-line therapeutic drugs used commonly to treat MDR TB: fluoroquinolones and at least one of three injectable second-line drugs used to treat TB (amikacin, kanamycin, or capreomycin). XDR TB has been identified in all regions of the world, including the United States.*

*In the United States, the cost of hospitalization for one XDR TB patient is estimated to average \$483,000, approximately twice the cost for MDR TB patients. Because of the limited responsiveness of XDR TB to available antibiotics, mortality rates among patients with XDR TB are similar to those of TB patients in the preantibiotic era.*

*In January 1992, CDC convened a Federal TB Task Force to draft an action plan to improve prevention and control of drug-resistant TB in the United States (CDC. National action plan to combat multidrug-resistant tuberculosis. MMWR 1992;41 [No. RR-11]). In November 2006, CDC reconvened the Task Force to draft an updated action plan to address the issue of MDR TB and XDR TB. Task Force members were divided into nine response areas and charged with articulating the most pressing problems, identifying barriers to improvement, and recommending specific action steps to improve prevention and control of XDR TB within their respective areas.*

*Although the first priority of the Federal TB Task Force convened in 2006 was to delineate objectives and action steps to address MDR TB and XDR TB domestically, members recognized the necessity for TB experts in the United States to work with the international community to help strengthen TB control efforts globally. TB represents a substantial public health problem in low- and middle-income countries, many of which might benefit from assistance by the United States. In addition, the global TB epidemic directly affects the United States because the majority of all cases of TB and 80% of cases of MDR TB reported in the United States occur among foreign-born persons. For these reasons, the Action Plan also outlines potential steps that U.S. government agencies can take to help solve global XDR TB problems. Unless the fundamental causes of MDR TB and XDR TB are addressed in the United States and internationally, the United States is likely to experience a growing number of cases of MDR TB and XDR TB that will be difficult, if not impossible, to treat or prevent.*

*The recommendations provided in this report include specific action steps and new activities that will require additional funding and a renewed commitment by government and nongovernment organizations involved in domestic and international TB control efforts to be implemented effectively. The Federal TB Task Force will coordinate activities of various federal agencies and partner with state and local health departments, nonprofit and TB advocacy organizations in implementing this plan to control and prevent XDR TB in the United States and to contribute to global efforts in the fight against this emerging public health crisis.*

The material in this report originated in the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Kevin Fenton, MD, PhD, Director, and the Division of Tuberculosis Elimination, Kenneth G. Castro, MD, Director.

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## Introduction

### Global Health Burden of Tuberculosis

Tuberculosis (TB) is among the most common infectious diseases and frequent causes of death worldwide (1). TB is caused by *Mycobacterium tuberculosis* and is spread most commonly by airborne transmission. *M. tuberculosis* can affect any part of the body but is found most often in the lungs. Persons with pulmonary TB generally have a cough that produces small airborne droplet nuclei containing tubercle bacilli that can remain in the air for hours. Vulnerable persons exposed to tubercle bacilli in airborne droplets might become infected. The majority of persons who become infected remain noncontagious and without a cough or other symptoms. These persons have latent *M. tuberculosis* infection (LTBI) and can be treated with a single drug (isoniazid) for 9 months to prevent disease.

Infected persons who do not have underlying medical problems and do not receive LTBI treatment have a 5%–10% lifetime risk for progressing to TB disease (2). However, the risk for disease progression increases substantially in the presence of immunosuppression, such as that caused by the human immunodeficiency virus (HIV) and immunosuppressive medications (2). Persons with pulmonary TB can be cured with a 6-month course of antibiotics that includes isoniazid, rifampin, pyrazinamide, and ethambutol during the first 2 months. In the United States, diagnosis and treatment for TB is accessible and effective (3). However, many developing countries have limited resources to diagnose TB illness and treat persons with TB. Worldwide, 2 billion persons (one third of the world's population) are thought to have LTBI. Nearly 9 million persons develop TB disease each year, and close to 2 million TB-related deaths occur annually (1). In the United States, approximately 13,000 new cases of TB are reported annually, and 650 persons die from TB each year (4). TB is the leading cause of mortality among persons infected with HIV (5).

### Emergence of Drug-Resistant Tuberculosis

During 1985–1992, the United States experienced an unprecedented TB resurgence marked by a substantial number of patients with TB who did not respond to treatment and who eventually died (6). Physicians and epidemiologists quickly determined that these persons had multidrug-resistant TB (MDR TB), which is defined as TB that is resistant to both isoniazid and rifampin (7). Although persons with MDR TB usually can be treated effectively by relying on second-line drugs (amikacin, kanamycin, or capreomycin), these have more side effects and are more expensive and less effective than first-

line drugs and require regimens lasting 18–24 months (3). In addition, the cure rate for persons with MDR TB is 50%–60%, compared with 95%–97% for persons with drug-susceptible TB (3). In response to several MDR TB outbreaks in hospitals and correctional facilities in New York and Florida during 1988–1991 (8,9), CDC convened a Federal TB Task Force\* with representatives from multiple U.S. agencies† to produce recommendations for a nationwide response to the MDR TB outbreaks. In June 1992, the Federal TB Task Force published an action plan that provided a framework for response and specific action steps for state and local health departments and federal agencies (7). These action steps were grouped into nine categories: 1) surveillance and epidemiology, 2) laboratory diagnosis, 3) patient management, 4) screening and preventive therapy, 5) infection control, 6) outbreak control, 7) program evaluation, 8) information dissemination/training and education, and 9) research. Emergency federal funding was appropriated to CDC in 1993 and again in 1994 to allow the Federal TB Task Force and state and local health departments to implement certain parts of the plan. For example, CDC investigative teams were deployed to assist local programs in defining and organizing appropriate response to MDR TB outbreaks (CDC, personal communication, 2007). State and local health departments enhanced diagnostic laboratory capacity, increased the sensitivity of their surveillance systems, improved infection-control practices, and reemphasized the need for optimal treatment of all forms of TB to prevent the development and further transmission of MDR TB. Other federal agencies that are members of the task force also contributed substantially to implementation of the plan; a description of their activities follows.

The need for increased biomedical research and product development for TB was recognized by the National Institutes of Health (NIH) as part of the implementation of the 1992 Action Plan. The National Institute for Allergy and Infectious Diseases (NIAID) established extramural and intramural research programs in all areas of fundamental, translational, and clinical research in TB to create a platform of knowledge and the research tools needed to study *M. tuberculosis* and its interaction with the host and to characterize TB in animal models and humans. In June 2007, NIAID released a research agenda describing the specific biomedical research challenges and priorities that should be addressed in response to the emergence of drug-resistant TB (10).

\* A list of the members of the task force as of March 2007 appears on page 43 of this report.

† CDC, Food and Drug Administration, National Institutes of Health, Health Resources and Services Administration, Bureau of Prisons, Occupational Safety and Health Administration, Health Care Financing Administration, Indian Health Service, and National Institute on Drug Abuse.

The National Heart, Lung, and Blood Institute (NHLBI) supported studies with a strong emphasis on pulmonary TB, including complications through coinfection with HIV, and developed a training curriculum in TB for health professionals at medical institutions through the National Tuberculosis Curriculum Consortium (NTCC) (11,12). The Fogarty International Center (FIC) supported TB research and research training for developing country scientists through collaborative grants with U.S. institutions (13). The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) focused on international clinical research for optimizing TB treatment in children and women coinfecting with HIV (14). The more recently created National Institute of Biomedical Imaging and Bioengineering (NIBIB) has a substantial investment in diagnostic platform technologies (point-of-care and imaging) that can help improve TB diagnosis through advances in medical imaging methods (15).

In May 1994, the Food and Drug Administration (FDA) approved Rifater (a fixed-dose combination of rifampin, isoniazid, and pyrazinamide) to facilitate patient adherence with lengthy and complex multidrug therapy (16). In addition, FDA granted a priority new drug application review for the drug rifapentine, which was approved in July 1998 for the treatment of TB (17). In 1993, the United States Marshals Service (USMS) established a formal medical program for prisoners with TB (USMS, personal communication, 2007). As part of this activity, USMS drafted a series of advisory memoranda to provide education information and guidance to USMS field offices to support TB screening for staff and prisoners. USMS also collaborated with the Texas Department of Health to conduct presentations on TB control in correctional facilities highlighting patient tracking and follow-up issues that arise when transferring prisoners between and outside jurisdictions. The Department of Housing and Urban Development (HUD) developed web-based information and training activities on acquired immune deficiency syndrome (AIDS) and TB (HUD, personal communication, 2007).

Since 1998, with the creation of specific international TB programs (e.g., directly observed treatment, short-course [DOTS] expansion; research; training; and TB/HIV coinfection), the U.S. Agency for International Development (USAID) has provided technical and financial support to strengthen TB control programs worldwide (18). USAID also has supported drug-resistance surveys with biannual global reports and pilot programs to optimize MDR TB treatment and the Green Light Committee (GLC), which helps countries gain access to high-quality second-line TB drugs so they can provide treatment for persons with MDR TB (19). More recently, the Division of Immigration Health Services (DIHS) of the Health Resources and Services Administration (HRSA)

implemented a national TB Continuity of Care Program for persons who are detained by U.S. Immigration and Customs Enforcement (ICE) agents in the Department of Homeland Security (DHS) and who are to be deported before completing TB therapy (20); in October 2007, DIHS was transferred from HRSA to ICE. In addition, U.S. government agencies have worked with their counterparts in Mexico and in U.S. state agencies to develop initiatives (e.g., Ten Against TB) to address TB, including drug-resistant TB, along the U.S.-Mexico border (21). During 1993–2007, as a result of implementation of the 1992 Action Plan, the reported annual incidence of MDR TB in the United States declined 75%, from 485 cases in 1993 to 119 cases in 2007 (4).

## Emergence of Extensively Drug-Resistant Tuberculosis

Since 1993, both incidence of TB and the total number of TB cases in the United States have decreased, although the rate of decline has slowed since 2000. Worldwide, the number of TB cases has continued to increase, but the incidence rate has decreased since 2003. Recently, highly drug-resistant forms of TB have emerged worldwide. In 2006, CDC, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) reported the results of a survey regarding drug-resistant TB conducted by 25 reference laboratories comprising the Global Supranational TB Reference Laboratory Network (2000–2004), the National TB Surveillance System in the United States (1993–2004), the national reference laboratory of South Korea (2004), and the national MDR TB patient registry in Latvia (2000–2002) (22). The findings indicated that 20% of *M. tuberculosis* isolates were MDR, and 2% also were resistant to multiple second-line drugs. This highly resistant form of TB was identified in every region of the world, including the United States, where 4% of MDR TB isolates also were resistant to multiple second-line drugs. In a report published in 2006, this highly resistant form of TB was named extensively drug-resistant TB (XDR TB) (22). XDR TB is a subset of MDR TB that is resistant both to isoniazid and rifampin and to any fluoroquinolone drug and at least one of three second-line injectable drugs (amikacin, kanamycin, or capreomycin) (23).

The emergence of XDR TB raises concerns about the possibility of epidemics of virtually untreatable TB. Such epidemics could result in excessive mortality and substantial financial and infrastructure burden for public health and TB control programs. XDR TB is much more expensive to treat, with hospitalization costs in the United States estimated to average \$483,000 per case. A major outbreak of XDR TB in the United States would constitute a substantial drain on public

health resources and could quickly deplete the existing state and local TB budgets and have a negative impact on progress toward TB elimination. This is especially true in an era of diminishing resources for TB control at the national, state, and local levels (6). Treatment failures and subsequent death are more common among patients with XDR TB, and the drugs available to treat XDR TB are associated with serious adverse effects. Because persons who are infected with HIV or who have other immune-compromising conditions (e.g., diabetes) are more vulnerable to progressing to active TB disease, infection with XDR TB is of particular concern among these persons. In countries with high rates of HIV and limited health-care resources, substantial numbers of XDR TB cases are likely present. As of April 2007, South Africa (where HIV prevalence was estimated at 10.8% in 2005) had reported 352 cases of XDR TB, with the actual prevalence likely being much higher (24) because cultures and susceptibility testing are performed on only a small fraction of TB patients, and many drug-resistant cases will go undetected.

## Methodology

After an outbreak of XDR TB among HIV-infected persons in Kwazulu Natal, South Africa, reported in August 2006, urgent expert consultations were organized by the South African Medical Research Council (SAMRC) and WHO in September and October 2006 (25). The result of these consultations was the 2007 publication of a global MDR TB and XDR TB response plan with eight overarching objectives (26). Several U.S. government agencies, including CDC, participated in the expert consultations. The U.S. Federal TB Task Force was recognized as the appropriate venue to coordinate U.S. involvement in the global response to XDR TB.

In November 2006, following participation in the SAMRC and WHO XDR TB consultations, CDC convened members of the Federal TB Task Force to discuss the emergence of XDR TB and coordinate U.S. government agency involvement in the domestic and international response to this problem. After several teleconferences, the Task Force agreed that a U.S. government agency action plan should be written. The action plan that had been published in 1992 to respond to MDR TB was selected as a basis for drafting the XDR TB response plan (7). Several members of the 2006 Task Force also had contributed to the 1992 Action Plan to combat MDR TB. This MDR TB expertise contributed substantially to a well-informed and effective discussion and the creation of an Action Plan to Combat Extensively Drug-Resistant TB. As had occurred in the process to create the 1992 Action Plan, members of the Federal TB Task Force were divided into sections to address critical areas of response. The 1992 action plan distributed

the objectives and implementation steps needed to address 38 problems among nine response areas (surveillance and epidemiology, laboratory diagnosis, patient management, screening and preventive therapy, infection control, outbreak control, program evaluation, information dissemination/training and education, and research). Although largely overlapping with the 1992 action plan, the response areas for the XDR TB plan were reorganized as follows: 1) diagnostic laboratory; 2) surveillance, epidemiology, and outbreak investigations; 3) infection control; 4) clinical and programmatic interventions; 5) ethical and legal issues; 6) communication and education; 7) research; 8) partnerships; and 9) cost analysis. These response areas also are closely aligned with WHO's seven-point Global Action Plan to Combat XDR TB (26), which calls for public health authorities to 1) conduct rapid surveys of XDR TB to determine the burden, 2) enhance laboratory capacity with an emphasis on rapid drug-sensitivity testing, 3) improve the technical capacity of clinical and public health practitioners to respond effectively to XDR TB outbreaks and manage patients, 4) implement infection-control precautions, 5) increase research support for TB drug development, 6) increase research support for rapid diagnostic test development, and 7) promote universal access to antiretroviral drugs under joint TB/HIV activities. In addition, the implementation steps were renamed "action steps."

In January 2007, each subgroup of the Federal TB Task Force that was responsible for addressing a critical response area began by reviewing the relevant sections of the 1992 action plan to determine which problems, objectives, and action (formerly implementation) steps needed to be deleted or updated and revised. The subgroups also determined if gaps existed requiring the identification of additional problems, objectives and action steps. In particular, because the 1992 plan had focused primarily on domestic MDR TB, the subgroups were instructed to expand the scope of the new plan to address the role of U.S. government agencies in the international response to XDR TB. To reflect this distinction, the new plan labels objectives as domestic, international, or both. The expanded scope and a greater emphasis on detail resulted in a substantial increase in the number of problems, objectives, and action steps identified compared with the 1992 plan. For example, the number of problems increased from 38 in 1992 to 67 in the current plan. An emphasis also was placed on being as inclusive as possible when designating lead federal agencies and potential external partners. To provide a basis for revisions, the subgroup members reviewed pertinent literature published since 1992, which is substantially more voluminous, especially for drug-resistant TB, compared with that available before 1992, and available unpublished data. After drafts of the sections were completed, the sections were compiled into a single document that was

distributed to the entire Federal TB Task Force for review and comment. In June 2007, the Federal TB Task Force met in Rockville, Maryland, to make additional revisions, especially to eliminate redundancies between sections. These revisions were incorporated into a final draft that was submitted for multiple agency clearance in September 2007.

## **Recommendations to Combat Extensively Drug-Resistant Tuberculosis**

### **Diagnostic Laboratory**

The diagnosis of XDR TB is established by laboratory methods. Accurate, reliable, and prompt TB laboratory services should be coordinated fully with provider and public health practitioners caring for persons with TB. Test results must be available in a time frame that allows clinicians to make prompt and informed patient management decisions. For this goal to be met, laboratory capacity for the diagnosis of TB and the detection of drug resistance must be rapidly enhanced, both in the United States and worldwide. Adequate infrastructure must be built where it does not exist, a stable and well-trained work force must be developed and maintained, and a systems approach (27) must be implemented to maximize efficiency and proficiency. Laboratory methods and reporting, especially for susceptibility to second-line drugs, should be standardized through expert consensus. Rapid tests for TB diagnosis and drug-susceptibility testing on the basis of newer molecular methods must be evaluated promptly to determine their feasibility, especially for low-resource settings, and, if appropriately validated, their use should be promoted and facilitated. Internationally, competent, high-quality reference laboratory services with capacity to perform required testing of samples and to report results in a prompt fashion to providers and health officials must be available to jurisdictions in need.

### **Surveillance, Epidemiology, and Outbreak Investigation**

Domestic XDR TB surveillance must include accurate and complete reporting of second-line drug-susceptibility testing, real-time reporting, and active case finding. Central notification of MDR TB and XDR TB is essential to identify cross-jurisdictional issues and to provide potential for rapid emergency federal support, when needed. Internationally, rapid drug-susceptibility test (DST) surveys and more sustained systematic capture of DST information are highlighted as areas to be addressed as part of a comprehensive response to XDR TB. Epidemiologic studies that make use of genotyping

tools are recommended to elucidate XDR TB risk factors and transmission dynamics. Strategies also are needed to rapidly identify and respond to domestic and international XDR TB outbreaks.

### **Infection Control**

Effective infection-control practices are critical to prevent the transmission and further spread of MDR and XDR TB in health-care settings and other congregate settings (e.g., correctional facilities and homeless shelters). CDC infection-control guidelines were updated in December 2005 and should continue to be updated as needed (28). Further studies are needed to assess the effectiveness and feasibility of various infection-control strategies in different institutional settings. Testing workers for TB in various institutional settings is an important strategy for identifying workers infected with TB and detecting unsuspected transmission.

### **Clinical and Programmatic Interventions**

Prevention and control of TB in the United States require a robust public health infrastructure that includes a workforce trained in TB prevention, diagnosis, treatment, and case management. Because some patients fail to recognize TB symptoms, health care often is not sought during early stages of disease. In addition, providers who are unfamiliar with signs and symptoms of TB and with diagnostic standards might not suspect TB, delaying the start of effective treatment. Access to comprehensive and affordable clinical TB services (i.e., preventive, diagnostic, and treatment/case management) should be provided to all persons with TB or those suspected to have TB. Health-care providers who screen persons for TB should use up-to-date diagnostic and treatment guidelines. More health-care workers are needed to provide directly observed therapy (DOT) for TB patients to ensure successful treatment and help prevent development of disease attributable to drug-resistant TB.

