USAID
FROM THE AMERICAN PEOPLE

NIH National Institute of Allergy and Infectious Diseases

CDC
Centers for Disease Control and Prevention

NATIONAL ACTION PLAN
FOR COMBATING MULTIDRUG-RESISTANT TUBERCULOSIS

YEAR ONE REPORT

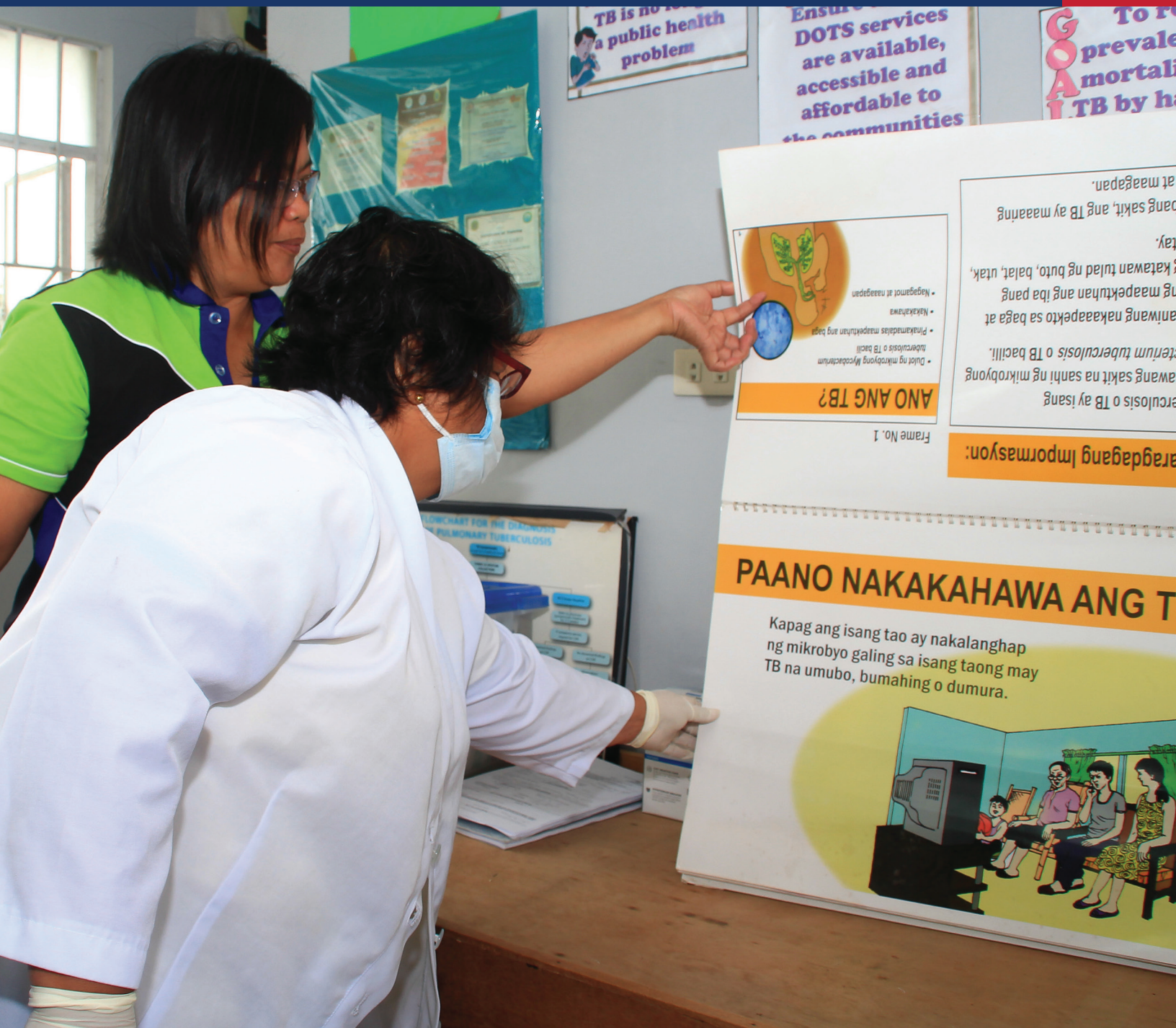


TABLE OF CONTENTS

Cover: A health provider examines an educational flipchart about tuberculosis at a health facility in Ibaan, Philippines. ©2016. Allan Castañeda. Courtesy of Photoshare.

ACRONYMS AND ABBREVIATIONS

BASICS	Building and Strengthening Infection Control Strategies for TB Prevention
BDQ	Bedaquiline
CDC	Centers for Disease Control and Prevention
CTB2	Consortium for Tuberculosis Biomarkers
DHHS	Department of Health and Human Services
DLM	Delamanid
DOH	Department of Health
DR-TB	Drug-Resistant Tuberculosis
EMBO	European Molecular Biology Organization
GDF	Global Drug Facility
GLI	Global Laboratory Initiative
H3Africa	Human Heredity and Health in Africa
HIV	Human Immunodeficiency Virus
KEMRI	Kenya Medical Research Institute
MDR-TB	Multidrug-Resistant Tuberculosis
MTB	*Mycobacterium tuberculosis*
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NITBRI	Intramural TB Research Initiative
NTP	National Tuberculosis Program
PEPFAR	President's Emergency Plan for AIDS Relief
R&D	Research and Development
RePORT	Observational International Research Cohorts
RNA	Ribonucleic Acid
SRS	Strategic Rotating Stockpile
STREAM	Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients With MDR-TB
TB	Tuberculosis
TBRU	Tuberculosis Research Units
USAID	United States Agency for International Development
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant Tuberculosis
Xpert	Xpert® MTB/RIF

A mother returns home after a several month inpatient stay at the beginning of her MDR-TB treatment in Ugu District, KwaZulu-Natal, South Africa. The newly initiated mobile injection team in this region allows her to be home to care for her children while still receiving adequate antibacterial coverage. © 2012 Amelia Rutter, Courtesy of Photoshare.

INTRODUCTION

Tuberculosis (TB) is the leading infectious disease killer globally, and in 2015 it claimed the lives of 1.8 million people. The deadly disease caused by *Mycobacterium tuberculosis* (MTB) is transmitted through the air from person to person and it occurs in the U.S. and around the world. TB is curable, but inappropriate treatment can lead to multidrug-resistant TB (MDR-TB), which is resistant to the two most effective anti-TB drugs, and extensively drug-resistant TB (XDR-TB), which is often deadly. An MDR-TB outbreak in the U.S. or in other countries will have serious consequences for individuals due to the long, difficult and toxic treatment regimen required, and for health systems and economies due to the very high cost of treatment and the burden that MDR-TB places on health providers and institutions.

In December 2015, the U.S. Government released a plan to address this growing crisis domestically and internationally and to advance research on this critical public health issue. The *National Action Plan for Combating Multidrug-Resistant Tuberculosis (National Action Plan)* is a five-year plan that not only builds on the U.S. Government's domestic and global TB strategies, as well as the World Health Organization's (WHO) END TB Strategy, but also contributes to the success of these existing strategies.

The goals of the *National Action Plan* are to:

1. Strengthen domestic capacity to combat MDR-TB;
2. Improve international capacity and collaboration to combat MDR-TB; and
3. Accelerate basic and applied research and development to combat MDR-TB.

From 2000 to 2015, an estimated 49 million lives were saved through global efforts to ensure TB diagnosis and treatment. The U.S. government has been a leader in these efforts, working through its lead agencies and programs to support implementation of high-quality services. The *National Action Plan* builds on these efforts to support the appropriate treatment of more than 16 million TB patients to ensure that 90 percent of them were cured and to prevent further development of MDR-TB. In addition to increased MDR-TB prevention efforts, the *National Action Plan* proposes increasing the number of MDR-TB treatment initiatives in countries with the highest MDR-TB burden. The *National Action Plan* is intended to promote greater coordination of U.S. Government resources—including domestic, bilateral and multilateral funding—to reduce the domestic and global risk of MDR-TB; increase the American public's awareness of the threats posed by MDR-TB; and serve as a call to action to encourage bilateral and multilateral donors, the private sector, and affected countries to increase investments in this critical area of worldwide concern. Additional investments in research and development will continue to contribute to improved treatment outcomes for individuals with MDR-TB through the discovery of new tools that are easy to implement in existing health systems; better use of existing and newly licensed TB drugs, an enhanced drug-development pipeline, increased availability of rapid assays for TB diagnosis and drug-susceptibility testing, effective vaccines and other preventative interventions, and improved disease surveillance. These actions help prevent the emergence of further resistance to TB drugs and significantly reduce the global spread of MDR-TB.

