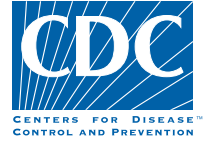




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# COMBATING MULTIDRUG-RESISTANT TUBERCULOSIS: YEAR FIVE REPORT OF THE NATIONAL ACTION PLAN

YEAR FIVE  
REPORT



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# ACRONYMS AND ABBREVIATIONS

<b>ACTG</b>	AIDS Clinical Trials Group	<b>NDoH</b>	National Department of Health
<b>ADRs</b>	Adverse Drug Reactions	<b>NIAID</b>	National Institute of Allergy and Infectious Diseases
<b>ATS</b>	American Thoracic Society	<b>NHLS</b>	National Health Laboratory Service
<b>BCG</b>	Bacille Calmette-Guérin	<b>NIH</b>	National Institutes of Health
<b>BDQ</b>	Bedaquiline	<b>NTP</b>	National Tuberculosis Program
<b>BPaL</b>	Bedaquiline, Pretomanid, and Linezoilid	<b>NTRLs</b>	National TB Reference Laboratories
<b>BV-BRC</b>	Bacterial and Viral Bioinformatics Resource Center	<b>NTMSC</b>	National TB Molecular Surveillance Center
<b>CAP</b>	Clinical Access Program	<b>PBMEF</b>	Performance-based Monitoring and Evaluation Framework
<b>CDC</b>	Centers for Disease Control and Prevention	<b>PHOENIX</b>	Protecting Households on Exposure to Newly Diagnosed Index Multidrug-resistant Tuberculosis Patients
<b>DLM</b>	Delamanid	<b>PLHIV</b>	People Living With HIV
<b>DMPA</b>	Depot Medroxyprogesterone Acetate	<b>PPE</b>	Personal Protective Equipment
<b>DOT</b>	Directly Observed Therapy	<b>PSM</b>	Procurement and Supply Chain Management
<b>DRA</b>	Drug Regulatory Authorities	<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>RR-TB</b>	Rifampicin-Resistant Tuberculosis
<b>eDOT</b>	Electronic Directly Observed Therapy	<b>RVCT</b>	Report of Verified Case of TB
<b>FDA</b>	U.S. Food and Drug Administration	<b>SGCID</b>	Structural Genomics Center for Infectious Diseases
<b>GDF</b>	Global Drug Facility	<b>STR</b>	Shorter treatment regimen
<b>GeneXpert</b>	Xpert® MTB/RIF	<b>TB</b>	Tuberculosis
<b>GRADE</b>	Grading of Recommendations Assessment, Development, and Evaluation	<b>TBDA</b>	TB Drug Accelerator
<b>GTBVP</b>	Global TB Vaccine Partnership	<b>TBIP</b>	TB Imaging Program
<b>HHS</b>	U.S. Department of Health and Human Services	<b>TBTC</b>	Tuberculosis Clinical Trials Consortium
<b>HIV</b>	Human Immunodeficiency Virus	<b>TBVI</b>	TuBerculosis Vaccine Initiative
<b>IDSA</b>	Infectious Disease Society of America	<b>TBRU-N</b>	Tuberculosis Research Unit Network
<b>IMPAACT</b>	International Maternal Pediatric Adolescent AIDS Clinical Trials Network	<b>U-LAM</b>	Urine TB Lipoarabinomannan
<b>IPC</b>	Infection Prevention and Control	<b>UNHLM</b>	United Nations High-Level Meeting
<b>ITIS</b>	Integrated TB Information System	<b>USAID</b>	United States Agency for International Development
<b>LPA</b>	Line probe assays	<b>VDOT</b>	Virtual Directly Observed Therapy
<b>MAIT</b>	Mucosal-Associated Invariant T	<b>WGS</b>	Whole-Genome Sequencing
<b>MIC</b>	Minimum Inhibitory Concentrations	<b>WHO</b>	World Health Organization
<b>MDDR</b>	Molecular Detection of Drug Resistance	<b>XDR-TB</b>	Extensively Drug-Resistant Tuberculosis
<b>MDR-TB</b>	Multidrug-Resistant Tuberculosis		
<b>MOH</b>	Ministry of Health		
<b>MTB</b>	Mycobacterium Tuberculosis		
<b>MTBVAC</b>	Mtb Whole Cell Vaccine Candidate		
<b>National Action Plan</b>	National Action Plan for Combating Multidrug-Resistant Tuberculosis		

# INTRODUCTION

Despite being preventable and curable, tuberculosis (TB) is one of the leading infectious disease killers, alongside COVID-19. In 2020, COVID-19 and associated measures to control it severely disrupted TB diagnosis and care services in the world's highest TB burden countries, threatening to reverse years of progress. In that year, an estimated 9.9 million (estimated range, 8.9–11.0 million) people fell ill with TB, and 1.5 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 is transmitted through the air from person to person. It is present in every country in the world, including the United States, which reported 7,174 cases of the disease in 2020.<sup>2</sup> While TB is curable, treatment is lengthy (at least six months) and requires multiple drugs; failure to treat the disease properly can lead to drug-resistant TB (DR-TB).

DR-TB refers to TB that is resistant to at least rifampicin (RR-TB), one of the most effective drugs required to treat TB. Multidrug-resistant TB (MDR-TB) is resistant to both isoniazid (the second-most vital drug) and rifampicin. 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. Those who suffer from DR-TB endure long, complicated, and toxic regimens; the fear of potentially transmitting the disease to loved ones; and income loss due to illness, isolation, and stigma. Beyond these devastating personal impacts, DR-TB poses a significant global health security threat to populations in the highest TB burden countries. DR-TB outbreaks wreak havoc on national economies and health care systems due to high treatment costs and the strain the disease puts on communities, families, and providers.

In 2020, an estimated 421,000 people developed DR-TB globally, including MDR-TB and XDR-TB. Only 37.5 percent of these DR-TB cases were diagnosed and reported to National TB Programs (NTPs), and of these cases, 95 percent started treatment. This equates to only an estimated 36 percent of DR-TB cases having access to appropriate treatment in 2020.<sup>3</sup> While an increasing number of individuals with DR-TB successfully complete treatment, progress has been slow, due to few new innovations in DR-TB therapy. 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 2020 in the United States, 513 people developed DR-TB; among these, 56 people were diagnosed with MDR-TB and one with XDR-TB.<sup>4</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>5</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>6</sup> In the United States, the cost to treat DR-TB is extremely high: more than \$182,000 per case for MDR-TB, and \$513,000 per case for XDR-TB.<sup>7</sup> Preventing, diagnosing, and treating TB in the United States, as in the rest of the world, requires better options to diagnose and treat every case of TB accurately, rapidly, and successfully.

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

<sup>1</sup> World Health Organization *Global Tuberculosis Report, 2021*.

<sup>2</sup> U.S. Centers for Disease Control and Prevention *Reported TB in the United States 2020*.

<sup>3</sup> *Ibid.*

<sup>4</sup> *Ibid.*

<sup>5</sup> *Ibid.*

<sup>6</sup> *Ibid.*

<sup>7</sup> *Ibid.*



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 builds on, and contributes to, the U.S. Government's *Global TB Strategy*, as well as the WHO *END TB Strategy*, the *United Nations High-Level Meeting on TB Targets*, 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 have saved an estimated 66 million lives.<sup>8</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 individuals with MDR-TB who are diagnosed and started on appropriate treatment, with a target of initiating treatment in 50 percent of individuals with MDR-TB in ten countries with the highest MDR-TB burdens in 2020.

In September 2018, the United Nations General Assembly High-Level Meeting (UNHLM) on TB 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 people with DR-TB. At the UNHLM, the U.S. Agency for International Development (USAID) launched the Global Accelerator to End TB to increase

commitment and build capacity of governments, civil society, and the private sector to accelerate countries' progress in reaching the global targets.

However, COVID-19's devastating impact on TB case finding and treatment in low- and middle-income countries, including the ten *National Action Plan* countries (Burma, China, India, Indonesia, Kazakhstan, Nigeria, Pakistan, the Philippines, South Africa, and Ukraine), has severely impeded progress in addressing TB and DR-TB. With the onset of the pandemic, many Ministries of Health redirected the limited resources for TB to respond to COVID-19, rolling back previously achieved gains. Furthermore, as a result of the pandemic, it is projected that TB will sicken an additional 6.3 million people and cause an additional 1.4 million TB deaths between 2020 and 2025.<sup>9</sup>

While COVID-19's impact will likely continue, this report outlines the U.S. Government Departments and Agencies progress toward the global targets and milestones of Year Five, the final year of the *National Action Plan*, and reviews accomplishments over the five-year implementation period of the *National Action Plan*.

<sup>8</sup> World Health Organization *Global Tuberculosis Report, 2021*.

<sup>9</sup> [http://www.stoptb.org/assets/documents/news/Modeling%20Report\\_1%20May%202020\\_FINAL.pdf](http://www.stoptb.org/assets/documents/news/Modeling%20Report_1%20May%202020_FINAL.pdf)

# 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 national surveillance to monitor progress toward TB elimination, and vital, unparalleled clinical trials and epidemiologic research that contributes to guidelines and drives strategies for eliminating TB in the United States and globally; 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.

Case finding, contact investigation, infection control practices in healthcare and other settings; combined with efforts to ensure people with TB disease complete treatment, and that contacts are tested and treated for latent TB infection are credited with annual reductions in TB cases since 1993. The United States' incidence of TB disease has decreased from 25,103 in 1993 to 7,174 in 2020.<sup>10</sup> The decline in the reported number of TB disease cases in 2020 is far larger compared to recent years and is likely due to multiple factors related to the COVID-19 pandemic, which have led to an under-ascertainment of cases and a true decline in TB incidence. Despite substantial declines in the rates of TB in the United States, disparities persist and have even increased

for certain racial and ethnic minority groups that have historically experienced greater obstacles to health and health care. The United States TB case rate (2.2 cases per 100,000<sup>11</sup>) remains well above the elimination threshold of less than one case per million persons.

In 2020, HHS/CDC launched a proactive initiative to better understand the effect of the COVID-19 pandemic on TB epidemiology in the United States, including close monitoring of real-time case report data through the National Tuberculosis Surveillance System, analysis of key TB case characteristics, and use of a range of complementary data sources (i.e., including public health and non-public health data). This work will provide context surrounding the greater-than-normal decline in a single year.

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>12</sup> The proportion of cases with reported mono-resistance to isoniazid has remained approximately nine percent over the last several years.<sup>13</sup>

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 (\$182,000) than a drug-susceptible TB (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.<sup>14-15</sup>

10 U.S. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report (MMWR) March 24, 2021.*

11 Ibid.

12 U.S. Centers for Disease Control and Prevention. *Reported TB in the United States 2020.*

13 Ibid.

14 Marks S et al. Treatment Practices, Outcomes, and Costs of Multidrug-resistant and Extensively Drug-resistant Tuberculosis in the United States. *Emerg Infect Dis.* 2014;20(5).

15 Aslam et al. Number and Cost of Hospitalizations with Principal and Secondary Diagnoses of Tuberculosis, United States. *Int J Tuberc Lung Dis.* 2018;22(12).

Because drug resistance can develop when an individual 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 education. U.S. state and local TB programs are responsible for TB elimination within their jurisdictions.

Access to TB drugs remains a challenge. U.S. state TB programs continue to report difficulty in obtaining drugs for treating latent TB infection, DS-TB, and MDR-TB. These drugs include rifapentine, ethambutol, rifampin, (costs doubling) pyrazinamide, rifabutin, and moxifloxacin.

### **OBJECTIVE 1.1: 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 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 funds the National TB Molecular Surveillance Center (NTMSC), part of the Antibiotic Resistance Laboratory Network, to perform universal WGS on isolates of Mtb gathered from newly diagnosed patients. HHS/CDC leverages WGS to identify new emerging DR-TB strains and better understand TB clusters and outbreaks. HHS/CDC flags WGS results that may indicate recent transmission of DS-TB and DR-TB and shares data with state and local jurisdictions in real time to facilitate targeted public health interventions to prevent outbreaks.

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

Completion of DR-TB treatment is challenging on many levels. HHS/CDC support for ensuring that individuals with DR-TB complete TB therapy includes a broad range of interventions. In 2020, HHS/CDC completed 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. Researchers found that TB treatment provided by eDOT was at least as effective as traditional in-person directly observed therapy (DOT) for ensuring high adherence to TB treatment and enabling people-centered care for TB disease. Safety for eDOT was similar to that of in-person DOT. In addition, an economic evaluation linked to this trial determined that eDOT was associated with lower costs from a societal perspective, and with lower or similar costs from a program perspective. Using electronic technologies, eDOT allows health providers to remotely monitor those with TB as they ingest their medication,

either in real time or recorded. Because eDOT uses remote observation in lieu of clinic visits by the individual (e.g., over smartphone video), it can improve treatment adherence and be more cost-efficient than traditional in-person DOT. Benefits can include convenience for those on treatment and staff, reduced staff travel cost and time, and prevention of exposure to other diseases, such as COVID-19.

Because the second-line drugs used to treat DR-TB are often available from only one manufacturer in the United States, HHS/CDC, in collaboration with the HHS Supply Service Center, maintains a small stockpile of drugs to ensure TB programs can keep people on critical treatment regimens if a manufacturing shortage arises. Since 2019, the HHS/CDC stockpile includes some of the critical drugs for all-oral regimens for DS-TB and 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 the risk of acquisition and spread of MDR-TB. More than 90 percent of state and local TB programs responding to point-in-time queries by the National TB Controllers Association reported having 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 on the shared goals of reaching every person with TB, curing those in need of treatment, and preventing the spread of new TB infections and the progression to active TB disease. Persistent challenges remain in the availability of effective tools, as well as in-country capacity and systems to further DR-TB detection, treatment, and prevention efforts. The far-reaching impacts of the COVID-19 pandemic on TB efforts has further exacerbated these challenges.

In many countries, Ministries of Health (MOHs) prioritized responding to COVID-19 over other health-related priorities. In 2020, globally and in *National Action Plan* countries, there were persistent challenges in accessing TB screening and testing services. Additionally, an overwhelmed and understaffed healthcare workforce, which was at the frontline of the pandemic response, had limited ability to conduct TB active case-finding and contact-tracing activities. Healthcare workers' capacity limitations were further exacerbated by pandemic-related quarantine measures, lockdowns, and movement restrictions. In a matter of months, COVID-19 threatened to reverse years of significant progress in combating TB. Data from countries in 2020 reported TB case notifications numbers last seen in 2016, indicating that countries have lost five or more years of progress due to COVID-19 and related mitigation measures. In some countries, TB notification rates dropped more than 20 percent, compared to 2019 results.<sup>16</sup> Such dramatic declines directly impacted DR-TB case detection and treatment enrollment.

