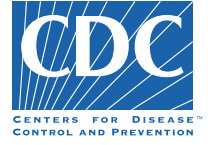




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National Institute of  
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# COMBATING MULTIDRUG-RESISTANT TUBERCULOSIS: YEAR FOUR OF THE NATIONAL ACTION PLAN REPORT

YEAR FOUR  
REPORT



# TABLE OF CONTENTS

ACRONYMS AND ABBREVIATIONS .....	2
INTRODUCTION .....	3
GOAL 1: STRENGTHEN DOMESTIC CAPACITY TO COMBAT MULTIDRUG-RESISTANT TUBERCULOSIS .....	5
GOAL 2: IMPROVE INTERNATIONAL CAPACITY AND COLLABORATION TO COMBAT MULTIDRUG-RESISTANT TUBERCULOSIS .....	7
GOAL 3: ACCELERATE BASIC AND APPLIED RESEARCH AND DEVELOPMENT TO COMBAT MULTIDRUG-RESISTANT TUBERCULOSIS .....	13
CONCLUSION .....	22

On the Cover: Doctors consulting on a TB diagnosis at the National TB Hospital in Almaty, Kazakhstan.  
Photo Credit: Victor Magdeyev for USAID

# ACRONYMS AND ABBREVIATIONS

<b>ACTG</b>	AIDS Clinical Trials Group	<b>NIAID</b>	National Institute of Allergy and Infectious Diseases
<b>BDQ</b>	Bedaquiline	<b>NIH</b>	National Institutes of Health
<b>CDC</b>	Centers for Disease Control and Prevention	<b>NTP</b>	National Tuberculosis Program
<b>CLICQ</b>	Clinic-Lab Interface Continuous Quality Improvement	<b>NTMSC</b>	National TB Molecular Surveillance Center
<b>DLM</b>	Delamanid	<b>PHOENIX</b>	Protecting Households on Exposure to Newly Diagnosed Index Multidrug-resistant Tuberculosis Patients
<b>DOT</b>	Directly Observed Therapy	<b>R&amp;D</b>	Research and development
<b>DR-TB</b>	Drug-Resistant Tuberculosis	<b>RePORT</b>	Regional Prospective Observational International Research for Tuberculosis Cohorts
<b>DS-TB</b>	Drug-Susceptible Tuberculosis	<b>STR</b>	Shorter treatment regimen
<b>eDOT</b>	Electronic Directly Observed Therapy	<b>TB</b>	Tuberculosis
<b>FDA</b>	U.S. Food and Drug Administration	<b>TB DIAH</b>	Tuberculosis Data, Impact Assessment and Communications Hub
<b>GDF</b>	Global Drug Facility	<b>TBTC</b>	Tuberculosis Clinical Trials Consortium
<b>GeneXpert</b>	Xpert® MTB/RIF	<b>TBRU-N</b>	Tuberculosis Research Unit Network
<b>HDT</b>	Host-Directed Therapy	<b>UNGA</b>	United Nations General Assembly
<b>HHS</b>	U.S. Department of Health and Human Services	<b>UNHLM</b>	United Nations High-Level Meeting
<b>HIV</b>	Human Immunodeficiency Virus	<b>USAID</b>	United States Agency for International Development
<b>IMPAACT</b>	International Maternal Pediatric Adolescent AIDS Clinical Trials Network	<b>WGS</b>	Whole-Genome Sequencing
<b>IPC</b>	Infection prevention and control	<b>WHO</b>	World Health Organization
<b>J2SR</b>	USAID's Journey to Self-Reliance	<b>WRD</b>	World Health Organization-Recommended Rapid Tuberculosis Diagnostic
<b>MDDR</b>	Molecular Detection of Drug Resistance	<b>XDR-TB</b>	Extensively Drug-Resistant Tuberculosis
<b>MDR-TB</b>	Multidrug-Resistant Tuberculosis		
<b>MTB</b>	Mycobacterium Tuberculosis		
<b>National Action Plan</b>	<i>National Action Plan for Combating Multidrug-Resistant Tuberculosis</i>		

# INTRODUCTION

Tuberculosis (TB) remains the world's deadliest infectious disease. In 2019, an estimated ten million (estimated range, 8.9–11.0 million) people developed this severely debilitating disease, and 1.4 million (estimated range, 1.3–1.5 million) died as a result.<sup>1</sup> TB is caused by *Mycobacterium tuberculosis* (Mtb), a bacterium that may be transmitted through the air from person to person. It is present in every country in the world, including the United States, which reported an estimated 9,000 cases of the disease in 2019.<sup>2</sup> TB is both curable and preventable, but treatment is lengthy (at least six months) and requires multiple drug combinations; failure to treat the disease properly can lead to drug-resistant TB (DR-TB).

As defined in this report, DR-TB refers to TB that is resistant to at least rifampicin (RR-TB), the most-effective drug required to treat TB. Multidrug-resistant TB (MDR-TB) is resistant to both isoniazid (the second-most vital drug) and rifampicin, and extensively drug-resistant TB (XDR-TB) is resistant to both rifampicin and isoniazid, and other drugs used to treat MDR-TB. Developing any type of DR-TB often has devastating effects on not only the individuals with the disease, but also their families and communities. DR-TB patients endure long, toxic, and complicated regimens; the anxiety of potentially transmitting the disease to loved ones; and the loss of income because of illness, isolation, and stigma. Beyond the impact on individuals, families, and communities, DR-TB poses a significant global health-security threat. DR-TB outbreaks wreak havoc on health care systems and economies due to high treatment costs and the strain the disease puts on providers, institutions, and national health budgets.

In 2019, an estimated 465,000 people developed DR-TB globally.<sup>3</sup> Of these, it is estimated that 78 percent had MDR-TB. However, only 44 percent of those DR-TB cases were

diagnosed and reported to National TB Programs (NTPs), of which 86 percent were enrolled on treatment—equating to only 38 percent of the estimated DR-TB cases in 2019.<sup>4</sup> While an increasing number of individuals with DR-TB have successfully completed treatment, progress has been slow. To drive further progress, intensified and consistent efforts are needed to ensure the development and rapid uptake of improved diagnostic methods, treatment regimens, and person-centered service-delivery models.

The percentage of U.S. DR-TB cases has remained stable for the last 20 years. In 2019 in the United States, 631 people developed DR-TB; among these, 90 people were diagnosed with MDR-TB and four with XDR-TB.<sup>5</sup> In the United States, treatment for DR-TB is difficult and costly. Among people who are treated for DR-TB, 73 percent require hospitalization, 37 percent require home isolation, 27 percent stop working, and nine percent die during treatment.<sup>6</sup> Many experience severe side effects, including depression and psychosis (19 percent), hearing impairment (13 percent), hepatitis (13 percent), kidney impairment (11 percent), loss of mobility (eight percent), vision impairment (seven percent), and seizures (one percent).<sup>7</sup> In the United States, the cost to treat DR-TB is extremely high: more than \$178,000 per case for MDR-TB, and \$553,000 per case for XDR-TB.<sup>8</sup> Preventing, diagnosing, and treating TB in the United States, as in the rest of the world, requires better options to diagnose and treat, accurately, rapidly, and successfully, every case of TB.

In December 2015, the U.S. Government released a plan to address the growing global TB crisis both 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

<sup>1</sup> World Health Organization *Global Tuberculosis Report, 2020*.

<sup>2</sup> U.S. Centers for Disease Control and Prevention *Reported TB in the United States 2019*.

<sup>3</sup> World Health Organization *Global Tuberculosis Report, 2020*.

<sup>4</sup> Ibid.

<sup>5</sup> U.S. Centers for Disease Control and Prevention *Reported TB in the United States 2019*.

<sup>6</sup> Ibid.

<sup>7</sup> Ibid.

<sup>8</sup> Ibid.

that builds on, and contributes to, the U.S. Government's [Global TB Strategy](#), as well as the World Health Organization's (WHO) [END TB Strategy](#) and the Stop TB Partnership's [Global Plan to End TB](#).

As outlined in the inaugural document, 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.

Since 2000, global efforts to ensure access to TB diagnosis, treatment, and care saved an estimated 60 million lives.<sup>9</sup> The U.S. Government is a leader in these efforts, working through its Departments and Agencies to support the implementation of, and research on, high-quality care, diagnostics, and treatment regimens. The [National Action Plan](#) is crucial to, and builds on, these efforts to support the successful treatment of TB and prevent the progression to DR-TB. In addition to increased efforts to diagnose, cure, and prevent MDR-TB, the [National Action Plan](#) works to increase the number of MDR-TB treatment initiatives in countries with the highest burden of DR-TB, with a target of a 25 percent increase by Year One, a 35 percent increase by Year Three, and a 50 percent increase by Year Five, as well as many other milestones in each of the three goals.