### **Ethical and Legal Issues**

Strict infection-control measures are necessary to prevent the spread of XDR TB. Patients with XDR TB might need to be placed in airborne infectious isolation while initial treatment response is monitored in order to prevent disease transmission to others. Guidance is needed regarding the ethical and legal issues involved in identifying and treating persons with XDR TB. The adequacy of current public health laws in the United States to address drug-resistant TB has not been studied comprehensively since 1993 (29). All states have laws to compel

isolation for persons with certain infectious diseases (including TB); however, these laws vary by state, and those for TB might be contingent on patient nonadherence and failure of voluntary measures. Public health authorities must balance the interests of the public with individual rights. Legal and ethical issues become even more complicated when persons have XDR TB because prolonged isolation might be necessary even when a patient is adherent. In addition, for some patients, no effective treatment is available that would allow for release from isolation on completion. Additional complexity also exists regarding non-U.S. citizens with infectious XDR TB who are scheduled to be repatriated to their native countries. U.S. public health officials might not be familiar with public health laws of other countries.

## Communication and Education

As a result of TB incidence rates decreasing in the United States, health-care providers have received little training regarding TB and consequently might not recognize the signs and symptoms of TB, which can lead to incorrect diagnosis and treatment, creation of drug resistance, and continued spread of TB in the community (30,31). Health-care providers should be educated about the signs and symptoms of TB, diagnostic methods, prevention, and treatment. In addition, education materials on MDR TB and XDR TB should be developed for the general public, populations at high-risk for TB on the basis of demographic and clinical characteristics, TB patients, TB prevention advocacy organizations, and policy makers, including legislators. Education materials should include informational pamphlets, instructions for therapy, behaviors to prevent transmission, medical alerts, and descriptions of TB programs. Distribution of these materials should be coordinated across federal and state agencies and updated as necessary. Advocacy is critical to make the public aware of the importance of TB control to the public's health, and to educate policy makers on the magnitude of the problems that will result if resources to state and local TB control programs continue to decline.

## Research

The biomedical research challenges represented by drug-resistant TB in the context of overall TB research activities have been described previously (10). Knowledge gaps remain regarding the genetics and growth characteristics of *M. tuberculosis*, the physiology and biochemistry of both the host and pathogen during infection, and the disease and genotypic and biologic markers that facilitate surveillance and indicate infection, disease, and drug resistance. Basic research needs to be supported to advance understanding of these issues and to help design new approaches to diagnosis and treatment. The

emergence of drug-resistant TB illustrates the pressing need to develop new and effective drug regimens for the treatment of TB, including drugs to cure MDR TB and XDR TB and to prevent development of active disease among persons who are infected latently with drug-resistant *M. tuberculosis*. Because poor patient adherence to therapy is one factor that can lead to development of MDR TB and XDR TB, research of associated behavioral and social factors should be conducted to identify ways to improve patient adherence and treatment completion. New, rapid, and cost-effective diagnostic methods are needed, particularly for use in rural areas and developing countries. Ultimately, an effective vaccine is needed to eliminate TB.

## Partnerships

To coordinate efforts to control XDR TB, existing partnerships must be strengthened, and new partnerships are needed between countries and within both the public and private sectors, including government and nongovernment organizations. Partnerships are necessary to focus existing resources on the most affected geographic areas, increase current public and private resources (both financial and human resources), coordinate the efforts (including research, education, laboratory, and programmatic), and raise awareness of the problem and consequences.

## Cost Analysis

Comprehensive information is not available on the cost of treating and implementing programs and interventions to prevent XDR TB. Research on the cost of treating and preventing XDR TB is needed to calculate the cost-effectiveness and benefits of interventions and strategies to combat XDR TB.

## Action Plan to Combat Extensively Drug-Resistant Tuberculosis

### Diagnostic Laboratory

The laboratory plays a critical role in the diagnosis and management of drug-resistant TB. Test results must be available in a time frame that allows clinicians to make prompt patient management decisions. Many laboratory techniques used to confirm a TB diagnosis and to identify drug resistance were developed in the 1950s, 1960s, and 1970s. Substantial improvements have been made in culture techniques and in rapid methods in the past decade. However, these more accurate, rapid, and sophisticated methods have not been implemented widely, particularly in regions of the world where MDR TB and XDR TB are common and optimized algorithms for providing rapid point-of-care laboratory confirmation of



TB and detection of drug resistance have not been established. To combat the growing problem of resistance to TB drugs, the most current methods need to be applied to their fullest capacity while better diagnostic tests are developed. The needs of the TB laboratory must be addressed to make laboratory services for TB, MDR TB, and XDR TB more rapid, sensitive, reliable, and more responsive to the needs for patient management, infection control, and TB control efforts. Although the challenges and potential solutions vary by setting, domestic and international TB laboratories face many of the same challenges.

## Problem 1

Many clinicians, laboratorians, health-care professionals, public health officials, and policy makers do not possess up-to-date knowledge of what constitutes appropriate laboratory capabilities and capacities or the appropriate use of tests to arrive at a prompt and accurate diagnosis of TB.

### Objective 1.1

Increase awareness of the need to develop necessary capacity and capabilities for the laboratory diagnosis of TB. This includes proper use of diagnostic tests, prompt reporting of results, and appropriate interpretation of test results for establishing a definite diagnosis and for guiding management of TB (domestic and international).

### Action Steps

1.1.1. Educate clinicians and public health officials about appropriate use of diagnostic services and tests, interpretation of laboratory test results, and the role of the diagnostic laboratory in monitoring treatment. Distribute current guidelines on TB diagnostic testing, drug-susceptibility testing, and laboratory services.

1.1.2. Conduct a survey of current practices and capabilities in private, hospital, commercial, and public TB laboratories to assess current methods and infrastructure used for direct detection of *M. tuberculosis* in patient specimens, and rapid testing for susceptibility to first- and second-line drugs.

1.1.3. Create or update self-assessment tools for private, hospital, commercial, and public laboratories to evaluate their practices in and knowledge of TB diagnosis and drug-susceptibility testing to facilitate planning of continuous quality improvements.

1.1.4. Educate policy makers, national health ministry officials, program officials, clinicians, laboratory managers, and laboratory directors about the role of prompt, reliable TB laboratory services in national and local health-care systems and public health programs.

1.1.5. Educate laboratorians, clinicians, and public health officials on the appropriate use of TB diagnostic laboratory services and the need for the integration of rapid tests into TB control programs to enhance patient care.

1.1.6. Identify and use resources available from regional jurisdictions in resource-limited settings with expected increases in MDR TB and XDR TB cases to help improve capacity for drug-susceptibility testing and care of patients with drug-resistant TB.

Lead federal agencies: U.S. Department of Health and Human Services (HHS) (CDC and NIH), USAID, and U.S. Department of Veterans Affairs (VA).

Suggested<sup>§</sup> collaborators: U.S. Department of Defense (DoD), American Thoracic Society (ATS), Infectious Diseases Society of America (IDSA), Association of Public Health Laboratories (APHL), National TB Controllers Association (NTCA), Regional Training and Medical Consultation Centers (RTMCCs), WHO, national health ministry, academia, and public health and private laboratories.

## Problem 2

Although the majority of domestic TB laboratories are prepared to respond to MDR TB, many have limited capacity to respond to XDR TB.

### Objective 2.1

Ensure that required laboratory services are available to respond properly to XDR TB (domestic).

### Action Steps

2.1.1. Assess current domestic laboratory resources and capacity to create an integrated network of TB diagnostic resources necessary for a prompt and robust response to XDR TB anywhere in the United States.

2.1.2. Develop centers of excellence for TB diagnosis as part of a network of laboratories and information/specimen management systems that use standardized procedures for reporting within 2 days of identification of MDR and XDR *M. tuberculosis* from clinical specimens, tracking and referral for TB cases, and shipping of specimens.

2.1.3. Develop enhanced biosafety level 3 laboratories with appropriate facilities, trained staff, administrative controls, and monitoring programs to handle XDR *M. tuberculosis* strains safely.

2.1.4. Ensure second-line drug-susceptibility testing of isolates from all patients identified with MDR TB.

2.1.5. Develop sufficient domestic laboratory capacity to accommodate rapid testing of *M. tuberculosis* strains in

<sup>§</sup> Organizations listed as suggested collaborators have not yet been approached to work on any recommended action steps.

case of domestic and international TB outbreaks (surge capacity) and to provide comprehensive, ongoing coverage for surveillance.

2.1.6. Develop a laboratory component for a rapid XDR TB outbreak response plan and provide training to local, state, and federal responders.

2.1.7. Coordinate the CDC Universal TB Genotyping Program with TB genotyping programs of the European Union (EU) and other international partners to identify genotypes associated with XDR *M. tuberculosis* strains and develop an early warning system for the spread of XDR *M. tuberculosis* strains.

Lead federal agencies: HHS (CDC and NIH).

Suggested collaborators: APHL, NTCA, academia, and public health and private laboratories.

### Problem 3

Current laboratory capacity is inadequate to identify, characterize and track drug resistant *M. tuberculosis* strains in response to the XDR TB epidemic.

#### Objective 3.1

Enhance laboratory capacity to support outbreak investigations and studies of XDR TB (domestic).

#### Action Steps

3.1.1. Provide support for MDR and XDR TB outbreak investigations through genotyping of *M. tuberculosis* isolates and rapid drug-susceptibility testing.

3.1.2. Fully implement the CDC Universal TB Genotyping Program to track and monitor *M. tuberculosis* strain transmission in the United States.

3.1.3. Establish and support a national *M. tuberculosis* genotype and isolate archive to compare strains, epidemiologic data, and clinical outcomes from different geographic regions.

3.1.4. Support efforts to determine genomic sequences of MDR and XDR *M. tuberculosis* strains to characterize resistance and aid in determining virulence mechanisms.

3.1.5. Provide overall technical laboratory assistance to investigate MDR TB and XDR TB outbreaks.

Lead federal agencies: HHS (CDC and NIH).

Suggested collaborators: NTCA, APHL, academia, and public health and private laboratories.

#### Objective 3.2

Determine laboratory capacity needed for rapid XDR TB surveys in WHO-designated high-burden (defined by WHO as

the 22 countries with the highest TB morbidity) and TB-focus countries<sup>‡</sup> (international).

#### Action Steps

3.2.1. Assess capacities of national and international academic, private, commercial, and public laboratories to provide laboratory services needed to conduct rapid XDR TB surveys.

3.2.2. Provide immediate (emergency) surge capacity through U.S. laboratory resources to affected countries in response to MDR TB and XDR TB outbreaks.

3.2.3. Develop a network of international quality-assured laboratories to conduct drug-susceptibility testing for XDR TB surveys.

3.2.4. Develop standardized methods for first- and second-line drug-susceptibility testing to be used in XDR TB surveys.

3.2.5. Develop external quality assessment programs for surveys.

Lead federal agencies: HHS (CDC and NIH) and USAID.

Suggested collaborators: U.S. Department of State (DOS), DoD, WHO, APHL, American Society for Microbiology (ASM), NTCA, IUATLD, Royal Netherlands Tuberculosis Association (KNCV), Research Institute of Tuberculosis (RIT), public health and private laboratories, and academia.

### Problem 4

The quality of and proficiency in TB laboratory diagnosis varies within the United States and internationally because a well-trained and stable laboratory workforce is not universally available.

#### Objective 4.1

Provide training in conventional and new diagnostic methods for TB (domestic and international).

#### Action Steps

4.1.1. Provide training to private, commercial, and public health laboratory managers and supervisors in laboratory management and systems.

4.1.2. Provide training to TB laboratory personnel for conventional and new diagnostic tests.

4.1.3. Provide training in biosafety and safe manipulation of pathogenic mycobacteria.

4.1.4. Develop training materials for current, new, and emerging technologies for TB laboratory personnel.

<sup>‡</sup> Countries that either 1) are WHO high-burden countries, 2) are countries from which the majority of foreign-born persons with TB in the United States originate (e.g. Mexico, the Philippines, and Vietnam), 3) have high HIV/TB prevalence, or 4) have a high prevalence of MDR TB.

4.1.5. Provide opportunities for exchange of personnel between laboratories in resource-limited settings to share knowledge about successful approaches to laboratory diagnosis.

4.1.6. Develop programs to assist laboratory managers in maintaining proficiency in TB laboratory services or to obtain services from referral laboratories.

4.1.7. Explore opportunities to integrate TB laboratory personnel into the general clinical laboratory workforce to strengthen overall human resource capacity at the local, district, and provincial levels.

4.1.8. Develop programs to inform and educate health-care providers about new tests for TB, their potential usefulness in establishing a diagnosis or monitoring therapy, and their cost/benefit over existing approaches.

4.1.9. Evaluate the effectiveness of newly developed training activities and programs to build laboratory capacity.

Lead federal agencies: HHS (CDC), and USAID.

Suggested collaborators: DoD, APHL, NTCA, National Laboratory Training Network (NLTN), STOP TB USA, WHO, IUATLD, Clinical Laboratory Standards Institute (CLSI), the Global Fund, and the World Bank.

## Problem 5

TB laboratory services at certain local public health laboratories are limited and might depend on access to networks of other public and private laboratories with better diagnostic capabilities, which often leads to substantial delays in diagnosis and treatment of TB.

### Objective 5.1

Develop a systems approach to improving TB laboratory services at the local level (domestic).

### Action Steps

5.1.1. Assess available TB laboratory services in a jurisdiction to determine the status and capacity of services and to identify unmet needs, obstacles to obtaining services, and opportunities for improvement.

5.1.2. Assess the actual costs of providing TB laboratory services through existing programs and develop a business plan for providing these services through an integrated system of laboratory services in the United States.

5.1.3. Develop a strategic plan for implementing and maintaining a systems approach to TB laboratory services.

5.1.4. Develop outcome measures to assess performance of and improvements in laboratory services and overall TB control programs.

Lead federal agencies: HHS (CDC).

Suggested collaborators: APHL, NTCA, state and local TB programs, academia, and public health and private laboratories.

### Objective 5.2

Develop integrated TB laboratory systems in high-burden countries and countries with limited resources (international).

### Action Steps

5.2.1. Inventory and assess available academic, private, commercial and public TB laboratory service providers to determine each country's domestic capacity to provide services for TB program and patient care activities.

5.2.2. Develop a network of public and private TB laboratories that use standardized and quality controlled methods for information and specimen management to meet the needs of the local and national TB treatment and control programs.

5.2.3. Provide training to develop national expertise in TB diagnostic laboratory services, patient care and TB control activities through engagement of national academic and clinical research programs.

5.2.4. Develop program-specific plans and phased approaches to improving laboratory services in national, country-level regional and peripheral (local) laboratories.

5.2.5. Develop local, district, regional, and national laboratories, including referral laboratories, that provide reliable services through conventional and rapid methods for TB diagnosis, drug-susceptibility testing and patient care.

5.2.6. Develop or ensure access to effective external quality assessment programs for laboratory services (e.g., acid fast bacillus [AFB]–smear microscopy, culture, and drug-susceptibility testing) provided at each level.

5.2.7. Support development of laboratory standards and accreditation programs with an emphasis on culture and drug-susceptibility testing to facilitate assessment and quality improvement of national and regional laboratories.

5.2.8. Explore options to increase TB laboratory capacity as part of efforts to improve general diagnostic laboratory service capacity and overall health sector reform.

5.2.9. Identify interim laboratory support services until local and regional capacity is developed.

5.2.10. Support research to develop inexpensive, high-quality diagnostic tools that can be used in resource-limited settings.

Lead federal agencies: HHS (CDC and NIH), and USAID.

Suggested collaborators: DoD, DOS, NTCA, APHL, ASM, WHO, and IUATLD.

## Problem 6

Culture-based laboratory tests to identify persons with XDR TB are slow, lack sensitivity, and have poor reliability, resulting in delayed diagnosis, treatment, and public health control efforts.

### Objective 6.1

Improve the ability of TB laboratories to identify and report drug-resistant *M. tuberculosis* (domestic).

### Action Steps

6.1.1. Develop local, district, state, regional, or referral laboratories that are able to rapidly identify *M. tuberculosis* bacteria in patient specimens and determine drug susceptibilities to first- and second-line agents using state-of-the-art conventional or rapid methods.

6.1.2. Encourage the use of state-of-the-art rapid tests for detection of *M. tuberculosis* and drug-susceptibility testing through focused laboratory funding.

6.1.3. Develop a bank of *M. tuberculosis* isolates for use in proficiency testing and research.

6.1.4. Implement proficiency testing programs and external quality assessment programs for new drug-susceptibility tests and rapid methods.

6.1.5. Assist laboratories in developing and implementing an integrated information management system for inventory, specimen tracking, reporting, and information sharing.

6.1.6. Identify interim laboratory support services until local and regional capacities are developed.

Lead federal agencies: HHS (CDC and NIH).

Suggested collaborators: APHL and NTCA.

## Problem 7

The lack of guidelines for the use of conventional and rapid culture-based or molecular methods for detection of *M. tuberculosis* and drug resistance impedes the widespread use of these tests.

### Objective 7.1

Develop consensus guidelines to address TB laboratory testing in the United States, in high-burden and in focus countries (domestic and international).

### Action Steps

7.1.1. Develop consensus guidelines for culture, drug-susceptibility, and rapid diagnostic testing to be used in local, district, state, national, and country-level regional laboratories.

7.1.2. Develop consensus guidelines for the use of rapid methods (e.g., nucleic acid amplification tests) to detect *M. tuberculosis* directly from patient specimens.

7.1.3. Develop consensus guidelines for the use of rapid, molecular methods for drug-susceptibility testing.

7.1.4. Develop consensus guidelines for culture-based methods to determine resistance to second-line TB drugs.

7.1.5. Conduct operational and implementation research to develop guidelines for optimal algorithms for TB laboratory testing, specimen referral, and reporting.

Lead federal agencies: HHS (CDC and NIH) and USAID.

Suggested collaborators: APHL, ATS, IDSA, CLSI, WHO, IUATLD, and academia.

## Problem 8

The current process for evaluating newly developed diagnostic tests can be time consuming and delay implementation for routine clinical use.

### Objective 8.1

Develop strategies for expedited evaluation and implementation of new rapid methods for laboratory confirmation of TB and identification of drug-resistance patterns (domestic and international).