GOAL 1: STRENGTHEN DOMESTIC CAPACITY TO COMBAT MULTIDRUG-RESISTANT TUBERCULOSIS

Following a resurgence that coincided with the onset of the HIV epidemic, the incidence of TB in the United States steadily declined from 1993 through 2014. However, the complexity of TB control and the challenges facing elimination of TB in the U.S. comparatively have not diminished. Progress appears to have leveled off recently, with 2014 experiencing only a 1.5 percent decrease in TB cases (the smallest decrease in a decade), and 2015 seeing a small increase in cases. Although rates of drug-resistant TB, particularly MDR-TB, have declined since 1993, these cases continue to complicate treatment and prevention efforts. Efforts to control and eventually eliminate TB in the United States are complicated by many factors. Annually, approximately one percent of U.S. TB cases are MDR-TB, with over 80 percent occurring among foreign-born persons. TB programs ensure continuity of care so that drug resistance does not develop among persons with lack of access to consistent health care services. This may includes provision of wraparound services such as patient education. Co-infection with HIV occurs in six percent of patients reported with TB. The TB programs in the state health department are responsible for coordination and oversight of activities to ensure that objectives related to TB prevention and control are achieved. The Centers for Disease Control and Prevention (CDC) provides funding and technical assistance to help TB programs address the burden of MDR-TB in each state. A single case of MDR-TB may present a heavy financial toll on a TB program; thus support for better treatment options, rapid diagnosis, and expert management are essential to not only prevent and control MDR-TB in the U.S., but also to keep the cost of TB management reasonable.

OBJECTIVE 1.1: UPGRADE TB SURVEILLANCE TO ENSURE COMPLETE AND ACCURATE DETECTION OF DRUG-RESISTANT TB

CDC is upgrading surveillance systems for tracking drug-resistant TB cases in the U.S. to capture molecular test results and more detailed clinical information about each case, which will enable better tracking of disease burden, targeting of resources, and linkages to care and contact investigations. CDC is working with state TB programs to standardize reporting for drug-resistant TB cases, improve methods for transitioning to next generation sequencing for molecular detection, and refining methods for culture-based drug susceptibility testing.

OBJECTIVE 1.2: STRENGTHEN STATE AND LOCAL CAPACITY TO PREVENT TRANSMISSION OF DRUG RESISTANT TB

CDC is also finalizing metrics for tracking TB transmission using molecular epidemiology. This will enable epidemiologists to identify related cases of drug-resistant and drug-susceptible TB that have been recently transmitted to enable targeted intervention and thus prevent additional transmission.

OBJECTIVE 1.3: ENSURE THAT PATIENTS WITH DRUG-RESISTANT TB RECEIVE TREATMENT UNTIL CURED

Completion of treatment for those with MDR-TB is challenging on many levels. The activities CDC supports to meet this objective encompass a broad

A doctor screens a newly arrived Tibetan refugee child Monk for tuberculosis in Dehradun, India. ©2012 J'Belle Foster. Courtesy of Photoshare.

range of interventions implemented by state and local health departments with funding and assistance from CDC. These include the development and implementation of such strategies as electronic directly observed therapy to ensure day-to-day support MDR-TB patients require to successfully complete the long, and often debilitating, treatment regimen. CDC is also strengthening the data collection and analysis needed to monitor treatment completion. CDC is now collaborating with the Department of Health and Human Services' (DHHS) Supply Service Center to manage and maintain a mini-stockpile of TB drugs to have on hand in the event of manufacturer shortages that could result in interruption of treatment. The stockpile is composed of a small supply of drugs that would be necessary to protect TB patients and communities in the event of a time-limited manufacturing shortage. Additionally, the CDC's Division of Tuberculosis Elimination is evaluating a U.S.-Mexico case definition for the national TB surveillance system that can be measured using current performance indicators, including completion of therapy. State and local TB programs continue to be responsible for caring for uninsured TB patients until they complete therapy for drug susceptible and drug resistant TB.

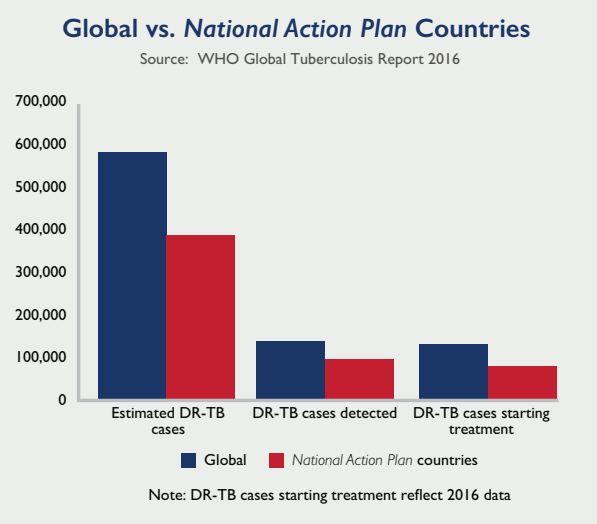
GOAL 2: IMPROVE INTERNATIONAL CAPACITY AND COLLABORATION TO COMBAT MULTIDRUG-RESISTANT TUBERCULOSIS

As the lead U.S. Government agency for global TB management efforts, the U.S. Agency for International Development (USAID) is working to reach every person with TB, cure those in need of treatment, and prevent new TB infections. In 2015, the most recent year for which complete data are available, there were an estimated 580,000 new cases of DR-TB globally. Of these estimated cases, only 132,120 (23 percent) were detected by National TB Programs (NTPs); of this total, almost 125,000 (22 percent) were enrolled for treatment. Unlike the high treatment success rates for TB, the detection of MDR-TB cases remains unacceptably low and only 52 percent of those put on treatment finish successfully. This means that of the 580,000 estimated TB cases, only 11 percent are enrolled in appropriate treatment regimens with a successful outcome. The *National Action Plan* will roll out new tools and approaches to dramatically address this issue in the highest burden MDR-TB countries. The main focus of Goal 2 is on 10 high MDR-TB countries[1] that make up more than 60 percent of the global MDR-TB burden.

There were an estimated 368,000 new cases of MDR-TB in the 10 prioritized *National Action Plan* countries, with 93,201 detected and 76,565 enrolled on treatment. Without success in these 10 prioritized *National Action Plan* countries, the global MDR-TB epidemic cannot be controlled. In 2016, more than 80,000 patients were enrolled in appropriate treatment programs, which puts these countries on track to reach the 2017 milestone of having at least 25 percent of all estimated MDR-TB patients in treatment. While this is a positive first step, a significantly increased effort will be required to achieve all milestones included in the *National Action Plan*. The substantial differences between each country's ability to detect and treat MDR-TB will significantly affect their ability to reach our future milestones.

1 Burma, China, India, Indonesia, Kazakhstan, Nigeria, Pakistan, Philippines, South Africa, and Ukraine

FIGURE 1: DR-TB Burden, Detection and Treatment Cascade



During the first year of the *National Action Plan*, USAID led the implementation of activities aimed at addressing these gaps, with CDC playing a collaborative role in key areas.

OBJECTIVE 2.1: IMPROVE ACCESS TO HIGH-QUALITY, PATIENT-CENTERED DIAGNOSTIC AND TREATMENT SERVICES

Expanding and increasing access to better quality TB diagnosis and treatment services are essential components of the *National Action Plan*. From

the patient's perspective, TB screening, diagnosis and treatment processes can be time-consuming, inconvenient, and expensive. Since all undiagnosed or untreated persons with TB are at risk of spreading the disease within their communities, timely detection and treatment are critical to stop the vicious circle of TB transmission. Yet, according to WHO, in 2015 more than 75 percent of all TB cases and just over 40 percent of DR-TB cases went undiagnosed or unreported. Scaling up and improving case detection methods, diagnostic capacities, and treatment options would have a significant impact on reducing the global TB burden and thus, the burden of drug resistant TB. These options must be adapted to meet patients' needs to be successful.

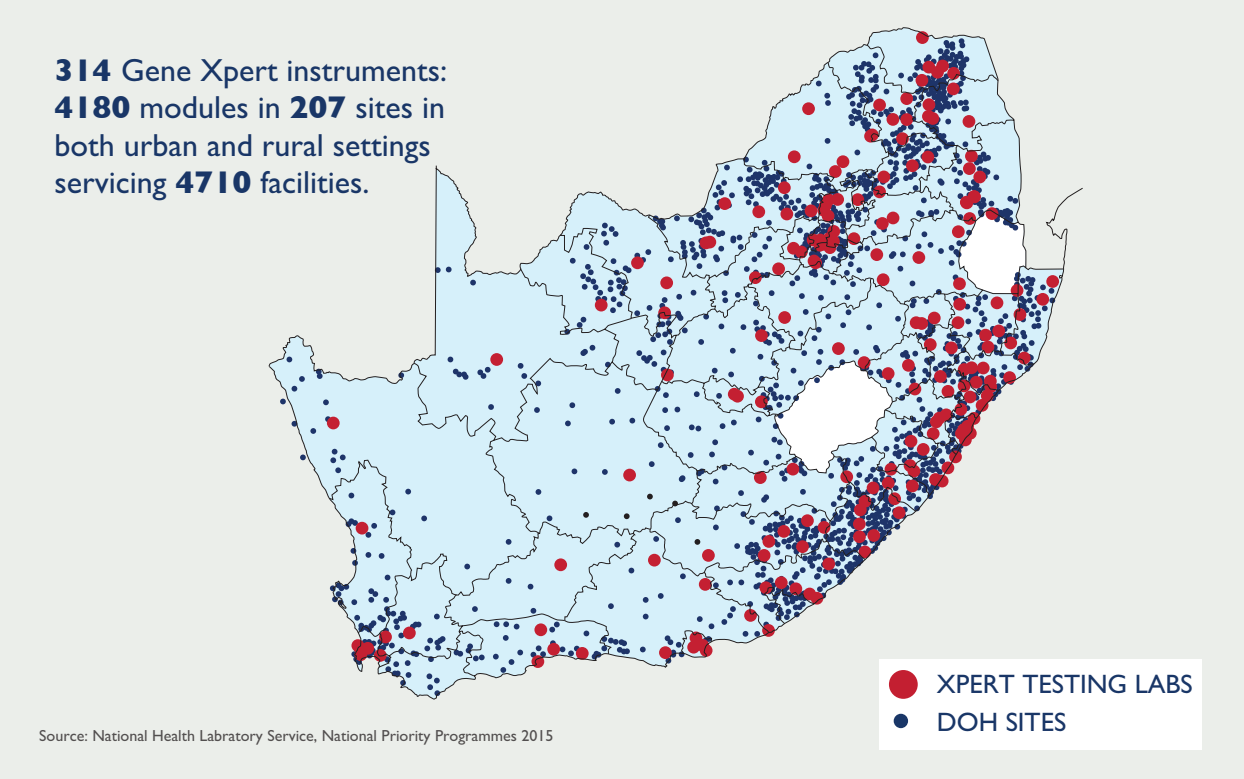
Any person exposed to TB can become infected, but it most often affects the poorest populations. While TB treatment may be offered at no cost to patients, it can still drive families further into poverty because many patients must take off work and travel far from home to receive medication. Additionally, people suffering from TB face stigma and discrimination. Care based on patient-centered models improves access to TB screening, diagnostic and treatment services and can significantly improve treatment outcomes. For example, patients are more likely to complete their treatment if they can receive it at home. Patient-centered models can include community-based treatment, ambulatory MDR-TB programs, increased screening at local and remote facilities and strengthening national and regional diagnostic networks. Improving access to high-quality, patient-centered diagnostic and treatment services ensures that NTPs have the capacity to reach every person with TB, cure those in need of treatment, and prevent the spread of disease and new infections.