In September 2018, the United Nations General Assembly High-Level Meeting (UNHLM) on TB set the stage for high-level attention and action on TB. This meeting established the ambitious target of enrolling an additional 40 million people on TB treatment by 2022 (commonly referred to as 40x22), to include 1.5 million patients with DR-TB. To help countries achieve this target, the U.S. Agency for International Development (USAID) launched the Global Accelerator to End TB at the UNHLM. In support of USAID's Journey to Self-Reliance (J2SR)<sup>10</sup> framework, the Accelerator increases commitment and builds capacity of governments, civil society, and the private sector to accelerate countries' progress in reaching the global targets. Both the Accelerator and J2SR initiatives work together to help achieve the [National Action Plan](#) goals and milestones set for 2020.

This report outlines the progress made by U.S. Government Departments and Agencies toward the global targets and milestones of Year Five, the final year of the [National Action Plan](#). There were 106,888 individuals enrolled on DR-TB treatment in Year Four, a seven percent increase from the previous year. The U.S. Government's activities under the [National Action Plan](#) are critical to these efforts.

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<sup>9</sup> World Health Organization *Global Tuberculosis Report, 2020*.

<sup>10</sup> USAID's Journey to Self-Reliance is an orientation of strategies, partnership models, and program practices to achieve greater development outcomes and work towards a time when foreign assistance is no longer necessary.

# GOAL I: STRENGTHEN DOMESTIC CAPACITY TO COMBAT MULTIDRUG-RESISTANT TUBERCULOSIS

The U.S. Centers for Disease Control and Prevention (CDC), within the U.S. Department of Health and Human Services (HHS), leads a state-of-the-art national TB program for the United States, which has achieved one of the lowest TB rates in the world.

HHS/CDC's domestic TB program conducts clinical trials and epidemiologic research that contributes to guidelines and strategies for eliminating TB throughout the world; provides funding and technical assistance to assure TB programs meet national indicators guiding progress toward TB elimination; supports laboratory services including molecular detection of drug resistance and universal whole genome sequencing (WGS); and provides training and education for diagnosis, treatment, and prevention of TB disease and latent TB infection.

Following an increase that coincided with both the onset of the HIV epidemic and decreasing support and resources for programs to prevent and control TB, HHS/CDC and its partners established an aggressive strategy credited with reducing U.S. incidence of TB disease from 25,103 in 1993 to less than 9,000 in 2019.<sup>11</sup> However, TB in the United States still causes preventable suffering and death, particularly among ethnic and racial minorities. The U.S. TB case rate (2.7 cases per 100,000<sup>12</sup>) remains well above the elimination threshold of less than one case per million persons.

The percentage of MDR-TB cases in the United States has remained steady for more than 20 years, at approximately one percent of U.S. TB cases; the majority (greater than 90 percent) of these cases occur among non-U.S.-born persons.<sup>13</sup> The proportion of cases with reported mono-resistance to isoniazid has remained approximately nine percent over the last several years.<sup>14</sup>

Eighty-three percent of U.S. state TB programs are reporting difficulty in obtaining drugs for treating latent TB infection, drug-susceptible TB (DS-TB), and MDR-TB. These include rifapentine, ethambutol, rifampin (costs doubling), pyrazinamide, rifabutin, and moxifloxacin. DR-TB cases complicate efforts to treat and prevent TB and are extremely expensive for state and local TB programs to manage. A single case of MDR-TB costs far more to treat (\$178,000) than a DS-TB case (approximately \$20,000); thus, support for better treatment options, rapid diagnosis, and expert management are essential to prevent and control DR-TB in the United States. Because drug resistance can develop when a patient does not complete a full treatment regimen, TB programs must ensure continuity of care among persons with TB disease; this includes the provision of wraparound services, food and temporary housing, and patient education. U.S. state and local TB programs are responsible for TB elimination within their jurisdictions.

## OBJECTIVE I.I: UPGRADE TB SURVEILLANCE TO ENSURE COMPLETE AND ACCURATE DETECTION OF DRUG-RESISTANT TB

HHS/CDC upgraded the U.S. domestic TB surveillance system for reporting DR-TB cases to capture molecular test results and more-detailed clinical information about each case, this will enable better tracking of disease burdens, targeting of resources, and linkages to care and contact investigations. Working with state and local TB programs to identify common language and protocols, HHS/CDC developed a method for reporting the results of molecular drug susceptibility tests to provide standardization within the

<sup>11</sup> U.S. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report (MMWR) March 24, 2020.*

<sup>12</sup> Ibid.

<sup>13</sup> U.S. Centers for Disease Control and Prevention *Reported TB in the United States 2019.*

<sup>14</sup> Ibid.

National TB Surveillance System, and has added related data collection fields to its revised Report of Verified Case of TB (RVCT) form.

HHS/CDC has developed guidance for states to use for reporting these and other new variables in its updated TB surveillance system. The implementation of electronic links between clinical laboratories and TB surveillance programs at the federal, state, and local levels is also under way. Enhancing platforms for laboratory reporting of molecular drug susceptibility tests allows HHS/CDC to capture drug resistance results more quickly and completely.

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

In addition to expanding the collection of molecular drug susceptibility test result data, HHS/CDC now conducts universal WGS on isolates of Mtb gathered from newly diagnosed patients. HHS/CDC flags WGS results that may indicate recent transmission of DR-TB and DS-TB, which epidemiologists can use at the state and local levels to facilitate targeted interventions to prevent outbreaks. HHS/CDC shares such data with state and local jurisdictions in real time.

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

Completion of treatment for patients with DR-TB is challenging on many levels. HHS/CDC support for ensuring that patients complete TB therapy includes a broad range of interventions. HHS/CDC is currently analyzing data from a randomized controlled trial of electronic directly observed therapy (eDOT) conducted in collaboration with partners at the New York City Department of Health and Mental Hygiene's Bureau of TB Control. Using electronic technologies,

eDOT allows health providers to remotely monitor TB patients as they ingest their medication, either in real time or recorded. Because eDOT uses remote observation in lieu of clinic visits by the patient (e.g., over smartphone video), it can improve treatment adherence and be more cost-efficient than traditional in-person directly observed therapy (DOT). Benefits can include convenience for patients and staff, reduced staff travel cost and time, and prevention of exposure to other diseases such as COVID-19. HHS/CDC is also currently analyzing the economic benefit of eDOT.

Because the second-line drugs used to treat DR-TB are often available from only one manufacturer in the U.S., HHS/CDC, in collaboration with the HHS Supply Service Center, maintains a small stockpile of drugs to ensure TB programs can keep patients on critical treatment regimens if a manufacturing shortage arises. In 2019, HHS/CDC updated its inventory to reflect treatment guidelines recommending all-oral regimens for DR-TB therapy.

## **MOVING FORWARD**

HHS/CDC is monitoring the effects that COVID-19 is having on TB elimination efforts in the United States. Decreased ability to contact trace, provide DOT, and ensure prompt diagnosis because of the strains on healthcare, public health and laboratory systems could increase risk of acquisition and spread of MDR-TB. More than 90 percent of state and local TB programs have staff deployed to COVID-19 because of their expertise in contact tracing/surveillance, infection control, monitoring the health of people in home isolation, including use of eDOT, and clinical care and treatment.

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

As the lead U.S. Government Agency for global TB efforts, USAID works with HHS/CDC and other U.S. Government Departments and Agencies to reach every person with TB, cure those in need of treatment, and prevent the spread of new TB infections and the progression to active TB disease. Persistent challenges remain in the limitations of existing tools, as well as in-country capacity and systems to further DR-TB detection, treatment, and prevention efforts.

This Report for Year Four provides a progress update on the *National Action Plan* activities implemented in 2019. It also provides preliminary data on the 2019 DR-TB case detection and treatment initiation rates and finalized 2018 DR-TB data<sup>15</sup> for the ten *National Action Plan* priority countries.<sup>16</sup>

From 2018 to 2019, the *National Action Plan* countries recorded an approximate five percent increase in the number of people diagnosed, and seven percent increase in the number of people enrolled on treatment for DR-TB. Additionally, these countries had a 76 percent increase in patients enrolled on regimens containing bedaquiline (BDQ), and a 69 percent increase in DR-TB patients enrolled on shorter treatment regimens (STR) in Year Four.

**Table 1: Detection and Treatment of DR-TB from Year Three and Year Four<sup>17</sup>**

	DR-TB Detected	DR-TB Enrolled	Enrolled on BDQ Regimen	Enrolled on STR
<b>Globally in 2018</b>	<b>186,772</b>	<b>156,071</b>	<b>22,392</b>	<b>41,403</b>
<b>10 National Action Plan Countries in 2018</b>	<b>127,866</b>	<b>99,532</b>	<b>12,785</b>	<b>34,162</b>
<b>10 National Action Plan Countries in 2019</b>	<b>134,216</b>	<b>106,888</b>	<b>22,453</b>	<b>57,630</b>

<sup>15</sup> World Health Organization *Global Tuberculosis Report, 2019*.