Within the first eight months of the COVID-19 pandemic, USAID conducted two surveys to better understand the pandemic's impact on TB services and identify interventions

that could be implemented to mitigate COVID-19-related setbacks on TB services. The surveys looked at the availability of guidelines, policies on TB and COVID-19, and COVID-19's effects on TB diagnostic services, in-person care, resources reallocation, and data reporting. The surveys revealed that due to the severity of the pandemic, most of the *National Action Plan* countries reallocated many healthcare systems and resources, including healthcare workers and GeneXpert instruments, to respond to COVID-19. Furthermore, due to TB and COVID-19 both being airborne infections, TB platforms were systematically utilized in the COVID-19 response, impacting the continuity of TB services. Countries transitioned TB resources—such as trained healthcare workers, equipped healthcare facilities, available personal protective equipment (PPE) and established diagnostic networks—to the pandemic response, resulting in major shortages across the TB service delivery system.

To help mitigate the pandemic's impact, USAID developed and disseminated technical guidance to the field that provided field staff with up-to-date information on COVID-19 (clinical manifestation, prevention, diagnosis, and management) and on managing TB programs and those suffering from TB during the pandemic. In addition, USAID promoted simultaneous testing for both TB and COVID-19, supported the scale up of all-oral treatment regimens for DR-TB, and helped introduce innovative approaches, such as digital technologies, to support those with TB and monitor and manage adverse events.

Despite challenges presented by the pandemic, USAID continued to partner with HHS/CDC and other Federal Departments and Agencies to support the *National Action Plan* countries in making progress towards the goals and milestones set forth in the *National Action Plan*. USAID and other partner Agencies continued working with NTPs in nine of the ten *National Action Plan* countries.<sup>17</sup> In particular,

<sup>16</sup> World Health Organization, *Global Tuberculosis Report, 2021*.

<sup>17</sup> Burma, India, Indonesia, Kazakhstan, Nigeria, Pakistan, the Philippines, South Africa, and Ukraine.

USAID continued to urge local implementers to scale up TB and DR-TB screening and testing and support the rapid scale up and optimization of GeneXpert instruments and drug-resistance testing. In addition to the active case-finding and DR-TB detection activities, USAID and partner Agencies continued to support the *National Action Plan* countries in closing the gap between the number of people diagnosed with TB and those started on treatment. Unfortunately, due to COVID-19's impact and resource demands, the target of enrolling at least 50 percent of those DR-TB in the ten *National Action Plan* countries was not achieved.

This Year Five Report provides a progress update on the *National Action Plan* activities implemented in 2020, the last year of the *National Action Plan*, and a review of the overall progress made during the five-year implementation period of the *National Action Plan*.

In 2016, WHO introduced a shorter treatment regimen (STR), which is a more manageable treatment option for DR-TB patients. In Year One through Year Four, the *National Action Plan* reported data on individuals with DR-TB started on STR.<sup>18</sup> However, in 2020, WHO further updated its DR-TB treatment guidelines to recommend using all-oral regimens and to discontinue the use of injectables. This more tolerable DR-TB treatment option, which eliminates the need for daily injections, proved to be a more appropriate regimen for treating MDR-TB during the COVID-19 pandemic. Starting in 2020, only data on individuals with DR-TB enrolled on all-oral regimens<sup>19</sup> is available. Data on all-oral regimens is included for 2019 for comparison purposes.

Finalized 2019 global data<sup>20</sup> for Year Four of the *National Action Plan* implementation appear below:

- Globally, 206,030 DR-TB cases were detected, which reflects 44 percent of the estimated 465,000 DR-TB incident cases in 2019; and
- 177,099 individuals with DR-TB enrolled on treatment, which reflects 38 percent of the estimated DR-TB incident cases in 2019

- 37,296 individuals with DR-TB enrolled on a regimen that contains bedaquiline (BDQ);
- 15,884 individuals with DR-TB enrolled on all-oral long regimen; and
- 68,237 individuals with DR-TB enrolled on a STR.

In *National Action Plan* countries:

- 137,883 DR-TB cases were detected, which reflects 67 percent of the total DR-TB cases detected globally; and
- 113,275 individuals with DR-TB enrolled on treatment, which reflects 64 percent of the total individuals with DR-TB enrolled globally;
  - 22,889 individuals with DR-TB enrolled on a regimen that contains BDQ;
  - 8,968 individuals with DR-TB enrolled on an all-oral long regimen; and
  - 57,687 individuals with DR-TB enrolled on STR.

Finalized 2020 data<sup>21</sup> for Year Five of the *National Action Plan* implementation appear below:

- 102,688 DR-TB cases were detected in the ten *National Action Plan* countries, which reflects 65 percent of the total DR-TB cases detected globally; and
- 89,565 individuals with DR-TB enrolled on treatment in the ten *National Action Plan* countries, which reflects 60 percent of the total individuals with DR-TB enrolled globally;
  - 30,410 individuals with DR-TB enrolled on a regimen that contains BDQ;
  - 34,652 individuals with DR-TB enrolled on an all-oral regimen (an almost four-fold increase compared to 2019), of which 9,683 were on an all-oral STR.

<sup>18</sup> STR data previously reported (before 2020) includes both patients on oral and injectable treatment.

<sup>19</sup> As reported by WHO, all-oral regimens data include STR and long-term regimens.

<sup>20</sup> World Health Organization. *Global Tuberculosis Report, 2020* and Global TB Database.

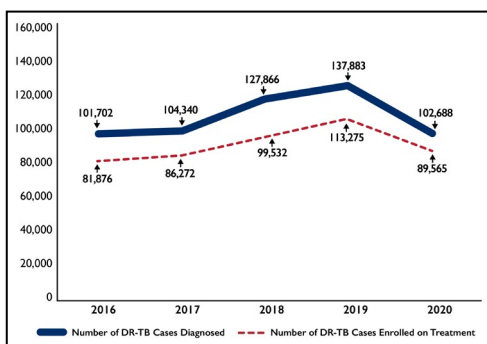
<sup>21</sup> Ibid.

**Table 1: Detection and Treatment of DR-TB from Year Four and Five<sup>22</sup>**

	DR-TB Detected	DR-TB Enrolled	Enrolled on BDQ Regimen	Enrolled on All-Oral Regimen <sup>23</sup>
Globally in 2019	206,030	177,099	37,296	15,884
Globally in 2020	157,947	150,382	51,750	48,138
10 National Action Plan Countries in 2019	137,883	113,275	22,889	8,968
10 National Action Plan Countries in 2020	102,688	89,565	30,410	34,652

As a result of many pandemic-related disruptions, Year Five was the first time in the five-year *National Action Plan* implementation period that countries recorded decreases in DR-TB detection and people enrolled on treatment (as compared to Year Four). In Year Five of the *National Action Plan*, 102,688 DR-TB cases were detected, representing a 26 percent decrease as compared to Year Four. Furthermore, only 89,565 of those individuals diagnosed with DR-TB were enrolled on appropriate treatment—a 21 percent decrease as compared to Year Four. The total number of individuals with DR-TB enrolled on treatment in Year Five represents 32 percent of the total estimated number of people with DR-TB in the ten *National Action Plan* countries; this is far below the 50 percent enrollment target. The results reported in Year Five are similar to those reported in Year One of the *National Action Plan* and are in line with 2020’s drastic overall declines in TB case notifications as a result of the COVID-19 pandemic (Figure 1).

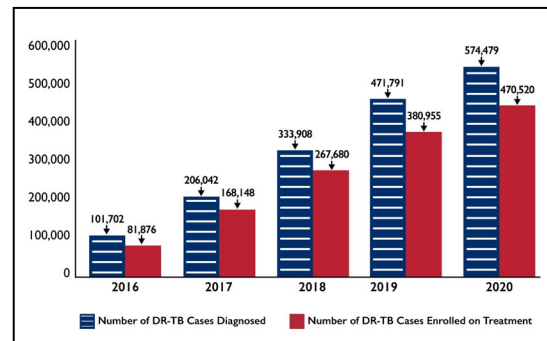
**Figure 1: Yearly DR-TB Detection and Treatment Results in National Action Plan Countries**



While the decrease in DR-TB case finding and treatment initiation is concerning, USAID and partner Agencies have recorded significant progress in the uptake of newly recommended treatment regimens, including BDQ-containing regimens. In Year Four of the *National Action Plan*, 22,889 people with DR-TB were enrolled on BDQ-containing treatments. In Year Five, 30,410 individuals with DR-TB were enrolled on BDQ-containing regimens—a 33 percent increase compared to the previous year.

During the five-year implementation of the National Action Plan, a total of 574,479 DR-TB cases were detected, and 470,520 people with DR-TB were enrolled on treatment (Figure 2). Furthermore, over the course of the *National Action Plan* implementation, 80,115 people with DR-TB were enrolled on a treatment regimen that contains BDQ.

**Figure 2: Cumulative DR-TB Detection and Treatment Results in National Action Plan Countries**



Since 2016, USAID and partners have successfully treated 17,064,883<sup>24</sup> people with TB, exceeding the *National Action Plan* target of successfully treating 16 million people. In addition, in high-burden countries, a treatment success rate of nearly 88 percent was achieved and maintained for individuals with DS-TB, and the global TB incidence dropped by 15 percent.<sup>25</sup> While neither the treatment success rate goal (of 90 percent) nor TB incidence decrease (of a 25 percent drop) was achieved through the *National Action Plan*, USAID and partners were able to achieve marked progress towards the global goal of ending TB by 2030.

<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.

<sup>23</sup> Data for 2019 only includes individuals enrolled on all-oral long regimens. Data for 2020 includes individuals on all-oral STR and long regimens.

<sup>24</sup> The cumulative number of people with TB who were successfully treated was calculated using data reported in 2016 (for cohort 2015) to data reported in 2020 (for cohort 2019).

<sup>25</sup> Note this is comparing the global TB incidence in 2015 to 2020 which is the latest publicly available data in the WHO database.

While 2020 was the final year of the *National Action Plan*, countries now face the greatest challenge yet of getting TB and DR-TB efforts back on track. Additional efforts, new innovations, and political commitment will be needed in 2021 and years after to mitigate gaps in the DR-TB response that emerged during COVID-19. Countries will not only need to recover from the devastating impacts of COVID-19, but will also need to accelerate progress towards achieving the ambitious UNHLM targets. Continued concerted efforts are required to achieve country-level targets as well as to leverage additional financial resources. USAID has taken the first step in recovering lost gains by helping countries to develop and implement targeted recovery plans in five of the *National Action Plan* countries (India, Indonesia, Philippines, South Africa, and Ukraine). Through these plans, USAID is supporting the introduction and scale-up of new tools to strengthen DR-TB diagnosis and treatment enrollment and adherence.

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

In Year Five, USAID and HHS/CDC continued working closely with the NTPs and National TB Diagnostic networks in nine countries<sup>26</sup> to develop quality-assured laboratory networks capable of detecting TB and DR-TB strains; expand access to rapid diagnostic tools and resources; implement nationwide screening of those with TB for MDR-TB through drug-resistance testing; and assist NTPs and in-country partners to scale-up quality facility- and community-based DR-TB care and treatment services, including the rapid uptake of novel, all-oral regimens, as well as improved pharmacovigilance.<sup>27</sup>

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

In 2020, USAID continued supporting nine countries<sup>28</sup> to strengthen and expand access to National TB Diagnostic networks by procuring and setting up additional GeneXpert instruments and expanding the number of sites equipped to perform line probe assays (LPA). With the support of USAID and partners, countries were able to successfully introduce novel, state-of-the-art laboratory tools to further expand easy access to rapid diagnostic tests for TB and DR-TB. For example, by the end of Year Five in South Africa, 166 sites were equipped with GeneXpert instruments, and 15 laboratories were performing TB culture procedures – with eight of these laboratories having drug-resistance testing capacity. In Nigeria, 399 GeneXpert instruments were installed across the country, which aided in providing testing services to vulnerable groups, as well as to communities in hard-to-reach areas. Furthermore, USAID has been assisting countries in conducting diagnostic network assessments, which include the implementation of important mapping exercises that aid the National TB Reference Laboratories (NTRLs) in strategically placing existing and new TB diagnostic instruments.

USAID has worked with the *National Action Plan* countries to scale up nationwide drug-resistance testing for all people with TB. Additionally, active case finding for TB activities has been implemented in many countries at the community level and in hard-to-reach areas to further improve TB case detection and peoples' access to free TB screening and DR-TB testing. Over the five-year implementation period of the *National Action Plan*, drug-resistant testing using a rapid diagnostic test among those with new TB cases has improved from as low as 11 percent of individuals with TB in 2015 (baseline year) to almost 35 percent on average across all ten *National Action Plan* countries—reaching as high as 60 to 96 percent of people with TB in a few *National Action*

26 Burma, India, Indonesia, Kazakhstan, Nigeria, Pakistan, the Philippines, South Africa, and Ukraine.

27 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.”

28 Ibid.

*Plan* countries (see Annex for more details).<sup>29</sup> With USAID support, many of the *National Action Plan* countries have modified their policies and protocols to allow more groups of people to get tested with rapid drug-susceptibility tests, like GeneXpert and first-line LPA. In countries like South Africa, the Philippines, Nigeria, Pakistan, Kazakhstan, and Ukraine, new policies allowed GeneXpert to be used as a screening TB test among people with TB signs and symptoms, instead of smear microscopy. This significantly improved the TB notification yield and allowed for simultaneous detection of DR-TB.

In South Africa, HHS/CDC has been supporting the National Health Laboratory Service (NHLS) to strengthen delivery of, and to expand access to, quality laboratory services, as well as enhancing healthcare worker and laboratory safety. HHS/CDC works collaboratively with other partners to provide technical support to the South African National Department of Health (NDoH) with scale-up of Urine TB Lipoarabinomannan (U-LAM) test as part of the screening approach for TB for people living with HIV (PLHIV), per WHO guidelines. HHS/CDC is currently supporting finalization of the revision of U-LAM guidelines in South Africa. HHS/CDC has also continued to support TB reference laboratories conducting TB drug susceptibility testing by strengthening their quality management systems through the implementation of structured, mentorship-based quality management programs. These programs lead to improved accuracy of test results and support laboratories to work toward international accreditation.

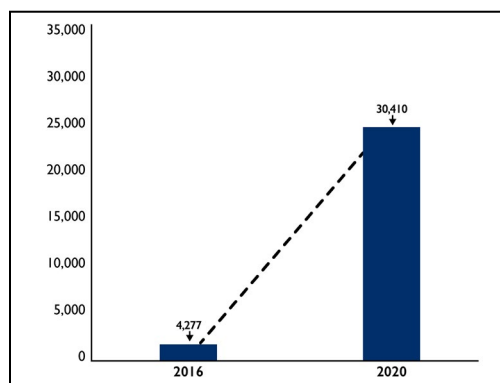
In India, HHS/CDC and USAID supported the first pan-India external quality-assurance program for 1187 GeneXpert instruments from 1130 sites. Training through NTRLs and partners for all states' TB programs and intermediate reference laboratories were done initially in person then transitioned to virtual, due to COVID-19 lockdowns and travel restrictions. An electronic external quality assurance (EQA) portal was piloted and modified, allowing state programs to submit EQA results online and receive feedback. EQA methods for TrueNat, a new rapid molecular test, were pilot tested in late 2020.