### Action Steps

8.1.1. Evaluate and deploy methods to optimize AFB sputum smear microscopy.

8.1.2. Evaluate and deploy sensitive and rapid molecular tests to detect *M. tuberculosis* directly in sputum specimens.

8.1.3. Evaluate and deploy rapid culture methods for isolating *M. tuberculosis*.

8.1.4. Evaluate and deploy rapid culture-based or molecular drug-susceptibility testing methods.

8.1.5. Develop methods to validate genotypic indicators of resistance through phenotypic susceptibility results and the patient's response to treatment.

8.1.6. Develop consensus methods and guidelines for the introduction and use of new diagnostic methods, including in resource-limited settings.

8.1.7. Provide access to well-characterized drug-susceptible and drug resistant-strains of *M. tuberculosis* for identification of drug-resistance markers.

8.1.8. Expand the genomic characterization of drug-resistant *M. tuberculosis* strains to identify new markers of resistance to second-line drugs.

8.1.9. Evaluate the cost effectiveness and appropriate use of available and new rapid methods and approaches to identify of MDR/XDR *M. tuberculosis*.

8.1.10. Determine and promote the most effective point-of-care drug-susceptibility testing methods and diagnostic algorithms and strategies, including molecular testing at the

local level followed by transport of positive specimens to full-service laboratories for further evaluation.

8.1.11. Provide access to or conduct clinical trials in partnership with high-burden countries to validate new microbiologic drug-susceptibility tests as part of local diagnostic procedures/algorithms.

8.1.12. Discuss with FDA criteria that will be required for approval of new tests for identification of drug-resistant TB and to perform rapid drug-susceptibility testing.

Lead federal agencies: HHS (CDC, FDA, and NIH), and USAID.

Suggested collaborators: DoD, Foundation for Innovative New Diagnostics (FIND), WHO Special Programme for Research and Training in Tropical Diseases [TDR], academia, public health laboratories, and IUATLD.

## Problem 9

The laboratory confirmation of TB in HIV-infected persons is difficult and time consuming because of the need for highly sensitive, sophisticated and technically challenging diagnostic tests that are not universally available in all settings with a high burden of HIV and TB.

### Objective 9.1

Improve laboratory confirmation of TB, MDR TB, and XDR TB in HIV-infected persons (domestic and international).

#### Action Steps

9.1.1. Strengthen TB laboratory capacity to detect AFB-smear negative TB through support of global efforts to build culture capacity in TB laboratories and develop methods to increase sensitivity of AFB-smear microscopy.

9.1.2. Develop and evaluate effective laboratory testing algorithms and specimen referral systems to prioritize specimens from HIV-infected persons appropriately.

9.1.3. Integrate TB laboratory capacity building with HIV laboratory capacity building.

9.1.4. Evaluate and deploy the use of sensitive and rapid molecular tests to detect *M. tuberculosis* directly in sputum and other clinical specimens from HIV-positive persons.

Lead federal agencies: HHS (CDC and NIH), and USAID.

Suggested collaborators: DOS, DoD, FIND, WHO (TDR), ASM, APHL, academia, IUATLD, and public health laboratories.

## Problem 10

Current technical assistance for laboratory capacity building is sporadic and not well coordinated or integrated often leading to unclear and inconsistent guidance.

## Objective 10.1

Develop consistent and well-coordinated approaches to technical assistance and consultation for TB laboratories in high-burden and focus countries (international).

### Action Steps

10.1.1. Develop technical assistance approaches and practices that are coordinated, consistent, and compatible with the efforts of international partners such as WHO and IUATLD.

10.1.2. Establish a cadre of well-trained consultants to help guide coordinated approaches to building TB laboratory capacity in high-burden and focus countries.

10.1.3. Contribute to the coordinated development of standardized checklists and templates for laboratory evaluation and training materials for laboratory capacity building efforts.

10.1.4. Contribute to the coordinated development of external quality assessment guidance and documents for microscopic and culture identification of *M. tuberculosis* and drug-susceptibility testing.

10.1.5. Contribute to the coordinated development of widely compatible laboratory information systems to facilitate transfer of information within and between TB control programs.

10.1.6. Promote expansion of the Supranational Laboratory Network through inclusion of reference laboratories that can assist in capacity building and external quality assessment.

10.1.7. Promote expansion of the Supranational Laboratory Network proficiency testing to include second-line drug-susceptibility testing.

10.1.8. Promote and coordinate partnering of public health laboratories in the United States with public health laboratories in high-burden and focus countries.

Lead federal agencies: HHS (CDC and NIH), and USAID.

Suggested collaborators: DoD, DOS, NTCA, APHL, ASM, WHO, and IUATLD.

## Problem 11

Providing technical assistance is logistically difficult.

### Objective 11.1

Establish international regional centers of excellence to facilitate implementation of technical assistance provided by the United States to TB endemic or TB-focus countries (international).

#### Action Steps

11.1.1. Build expertise for technical assistance to TB laboratories at selected centers of excellence in high-burden countries.

11.1.2. Provide opportunities for peer-to-peer training and exchange of laboratory personnel in resource limited settings.

11.1.3. Assist centers of excellence in developing training programs for program staff, laboratory managers and bench workers on establishing methods for external quality assessment processes through site visits and monitoring.

11.1.4. Assist centers of excellence in establishing reference laboratory services for identification of *M. tuberculosis* and susceptibility testing for first- and second-line drugs that would qualify them as Supranational Reference Laboratories and that could be made available to partner programs.

Lead federal agencies: HHS (CDC and NIH) and USAID.

Suggested collaborators: DOS, DoD, WHO, IUATLD, APHL, ASM, KNCV, RIT, academia, and public health laboratories.

## Problem 12

Resources available to TB laboratories are often inadequate for building and maintaining the necessary infrastructure and competencies to provide consistently high-quality diagnostic services.

### Objective 12.1

Mobilize resources and support international efforts to strengthen and sustain TB laboratory capacity (international).

#### Action Steps

12.1.1. Identify funding opportunities through the President's Emergency Plan for AIDS Relief, USAID, and the Global Fund to contribute to strengthening international laboratory efforts.

12.1.2. Support global efforts (e.g., WHO's strategic approach to the strengthening of laboratory services for TB control).

12.1.3. Support the Stop TB Partnership's Global Laboratory Initiative and the DOTS (directly observed therapy, short course) Expansion Working Group.

Lead federal agencies: USAID and HHS (CDC).

Suggested collaborators: DOS, WHO, the Bill & Melinda Gates Foundation, APHL, and the American Lung Association (ALA).

## Problem 13

The role of public and private TB laboratories in the diagnosis of persons latently infected with XDR *M. tuberculosis* has not been defined clearly.

## Objective 13.1

Develop laboratory services to identify persons with drug-resistant latent *M. tuberculosis* infection (DR LTBI) (domestic).

#### Action Steps

13.1.1. Assess the capacity of public and private TB laboratories to support DR LTBI diagnostic testing by determining the status and capacity of currently available services and identifying gaps, obstacles and opportunities for improvement.

13.1.2. Develop materials and programs to train laboratory personnel in DR LTBI diagnostic testing.

13.1.3. Develop consensus laboratory guidelines for DR LTBI testing methods.

13.1.4. Conduct operational research to optimize testing and referral algorithms.

13.1.5. Develop proficiency testing and external quality assessment modules for DR LTBI diagnosis.

13.1.6. Conduct Phase 4 clinical studies of new technologies for DR LTBI diagnosis and management.

Lead federal agencies: HHS (CDC, FDA, NIH).

Suggested collaborators: DoD, NTCA, APHL, CLSI, ATS, and IDSA.

## Problem 14

International laboratory services used by physicians under provisions of the United States Immigration and Nationality Act often are not equipped to the standards of U.S. TB programs and might not be able to reliably identify persons with drug-susceptible or MDR TB and XDR TB.

### Objective 14.1

Evaluate and improve the ability of international laboratories employed to identify *M. tuberculosis* and perform drug-susceptibility testing for potential U.S. immigrants (international).

#### Action Steps

14.1.1. Determine which high-burden country issues the largest number of immigrant visas and identify the top 20 immigrant visa processing posts.

14.1.2. Identify and assess the diagnostic capabilities of laboratories used by physicians affiliated with these visa processing posts.

14.1.3. Assure that evaluations and improvements in TB laboratory services used for medical evaluation of visa applicants are coordinated with overall efforts to improve national TB programs.

14.1.4. Provide training on the basis of U.S. government policies for the medical examination of aliens (available at

<http://www.cdc.gov/ncidod/dq/health.htm>) to TB laboratories used by examining physicians to facilitate improvement of laboratory proficiency for identification of *M. tuberculosis* and diagnosis of drug-susceptible and drug-resistant TB.

14.1.5. Provide oversight, proficiency testing, and consultation to ensure adequate TB diagnostic and drug-susceptibility testing capability are available for visa applicants in international screening laboratories.

Lead federal agencies: U.S. Department of Homeland Security (DHS), and HHS (CDC).

Suggested collaborators: DOS and the International Organization for Migration.

### **Problem 15**

Limited capacity exists for the evaluation of new TB diagnostic tests (see Problem 54).

#### **Objective 15.1**

Evaluate new methods to provide rapid and reliable laboratory confirmation of TB and identify patterns of drug resistance (domestic).

#### **Action Steps**

15.1.1. Contribute to the development and clinical evaluation of rapid and simple methods to identify and characterize MDR/XDR strains of *M. tuberculosis*.

15.1.2. Facilitate the development of improved diagnostic tests for rapid diagnosis of TB disease in persons with either compromised or intact immune systems.

15.1.3. Evaluate the specificity and sensitivity of candidate tests to rapidly diagnose and identify resistant *M. tuberculosis* strains in field settings.

15.1.4. Provide training in implementation research and field evaluations, and build clinical trial capacity to evaluate new laboratory tests.

Lead federal agencies: HHS (CDC, FDA, and NIH), and USAID.

Suggested collaborators: DoD, FIND, and academia.

## **Surveillance, Epidemiology, and Outbreak Investigations**

Identifying outbreaks of XDR TB to prevent further transmission requires a rapid, accurate, and adaptable surveillance system and coordinated response strategies. In the United States, individual states require reporting of TB cases by health-care providers and facilities to public health authorities. By mutual agreement, state health authorities report TB cases to CDC. Substantial delays can occur in reporting to CDC because many states report on a quarterly basis or at the end of the year. Key domestic surveillance needs include immediate

case reporting, accurate and complete reporting of second-line drug susceptibility and genotyping results, and active case finding among contacts and other high risk groups. Central notification of MDR and XDR TB is essential to identify cross-jurisdictional issues and to outline specific areas that should be targeted for rapid emergency (federal) support. Improved, unambiguous technical guidance (including outcome standards) is needed for collection, reporting, and data-quality procedures at the local, state, and federal levels. Internationally, areas that require increased attention and improvement include capacity for rapid DST surveys and more sustained, systematic capture of DST information. Epidemiologic studies, including genetic analyses of host and pathogen, are recommended to elucidate risk factors for acquiring XDR TB, transmission dynamics and determinants of host survival.

### **Problem 16**

No requirement exists for rapid reporting of TB cases to the National TB Surveillance System (NTSS), and many state and city TB programs report to NTSS only quarterly or at the end of the year, thus substantially limiting the ability to identify rapidly and respond promptly to outbreaks of MDR TB and XDR TB.

#### **Objective 16.1**

Develop a plan for reporting known or suspect MDR TB and XDR TB cases to the NTSS with no time lag (domestic).

#### **Action Steps**

16.1.1. Convene a working group of stakeholders (CDC, NTCA, local and state TB control programs, laboratorians) to develop an integrated plan for immediate notification of MDR TB and XDR TB cases.

16.1.2. Establish clear requirements and methods for reporting of MDR TB and XDR TB cases from local clinics to laboratories, hospitals, and other partners who might diagnose TB in patients to the state TB program and to NTSS.

16.1.3. Develop standard reports of aggregated XDR TB case data within the NTSS to provide to local and state TB programs.

16.1.4. Define mechanisms to provide feedback to state and local programs and partners regarding missing data, incomplete diagnostic information, and needed follow-up information.

16.1.5. Develop procedures and data requirements that allow public health agencies to identify and address large-scale and interjurisdictional issues and to request rapid mobilization of a federal response in case of emergencies.

16.1.6. Develop and maintain a national registry for MDR TB and XDR TB outside the NTSS that is linked to the national genotyping database or contains genotyping results

from the state TB programs. The registry should include persons with reported cases and with nonreportable (noncounted) cases of MDR TB and XDR TB and persons with cases of TB identified by clinical diagnosis alone who are known contacts to culture-confirmed MDR TB or XDR TB.

16.1.7. Develop required data elements for the national registry that include relevant clinical data, information about primary or secondary MDR TB and XDR TB cases, detailed history of prior and current drug treatment and susceptibility test results incorporating expanded second-line drug panels.

16.1.8. Develop web-based access to the national registry for state and local health departments, diagnostic laboratories and relevant public health officials with appropriate safeguards to protect sensitive information and personal identifiers.

Lead federal agencies: HHS (CDC and Health Resources and Services Administration [HRSA]), Bureau of Prisons (BOP), and DHS (Immigration and Customs Enforcement [ICE]).

Suggested collaborators: state TB program directors, TB controllers, TB program surveillance coordinators, state border health offices, NTCA, and private and state public health laboratories.

## Problem 17

Data reported to the NTSS, including data for XDR TB cases, often are not fully validated for accuracy and completeness.

### Objective 17.1

Develop a plan to determine and assure completeness and accuracy of all reported TB data, including those for XDR TB cases (domestic).

### Action Steps

17.1.1. Review the data currently required for reports of completeness of information collection for each variable that is requested of state TB programs by NTSS and expand these reports to reflect critical information pertinent to XDR TB (e.g., initial and final DST results and initial treatment strategy).

17.1.2. Conduct site visits or standardized surveys to review current surveillance procedures for state and local health departments and identify opportunities for improvement.

17.1.3. Develop a standardized plan to validate Report of Verified Case of TB (RVCT) data among persons with cases of MDR TB and XDR TB, using medical and clinic record review at the local reporting area.

Lead federal agencies: HHS (CDC).

Suggested collaborators: state TB program directors, TB controllers and surveillance coordinators, NTCA, private commercial laboratories, and state public health laboratories.

## Problem 18

For 66% of MDR TB cases reported to the NTSS during 2000–2006, DST results were incomplete and not sufficient to estimate the proportion of XDR TB among MDR cases, and 20% of MDR TB cases lacked information about susceptibility to any of the second-line drugs.\*\*

### Objective 18.1

Increase testing for and reporting of DST results to the NTSS (domestic).

### Action Steps

18.1.1. Analyze annually the completeness of second-line drug-susceptibility testing for all MDR *M. tuberculosis* isolates by state and contact each state with less than 100% completeness for second-line drug-susceptibility testing.

18.1.2. Determine whether incomplete DST data are the result of incomplete testing or incomplete reporting.

18.1.3. Establish a notification system through which CDC's Division of Tuberculosis Elimination (DTBE) program consultants are alerted to visit state TB programs to discuss improvements in drug-susceptibility testing and reporting, including review of instructions for reporting DST results to the current RVCT and the newly-formed MDR TB and XDR TB national registry.

18.1.4. Develop a process through which routine requests for missing DST results for MDR TB cases are requested from state TB programs.

18.1.5. Develop programs to ensure that personnel at the local and state TB programs are adequately trained in necessary procedures and reporting requirements for drug-susceptibility testing.

Lead federal agencies: HHS (CDC).

Suggested collaborators: state TB program directors, TB controllers and surveillance coordinators, NTCA, private and state public health laboratories, and APHL.

## Problem 19

Laboratory reporting of DST results to the state health department is not standardized across the United States.

### Objective 19.1

Standardize laboratory reporting to the state health departments by state and private laboratories throughout the United States (domestic).

\*\* Percentages are based on reported drug-susceptibility test results in the 2006 NTSS database. Adequate testing for XDR TB uses the WHO definition: TB that is resistant 1) to isoniazid and rifampin and 2) to any fluoroquinolone and at least one of three injectable second-line drugs (amikacin, kanamycin, or capreomycin).



### Action Steps

19.1.1. Convene a working group of TB program and laboratory experts to develop a standardized format for laboratory reporting. Disseminate the recommended reporting method to TB programs and public health and private laboratories via their professional associations.

Lead federal agencies: HHS (CDC).

Suggested collaborators: state TB program directors, TB controllers and surveillance coordinators, NTCA, private and state public health laboratories, and APHL.

### Problem 20

Active case-finding procedures for XDR TB and MDR TB at the state and local level are not standardized.

#### Objective 20.1

Develop standard guidelines for state and local TB programs to ensure prompt identification and reporting of newly diagnosed cases of XDR TB and MDR TB (domestic).

### Action Steps

20.1.1. Review case-finding and reporting procedures among local and state TB programs and evaluate their effectiveness and promptness.

20.1.2. Convene a working group of state TB program personnel to develop standardized guidelines for prompt case finding and reporting at the state and local level.

20.1.3. Develop guidelines for contact tracing during investigations of XDR TB patients (see Problem 26) that facilitate rapid identification of close contacts at highest risk for active disease.

Lead federal agencies: HHS (CDC), BOP, and DHS (ICE).

Suggested collaborators: state TB program directors, TB controllers and surveillance coordinators, NTCA, and private and state public health laboratories.

### Problem 21

Certain groups of foreign-born persons, persons living in correctional facilities, and marginalized persons (i.e., persons who are isolated, excluded, or alienated from mainstream society) are at increased risk for TB and XDR TB.

#### Objective 21.1

Enhance surveillance for MDR TB and XDR TB among risk groups of foreign-born persons, incarcerated persons, and other marginalized at-risk persons (domestic).

### Action Steps

21.1.1. Develop procedures for enhanced TB disease surveillance among inmates who are either foreign-born or belong to other groups with high rates of tuberculosis who have resided outside the United States or Canada for >6 months before their incarceration.

21.1.2. Develop guidelines for medical follow-up and referral of persons with abnormal chest radiographs for microbiologic diagnosis and treatment for TB during incarceration and after release.

21.1.3. Develop recommendations and guidelines for diagnosis, treatment, and medical management of incoming and existing inmates, transfers, and those who are released from prison.

21.1.4. Contribute to the establishment of partner programs for evaluation of routine intake processes and surveillance used by all types of correctional facilities and detention centers to facilitate implementation of the recommended action plans for identification and management of XDR TB.

Lead federal agencies: HHS (CDC), DHS (ICE and Customs and Border Protection [CBP]), and U.S. Department of Justice (DOJ) (BOP and USMS).