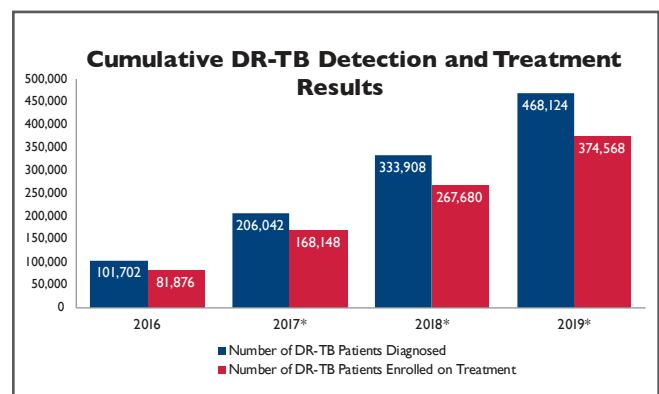
<sup>16</sup> National Action Plan countries: Burma, the People’s Republic of China, India, Indonesia, Kazakhstan, Nigeria, Pakistan, the Philippines, South Africa, and Ukraine.

<sup>17</sup> 2018 numbers have been updated from the Year 3 report, based on the latest information from WHO. 2019 data is subject to be updated similarly next year.

With the increase in resources in some of the *National Action Plan* countries for DR-TB, USAID and partner U.S. Government Agencies continue to assist countries in scaling up DR-TB case detection and treatment enrollment. Since the inception of the *National Action Plan*, the ten priority countries have prioritized rapid scale-up of GeneXpert, a molecular test, instrument capacity, and use and expansion of DR-TB testing. In 2019, 106,888 DR-TB patients were diagnosed and enrolled on treatment in the ten countries. This is a seven percent increase in the number of patients enrolled on treatment from Year Three. USAID continues to support active case-finding efforts for DR-TB in countries covered by the *National Action Plan*, with highlights of efforts in Nigeria and Burma included in this chapter.

While impressive, as DR-TB care is more complex than regular TB care, we are not on track to meet the Year Five target. Treating DR-TB requires more expensive medications, longer treatment regimens, dedicated treatment sites, trained medical personnel, measures for infection control, and a system for managing ambulatory patients with adverse events. Over the course of the *National Action Plan*, 468,124 individuals with DR-TB were detected and 374,568 were enrolled on treatment (Figure 1).

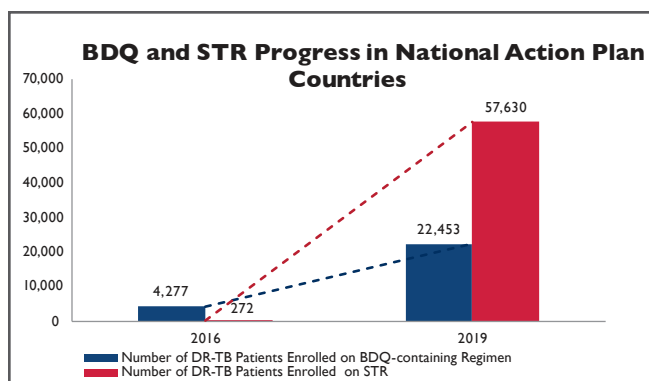
**Figure 1: Cumulative\* Detection and Treatment of DR-TB in Countries Covered by the National Action Plan, Year One to Year Four**





While significant progress has been made in the uptake of regimens containing BDQ and STR, USAID and partner U.S. Government Agencies are not on track to meet the 50 percent enrollment target for Year Five. During the implementation of Year One of the *National Action Plan*, only 4,277 DR-TB patients received BDQ treatments. In Year Four, the number increased to 22,453 DR-TB patients—a five-fold increase. In 2016, WHO introduced the shorter treatment regimen (STR), a safer, shorter treatment option for DR-TB patients. Initially countries were reluctant to scale-up the new regimen rapidly, but with USAID support, significant progress has been made. In 2016, only 272 DR-TB patients were enrolled on STR while in 2019, that number increased to 57,630 DR-TB patients—a 200-fold increase.

**Figure 2: Progress in Adopting BDQ and STR in Countries Covered by the *National Action Plan*, Year One to Year Four**



Despite the measurable progress made in DR-TB control, the proportion of patients who have been diagnosed and enrolled on treatment in 2019 is not on track to reach the Year Five targets of the *National Action Plan*. Furthermore, considering the negative impact of COVID-19 mitigation efforts on TB programs, it is unlikely that *National Action Plan* countries will meet the target of enrolling 50 percent of the total estimated DR-TB cases on treatment. To achieve these targets (and other targets listed in the *National Action Plan*) and mitigate against the COVID-19 impact, countries will need to mobilize additional resources, greater political will, and bold actions to control the DR-TB epidemic.

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

In Year Four, USAID and HHS/CDC provided assistance to NTPs and National TB Laboratory networks in the ten countries to increase procurement and installation of GeneXpert instruments and expand the algorithm for TB and DR-TB screening, in light of international recommendations. In addition, USAID worked with local partners to improve access to TB screening at the primary health care level, improve access to TB detection, and link detected patients to care and support. To improve the quality of DR-TB care, USAID has scaled-up implementation of the [DR-TB Care Package](#) and community-based DR-TB services, as well as improved pharmacovigilance<sup>18</sup> for TB. USAID remains committed to addressing treatment side effects across the *National Action Plan* countries. Through the BDQ donation program, USAID organized workshops on the detection, management, and reporting of drug-related adverse events. The workshops brought together NTP managers, clinicians, pharmacists, and representatives from drug regulatory authorities and resulted in the development of country-specific frameworks for pharmacovigilance. The results have been improved patient care and increased reporting of adverse events. Going forward, USAID will focus on strengthening NTPs' electronic reporting.

### SUB-OBJECTIVE 2.1.1: STRENGTHEN THE CAPACITY OF NATIONAL TB LABORATORY NETWORKS TO DIAGNOSE TB AND MDR-TB

In 2019, USAID continued strengthening the diagnostic capacity of TB laboratory networks by supporting diagnostic network assessments with NTPs and TB diagnostic networks to identify gaps and develop recommendations toward increasing access to high-quality TB detection at all levels. The diagnostic network assessments prioritize recommendations for achieving countries' National Strategic Plan (NSP) and End TB Strategy targets, including guidance on scale-up of the

<sup>18</sup> Pharmacovigilance is defined by WHO as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem."

WHO-recommended rapid TB diagnostic (WRD), the Xpert Ultra test, as the initial diagnostic test and universal drug-susceptibility test for persons with presumed TB.

Additionally, USAID and HHS/CDC has supported country activities in further strengthening diagnostic networks by: providing diagnostic technical support for NTP reviews; developing diagnostic network design processes, including mapping of diagnostic networks; standardizing specimen referral system tools to increase access to both GeneXpert as well as culture and drug susceptibility testing for all eligible individuals; evaluating the technical impact of the Cepheid GeneXpert buy-down agreement; developing and revising global guidelines regarding molecular assays for diagnosis of pulmonary and extrapulmonary TB in adults and children; and conducting assessments of readiness for reference laboratories to conduct second-line line-probe assays (SL-LPA). All of these efforts have increased countries' capacities to actively find more cases.

In Nigeria, HHS/CDC collaborated with the Ministry of Health (MoH) to scale up the Clinic-Lab Interface Continuous Quality Improvement (CLICQ) project. The CLICQ project works to actively identify and address the gaps in TB case-finding and treatment outcomes. The goals of CLICQ are to improve TB case finding and initiation of TB treatment among persons with signs or symptoms of TB, and to improve time-to-TB diagnosis and time-to-initiation of TB treatment for persons with confirmed TB. In China, HHS/CDC evaluated data-driven strategies to increase high-risk patient access to universal drug-susceptibility testing for improved TB and DR-TB bacteriological confirmation.

To continue strengthening regional quality of TB laboratories that provide drug sensitivity testing services for DR-TB surveillance, HHS/CDC continued supporting the provision of external quality-assurance materials to more than 1,000 testing sites across 24 countries in Africa and Asia and established four new, national, external quality-assurance programs across the African region to ensure accurate, reliable, and timely drug susceptibility testing results for patient impact and programmatic management

of DR-TB. HHS/CDC also supported TB reference laboratories conducting TB drug susceptibility testing by strengthening their quality management systems through the implementation of structured, mentorship-based quality management programs that lead to improved accuracy of test results and supported laboratories to work toward international accreditation.