## 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 Five, with the international approval and WHO recommendation of a novel, all-oral treatment regimen, USAID and HHS/CDC collaborated with NTPs and local and international partners to quickly roll out the new regimen in all USAID TB priority countries.<sup>30</sup> The novel regimen will be extremely beneficial for all people with DR-TB, who will no longer need to endure an injectable agent that has long been part of DR-TB treatment regimens.

This will mean that people with DR-TB will be able to tolerate the treatment much better, thus helping to ensure greater treatment adherence, as demonstrated during the pandemic. Additionally, by eliminating daily injections, along with the scale up of digital adherence technologies, those with DR-TB will be able to take the treatment and be monitored while remaining in their community or at home.

**Figure 3: Number of DR-TB Cases Enrolled on a BDQ Regimen in National Action Plan Countries**



As a result of this, in 2020, 34,652 individuals with DR-TB were initiated on all-oral treatment regimens. With USAID support, National Action Plan countries were also able to expand access to DR-TB treatment sites, scale-up home-based care models, introduce innovative treatment adherence tools, and provide technical assistance to improve quality of DR-TB care.

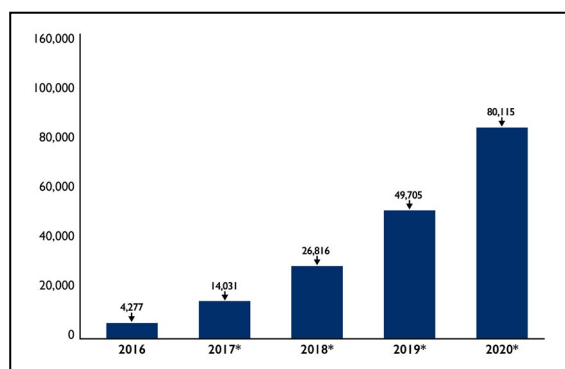
<sup>29</sup> World Health Organization. Global TB Database.

<sup>30</sup> <https://www.usaid.gov/global-health/health-areas/tuberculosis/countries>



In the five-year implementation period of the *National Action Plan*, USAID also supported the uptake of BDQ-containing regimens. Resulting in a seven-fold increase in people with DR-TB enrolled on BDQ-containing treatments in Year Five as compared to Year One. Further, over the course of the National Action Plan, 80,115 individuals with DR-TB were enrolled on BDQ-containing treatments.

**Figure 4: Cumulative Number of DR-TB Cases Enrolled on a BDQ Regimen in National Action Plan Countries**



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

A strong and robust monitoring and surveillance system is required to effectively manage large-scale programs. USAID prioritizes ensuring that quality TB data is collected, monitored, and used for decision-making in real time; data-driven decision making is at the core of USAID's Global Accelerator to End TB. As part of this, USAID has developed a performance-based monitoring and evaluation framework (PBMEF) that countries can adopt to better improve standardized TB data reporting and monitoring.

In 2020, USAID assisted countries to initiate and scale up connectivity solutions such as GX Alert, DataToCare, C360, and SMS-reporting systems, among others, in order to ensure the proper linkage of laboratory equipment to national database systems. This will make faster transmission of laboratory test results possible, to allow for those with TB to be initiated on appropriate treatment more quickly. Furthermore, USAID supported the scale up of person-based digital electronic recording and reporting systems, as well as systems for active TB surveillance and vital registration.

### 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

In 2020, USAID technical assistance focused on the scale-up of an early warning drug procurement and management system for DR-TB medicines in *National Action Plan* countries, and providing support related to in-country regulatory approval processes for first- and second-line drugs. In order to improve drug management systems, USAID assisted countries with the development of robust TB procurement and supply chain management (PSM) systems that can track drug stock and provide countries with an early warning if the stock level of medicines falls too low. This assists NTPs in preparing drug quantification for procurement.

Additionally, to ensure people have access to novel medications for TB and DR-TB treatment, USAID worked with NTPs and local counterparts to support the registration process of new anti-TB medications. As a result, drug regulatory authorities (DRA) in multiple *National Action Plan* countries were able to register several new TB and DR-TB medications. For example: in the Philippines, ten new medications dossiers were submitted for registration; in Kazakhstan, delamanid (DLM) was registered; and in Burma, two first-line TB medications were submitted for approval.

During the five-year *National Action Plan* period, USAID continued its support of the Stop TB Partnership's Global Drug Facility (GDF). In 2020, GDF assisted NTPs with: ensuring intensified supply monitoring and production planning; deployment of medicines from the GDF strategic rotating stockpile; equitable medicine rationing; pooled procurement; and extensive technical assistance. GDF also conducted six on-site missions pre-COVID, and from March 2020 onward, provided remote technical assistance to NTPs by holding 80 remote meetings, eight training workshops, and four missions.

Despite the COVID-19 pandemic, in 2020, with USAID support, GDF averted 109 potential stockouts and significantly decreased delivery times from the standard six months to two months for shipments to 65 countries for emergency orders, and from six months to two to four months for shipments to 102 countries for urgent orders.<sup>31</sup> GDF was also able to deliver 2,121 shipments of TB medicines and/or diagnostics totaling \$307 million to 123 countries. GDF continued to expand its client base, serving principal recipients of Global Fund grants in 87 countries; clients using other donor funding in 70 countries; and 55 countries using domestic funding to buy TB medicines and/or diagnostics—the highest number ever. GDF also provided procurement services for 20 clinical research projects in 2020—a 67 percent increase compared to 2019.

## OBJECTIVE 2.2: PREVENT MDR-TB TRANSMISSION

DR-TB case finding and proper case management are two cornerstones of DR-TB efforts and have been prioritized for the implementation of the *National Action Plan* in all ten countries. For Year Five, the main priorities were improving treatment adherence and overall quality of care. Building on the successful development of the DR-TB Care Package in previous years of the *National Action Plan*, as well as on launching breakthrough digital adherence technologies, in 2020, USAID continued to provide critical technical assistance to nine countries.<sup>32</sup> To support NTPs during the pandemic, USAID supported the implementation of new treatment regimens and scaling up of innovative digital treatment adherence and support technologies.

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

In Year Five, USAID worked closely with the *National Action Plan* countries to improve screening for, and detection of, DR-TB via rapid, high-quality diagnostic tools. For example, in India, the TrueNat instrument—a novel, rapid diagnostic

laboratory instrument—was developed and approved for global use. In other countries, USAID assisted NTPs and NTRLs in the scale up and optimization of GeneXpert instruments and increased access to drug susceptibility testing. However, due to COVID-19, national lockdowns and the shifting of healthcare resources for the pandemic, TB and DR-TB case detection were significantly affected.

Nevertheless, in order to continue to improve quality of care, USAID-funded partners worked with NTPs to perform regular treatment site monitoring, supervision visits, and cohort reviews—essential tools for ensuring quality of DR-TB care. Because of the lengthy nature of DR-TB treatment regimens and to ensure that treatment-related gaps and issues were quickly identified, USAID established systems to support people through regular in-person or virtual visits.

For example, in the Philippines, USAID has supported the implementation of the Integrated TB Information System (ITIS) nationwide since 2017, and 100 percent of people with DR-TB are monitored in the system. In 2020, through USAID support, the NTP introduced and implemented ConnectTB—a mobile health application that allows community health workers to track treatment adherence, proactively manage adverse drug reactions (ADRs), conduct contact tracing, and remind people about scheduled laboratory and clinical visits—in six satellite treatment centers with the highest loss to follow-up and lowest ADRs reporting rates.

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

According to the WHO's 2021 Global TB Report, the global treatment success rate for DR-TB is only 59 percent. This is unacceptably low. Beginning in Year One of the *National Action Plan* and continuing over its implementation period, USAID has prioritized activities that work towards improving treatment adherence via person-centered care that supports both medical and non-medical needs of people with DR-TB. In Year One of the *National Action Plan*, USAID introduced the DR-TB Care Package, which focuses on providing holistic

<sup>31</sup> Emergency orders apply to situations that arise as a result of there being inadequate supplies available and are likely to result in stock-outs and thus interruption of treatment/services. Urgent orders apply to orders impacted by delays.

<sup>32</sup> Burma, India, Indonesia, Kazakhstan, Nigeria, Pakistan, the Philippines, South Africa, and Ukraine.

support for those who are receiving DR-TB treatment. By the end of 2019, this package had been expanded to nine countries covered by the *National Action Plan*; in 2020, USAID continued to further scale up adoption and implementation of the care package.

As a result of COVID-19 mitigation efforts, it was increasingly more difficult to monitor and support treatment and care for those with DR-TB in 2020. To combat this, USAID supported NTPs in *National Action Plan* countries to rapidly implement and scale up digital adherence technologies that had been piloted in 2018 and 2019. For example, during Year Five, USAID assisted countries with implementation of 99DOTS (a low-cost, mobile phone-based technology that supports people's treatment adherence), virtual directly observed therapy (VDOT), SMS-reminders, and smart pill boxes. All these tools allowed people to receive treatment from the comfort and safety of their homes, while also allowing healthcare providers to continue to support and monitor treatment. These tools allowed those with DR-TB to continue, and even complete, treatment during the pandemic.

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

In 2020, USAID provided focused technical assistance to improve TB surveillance and screening among all healthcare workers in facilities responsible for diagnosis and treatment of people with, and at high risk for, MDR-TB. Beginning in Year Two of the *National Action Plan*, USAID partnered with the NTPs in *National Action Plan* countries to develop national policies, protocols, and standard operating procedures related to active and continued TB screening of healthcare workers, as well as the implementation of measures to ensure healthcare protection in the workplace. In 2020, the programmatic implementation of TB screening for healthcare staff was rapidly expanded; this resulted in better early detection of TB among healthcare workers. An increasing number of NTPs implemented routine TB screening of medical personnel and improved systems for registration and reporting of TB cases in the workplace. In the wake of the COVID-19 pandemic, improved screening systems are, and will continue to be, especially important in facilitating the early detection and prevention of airborne infections.

In South Africa, HHS/CDC assisted the NDoH and Provincial Departments of Health to strengthen infection prevention and control (IPC). The key focus areas for reducing nosocomial and community-acquired TB through IPC measures included capacity building, implementation support, enabling systems, and education support. During the COVID-19 pandemic, HHS/CDC provided assistance in developing a national-level IPC tool and trainings, and supported facility assessments for IPC readiness. In addition, HHS/CDC supported health facilities in implementing IPC measures to capacitate them to an advanced level of IPC promotion and practice, ensuring the continuation of care for those with TB and HIV, and creating a safe working environment for health care workers.

# 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. As promising products advance through the development pipeline, HHS/NIH supports extensive clinical research activities and leverages established clinical trials networks and global collaborations, including in TB-endemic countries. Through these studies, researchers are examining novel strategies to prevent, treat, and diagnose TB across different populations, including adults with latent and active TB, adolescents, children, pregnant women, and individuals with TB and HIV co-infection. In September 2018, NIAID released the [NIAID Strategic Plan For Tuberculosis Research](#), which focuses on the highest research priorities needed to develop new TB treatment and prevention tools and emphasizes the significance of global collaborations. Many of these collaborations 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. For example, the antibacterial drug pretomanid and the diagnostic assays run on the GenXpert instrument, are being tested in HHS/NIH, HHS/CDC, and USAID-supported clinical trials to optimize their use or are being implemented in TB-endemic countries as part of WHO-recommended regimens. 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

receiving assistance from USAID, HHS/CDC, and other U.S. Government Agencies—are being used to initiate country-based biomedical research.

HHS/NIH, HHS/CDC, and USAID support clinical research to improve therapeutics and prevention. As part of its support for programmatically relevant TB research, HHS/CDC funds and provides scientific leadership for the TB Clinical Trials Consortium (TBTC), a group of competitively-awarded contracts with investigators from the HHS/CDC, U.S. academic medical centers and health departments, and selected U.S. Department of Veterans Affairs medical centers. HHS/CDC's clinical trials translate basic research findings into the diagnostic and treatment tests and regimens that directly help people in the United States and globally. 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 collaborates with the NIAID-funded AIDS Clinical Trials Group (ACTG). As part of this collaboration, ACTG sites enrolled participants for Study 31, a trial funded by the HHS/CDC. Study 31 found that “Efficacy of a 4-month rifapentine-based regimen containing moxifloxacin was noninferior to the standard 6-month regimen in the treatment of tuberculosis.”<sup>33</sup> This new treatment strategy is the first shortened regimen to be developed in almost 40 years. Shortened regimens have the potential to enhance compliance, reduce side effects, and lower the probability of drug resistance emerging.

In 2021, HHS/CDC announced the awardees for the next ten-year cycle of TBTC studies, which will emphasize latent TB infection in the United States, and TB disease both domestically and internationally.

HHS/CDC, HHS/NIH, and USAID advise WHO and other international advisory groups to strengthen coordination of

33 <https://www.nejm.org/doi/full/10.1056/NEJMoa2033400>

global TB activities. HHS/CDC provides recommendations on global TB policy, programs, research, and laboratory guidelines. In 2021, HHS/CDC participated in the revision of the definition of XDR-TB and to the WHO Mtb mutation catalog.<sup>34</sup> HHS/NIH shares scientific expertise with WHO and other partners, such as the Stop TB Partnership, Bill and Melinda Gates Foundation, and Global TB Vaccine Partnership, to inform coordinated research and development strategies for new TB drugs and vaccines.

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 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 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 the spread of 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 response strategies.

Building on the most recent scientific progress and the renewed commitment to end the TB epidemic, USAID, HHS/NIH, and HHS/CDC TB research priorities include: the development of novel combinations of therapies to treat those with TB and DR-TB with the goal of improving outcomes, safety, and reducing treatment duration; evaluation of treatment regimens for latent TB infection; supporting the development of new diagnostic tools for DR-TB through collaboration with private biotechnology companies; evaluation of factors associated with TB transmission, and

provision of technical support; and guidance for local clinical trial and operational research capacity building. Additionally, USAID works directly with national governments at a country level to inform national programs and strategies. Throughout the COVID-19 pandemic, USAID research projects have maintained activities through the introduction of innovative strategies that prioritize the safety of participants and research teams and maintain the integrity of research projects.

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 U.S. Government TB Working Group, 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 TRANSMISSION OF TB**

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 significant impact on individual and public health.