Suggested collaborators: state TB program directors, TB controllers and surveillance coordinators, NTCA, correctional health systems administrators and providers, and private and state public health laboratories.

### Problem 22

Reporting criteria for national surveillance of TB currently exclude patients who are expected to be in the United States for <90 days and persons who cross the border frequently.

#### Objective 22.1

Develop a mechanism at the federal level for recording and tracking of cases that are not officially included in national case counts (see Problem 16, action step 16.1.6) (domestic).

### Action Steps

22.1.1. Establish a mechanism to report all TB cases in persons identified or treated in the United States who do not meet current reporting criteria for national surveillance (e.g., are not residents).

Lead federal agencies: (CDC and HRSA), DHS (ICE and CBP), and DOJ (BOP and USMS).

Suggested collaborators: state TB program directors, TB controllers and surveillance coordinators, state border health offices, NTCA, private, and state public health and hospital laboratories.

## Problem 23

In areas where XDR TB has been identified, the actual prevalence of resistance to first- and second-line drugs among TB cases is unknown.

### Objective 23.1

Estimate the prevalence of resistance to first- and second-line drugs among reported TB cases (international).

#### Action Steps

23.1.1. Conduct rapid drug-susceptibility surveys in areas where XDR TB has been identified.

23.1.2. Contribute to the development of international guidelines for standardized drug-susceptibility testing.

23.1.3. In collaboration with international partners, identify barriers to conducting drug-susceptibility testing and develop solutions to overcome these obstacles.

Lead federal agencies: HHS (CDC) and USAID.

Suggested collaborators: WHO, national health ministries, supranational reference laboratories, and IUATLD.

### Objective 23.2

Increase capacity to perform sustained drug-susceptibility testing on a routine basis and develop procedures and methods for systematic recording and tracking of data trends (international).

#### Action Steps

23.2.1. Develop national TB registries/surveillance systems that include DST results for each case.

23.2.2. Identify barriers to increasing capacity for drug-susceptibility testing in resource-limited settings.

23.2.3. Increase laboratory capacity (see Problems 2, 3, 6, and 10).

23.2.4. Support clinical evaluation of novel rapid diagnostic tools and drug-susceptibility testing (see Problem 15).

Lead federal agencies: HHS (CDC) and USAID.

Suggested collaborators: WHO, national health ministries, APHL, and IUATLD.

## Problem 24

The risk factors for and transmission dynamics of XDR TB in domestic and international settings are not completely understood.

### Objective 24.1

Determine global epidemiologic profiles and transmission dynamics of XDR TB in different geographic areas (domestic and international).

## Action Steps

24.1.1. Conduct retrospective analyses of epidemiologic and genotyping data and linkages from existing XDR TB contact investigations and national genotyping databases.

24.1.2. Develop an approach for regular and systematic analysis of national genotyping data for XDR *M. tuberculosis* isolates.

24.1.3. Compare drug-resistance profiles and treatment histories among previously treated and newly diagnosed cases of drug-resistant TB and establish the proportion of XDR TB and MDR TB among these different patient groups.

24.1.4. Determine and report the relationship between virulence factors identified for XDR *M. tuberculosis* and clinical disease manifestation of XDR TB (see Problem 52).

Lead federal agencies: HHS (CDC and NIH).

Suggested collaborators: state and local health departments, WHO, and national health ministries.

### Objective 24.2

Determine the proportion of XDR TB cases occurring among newly diagnosed and previously treated TB cases, and how this distribution varies by geographic region and within separate patient groups (domestic).

#### Action Steps

24.2.1. Conduct retrospective analyses of patterns of drug resistance and treatment histories for MDR TB and XDR TB cases from national surveillance system and cohort studies to identify risk factors for the development of secondary XDR TB.

24.2.2. Design multisite prospective studies to evaluate the impact of treatment strategies on the development and clinical outcomes for MDR TB and XDR TB patients on the basis of the results from retrospective analyses of relevant cohorts.

Lead federal agencies: HHS (CDC and NIH).

Suggested collaborators: state and local health departments, public health laboratories, private physicians, and academia.

### Objective 24.3

Describe transmission dynamics of MDR TB and XDR TB (domestic).

#### Action Steps

24.3.1. Analyze data from existing XDR TB contact investigations and national genotyping data to identify factors driving the transmission of XDR TB in high and low TB incidence settings.

Lead federal agencies: HHS (CDC).

Suggested collaborators: state and local health departments.

**Objective 24.4**

Identify strains of XDR *M. tuberculosis* that are associated with increased transmissibility and virulence (domestic).

**Action Steps**

24.4.1. Conduct retrospective in-depth analyses of XDR TB cases for which linked clinical and *M. tuberculosis* strain genotyping information is available from national and other genotyping databases.

24.4.2. Develop protocols to follow these cases prospectively and to add new cases to the cohort as they receive a diagnosis.

Lead federal agencies: HHS (CDC and NIH).

Suggested collaborators: state and local health departments, private and state public health laboratories, and APHL.

**Problem 25**

The survival rates among patients with TB that is resistant to first- and second-line therapeutics have not been adequately analyzed, and host/pathogen determinants of survival, including the effect of co-morbidities, remain to be elucidated.

**Objective 25.1**

Conduct studies to identify determinants of survival among MDR TB and XDR TB patients, and how survival varies by host and pathogen factors (domestic and international).

**Action Steps**

25.1.1. Conduct retrospective analyses of national surveillance data and other cohort studies to understand differences in and factors affecting survival among drug-susceptible and MDR TB and XDR TB patients.

25.1.2. Design multisite prospective studies of treatment practices and other factors that affect clinical outcomes for MDR TB and XDR TB patient on the basis of results from retrospective analyses in relevant cohorts.

Lead federal agencies: HHS (CDC and NIH) and USAID.

Suggested collaborators: DOS, state and local health departments, WHO, national health ministries, IUATLD, and academia.

**Problem 26**

Methods for detecting and documenting outbreaks of XDR TB both domestically and internationally are not currently optimized to allow a rapid response.

**Objective 26.1**

Improve speed and accuracy of detection and investigation of MDR TB and XDR TB outbreaks in the United States to include rapid identification of risk factors for transmis-

sion and recommendations to interrupt further transmission (domestic).

**Action Steps**

26.1.1. Develop systems to use surveillance data in combination with strain genotyping for detection of MDR TB and XDR TB transmission events immediately as they become known to the local TB clinic or local provider.

26.1.2. Establish rapid and enhanced procedures for reporting of MDR TB and XDR TB cases to CDC by TB controllers and for identification and reporting of MDR TB and XDR TB clusters on the basis of monthly review of the genotyping database combined with the RVCT.

26.1.3. Expand processes available for triggering rapid investigation of TB clusters to include MDR TB and XDR TB through generation of MDR TB and XDR TB cluster reports to be shared among DTBE senior staff; establish procedures to alert the respective State TB Controllers and other relevant interjurisdictional areas and rapidly review available data to prioritize on-site responses.

26.1.4. Establish plans to initiate case contact investigations through state TB programs and establish procedures for reporting of aggregate data (numbers of cases, contacts, numbers tested, numbers treated for LTBI and numbers completing treatment) to DTBE for each contact investigation of an MDR TB and XDR TB patient.

26.1.5. Develop policies to ensure complete evaluation and follow-up for all close and high-priority contacts of MDR TB AND XDR TB cases if state or local health departments are unable to complete contact investigations without outside assistance.

26.1.6. Develop a federal plan with clearly defined roles within and among federal agencies to allow identification of interjurisdictional issues in the tracing and management of MDR TB and XDR TB cases to ensure rapid and coordinated management of patients that travel to and from, or within the United States.

Lead federal agencies: HHS (CDC) and DHS.

Suggested collaborators: state and local health departments and state public health laboratories.

**Objective 26.2**

Provide assistance to WHO and countries outside the United States for rapid investigation of MDR TB and XDR TB outbreaks, including the identification of risk factors for transmission and the recommendation of responses to interrupt transmission and contain outbreaks (international).

## Action Steps

26.2.1. Establish procedures for prioritization of invited responses to assist in the investigation of MDR TB and XDR TB cases by host countries on the basis of available information.

26.2.2. Formulate goals and objectives for the outbreak response team that are consistent with the specific request for assistance by the host country.

26.2.3. Establish a rapid response team to investigate the outbreak and define procedures for communication between the host country's ministry of health, the CDC Director's Emergency Operation Center, DTBE, and WHO that include consideration for potential large-scale interjurisdictional issues that will require rapid resolution.

Lead federal agencies: HHS (CDC) and USAID.

Suggested collaborators: DOS, WHO, and national health ministries.

## Infection Control

Because TB is spread by the airborne route, anyone who breathes air containing viable tubercle bacilli is at risk for acquiring *M. tuberculosis* infection. This includes persons caring for and exposed to infectious TB patients, especially patients without an established diagnosis. To prevent the spread of disease and maintain the best possible care for patients, special infection-control practices and procedures must be available.

Effective infection control depends on early detection and diagnosis of TB disease, prompt initiation of effective therapy, and airborne infection isolation to prevent further disease transmission. Each institutional setting that might house persons with undiagnosed TB disease or in which TB patients are treated should have infection-control programs available that minimize the risk for TB transmission, including MDR TB and XDR TB, to patients, workers, and others within the institutional setting.

Various infection-control strategies are available depending on whether a setting will provide primary care or triage and refer patients with suspected or confirmed TB disease. All infection-control strategies should be on the basis of a three-level hierarchy: administrative controls, environmental controls, and personal respiratory protection. Combinations of these infection-control strategies have been demonstrated to be effective at preventing TB transmission. However, these strategies are not implemented consistently, and their individual effectiveness and feasibility are not well-characterized.

## Problem 27

Although administrative controls, environmental controls, and respiratory protection have been effective when used in

combination, ethical issues have prevented assessment of their individual effectiveness in settings in which TB transmission occurs. Resulting knowledge gaps hamper efforts to prioritize interventions for optimal cost-benefit in resource-limited settings.

### Objective 27.1

Ensure dissemination and implementation of currently recommended infection-control strategies across a range of high-risk institutional settings (e.g., health-care facilities, substance abuse clinics, residential treatment centers, homeless shelters, and correctional and detention facilities) through education and regulatory programs (domestic and international).

### Action Steps

27.1.1. Conduct a public health information campaign to encourage dissemination of recommended TB infection-control procedures to U.S. health-care settings (inpatient and outpatient) that provide TB care, institute measures to track implementation of these measures, and identify barriers to implementation.

27.1.2. In collaboration with high-burden country health-care providers, identify and prioritize TB infection-control procedures appropriate for health-care settings (inpatient and outpatient) in resource-limited areas where TB care is provided.

27.1.3. Provide regularly scheduled updates to CDC's infection-control guidelines for health-care settings and related documents (e.g., guidelines for correctional and detention facilities) (26,30) and provide clarification as needed.

27.1.4. Develop guidance statements on TB prevention in HIV-infected and other immunocompromised health-care workers.

27.1.5. Disseminate and implement recommendations for use of airborne infection isolation rooms for known or suspected TB patients and use of local exhaust ventilation for aerosol generating procedures on these patients.

27.1.6. Disseminate and implement guidelines for selection, use, and appropriate re-use of certified respiratory protective devices used to protect against infection with *M. tuberculosis* in domestic and international settings including those with resource constraints.

27.1.7. Disseminate, implement, and regularly update recommendations for design, application, installation, monitoring, and maintenance of both upper air and in-duct ultraviolet germicidal irradiation (UVGI) fixtures.

27.1.8. Develop guidelines for effective administrative and environmental measures to prevent *M. tuberculosis* transmission in homeless shelters, community residences for special needs populations, correctional and detention facilities, and

substance-abuse treatment centers. Guidelines are needed for correctional and detention facilities that can be applied internationally; guidelines for domestic correctional and detention facilities were published in 2006 (32) but might be relevant only to other industrialized countries with similar correctional systems and similar TB case rates.

27.1.9. Provide technical assistance to substance-abuse centers, shelters for the homeless, community residences for special needs populations, correctional and detention facilities, and health-care settings to determine the adequacy of local administrative controls, environmental controls and respiratory protection to minimize transmission of *M. tuberculosis*.

27.1.10. Regularly interact and communicate with regulatory agencies (e.g., Occupational Safety and Health Administration [OSHA]) and standard-setting organizations (e.g., the Joint Commission [formerly the Joint Commission on Accreditation of Healthcare Organizations (JCAHO)]; the American Society of Heating, Refrigerating and Air-Conditioning Engineers [ASHRAE]; and the American Institute of Architects [AIA]) to ensure that infection-control standards and guidelines for preventing *M. tuberculosis* transmission are consistent.

Lead federal agencies: HHS (CDC, FDA, HRSA, and Substance Abuse and Mental Health Services Administration [SAMHSA]), USAID, DHS (ICE), DOJ (BOP and USMS), VA, and HUD.

Suggested collaborators: OSHA, Healthcare Infection Control Practices Advisory Committee (HICPAC), Association for Professionals in Infection Control and Epidemiology (APIC), JCAHO, ASHRAE, AIA, state and local health departments, WHO, IUATLD, and national health ministries.

## Problem 28

Tuberculin skin-testing programs are not implemented consistently in the United States.

### Objective 28.1

Ensure adequate TB testing programs for workers are available on site in settings with a substantial risk for transmission of *M. tuberculosis* (domestic).

### Action Steps

28.1.1. Implement guidelines and requirements for improved institutional TB risk assessments in collaboration with OSHA and JCAHO to enhanced TB screening and monitoring procedures.

28.1.2. Recommend considering positive tuberculin skin test (TST) or blood assay (BAMT) for identification of *M. tuberculosis* infection among health-care workers as an outcome measure of the effectiveness of TB infection-control programs in health-care facilities that are in the medium risk

category or have been classified as having potential ongoing transmission.

28.1.3. Provide health departments with support in recruitment of and assistance to health-care centers, correctional facilities, homeless shelters, and substance-abuse treatment centers to implement and assess the effectiveness of programs for systematic TB screening of workers employed in medium- or high-risk settings.

Lead federal agencies: HHS (CDC).

Suggested collaborators: OSHA, JCAHO, and state and local health departments.

## Clinical and Programmatic Interventions

The fundamental principles and practices of TB control have been described previously (3,33). These principles and practices underlie the clinical and programmatic components of diagnosis, reporting, treatment and prevention of drug-resistant TB addressed in this Task Force Plan

Persons at risk for TB disease often fail to access health-care systems for a variety of complex reasons. A lack of understanding of TB and its symptoms, lack of financial resources (e.g., health insurance or transportation to the clinic), lack of awareness of free clinical services for TB, concerns of deportation and stigmatization, and existence of competing priorities (e.g., shelter and food) all contribute to delays in TB diagnosis and result in prolonged TB transmission in the community. Clinical and programmatic services must be integrated with and closely coordinated with TB laboratory services through a systems approach to ensure successful diagnosis and case management. Once patients access care, lack of familiarity with TB by health-care providers might result in misdiagnosis and inappropriate treatment, which in turn can lead to development of drug resistance and continued transmission of *M. tuberculosis*. Once a TB diagnosis has been established, providing clinical TB services (preventive, diagnostic, and treatment/case-management) that are culturally acceptable, affordable and logistically accessible to patients is a prerequisite for successful TB management and treatment completion.

Throughout the process of clinical care of TB patients, infection-control practices must be implemented properly, and health-care providers (physicians, nurses, pharmacists, dentists, laboratorians, other allied health professionals, traditional healers) must be educated thoroughly and trained in all principles and practices of TB care. To sustain consistent high quality and prompt care of TB patients, monitoring and evaluation programs must be established to identify rapidly systems failures and implement corrective measures. The elements of the health system that are necessary to prevent the

development and transmission of MDR TB and XDR TB have been identified (Figure). Failures at any of the necessary steps related to proper TB diagnosis, treatment and infection-control measures can lead to the development or transmission of drug-resistant TB.

The United States needs to assist international TB control programs in the development of clinical and programmatic practices that follow international standards for TB diagnosis and care, laboratory services, and infection control. Support should be provided to ensure that TB patients receive services free of charge and have access to DOT through the completion of treatment. The implementation of international informa-

tion sharing mechanisms is critical for the prevention of drug resistance and the successful control of TB worldwide.

**Problem 29**

TB patients might not have access to care.

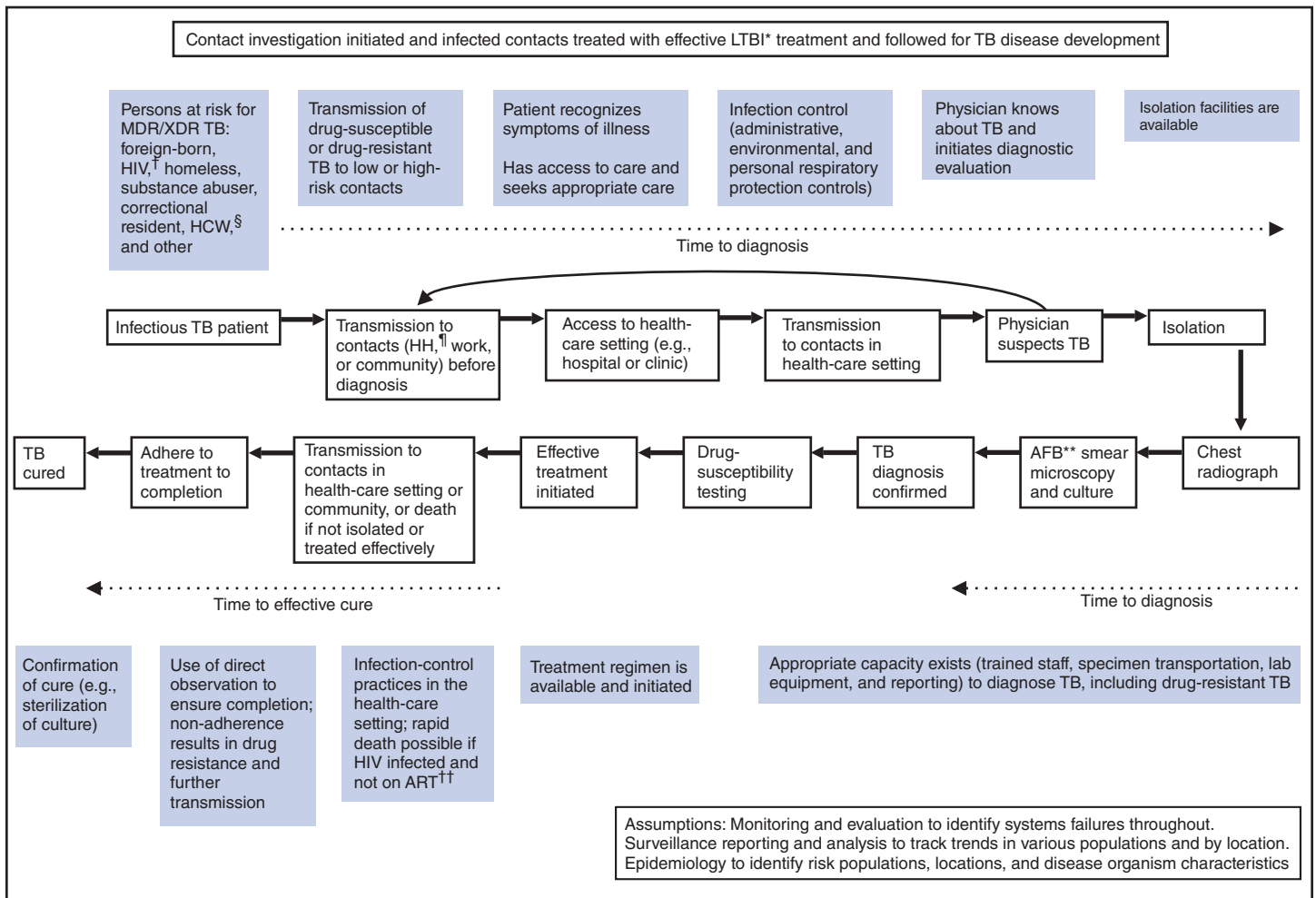
**Objective 29.1**

Increase the number of TB suspects at risk for MDR TB and XDR TB who seek and access care (domestic).