In Burma, USAID has engaged non-government and private providers, including Ethnic Health Organizations (EHOs) and Ethnic and Community-Based Health Organizations (ECBHOs), and partnered with the private sector for mandatory case notification and to explore opportunities for expanding access to DR-TB diagnostics.

## **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 Year Four, USAID collaborated with NTPs and local and international partners to implement necessary changes in TB treatment guidelines and protocols quickly in nine out of the ten *National Action Plan* countries in order to scale up implementation of novel drugs and shorter treatment regimens. As a result, by the end of 2019, all ten countries implemented BDQ-containing regimens and enrolled approximately 22,500 DR-TB patients on treatment. To reduce the length of treatment,<sup>19</sup> USAID provided countries with technical assistance to scale up STR.<sup>20</sup> This technical assistance contributed to the significant progress made in the *National Action Plan* countries, including enrolling approximately 58,000 patients on such treatment regimens in nine countries (all *National Action Plan* countries except China). In December 2019, based on initial evidence from South Africa,<sup>21</sup> WHO recommended the all-oral treatment regimen for both long- and short-term regimens. To improve the safety and quality of care provided and consequently improve the long-term treatment outcomes, starting in 2020, USAID will embark on an ambitious plan to ensure that all DR-TB patients transition to all-oral treatment regimens.

<sup>19</sup> As of 2019, 20 months is the standard duration for treatment.

<sup>20</sup> The standard duration for STR is nine to 11 months.

<sup>21</sup> South Africa is one of the ten NAP priority countries.

### **SUB-OBJECTIVE 2.1.3: STRENGTHEN TB/MDR-TB SURVEILLANCE AND MONITORING SYSTEMS**

To end TB, improving recording and reporting systems and the analysis of TB data is a priority for USAID. In late 2018, former USAID Administrator Mark Green launched USAID's Global Accelerator to End TB. The Accelerator relies on standardized data collection to inform decisions. In 2019, USAID, directly and in collaboration with WHO, continued assisting *National Action Plan* countries in improving TB data systems for surveillance, monitoring, and evaluation. The TB Data, Impact Assessment, and Communications Hub (TB DIAH) Project, awarded by USAID, will be integral in ensuring the timely collection and analysis of more reliable TB data and analysis; TB DIAH will also assist USAID Missions in the implementation of an improved performance-based framework. On a global level, USAID has partnered with WHO in the collection, analysis, and reporting of annual TB data and statistics, including for the *National Action Plan* countries. The results of this work are published annually in the WHO Global TB Report and the open-source WHO Global TB database.

HHS/CDC also supported programs to strengthen DR-TB surveillance through the establishment of sequencing-based detection of mutations associated with DR-TB. In India, HHS/CDC worked to initiate the development of a national sample collection and laboratory referral network for sequencing-based detection of DR-TB for surveillance across the country. Additionally, in 2019, USAID augmented this work by ensuring that the five WGS sites in India are proficient in conducting WGS to predict drug resistance and strain lineage. With support from USAID, HHS/CDC also conducted two collaborative data-use workshops to engage and build capacity of local staff in Mumbai, India, to improve surveillance and quality, analysis, and use of program data for program improvement. In Tamil Nadu, India, HHS/CDC worked to support the formation of a sequencing-based, retrospective DR-TB database to better understand local mutations associated with DR-TB. In Nigeria, HHS/CDC began a Global Health Security Agenda (GHSA) collaboration with the Nigerian Federal Ministry of Health to establish sequencing-based surveillance of DR-TB patient isolates for enhanced epidemic monitoring and action for DR-TB disease control.

### **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**

As a key component of achieving the *National Action Plan* targets, USAID dedicates significant attention to ensuring equitable access to quality-assured second-line TB medications, a small and fragmented market. In 2019, USAID continued collaboration with, and support to, the Stop TB Partnership's Global Drug Facility (GDF); this resulted in the delivery of \$243 million worth of TB products to 121 countries, including \$194 million worth of medicines and \$49 million worth of diagnostics. In 2019, there was a 17 percent increase in the number of GDF-delivered shipments as compared to 2018, increasing from 1,755 to 2,061 shipments.

As part of the J2SR approach, the GDF assisted eight countries (adding two countries from 2017) in using their domestic funding to buy diagnostics through the GDF. The GDF also successfully implemented the USAID-Janssen Bedaquiline Donation Program by managing received orders of more than 45,000 treatment courses during the program's final five weeks in 2019. Additionally, the GDF coordinated the introduction of the newly available, child-friendly formulations of delamanid (DLM) for DR-TB treatment in children by working with partners to prepare countries, negotiating supply terms, and providing the medicines in 56 countries.<sup>22</sup> Building on its successful partnership with Janssen, USAID is focused on accelerating the detection and treatment of TB in children and supporting the introduction of the newly FDA-approved pediatric formulation of BDQ.

To ensure countries have uninterrupted access to TB products, the GDF significantly decreased shipment lead times from the standard six months to two months for 69 countries, and to four months for another 110 countries. The GDF conducted 41 missions to provide technical assistance to countries on procurement and supply planning, including five training sessions on quantification; this reflects a 28 percent increase, as compared to 2018, in the number of missions for technical assistance. To align with the latest

<sup>22</sup> While the U.S. Government agencies work to treat children with MDR-TB, currently data is not widely available across National Action Plan countries differentiating between child and adult MDR-TB cases.

WHO guidelines for DR-TB treatment, the GDF assisted 48 priority countries in the development and implementation of costed procurement and supply transition plans.

Lastly, the GDF facilitated the registration of 86 TB medicines in nine countries, including two *National Action Plan* countries, Ukraine and the Philippines.

## **OBJECTIVE 2.2: PREVENT MDR-TB TRANSMISSION**

To reduce DR-TB transmission at the local and global level, it is imperative to find TB cases early (before they become infectious), enroll all detected patients on treatment, and support treatment completion. In Year Four of the *National Action Plan*, USAID and HHS/CDC supported NTPs and other partners to: expand services to DR-TB patients and their families through the DR-TB Care Package; assist with the uptake of community- and home-based care; and provide further support in the introduction of digital tools in nine *National Action Plan* countries to improve DR-TB treatment adherence and monitoring.

### **SUB-OBJECTIVE 2.2.1: IMPROVE ACCESS TO HIGH-QUALITY, PATIENT-CENTERED MDR-TB CARE**

In Year Four, USAID worked closely with seven *National Action Plan* countries (Burma, India, Indonesia, Kazakhstan, Philippines, South Africa, and Ukraine) to expedite uptake of the TB risk prioritization screening tool. While WHO developed this tool for DS-TB case finding, countries have been successfully using it to detect more DS- and DR-TB patients. To improve DR-TB case management, countries are implementing regular site supervision and cohort-monitoring approaches, as well as utilizing WHO standards and benchmarks.

### **SUB-OBJECTIVE 2.2.2: ENHANCE ADHERENCE TO TREATMENT FOR TB AND MDR-TB**

The 55 percent global treatment success rate for DR-TB remains unacceptable to patients, families, and health providers. Since Year One of the *National Action Plan*, USAID has given greater attention to programs and activities focused

on improving treatment adherence, treatment support, and both medical and non-medical care. In 2016, USAID introduced the [DR-TB Care Package](#), a holistic package to support DR-TB patients who are receiving care. By the end of 2019, the package was expanded to nine *National Action Plan* countries.

In 2019, USAID continued the scale-up of digital solutions to improve treatment adherence and monitoring for DR-TB patients. The number of digital approaches—such as video directly observed therapy (VDOT), SMS reminders, pill boxes, phone applications, and others—was expanded in *National Action Plan* countries. In 2019, USAID/Burma partnered with private-sector providers to test “99DOTS”; the Philippines and Indonesia scaled up the application of digital tools for a larger cohort of DR-TB patients; and India expanded the portfolio of tools to include “99DOTS,” Medication Event Reminder Monitor System (MERM), virtual DOT (VDOT), and Operation ASHA (OP-ASHA).

### **SUB-OBJECTIVE 2.2.3: PREVENT THE TRANSMISSION OF TB AND MDR-TB WITHIN HEALTH-CARE FACILITIES**

In 2019, USAID worked with the *National Action Plan* countries to address TB and DR-TB transmission in facilities, improve effectiveness and quality of infection prevention and control (IPC) programs, and set up indicators and targets to measure the performance of those interventions. USAID provided targeted technical assistance through global consultations and meetings with *National Action Plan* countries to develop and implement TB IPC action plans, focusing on improving data collection, flow, and reporting to expand IPC programming in these countries. Additionally, USAID supported the development and release of a number of webinars on interventions for preventing TB transmission in health care facilities. Webinar topics included: IPC roadmap development; IPC roadmap implementation; the development of priority IPC indicators; reducing TB transmission among health-care workers; Finding cases Actively, Separating safely, and Treating effectively (FAST); and ultraviolet germicidal irradiation (UVGI). These webinars were shared with more than 260 NTP leaders, TB program managers, IPC professionals, and other clinical staff around the world, including stakeholders in *National Action Plan* countries.