<sup>34</sup> <https://www.who.int/publications/i/item/9789240028173>, <https://www.who.int/publications/i/item/meeting-report-of-the-who-expert-consultation-on-the-definition-of-extensively-drug-resistant-tuberculosis>



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

Building on a robust and comprehensive TB research portfolio, HHS/NIH continues to expand its immunology and TB vaccine research program, including novel vaccine development. HHS/NIH is supporting the clinical evaluation of several investigational TB vaccines, including a thermostable adjuvanted subunit vaccine (ID93+GLA-SE), an attenuated Mtb whole cell vaccine candidate (MTBVAC), which may be more protective than the Bacille Calmette-Guérin (BCG) vaccine, and a recombinant BCG vaccine candidate, VPM1002, which is designed to be safer and more efficacious than BCG. 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 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. Researchers are now using this model to define immune correlates and mechanisms of protection, which will inform the basis of the next generation of vaccines either with attenuated whole organism or subunit approaches.

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. With U.S. Government support, TB researchers are exploring novel prevention approaches that leverage recent advances, including COVID-19 vaccine technologies, and evaluating innovative vaccine concepts. In September 2020, NIAID's Advisory Council approved a FY 2022 concept entitled

"Innovation for TB Vaccine Discovery." Concepts represent early planning stages for dedicated programs targeting specific scientific gaps in the NIAID research portfolio. This concept's main goal is to support the design of novel TB vaccine candidates that exploit innovative approaches and their advancement into preclinical animal model testing. 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.

Coordination of research efforts through national and global partnerships is critical to ultimately eradicate TB disease. USAID has 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/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. HHS/CDC and USAID have 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. HHS/NIH is engaged in a partnership with the Bill and Melinda Gates Foundation and the Gates Medical Research Institute to identify vaccine-elicited correlates of protection using samples from a GlaxoSmithKline and AERAS-sponsored Phase 2 trial of the candidate TB vaccine M72/AS01. HHS/NIH has supported the early, pre-clinical and clinical development of M72. A final analysis of the Phase 2 trial recently found the vaccine provided 54 percent protection against active pulmonary TB. In addition, HHS/NIH staff serve as members of the Global TB Vaccine Partnership (GTBVP), a forum for key stakeholders in TB vaccine R&D to identify and address barriers and create opportunities to help accelerate the development of safe and effective TB vaccines.

HHS/NIH is supporting research to develop novel adjuvants and to test adjuvants in combination with Mtb immunogens to determine if they elicit protective immune responses. In September 2020, NIAID's Advisory Council approved a FY 2022 concept entitled "Advancing Vaccine Adjuvant Research

for Tuberculosis (TB).” Concepts represent early planning stages for dedicated programs targeting specific scientific gaps in the NIAID research portfolio. This concept’s main goal is to further the development of preventive, including post-exposure, TB vaccines through side-by-side comparisons of adjuvants in combination with Mtb immunogens, facilitating the identification of Mtb immunogen candidates for clinical development and potential immune correlates of protection.

HHS/NIH is also supporting the “Immune Mechanisms of Protection against Mycobacterium Tuberculosis Center (IMPAC-TB)” program 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 program will also support studies in several animal models to inform vaccine design and undertake in-depth immunological analysis of promising vaccine candidates. 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.

HHS/NIH researchers identified several differences in cytokines in vitro between infected and uninfected lymph nodes, showing a significant role for Mtb in driving the cytokine response at the site of infection. The discovery may offer new immunotherapy targets for vaccine assessment.

### **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, HHS/NIH supports

clinical research to inform the prevention, treatment, and management of TB through NIAID’s AIDS Clinical Trials Group (ACTG) and the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT). The Brief Rifampine-Isoniazid Evaluation for TB Prevention (BRIEF-TB) study, conducted by the ACTG and IMPAACT networks, showed that a one-month regimen of daily rifampine and isoniazid was as safe and effective as the standard treatment of 9 months of isoniazid alone for preventing TB in those infected with HIV. The shorter regimen had a higher degree of adherence than in the nine-month study group. In another 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 delamanid (DLM) versus 26 weeks of isoniazid for preventing confirmed or probable active TB in high-risk household contacts of individuals with MDR-TB. HHS/NIH also supports projects to better understand the immune response to TB in pregnant women and their children and identify immune correlates during pregnancy that predict development of active TB in post-partum HIV-infected women.

HHS/NIH 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 to inform enhanced approaches for preventing TB infections and subsequent disease.

USAID is supporting a study aimed at characterizing 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 spread 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 programs in the U.S. and around the world. 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 people 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 programs, are required to determine whether a diagnostic test improves the accuracy and speed at which individuals of all ages with TB 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 people with DR-TB. The Bacterial and Viral Bioinformatics Resource Center (BV-BRC), which has more than 29,000 Mtb genomes and associated clinical data, provides tools to analyze genomic data. The TBTC and the 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.

The HHS/NIH-supported [TB Portals Program](#) is a web-based, open-access repository of socioeconomic/geographic, clinical, laboratory, radiological, and genomic data from people with DR-TB to facilitate multinational collaboration for data sharing and analysis. These data feed directly into meta-domain and domain-specific tools. Users can view and analyze all domains of TB Portals data together in [Case Browser](#) and [Data Exploration Portal \(DEPOT\)](#); genomics and radiomics data can be singularly explored in [Genomic Analysis Portal \(GAP\)](#) and [Radiomics Analysis Portal \(RAP\)](#), respectively. The newest tool in the TB Portals platform is an [interactive 3D case viewer](#), which launched on March 24, 2021 for World TB Day. Chest CT images housed in the TB Portals with radiologist-provided descriptors and machine learning derived maps of abnormalities allow users to interactively explore changes in the lungs over the course of a clinical MDR-TB treatment.

Scientists in the HHS/NIH-supported Tuberculosis Research Units (TBRU) network developed a time-lapse microscopy tool, ODELAM, that observes individual cells growing into microcolonies. ODELAM enables quantitative measures of growth kinetics and can be utilized to rapidly evaluate Mtb drug resistance in laboratory settings. HHS/NIH supported the development of an Mtb ribonucleic acid (RNA)-based assay that proved promising as a predictive

TB treatment biomarker: Serum diagnostics for pediatric TB are being evaluated as is a novel breath sensor for rapid, low-cost diagnosis of TB in children. HHS/NIH is also supporting research on PCR-based approaches, including the development of a diagnostic using amplicon reconstruction for detection of DNA fragments in urine samples. Finally, within the "Feasibility of Novel Diagnostics for TB in Endemic Countries (FEND for TB) program," HHS/NIH supports clinical evaluation of early-stage TB diagnostics in TB-endemic countries. FEND for TB centers will evaluate many different assays and biomarkers, including diagnostics for triage testing and rapid point-of-care diagnosis and drug susceptibility testing, and will include testing for different populations, such as children and people living with HIV. These centers will also accept requests from diagnostic developers to evaluate early-stage TB diagnostic technologies.

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 THE PROGRESSION TO ACTIVE TB IN CHILDREN AND ADULTS**

HHS/NIH recently awarded projects to support the TBRU network that operates 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. HHS/NIH researchers are working to identify biomarkers that may be useful in differentiating between latency and persistence of TB in individuals in endemic countries. A clinical study was recently launched in India to evaluate why ninety percent of those infected with TB have latent TB infection and why some progress to active TB. The study will assess how risk factors like malnutrition, diabetes mellitus, and helminth infection can affect the biosignatures and impact the development of active TB.

To enable coordinated and comparable research in TB-endemic countries, HHS/NIH has made substantial investments in global TB research programs focused on adults and children. The RePORT Consortium utilizes standardized protocols and is contributing critical resources to other HHS/NIH-funded studies. The development of novel approaches to detect TB in pediatric populations remains a high priority. These efforts include the evaluation of new assays and research to understand biomarkers for risk progression. For example, a comprehensive evaluation of TB biomarkers for children using a novel, hand-held device was recently conducted. 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. Additionally, a study was launched to identify biomarkers, clinical signs, and molecular explanations for paradoxical reactions to TB treatment. Research is being conducted to identify host biomarkers in HIV-infected adults and children, as well as biomarkers for paucibacillary and latent TB. Additionally, novel technologies using biomarkers such as the nanotrap platform are being evaluated for the diagnosis of TB.

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

Improving treatment options for TB 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 care.

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

Basic studies on mycobacterial dynamics remain important to the application of improved DR-TB treatment options. One such study was conducted by the HHS/CDCTBTC and NIAID's ACTG networks to compare mycobacterial isolates before 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 for those with MDR-TB. These efforts include re-mining traditional classes of drugs, such as beta-lactams, and evaluating previously limited-utility antibiotics with new routes of administration, such as inhaled delivery approaches. 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 ACTG conducts clinical trials of existing drugs, including comparison of standard treatments, drug interactions, and pharmacokinetics. Studies are being conducted to evaluate single and combination therapies of new and repurposed drugs and the development of new models to guide optimal TB drug combinations are underway. For example, the first Phase IIc three-month treatment trial for DS-TB (CLOFAST) is being conducted by the ACTG, and research is being pursued on depot medroxyprogesterone acetate (DMPA) in African women receiving treatment for HIV and TB.

Shortening TB drug regimens is critical for treatment adherence, which improves the effectiveness of the treatment. The TBTC and ACTG networks partnered to further investigate improved treatment options for DS-TB disease. As mentioned earlier in this report, 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 whether high-dose (1,200 mg) daily rifapentine can shorten the necessary duration of treatment to four months, with or without moxifloxacin (rather than ethambutol). 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 treatment option is the first successful shorter-course regimen for DS-TB disease in almost 40 years. Additionally, TBTC Study 37 is a Phase III trial to evaluate shortened treatment regimens for latent TB infection. It will compare six weeks of daily rifapentine to the currently recommended three-to-four-month rifamycin-containing regimens.

Both HHS/NIH and HHS/CDC are evaluating novel drug formulations tailored for pediatric populations. 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/NIH is supporting the development of pediatric formulations of fixed-dose combinations of first-line TB drugs. The IMPAACT-led TASK-002 study demonstrated that the bioavailability of bedaquiline (BDQ) tablets suspended in water was equivalent to tablets swallowed whole, suggesting the current formulation could be used to treat MDR-TB in children. Additionally, HHS/NIH is supporting a clinical trial in Vietnam and the Philippines exploring shortening of treatment duration for MDR-TB with the most potent new drugs available.

### **SUB-OBJECTIVE 3.3.2: ENHANCE KNOWLEDGE TO ENABLE THE 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 in decades, BDQ and DLM. 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 people benefit from new drugs. An HHS/NIH-sponsored clinical trial evaluated use of BDQ and DLM, alone and in combination, in adults with and without HIV co-infection, taking multidrug treatment for MDR-TB or rifampicin-resistant TB (RR-TB), and established the safety of using the two drugs in combination. HHS/NIH is also sponsoring Phase I/II trials to evaluate the use of BDQ in combination with optimized individualized MDR-TB therapy in HIV-infected and uninfected infants, children, and adolescents with MDR-TB disease, and the use of DLM in combination with optimized multidrug regimen for MDR-TB in children with and without HIV co-infection.

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 individuals with MDR-TB. 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. 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 those with MDR-TB with additional resistance to fluoroquinolones in South Africa (BEAT Tuberculosis Study) and in those with pre-XDR and XDR-TB in India (BEAT TB). The USAID-supported BEAT studies are currently enrolling people. Finally, to support the use of the recently FDA-approved bedaquiline, pretomanid, and linezolid (BPaL) regimen, USAID is supporting the clinical access program (CAP) for the BPaL regimen in South Africa. The BPaL CAP will generate programmatic evidence to inform the successful introduction of the regimen in countries.

HHS/NIH is pursuing studies of additional TB drug candidates. One such trial is evaluating the pharmacokinetics, safety and acceptability of pretomanid in children with RR-TB. Another is supporting a Phase II study of an all-oral treatment regimen for multidrug resistant pulmonary TB in the Philippines and Vietnam. The study will evaluate the efficacy and tolerability of the regimen and determine the optimal duration of treatment.

In collaboration with the Global Alliance for TB Drug Development, HHS/CDC is working to determine pretomanid minimum inhibitory concentrations (MIC) for multidrug-resistant isolates of *M. tb* from those with TB in the United States. HHS/CDC is also working with U.S. TB programs and CDC-funded TB Centers of Excellence to identify and monitor those who are being treated with bedaquiline, pretomanid, and linezolid (BPaL).

HHS/NIH investigators have identified a plasma chemokine signature that can be used as a novel biomarker for predicting

adverse treatment outcomes in pulmonary TB, and recently launched a clinical study to better understand paradoxical reactions in people with TB and associated sequelae.

### **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 to select the most promising new compounds for further advancement, including spectinomides, nucleoside antibiotics, beta-lactams, oxazolidinones, and other new classes of experimental 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 also continues to participate in the TB Drug Accelerator (TBDA) 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 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 clinical trials of host-directed therapies, including a Phase IIb dose-finding study of pravastatin in adults, a Phase II trial of the safety, pharmacokinetics, and hematologic effects of imatinib on myelopoiesis in adults when given with and without isoniazid and rifabutin, and a prospective Phase II study of metformin in combination with standard treatment regimens of pulmonary TB in people coinfecting with HIV. Additionally, researchers are conducting a study to assess if those with less severe TB might not require the standard six-month treatment duration. By using PET/CT lung scans with estimates of TB burden, researchers hope to reduce treatment time to four months.

HHS/NIH is advancing pre-clinical studies to identify completely novel therapeutic targets and new approaches to

improve treatment outcomes. Scientists recently elucidated the role of mucosal-associated invariant T (MAIT) cells during TB infection. The research team showed that during early infection MAIT cells directly contribute to the slow priming of CD4 T cells, but during later infection MAIT cell stimulation may be an effective host-directed therapy for TB. HHS/NIH also issued a new funding opportunity in 2020 to support pre-clinical studies of vaccines as an adjuvant to improve treatment of active TB in people living with and without HIV. Since 2013, HHS/NIH has led an effort to reintroduce the concept of therapeutic bacteriophage for treatment of infectious diseases. This concept has been expanded through a new funding opportunity to support the development of bacteriophage therapy bacterial pathogens, including TB.

HHS/NIH is supporting several innovative approaches to new TB treatments, including the development of new in silico models and pharmacokinetic methodologies 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 experimental antibiotics, and pediatric-friendly formulations. A new funding opportunity announcement was recently issued to support the development of new long acting or extended-release formulations of existing drugs for the treatment of TB. HHS/NIH has supported studies to further investigate the mechanism of action of TB drugs, like pyrazinamide, and experimental antibiotics, which helped prioritize new TB drug regimens for further development. HHS/NIH has provided pre-clinical and clinical support, including animal model support, for development of novel classes of antibiotics and supports clinical trials on a shortened treatment regimen for MDR-TB and pharmacokinetics during pregnancy and the post-partum period. The Structural Genomics Center for Infectious Diseases (SGCID) 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 places a strong emphasis on pre-clinical development of therapeutic candidates through a variety of mechanisms. Contracts that test and help develop pre-clinical therapeutics have been utilized by over 100 research groups in more than 40 countries. The TB Imaging Program (TBIP)

uses predictive Mtb infection models and the application of medical imaging techniques. TBIP uses CT and PET with functional markers for inflammation or other indicators to follow TB disease development and responses to preventative or therapeutic interventions, and evaluates potential chemotherapeutic and novel regimens for TB treatment in pre-clinical models. HHS/NIH assisted the TB Alliance in the pre-clinical development of a new oxazolidinone antibiotic by providing evaluations and administrative assistance in preparation for a safety study. HHS/NIH collaborated with Merck to develop a TB-selective oxazolidinone that should have none of the safety concerns of linezolid which will enter Phase I testing in 2022.