GeneXpert: One step closer to a point-of-care diagnostic

GeneXpert is a diagnostic tool that tests sputum samples for the presence of TB. The introduction of GeneXpert revolutionized TB diagnosis and care because it is more accurate than current testing methods and detects difficult-to-diagnose forms of TB, such as drug-resistant TB and HIV-associated TB, in less than two hours at more accessible decentralized facilities. Accurately diagnosing drug resistant and HIV-associated TB at the first patient interaction improves treatment outcomes and reduces the spread of infectious TB to families and communities.

Cartridges prepared for Xpert MTB/RIF (tuberculosis) testing at the Quezon Institute in Manila, Phillipines. ©2013 Michael Tran. Interactive Research and Development. Courtesy of Photoshare.

FIGURE 2: National distribution of GeneXpert in South Africa's Department of Health sites



Sub-objective 2.1.1: Strengthen the capacity of national TB laboratory networks to diagnose TB and MDR-TB

USAID and CDC have worked with *National Action Plan* countries to develop comprehensive National TB Strategic Plans that address provision and placement of TB and MDR-TB laboratory services at each level, an important step in planning much needed improvements to the overall laboratory network to find cases earlier and stop TB transmission. Mapping of diagnostic networks is also underway in several countries to lay the groundwork for upcoming comprehensive mapping that will be conducted in the *National Action Plan* countries. The U.S. Government is working with the Global Laboratory Initiative (GLI) to promote best practices and accelerate scale up of MDR-TB diagnostics in priority countries. In Nigeria, USAID and CDC developed an operational framework for assessing TB laboratory and diagnostic networks in March 2016 using tools adapted during a USAID-led comprehensive international review of Nigeria's TB diagnostic network. This review resulted in revisions to the DR-TB diagnostic algorithm and the framework represents a key step toward prioritizing and planning laboratory strengthening and monitoring which will contribute to the *National Action Plan*. The framework will be adapted for use in additional *National Action Plan* countries.

South Africa's National TB Program has introduced and scaled up use of Xpert with technical assistance from USAID and CDC. The number of health facilities with an Xpert machine has quickly increased since 2012, reaching 309 sites in 2015 to achieve national coverage. Due to the availability of Xpert, the number of patients screened for TB has significantly increased, with 196,783 people screened in 2015.

Sub-objective 2.1.2: Expand and strengthen national MDR-TB care and treatment capacity to optimize the use of current and novel regimens

In early 2016, the first new major DR-TB treatment guidelines released by WHO dramatically shortened the length of the treatment regimen. In addition to the approval of bedaquiline (BDQ) and delamanid (DLM) for the treatment of MDR-TB, this is one of the most critical steps for improving MDR-TB treatment outcomes and adherence globally. Following the release of the guidelines, USAID ramped up support to countries to ensure the implementation guidance was rapidly available through innovative learning and communication platforms. This guidance will help countries plan, implement, and introduce the shortened treatment regimen and new TB drugs for MDR-TB more rapidly. USAID is also supporting the introduction and roll-out of BDQ through a public-private partnership with Janssen Pharmaceuticals Inc., the pharmaceutical arm of Johnson & Johnson. To date, 43 countries have ordered BDQ through the partnership, with several countries placing subsequent orders and scaling up their treatment plans.

Sub-objective 2.1.3: Strengthen TB/MDR-TB surveillance and monitoring systems

The analysis of accurate and timely data is a cornerstone of the response to disease outbreaks and is necessary to inform interventions to reduce the burden of disease throughout the population. USAID and CDC are working together with NTPs and other key partners, such as disease surveillance programs, to improve the data on which the TB and MDR-TB programs are based and to improve understanding of the location and distribution of disease. A large amount of information on MDR-TB global surveillance is available due to early support from USAID to WHO 20 years ago, as highlighted in a 2016 *New England Journal of Medicine* Special Report.[2] USAID and CDC support ongoing collection and analysis of data on all forms of TB, including prevalence surveys and drug resistance in countries where the burden is highest. CDC is supporting multiple efforts to improve TB surveillance in China, including an inventory study designed to identify the extent to which the disease is under-reported and overall coordination of multiple data systems that include information about TB.

Sub-objective 2.1.4: Improve the global availability and affordability of quality-assured, second-line drugs and improve country-level procurement and supply chain management systems

Ensuring that countries have access to affordable, high-quality TB treatment is a global challenge, especially with regard to the second-line drugs needed to treat drug resistant TB. USAID works closely with the Global Drug Facility (GDF) to support the continued

2 *New England Journal of Medicine* http://www.nejm.org/doi/full/10.1056/NEJMsr1512438#t=article

BEDAQUILINE DONATION PROGRAM

Bedaquiline, the first of a new class of FDA approved drugs to treat TB in more than 40 years, brings new hope to patients fighting MDR-TB with little to no other treatment options.

The bedaquiline donation program is an innovative public-private partnership between USAID and Janssen Therapeutics of Johnson & Johnson. The donation of bedaquiline, combined with technical support provided by USAID, will enable patients in nearly 100 countries to access this life-saving medication and fight MDR-TB.

development and maintenance of a global supply of affordable, quality-assured second-line drugs. USAID continues to ensure critical MDR-TB drugs are available and quality assured. Over the last year, USAID assisted in developing and securing the availability, affordability and quality of two critical MDR-TB drugs. In addition, USAID has worked with GDF to re-design the global Strategic Rotating Stockpile (SRS) of second-line drugs for the treatment of MDR-TB to ensure it is functioning efficiently and effectively. The SRS is a critical element in the global response to MDR-TB because most of the drugs are orphan products with low global volumes. The SRS allows countries to have quick access to the medications to ensure uninterrupted continuity of treatment for patients at an affordable price.

OBJECTIVE 2.2: PREVENT MDR-TB TRANSMISSION

The most important steps in preventing MDR-TB transmission are timely detection and treatment of all forms of TB and use of infection control interventions at facilities that diagnose and treat TB. USAID is working with NTPs and partners to promote patient-centered care aimed at ensuring the timely diagnosis and treatment. Additionally, USAID and CDC support NTPs to implement interventions to reduce transmission at the facility level.