In 2019, HHS/CDC worked directly with the NTPs in India and China to implement, monitor, and assess different models of infection control interventions. With support from USAID, HHS/CDC worked with the Municipal Corporation of Greater Mumbai (MCGM) in Mumbai, India, to embed a multi-disciplinary airborne infection control (AIC) unit, which provides baseline assessments for facilities, ongoing mentoring, and follow-up assessments to track AIC changes and improvements. The unit has expanded to work in 13 wards and has completed its fourth round of follow-up assessments at MCGM health facilities. HHS/CDC is also now working with the Municipal Corporation of Chennai, another megacity in India, which has also started a pilot for AIC implementation with the intent to expand it citywide. HHS/CDC is collaborating with India's Central TB Division to adopt and adapt lessons learned from these experiences and to expand the implementation of TB infection control widely through the National TB Elimination Program.

HHS/CDC, in collaboration with Chinese National TB Program (NCTB) and China CDC has completed implementation of TB infection control interventions in six counties (nine TB designated health facilities) and two municipalities (four MDR-TB designated health facilities) to improve practices for infection control and to understand the feasibility and acceptability of these practices in China. HHS/CDC assisted in the development of TB infection control assessment checklists, standard operating procedures, and dashboards. Training-of-trainers workshops were conducted for national and provincial China CDC and NCTB staff. These staff then led regional training sessions for the county China CDC and health facility staff. All facilities have completed baseline and final knowledge, attitudes, and practices surveys; baseline facility assessments, routine monitoring and mentoring visits; final facility assessments; and in-depth interviews with health facility staff. Data are currently analyzed to better understand the acceptability and feasibility of future scale up of TB interventions for infection control throughout China.

## MOVING FORWARD

USAID and HHS/CDC are monitoring the effects of COVID-19 on global TB efforts, as initial data suggest dramatic reductions on DR-TB case finding, treatment initiation, and completion. In collaboration with in-country partners and Ministries of Health, USAID is closely monitoring the performance of DR-TB indicators and *National Action Plan* milestones and developing a response plan to address new challenges. While it is hard to predict the full impact of COVID-19 on TB in general, and DR-TB in particular, the pandemic has already had a dramatic impact on overall health care systems and vulnerable and marginalized populations. Once the COVID-19 pandemic is under control, NTPs in the ten *National Action Plan* countries will be able to assess the situation and deploy additional efforts to revert declining trends for DR-TB case finding and treatment initiation to the 2019 levels. Additional efforts, funding, and political commitment will be needed in early 2021 to mitigate the gaps in DR-TB control that emerged during the pandemic of COVID-19.

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

The National Institutes of Health (NIH) within HHS has a mission to fund and conduct domestic and international biomedical research on TB. Within HHS/NIH, the National Institute of Allergy and Infectious Diseases (NIAID) is the lead institute for TB research, complemented by programs supported by other HHS/NIH Institutes and Centers. This comprehensive research portfolio provides opportunities to contribute strategically to key areas of basic science leading to the discovery, development, and evaluation of new vaccines, drugs, and diagnostics. In September 2018, NIAID released the [NIAID Strategic Plan For Tuberculosis Research](#), which prioritizes expanding fundamental knowledge of TB by using modern tools, such as state-of-the-art imaging and systems biology methods, to better understand how TB infection remains latent in some individuals and then progresses to active disease, as well as the host and microbial factors that affect TB disease, transmission, and epidemiology. Many of these research projects highlight the synergy between U.S. Government Agencies' TB activities. Diagnosis, treatment, and care strategies and tools developed with HHS/NIH support continue to be evaluated or implemented through USAID and HHS/CDC programs. Many tools developed with HHS/NIH funding, such as the investigational antibacterial drug pretomanid and the diagnostic tool GeneXpert MTB/RIF, are being tested in clinical trials or are implemented in TB-endemic countries with HHS/CDC and USAID support. Observational international research cohorts, such as the [Regional Prospective Observational International Research for Tuberculosis Cohorts \(RePORT\) Network](#) – a cooperative strategy between HHS/NIH and interested governments that benefit from investments made by USAID, HHS/CDC, and other U.S. Government Agencies – are being used to initiate country-based biomedical research. HHS/NIH contributes to research on TB diagnostics, vaccines, and therapeutics using several funding mechanisms.

The HHS/NIH International Centre for Excellence in Research (ICER) in Chennai, India, is located at the National

Institute for Research in Tuberculosis, a permanent institute under the Indian Council of Medical Research. NIH researchers and collaborators at the ICER are revealing the role of host immune responses in pulmonary TB and extrapulmonary forms of TB. Efforts include uncovering the interaction of TB with other chronic conditions, such as diabetes mellitus, and identifying biomarkers of disease state and treatment success. HHS/NIH researchers recently described a plasma chemokine signature that can be used as a novel biomarker for predicting adverse treatment outcomes in pulmonary TB.

In the United States, HHS/CDC contributes applied research to improve understanding of drug resistance, aid optimal use of state-of-the-art approaches for surveillance, and develop and evaluate novel therapeutic approaches. HHS/CDC funds and provides scientific leadership for the TB Clinical Trials Consortium (TBTC), which translates basic research findings into the diagnostic and treatment tests and regimens that directly help patients. For example, TBTC identified the isoniazid and rifapentine (3HP) regimen now used to prevent progression to TB disease among persons with latent TB infection. TBTC researchers include investigators from the HHS/CDC, U.S. and international public health departments, academic medical centers, and selected U.S. Department of Veterans Affairs medical centers. HHS/CDC also funds the TBTC to expand diagnosis and treatment of latent TB infection.

In November 2019, HHS/CDC, the [American Thoracic Society](#) (ATS), European Respiratory Society, and Infectious Diseases Society of America (IDSA) published [clinical guidelines on the treatment of DR-TB](#) in the American Journal of Respiratory and Critical Care Medicine. The guidelines prioritize use of medications that can be administered orally. The guidelines are evidence-based, and were developed with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. The recommendations prioritize orally-

administered medications to make treatment more tolerable and improve patient outcomes, and provide guidance on the choice and number of drugs to use during treatment. Importantly, the recommendations address treatment of contacts to DR-TB cases to prevent future DR-TB disease. Recommendations also cover treatment length, the role of surgery, practices for treating special populations, and monitoring treatment. The same month, HHS/CDC released a new report, [Antibiotic Resistance Threats in the United States, 2019](#), which categorizes 18 antibiotic-resistant bacteria and fungi based on level of concern to human health. The report lists [DR-TB](#) as a “serious threat” that requires continued vigilance to maintain the progress made from effective TB control strategies.

Building on the most recent scientific progress and opportunities that contribute to ending the TB epidemic, USAID’s TB research priorities are: development of novel combinations of therapies to treat TB and DR-TB patients with improved safety and reduced treatment duration; assessment of treatments for preventing people at high-risk from developing TB; optimization of DR-TB diagnostics through collaboration with private biotechnology companies, creating cohesion between different actors in the development of new TB diagnostic solutions; escalation of evidence from high TB burden countries with high levels of DR-TB linking ongoing DR-TB transmission as the driving force to maintaining high levels of DR-TB incidence; and provision of technical support and guidance for local clinical trial and operational research capacity building. Additionally, USAID, at a country level, works directly with national governments to inform national programs and strategies.

Since many global donors support TB research and development (R&D), HHS/NIH scientists ensure that U.S. Government investments are optimally applied and complement other Agencies’ international programs. To facilitate coordination, HHS/NIH, USAID, and HHS/CDC continue to participate in the WHO-led Funder’s Forum for TB R&D and WHO’s Global TB Research Task Force.

## 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 TB transmission and progression of latent Mtb infection to active TB disease, developing new preventive strategies and tools requires a better understanding of the biological mechanisms and dynamics of TB, as well as strategic support of critical product development and clinical testing activities. Prevention and treatment strategies that target persons at highest risk of developing transmissible forms of the disease are expected to have a significant impact on individual and public health.

### SUB-OBJECTIVE 3.1.1: ADVANCE RESEARCH AND DEVELOPMENT OF NOVEL VACCINES

Building on a robust and comprehensive TB research portfolio, HHS/NIH continues to support multiple grants and contracts to expand its immunology and TB vaccine research program, including novel vaccine development. HHS/NIH is supporting several clinical trials evaluating investigational TB vaccines, including a Phase I trial of a thermostable vaccine and a Phase 1b/2a trial of the MTBVAC vaccine candidate in adults. In addition, HHS/NIH’s Vaccine Research Center has established a TB Vaccine Unit dedicated to the scientific investigation and clinical development of new vaccine and adjuvant strategies for preventing TB infection and disease. Researchers at HHS/NIH’s Vaccine Research Center found that administration of the TB Bacille Calmette-Guérin (BCG) vaccine, which has been in use for over a century, by intravenous instead of intradermal administration greatly increases the vaccine’s ability to protect rhesus macaques from Mtb infection. This work provides new insights into the mechanisms of BCG vaccine-elicited protection against TB.