The development of novel and shorter treatment regimens is critical to prevent, treat, 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 more than 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 to build research capacity in TB-endemic countries. 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 to build research capacity in TB-endemic countries. Through the FEND for TB program, HHS/NIH is strengthening capacity for TB diagnostics research in TB-endemic countries. The network includes three centers that will provide clinical site capacity in 12 TB-endemic countries. In addition, HHS/NIH recently announced the "Tuberculosis Research Advancement Centers" initiative, which will establish multidisciplinary collaborative research teams in the U.S. and TB-endemic areas to recruit and mentor the next generation of TB investigators and attract investigators to the TB field. 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 these funding opportunities, HHS/NIH continues to provide training in grant writing, financial administration, bioethics, and implementation research.

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. The ICER program is focused on infectious disease clinical research, with centers that can address the research and training needs of greatest relevance to the local population. Due to the high prevalence of TB in India, significant research efforts are focused on this area. The ICER holds long-term collaborations in country and has developed a core research program that includes the improvement of laboratory and clinical field site infrastructure and enhancement of information technology capability.

HHS/NIH continues to support the International Tuberculosis Research Center, an ongoing collaboration between NIAID and the South Korean Ministry of Health and Welfare that is focused on clinical trials of TB, particularly MDR-TB

and XDR-TB. HHS/NIH also continues to conduct clinical research on TB in TB-endemic countries in areas to improve treatment outcomes, evaluate mechanisms of drug resistance, and study the impact of improved screening on TB incidence.

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 (including 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 disease research, TB research has been affected by the COVID-19 pandemic. Many laboratories needed for TB research were temporarily closed in 2020 and re-opened with minimal personnel to

maintain social distancing. Labs continue to be affected in 2021, and some researchers still have restricted or limited access to facilities, equipment, and animal models. Additionally, the pandemic is contributing to supply chain disruptions, particularly in TB-endemic countries, and many resources have been diverted to support the response to COVID-19. The pandemic has also created uncertainty among the research workforce, including for trainees and early career scientists. HHS/NIH supports clinical trials and studies on TB, which have been significantly impacted as focus in many parts of the world has shifted to COVID-19 and trial enrollment was often not permitted due to safety concerns. HHS/NIH is supporting limited studies on COVID-19 and TB, including a natural history study of COVID-19 and interactions with HIV, TB, and hypertension in Haiti and Tanzania. HHS/NIH also is supporting two studies in South Africa to help understand the impact of COVID-19 on TB. The studies will test the hypothesis that co-infection with SARS-CoV-2 will have a significant impact on protective innate immunity in people with TB spanning the Mtb infection spectrum and assess the association between SARS-CoV-2 infection and an increased risk of primary TB infection and/or TB reactivation.

With the pandemic's negative impact on TB case detection, USAID and HHS/NIH will invest in research to find new TB diagnosis tools and approaches for increasing the detection of all forms of TB in adults and children—as well as continue research that will evaluate new anti-TB medications, treatment, and prevention regimens. In addition, COVID-19 and TB's impact on quality of life, the potential need for pulmonary rehabilitation, and long-term socioeconomic and mental health support are future challenges needing further evaluation. Working with local organizations, USAID research projects will address social, behavioral, and other determinants of TB and TB/COVID-19 to improve program performance and TB care delivery.

# CONCLUSION

While the U.S. Government Departments and Agencies charged with implementing the *National Action Plan* have met all Year Five milestones, the COVID-19 pandemic has negatively impacted activities related to the detection and treatment of DR-TB. In 2020, data showed a 26 percent decline in DR-TB case detection in *National Action Plan* countries compared to 2019, when there was a seven percent increase, as compared to 2018.

To address this serious situation, five USAID-supported *National Action Plan* countries (India, Indonesia, Philippines, South Africa, and Ukraine) are among the countries that have developed and implemented plans to recover from COVID-19's devastating impact on TB and DR-TB programs. These recovery efforts are utilizing innovative approaches to target barriers to TB case finding and treatment enrollment and adherence.

Despite setbacks from the COVID-19 pandemic, the *National Action Plan* countries have made significant contributions to global efforts in scaling up DR-TB detection and treatment, and the uptake of new DR-TB treatment regimens over the five-year implementation of the *National Action Plan*.

The *National Action Plan* has paved the way for the rapid introduction and scaling up of new tools to diagnose and treat DR-TB. Over the five years of its implementation, the number of people who started on the new BDQ-containing treatment regimen increased by almost seven times, from 4,277 in 2016 to 30,410 in 2020. The *National Action Plan* also provided U.S. Government Departments and Agencies with the opportunity to support research and development and to closely monitor the progress made by implementing these research activities. Moving forward, the *National Action Plan* could prove to be an important tool in advocating for increasing commitments to address DR-TB.

While this five-year plan has concluded, it is critical to build on the progress and structures established through the *National Action Plan*—expanding to more countries and further scaling up interventions to ultimately have a

greater impact on detecting and treating DR-TB. 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, DR-TB remains a dire global health security threat. Because of this, it is increasingly vital that high DR-TB burden countries, partners, and donors accelerate efforts and investments to mitigate the setbacks caused by COVID-19 and further accelerate progress to address and eliminate TB and DR-TB.



# APPENDIX: MILESTONES AND ADVANCES

## GOAL I

<b>Objective 1.1 Upgrade TB surveillance to ensure complete and accurate detection of drug-resistant TB</b>	
<b>Year Five Milestones</b>	<b>Year Five Progress</b>
CDC will work with its partners to establish an updated electronic surveillance system for collecting, analyzing, and storing national and State-level TB clinical data.	<ul style="list-style-type: none"> <li>▪ CDC upgraded the U.S. domestic TB surveillance system to collect and report the results of new methods for identifying drug resistance. Specifically, CDC has developed and tested the molecular drug susceptibility testing reporting (MDSTR) form to provide standardization within the National TB Surveillance System. These new variables will be included in the updated Report of Verified TB form used in collecting data on all U.S. TB disease cases.</li> <li>▪ CDC is pilot testing HL7 standardized coding for Electronic Laboratory Reporting (ELR) into state surveillance systems, as well as standardized coding for electronic transmission from state surveillance systems into MDSTR data collection systems. Nationwide standardized coding will improve the validity of all data on drug resistance.</li> </ul>
<b>Objective 1.2 Strengthen State and local capacity to prevent transmission of drug-resistant TB</b>	
<b>Year Five Milestones</b>	<b>Year Five Progress</b>
CDC will work with its partners to develop new tools to facilitate contact investigations.	<ul style="list-style-type: none"> <li>▪ HHS/CDC finalized new metrics for tracking TB transmission that can be applied to DS-TB and DR-TB.</li> <li>▪ HHS/CDC postponed expanding data collection for drug susceptibility testing results in the new version of Report of Verified Case of TB (RVCT) in 2020, because TB programs lacked capacity for making this change while addressing the pandemic. This work will continue in 2021</li> </ul>
CDC will work with the National TB Controllers Association to develop a surge-capacity plan for rapid response to control cases, clusters, and outbreaks of drug-resistant TB.	<ul style="list-style-type: none"> <li>▪ HHS/CDC and state and local partners are coordinating investments from the American Rescue Plan to strengthen the disease intervention specialists (DIS) workforce to respond to COVID-19 and other infectious diseases.</li> </ul>
<b>Objective 1.3 Ensure that patients with drug-resistant TB receive treatment until cured</b>	
<b>Sub-objective 1.3.1 Explore the potential use of a national TB stockpile to ensure the availability of TB medicines and screening tests</b>	
<b>Year Five Milestones</b>	<b>Year Five Progress</b>
CDC will work with public and private sector organizations to maintain a supply of TB drugs.	<ul style="list-style-type: none"> <li>▪ HHS/CDC, in collaboration with the HHS Supply Service Center, maintains a small stockpile of crucial drugs for treating TB disease and TB infection. In the event of a national shortage, TB programs can request drugs to ensure those with TB can remain on TB treatment without interruption.</li> </ul>

<b>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.</b>	
<b>Year Five Milestones</b>	<b>Year Five Progress</b>
CDC and other State and Federal agencies will identify mechanisms for providing resources to or care for patients with MDR-TB or XDR-TB.	<ul style="list-style-type: none"> <li>In 2020, HHS/CDC completed a randomized controlled trial of eDOT conducted in collaboration with partners at the New York City Department of Health and Mental Hygiene's Bureau of TB Control. Researchers found that TB treatment provided by eDOT was at least as effective as traditional in-person DOT for ensuring high adherence to TB treatment and enabling patient-centered care for TB disease. Patient safety for eDOT was similar to that of in-person DOT. An economic evaluation linked to this trial determined that eDOT was associated with lower costs from a societal perspective, and with lower or similar costs from a program perspective.</li> </ul>
<b>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</b>	
<b>Year Five Milestones</b>	<b>Year Five Progress</b>
CDC will work with the State and local programs and other partners to identify mechanisms for improving U.S. management for transnational cases of TB disease	<ul style="list-style-type: none"> <li>Ongoing.</li> </ul>
CDC will work with State and local programs and other partners to develop a case definition for transnational (or binational) TB disease cases.	<ul style="list-style-type: none"> <li>HHS/CDC and state and local partners identified a surveillance definition for describing binational TB cases. The new definition includes cases that include "crossed border while on TB treatment" and "received treatment in another country, coordinated by an established, US-funded, binational TB program." <a href="https://pubmed.ncbi.nlm.nih.gov/29570435/">https://pubmed.ncbi.nlm.nih.gov/29570435/</a></li> </ul>
CDC will work with State and local programs and other partners to establish indicators to measure treatment completion rate for transnational TB cases.	<ul style="list-style-type: none"> <li>HHS/CDC has added a variable for reporting binational cases to its Report of Verified Case of TB (RVCT). Due to TB programs' involvement in addressing COVID-19 cases, State and local health departments have not fully implemented the new form, and HHS/CDC and partners have not developed an indicator for completion of treatment for these cases.</li> </ul>
CDC will establish national baseline data to measure improvements in treatment completion rates.	<ul style="list-style-type: none"> <li><a href="#">National TB Indicators</a> are key process and outcome measures for TB control programs in the United States, including treatment completion. HHS/CDC publishes progress towards these indicators annually at <a href="https://www.cdc.gov/tb/statistics/indicators/2019/StateCity-TBReport.htm">https://www.cdc.gov/tb/statistics/indicators/2019/StateCity-TBReport.htm</a>.</li> </ul>
CDC will explore the possibility of extending medical exams and treatment overseas to persons who are likely to remain in the United States for 6 months or longer.	<ul style="list-style-type: none"> <li>On hold due to COVID-19.</li> </ul>

## 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 Five Milestones	Year Five Progress
<p>USAID and CDC will work with up to 10 countries to implement nationwide screening of TB patients for MDR-TB through drug-resistance testing.</p>	<p>USAID-led achievements:</p> <ul style="list-style-type: none"> <li>▪ TB case finding and identification of DS-TB and DR-TB strains are key components of every national TB response and an integral part of USAID support in the country.</li> <li>▪ Over the period of the National Action Plan (NAP) implementation in the 10 priority countries, USAID achieved significant progress in expanding access to DR-TB screening and testing. Drug-resistant testing has improved from as low as 11 percent in 2015 to almost 84 percent among bacteriologically confirmed individuals with new TB on average and reached 100 percent in two NAP countries (Kazakhstan and South Africa).</li> <li>▪ With USAID support, countries have modified policies and protocols to allow more patient groups to get tested with rapid drug-susceptibility tests like GeneXpert (GX) and first-line lane probe assay (LPA). In countries like South Africa, Philippines, Nigeria, Pakistan, Kazakhstan, and Ukraine, new policy allowed GX to be used as a screening TB test among people with TB signs and symptoms, instead of smear microscopy, which significantly improved the yield of TB notification and allowed simultaneous detection of DR-TB.</li> <li>▪ Overall, during the five years of NAP implementation, all 10 priority countries have implemented activities aimed at DR-TB case finding and early diagnosis, improved policy to expand testing coverage, and achieved notable progress in expanding testing services nationwide.</li> </ul> <p>CDC-led achievements:</p> <ul style="list-style-type: none"> <li>▪ None to report.</li> </ul>