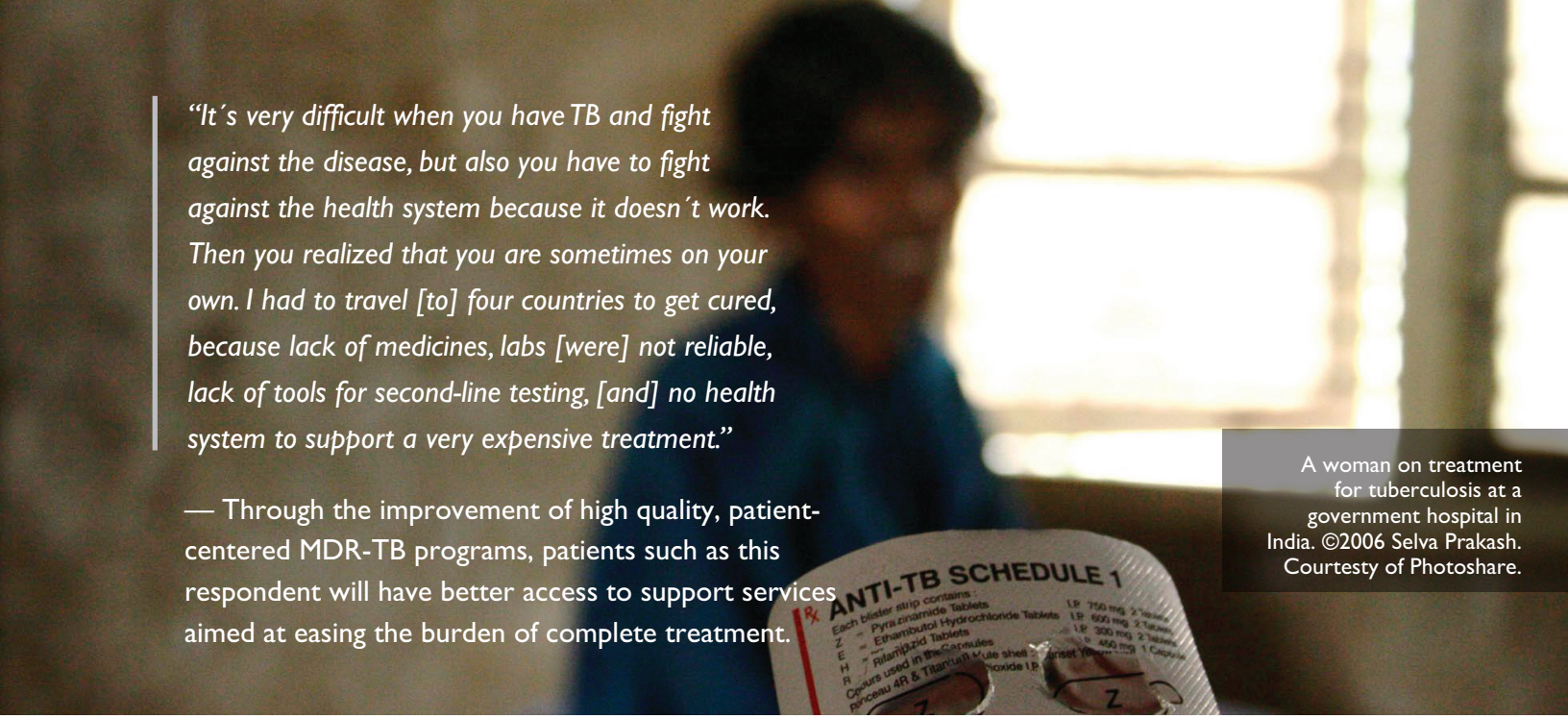
Sub-objective 2.2.1: Improve access to high-quality, patient-centered MDR-TB services

Standard MDR-TB treatment regimens range from 18-24 months and require patients to return to health facilities on a regular basis. Patients often experience debilitating side effects and can become disabled after completing treatment, for example, they may experience permanent hearing loss. To address this challenge, USAID has developed an ancillary care package designed to define essential services needed to support patients during treatment. Over the past year, USAID conducted a survey among stakeholders to gather information on the challenges patients face during MDR-TB treatment so that programs can better respond to their needs.

The MDR-TB ancillary care package will be launched in 2017 in four *National Action Plan* countries to help TB programs improve patient-centered services, such as nutrition support, transport vouchers and psychosocial services, for MDR-TB patients. By addressing the needs of patients beyond medications, the ancillary care package will help countries provide a comprehensive patient-centered MDR-TB treatment approach that will increase treatment adherence and consequently decrease MDR-TB transmission.

Stop TB Partnership
GLOBAL DRUG FACILITY
TB PROGRAMME

The Global Drug Facility (GDF) was established in 2001 by the Stop TB Partnership as a unique pooled procurement system, with the goal of expanding access to and the availability of high-quality TB drugs. The GDF mechanism provides countries with technical assistance in TB drug management and pharmacovigilance and assists with the procurement of low-cost of TB drugs. Since inception over $1.1 billion of TB commodities have been procured through GDF in over 137 countries for over 25 million adults and 1.3 million children.



"It´s very difficult when you have TB and fight against the disease, but also you have to fight against the health system because it doesn´t work. Then you realized that you are sometimes on your own. I had to travel [to] four countries to get cured, because lack of medicines, labs [were] not reliable, lack of tools for second-line testing, [and] no health system to support a very expensive treatment."

— Through the improvement of high quality, patient-centered MDR-TB programs, patients such as this respondent will have better access to support services aimed at easing the burden of complete treatment.

A woman on treatment for tuberculosis at a government hospital in India. ©2006 Selva Prakash. Courtesy of Photoshare.

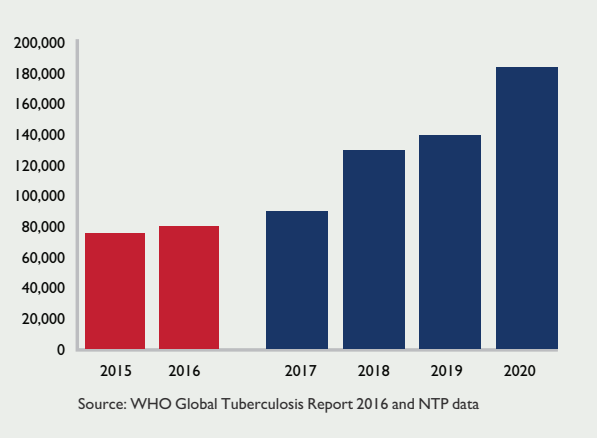
Sub-objective 2.2.2: Enhance adherence to TB and MDR-TB treatment

Given the unacceptably low MDR-TB treatment success rates throughout the world, there is an urgent need to identify practical tools for health care providers to determine whether or not patients are able to complete difficult treatment regimens. In addition to the ancillary support package described above, USAID has worked with partners to develop a case management and review system that will allow providers to assess short term treatment outcomes and side effects, as well as specific patient needs, on a routine basis. Ongoing analysis of TB and MDR-TB treatment will provide insights on the barriers to successful completion and help providers to identify where support is needed the most and who is at the highest risk of unfavorable outcomes.

Sub-objective 2.2.3: Prevent the transmission of TB and MDR-TB with health care facilities

Poor infection control in health care facilities where people with TB receive in- and out-patient care is responsible for spreading drug-resistant TB. To address this challenge, USAID and CDC are supporting a wide array of interventions to improve infection control and reduce the risk of transmission in these settings. For example, USAID has supported the development of quality infection control guidelines in *National Action Plan* priority countries. All guidelines are based on WHO recommendations and evidence-based approaches. CDC has developed a toolkit to identify key gaps in infection control practices and implement continuous quality improvement (BASICS), which is being implemented and rolled out in Nigeria, China and India.

FIGURE 3: *National Action Plan* Enrollment Results and Targets



Source: WHO Global Tuberculosis Report 2016 and NTP data

GOAL 3: ACCELERATE BASIC AND APPLIED RESEARCH AND DEVELOPMENT TO COMBAT MULTIDRUG-RESISTANT TUBERCULOSIS

The National Institutes of Health (NIH) has a mission to fund and conduct domestic and international biomedical research on TB. Within NIH, the National Institute of Allergy and Infectious Diseases (NIAID) is the lead institute for TB research, complemented by programs supported through other Institutes and Centers. This broad engagement provides opportunities to contribute strategically to key areas of science underpinning the discovery of new vaccines, drugs and diagnostics, as well as to conduct and support studies to identify product candidates and prepare them for clinical evaluation. Many research projects highlight the synergy between U.S. Government agencies' TB activities. For example, international projects NIH supports, such as its Tuberculosis Research Units (TBRU) and observational international research cohorts (RePORT) benefit from investments made by USAID, CDC and other U.S. Government agencies. Strategies and tools developed with NIH support may also be evaluated or implemented through USAID and CDC programs. NIH contributes to TB product development through a variety of funding mechanisms. Since many funders support global TB R&D, NIH officials and scientists ensure that U.S. Government investments are optimally applied and complement other U.S. Government or international programs. To facilitate coordination, NIH, USAID and CDC also participate in the WHO-led Funder's Forum for TB R&D and have spearheaded the development of a comprehensive Funders' Compendium to guide access to project support.

OBJECTIVE 3.1: INCREASE OPTIONS FOR PREVENTING ACTIVE TB, LATENT TB INFECTION, AND TB TRANSMISSION

Due to the complexity of the host/pathogen interactions underlying the progression of latent MTB infection to active TB disease, developing new preventive strategies requires a thorough understanding of the biological mechanisms and dynamics of TB, strategic support of critical product development, and clinical testing activities. Effective products and care strategies that specifically prevent transmissible forms of the disease are expected to have a significant impact on personal and public health, and their development requires multidisciplinary partnerships and collaborations.

Sub-Objective 3.1.1: Advance research and development of novel vaccines

Building on a robust and broad TB portfolio of extramural grants awarded to external institutions and intramural projects conducted by NIH scientists, NIH issued new funding opportunities in 2016 to study topics critical to the development of novel TB vaccines, including host responses during MTB infection, immune evasive strategies employed by the pathogen, and mechanisms underlying the transition to active disease. Findings from current NIH-funded biomedical studies will inform how these host responses can be leveraged for design of new vaccines and other preventive strategies, including host directed therapy. NIH supported studies also are defining biological markers that indicate whether or not a person is protected from infection or disease. These funding

opportunities complement ongoing NIH support for a variety of vaccine and adjuvant approaches. NIH continues to provide various resources to the research and product development community to facilitate transition of basic biomedical research findings into candidate products. These resources include microbial, biochemical and immunological reagents, bioinformatics tools and technologies to support data integration, and animal testing services and clinical trials capacity. These resources also contribute to the development of more predictive animal models and clinical trials to study the safety and efficacy of vaccine candidates. During the reporting period, NIH conducted workshops and seminars for academic and product development scientists and presented posters to discuss key issues and programs in TB host/pathogen interactions, their relevance for vaccines and preventive strategies, and opportunities for accessing NIH resources. NIH staff also participated in discussions with other key funders/supporters of TB R&D and engaged with product developers to ensure that resources are optimally aligned to fill key gaps in vaccine development.