HHS/NIH continues to provide resources to the academic and industry communities to facilitate translation of basic biomedical research findings into vaccine candidates. These resources include microbial, biochemical and immunological

reagents, bioinformatics tools, and technologies to support data integration, and animal testing services and clinical trials capacity. HHS/NIH's resources also contribute to the development of better predictive animal models and clinical trials to study the safety and efficacy of vaccine candidates. Through the U.S. Government's investments in vaccine development and clinical research activities, researchers are exploring novel approaches for the prevention of TB and evaluating innovative vaccine concepts. Continued, iterative development and testing of vaccine candidates is critical for advancing approaches developed in the laboratory and in animal models to those that will prevent TB in humans.

Among many collaborative public-private partnerships, HHS/NIH is a member of the Stop TB Partnership's [Working Group on New TB Vaccines](#), whose mission is to facilitate research and development of new vaccines to prevent TB, and collaborates with the European Tuberculosis Vaccine Initiative (TBVI), a non-profit foundation that facilitates the discovery and development of new, safe, and effective TB vaccines that are accessible and affordable for all people. USAID has also continued to support the function of the Stop TB Partnership's Working Group on New TB Vaccines to ensure ongoing collaboration between researchers working on TB vaccines. HHS/CDC has participated in and provided subject matter expertise to two WHO-related meetings on the public health value and the R&D roadmap for TB vaccines. In addition, HHS/NIH staff serve as Observers on the Global TB Vaccine Partnership, a forum for key stakeholders in TB vaccine R&D to identify and address barriers and to discuss priorities in order to help inform funding decisions.

HHS/NIH is supporting research, including clinical trials, on protective and novel immune responses and development of novel drugs. HHS/NIH also continues to participate in the TB Drug Accelerator program – an international collaborative effort among governments, companies, academia, hospitals, and non-government organizations to accelerate the discovery and development of novel TB drugs. HHS/NIH is supporting research which will develop and test novel adjuvants in combination with several Mtb antigens.

HHS/NIH researchers identified a series of compounds that inhibit Mtb growth through inhibition of Mg<sup>2+</sup> uptake via direct binding to the CorA transporter. Inhibition of Mg<sup>2+</sup> homeostasis by CorA is an attractive target for TB drug discovery. Additionally, several differences in cytokine profiles have been identified in vitro between infected and uninfected lymph nodes, showing a significant role for Mtb in driving the cytokine response at the site of infection. These differences may be key in developing new immunotherapy targets.

HHS/NIH is supporting awards under the "Immune Mechanisms of Protection against Mycobacterium Tuberculosis Center (IMPACT-TB)" solicitation to support research to gain a comprehensive understanding of the nature, location and timing of protective immune responses required to prevent initial Mtb infection, establishment of latent infection or progression to active disease. The awards will also support in-depth immunological analysis of promising vaccine candidates. Studies in several animal models will help inform vaccine design. Other recent funding opportunities include "Notice of Special Interest (NOSI): Mechanisms of Mycobacterial-Induced Immunity in HIV-Infected and/or Uninfected Individuals to Inform Innovative Tuberculosis Vaccine Design." HHS/NIH research on immune protection from TB among HIV-infected individuals has demonstrated that at least ten percent of individuals exposed to TB are "resisters" who do not develop a positive Purified Protein Derivative (PPD) or Interferon Gamma Release Assay (IGRA) for several years past exposure. Resisters develop interferon-gamma-independent markers of Mtb exposures with antibody responses distinctive for resistance versus latent infection.

### **SUB-OBJECTIVE 3.1.2: SUPPORT THE DEVELOPMENT OF METHODOLOGIES TO PREVENT TRANSMISSION AND DEVELOPMENT OF TB AND MDR-TB**

In addition to the basic research necessary for new diagnostics, therapeutics, and vaccines, NIH supports clinical research to inform the prevention, treatment, and management of TB through the NIH-sponsored AIDS Clinical Trials Group (ACTG) and the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT). For example, IMPAACT is conducting the



“Protecting Households on Exposure to Newly Diagnosed Index Multidrug-resistant Tuberculosis Patients (PHOENIX)” clinical trial. PHOENIX is a Phase 3 trial to compare the efficacy and safety of 26 weeks of DLM versus 26 weeks of isoniazid for preventing confirmed or probable active TB in high-risk household contacts of MDR-TB patients. HHS/NIH, as well as HHS/CDC, is supporting research to improve the understanding of where, when, and how TB transmission occurs to gain a better understanding of the factors that influence transmission so that more efficacious approaches for preventing TB infections and subsequent disease can be developed or improved.

USAID is supporting the implementation of a study that is aiming to characterize the transmission of MDR-TB using Mtb WGS technology in Moldova. Genomic data, combined with detailed epidemiological data, will enable the understanding of risk factors and epidemiological characteristics that are driving TB spreading in a community to allow for a better prioritization of TB prevention. The project has reached its goal of collecting 1,800 culture positive specimens; these specimens are currently undergoing WGS.

HHS/CDC has evaluated and implemented WGS approaches for improving cluster investigation and detection by establishing the National TB Molecular Surveillance Center (NTMSC) at the Michigan public health laboratory. The NTMSC provides conventional genotyping and WGS for approximately 9,000 Mtb isolates per year. HHS/CDC has developed analytic tools to analyze the vast amount of WGS data so that it can be combined efficiently with epidemiological data to improve outbreak detection and investigation. The WGS data provides higher resolution and allows U.S. state TB programs to focus their resources to stop and prevent ongoing transmission within communities.

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

Rapid and accurate diagnosis of acute and latent Mtb infection, MDR-TB, and XDR-TB is the cornerstone of TB care and control programs in the U.S. and globally. A variety

of technologies are being developed to confirm or rule out active TB and to quickly determine which antibiotics will constitute the most effective treatment regimen. Clinical studies to evaluate these technologies are being conducted in countries where TB is endemic. Diagnosis of latent Mtb infection offers the opportunity to provide patients with preventive therapy to lower their immediate risk of developing active TB. The development of TB diagnostics involves research to detect DS-TB and DR-TB or biomarkers that can be identified in sputum, blood, or other body fluids or excretions, and pairing those with novel, rapid technologies that can be utilized in healthcare settings where they are needed most urgently. Unique collaborations among multiple partners, including healthcare providers and TB control programs, are required to determine whether a diagnostic test improves the accuracy and speed at which TB patients of all ages can be identified and offered effective treatment.

### **SUB-OBJECTIVE 3.2.1: SUPPORT THE DEVELOPMENT OF NEW TOOLS AND APPROACHES FOR DETECTION OF DRUG-RESISTANT TB**

HHS/NIH currently supports research using a broad and diverse range of technologies and approaches aimed at improving the identification of DS-TB and MDR-TB/XDR-TB, as well as the identification of human biomarkers suitable to determine whether a person is infected with Mtb and who may have the highest risk for developing active TB disease. A continued area of focus is the creation of comprehensive datasets that give insight into the diversity of the biology and drug-resistance profiles of Mtb strains and how they affect patients. The HHS/NIH-supported Pathosystems Resource Integration Center (PATRIC), which has over 10,000 Mtb genomes and associated clinical data, provides tools to analyze genomic data. The HHS/CDC TBTC and the HHS/NIH-supported ACTG are contributing specimens to a collaborative registry as part of the search for biomarkers of progression from latent infection to active TB disease. With the emergence of new diagnostic platforms, collaborations among clinicians, public health scientists, bioinformatics specialists, and medical diagnostic developers provide opportunities for development and strengthening of reference laboratories in TB-endemic countries to evaluate promising new diagnostic tests.

HHS/NIH supported the development of an Mtb ribonucleic acid (RNA)-based assay that proved promising as a predictive TB treatment biomarker; it will be validated using samples from ACTG trials. Human RNA-based prognostic biosignatures for development of active TB are also being validated. HHS/NIH is supporting research using nanotechnology to study the translation of a set of Mtb-derived urinary markers and serum, as well as using a novel, low-cost, handheld device to generate high-quality data for future non-invasive diagnosis of TB in children. HHS/NIH is also supporting acceptance and usability of a mobile diagnostic platform by local general practitioners in India, and evaluating it against diagnoses from trained pulmonologists using traditional stethoscopes and standard lung function. HHS/NIH is supporting the development of Oral Swab Analysis (OSA) methods for diagnosis, which may be more suitable for children. Finally, NIH funded three projects under the “Feasibility of Novel Diagnostics for TB in Endemic Countries (FEND for TB)” opportunity to support clinical evaluation of early stage TB diagnostics in TB-endemic countries, with an emphasis on diagnostics that target special populations, including pediatric populations and people living with HIV.