**Action Steps**

29.1.1. Develop and disseminate education materials for groups at risk for TB and MDR TB and XDR TB to increase

**Figure. Prevention of development and transmission of drug-resistant tuberculosis (TB)**



\* Latent TB infection.  
 † Human immunodeficiency syndrome-positive.  
 § Health-care worker.  
 † Household.  
 \*\* Acid fast bacillus.  
 †† Antiretroviral therapy.

understanding of TB symptoms (especially early symptoms), transmission, and treatment. Materials and interventions should be presented in a way that engenders trust in health-care institutions and helps to destigmatize patients with TB disease.

29.1.2. Provide support and consultation to groups using culturally appropriate education formats and language (including those geared to persons who are illiterate) to promote an understanding of the availability of and how to access TB treatment free of charge.

29.1.3. Distribute the Patients' Charter for Tuberculosis Care (34), which describes patients' rights and responsibilities in languages appropriate to the patient population.

29.1.4. Develop interventions that are culturally and linguistically appropriate to remove barriers or obstacles and assist patients in accessing care in a continuous manner, emphasizing clinic hours, transportation, and overcoming other barriers to improve treatment adherence and prevent the development and transmission of drug-resistant strains.

29.1.5. Evaluate interventions to ensure that they are culturally appropriate and effective in increasing patient access to TB diagnosis and treatment.

Lead federal agencies: HHS (CDC and HRSA).

Suggested collaborators: state and local health departments and RTMCCs.

### Problem 30

Initial point-of-contact (POC) providers (e.g., emergency, urgent, primary, and correctional care providers; university health service and occupational medicine clinicians; health department clinicians; civil surgeons<sup>††</sup>; and traditional healers) might not suspect TB or have current or complete information about the diagnosis and/or treatment of TB (see Problem 44).

#### Objective 30.1

Provide POC providers who serve at-risk persons with education and guidance to increase their knowledge of TB and increase their access to resources to avoid misdiagnosis, prolonged transmission, and inappropriate treatment (domestic).

#### Action Steps

30.1.1. Promote general knowledge of TB among providers through specific TB curricula and self-study modules. Educate providers about the critical importance of patient-centered case management and how to deliver high-quality services needed to ensure patient adherence and treatment completion.

Explain the risks associated with undiagnosed, misdiagnosed, and inappropriately or inadequately treated TB.

30.1.2. Promote practices such as use of treatment regimens on the basis of national guidelines, DOT, prompt adjustment of treatment in response to DST results, patient incentives and enablers to maintain adherence, monitoring of response to treatment, and comprehensive case management in close collaboration with the local TB control program and treatment experts to prevent development and amplification of drug resistance among all TB patients.

30.1.3. Conduct a national media campaign to raise awareness of TB for the general public and health-care providers.

30.1.4. Engage medical professional associations to raise awareness of TB and TB guidelines.

30.1.5. Review TB screening procedures and protocols for institutional facilities and primary care providers to assure competency and develop links between POC providers, local and state health departments and RTMCCs for diagnosis and referral of suspects.

30.1.6. Develop and distribute current regional, national and international MDR/XDR surveillance charts to health-care providers and public health programs to inform them of high-prevalence areas for MDR TB and XDR TB.

30.1.7. Address health-care provider fears about MDR TB and XDR TB through discussions with medical societies, formal and informal presentations with health-care professionals at meetings, and through targeted mailings.

30.1.8. Evaluate changes in POC awareness of diagnostic and treatment issues related to susceptible and resistant TB (see Problem 44 for additional action steps).

Lead federal agencies: HHS (CDC and HRSA), and BOP.

Suggested collaborators: NTCA, state and local health departments, health-care professional associations, state and local correctional facilities, homeless shelters, and RTMCCs.

### Problem 31

Clinicians' ability to diagnose XDR TB often is inadequate.

#### Objective 31.1

Improve clinicians' ability to diagnosis XDR TB, especially in immunocompromised persons (domestic).

#### Action Steps

31.1.1. Address provider concerns or fears about transmission and treatment of XDR TB.

31.1.2. Evaluate provider ability to diagnose TB and drug-resistant TB.

<sup>††</sup> Designated physicians who examine aliens in the United States who apply for adjustment of their immigration status to that of permanent residents.

31.1.3. Educate health-care providers on the need for expedited drug-susceptibility testing immediately after an initial TB diagnosis, especially in high-risk congregate settings and in immunocompromised persons, to reduce morbidity and mortality in persons with drug-resistant TB.

31.1.4. Update TB care guidelines to recommend routine HIV testing during initial patient evaluation for TB on the basis of opt-out testing<sup>§§</sup> recommended by CDC.

31.1.5. Develop and distribute regularly updated regional, national and international MDR TB and XDR TB surveillance charts to health-care providers and public health programs to increase awareness of the extent of drug-resistant disease in patients who do not respond to first-line therapy.

31.1.6. Develop a system of consultation and patient referral between primary care physicians (including HRSA Community Health Centers, primary care HIV clinics, and homeless programs), physicians in correctional or detention settings, departments of health, and RTMCCs to improve diagnosis and management of TB patients, especially those with MDR TB and XDR TB.

31.1.7. Discuss with FDA requirements for review and approval of rapid tests to detect rifampin resistance (RIF) as a primary/surrogate indicator for MDR TB and XDR TB and define special situation where use of rapid RIF assays and other molecular tests to diagnose drug resistance would be appropriate.

Lead federal agencies: HHS (CDC, FDA, and HRSA).

Suggested collaborators: NTCA, RTMCCs, state and local health departments, and health-care provider professional societies.

### **Problem 32**

Existing diagnostic protocols used for screening foreign-born persons entering, or already residing in the United States, are not sufficient to detect XDR reliably.

#### **Objective 32.1**

Improve currently used protocols for TB screening among foreign-born persons to facilitate rapid detection of XDR TB (Domestic)

#### **Action Steps**

32.1.1. Review and update instructions for civil surgeons and other health-care providers involved in screening of foreign-born persons after arrival in the United States to facilitate early identification and prompt treatment of drug-resistant TB.

32.1.2. Develop certification processes for Civil Surgeons and others health-care providers who provide TB screening to assure consistency and proficiency in diagnostic procedures.

32.1.3. Evaluate procedures for monitoring and quality control of updated screening procedures for TB and MDR TB and XDR TB to assure adequate and consistent implementation.

Lead federal agencies: HHS (CDC, HRSA), and DHS (ICE).

Suggested collaborators: DOS, state and local and health departments, and civil surgeons.

### **Problem 33**

Effective and safe treatment regimens for XDR TB have not been established.

#### **Objective 33.1**

Identify appropriate treatment regimens for TB resistant to various types and combinations of chemotherapeutic agents (domestic and international).

#### **Action Steps**

33.1.1. Perform literature analysis to document and summarize experience with treatment regimes and associated clinical outcomes for patients with XDR TB.

33.1.2. Develop guidance for empiric treatment of persons with suspected XDR TB before availability of DST results with regionally appropriate standardized regimens.

33.1.3. Develop recommendations for treatment of XDR TB on the basis of available resistance patterns.

Lead federal agencies: HHS (CDC) and USAID.

Suggested collaborators: WHO, IUATLD, state and local health departments, and national ministries of health.

### **Problem 34**

The quality of currently available services and treatment for XDR TB patients has not been monitored or evaluated sufficiently.

#### **Objective 34.1**

Improve the quality and effectiveness of free clinical services, medications and treatment regimens as part of patient-centered management for patients with XDR TB (domestic).

#### **Action Steps**

34.1.1. Develop and implement fully supported, improved patient-centered clinical services for outpatient management of persons with XDR TB that ensure full cooperation and maximum chance of success.

34.1.2. Develop and implement procedures and due process and recommendations for legal recourse for management of

<sup>§§</sup> Defined as performing HIV testing after notifying the patient that the test will be performed and consent is inferred unless the patient specifically declines.



XDR TB patients refusing treatment or care to minimize risk to communities (see Problems 39, 41, and 42).

34.1.3. Identify centers of excellence for in-patient treatment of MDR TB and XDR TB that are available for consultation on and referral of XDR TB patients to optimize care and increase likelihood of cure.

34.1.4. Evaluate whether XDR TB centers of excellence might be developed as national referral centers for all patients with XDR TB to provide the best possible care, increase treatment success and reduce transmission to others.

34.1.5. Develop procedures for transfer of patients to referral centers and identify funding to support the cost of treating and managing XDR TB patients.

34.1.6. Establish programs to facilitate collaboration between XDR TB centers of excellence and the RTMCCs for ongoing medical education, consultation, and technical assistance to community providers on all aspects of care of MDR TB and XDR TB patients.

34.1.7. Develop processes and procedures for referral and care of patients who are in legal custody during inpatient or outpatient treatment to ensure appropriate discharge and continuity of care when released from custody or transferred to a different detention facility or law enforcement agency.

34.1.8. Develop processes to request a stay of removal for patients slated for deportation to a country where treatment is not likely to be available and establish procedures and resources to complete TB treatment in the United States, including provision of secure environments, if appropriate.

Lead federal agencies: HHS (CDC and HRSA), DHS (ICE), and DOJ (BOP and USMS).

Suggested collaborators: state and local health departments, RTMCCs, existing specialized TB treatment centers (e.g., National Jewish Research and Medical Center, Shattuck Hospital, AG Holley Hospital, and Texas Center for Infectious Diseases), ATS, and IDSA.

### **Problem 35**

MDR TB patients most at risk for XDR TB might not adhere to treatment.

#### **Objective 35.1**

Address known barriers to treatment adherence for MDR TB patients at risk for XDR TB through sustainable solutions (domestic).

#### **Action Steps**

35.1.1. Implement routine program evaluations and technical assistance for domestic TB programs to identify weaknesses that might lead to inappropriate therapy, treatment failures and the development of drug resistance.

35.1.2. When appropriate, assure the use of DOT throughout treatment for patients with MDR TB and XDR TB.

35.1.3. Recommend the use of fixed-dose drug combinations (pills that contain a fixed dose of multiple medications) in the United States to facilitate treatment adherence.

35.1.4. Provide appropriate incentives and enablers to facilitate treatment adherence.

35.1.5. Ensure continuity of care for foreign-born and other high-risk patients who might face deportation or who are traveling frequently between jurisdictions.

Lead federal agencies: HHS (CDC and HRSA), DHS (ICE), and DOJ (BOP and USMS).

Suggested collaborators: state and local health departments, TBNET, and CureTB.

### **Problem 36**

Experienced health-care workers and health-care providers with substantial expertise in TB care and management have left the workforce for retirement and have not been replaced in sufficient numbers to assure continuity of quality care.

#### **Objective 36.1**

Increase the number of trained TB health-care workers (domestic and international).

#### **Action Steps**

36.1.1. Develop, disseminate and endorse use of model TB curricula in nursing, medical, and allied health education institutions.

36.1.2. Post TB job openings at universities that are teaching TB curricula.

36.1.3. Provide academic awards for exceptional performance in TB research, interventions, and communications.

36.1.4. Conduct pre-service and in-service training of health personnel.

Lead federal agencies: HHS (CDC, NIH, and HRSA) and USAID.

Suggested collaborators: NTCA, nursing, medical, and allied health professional associations and education institutions, Association of State and Territorial Health Officers (ASTHO), APHL, Association of Schools of Public Health, and academia (including historically black colleges and universities to address workforce diversity).

### **Problem 37**

Safe, effective treatment regimens and appropriate follow-up procedures for managing contacts of XDR TB patients have not been established.

### Objective 37.1

Prevent transmission to and development of XDR TB among contacts of XDR TB patients.

#### Action Steps

37.1.1. Evaluate the effectiveness and safety of proposed regimens and/or follow-up procedures for contacts of XDR TB patients.

37.1.2. Develop and disseminate to private and public health-care providers CDC recommendations for treatment and follow up of contacts of patients with XDR TB and enlist the endorsement of medical and nursing societies to ensure compliance with treatment recommendations.

37.1.3. Encourage community physicians and others with limited experience or expertise in managing MDR TB and XDR TB to consult with centers of excellence for possible referral of patients for treatment and management.

Lead federal agencies: HHS (CDC).

Collaborators: state and local health departments, RTMCCs, ATS, IDSA, and NTCA.

### Problem 38

Resources and/or technical capacity to adequately address TB and XDR TB are not universally available outside the United States.

### Objective 38.1

Increase U.S. assistance to TB and XDR TB programs, especially to TB-endemic countries from which substantial numbers of persons immigrate to the United States (international).

#### Action Steps

38.1.1. Support WHO's plan to respond to the global problem of XDR TB (26).

38.1.2. Contribute to international efforts to strengthen TB and TB/HIV control activities such as universal use of DOT to reduce default rates, improvement of laboratory/diagnostics capacity and quality, provision of antiretroviral treatment for persons co-infected with HIV, targeted TB screening in at-risk persons and support for the creation of regional training and treatment centers to optimize care and prevent the development of drug resistance.

38.1.3. Contribute to the expansion of supranational laboratory capacity, quality assessment programs and training to ensure rapid and accurate diagnosis of TB and drug-resistant TB.

38.1.4. Assist in the recruitment and training of health-care workers in basic TB management and the early recognition of indicators suggestive of drug-resistant TB.

38.1.5. Review the technical instructions for panel physicians<sup>44</sup> who conduct TB screening as part of immigration procedures with regard to XDR TB diagnosis and contact management and develop a process to certify panel physicians.

38.1.6. Support and recommend the use of fixed-dose drug combinations when appropriate and provide training and technical assistance to improve TB drug management.

38.1.7. Provide technical assistance through full-time consultants to ministries of health in countries that are sources of large numbers of U.S. immigrants and countries with a high burden of drug-resistant TB to support completion of ongoing drug-resistance surveys and the establishment of drug-resistance surveillance systems.

38.1.8. Provide resources and support to establish U.S.-transnational TB case management programs such as international referral programs and information-sharing system.

Lead federal agencies: USAID, HHS (CDC, HRSA), and DHS (ICE).

Suggested collaborators: DOS, WHO, IUATLD, Green Light Committee (GLC), Medicins Sans Frontieres (MSF), and KNCV.

## Ethical and Legal Issues

TB is a reportable infectious disease, and public health protection and TB control activities are described in specific state laws. Many existing laws were established before the contemporary public health recommendations for the prevention and control of TB became available (6,35). As a result, the Advisory Committee for the Elimination of Tuberculosis (ACET) and CDC conducted a survey of state TB control laws and regulations and developed recommendations that addressed legal issues of TB control in the United States. Since these recommendations were published (29), no systematic follow up has been conducted to determine the extent to which these recommendations were implemented.

### Problem 39

Laws and regulations permitting authorities to compel treatment and isolation of patients with tuberculosis vary by state.

### Objective 39.1

Encourage states to review existing laws to ensure they are adequate to deal with XDR TB patients (domestic).

<sup>44</sup> Designated physicians who examine all refugees coming to the United States and all applicants outside the United States applying for immigrant visas before travel to the United States.

## Action Steps

39.1.1. Encourage states to develop a contemporary model state law through a public process that defines criteria, situations and conditions under which compulsory treatment and isolation of patients with infectious TB should be considered.

39.1.2. Provide support and recommendations for review, clarification and update of state and local tuberculosis control laws.

Lead federal agencies: HHS (CDC).

Suggested collaborators: state and local health departments, law schools and state legislatures.

## Problem 40

Public health authorities in the United States have only limited understanding of public health law pertaining to infectious diseases of public health significance in Mexico and other neighboring countries.

### Objective 40.1

Increase knowledge among U.S. state public health officials regarding public health laws pertaining to infectious diseases in countries neighboring the United States (domestic and international).

## Action Steps

40.1.1. Convene a legal forum to address legal requirements and interventions to avert public health threats that might arise from patients crossing international jurisdictional boundaries.

40.1.2. Translate public health laws from countries neighboring the United States into English for distribution to U.S. public health officials.

40.1.3. Establish a repository of binational and transnational public health legal information in English and Spanish.

Lead federal agencies: HHS (CDC and HRSA), DHS (ICE and CBP), and DOJ.

Suggested collaborators: state and local health departments, law schools, and national justice and health ministries.

## Problem 41

The effectiveness of mandated isolation or quarantine to compel treatment for TB patients as compared to less restrictive measures, and the ethical issues associated with these measures, have not been evaluated closely.

### Objective 41.1

Develop guidelines and a research agenda to determine the effectiveness of and ethical issues associated with compelling

treatment and isolation for TB patients who are considered a threat to public health (domestic).

## Action Steps

41.1.1. Conduct research to determine the impact and effectiveness of mandatory isolation to compel treatment for tuberculosis as compared with less restrictive measures.

41.1.2. Conduct research on ethical issues of mandated isolation (or quarantine) and less restrictive measures to compel treatment for tuberculosis.

41.1.3. Convene a workshop for bioethicists and TB control, care, and research professionals to identify and catalog key ethical issues likely to be confronted as part of the XDR TB response.

Lead federal agencies: HHS (CDC and NIH), DHS, and DOJ.