<p>USAID and CDC will work with up to 10 countries to develop quality-assured laboratories capable of diagnosing and monitoring MDR-TB consistent with international standards using the latest tools and technology.</p>	<p>USAID-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ In 2020, support was provided to nine countries ( Burma, India, Indonesia, Kazakhstan, Nigeria, Pakistan, the Philippines, South Africa, and Ukraine) to expand the national TB laboratory networks, add more GeneXpert instruments, and expand LPA sites. With the support of USAID and other donors, countries have been able to add more laboratory tools to ease access to rapid diagnostic tests for TB and DR-TB. For example, in South Africa, by the end of Year Five, 166 sites were equipped with GX instruments and 15 laboratories were performing TB culture procedures, with eight of them having capacity for drug-resistance testing. Nigeria was able to install 399 GX instruments across the country, which enabled them to reach vulnerable groups as well as communities in hard-to-reach areas.</li> <li>▪ Quality assurance is an integral part of any TB laboratory practice, and USAID has been working with its partners on the ground in the NAP countries to set up policies and practices according to the international standards. Trainings and capacity building have been provided to laboratory staff on panel testing, training of trainers, on-site supervision and monitoring &amp; evaluation. As a result, by the end of 2020, most of countries LPA laboratories, as well as DST culture laboratories, introduced quality assurance standards and participated in the quality monitoring system. For example in India, 100 percent of DST laboratories had quality assurance in place, and most of the GX sites implement protocols aimed at reducing errors and following international best practices.</li> </ul> <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ In 2020, HHS/CDC supported India to conduct its first pan-India external quality-assurance program for 1187 GX instruments from 1130 sites. Training through national TB reference laboratories and partners for all states TB programs and intermediate reference laboratories were done initially in person and transitioned virtually due to lockdowns and travel restrictions due to the COVID-19 pandemic. An electronic EQA portal was piloted and modified, allowing state programs to submit EQA results and receive feedback. External quality methods for TrueNat, the new rapid molecular test that will be replacing sputum smear, were pilot tested in late 2020.</li> <li>▪ HHS/CDC has been supporting the National Health Laboratory Service (NHLS) to strengthen delivery of and to expand access to quality laboratory services and enhancing healthcare worker and laboratory safety in South Africa.</li> <li>▪ HHS/CDC also supported TB reference laboratories in South Africa 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.</li> </ul>
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<b>Sub-Objective 2.1.2 Expand and strengthen national MDR-TB care and treatment capacity to optimize the use of current and novel regimens</b>	
Year Five Milestones	Year Five Progress
<p>USAID will work with up to 10 countries to introduce shortened MDR-TB regimens.</p>	<ul style="list-style-type: none"> <li>▪ Since 1997, WHO has been recommending treatment options for people with MDR-TB via a mixture of first- and second-line medications. Initial regimens contained both injectable and oral medications, consisting of five to seven drugs and lasting for 18 to 20 months. Only in 2016, WHO reviewed evidence from the nine-month treatment regimen implementation in 20 countries and issued a 2016 update to the MDR-TB treatment guidelines, specifically recommending the implementation of the standard shorter regimen under programmatic conditions.</li> <li>▪ In 2020, further modifications to the shorter regimens have been applied and injectable agents were removed to improve safety and quality of DR-TB care provided. All NAP countries introduced the change and achieved different levels of progress by the end of the year. For example in Pakistan, 80 percent those with DR-TB enrolled on all-oral regimen, and in South Africa it reached 89 percent. Overall, 34,652 individuals with DR-TB have been provided with the novel treatment option in 2020.</li> </ul>
<p>USAID will work with up to 10 countries to scale-up quality facility and community-based MDR-TB care and treatment services.</p>	<p>USAID-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ In 2020, USAID supported NAP countries to expand DR-TB treatment sites, scale up of home-based care, introduce innovative treatment monitoring tools, and provide technical assistance to improve the quality of DR-TB care. For example, Indonesia increased the number of treatment initiation sites from 153 sites in 2018 to 282 in 2020, with about 42 percent of those receiving ambulatory-level care. In South Africa, 650 treatment initiation sites were operational by the end of 2020, and DR-TB care was decentralized to the primary health care level in order to improve access to care and adherence to treatment. In the Philippines, the number of DR-TB treatment sites increased from 171 in 2018 to 199 in 2020, and 100 percent of those with DR-TB receive treatment at the community or ambulatory level.</li> </ul>



Sub-Objective 2.1.3 Strengthen TB and MDR-TB surveillance	
Year Five Milestones	Year Five Progress
<p>USAID and CDC will work with up to 10 countries to implement standards and benchmarks to improve surveillance and vital registration systems to directly measure TB burden.</p>	<p>USAID-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ To correctly measure TB incidence and TB notifications countries must implement active TB surveillance as well as vital registration systems. In 2020, USAID supported nine NAP countries (Burma, India, Indonesia, Kazakhstan, Nigeria, Pakistan, the Philippines, South Africa, and Ukraine) to further improve monitoring and evaluation (M&amp;E) of DR-TB case detection and registration. Also, National TB Programs further utilized the standards and benchmarks (S&amp;B) tool, which were introduced by WHO in order to help countries improve their M&amp;E system for TB data collection and analysis.</li> <li>▪ As of December 2020, the following countries had completed the standards and benchmark checklist: Burma (2016), Indonesia (2017), Kazakhstan (2017), Nigeria (2017), Pakistan (2016), Philippines (2017), South African (2015), Ukraine (2014), China (2018), and India (2018). Also, all NAP countries have been participating in annual TB data collection exercises, led by WHO, which helped to populate the global TB database and is the basis for Annual Global TB Report.</li> </ul> <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ HHS/CDC led the national mini-epidemiological review in support of the India Joint Monitoring Mission (JMM) in 2019. A systematic assessment of the TB surveillance system at the district and state levels was done for 10 sites, using the WHO standardized standards and benchmarks.</li> </ul>
<p>USAID will work with up to 10 countries to scale-up patient-based electronic recording and reporting systems;</p>	<p>USAID-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ USAID has been supporting NAP countries to implement, expand, and scale up an electronic recording and reporting system for individuals with DR-TB since 2016, and has continued the technical support through 2020. A lot of progress has been made in most NAP countries over the five years of the NAP implementation. Significant shift into digital area was done in 2020, due to the COVID-19 pandemic, which catalyzed the utilization of digital systems for all aspects of TB care, from registration and treatment initiation, to monitoring the treatment adherence and establishing remote communication with those with DR-TB and the caregivers.</li> <li>▪ In Burma, two M&amp;E digital systems are used for those with DR-TB: an Excel-based recording (ENRS) and OpenMRS. In 2020, 100 percent of those with DR-TB were monitored in the excel-based system and further assistance from donors would be needed to achieve full transition to OpenMRS by 2022. In Ukraine, 100 percent of those with DR-TB were monitored via the E-TB manager system, which was developed by a USAID-funded project. India has scaled-up the NIKSHAY system to record and monitor all those with TB, including, DR-TB. USAID is ensuring that any new, innovative diagnostic models are integrated with this system. In the Philippines the Integrated TB Information System (ITIS) has been implemented nationwide since 2017, and 100 percent of individuals with DR-TB are monitored in the system. In 2020, USAID support continued to roll-out mandatory TB notification, particularly in the private sector.</li> </ul>

<p>DOD will work with other U.S. departments and agencies to enhance collection and sharing of TB and MDR-TB data in strategically relevant areas where the U.S. military may be deployed.</p>	<p>DOD-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ No international surveillance data to report.</li> </ul>
<p>USAID and CDC will work with up to 10 countries to implement an approach to link laboratory and TB and MDR-TB program-surveillance systems using novel approaches that enable more rapid diagnosis and initiation of treatment nationwide.</p>	<p>USAID-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ Installation and scale up of rapid TB diagnostic tools, such as GX or TrueNat requires rapid registration of notified DR-TB cases and immediate treatment initiation. However, given that most of the diagnostic instruments located at the primary healthcare level, only digital connectivity allows such actions during the 5 years of NAP implementation USAID has been assisting NAP countries to initiate and scale up connectivity solutions such as GX Alert, DataToCare, SMS-reporting systems, and others.</li> <li>▪ For example, in South Africa an automated, weekly alert systems was in place for any rifampicin-resistant cases. Alerts are sent to NTP managers at provincial and district level. In Nigeria an electronic, real-time reporting system was in place for GX results, with most GX tests being reported with the exception of some GX machines with poor internet connectivity. In Indonesia, USAID supported implementation of GX connectivity and made it link with NTP information system.</li> <li>▪ However, not all countries have been successful in the implementation. No significant progress has been made in China, Pakistan, and Kazakhstan. In Nigeria and Ukraine, the pilots were initiated but will require more assistance and support for the national scale up.</li> </ul> <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ 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. Prospective DR-TB samples across India are being sampled to refine the DR-TB database for DR-TB mutations.</li> <li>▪ 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.</li> <li>▪ HHS/CDC supported the Whole Genome Sequencing (WGS) project in South Africa which aims to enhance microbiological and epidemiological surveillance of TB. MDR TB transmission surveillance serves as an early warning system for detection of high-risk clusters of DR-TB using traditional typing methods and has been established at the Centre for Tuberculosis in selected districts in South Africa.</li> <li>▪ In South Africa, HHS/CDC continues to support the monitoring and evaluation of TB activities by NDoH, including EDR-Web, a Health Management Information System for reporting and monitoring of DR-TB data.</li> </ul>

- HHS/CDC is collaborating with the National TB and Leprosy Control Program (NTBLCP) and the National HIV Program in the Nigerian Federal Ministry of Health (FMOH), to develop capacity for **Sequencing-based Sentinel Surveillance for Drug Resistant Tuberculosis in Nigeria**. The ultimate goal of this initiative is to develop a **Regional Sequencing hub for drug-resistant Tuberculosis (REST Hub)** in Nigeria, by leveraging existing HIV sequencing capacity.

**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 Five Milestones	Year Five Progress
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USAID will work with up to 10 countries to scale up an MDR-TB early warning drug procurement and management system.

- USAID-led Achievements:
- In 2020, USAID worked with nine NAP countries (Burma, India, Indonesia, Kazakhstan, Nigeria, Pakistan, the Philippines, South Africa, and Ukraine) to assist with the TB drug procurement, management, and monitoring system. The immediate goal was to set up a robust TB procurement and supply chain system (PSM), which can track the drug stock, provide an early warning if the stock level of medications is low, and assist the NTP to prepare drug quantification for the procurement.
  - In Burma and Indonesia, the USAID-funded GHSC-PSM Project assisted NTPs to implement drug stock and monitoring systems at the national levels and improve international drug orders. In Ukraine and the Philippines, the QuanTB tool has been used for several years, after being installed by a USAID project. In India, Kazakhstan, South Africa, Pakistan, and Nigeria, locally designed solutions have been used to monitor the drug stock, and USAID provided technical support for expansion and maintaining the progress.
  - Due to the COVID-19 pandemic, four of NAP countries experienced temporarily TB drug stockouts, which were immediately mitigated by the PSM system: Burma experienced stockouts of INH and Para-aminosalicylic acid; the Philippines, with TB medications for children and Delamanid for DR-TB; Ukraine with several second-line medications; South Africa with several first-line medications, as well as with Moxifloxacin, Ethionamide, and Levofloxacin for DR-TB.

USAID will work with up to 10 countries to assist them with their in-country regulatory approval processes of first-line and second-line drugs.

- USAID implementing partners have been working with local drug regulatory authorities (national FDAs) to strengthen regulatory systems for the approval of the first-line and second-line anti-TB drugs and ensuring rational use of anti-TB drugs. USAID provided support, depending on country needs, as well as available partners and experience on the ground, which varied from country to country. In general, USAID partners have been assisting national counterparts with finding mechanisms for registering essential unregistered drugs in the country, supporting health technology assessment for new TB medicines and short-term treatment regimens, conducting a feasibility assessment for regulatory system strengthening for ensuring rational use of TB drugs by the private TB providers, and implementing a multi-pronged approach for successful implementation of regulatory control for the selection, procurement and warehousing, distribution, and rational use of anti-TB medicine.

	<ul style="list-style-type: none"> <li>In 2020, national medicine regulatory authorities/agencies in multiple NAP countries registered many TB and DR-TB medications. For example: in the Philippines, 10 new medications dossiers were submitted for registration; in Kazakhstan, the Delamanid medicine was registered; in Burma, two first-line TB medications submitted for approval.</li> </ul>
<b>Objective 2.2 Prevent MDR-TB Transmission</b>	
<b>Sub-Objective 2.2.1 Improve access to high-quality, patient-centered MDR-TB services</b>	
<b>Year Five Milestones</b>	<b>Year Five Progress</b>
<p>USAID will work with up to 10 countries to further increase, beyond the 3-year milestones, enhanced patient identification and medical screening of individuals at high risk for MDR-TB.</p>	<ul style="list-style-type: none"> <li>In 2020, USAID support was aimed at expanding access to GeneXpert tests (for rapid TB and DR-TB detection) by operationalizing additional GX instruments, providing TA for installation of new instruments, improving system on sample transportation, and expanding diagnostic algorithms for better access and coverage.</li> <li>In India, for example, the government was able to implement universal DST via GX and TrueNat instruments and expand sequential DSTs to guide appropriate treatment initiation. In Kazakhstan, contacts with individuals with TB, people with pulmonary sequelae, people with some medical conditions (HIV/AIDS, under immunosuppressive treatment, diabetes, drug users, pulmonary chronic diseases) and prisoners have been selected for expanded access to rapid DST. In South Africa and the Philippines, new policies allow rapid DST to be used for TB suspects as well as TB contacts and people with HIV.</li> <li>However, due to the COVID-19 pandemic, most NAP countries experienced strict lockdowns, limited access to healthcare facilities for TB screening and testing, and significant reductions of rapid TB diagnostic tests performed. For example, in Burma, in 2020, only 74,799 people were tested for DR-TB, compared to 126,328 in 2018. In India, 1,170,646 people were tested for DR-TB in 2020, compared to 1,405,396 in 2018. In South Africa, 308,967 fewer tests were performed than estimated.</li> </ul>
<p>USAID will work with up to 10 countries to scale-up patient-centered MDR-TB quality service delivery site monitoring.</p>	<ul style="list-style-type: none"> <li>In 2020, USAID supported countries in implementing a proactive system of quality monitoring in order to improve quality of DR-TB treatment and improve adherence and treatment response. Regular treatment site monitoring, supervision visits, and regular cohort reviews are essential tools for DR-TB quality assurance. Since DR-TB treatment takes many months, early assessment (ideally each quarter) help TB specialists to identify hidden gaps and issues and correct them before individuals are lost to follow up.</li> <li>USAID has been supporting NAP countries to improve the quality of DR-TB care and person-centered approaches since 2016. By the end of 2019, all 10 priority countries established an enhanced system of adherence and treatment monitoring. In 2020, NTPs and partners were expanding the cohort review approaches to the national level and expanded the cohort sizes. With the exception of China, all other countries expanded outpatient and ambulatory-based care in 2020, and the COVID-19 pandemic catalyzed the approach, when limited face-to-face interaction was possible.</li> </ul>

Sub-Objective 2.2.2 Enhance adherence to TB and MDR-TB treatment	
Year Five Milestones	Year Five Progress
USAID will work with up to 10 countries to scale-up ancillary care packages to improve MDR-TB patient treatment outcomes.	<ul style="list-style-type: none"> <li>▪ In 2016, USAID developed the DR-TB Care Package Tool with the aim to provide comprehensive treatment and social and psychological support to all those with DR-TB in NAP priority countries and globally. In 2018, the pilot activity was initiated in China, Pakistan, South Africa, and Ukraine, and 1,081 individuals with DR-TB were enrolled to test the developed approach and assess effectiveness and feasibility before the global scale up.</li> <li>▪ In 2018, USAID has brought together DR-TB experts from 10 NAP countries to disseminate results of the pilot and train and support the adaptation of the DR-TB Care Package. By the end of 2018, eight countries had either implemented or introduced the approach at the national level: Burma, China, India, Indonesia, Nigeria, Pakistan, South Africa, and Ukraine.</li> <li>▪ In 2020, NTPs and national partners expanded access to adherence support for those with DR-TB via either the DR-TB Care Package or other interventions. Even with the COVID-19 pandemic, most of the NAP countries provided and further expanded support. For example, in Burma 98 percent of those with DR-TB received non-medical treatment support, and the treatment success rate reached 80 percent for those with DR-TB (cohort of 2017). In India, implementation of adherence support with the combination of shorter regimen improved treatment success rate from 48 to 76 percent (cohort of 2018). In Nigeria, all people with DR-TB receiving non-medical adherence support and treatment success rate reached 77% and lost to follow up rate reduced to five percent (cohort of 2017).</li> </ul>
USAID will work with up to 10 countries to address gaps identified by the TB treatment adherence assessment tool.	<ul style="list-style-type: none"> <li>▪ Starting 2018, USAID began working with NAP countries to fast-track and bring new digital TB innovations into life. Together with partners, USAID identified digital solutions to support monitoring of TB adherence as well as assist TB providers with treatment monitoring. Number of digital tools, smartphone apps and software have been developed globally with the aim at supporting individuals with TB to stay adherent and for providers to monitor them electronically. In 2018, USAID brought together experts from 10 NAP countries in India, demonstrated novel digital solutions and assisted countries to select top-three innovations for piloting and further scale up.</li> <li>▪ In 2019 and 2020, USAID supported partners and the NTPs to implement and scale up digital and other innovative solutions, aimed at improved adherence to DR-TB treatment. USAID assisted countries with implementation of 99DOTS, Video DOT, SMS-reminders and smart pill boxes. By the end of 2020, eight countries achieved significant progress in implementation of digital adherence tools (all except Pakistan and China).</li> <li>▪ With the COVID-19 pandemic affecting TB case finding and treatment monitoring, countries emphasized remote treatment monitoring, using digital tools and technologies.</li> </ul>