U.S. Government-supported research has contributed to our understanding of how the pathogen subverts the immune system and repeatedly causes disease without the host developing natural immunity. This understanding is critical for the development of vaccines and will require continued, proactive interaction and collaboration with product developers and academic institutions and will continue beyond the current reporting year.

Sub-Objective 3.1.2: Support the development of methodologies to prevent transmission and development of TB and MDR-TB

In addition to biomedical basic and translational R&D activities necessary for new product development, U.S. Government agencies (USAID, CDC, and NIH) engage in patient-oriented public health research to inform prevention, treatment, and management of TB. Strategies under investigation during 2016 included shorter courses of more effective therapies and treatment schedules for persons latently infected with MTB and effectiveness of prophylactic treatment to protect contacts of patients with MDR-TB. CDC is assessing an enhanced infection control intervention package for its impact in reducing TB transmission in health care facilities and communities and supporting a project that uses active cough surveillance, temporary isolation and tailored treatment to prevent the spread of MDR-TB in hospitals and other congregate settings. In 2016, USAID initiated studies to evaluate a three month, once-a-week treatment intended to prevent the development of drug-sensitive TB after MTB infection in HIV-infected individuals. In addition, NIH is conducting a Phase III clinical trial of ultra-short-course of rifapentine and isoniazid for the prevention of active TB in HIV-infected individuals with latent TB infection.

Each country and community affected by TB presents unique challenges and opportunities for intervention. While U.S. Government support has contributed to the development of novel strategies to prevent transmission, evidence of their effectiveness and appropriateness will require additional studies and continued investment.

OBJECTIVE 3.2: IMPROVE THE DIAGNOSIS OF DRUG-RESISTANT AND DRUG-SUSCEPTIBLE LATENT AND ACTIVE TB

Rapid and accurate diagnosis of latent MTB infection and TB disease is the cornerstone of TB care and control programs in the U.S. and worldwide. A variety of technologies are being developed and evaluated in countries where TB is endemic to confirm or rule out active TB and to quickly determine which antibiotics will constitute the most effective treatment regimen. Diagnosis of latent MTB infection

offers the opportunity to provide patients with preventive therapy and to lower their immediate risk of developing active, transmissible TB. Diagnostic development requires unique collaborations among multiple partners since biological markers need to be identified and combined with engineered technologies, and then evaluated for their contribution to specific diagnostic algorithms.

Sub-Objective 3.2.1: Support the development of new tools and approaches for detection of drug-resistant TB

NIH currently supports research on a broad and diverse range of technologies and approaches aimed at improving the identification of drug-sensitive and multidrug-resistant/extensively drug-resistant TB, as well as the identification of human biomarkers suitable to determine whether a person has MTB infection and may be at risk for developing active TB disease. Whole genome sequencing of strains of MTB isolated from patients all over the world continues to yield data to characterize the genetic diversity, evolution and patterns of drug resistance of the pathogen. NIH and CDC continue to support and participate in collaborations among international researchers to sequence and process genomes of MTB isolated from patients in Africa, Asia, Europe, Latin America and the Middle East. Data from several thousand bacterial isolates are continuously being integrated into global databases benefiting the development of molecular diagnostic technologies. To facilitate integration of promising new diagnostics at the most impactful stage of patient care, U.S. Government agencies (NIH, USAID, and CDC) also support clinical performance and feasibility testing of new tools. During the first year of the *National Action Plan*, a variety of funding announcements were made available by NIH to the R&D community to facilitate development of diagnostic relevant technologies.

A challenge for the development of genetic technologies for detection of drug-resistant TB is the relationship between genetic mutations, extent of resistance and response to therapy. This is an expanding area of research and requires continued collaboration among clinicians, public health programs, bioinformatics specialists and diagnostic developers.

Sub-Objective 3.2.2: Support research to identify biological markers to help detect latent TB and progression to active TB in children and adults

NIH expanded its Tuberculosis Research Unit (TBRU) to four centers in 2014, studying latency and persistence of TB in individuals and endemic countries. During this reporting period, ongoing studies focused on elucidating human and bacterial factors that may indicate who is at highest risk for developing TB and why some individuals are able to control the infection. CDC-supported clinical trial sites participate in these and other studies that are identifying biological markers for improved detection of latently infected persons. In collaboration with NIH, CDC contributes to the Consortium for Tuberculosis Biomarkers (CTB2) which may speed the clinical trials of new drugs and contribute to the search for biomarkers that will help predict or identify progression from infection to disease. NIH is expanding its programs to include targeted biomarker identification studies for pediatric TB. During the first year of the *National Action Plan*, NIH contributed to an international publication that describes biological markers in the blood of individuals with latent TB infection, an important accomplishment that may provide better ways to predict who is at risk of progressing to TB disease[3]. In addition, NIH co-sponsored a comprehensive analysis of publicly available human gene expression datasets to identify a diagnostic signature of active tuberculosis from blood

3 *Lancet*, http://dx.doi.org/10.1016/S0140-6736(15)01316-1)

samples. This identified three genes that distinguished individuals with active TB from healthy controls, which could be used to aid diagnosis and to monitor treatment response[4].

The discovery of biological markers indicating latent infection and risk of developing active TB requires collaboration with and participation of volunteers from communities in TB-endemic countries. Robust longitudinal clinical cohorts are being established in India, Brazil, Indonesia, South Africa, China and the Philippines that have the potential to serve as study sites for targeted, integrated and well-coordinated research programs to better understand the regional differences in the TB epidemics and serve as platforms for new research programs.

4 *Lancet Respir Med*: http://www.sciencedirect.com/science/article/pii/S2213260016000485

OBJECTIVE 3.3: IMPROVE TREATMENT OPTIONS FOR DRUG-SUSCEPTIBLE AND DRUG-RESISTANT TB

While effective drugs and regimens exist to treat drug-sensitive and drug resistant TB, these regimens are lengthy, prescribed in a standard way rather than tailored to the drug susceptibility profile of the infecting strain of MTB, and often cause temporary or life-long side effects in patients. Because improving treatment options for TB requires engagement across the full spectrum of TB research, from basic science to implementation, U.S. Government agencies are contributing multiple kinds of support, expertise and research to provide short, medium and long term improvement of TB care. To provide improvements

IMPROVING THE USE OF A FLUOROQUINOLONE ANTIBIOTIC FOR TREATMENT OF MDR-TB

When used as part of second-line therapy for MDR-TB, fluoroquinolone antibiotics, particularly levofloxacin, gatifloxacin and moxifloxacin, have consistently improved treatment outcomes. Of these, levofloxacin shows the least serious side effects. However, the most efficacious and well-tolerated oral dose of levofloxacin as part of a standard second-line treatment regimen had not been established in standard clinical trials. To address this question, NIH is funding a Phase 2 clinical trial[5] to investigate the amount of drug circulating in the blood of patients who take different oral doses of levofloxacin and how these amounts are related to elimination of MTB in their sputum. Results from this study have the potential to indicate the best oral dose of levofloxacin recommended for patient treatment. This trial leverages resources from multiple U.S. Government partners, including NIH-funded Grant U19-AI100805[6], parallel enrollment through CDC's TB Trials Consortium Study 32, and infrastructure in Peru and South Africa built with NIH, CDC and USAID support. The participating pharmaceutical company, MacLeods Pharmaceuticals in Mumbai, India, is the regulatory sponsor. This trial highlights how U.S. Government investment in public health research infrastructure in TB-endemic countries made it possible to initiate multi-disciplinary, multi-national collaborations. These collaborations can be utilized to help generate knowledge to improve treatment recommendations for MDR-TB.

5 https://clinicaltrials.gov/ct2/show/NCT01918397

6 https://projectreporter.nih.gov/project_info_description.cfm?aid=8544616

in therapy to patients, studies are being conducted to optimize the use of current drugs. At the same time, new therapies are being evaluated in the field and innovative research is in place to identify better treatments and produce new drug candidates.

Sub-Objective 3.3.1: Improve the use of existing TB drugs for treatment of drug-susceptible and drug-resistant TB

U.S. Government agencies (USAID, CDC, and NIH) are conducting studies to assess the utility and effectiveness of several regimens that may result in fewer serious side effects and/or shorter treatment durations for patients with MDR-TB. This includes studies to investigate whether existing antibiotics can be administered at different doses to improve treatment of TB. NIH is contributing to these activities by supporting studies designed to improve understanding of the pharmacological basis of action for current first and second-line TB drugs, and to explore whether other antibiotics can be repurposed for TB. USAID is supporting the STREAM (Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB) study, a randomized clinical study that is evaluating the efficacy and safety of a nine month MDR-TB treatment regimen composed of existing TB drugs. These studies also contribute to capacity building with other nations' TB programs and help ensure that the most recent scientific findings are integrated with treatment policies.