Suggested collaborators: state and local health departments, law schools, and academia (biomedical ethicists).

## Problem 42

Patients with XDR TB could require prolonged isolation measures regardless of the patient's adherence to treatment, which might present an ethical dilemma in balancing the interests of public health with those of the patient.

### Objective 42.1

Develop guidance on ethical issues pertaining to prolonged isolation of patients with XDR TB who are fully adherent to treatment (domestic).

## Action Steps

42.1.1. Conduct research on ethical considerations of prolonged, mandated isolation including contexts of fully adherent patients and those who are in the terminal stages of disease.

Lead federal agencies: HHS (CDC and NIH), DHS, and DOJ.

Suggested collaborators: state and local health departments, law schools, and academia (biomedical ethicists).

## Problem 43

Obstacles to compassionate use of experimental chemotherapeutic agents for patients with XDR TB limit critically important therapeutic options.

### Objective 43.1

Address the obstacles to and identify solutions for compassionate use access of new experimental therapeutic agents for treatment of XDR TB patients (domestic).

## Action Steps

43.1.1. Initiate discussion with public and private sector organizations involved in TB drug development to define components of viable compassionate use programs to access experimental chemotherapeutics for XDR TB patients.

43.1.2. Contribute to the development of compassionate access programs in collaboration with pharmaceutical partners and FDA.

Lead federal agencies: HHS (CDC, FDA, and NIH).

Suggested collaborators: state and local health departments, RTMCCs, academia, and the pharmaceutical industry.

## Communication and Education

Comprehensive and tailored information on TB and drug-resistant TB including XDR is needed for many different audiences. In the United States, private health-care providers (i.e., those not in public health departments) receive little education or training on detection and appropriate treatment of TB (11,30,31,36–38). As a consequence, infectious TB often goes unrecognized, even if a patient presents to a physician with apparent signs and symptoms of active disease. This has led to incorrect treatment, prolonged transmission of TB in the community, and creation of drug-resistant organisms.

Education and communication must be appropriately targeted to health-care providers and patients to improve awareness and guide access to competent clinical services. Community leaders and health policy makers, including public health officials, must be well informed about the need to communicate and address issues that can fuel the development and spread of drug-resistant TB in their communities. Education efforts should clearly outline the critical elements that must be applied to prevent and control TB in various settings and risk populations (34).

Clear, concise messages, easy to understand yet comprehensive education materials and medical alerts should be developed and disseminated to the general public, TB patients, physicians and other health-care workers, health advocacy organizations, and decision makers, including legislators. These communications should be coordinated across Federal agencies and updated as necessary. Increasing awareness of the signs and symptoms of TB and the appropriate treatment and control strategies, must become a priority in the United States to ensure TB is recognized and treated as a public health threat with the potential to result in virtually untreatable forms of disease, such as XDR TB.

In TB-endemic countries where cases of drug-resistant TB are increasing, health authorities must also remain informed about the risk for and incidence of XDR TB. There, provider education initiatives must also focus on the need for appropri-

ate case management, including knowledge regarding locally and regionally available specialty resources and medications and the consequences of inappropriate or inadequate treatment of drug-resistant TB.

## Problem 44

Health-care providers and the general public are not well-informed about the symptoms, appropriate, diagnosis, treatment, and prevention of drug-susceptible and drug-resistant TB including XDR TB.

### Objective 44.1

Develop education mechanisms and materials, targeted to public and private health-care providers and other workers who might come into contact with populations with a high prevalence of TB infection and disease in settings such as health-care facilities, homeless shelters and correctional facilities, about drug-susceptible and drug-resistant TB including XDR, heighten awareness and encourage appropriate prevention, diagnosis, treatment, and referral (domestic).

## Action Steps

44.1.1. Review and update existing education materials and communication products on TB to include relevant information about drug-resistant forms of disease.

44.1.2. Identify communication gaps and special needs for education and communication products regarding drug-susceptible and drug-resistant TB and develop new materials as needed.

44.1.3. Communicate to health-care providers appropriate measures to prevent MDR TB and XDR TB, including the importance of detecting and treating LTBI and TB disease and the importance of prompt reporting of TB cases to proper health authorities.

44.1.4. Communicate to health-care providers the importance of consulting and engaging TB experts in the medical management of MDR TB patients to avoid the development of XDR TB and to ensure that appropriate specialized resources for treatment of drug-resistant TB are optimally used.

44.1.5. Familiarize health-care providers serving high-risk patients with TB training and medical consultation resources that are available through the RTMCCs.

44.1.6. Contribute to the dissemination and promotion of infection-control guidelines and supporting education materials in the United States (28) and globally (39).

44.1.7. Develop strategies and materials on TB and MDR TB and XDR TB diagnosis, treatment, and reporting for dissemination at national medical and laboratory meetings.

44.1.8. Develop education materials for digital mass media, such as the Internet, personal digital assistants, and podcasts

to reach and inform health-care providers about control of all forms of TB.

44.1.9. Develop and distribute targeted education material to health-care providers and nontraditional partners who are not usually engaged in TB control activities such as primary care and nurse practitioners, physician assistants, emergency care and urgent care specialists, health-care providers in correctional facilities, civil surgeons, pharmacists, foreign-trained clinicians, non-U.S. health-care providers, university health service, occupational medicine specialists, rheumatologists, oncologists, radiologists, laboratories, traditional healers, NGOs, and CBOs.

44.1.10. Present specialty-specific information about care and control of all forms of TB at professional conferences.

44.1.11. Develop targeted TB training and education for other workers who might be exposed to TB in settings such as health-care facilities, homeless shelters and correctional facilities.

Lead federal agencies: HHS (CDC, NIH, and HRSA).

Suggested collaborators: RTMCCs, NTCA, ATS, American College of Chest Physicians (ACCP), IDSA, American Medical Association (AMA), American Association of Family Practitioners (AAFP), and APHL.

### **Objective 44.2**

Develop education mechanisms and materials to inform decision makers in the public and private sectors about priorities and strategies for the prevention and control of TB and MDR TB and XDR TB (domestic).

#### **Action Steps**

44.2.1. Develop strategic plans for advocacy and communications in collaboration with National TB Controllers Association, Results International, STOP TB USA, the American Thoracic Society, and other relevant organizations.

44.2.2. Provide assistance to federal and state TB programs to develop and use coordinated communication mechanisms to disseminate information about drug-susceptible and MDR/XDR (e.g., California TB Controller Association newsletter, TB Notes, letters to colleagues, or TB Educate listserv).

44.2.3. Identify a designated contact person in health departments for states with a high incidence of TB disease to help facilitate media communications.

44.2.4. Develop mechanisms for networking and communications between state TB controllers, legislators and community leaders for populations affected by TB.

44.2.5. Establish conduits for regular and systematic communication of relevant data on all forms of TB, TB control program successes and needs, and federal agency efforts related to MDR TB and XDR TB to policy makers.

44.2.6. Encourage TB programs to include policy makers and their staff on state and local advisory committees.

44.2.7. Identify resources to develop and promote public education/information campaigns.

Lead federal agencies: HHS (CDC, NIH, and HRSA).

Suggested collaborators: NTCA, ATS, IDSA, STOP TB USA, Results International, and state and local health departments.

### **Objective 44.3**

Integrate information on TB, MDR-TB, and XDR-TB prevention, diagnosis, and treatment into health promotion strategies of organizations with common interests in public health issues (domestic and international).

#### **Action Steps**

44.3.1. Develop strategic plans for advocacy and communications in collaboration with NTCA, Results International, STOP TB USA, ATS, and other relevant organizations.

44.3.2. Identify resources to develop and disseminate public education/information materials to inform community groups, managed care organizations, and provider groups about TB and MDR TB and XDR TB.

44.3.3. Identify resources to develop and disseminate public education/information materials on TB and MDR TB and XDR TB to inform staff and law enforcement officials in correctional and detention facilities, including ICE and CBP.

44.3.4. Establish communication channels through managed care organizations, medical and nursing societies and local chapters of professional organizations to disseminate information about TB and MDR TB and XDR TB.

44.3.5. Develop mechanisms and collaborations to integrate information on XDR TB in education materials being developed for health-care providers in training through NTCC.

44.3.6. Contribute to the development and implementation of a strategic plan for advocacy and media communication with STOP TB Partnership working groups and TB patient representatives, high-burden country TB and HIV control managers, and other global advocates for TB.

Lead federal agencies: HHS (CDC, NIH, and HRSA), DHS (ICE and CBP), DOJ (BOP and USMS), and USAID.

Suggested collaborators: NTCA, Results International, STOP TB USA, NTCC, STOP TB Partnership, and state and local health departments.

### **Objective 44.4**

Establish and maintain mechanisms to facilitate regular communication among federal agencies, and with state and local TB control programs (domestic).

## Action Steps

44.4.1. Regularly update and disseminate information by the CDC, WHO, and other agencies on MDR TB and XDR TB to federal staff, TB control programs, HIV/AIDS programs, and other public health agencies and interested organizations to ensure that U.S. public health programs are well informed about the incidence and prevalence of drug-resistant TB in the United States and globally.

44.4.2. Identify federal TB Task Force members to serve as key spokespersons for issues related to MDR TB and XDR TB while ensuring that all Task Force members are well informed to contribute to the ongoing dissemination of information on all forms of TB.

44.4.3. Communicate on a regular basis efforts and relevant results and outcomes related to prevention and control of MDR TB and XDR TB by federal agencies.

Lead federal agencies: HHS (CDC and NIH).

Suggested collaborators: NTCA and state and local health departments.

## Research

Biomedical research in TB creates a foundation of knowledge that informs the development of new health-care interventions as well as control and prevention strategies for drug-resistant TB. While U.S. federal agencies have substantially contributed to research in TB and the identification of drugs, vaccines and diagnostics, the emergence of more difficult to treat forms of drug-resistant TB will require renewed and more targeted efforts to help control and prevent the development and transmission of drug-resistant forms of TB. One compilation of biomedical research priorities related to MDR TB and XDR TB has been published (7).

TB therapy was revolutionized in the 1940s by the development of antibiotics by academic and for-profit organizations, and the demonstration of their efficacy and safety in randomized clinical trials largely conducted by the public sector. These therapies became the basis for the global DOTS strategy for TB control. Although initially highly effective in reducing the incidence and prevalence of TB in endemic countries, the continued success of the DOTS strategy is now seriously threatened by the emergence of highly drug-resistant strains of *M. tuberculosis*. Furthermore, interactions between TB and HIV medications and drugs used in the treatment of specialized problems such as diabetes, drug addiction and mental disorders (conditions that are encountered in populations at risk for TB) might substantially complicate the development of effective new TB drugs. To ensure the continued availability of effective therapeutics against all forms of TB, the development of new, safe, and effective TB drugs must remain a high

priority. Success in TB drug development will also heavily rely on the establishment and continued support of competent, experienced trial sites in TB and TB/HIV endemic countries for all phases of clinical testing.

## Problem 45

Few new TB drugs are in preclinical and clinical development.

### Objective 45.1

Increase the number of candidates in all stages of the TB drug development pipeline to increase the likelihood that new agents will become available for clinical use within the next 5-10 years (domestic and international).

## Action Steps

45.1.1. Increase communication between private not-for-profit and commercial organizations and relevant public sector agencies to identify opportunities for public/private collaborations in TB drug development.

45.1.2. Reevaluate, refine, and optimize support for drug discovery and preclinical studies for pharmaceutical companies and academic/not-for profit organizations (in vitro and animal models).

45.1.3. Encourage pharmaceutical companies, academic researchers and nonprofit organizations to engage in TB drug development research and development efforts.

Lead federal agencies: HHS (CDC, FDA, and NIH) and USAID.

Suggested collaborators: Global Alliance for TB Drug Development, pharmaceutical industry, and academia.

## Problem 46

The global capacity to conduct clinical trials for new drugs that treat TB and MDR TB and XDR TB is limited.

### Objective 46.1

Contribute to the development and support of global TB clinical trials sites and resources to facilitate clinical evaluation of new drugs for TB and MDR TB and XDR TB (domestic and international).

## Action Steps

46.1.1. Participate in the assessment and evaluation of current clinical trials sites for TB.

46.1.2. Establish collaborations to develop strategies for expansion of global TB trials, and associated laboratory capacity within national and local TB control programs.

46.1.3. Establish collaborations to develop international standards and protocols to facilitate TB drug trials in MDR TB

and XDR TB patients and develop mechanisms to coordinate efforts with WHO and GLC.

46.1.4. Expand U.S. government funded clinical TB research efforts to include MDR TB and XDR TB when appropriate.

46.1.5. Establish collaborations to define laboratory standards for MDR TB and XDR TB clinical trials.

Lead federal agencies: HHS (CDC, FDA, and NIH) and USAID.

Suggested collaborators: Global Alliance for TB Drug Development, European and Developing Countries Clinical Trials Partnership (EDCTP), other national research agencies (e.g., British Medical Research Council (BMRC), SAMRC, and Tuberculosis Research Centre (TRC)-Chennai), academia, GLC, and WHO.

### **Problem 47**

Well-validated surrogate markers do not exist to rapidly assess clinical efficacy of new chemotherapeutic agents and regimens against drug-susceptible and MDR TB and XDR TB.

#### **Objective 47.1**

Contribute to the clinical definition and validation of surrogate markers to shorten the duration of clinical trials to estimate the efficacy of new chemotherapeutic agents and regimens (domestic and international).

#### **Action Steps**

47.1.1. Encourage and support collaboration between researchers in diagnostics and immunology and TB clinical trials groups to facilitate access to well-characterized clinical specimens.

47.1.2. Initiate discussion with U.S. and other national regulatory agencies to define minimally acceptable data sets needed to accept surrogate markers for registration of new chemotherapeutic agents and regimens.

Lead federal agencies: HHS (CDC, FDA, and NIH).

Suggested collaborators: Global Alliance for TB Drug Development, pharmaceutical industry, other national research agencies (e.g., BMRC, SAMRC, and TRC-Chennai), and academia.

### **Problem 48**

Effective treatments for latent MDR/XDR *M. tuberculosis* infection have not been established.

#### **Objective 48.1**

Support clinical studies to identify effective treatment strategies for LTBI caused by MDR and XDR *M. tuberculosis*.

### **Action Steps**

48.1.1. Contribute to and support protocol development and clinical studies to evaluate new chemotherapeutic agents that were developed for active TB for treatment of drug-resistant LTBI.

Lead federal agencies: HHS (CDC, FDA, and NIH).

Suggested collaborators: Global Alliance for TB Drug Development, pharmaceutical industry, other national research agencies (e.g., BMRC, SAMRC, and TRC-Chennai), and academia.

### **Problem 49**

The types of clinical data needed to support registration of new chemotherapeutic agents against TB have not been clearly defined making it difficult to design effective clinical development plans and timelines.

#### **Objective 49.1**

Establish a forum for discussion between U.S. and international regulatory agencies to define specific guidance for clinical development and approval of chemotherapeutic agents indicated for use in MDR TB and XDR TB (domestic and international).

#### **Action Steps**

49.1.1. Contribute to and support workshops and discussion among organizations involved in TB drug development and regulatory agencies to better define guidelines for clinical development and approval of new TB agents.

49.1.2. Encourage and support discussions between regulatory agencies and the private sector to facilitate development of compassionate use protocols for new TB drugs.

Lead federal agencies: HHS (CDC, FDA, and NIH).

Suggested collaborators: Global Alliance for TB Drug Development, pharmaceutical industry, European Medicines Agency, and other international regulatory bodies.

### **Problem 50**

Pharmacology of existing and new TB drugs, including interactions with antiretroviral medications commonly used among at-risk populations, has not been adequately assessed.

#### **Objective 50.1**

Support extended pharmacologic studies (pharmacokinetics, pharmacodynamics, and pharmacogenetics), including those that better characterize drug exposure profiles of first-line, second-line, and new drugs and combination regimens among at-risk populations and TB and HIV/TB patients (domestic and international).

## Action Steps

50.1.1. Support pharmacologic studies of drugs and relevant combination therapies either independently or nested within ongoing clinical trials.

50.1.2. Encourage and support pediatric studies of individual drugs and relevant combination therapies.

Lead federal agencies: HHS (CDC, FDA, and NIH).

Suggested collaborators: Global Alliance for TB Drug Development, pharmaceutical industry, other national research agencies (e.g., BMRC, SAMRC, and TRC-Chennai), and academia.

## Problem 51

Efficacy, safety and pharmacology of TB chemotherapeutics are not well characterized in special populations such as children, injection drug users, persons with HIV/AIDS, and others.

### Objective 51.1

Encourage and support inclusion of special populations in clinical trials that investigate new and improved drug treatment strategies for TB and MDR TB and XDR TB (domestic and international).

## Action Steps

51.1.1. Initiate collaborations to develop clinical trial protocols for evaluation of existing and new TB treatment regimens in special populations.

51.1.2. Encourage and support early and late stage clinical trials in special populations.

Lead federal agencies: HHS (CDC, FDA, and NIH).

Suggested collaborators: Global Alliance for TB Drug Development, pharmaceutical industry, other national research agencies (e.g., BMRC, SAMRC, and TRC-Chennai), and academia.

## Fundamental Science

The foundation for development of new health-care interventions in TB is a solid understanding of the interaction between *M. tuberculosis* and the host and how infection transitions to active disease. Knowledge acquired through basic research in these areas must be effectively leveraged in translational science (i.e., research that translates basic scientific discoveries into clinical applications). As a consequence of the sequencing of the genome of both the host and pathogen, the development of molecular tools to manipulate the pathogen, the establishment of genomic and postgenomic technologies and tools, and the expansion of animal models available to study TB,

many important questions in the pathogenicity of TB now can be addressed.

Although considerable progress in fundamental science (basic and translational) of TB has been made over the past decade, the availability of more tools, technologies and advanced methodologies has made it possible to create new hypotheses and revisit earlier observations to contribute to a more detailed understanding of the best points of intervention in TB treatment, necessary characteristics of potential new TB vaccines, and what host/pathogen factors might be early indicators of infection, disease, drug resistance, and transmission. In addition, the effectiveness of current and new infection-control measures, such as negative pressure, high-efficiency particulate air filters, laminar flow, ventilation design on the basis of modeling approaches (e.g., computational fluid dynamics, ultraviolet germicidal irradiation, room air cleaners, and alternative air disinfection methodologies) should be evaluated in appropriate research settings.

## Problem 52

The characteristics of *M. tuberculosis* (e.g., growth, physiology, biochemistry, genetics, and molecular biology) are incompletely understood.

### Objective 52.1

Continue to support fundamental research on the biology of *M. tuberculosis* and the host responses to infection and disease (domestic and international).