**Sub-Objective 2.2.3 Prevent the transmission of TB and MDR-TB within health care facilities**

Year Five Milestones	Year Five Progress
<p>USAID and CDC will work with up to 10 countries to ensure surveillance and screening of all health-care workers in facilities responsible for diagnosis and treatment of individuals with, and at high risk for, MDR-TB.</p>	<p>USAID-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ Beginning in 2017, USAID started to assist NTPs and local partners with the implementation of policies and practices related to screening and testing healthcare workers for TB. New protocols, policies, and executive orders have been created and approved for implementation in many NAP countries. Regular screening and testing for TB among healthcare workers improved and resulted in better detection of TB at the early stages.</li> <li>▪ For example, in Kazakhstan the number of TB staff that were diagnosed with TB decreased from 38 people (221.6 per 100,000) in 2013 to 12 in 2017 (103.4 per 100,000), to 11 in 2019 (115,9 per 100,000). In 2020, 8,579 health and auxiliary staff of the TB service were screened for TB, and only four people have been detected with TB. In South Africa, the number of healthcare staff screened from TB has increased from 967 in 2017 to 19,076 in 2019. The number of confirmed cases also increased in 2019 to 28.</li> <li>▪ By the end of 2020, five countries have policies in place for healthcare worker screening: Burma, Philippines, India, Kazakhstan, South Africa (awaiting cabinet approval), and Ukraine. In Indonesia, a general screening guideline exists in the national infection control and prevention protocol, not specific to TB.</li> </ul> <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ HHS/CDC has supported activities related to health-care worker screening for TB in primary and secondary facilities for 10 wards in Mumbai.</li> <li>▪ HHS/CDC supported implementation of infection prevention and control in cities of Mumbai and Chennai in collaboration with the city Municipal Corporations. 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.</li> <li>▪ HHS/CDC assisted the NDoH and Provincial Departments of Health in South Africa to strengthen infection prevention and control. The key focus areas to reduce nosocomial and community-acquired TB through IPC measures included capacity building, implementation support, enabling systems and education support.</li> </ul>

# 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 Five Milestones	Year Five Progress
<p>NIH will continue to support research, pre-clinical studies, and clinical trials and studies for the evaluation of new vaccines, adjuvants, and preventive drugs.</p>	<p>NIH-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ The Vaccine Research Center's (VRC) Tuberculosis Vaccine Unit continues to support scientific investigation and clinical development of new vaccine strategies for preventing TB infection and disease.</li> <li>▪ VRC researchers found that nine out of ten macaques w/ IV BCG vaccination were highly protected, with six macaques showing no detectable levels of infection. This level of sterile protection is unprecedented (Nature, <a href="https://www.nature.com/articles/s41586-019-1817-8">https://www.nature.com/articles/s41586-019-1817-8</a>); ongoing work is using this model to define immune correlates and mechanisms of protection. This will inform the basis of next generation vaccines either with attenuated whole organism or subunit approaches.</li> <li>▪ Recent Funding Opportunities:               <ul style="list-style-type: none"> <li>• Release of RFA-AI-21-007 "Innovation for Tuberculosis Vaccine Discovery (ITVD) (R61/R33 Clinical Trial Not Allowed)." The goal of this initiative is to support the design of novel TB vaccine candidates that exploit innovative approaches and their advancement into preclinical animal model testing. This funding opportunity will use a milestone driven, biphasic award mechanism to fund high risk/exploratory research. Transition to the second phase depends on the successful completion of milestones.</li> <li>• Release of BAA-DAIT-75N93021R00008: Advancing Vaccine Adjuvant Research for Tuberculosis (AVAR-T). The goal of this initiative is to further the development of preventive, including post-exposure, TB vaccines through side-by-side comparisons of adjuvants in combination with Mycobacterium tuberculosis (Mtb) immunogens, and to establish immunological profiles of adjuvants that work through different mechanisms, facilitating the identification of the most promising adjuvant: Mtb immunogen candidates for clinical development and potential immune correlates of protection.</li> </ul> </li> <li>▪ Supporting five awards made in response to RFA-AI-16-079: Partnerships for Development of Vaccines to Prevent Mycobacterium tuberculosis (R01AI135721; R01AI135629; R01AI135631; R01AI135720; R01AI135723).</li> <li>▪ Support awards received in response to PAR-18-923: Characterization of Mycobacterial Induced Immunity in HIV-infected and Uninfected Individuals (R21 Clinical Trial Not Allowed).</li> <li>▪ Support awards received in response to PAR-16-254: Mechanisms of Mycobacterial-Induced Immunity in HIV-Infected and Uninfected Individuals to Inform Innovative Tuberculosis Vaccine Design (R01).</li> <li>▪ PAR-19-307: Mechanisms of Mycobacterial-Induced Immunity in HIV-Infected and Uninfected Individuals to Inform Innovative Tuberculosis Vaccine Design (R01).</li> <li>▪ Issued Notice of Special Interest (NOSI): Mechanisms of Mycobacterial-Induced Immunity in HIV-Infected and/or Uninfected Individuals to Inform Innovative Tuberculosis Vaccine Design (NOT-AI-20-071). This NOSI replaced the expired PAR-18-923 (R21) and PAR-19-307 (R01).</li> <li>▪ Supporting awards under RFA-AI-17-039: Understanding Immunopathogenesis of Tuberculosis in HIV-1 Infected and exposed Children (R01 Clinical Trial Not Allowed) (R01AI142670, R01AI142662, R01AI142647).</li> </ul>

NIH will continue to support research, pre-clinical studies, and clinical trials and studies for the evaluation of new vaccines, adjuvants, and preventive drugs.

- Immune Correlates of LTBI In HIV-Exposed Infants (R01AI142669).
- Supporting awards under PAR-19-357 (R01) and 364 (R24): Myeloid-Derived Suppressor Cells (MDSCs) as Potential Therapeutic Targets in TB/HIV.
- Currently support contract awards made in response to NIAID-DAIT-NIH AI-201700104: Immune Mechanisms of Protection Against Mycobacterium tuberculosis Center (IMPAC-TB) (75N93019C00070; 75N93019C00071; 75N93021C00029). The goals of the program are to define immune mechanisms required for protection against Mtb infection, establishment of latent infection or progression to active TB disease to guide TB vaccine development. The scientific teams will take a comprehensive, multidisciplinary approach and conduct intensive, iterative analysis of immune responses following Mtb exposure, infection, or vaccination. In-depth immunologic analyses of tissue specific and systemic responses against Mtb will be done in small animals, non-human primates, and humans.
- The Harvard IMPAC-TB Center (75N93019C00071):
  - Characterizing antigen specific antibodies from plasma and broncho-alveolar lavage in NHP given intravenous BCG-vaccinated versus intradermal BCG administration; determine whether there is an association between antibody levels and bacterial burden following Mtb challenge. This work is funded in part by IMPAC-TB and a manuscript is in preparation.
  - Examining the role of CD8 T EMRA cells (T cell effector memory re-express CD45RA) in unstimulated PMBCs from LTBI individuals relative to resister (RSTR) individuals. Manuscript in development.
  - Discovered that generation of anti-IgM antibodies following BCG vaccination protect NHPs from challenge compared to animals without IgM. This work is funded in part by IMPAC-TB and has been submitted for publication.
  - Showed that resister (RSTR) mice, which are able to clear Mtb without a detectable interferon gamma response, exhibited increases in particular lung cell subsets, including regulatory T cells and distinct macrophage, dendritic cell and eosinophil subsets.
  - Conducted retrospective analysis of PBMC samples from an adolescent reverter (RVRTR) cohort and showed that RVRTRs maintain a detectable Mtb-specific IFN-gamma response, but that their CD4 T cells have a reduced response compared to persistently IGRA+ individuals. The data suggest that spontaneous RVRTRs may have experienced low antigen burden at exposure and controlled Mtb infection.
  - Developing and applying integrative computational models to 1) identify shared features of BCG vaccination across diverse mouse strains that include RSTR-like animals, and 2) characterize responses that associate with protection in an NHP IV-BCG dose down study at the NIH.
- The Cascade IMPAC-TB Center (75N93019C00070):
  - Found that ultra-low dose infection in mice results in heterogeneous outcomes, including single, well-organized granulomas and unilateral lung containment (Cell Host & Microbe, <https://www.sciencedirect.com/science/article/pii/S1931312820305618>). Blood transcriptional signatures derived to correlate with pulmonary bacterial burdens in Mtb-infected mice can predict human TB risk. This work is funded in part by IMPAC-TB.

NIH will continue to support research, pre-clinical studies, and clinical trials and studies for the evaluation of new vaccines, adjuvants, and preventive drugs.

- Conducting a screen for improved models of protection against Mtb infection in mice.
- Defined the optimal time point to assess protective immune responses in Mtb-infected rhesus macaques. Assessment of immune responses in BCG-vaccinated Mtb-infected Rhesus macaques has been initiated.
- In collaboration with the University of Stellenbosch in South Africa initiated household contact study. Conducting PET/CT, bronchoscopy and phlebotomy in all cohorts and obtaining BAL and PBMC samples from each participant for high resolution immunological and transcriptional analysis.
- Designed and initiated a center-wide data and resource management system to capture, store, catalog, and disseminate contract-generated reagents, processed datasets and other resources.
- Supporting contract award in response to BAA-NIAID-DAIT-NIH-AI201800007: Large-Scale T cell Epitope Discovery to characterize Mycobacterium tuberculosis T cell epitopes in vaccination and active infection (75N93019C00067).
- Supporting contract in response to HHS-NIH-NIAID-BAA2017-1 (Adjuvant Development Program) to develop and test novel combination adjuvants and apply them to the development of effective tuberculosis vaccines (HHSN272201800044C).
- Supporting contract in response to HHS-NIH-NIAID-AI2013168 (Adjuvant Discovery Program), to identify novel C-type lectin receptor (CLR) agonists as adjuvants for use with the M72 Mtb vaccine (HHSN272201400050C): A lead CLR-agonist (UM-1098) formulated with SNP nanoparticles, delivered with the M72 subunit TB antigen, induced strong Th17-dependent protection against TB challenge in mice.
- Supplementing an Adjuvant Discovery Program contract award in response to BAA-NIAID-DAIT-NIH-AI-2013168 to test newly identified CLR-targeting adjuvants with additional, novel Mycobacterium tuberculosis antigens (HHSN272201400050C): immunization with Ag85B/ESAT6 with one of three small-molecule adjuvants that target CLR, TLR7 or TLR4 (UM-1098, UM-1007, INI-2002, respectively) all demonstrated superior protection. Efficacy elicited by UM-1098 SNP or INI-2002-adjuvanted Ag85b/ESAT6 is comparable to that of BCG.
- SBIR Adjuvant Development contract award is testing an advanced synthetic saponin adjuvant with novel *Mycobacterium tuberculosis* antigens (75N93019C00016).
- Support investigator-initiated awards focusing on the preclinical development of novel TB vaccine candidates.
- Supporting two investigator-initiated awards focusing on the innate immune response to Mtb of children living with HIV with LTBI with a focus on memory-like NK cell responses (R01AI142672) and adaptive immune responses to Mtb infection and TB disease among young children with and without HIV-exposure (R01AI157807).
- Supporting investigator-initiated award focusing on the identification of immune correlates of protection from TB in BCG-IV vaccinated SIV+ macaques (R01AI155345).
- Continued to support the study of the body's response to TB infection and damage to the lungs (R01HL127384).
- Supports identifying novel ways to improve IL-17 and Th17 vaccine-induced cells to provide sterilizing vaccine-induced immunity against TB (R01HL105427).

NIH will continue to support research, pre-clinical studies, and clinical trials and studies for the evaluation of new vaccines, adjuvants, and preventive drugs.

- PAR-18-489: One project including an award to investigate application of synthetic vaccine depot loaded with strategically selected adjuvant combinations and possessing highly tunable release kinetics to mimic key pathways and duration of immunostimulation of BCG and their effect on the immune modulation (R21AI137932).
- The anti-tubercular activity of simvastatin is mediated by cholesterol-driven autophagy via the AMPK-mTORC1-TFEB axis (J Lipid Res, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7707180/>).
- Supporting clinical trial through U01AI131861, "MTBVAC Phase 1b/2a Randomized, Double-blind, Active-controlled, Safety, Immunogenicity, and Dose-escalation Study in Adults with and without Latent Tuberculosis Infection in South Africa" (<https://clinicaltrials.gov/ct2/show/NCT02933281>).
- Supported early-stage studies of a candidate TB vaccine called M72/AS01 E (manufactured by GlaxoSmithKline). A Phase 2b trial found the candidate significantly reduced the incidence of pulmonary TB disease in HIV-negative adults with latent TB infection for three years following vaccination. In collaboration with the Bill and Melinda Gates Foundation and the Gates Medical Research Institute, NIH is supporting supplements to identify M72/AS01 E vaccine-elicited correlates of protection R01AI141315 R01AI118608, R01AI141549, R01AI143636, P01AI120756).
- In collaboration with the Bill and Melinda Gates Foundation and the Gates Medical Research Institute, IAVI and other stakeholders, NIH is supporting a supplement to identify BCG revaccination-elicited correlates of protection in samples from the AERAS C-040-404 Phase 2 trial which showed that BCG revaccination prevented sustained Quantiferon conversion with an efficacy of 45.4% in HIV(-) adolescents (UM1AI068618). The NIH-funded HIV Vaccine Trials Network (HVTN), supported HVTN 602/Aeras A-042 (<https://clinicaltrials.gov/ct2/show/NCT02378207>), a Phase 1b clinical trial designed to characterize the immunogenicity of H4:IC31 and BCG revaccination, in addition to a third vaccine candidate, H56:IC31, to help identify candidate vaccine response biomarkers and to optimize immune assays that could be evaluated as correlates of protection against Mtb infection in Aeras C-040-404 and H56:IC31 efficacy trials (UM1AI068614, UM1AI068618, UM1AI068635, UM1AI069519, P30AI064518) (EClinicalMedicine, <https://www.ncbi.nlm.nih.gov/pubmed/32382714>).
- HVTN 602/Aeras A-042 (<https://clinicaltrials.gov/ct2/show/NCT02378207>) is a Phase 1b clinical trial designed to characterize the immunogenicity of H4:IC31 and BCG revaccination, in addition to a third vaccine candidate, H56:IC31, to help identify candidate vaccine response biomarkers and to optimize immune assays that could be evaluated as correlates of protection against Mtb infection in C-040-404 and H56:IC31 efficacy trials (EClinicalMedicine, <https://www.ncbi.nlm.nih.gov/pubmed/32382714>).
- IMPAACT 2035/HVTN 604: Phase I/II Study of the Safety and Immunogenicity of VPM1002 Vaccination and BCG Re-Vaccination against Tuberculosis in South African Pre-Adolescents Living with and without HIV (<https://www.impactnetwork.org/studies/impact2035hvt604>).