Sub-Objective 3.3.2: Enhance knowledge to enable optimal and safe use of newly registered TB drugs

In 2012 and 2014, biomedical R&D in TB resulted in the licensure of new classes of drugs for the first time in decades. The integration of these new drugs into existing regimens to replace or improve therapy requires efficacy and safety studies to ensure that treatment is effective and that patients benefit from new drugs. During this reporting period, several ongoing clinical trials were supported to determine whether the newly registered TB drugs BDQ-DLM can safely be administered with other second-line TB drugs. NIH is planning a study to determine whether BDQ and DLM may be used together safely for the treatment of MDR-TB, and is conducting a trial to evaluate the pharmacokinetics, safety, and tolerability of DLM in combination with optimized second-line drugs for treatment of MDR-TB in HIV infected and uninfected children. Furthermore, additional studies were supported to determine whether novel combinations of these drugs can be used for a shorter duration of treatment for drug resistant TB. Such studies include the second phase of the USAID's supported STREAM study which is evaluating safety and efficacy of two treatment regimens using BDQ to replace or reduce exposure to injectable and their associated side effects. As new drugs licensed for TB roll out, clinical trials must be conducted to evaluate how they perform in combination and determine what side effects may occur.

Sub-Objective 3.3.3: Develop novel drugs and shorter regimens to treat drug-resistant TB and improve the selection of drug candidates for clinical trials

Development of new chemical entities requires a thorough understanding of the biology of MTB, where it resides in organs, and how best to target drugs to these locations for maximum efficacy. In the first year of *National Action Plan* implementation, NIH continued to support all aspects of basic and translational research, including the provision of preclinical and clinical resources to product development partners aimed at filling the pipeline of new drugs and to assist in their transition to clinical trials and registration. NIH continues to encourage and support rational, pharmacologically driven approaches to drug discovery, development of animal models, regimen selection and clinical trial design to

improve the state of the science of TB drug discovery and lower risks for product developers. NIH scientists continue to make advances in drug discovery through participation in global drug development consortia, which are emerging as effective models for academic/pharmaceutical collaborations.

While significant innovation has occurred and important research discoveries have the potential to improve TB therapy, turning new knowledge into promising new approaches will require long-term investment and sustained research partnerships among U.S. Government agencies, academia, not-for-profit and for-profit organizations.

OBJECTIVE 3.4: INCREASE CAPACITY TO CONDUCT BIOMEDICAL AND CLINICAL RESEARCH ON TB IN TB-ENDEMIC COUNTRIES

Research studies involving human volunteers are the cornerstone of applied biomedical research and require close collaboration with TB-endemic countries to be successful. To ensure that U.S. Government investments in biomedical research have tangible benefits for communities worldwide, NIH, CDC and USAID continue to support partnerships with local scientists and universities, as well as bilateral programs with governments to advance research capacity building and investigator training. The need to engage countries with a significant burden of TB to support all aspects of research is articulated in the third pillar of WHO's End TB Strategy. Because general infectious disease training benefits scientists who conduct TB research by improving their research and clinical skills, numerous NIH funding opportunities for training were issued during the reporting period that are not specifically directed toward TB, but will have positive benefits for TB programs. To help facilitate applications for NIH funding opportunities, NIH continues to provide training in grant writing, financial administration, bioethics and implementation research, particularly through its ongoing Human Heredity and Health in Africa (H3Africa) program. Infrastructure developed with USAID and CDC support is leveraged by local scientists in international research projects and collaborations in NIH-supported grants.

CONCLUSION

During the first full year of the *National Action Plan*, U.S. Government agencies made a significant contribution to addressing the challenges posed by drug-resistant TB in the United States and globally, working with NTPs, technical partners and other key stakeholders to improve screening, diagnosis and treatment services at home and abroad. While major challenges remain in countries where the burden is highest, first-year results are promising in terms of enrollment on second-line treatment and strengthening health systems to support the ongoing response. All year one milestones were achieved. The U.S. Government in collaboration with key technical partners will continue to build on our existing platforms to bring about sustainable impact and save lives. By continuing the well-coordinated implementation of the *National Action Plan,* the U.S. Government will work with states and international partners to further reduce the burden of global TB.

Mycobacterium Tuberculosis. Credit: NIAID.

APPENDIX: MILESTONES AND ADVANCES, GOAL 1

Objective 1.1 Upgrade TB surveillance to ensure complete and accurate detection of drug-resistant TB	
Year 1 Milestones	**Advances**
Identify common language and protocols for reporting drug resistance to anti-TB drugs.	▪ Development of standardized reporting underway.
Objective 1.2 Strengthen state and local capacity to prevent transmission of drug-resistant TB	
Year 1 Milestones	**Advances**
Work with the National TB Controllers Association to develop surge capacity for controlling transmission of drug resistant TB.	▪ Finalizing new metrics for tracking TB transmission that can be applied to drug resistant TB as well as drug-sensitive TB.
Explore ways to increase staffing at State and local health departments during TB contact investigations.	▪ Unable to address surge capacity, increased staffing, or development of other new tools without additional funding.
Objective 1.3 Ensure that patients with drug-resistant TB receive treatment until cured	
Sub-objective 1.3.1 Explore the potential use of a national TB stockpile to ensure the availability of TB medicines and screening tests	
Year 1 Milestones	**Advances**
CDC will explore the development of a National TB Stockpile that could store and rotate TB supplies that can be ordered by State and local TB programs.	▪ Stockpile, managed by the DHHS Supply Service Center, is operational in the event of a national drug shortage.
Sub-objective 1.3.2 Explore options for providing care for persons with MDR-TB or XDR-TB who do not have a medical home	
Year 1 Milestones	**Advances**
CDC and State and local TB programs will work together on plans for completion of therapy once MDR-TB or XDR-TB patients are released from a hospital.	▪ Clinical trial design to evaluate electronic directly observed therapy (eDOT) for treating TB disease.
Sub-objective 1.3.3 Improve completion of therapy for persons who travel in or out of the United States while on treatment for TB disease	
Year 1 Milestones	**Advances**
CDC and others will explore ways to strengthen medical management of transnational TB disease cases.	▪ Evaluation of binational (U.S.-Mexico) case definition for surveillance system in progress.

APPENDIX: MILESTONES AND ADVANCES, GOAL 2

Objective 2.1 Improve access to high-quality, patient-centered diagnostic and treatment services	
Sub-Objective 2.1.1 Strengthen the capacity of national TB laboratory networks to diagnose and treat TB and MDR-TB	
Year 1 Milestones	**Advances**
USAID and CDC will work with up to 10 countries to develop comprehensive national TB/MDR-TB laboratory strategic plans addressing provision and placement of services at each level, as part of each country's National TB Strategic Plan.	▪ The NTPs of Burma, India, Indonesia, Kazakhstan, Pakistan, Philippines, South Africa, and Ukraine have National Laboratory Strategic Plans that address TB and MDR-TB. ▪ USAID and CDC developed a framework for assessing TB laboratory and diagnostic networks in multiple countries using tools adapted through a USAID-led comprehensive international review of Nigeria's TB diagnostic network in March 2016. This framework is a key step towards prioritizing and planning laboratory strengthening and monitoring. ▪ In Nigeria, USAID and CDC developed an operational plan/work plan in response to the TB diagnostic network assessment, including revisions to the DR TB diagnostic algorithm. ▪ Mapping of diagnostic networks is also underway in several countries in Africa, and U.S. Government is working with the Global Laboratory Initiative (GLI) and GLI Africa to promote best practices and accelerate scale up of MDR-TB diagnostics in priority countries.
Sub-Objective 2.1.2 Expand and strengthen national MDR-TB care and treatment capacity to optimize the use of current and novel regimens	
Year 1 Milestones	**Advances**
USAID will work with up to five countries to introduce a new MDR-TB drug (BDQ, DLM, or both).	▪ USAID supported NTPs in Burma, India, Indonesia, Kazakhstan, Pakistan, Philippines and South Africa to introduce BDQ for treatment of MDR-TB. This support encompassed a wide variety of activities; for example, revision of NTP treatment guidelines to include BDQ, training of clinicians on the appropriate use of BDQ, coordination with pharmaceutical regulatory agencies to facilitate importation and development of systems to monitor adverse events. Additionally, Burma and South Africa introduced DLM in limited research conditions.
USAID will work with one country to scale-up use of BDQ or DLM.	▪ South Africa is an early adopter of BDQ for treatment of drug-resistant TB. Since the inception of the BDQ program, almost 4,000 patients have received the drug as part of their treatment regimen. With technical assistance from USAID, the NTP in South Africa has greatly increased access to the drug.
Sub-Objective 2.1.3 Strengthen TB and MDR-TB surveillance	
Year 1 Milestones	**Advances**
USAID will enhance tracking of MDR-TB disease burden and surveillance data for dissemination.	▪ USAID developed and provides ongoing financial and technical support to WHO's Tuberculosis Monitoring and Evaluation Unit to perform annual collection and analysis of TB data, including routine data on MDR-TB in over 200 countries.
CDC will assist one country in the completion of an inventory study to determine gaps in the TB surveillance system.	▪ CDC supported China's National Center for TB (NCTB) to conduct a pilot inventory study in nine provinces, review lessons learned, and develop a standardized process for routinely matching laboratory, hospital, and surveillance records to identify TB cases that were not reported to the national system. In 2016, CDC assisted the NTP in the Philippines in planning its national inventory study to measure the level of under-reporting of diagnosed TB cases to the surveillance system. USAID also provided technical assistance to the state TB program in Lagos, Nigeria, to plan an inventory study.
Sub-Objective 2.1.4 Improve the global availability and affordability of quality-assured, second-line drugs and improve country-level procurement and supply chain management	
Year 1 Milestones	**Advances**
USAID will support the continued development and maintenance of a global supply of affordable, quality-assured, second-line drugs to ensure access to life-saving drugs.	▪ USAID has provided ongoing support to the GDF to maintain a strategic rotating stockpile of second-line medications that NTPs can access to ensure timely and affordable supply of second-line drugs at all times. The SRS is also available for emergency orders. The GDF is able to turn around requests to the SRS very quickly to ensure that patients can stay on life saving treatment. Additionally, USAID works with the GDF to improve procurement and distribution systems in countries.