## Action Steps

52.1.1. Encourage and support studies to determine mechanisms of acquisition of drug resistance by *M. tuberculosis*.

52.1.2. Encourage and support expanded research on the physiology, biochemistry, and structural biology of *M. tuberculosis* virulence factors and pathogenic mechanisms.

52.1.3. Encourage and support studies to determine the mechanisms of immunopathogenesis of TB.

52.1.4. Encourage and support increased efforts to determine the immunologic and biologic factors associated with or responsible for latency and reactivation of *M. tuberculosis* infection.

52.1.5. Support the development of advanced animal and computational model systems to support fundamental research in TB, taking advantage of new disciplines (e.g., genomics, postgenomics, and proteomics) and system biology techniques.

52.1.6. Continue to provide high quality research reagents to facilitate TB research.



52.1.7. Expand efforts to identify and validate novel drug targets, vaccine strategies, diagnostic markers and research tools.

52.1.8. Encourage and support research on genomics of both *M. tuberculosis* and human/animal hosts, linking to genetic epidemiologic research to direct studies in transmission, pathogenicity, microbial host interactions, and disease progression.

52.1.9. Support studies to characterize manifestations of TB in pediatric and immunocompromised populations.

Lead federal agencies: HHS (CDC and NIH)

Suggested collaborators: Global Alliance for TB Drug Development, pharmaceutical industry, other national research agencies (e.g., BMRC, SAMRC, and TRC-Chennai), and academia.

### Problem 53

The effectiveness of various individual strategies for preventing TB transmission has not been sufficiently evaluated in domestic and international health-care settings.

#### Objective 53.1

Support basic and applied research to assess and/or improve the efficacy of various control methods for preventing transmission of TB in health-care settings and in communities to contribute to evidence-based public health recommendations (domestic and international).

#### Action Steps

53.1.1. Review the efficacy and cost effectiveness of administrative and environmental controls and respiratory protection strategies used to prevent infection within relevant programs and recommend areas of improvement.

53.1.2. Support research to develop improved tools to elucidate the environmental viability of airborne *M. tuberculosis* and design new and improved air disinfection methods.

53.1.3. Support research and efforts to develop effective, affordable methods for expedient isolation of contagious patients that do not require major facility modifications.

53.1.4. Encourage and support cost analyses for modifying existing health-care settings, correctional and detention facilities, homeless shelters, community residences for special needs populations and other high-risk institutional settings to achieve compliance with current and future infection-control requirements.

53.1.5. Support research to characterize dose-infection relationships for airborne *M. tuberculosis* to inform risk assessment of infection in relation to reductions in exposure.

53.1.6. Develop protocols and support studies to evaluate the effectiveness of various administrative controls on the reduction of TB transmission.

53.1.7. Support research to objectively document and improve the ability of various environmental controls to reduce exposure to airborne *M. tuberculosis*.

53.1.8. Support research to develop objective measures to document and compare the ability of various respiratory protective devices to reduce exposure to *M. tuberculosis* and to establish evidence-based recommendations for use of nationally certified respirators providing the appropriate level of protection.

Lead federal agencies: HHS (CDC and NIH), DHS (ICE), and DOJ (USMS and BOP).

Suggested collaborators: OSHA, WHO, health-care facilities, academia, other national research agencies (e.g., BMRC, SAMRC, and TRC-Chennai)

### Diagnostics

The prompt and correct diagnosis of drug-susceptible and drug-resistant TB is one of the cornerstones of effective TB control. Current diagnosis of pulmonary TB in endemic countries is limited to clinical evaluation combined with low sensitivity microbiologic tests. Available diagnostics do not offer the speed and sophistication needed to provide physicians in the field in high-burden countries with the information required to accurately diagnose drug-susceptible and drug-resistant TB and to prescribe the most appropriate treatment regimens. Three distinct research and development areas need to be addressed:

- microbiological diagnostics: rapid identification of drug-resistance or drug-sensitive TB and levels/types of drug resistance;
- clinical diagnostics: rapid identification of pulmonary and nonpulmonary TB, accurate diagnosis of TB in HIV infected patients, reliable identification of latent *M. tuberculosis* infection and accurate exclusion of TB disease; and
- response to treatment: follow-up of patients on empiric therapy when drug resistance testing was not possible/feasible (e.g., extrapulmonary TB).

Although certain diagnostics platforms might be technologically too advanced for field use in resource limited countries, these tests might nevertheless provide a substantial contribution to the advancement of new therapeutics for TB by allowing rapid assessment of response to therapy in clinical trials. Such measures are critical in settings with patients with extrapulmonary TB and those where drug-susceptibility testing is not possible or delayed. Furthermore, rapid assessment of response

to therapy will help determine whether adequate regimens have been prescribed and might contribute to limiting the development of drug resistance.

### **Problem 54**

Rapid, point-of-care identification of drug-sensitive and drug-resistant pulmonary and extrapulmonary TB among HIV-negative and HIV-positive adults and pediatric populations and reliable early identification of latent *M. tuberculosis* infection are not yet possible (see Problem 15).

#### **Objective 54.1**

Develop rapid, point-of-care diagnostics for the reliable identification of drug-sensitive and drug-resistant pulmonary and extrapulmonary TB disease and latent infection including in HIV infected patients and pediatric populations (domestic and international).

#### **Action Steps**

54.1.1. Provide increased support for basic research on the biology of *M. tuberculosis*, the host responses to infection and progression to active disease, and epidemiologic studies to identify immunologic and microbiologic markers of infection and progression to active disease for diagnostic development.

54.1.2. Encourage development of new TB diagnostics by the small business community under mechanisms available through U.S. government funding.

54.1.3. Facilitate the development of serological and immunological tests specific to *M. tuberculosis* infection, and the development of genotypic markers for the point-of-care identification of drug-resistant TB through access to well characterized patient specimens to determine sensitivity of different diagnostic tests for TB in patients with different levels of immune function and at different stages of clinical disease.

54.1.4. Encourage and support research, including research into advanced imaging technologies to improve currently available diagnostic tests for the identification of pulmonary and extrapulmonary TB and latent *M. tuberculosis* infection.

54.1.5. Support the evaluation of cost effectiveness and appropriate use of available and newly developed rapid methods for diagnosis of drug-sensitive and drug-resistant pulmonary and extrapulmonary TB and latent *M. tuberculosis* infection.

54.1.6. Support studies to determine the most effective diagnostic combination/algorithms for latent *M. tuberculosis* infection and promote their inclusion in ongoing TB control programs.

54.1.7. Support and provide training to health-care providers for new diagnostic tests in high-burden countries to expand the use of new tests.

54.1.8. Support studies to improve molecular epidemiologic tools and databases for contact investigation and to assess the impact of new diagnostics, drugs and vaccines.

54.1.9. Establish partnerships and contribute to collaborative networks to facilitate validation of new diagnostic tests as part of clinical trials in partnership with high-burden countries.

54.1.10. Initiate discussions with FDA to identify criteria that will have to be met for approval of new diagnostic tests for identification of drug-sensitive and drug-resistant pulmonary and extrapulmonary TB and latent *M. tuberculosis* infection.

54.1.12. Support clinical and operational studies to evaluate the contribution of new diagnostic strategies to the management and treatment of HIV-associated TB and pediatric TB.

Lead federal agencies: HHS (CDC and NIH).

Suggested collaborators: FIND, Aeras Global TB Vaccine Foundation (AERAS), academia, and other national research agencies (e.g., BMRC, SAMRC, and TRC-Chennai).

### **Problem 55**

Efforts to develop tests to rapidly characterize clinical response to new and improved drug regimens in clinical trials are limited.

#### **Objective 55.1**

Develop serologic, immunologic, and microbiologic tests to assess response to treatment. Evaluate technologically advanced tests, which might or might not be feasible to implement in endemic countries, for measuring drug efficacy in clinical trials of new therapeutics and regimens for TB (domestic and international).

#### **Action Steps**

55.1.1. Encourage and support basic research on the changes in host immunology as a result of drug treatment in TB patients.

55.1.2. Encourage and support evaluation of serologic tests in the context of drug treatment and response to therapy.

55.1.3. Establish partnerships and encourage collaborations to facilitate access to well characterized, longitudinally collected patient specimens from drug treatment trials to determine suitability of diagnostic tests for measuring response to therapy.

55.1.4. Support studies to evaluate the cost effectiveness of including tests to assess response to therapy with empiric drug treatment.

55.1.5. Support studies to determine the most effective diagnostic combination/algorithms to measure response to therapy and promote inclusion in ongoing TB control programs, when appropriate.

55.1.6. Establish partnerships and contribute to collaborative networks to facilitate validation of tests to determine response

to therapy as part of clinical trials in partnership with high-burden countries.

55.1.7. Establish partnerships and contribute to collaborative networks to use response tests in clinical trials to assess the early efficacy of new drug regimens.

55.1.8. Initiate discussions with FDA to identify criteria that will have to be met for diagnostic tests to assess early response to therapy as part of the data provided for new drug registration.

Lead federal agencies: HHS (CDC, FDA, and NIH) and USAID.

Suggested collaborators: FIND, AERAS, academia, and other national research agencies (e.g., BMRC, SA-MRC, and TRC-Chennai).

## Vaccines

Long-term control and ultimate elimination of TB likely will require an effective vaccine (40). Research to characterize needs for an effective vaccine, on the basis of immunological responses of persons infected with *M. tuberculosis* who do not become ill and animal models and comparisons with the currently used vaccine *M. bovis* Bacille Calmette-Guerin (BCG) have been supported for over a decade. BCG vaccine, usually administered once in infancy in countries with a moderate and high incidence of TB, is effective in preventing TB meningitis and disseminated TB in children but has highly variable efficacy in preventing other forms of TB, especially in adults (41). Strategic plans for a TB vaccine have been developed, and support for biomedical research for the development of new, more effective vaccines and vaccinations strategies has resulted in progress to the point where several new vaccine candidates are now being evaluated in clinical trials. Nevertheless, a highly effective vaccine has remained elusive.

Increased capacity to allow entry of novel vaccine candidates into Phase I clinical studies and comparative studies of vaccine platforms in human trials will contribute substantially to understanding development needs for effective TB vaccines. However, assays and methodologies for preclinical validation and clinical characterization need to be standardized globally. Clinical trial protocols for the assessment of vaccination strategies and the development of expertise to conduct clinical trials and immunological assays in TB endemic countries are needed to establish a robust infrastructure for TB vaccine research and development (R&D).

### Problem 56

Current preclinical and clinical efforts in TB vaccine development are not optimally coordinated.

### Objective 56.1

Facilitate and expedite the identification and clinical testing of new vaccine candidates and vaccination strategies (domestic and international).

#### Action Steps

56.1.1. Discuss the role of U.S. government partners in contributing to global TB vaccine R&D and identify areas of contribution.

56.1.2. Contribute to and assist in the global coordination of TB vaccine development and clinical testing.

56.1.3. Encourage and support clinical studies to assess the potential role of BCG vaccination in MDR TB and XDR TB outbreaks where no effective antibiotics are available to contribute to control strategies.

56.1.4. Encourage and support studies with subunit, peptide, vectored and DNA vaccines as adjuncts to therapy for MDR TB and XDR TB.

56.1.5. Establish collaborations with regulatory agencies worldwide to discuss harmonization of regulatory pathways for clinical development and approval of new drugs, vaccines and diagnostics for TB.

56.1.6. Encourage and support research on postexposure vaccination.

56.1.7. Continue to support resources and facilities for testing of new TB vaccines in animal models.

56.1.8. Establish collaborations with U.S. government sponsored HIV immunology testing programs to discuss access to clinical specimens from TB vaccine trials.

56.1.9. Sponsor a workshop to update the U.S. Blueprint for TB Vaccine Development (40).

56.1.10. Encourage and support research on biological response modifiers, adjuvants, and therapeutic vaccines and vaccination strategies (immunotherapeutics of TB).

Lead federal agencies: HHS (CDC, FDA, and NIH).

Suggested collaborators: WHO, EU, AERAS, academia, and other national research agencies (e.g., BMRC, SAMRC, and TRC-Chennai).

## Behavioral, Social, Clinical, and Operational Science

Current TB therapy is complex and lengthy, and it can be associated with adverse reactions to medications. Patient adherence often is difficult, leading to discontinuation of therapy; this results in relapse, continued transmission of disease, and, in some cases, the development of drug-resistant TB. Adherence is influenced by patient characteristics, differences in health-care seeking behavior, assumptions about disease, the health-care environment, the availability of adherence-enhancing

interventions, the quality of communication between patients and providers, the availability and use of education materials to inform patients and families about TB, treatment and consequences of defaulting, the convenience of access to drugs for supervised treatment, and the quality of drugs available through TB control programs.

The complexity of factors underlying patient adherence and the importance of completing treatment for TB necessitates increased emphasis on patient-centered treatment options and a thorough understanding of behavioral and social interventions that have to be in place to augment traditional TB control approaches. Operational research to improve care programs must include studies to characterize TB health services, case and data management practices, staff selection, training and retention incentives, physician training, management and organizational structure, relationships with the community, community perceptions of services, community resistance to public health services, and clinic policies and practices to provide the best possible environment for ensuring patient trust and treatment completion.

### **Problem 57**

Patient adherence to TB chemotherapy is not optimal, and alternative methods for ensuring completion of therapy are not fully developed.

#### **Objective 57.1**

Identify alternatives and adjuncts to currently used treatment protocols through behavioral research to improve adherence to therapy (domestic and international).

#### **Action Steps**

57.1.1. Encourage and support studies to develop and validate predictor instruments to identify patient, social and cultural factors associated with poor adherence to therapy and development of drug-resistant TB.

57.1.2. Continue to support research on cultural influences on health-care utilization and adherence among foreign-born persons and minority groups at risk for drug-resistant TB.

57.1.3. Encourage and support studies to determine the effectiveness of interventions to increase adherence, including incentives, supports (enablers), and provision of social and other health-care services offered through TB programs.

57.1.4. Support studies to evaluate the contribution of communication styles of TB health-care providers to treatment outcomes.

57.1.5. Facilitate surveys of TB treatment practices of various health-care providers to determine discrepancies in practices that might contribute to poor adherence and development of drug-resistant TB.

57.1.6. Support studies to identify barriers to effective communication and implementation of effective practices by providers most likely to treat patients at risk for drug-resistant TB.

57.1.7. Support review of prior formative communications research and conduct new studies to identify innovative and effective education methods to reach populations with high disease prevalence.

57.1.8. Evaluate education strategies for targeting the health-care providers of patients at risk for drug-resistant TB and identify shortcomings and barriers to communication.

Lead federal agencies: HHS (CDC, FDA, and NIH).

Suggested collaborators: state and local health departments, WHO, other national research agencies (e.g., BMRC, SAMRC, and TRC-Chennai), and academia.

### **Problem 58**

Operational and clinical questions related to patient adherence and optimal organization and structure of health services to ensure effective TB care remain unanswered.

#### **Objective 58.1**

Identify operational, clinical and systems barriers to providing effective TB care and develop strategies for improvement (domestic and international).

#### **Action Steps**

58.1.1. Support the design and implementation of operational research studies to improve TB control programs and patient/provider communication and relationships.

Lead federal agencies: HHS (CDC, FDA, and NIH).

Suggested collaborators: WHO, other national research agencies (e.g., BMRC, SAMRC, and TRC-Chennai), and academia.

### **Partnerships**

Because XDR TB presents a worldwide threat, a coordinated international response will rely on effective partnerships between all organizations and governments that are involved in TB control programs, TB biomedical research and product development (Box). In addition, the establishment of new alliances is needed to fill the critical gaps in the global response identified in this report. Currently, government agencies at all levels, international organizations, nongovernment organizations (NGOs), academic institutions, and the private sector are coordinating their efforts as members of the STOP TB Partnership. Furthermore, cross-disciplinary research and product development efforts are brought together through various nonprofit organizations focused on developing affordable and effective drugs, vaccines and diagnostics. Representatives