HHS/CDC participates in international consortia to develop and improve molecular and phenotypic methods for DR-TB detection. For targeted molecular assays, the identification of specific genes and mutations involved in drug resistance is needed for the development and optimization of assays and interpretation criteria of the results. HHS/CDC continues to explore the molecular basis of drug resistance to old, new, and repurposed antibiotics used to treat TB. This information is critical to the development and continual improvement of molecular-based assays.

HHS/CDC has offered the Molecular Detection of Drug Resistance (MDDR) clinical service to all U.S. state programs since 2009. This clinical service provides rapid results for the prediction of drug resistance using molecular-based assays. The current MDDR assay is based on conventional sequencing of loci associated with resistance to both first- and second-line drugs, and HHS/CDC is currently transitioning to a targeted next generation sequencing-based assay using the latest technology. This assay will provide information on more genetic loci and allow better detection of heteroresistance.

### **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**

HHS/NIH is recompeting the TB Research Units Network (TBRU-N) that will operate as a collaborative network to improve understanding of Mtb-host interactions through characterization of bacterial and host determinants that are relevant during stages of infection and disease, and analyses of bacterial and host heterogeneity on disease outcomes. The current network includes clinical sites in Brazil, Ethiopia, Haiti, Kenya, Peru and South Africa. Other ongoing projects are working to identify biomarkers that may be useful in differentiating between latency and persistence of TB in individuals in endemic countries. HHS/NIH researchers discovered that pulmonary TB is associated with heightened levels of plasma proinflammatory cytokines, which are reversed after chemotherapy, and proinflammatory cytokines are markers of disease severity, bacterial burden, and delayed culture conversion.

To enable coordinated and comparable research in TB-endemic countries, HHS/NIH co-funded and continues to support the RePORT Consortium, which utilizes standardized protocols and is contributing critical resources to HHS/NIH-funded studies, including the development of diagnostic tools specifically for TB diagnosis in children. In addition, HHS/NIH is supporting the development of a novel stool-based assay to diagnose pediatric TB, as well as the validation of novel potential pediatric biomarkers. In collaboration with the Bill and Melinda Gates Foundation, HHS/NIH continues to support and analyze biomarkers to predict TB treatment duration in the PREDICT-TB trial in China. HHS/NIH researchers launched a study to identify biomarkers, clinical signs, and molecular explanations for paradoxical reactions to TB treatment. HHS/NIH is supporting research looking for host biomarkers in HIV-infected persons and children, as well as biomarkers for paucibacillary and latent TB. Additionally, HHS/NIH is supporting research predicting TB outcomes using genotypic and biomarker signatures and investigating the nanotrap platform using biomarkers to diagnose TB.

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

Improving treatment options for TB also requires the full spectrum of TB research, from basic science to implementation. U.S. Government Agencies are contributing multiple kinds of resources and expertise to support pre-clinical and clinical research to enable short-, medium- and long-term improvement of TB care. While global and domestic recommendations for the treatment of DS-TB and DR-TB are available, continued progress is needed to develop improved therapeutics and treatment regimens. The use of key drugs within these regimens is being optimized, new drugs are being studied for their ability to shorten therapy and provide safer treatment options, and completely new, innovative regimens and treatment approaches are being developed that would dramatically impact patient care.

### **SUB-OBJECTIVE 3.3.1: IMPROVE THE USE OF EXISTING TB DRUGS FOR TREATMENT OF DRUG-SUSCEPTIBLE AND DRUG-RESISTANT TB**

HHS/CDC's TBTC Study 31/ACTG 5349 evaluated shorter treatment regimens for DS-TB. Over 2,500 participants were enrolled at 34 clinical sites in 13 countries. The study aimed to evaluate if high-dose (1,200 mg) daily rifapentine can shorten the necessary duration of treatment to four months, with or without moxifloxacin (rather than ethambutol). Study 31 was conducted in partnership with HHS/NIH's ACTG network. The study showed that a four-month daily treatment regimen of high-dose rifapentine with moxifloxacin is as safe and effective as the existing standard six-month daily regimen at curing DS-TB disease. This regimen is the first successful short-course treatment regimen for DS-TB disease in almost 40 years.

HHS/CDC's TBTC Study 35 is a Phase I/II trial to evaluate the safety of giving rifapentine in combination with isoniazid to prevent TB in children, and to establish the dose at which rifapentine should be administered. A major obstacle to

dosing rifapentine in young children has been the lack of TB medicines specifically formulated for children, many of whom have difficulty swallowing tablets that were made for adults. The trial is making use of a new combined formulation of rifapentine and isoniazid that can be dissolved in water and tastes like mango, making it easier for children to swallow.

HHS/CDC's TBTC Study 37 is a Phase III trial evaluating shortening regimens for latent TB infection. It will compare six weeks of daily rifapentine to the currently recommended three to four-month rifamycin-containing regimens.

HHS/NIH-supported TBRU-N investigators collaborated with the HHS/CDC TBTC investigators to compare mycobacterial isolates before treatment and after treatment. Lower pre-treatment antimicrobial activity values for isoniazid and rifampin seen in the laboratory were associated with increased risk of later relapse. These data suggest that regimens that include higher-potency drugs at higher doses could be beneficial.

HHS/NIH continues to support research on treatments in MDR-TB patients, including standard of care and second-line drugs, that will be used to further optimize treatment regimens. HHS/NIH supports pharmacokinetic studies on TB drugs and is supporting studies to identify optimal regimens in vitro and in animal models that fulfill the requirements of shortening therapy. The HHS/NIH-funded ACTG conducts clinical trials of existing drugs, including comparison of standard treatments, drug interactions, and pharmacokinetics. HHS/NIH, in collaboration with the HHS/CDC, is supporting re-evaluation of existing drugs such as rifapentine and moxifloxacin for DS-TB. HHS/NIH supports studies to evaluate single and combination therapies of new and repurposed drugs and is funding the development of new models to guide the development of optimal TB drug combinations. For example, HHS/NIH is supporting the first Phase IIc three-month treatment trial for DS-TB (CLOFAST) in the ACTG evaluating a new regimen, and is supporting research on depot medroxyprogesterone acetate (DMPA) in African women receiving treatment for HIV and TB. HHS/NIH is also supporting the development of pediatric formulations of fixed-dose combinations of first-line TB drugs.

### **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 resulted in the licensure of the first two new TB drugs, BDQ and DLM, in decades. The integration of these new drugs into regimens to replace or improve therapy requires efficacy and safety studies that ensure treatment is effective and that patients benefit from new drugs. An HHS/NIH-sponsored clinical trial is evaluating the safety and tolerability of BDQ in infants, children, and adolescents who may or may not be co-infected with HIV, contributing data for the safe use of this drug in these important populations. Another clinical trial is evaluating the safety and tolerability of DLM in HIV-infected and uninfected children with MDR-TB. HHS/NIH is conducting a pharmacokinetic and safety study of BDQ and DLM in patients with MDR-TB. HHS/NIH is also supporting study of the emergence of BDQ- and clofazimine-resistance after interruption of DR-TB therapy in South Africa – a high HIV prevalent setting. HHS/CDC will be participating as part of a global surveillance study to monitor potential emergence of pretomanid resistance.

The USAID-supported STREAM-II study is evaluating safety and efficacy of BDQ in an all-oral, shorter regimen for the treatment of RR-TB. More broadly, the STREAM trial is a Phase III randomized control trial that is studying the efficacy, safety, and economic impact of shortened MDR-TB treatment regimens. Per the newly updated WHO [DR-TB Treatment Guidelines](#), the use of shorter, all-oral, BDQ-containing regimens are recommended for MDR-TB patients. BDQ-containing regimens (as opposed to injectables) are believed to be more cost effective and lead to increased treatment adherence and success. This randomized control trial hopes to better test these hypotheses in multiple settings. Furthermore, STREAM is the first trial to provide an economic analysis of this treatment regimen, and the result would be an important tool for policymakers to better assess the economic and financial impact of adopting these new regimens. Patient enrollment has been completed and data are expected in early 2022.

In collaboration with Janssen and Otsuka pharmaceutical companies, USAID is also supporting an open label Phase III randomized control trial to evaluate the efficacy and safety of a combination regimen of BDQ, DLM, linezolid, and clofazimine in MDR-TB patients with additional resistance to fluoroquinolones in South Africa (BEAT Tuberculosis Study) and in pre-XDR and XDR-TB patients in India (BEAT TB). The USAID-supported BEAT studies are currently enrolling patients.