Objective 2.2 Prevent MDR-TB Transmission	
Sub-Objective 2.2.1 Improve access to high-quality, patient-centered MDR-TB services	
Year 1 Milestones	**Advances**
USAID will work with up to 10 countries to validate and introduce a risk prioritization screening tool.	▪ In Burma, Indonesia, Kazakhstan, Nigeria and South Africa, USAID has implemented a risk prioritization tool to identify the important populations and screening strategies to maximize detection of additional TB cases that might not otherwise be found.
Sub-Objective 2.2.2 Enhance adherence to TB and MDR-TB treatment	
Year 1 Milestones	**Advances**
USAID will develop generic ancillary care packages (e.g., services and supplies not directly related to treatment, but which enable patients to continue therapy, such as pain or nausea medicine, food rations and supportive services) for MDR-TB patients.	▪ USAID has developed an ancillary care package to identify key services and interventions needed to support MDR-TB patients through the diagnosis and treatment processes. During the first year of the *National Action Plan*, USAID undertook a survey of patients, providers and technical partners to identify the key barriers to successful MDR-TB diagnosis and treatment.
USAID will develop a quality-care monitoring tool to improve the rates of treatment adherence in TB programs.	▪ USAID worked with partners to develop the expanded cohort review tool, a standardized process for routinely assessing patients on TB treatment to identify challenges to treatment adherence and generate an action plan for overcoming barriers to successful treatment completion.
Sub-Objective 2.2.3 Prevent the transmission of TB and MDR-TB within health care facilities	
Year 1 Milestones	**Advances**
USAID will work with up to 10 countries to develop quality national infection control guidelines.	▪ Building on the existing TB portfolio, USAID has supported the development of quality national infection control guidelines in Burma, India, Indonesia, Kazakhstan, Nigeria, Pakistan, South Africa and Ukraine. All infection control guidelines are based on WHO recommended standards and a subset integrate the USAID supported FAST strategy, as requested by NTPs.
CDC will develop a tool for assessing implementation and impact of TB infection control interventions.	▪ CDC designed an intervention package and toolkit to identify and address TB infection control gaps, implement routine monitoring and evaluation, and ensure continuous program improvement called Building and Strengthening Infection Control Strategies for TB Prevention (TB BASICS) in health care facilities. ▪ In Nigeria, CDC and USAID provided support to improve infection control practices, including incorporating TB BASICS into national guidelines and curricula for health care workers, which is being scaled-up nationwide. In India, CDC is supporting the establishment of a novel Airborne Infection Control Unit to assess, implement and evaluate infection control interventions in health care facilities treating TB using the TB BASICS tool. CDC/PEPFAR is also supporting the scale-up of infection control interventions using the TB BASICS tool in antiretroviral therapy (ART) Centres throughout India.

APPENDIX: MILESTONES AND ADVANCES, GOAL 3

Objective 3.1 Increase options for preventing active TB, latent TB infection, and TB transmission	
Sub-Objective 3.1.1 Advance research and development of novel vaccines	
Year 1 Milestones	**Advances**
NIH will expand its dialogue among basic scientists, funders, and vaccine developers to identify novel strategies for vaccine development, encourage research related to vaccine design, and educate partners about resources available to contribute to vaccine development.	▪ Workshop on March 7-8, 2016 on "The Impact of Mycobacterial Immune Evasion on Protective Immunity: Implications for TB Vaccine Design." ▪ Poster presentation on clinical resources for TB at the June 21-23, 2016 TB Summit in London, and on preclinical R&D resources at the EMBO Conference on Tuberculosis in September 2016 in Paris. ▪ Established the Intramural TB Research Initiative (NITBRI) and held kick-off symposium on June 27, 2016 "New Approaches to Combating Tuberculosis. Leveraging NIH Intramural TB Research for the Global Effort." ▪ Participated in the second "Collaboration for TB Vaccine Discovery" (CTVD) meeting in July 2016, hosted by the Bill and Melinda Gates Foundation in Seattle, WA. ▪ Workshop on September 28-29, 2016 on "Developing Functional Assays for TB Vaccine R&D: An Aeras/NIAID Workshop." ▪ Ongoing participation in R&D discussions/leveraging resources with TB vaccine development product development partnerships and for-profit organization.
NIH will continue to support studies to map the diversity of immune responses required for vaccine efficacy.	▪ TB Research Portfolio (https://report.nih.gov/categorical_spending.aspx). ▪ Recent funding opportunities: - PAR-15-360: Characterization of Mycobacterial Induced Immunity in HIV-infected and Uninfected Individuals (R21). - PAR-16-254: Mechanisms of Mycobacterial-Induced Immunity in HIV-Infected and Uninfected Individuals to Inform Innovative Tuberculosis Vaccine Design (R01). - RFA-AI-16-079: Partnerships for Development of Vaccines to Prevent *Mycobacterium tuberculosis* Infection and/or Tuberculosis Disease (R01). - RFA-AI-16-047: Partnerships for Structure-Based Design of Novel Immunogens for Vaccine Development (R01). - RFA-AI-16-034: Partnerships for Countermeasures Against Select Pathogens (R01) ▪ Clinical Challenge Model for Assessment of Human TB Immunity (https://clinicaltrials.gov/ct2/show/NCT01868464).
Sub-Objective: 3.1.2 Support the development of methodologies to prevent transmission and development of TB and MDR-TB	
Year 1 Milestones	**Advances**
USAID will initiate at least one study to evaluate the impact and cost-effectiveness of at least one TB prevention measure on TB and MDR-TB transmission in different care settings in high-burden TB countries.	▪ USAID: Weekly High dose isoniazid and rifapentine. ▪ Periodic Prophylaxis for TB ($WHIP_3TB$) (https://www.clinicaltrials.gov/ct2/show/NCT02980016). Other U.S. Government-supported ongoing or planned clinical trials/studies: ▪ NIH: Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx) (http://www.impaactnetwork.org/studies/IMPAACT2003B.asp). ▪ CDC/PEPFAR: Evaluation of an Enhanced Tuberculosis Infection Control Intervention in Healthcare Facilities in Vietnam and Thailand (EnTIC) (www.clinicaltrials.gov/ct2/show/NCT02073240). ▪ NIH: Evaluating the Pharmacokinetics, Tolerability, and Safety of Once-Weekly Rifapentine and Isoniazid in HIV-1-Infected and HIV-1-Uninfected Pregnant and Postpartum Women with Latent Tuberculosis Infection (www.clinicaltrials.gov/ct2/show/NCT02651259). ▪ NIH: Finding and Treating Unsuspected and Resistant TB to Reduce Hospital Transmission (R01-AI112748). ▪ NIH: Cell Phone Video Directly Observed Therapy to Monitor Short Course LTBI Treatment (https://www.clinicaltrials.gov/ct2/show/NCT02641106). ▪ NIH: Innovative Interdisciplinary Approaches to Sustainable Airborne Infection Control (D43-TW9379).