**BOX. Domestic and international partner organizations involved in tuberculosis (TB) research and control programs\***

<b>Organization</b>	<b>Website</b>
Aeras Global TB Vaccine Foundation	<a href="http://www.aeras.org">http://www.aeras.org</a>
American College of Chest Physicians	<a href="http://www.chestnet.org">http://www.chestnet.org</a>
American Medical Association	<a href="http://www.ama-assn.org">http://www.ama-assn.org</a>
American Thoracic Society	<a href="http://www.thoracic.org">http://www.thoracic.org</a>
Association for Professionals in Infection Control and Epidemiology	<a href="http://www.apic.org">http://www.apic.org</a>
Association of Public Health Laboratories	<a href="http://www.aphl.org">http://www.aphl.org</a>
Bill & Melinda Gates Foundation	<a href="http://www.gatesfoundation.org">http://www.gatesfoundation.org</a>
Centers for Disease Control and Prevention	<a href="http://www.cdc.gov">http://www.cdc.gov</a>
CDC Foundation	<a href="http://www.cdcfoundation.org">http://www.cdcfoundation.org</a>
Centers for Medicare and Medicaid Services	<a href="http://www.cms.hhs.gov">http://www.cms.hhs.gov</a>
CureTB	<a href="http://www.cureTB.org">http://www.cureTB.org</a>
Executive Office of Immigration Review	<a href="http://www.usdoj.gov/eoir">http://www.usdoj.gov/eoir</a>
Federal courts	<a href="http://www.uscourts.gov">http://www.uscourts.gov</a>
Food and Drug Administration	<a href="http://www.fda.gov">http://www.fda.gov</a>
Foundation for Innovative New Diagnostics	<a href="http://www.finddiagnostics.org">http://www.finddiagnostics.org</a>
Global Alliance for TB Drug Development	<a href="http://www.tballiance.org">http://www.tballiance.org</a>
Global Drug facility	<a href="http://www.stoptb.org/gdf">http://www.stoptb.org/gdf</a>
Green Light Committee	<a href="http://www.who.int/tb/challenges/mdr/greenlightcommittee/en/index.html">http://www.who.int/tb/challenges/mdr/greenlightcommittee/en/index.html</a>
Health Resources and Services Administration	<a href="http://www.hrsa.gov">http://www.hrsa.gov</a>
Hospital Infection Control Practices Advisory Committee	<a href="http://www.cdc.gov/ncidod/dhqp/hicpac.html">http://www.cdc.gov/ncidod/dhqp/hicpac.html</a>
Immigration and Customs Enforcement	<a href="http://www.ice.gov">http://www.ice.gov</a>
Infectious Diseases Society of America	<a href="http://www.idsociety.org">http://www.idsociety.org</a>
International Council of Nurses	<a href="http://www.icn.ch">http://www.icn.ch</a>
International Union against Tuberculosis and Lung Diseases	<a href="http://www.iuatld.org">http://www.iuatld.org</a>
KNCV Tuberculosis Foundation	<a href="http://www.kncvtbc.nl/Site/Professional.aspx?language=en-GB">http://www.kncvtbc.nl/Site/Professional.aspx?language=en-GB</a>
Médecins sans Frontières	<a href="http://www.msf.org">http://www.msf.org</a>
National Institutes of Health	<a href="http://www.nih.gov">http://www.nih.gov</a>
National Ministries of Health	
National TB Programs	
Occupational Health and Safety Administration	<a href="http://www.osha.gov">http://www.osha.gov</a>
RESULTS International	<a href="http://www.results.org">http://www.results.org</a>
StopTB	<a href="http://www.stoptb.org">http://www.stoptb.org</a>
Task Force for Child Survival & Development	<a href="http://www.taskforce.org">http://www.taskforce.org</a>
TBNet	<a href="http://www.migrantclinician.org/network/tbnet">http://www.migrantclinician.org/network/tbnet</a>
Treatment Action Group	<a href="http://www.aidsinfonyc.org/tag">http://www.aidsinfonyc.org/tag</a>
U.S. Agency for International Development	<a href="http://www.usaid.gov">http://www.usaid.gov</a>
U.S. Department of Health and Human Services	<a href="http://www.dhhs.gov">http://www.dhhs.gov</a>
U.S. Customs and Border Protection	<a href="http://www.cbp.gov">http://www.cbp.gov</a>
U.S. Department of Homeland Security	<a href="http://www.dhs.gov">http://www.dhs.gov</a>
U.S. Department of Housing and Urban Development	<a href="http://www.hud.gov">http://www.hud.gov</a>
U.S. Department of Veterans Affairs	<a href="http://www.va.gov">http://www.va.gov</a>
U.S. local and state TB control programs	<a href="http://www.cdc.gov/tb/pubs/tboffices.htm">http://www.cdc.gov/tb/pubs/tboffices.htm</a>
U.S. Marshals Service	<a href="http://www.usmarshals.gov">http://www.usmarshals.gov</a>
U.S. National TB Controllers Association	<a href="http://tbcontrollers.org/">http://tbcontrollers.org/</a>
U.S. National Tuberculosis Nurse Coalition	<a href="http://tbcontrollers.org/">http://tbcontrollers.org/</a>
U.S. Regional Training and Medical Consultations Centers	<a href="http://www.cdc.gov/tb/rtmcc.htm">http://www.cdc.gov/tb/rtmcc.htm</a>
World Health Organization	<a href="http://www.who.int">http://www.who.int</a>
Pharmaceutical companies	
Academic institutions	

\*This list is not intended to be exhaustive but rather provides examples of entities that partner with the U.S. government in U.S. domestic and international TB control efforts.

from United States government agencies are actively involved in these partnerships and contribute their knowledge and expertise to help address the national and global aspects of XDR TB.

The U.S. Federal Tuberculosis Task Force serves as a mechanism to coordinate activities of various federal agencies that are involved in domestic and international TB prevention and elimination programs. Domestically, U.S. government agencies work closely with local and state TB control programs, academic institutions, professional associations, and pharmaceutical companies to assure the most effective use of available resources and to minimize duplication of effort. The expansion of existing partnerships to include management and prevention of XDR TB and other forms of drug-resistant TB will be important if TB is to be eliminated in the United States and worldwide.

### **Problem 59**

Differing jurisdictions among public health agencies, scopes of work among nongovernment organizations, and varying country-specific public health policies, economic conditions, and political commitments pose a substantial barrier to launching and focusing a coordinated response to TB (MDR TB and XDR TB and HIV/TB) in high-burden settings with the greatest needs.

#### **Objective 59.1**

Optimize integration, coordination and synergy between U.S. government agencies, international organizations, and national TB/HIV programs to achieve reduction in disease rates through more focused prevention/intervention activities for MDR TB and XDR TB and HIV/TB and nonduplicative allocation of funding, staff and resources (international).

#### **Action Steps**

59.1.1. Develop programs or working groups to maximize cooperation between international organizations and to align resources for an efficient, resource sparing response in high-burden countries.

59.1.2. Establish additional interagency agreements to formalize existing cooperative efforts, where feasible.

Lead federal agencies: USAID and HHS (CDC).

Suggested collaborators: WHO, STOP TB, IUATLD, KNCV, ministries of health, and national and local National TB Program (NTP) staff.

### **Problem 60**

Currently available global funds are insufficient to mount a comprehensive response to XDR TB, particularly in settings with high rates of HIV/TB co-infection. Resources need to be

focused on this emerging threat, on the basis of identification of specific needs.

#### **Objective 60.1**

Educate global and domestic partners on the international problem of TB, what activities are ongoing and what gaps remain to provide an effective response to MDR TB, XDR TB, and HIV/TB (domestic and international).

#### **Action Steps**

60.1.1. Increase interactions within existing partnerships and with private sector organizations, companies, and foundations to increase awareness of the current gaps that affect a global response to TB.

60.1.1. Develop media projects to call attention to the global problem of TB and HIV/TB and the rise in drug-resistant TB and outline the limitations of current ongoing efforts.

Lead federal agencies: USAID and HHS.

Suggested collaborators: WHO, STOP TB, IUATLD, Treatment Action Group (TAG), MSE, ATS, NTCA, Task Force for Childhood Survival and Development, IDSA, and the Bill & Melinda Gates Foundation.

### **Problem 61**

Globally, human resources at all levels in national TB programs are insufficient and maintaining a well qualified workforce has been difficult due to the continuous exodus of qualified, experienced TB and/or HIV staff. Domestically, the number of medical professionals with experience in managing TB patients, much less MDR TB and XDR TB patients, has declined in parallel with TB cases. A critical need is to strengthen human resources at the local and state/provincial/district level.

#### **Objective 61.1**

Develop and use partnerships between organizations involved in workforce training and retention to increase the number of qualified personnel available to international TB and HIV/TB programs (domestic and international).

#### **Action Steps**

61.1.1. Contribute to the identification of appropriate partner organizations and the establishment of programs to describe barriers to effective hiring and retention of qualified personnel in high-burden countries.

61.1.2. Participate in the development of recommendations to improve hiring, training, and retention practices for personnel employed in TB and HIV/TB programs.

61.1.3. Provide technical assistance for assessing and updating current infection-control procedures and processes to create

a safe work place for health-care personnel with the ultimate goal to increase retention of employees.

Lead federal agencies: USAID and HHS (CDC and NIH).

Suggested collaborators: WHO, KNCV, Family Health International (FHI), Peace Corps, MSF, NTCA, RTMCCs, local and state TB control programs, Association of Schools of Public Health, and academia (including historically black colleges and universities to address workforce diversity).

## Problem 62

Government and private biomedical research and product development activities in the United States might be duplicative, limiting the effective use of available funds and the efficiency by which fundamental research findings can be translated into new health-care interventions.

### Objective 62.1

Establish a forum among U.S. organizations, government and private, providing funding, regulatory oversight and research direction for TB science and product development to coordinate efforts and ensure optimal use of available resources (domestic).

#### Action Steps

62.1.1. Convene representatives from U.S. organizations involved in TB research and product development to identify current barriers and needs for improved coordination of programs.

62.1.2. Establish and articulate the roles and responsibilities of each partner in furthering specific aspects of TB research and product development.

62.1.3. Identify key gap areas in translational research and develop recommendations for programs or new partnerships to address these gaps.

Lead federal agencies: HHS (CDC, FDA, and NIH) and USAID.

Suggested collaborators: NGOs, academia, local and state health departments, ATS, IDSA, and the pharmaceutical industry.

## Problem 63

Biomedical and product development activities and regulatory activities are not coordinated optimally between U.S. and international governmental and private agencies. Insufficient coordination of research activities exists among the various international entities with commitments to support TB research, or with involvement in related activities such as medical regulation.

### Objective 63.1

Develop or support working groups or other mechanism to facilitate coordination of research activities among U.S. and international governmental and private agencies (international).

#### Action Steps

63.1.1. Develop an effective and sustainable forum for coordinating TB research between U.S. and international agencies.

63.1.2. Establish and articulate the roles and responsibilities of each partner in furthering specific aspects of TB research and product development.

63.1.3. Identify key gap areas in translational research and develop recommendations for programs or new partnerships to address these gaps.

Lead federal agencies: USAID and HHS (CDC, FDA, and NIH).

Suggested collaborators: WHO, IUATLD, academia, ATS, IDSA, national ministries of health, Non-Governmental Organizations (NGOs), pharmaceutical industry, and KNCV.

## Problem 64

Outside of the public health community, only limited awareness exists of the potential consequences of XDR TB for the United States and globally (see Problem 44).

### Objective 64.1

Establish and maintain partnerships with appropriate organizations within and outside the public health community to increase awareness of XDR TB among policy makers and the general public (domestic and international).

#### Action Steps

64.1.1. In collaboration with appropriate partners, develop coordinated and consistent education material to promote informed awareness of XDR TB in the U.S. and internationally.

Lead federal agencies: HHS (CDC, NIH, and HRSA), USAID, and HUD.

Suggested collaborators: WHO, IUATLD, Results International, American Lung Association, Treatment Action Group, local and state health departments, academia, and national ministries of health.

## Problem 65

Current public health partnerships are not sufficient to ensure continuity of care for TB patients and their contacts who either reside temporarily in the United States or frequently

cross its borders. More than half the TB cases in the United States occur among immigrants who become infected before their arrival in the United States. Lack of continuity of care contributes to treatment default, ongoing transmission, and prolonged illness. Partnerships are needed for effective transnational case management.

### **Objective 65.1**

Identify appropriate partners and programs to contribute to projects and strategies that ensure continuity of TB care for patients traveling or migrating into or out of the United States (domestic and international).

### **Action Steps**

65.1.1. Identify domestic and international partners to participate in an assessment of barriers to continuity of care for migrants or traveling TB patients.

65.1.2. Develop and implement transnational partnerships that allow establishment of cross-border TB care and management programs, such as the Bi-National TB Card and transnational referral programs for continuity of TB therapy.

65.1.3. Strengthen partnerships between ICE and TB Programs in countries to which patients are deported while on TB treatment that was initiated in the United States.

Lead federal agencies: HHS (CDC and HRSA), USAID, DHS (ICE, CBP), federal courts, and USMS.

Suggested collaborators: foreign NTPs and ministries of health, local and state TB programs in the United States and other countries, Cure TB, and TB Net.

### **Cost Analysis**

A realistic national estimate of the costs of diagnosing, treating, and managing XDR TB will be an important prerequisite for measuring the benefit and savings to the United States that would be realized through prevention of XDR TB. CDC has estimated the costs for hospitalization of one XDR TB patient at approximately \$483,000 (CDC, unpublished data 2007) whereas outpatient treatment costs, productivity losses, patient out-of-pocket expenses, and quality of life changes attributable to XDR TB are unknown.

Some of the existing interventions and strategies for TB care and management, such as the use of DOT, already have been demonstrated to be cost effective in preventing the development of MDR TB, but information about additional strategies is currently not available. Analysis of such cost-benefit and cost-effectiveness data will be critical to prioritize programs and advocate for resources to implement specific interventions to help prevent XDR TB.

### **Problem 66**

A comprehensive and up-to-date estimate of the costs of diagnosing, treating, and managing XDR TB in the United States is not available.

### **Objective 66.1**

Conduct a study on the basis of health-care system and societal perspectives to calculate the costs of diagnosing, treating, and managing all cases of XDR TB identified through surveillance for patients and their contacts (domestic).

### **Action Steps**

66.1.1. Identify representative samples or cohorts of XDR TB patients during 2004–2007 (verified and reported, unreported incident and prevalent cases), and their contacts for estimating costs associated with health care and personal productivity.

66.1.2. Estimate from representative samples or cohorts of XDR TB patients the average medical costs incurred on the basis of the extent and pattern of drug resistance, medically indicated procedures and examinations needed to diagnose drug-resistant TB, the length of inpatient and outpatient treatment, management of adverse events and treatment and disease associated chronic sequelae, and the cost of case management of contacts.

66.1.3. Estimate from representative samples or cohorts of XDR TB patients that were employed prior or during XDR TB diagnosis associated losses in personal productivity and salary losses on the basis of the extent and pattern of drug resistance, chronic disease, and the impact of patient mortality (age at death and time to death).

66.1.4. From a survey of XDR TB survivors and their family members, estimate loss of quality-adjusted life years on the basis of extent and patterns of drug-resistant TB disease.

66.1.5. Conduct patient interviews to estimate out-of-pocket medical expenses associated with XDR TB disease.

Lead federal agencies: HHS (CDC).

Suggested collaborators: state/local Departments of Health, public and private outpatient providers and hospitals, laboratories, former patients, and family members.

### **Problem 67**

Cost-effective strategies to prevent XDR TB remain to be established.

### **Objective 67.1**

Determine the costs of interventions or strategies to prevent XDR TB in the United States (domestic).



## Action Steps

67.1.1. On the basis of a review of the literature of recommended interventions and strategies to prevent XDR TB in the U.S, identify those interventions and strategies that might offer the greatest cost effectiveness.

67.1.3. Determine implementation costs for interventions that have not previously been assessed.

67.1.4. Determine the cost benefit for each prevention strategy in relation to cost that would have been incurred to treat XDR TB.

Lead federal agencies: HHS (CDC).

Suggested collaborators: state and local health departments, and academia.

## Conclusion

The nine response areas addressed in this report are closely aligned with WHO's seven-point Global Action Plan to Combat XDR TB (26), which calls for public health authorities to 1) conduct rapid surveys of XDR TB to determine the burden, 2) enhance laboratory capacity with an emphasis on rapid drug sensitivity testing, 3) improve technical capacity of clinical and public health practitioners to respond effectively to XDR TB outbreaks and manage patients, 4) implement infection-control precautions, 5) increase research support for TB drug development, 6) increase research support for rapid diagnostic test development, and 7) promote universal access to antiretroviral drugs under joint TB/HIV activities.

The Federal TB Task Force Plan and the Global Action Plan will require a renewed commitment by all public health workers as well as new resources from both the public and private sectors. In the United States, federal funding has remained relatively level since 2000, and state and local funding has declined in many states since 2000. As a result, TB prevention and control capacity in the United States has eroded. For example, many states have decided to implement selective rather than universal patient-centered DOT to ensure adherence to treatment until complete. These decisions are made on the basis of financial constraints but place the patient at high risk for treatment failure and subsequently the potential creation of MDR TB or XDR TB. In the absence of shorter treatment regimens, and without adherence-promoting measures such as DOT, the TB patient is more likely to experience drug resistance that could result from interruptions in treatment. These choices place the public and the nation in a vulnerable position, risking outbreaks of MDR or XDR TB if conditions facilitate rapid spread and possibly causing public health crises. (42,43)

The Federal TB Task Force Plan provides an effective framework to detect, prevent, and control XDR TB, but it also

highlights the existence of substantial unmet needs. There is concern that progress in TB prevention and control is waning as manifested by the decrease in the rate of decline in TB incidence since 2000. The United States responded successfully to the MDR TB problem in the 1990s and is capable of preventing and controlling XDR TB; however, this will require a united commitment and effort similar to that which occurred in 1992.

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## Appendix

### Acronyms and Abbreviations Used in This Report

AAFP	American Academy of Family Physicians
ACCP	American College of Chest Physicians
ACET	Advisory Council for the Elimination of Tuberculosis
AERAS	Aeras Global TB Vaccine Foundation
AFB	Acid fast bacillus
AIA	American Institute of Architects
AIDS	Acquired immunodeficiency syndrome
ALA	American Lung Association
AM	American Medical Association
APHL	Association of Public Health Laboratories
APIC	Association for Professionals in Infection Control and Epidemiology
ASHRAE	American Society of Heating, Refrigerating and Air-Conditioning Engineers
ASM	American Society for Microbiology
ASTHO	Association of State and Territorial Health Officers
ATS	American Thoracic Society
BAMT	Blood assays for Mycobacterium tuberculosis
BOP	Federal Bureau of Prisons
CBP	U.S. Customs and Border Protection
CLSI	Clinical and Laboratory Standards Institute
DHS	Department of Homeland Security
DIHS	Division of Immigration Health Services
DOD	Department of Defense
DOJ	Department of Justice
DOS	Department of State
DOT	Directly observed therapy
DOTS	Directly observed therapy, short-course
DR LTBI	Drug-resistant latent tuberculosis infection
DST	Drug susceptibility testing
DTBE	Division of Tuberculosis Elimination
EQA	External quality assurance
EU	European Union
FDA	Food and Drug Administration
FIC	Fogarty International Center
FIND	Foundation for Innovative New Diagnostics
FHI	Family Health International
GLC	Green Light Committee
HHS	Department of Health and Human Services
HICPAC	Hospital Infection Control Practices Advisory Committee
HIV	Human immunodeficiency virus
HRSA	Health Resources and Services Administration
HUD	Department of Housing and Urban Development
ICE	U.S. Immigration and Customs Enforcement
IDSA	Infectious Diseases Society of America
IUATLD	International Union Against Tuberculosis and Lung Disease
JCAHO	Joint Commission (formerly Joint Commission on Accreditation of Healthcare Organizations)
KNCV	Royal Netherlands Tuberculosis Association

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LTBI	Latent tuberculosis infection
MDR TB	Multidrug-resistant tuberculosis
MSF	Doctors Without Borders/Medecins Sans Frontieres
NCET	National Coalition for the Elimination of Tuberculosis
NGO	Non-governmental organization
NIH	National Institutes of Health
NLTN	National Laboratory Training Network
NTCA	National TB Controllers Association
NTCC	National Tuberculosis Curriculum Consortium
NTP	National TB Program
NTSS	National TB Surveillance System
OHSA	Occupational Safety and Health Administration
POC	Point-of-contact
RIF	Rifampin resistance
RIT	Research Institute of Tuberculosis
RTMCC	Regional Training and Medical Consultation Center
RVCT	Report of verified case of tuberculosis
SAMHSA	Substance Abuse and Mental Health Services Administration
TAG	Treatment Action Group
TB	Tuberculosis
TST	Tuberculin skin test
USAID	U.S. Agency for International Development
USMS	United States Marshals Service
UVGI	Ultraviolet germicidal irradiation
VA	Department of Veterans Affairs
WHO	World Health Organization
WHO (TDR)	World Health Organization Research and Training in Tropical Diseases
XDR TB	Extensively drug-resistant tuberculosis

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