### **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**

HHS/NIH is continuing to support pre-clinical studies in order to select the most promising new compounds for further advancement, including the pre-clinical development of a new beta-lactam-class, rifamycin-class, and diarylquinoline-class antibiotics. HHS/NIH, HHS/CDC, and USAID staff participate in the Stop TB Partnership's [Working Group on New TB Drugs](#), which tracks progress in the global landscape of TB drug development. HHS/NIH and USAID assisted in the development of the new TB drug pretomanid, approved by the FDA as part of a three-drug oral regimen for the treatment of XDR-TB. HHS/NIH is currently evaluating pretomanid's safety for patients with renal or hepatic impairment.

HHS/NIH is funding the development of new *in silico* models and pharmacokinetic studies to guide development of treatment shortening combinations of drugs. HHS/NIH is funding formulations research, especially in the area of inhaled pulmonary delivery methods for drugs, as well as longer-acting delivery approaches and pediatric-friendly formulations of existing drugs. HHS/NIH has supported studies to further investigate the mechanism of action of TB drugs, like pyrazinamide, that may inform development of new TB treatment regimens. HHS/NIH has provided pre-clinical and clinical support, including animal model support, for development of novel classes of antibiotics, including spectinomycin and caprazene class antibiotics. HHS/NIH supports clinical trials on a shortened treatment regimen for MDR-TB (PREDICT-TB) and pharmacokinetics during pregnancy and the post-partum period. HHS/NIH supports

the Structural Genomics Center for Infectious Diseases (SGCID), which uses a structure-guided approach to evaluate drug targets and candidate drugs against TB and has established an expanded facility for imaging of Mtb infection in animal models.

HHS/NIH-sponsored scientists continue to make advances in drug discovery through participation in global drug development consortia, such as the Lilly TB Drug Discovery Initiative (LTI), which are emerging as effective models for academic-pharmaceutical collaborations. These research partnerships are increasingly utilizing rational, pharmacologically-driven approaches to drug discovery, development of animal models, regimen selection and clinical trial design to improve the state of the science for TB drug discovery and lower risks for industry. For example, HHS/NIH is contributing to the pre-clinical development of a novel chemical entity for DR-TB from a not-for-profit collaboration with Eli Lilly and Company and PAI Life Sciences. Pre-clinical safety and efficacy studies have supported CPZEN-45's candidacy as a novel anti-TB antibiotic.

HHS/NIH contracts that test and help develop pre-clinical therapeutic candidates have been awarded and utilized by over 100 research groups in more than 40 countries. NIH assisted in the preclinical development of a new oxazolidinone by providing evaluations and administrative assistance in preparation for a safety study. HHS/NIH assisted the TB Alliance in the pre-clinical development of a new oxazolidinone by providing evaluations and administrative assistance in preparation for a safety study. HHS/NIH initiated two Phase II trials of innovative host-directed therapy (HDT) agents (imatinib and pravastatin) as adjunctive treatments for TB and an additional trial to study metformin as an adjunctive HDT for TB treatment.

The development of novel and shorter treatment regimens is critical to prevent, control, and eliminate DS-TB and DR-TB. The ability to screen large potential therapeutic compound libraries in an efficient and biologically relevant manner are limited and not readily available to most research laboratories. HHS/CDC has recently developed a three-dimensional bioplatfrom to screen anti-tubercular and host-directed therapies to aid in the development of novel and shorter regimens and has screened over 1,200 compounds while identifying more than 50 promising candidates that will be further screened in animal models.

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

To ensure that U.S. Government investments in biomedical research have tangible benefits for communities worldwide, HHS/NIH continues to support partnerships with scientists and universities in TB-endemic countries and local affected communities, 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 the WHO's [End TB Strategy](#). HHS/NIH has issued multiple funding opportunities targeted at TB research in endemic countries. As general infectious disease training benefits scientists who conduct TB research by improving their research and clinical skills, numerous HHS/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. Some are designed to support career tracks and span multiple phases, from junior faculty through emerging leaders and senior investigators, and include training for health professionals. To help facilitate applications for HHS/NIH funding opportunities, HHS/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 and similar initiatives.

USAID is supporting capacity building efforts of clinical trial sites in South Africa's Eastern Cape through the BEAT study and in Eastern Europe through a grant with [WHO/ Special Programme for Research and Training in Tropical Disease \(TDR\)](#). These studies support capacity building efforts of clinical trial sites in South Africa's Eastern Cape and India. These activities have been building the local clinical research networks as a joint collaboration of academic institutions, clinical hospitals, national research organizations, NTPs and community organizations (community advisory boards) with the goal of advancing clinical studies, as well as facilitating education and training, study results implementations, and data sharing. Through another grant

with WHO/TDR, Structured Operational Research and Training Initiative (SORT IT), USAID has been supporting building operational and implementation research capacity in Africa, Asia, and Eastern Europe generating evidence that is useful for policy making.

In collaboration with China CDC's Field Epidemiology Training Program (FETP) and National Center for TB Control, HHS/CDC has developed a TB-specific cohort for China's national FETP. As part of this two-year intensive training and mentoring program, FETP residents receive didactic training in general epidemiology, surveillance, and outbreak response, as well as TB-specific workshops that provide an overview of TB public health strategies. The 2019 TB FETP cohort also developed and implemented operations research projects that focused on developing methods to improve TB diagnosis, identifying gaps and challenges in reporting of pediatric TB, improving TB infection control knowledge and practices, and identifying risk factors for TB treatment non-adherence.

## MOVING FORWARD

Like other areas of infectious respiratory disease research, TB research will be affected by the COVID-19 pandemic. Many laboratories needed for TB research are temporarily closed due to the pandemic and many researchers have restricted or limited access to facilities and equipment. Additionally, the pandemic is contributing to supply chain disruptions and difficulty in obtaining new equipment. COVID-19 has also created uncertainty among the research workforce, including for trainees and early career scientists. NIH supports numerous clinical trials and studies on TB, and they are being impacted significantly as focus in many parts of the world has shifted to COVID-19. NIH is supporting [limited studies](#) to understand the impact of COVID-19 on TB and conversely, how TB affects COVID-19.

# CONCLUSION

U.S. Government Departments and Agencies charged with implementing the *National Action Plan* have made significant progress in the fight against DR-TB to date. In Year Four, the *National Action Plan* countries reported a five percent increase in the number of patients diagnosed with DR-TB and a seven percent increase in the number of DR-TB patients enrolled on treatment. The U.S. Government and its partners continue to advance innovative research required for the development for countermeasures against DR-TB. Since the launch of the Plan, 468,124 individuals with DR-TB were detected, and 374,568 were enrolled on treatment. The work of national governments and partners in *National Action Plan* countries, along with expanded access and uptake of shorter DR-TB treatment regimens, including those that contain BDQ, have driven this progress. The U.S. Government Departments and Agencies implementing the *National Action Plan* have been instrumental in supporting this uptake, and in Year Five, will continue to develop, roll out, and scale up newly approved diagnostic tools and treatments.

However, overall progress in Year Four has been less than in the previous year, with the ten *National Action Plan* countries reporting a smaller increase in treatment enrollment. In the United States, nearly 90 percent of state TB programs continue to experience difficulties accessing TB medicines, especially medicines to treat DR-TB. Intensive efforts will be needed in the United States, *National Action Plan* countries, and globally to address barriers to case finding, treatment enrollment, and treatment adherence, particularly with the predicted impact of COVID-19 on TB.

The unprecedented global response to the COVID-19 pandemic will have far-reaching effects on progress made toward eliminating TB by 2030. While the short- and long-term impacts of the pandemic have not yet been quantified, various modeling efforts highlight the serious disruption the global pandemic of COVID-19 may cause for TB programs and progress. One of these efforts is a [modeling study](#) commissioned by the Stop TB Partnership in collaboration with the Imperial College, Avenir Health, Johns Hopkins University, and USAID. This study cites that a minimum of five years of progress will be lost, with global TB incidence and deaths increasing to levels seen between 2013 and 2016. This will equate to an additional six million people falling ill with TB and an additional 1.4 million TB deaths between 2020 and 2025. In addition, the pandemic will also disrupt TB research and development activities, as well as TB clinical research worldwide.

To mitigate the unintended impacts of the global COVID-19 pandemic and further accelerate progress to DR-TB control and TB elimination, even greater increased efforts and investments will be required by high DR-TB burden countries, partners, and donors. The U.S. Government Departments and Agencies implementing the *National Action Plan* remain committed to working together to drive continued progress in DR-TB diagnosis and care. However, without the allocation of additional financial and technical resources, it will not be possible to maintain the progress to date, let alone achieve the lifesaving milestones targeted for the last year of the *National Action Plan*.