	▪ NIH: Impact of Effective Chemotherapy on Transmission of Drug-Resistant Tuberculosis (R01-AI099603). ▪ NIH: Development and Clinical Evaluation of a Lyophilized, Thermostable Tuberculosis Vaccine (HHSN272201400041C). ▪ DoD: Planning a randomized clinical trial of proof-of-concept of BCG immunization to prevent MTB infection in healthy adults.
Objective: 3.2 Improve the diagnosis of drug-resistant and drug-susceptible latent and active TB	
Sub-Objective: 3.2.1 Support the development of new tools and approaches for detection of drug-resistant TB	
Year 1 Milestones	**Advances**
NIH will continue to support large-scale sequencing efforts to map the global genetic diversity of drug resistance in MTB to define genetic markers that can be included in diagnostic tests to improve the identification of MDR-TB and XDR-TB.	▪ TB portal at "Pathosystems Resource Integration System" (PATRIC) (https://www.legacy.patricbrc.org/portal/portal/patric/TB). ▪ Center of Excellence for Translational Research – Integrated discovery and development of innovative TB Diagnostics (U19-AI109755).
NIH will continue to support non-clinical and clinical studies to evaluate early-stage diagnostic tests and will educate partners about resources available to contribute to diagnostic development.	▪ RFA-AI-16-034: Partnerships for Countermeasures Against Select Pathogens (R01).
USAID will initiate an evaluation of at least one promising (preferably point-of-care) TB and MDR-TB diagnostic tool in adults and children.	▪ Planning an evaluation of the Cepheid "OMNI" point of contact diagnostic platform in low resource settings.
CDC will initiate baseline assessments of the entire diagnostic and treatment cascade for MDR-TB to identify factors that affect the time between first patient contact, diagnosis, and treatment initiation.	▪ Supported an assessment of diagnostic and treatment cascade for MDR-TB in Mumbai to identify factors affecting time between first patient contact, diagnosis and treatment initiation. CDC in collaboration with the government of India has initiated interventions to address barriers to diagnosis and improve treatment initiation and adherence.
Sub-Objective 3.2.2 Support research to identify biological markers to help detect latent TB and progression to active TB in children and adults	
Year 1 Milestones	**Advances**
NIH will continue to support biomedical research studies to identify novel biological markers and signatures to detect the likelihood of progression from infection to active TB.	▪ A blood RNA signature for tuberculosis disease risk: a prospective cohort study (*Lancet*, http://dx.doi.org/10.1016/S0140-6736(15)01316-1). ▪ Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis (*Lancet Respir Med*, http://www.sciencedirect.com/science/article/pii/S2213260016000485). ▪ PET CT Identifies Reactivation Risk in Cynomolgus Macaques with *Latent M. tuberculosis* (*PLoS Pathogen*, http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1005739).
NIH, CDC, and USAID will expand clinical cohorts in TB-endemic countries to study correlates of progression from TB infection to active disease.	▪ NIH's TBRU-N (https://www.niaid.nih.gov/research/tuberculosis-research-units-network). The CDC-supported Kenya Medical Research Institute (KEMRI) in Kisumu is a clinical site for a TBRU that is enrolling a clinical cohort to identify immune markers that predict progression from latent TB infection to active disease. ▪ NIH's RePORT network. ▪ CDC's TB Trials Consortium, in collaboration with NIH, is contributing specimens to a collaborative repository (CTB2 http://www.tbbiorepository.org/about-ctb2) to contribute to the search for markers of progression from latent TB infection to active TB disease and to monitor treatment response.

Objective: 3.3 Improve treatment options for drug-susceptible and drug-resistant TB	
Sub-Objective 3.3.1 Improve the use of existing TB drugs for treatment of drug-susceptible and drug-resistant TB	
Year 1 Milestones	**Advances**
NIH will discuss innovative and pharmacologically-based strategies for the development of new, shorter regimens with the research and product development community and will educate partners about resources available to contribute to drug development.	▪ Co-hosted two workshops on "Optimization of Oxazolidinones for Use in TB Drug Regimens" with the Stop TB Partnership's Working Group on New Drugs (http://www.newtbdrugs.org/) in July and December 2016. ▪ Poster presentation on clinical resources for TB at the June 21/23, 2016 TB Summit in London, and on preclinical R&D resources at the EMBO Conference on Tuberculosis in September 2016 in Paris. ▪ NITBRI held kick-off symposium on June 27, 2016 "New Approaches to Combating Tuberculosis. Leveraging NIH Intramural TB Research for the Global Effort." ▪ Provided preclinical resources to the Lilly TB Drug Discovery Initiative to study the antiparasitic drug Nitazoxanide for use against MTB.
USAID will initiate an assessment of new methods or packages of care to enhance treatment success.	▪ USAID has developed an ancillary care package to identify key services and interventions needed to support MDR-TB patients through the diagnosis and treatment processes. During the first year of the *National Action Plan*, USAID undertook a survey of patients, providers and technical partners to identify the key barriers to successful MDR-TB diagnosis and treatment. The results of this survey were used to draft a simple tool that will allow providers to assess the needs of specific patients and prioritize support activities that best fit those needs, with the ultimvate aim of improving treatment outcomes.
USAID and CDC will continue to support ongoing studies in adults to assess shorter MDR-TB regimens using existing TB drugs.	▪ Provided technical assistance to initiate a clinical protocol assessing feasibility, effectiveness, and safety of the newly recommended 9-month treatment regimen for MDR TB in the National TB Control Program of the Philippines. ▪ CDC: a multi-site clinical trial to assess the bactericidal activity of specific anti-TB drugs to guide treatment decisions when susceptibility test results differ between closely related drugs, which occurs in a large fraction of patients. This study should inform clinical and laboratory practice and guidelines and may expand options for treatment for certain patients. ▪ USAID is leading a clinical trial to evaluate the efficacy and safety of oral 9-month regimen and 6-month regimen containing new drug BDQ for the treatment of MDR-TB (STREAM II study).(https://www.clinicaltrials.gov/ct2/show/NCT02409290). ▪ NIH: Efficacy and Safety of Levofloxacin for the Treatment of MDR-TB (Opti-Q) (https://www.clinicaltrials.gov/ct2/show/NCT01918397). ▪ NIH: Trial of High-Dose Rifampin in Patients With TB (HIRIF) (https://www.clinicaltrials.gov/ct2/show/NCT01408914).
Sub-Objective 3.3.2 Enhance knowledge to enable optimal and safe use of newly registered TB drugs	
Year 1 Milestones	**Advances**
USAID will support the evaluation of new and shorter TB regimens containing novel anti-TB drugs in adults.	▪ USAID is co-sponsoring "A Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 Plus Linezolid in Subjects With Drug Resistant Pulmonary Tuberculosis (NiX-TB, https://clinicaltrials.gov/ct2/show/NCT02333799). ▪ USAID is leading a clinical trial to evaluate the efficacy and safety of oral 9-month regiment and 6-month regimen containing new drug BDQ for the treatment of MDR-TB (STREAM II study). Other U.S. Government-supported ongoing or planned clinical trials/studies: ▪ NIH: A Trial of the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, among Participants Taking Multidrug Treatment for Drug-Resistant Pulmonary Tuberculosis. (https://clinicaltrials.gov/show/NCT02583048). ▪ NIH: Evaluating the Pharmacokinetics, Safety, and Tolerability of Bedaquiline in HIV-Infected and HIV-Uninfected Infants, Children, and Adolescents With Multidrug-Resistant Tuberculosis (https://clinicaltrials.gov/ct2/show/NCT02906007). ▪ NIH: Planning a clinical trial to evaluate the Safety, Tolerability, and Initial Efficacy of Linezolid Combined with Delamanid and Optimized Background Therapy (OBT) for the Treatment of Multidrug-Resistant Tuberculosis.

Sub-Objective 3.3.3 Develop novel drugs and shorter regimens to treat drug-resistant TB and improve the selection of drug candidates for clinical trials	
Year 1 Milestones	**Advances**
NIH will support novel therapeutic approaches for the treatment of TB, such as host-directed therapeutics (HDT).	▪ RFA-AI-16-034: Partnerships for Countermeasures Against Select Pathogens (R01) ▪ Supporting four awards under the Initiative "Host Directed TB Therapy: New Approaches (UH2/UH3). ▪ Preclinical TB drug discovery services are currently accessed by more than 100 research groups annually in more than 30 countries. ▪ Exploratory research in immune targeted adjuncts to TB chemotherapy. ▪ Collaborating agency in the Bill and Melinda Gates Foundation's Drug Accelerator Program. ▪ Optimizing Combination Therapy to Accelerate Clinical Cure of Tuberculosis (P01 AI123036). ▪ New chemical entities are entering preclinical studies through the NIH supported Lilly TB Drug Discovery Partnership (https://www.niaid.nih.gov/research/partnership-eli-lilly).
Objective: 3.4 Increase capacity to conduct biomedical and clinical research on TB in TB-endemic countries	
Year 1 Milestones	**Advances**
USAID will create an inventory (map) of potential sites and initiate needs-based procurement of equipment to prepare study sites.	▪ Through the TREAT TB project has identified new potential sites in five countries that could be strengthened to implement the STREAM II study.
NIH, CDC and USAID will provide training in clinical research to high-burden TB countries with the capacity to conduct biomedical clinical research to facilitate their active participation in trials and studies.	▪ CDC: Providing technical assistance to the KEMRI in Kisumu for oversight and conduct of therapeutic, preventative, diagnostic and implementation clinical trials for TB and TB/HIV. ▪ NIH: Targeted training programs relevant for TB and HIV/TB are supported under seven framework programs. ▪ NIH Supported Funding Opportunities: - PAR-17-057 – Global Infectious Disease Research Training Program (D43) - PAR-16-279/2801281 – NIH HIV Research Training Program for Low- and Middle-Income Country Institutions (D43) - PAR-16-082 – International Bioethics Research Training Program (D43) - PAR16-081 – International research Ethics Education and Curriculum Development Awards (R25) - RFA-AI-16-082/083 – Revision Applications for U.S. South Africa Program for Collaborative Biomedical Research (various funding mechanisms) - PAR-15-291 – International Research Scientist Development Award (IRSDA) (K01) - PAR-15-292 – Emerging Global Leader Award (K43) - PAR-14-080 – International Research in Infectious Diseases, Including AIDS (IRIDA) (R01) ▪ NIH: Fogarty International Center held a "Tuberculosis Network Meeting" on June 21, 2016 to expand their dialog among international trainees and grantees supported through their training grants.
NIH will expand opportunities for funding of biomedical clinical research in TB-endemic countries.	▪ Expanding Regional, Observational TB Cohorts in high burden TB countries to facilitate collaborative, clinical research. *Clin Infect Dis* (https://academic.oup.com/cid/article/61/suppl_3/S155/356154/RePORT-International-Advancing-Tuberculosis). ▪ H3 Africa Program (http://www.h3africa.org/).