NIH will continue to support research, pre-clinical studies, and clinical trials and studies for the evaluation of new vaccines, adjuvants, and preventive drugs.

- RePORT international consortium is conducting longitudinal studies to interrogate the biological and clinical significance of QuantiFERON (QFT) reversion in Mtb infected individuals. QFT tests are used to diagnose TB infections and these studies will help address whether QFT reversion correlates with protection from infection and progression to disease.
- Supports finding every detectable TB case in a small, well-circumscribed urban Ugandan district, using whole-genome sequencing to identify cases, even those without symptoms (R01HL138728).
- Supports investigating several host pathways that are involved in forming or degrading the lipids deposited in foam cells by using clinical samples from donors with TB, cell culture systems, and animal models, to test the hypothesis that blocking formation of foam cells improves TB infection outcomes (R01HL149450).
- Costing the implementation of public health interventions in resource-limited settings: a conceptual framework (Implementation Science, <https://doi.org/10.1186/s13012-020-01047-2>).
- Supports a retrospective cohort study in Kampala, Uganda to determine if distance is associated with TB treatment outcomes (BMC Infectious Diseases, <https://doi.org/10.1186/s12879-020-05099-z>).
- The TB Portals Program is a web-based open-access repository of socioeconomic/geographic, clinical, laboratory, radiological, and genomic data from patients with drug-resistant TB to facilitate multinational collaboration for data sharing and analysis. The newest tool in the platform is an interactive case viewer which uses chest CT images with descriptors and maps of abnormalities to illustrate changes in the lungs over the course of clinical MDR-TB treatment.

<p>NIH and CDC will intensify collaborations with domestic and international vaccine developers to leverage pre-clinical and clinical resources for vaccine development.</p>	<p>NIH-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ Joint India-U.S. collaboration under the Indo-U.S. Vaccine Action Program (VAP) to support development of an adjuvanted BCG vaccine to enhance protective efficacy against Mtb.</li> <li>▪ Serving as a member of the Stop TB Partnership Working Group on New TB Vaccines to facilitate research and development of new vaccines to prevent TB (<a href="http://www.newtbvaccines.org/">http://www.newtbvaccines.org/</a>).</li> <li>▪ Collaborating 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.</li> <li>▪ Serving as members of the BMGF led Collaboration for TB Vaccine Discovery (CTVD - <a href="https://www.ctvd.co/Pages/default.aspx">https://www.ctvd.co/Pages/default.aspx</a>).</li> <li>▪ Serving as members of the Global Tuberculosis Vaccine Partnership (GTBVP). GTBVP is a forum for key stakeholders in TB vaccine R&amp;D with the aim to bring together funders, product developers and policymakers working jointly to address barriers and create opportunities to help accelerate the development of safe and effective TB vaccines (<a href="https://www.gtbvp.org/">https://www.gtbvp.org/</a>).</li> </ul> <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ Participation in XDR definition revision <a href="https://www.who.int/publications/i/item/meeting-report-of-the-who-expert-consultation-on-the-definition-of-extensively-drug-resistant-tuberculosis">https://www.who.int/publications/i/item/meeting-report-of-the-who-expert-consultation-on-the-definition-of-extensively-drug-resistant-tuberculosis</a></li> <li>▪ Developing novel physiological 3-D tuberculoma model to study host-directed therapy.</li> </ul>
<p>USAID will support platforms for TB vaccine researchers and key stakeholders in countries to facilitate collaboration and increase knowledge on TB vaccine research.</p>	<p>USAID continues to support the work of the Global TB Vaccine Working group of the STOP TB Partnership (<a href="http://www.newtbvaccines.org/">http://www.newtbvaccines.org/</a>)</p>
<p>The Department of State (State) and the Department of Defense (DOD) will explore a proof-of concept randomized controlled study to assess whether Calmette-Guerin (BCG) can provide short term protection to adults for prevention of TB infection during extended travel to high-risk countries.</p>	<p>DOD-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ DOD is poised to start this 2000 person clinical trial "TB Immunization to Prevent Infection [TIPI trial]" using BCG-Tokyo in September 2021. COVID-19 has restricted international travel over the past 18 months, resulting in a temporary halt to starting the study.</li> </ul> <p>State-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ None to report.</li> </ul>

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

Year Five Milestones	Year Five Progress
<p>USAID will evaluate at least one intervention to prevent the spread of MDR-TB based on assessments of probable transmission routes.</p>	<p>USAID-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ USAID has been supporting the implementation of a project in Moldova that is aiming at characterizing the transmission of MDR-TB using MTB genome sequencing. The project studies nosocomial and community transmission of MDR-TB through combined analysis of whole genome sequencing data with spatial, epidemiologic, demographic and laboratory information to understand the relative contribution of acquired and transmitted resistance to the MDR-TB epidemic in the country; and contribute to active case finding and outbreak surveillance for community transmission. The ultimate goal is to create data regarding TB transmission to guide effective risk management of TB and MDR-TB. The study has collected 1,800 culture-positive sputum specimens from newly diagnosed individuals with TB. Detailed maps that combine spatial and genomic information to reveal geographic patterns of transmission of TB and MDR-TB across Moldova were developed and submitted for publication.</li> </ul> <p>NIH-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ Continues to support eight awards made in response to RFA-AI-18-037: Halting TB Transmission in HIV-Endemic and Other High-Transmission Settings. These awards address a variety of questions to understand bacterial and host factors driving transmission, identify potential interventions to reduce transmission and to develop of novel tools to monitor TB transmission (R01AI147345, R01AI147319, R01AI147346, R01AI147321, R01AI147316, R01AI147349, R01AI147336, R01AI147347).</li> <li>▪ RFA-AI-20-023: International epidemiology Databases to Evaluate AIDS (leDEA) - Supporting 7 regional data center awards that bring clinical and research data and monitor and guide response to HIV/AIDS epidemic. This program also asks leDEA to include a TB cohort for evaluating TB treatment outcomes, creating data tools and facilitating access to data at a global level.</li> <li>▪ PAR-19-283: A project supporting novel research and public health strategies to be developed and coupled with enhanced training and local capacity building in Kenya (TW011817-01).</li> <li>▪ PAR-20-248: Ruth L. Kirschstein National Research Service Award (NRSA) Individual Fellowship (F30) - Supported spatial and decision analytic models for addressing challenges in pediatric TB control and care (F30HD105440).</li> <li>▪ HD-20-008: Innovative Epidemiologic Approaches for Understanding Long-term Health Outcomes of HIV-exposed Uninfected (HEU) Populations - supported screening pregnant women, enrolling infants and intensive analysis of neonatal adaptive immunity among infants in HEUs and neurocognitive development and background TB status (HD103066-01).</li> <li>▪ PA-19-191: One project is supporting a fellowship investigating transmission risk and incidence of extensive drug resistant TB in South Africa (F30AI152342).</li> </ul>

	<ul style="list-style-type: none"> <li>▪ PA-19-126: One project is supporting a mentoring award to measure the prevalence of undiagnosed TB and characteristics of TB among Brazilian prisoners who are unable to provide sputum samples, to optimize Mark Aerosol Sampling and to identify algorithms for TB screening in prisons (K01AI156022). Another project is supporting a mentoring award to determine TB transmission and preventive therapy outcome in boarding schools and monasteries in Tibetan refugees in India (K01AI148583).</li> <li>▪ PA-20-185: Investigating how Mtb induces cough and facilitates disease transmission (R01AI158688).</li> <li>▪ In a serial interval model for TB, optimized to determine the time between symptom onset in an infector and infectee to understand disease transmission, it was estimated to be 0.5 year for the US and Canada and 2.0 years in Brazil (K01AI102944) (Am J Epidemiol), <a href="https://pubmed.ncbi.nlm.nih.gov/32458995/">https://pubmed.ncbi.nlm.nih.gov/32458995/</a>.</li> <li>▪ A model was built to estimate the relative transmission probability for all case-pairs from demographic, spatial and clinical data, and it was found that the probabilities estimated using genetic distance between cases to define training transmission events are able to distinguish between truly linked and unlinked pairs with high accuracy in a TB outbreak in Hamburg, Germany (U19AI111276) (Int J Epidemiol., <a href="https://pubmed.ncbi.nlm.nih.gov/32211747/">https://pubmed.ncbi.nlm.nih.gov/32211747/</a>).</li> </ul>
<p>USAID and CDC will evaluate at least one new TB treatment regimen to prevent TB and MDR-TB in adults and children.</p>	<p>USAID-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ Results from the WHIP3TB trial presented at CROI 2020 (Boston, MA). WHIP3TB compared the effectiveness and safety of 3HP given once versus 3HP given once a year for two years (an approach called periodic 3HP, or p3HP) among people living with HIV (PLHIV) ages 2 years and older in South Africa, Ethiopia, and Mozambique. TB incidence was similar among participants taking 3HP and those receiving p3HP over 24 months. Abstract available from: <a href="http://www.croiconference.org/sessions/effectiveness-3hp-annually-vs-once-hiv-positive-people-whip3tb-trial">http://www.croiconference.org/sessions/effectiveness-3hp-annually-vs-once-hiv-positive-people-whip3tb-trial</a>, and the study was published in the annals of internal medicine: <a href="https://doi.org/10.7326/m20-7577">https://doi.org/10.7326/m20-7577</a>.</li> </ul> <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ In November 2019, the CDC, the American Thoracic Society (ATS), European Respiratory Society, and Infectious Diseases Society of America (IDSA) published new clinical guidelines for treatment of drug resistant TB, including new recommendations on treatment of multidrug-resistant TB (MDR-TB) and isoniazid-resistant but rifampin-susceptible TB. In May 2020, CDC sent out a communication update to U.S. TB programs on the approval of pretomanid as part of a 6-month, all-oral BPaL (bedaquiline, pretomanid, and linezolid) regimen for the treatment of adults with pulmonary extensively drug-resistant tuberculosis (XDR-TB) or with treatment-intolerant or non-responsive MDR TB by the U.S. FDA under the Limited Population Pathway for Antibacterial and Antifungal Drugs.</li> </ul>

- TBTC Study 31/ACTG A5349: In 2020, CDC completed an international, randomized, controlled, open label, phase 3 non-inferiority clinical trial that identified a four-month daily treatment regimen containing a combination of high-dose rifapentine and moxifloxacin is as effective as the standard daily 6-month regimen in curing drug-susceptible TB disease. This is the first successful short treatment regimen for drug-susceptible tuberculosis disease identified in almost 40 years. It was the largest drug-susceptible TB disease treatment trial sponsored by CDC, with more than 2,500 participants enrolled at 34 clinical sites in 13 countries. CDC published “Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis” in The New England Journal of Medicine (DOI: 10.1056/NEJMoa2033400).
- CDC’s TBTC Study 37: CDC is supporting an open label, multi-center, phase 3 randomized controlled non-inferiority trial evaluating shortening regimens for latent TB infection. It will compare the safety and efficacy of a 6-week regimen of daily rifapentine against the current standard of 12-16 weeks of rifamycin-containing treatment regimens. The treatment of latent TB infection is essential to controlling TB in the United States because it substantially reduces the risk that latent TB infection will progress to active TB disease among children and adults.
- [Comparing rates of mycobacterial clearance in sputum smear-negative and smear-positive adults living with HIV](#). BMC Infect Dis. 2021 May 22;21(1):466. doi: 10.1186/s12879-021-06133-4
- Contributed to Lancet 2018 publication: Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis, which formed the basis of updated drug-resistant TB guidelines (<https://www.sciencedirect.com/science/article/pii/S0140673618316441?via%3Dihub>).

NIH-led Achievements:

- Protecting Households on Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIX – ACTG 5300B/IMPACT 2003B): A Phase III trial comparing efficacy and safety 26 weeks delamanid versus isoniazid for preventing active TB among high-risk drug-resistant tuberculosis household contacts (adults and children) with or without HIV (<http://www.impactnetwork.org/studies/IMPACT2003B.asp>).
- IMPACT 2024: Phase I/II Dose Finding and Safety Study of Daily Rifapentine Combined with Isoniazid (IHP) for Tuberculosis Prevention in Infants, Children and Adolescents (<https://www.impactnetwork.org/studies/impact2024>).
- IMPACT 2025: A Phase I/II Trial of 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.
- NIH supported the TB APPRISE study (IMPACT P1078), which compared the safety and efficacy of initiating isoniazid preventive therapy during pregnancy versus 3 months post partum, in women living with HIV in countries with high tuberculosis prevalence (<https://www.clinicaltrials.gov/ct2/show/NCT01494038>). Although there were no significant differences in maternal safety outcomes between the groups, the study did observe a higher incidence of adverse pregnancy outcomes in the group treated during pregnancy. This finding is concerning and merits research into alternative approaches to tuberculosis preventive therapy in pregnant women (N Engl J Med, <https://www.nejm.org/doi/full/10.1056/NEJMoa1813060>).

- A Phase 2 trial evaluating the efficacy and tolerability of duration randomized treatment of multidrug resistant pulmonary TB in the Philippines and Vietnam (U01AI152980).
- Supports a Phase 4 clinical trial to evaluate treatment success, safety, and cost effectiveness of 4 weeks of daily rifapentine and isoniazid (IHP) for prevention of TB in HIV-uninfected individuals in Brazil (U01AI152961) (<https://www.clinicaltrials.gov/ct2/show/NCT04703075>).
- Supports research to explore host mechanisms responsible for necrotization of TB granulomas and to develop corrective measures to prevent, reduce or reverse the necrotization as well as inhibit the spread of drug resistance (R01HL126066).

**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 Five Milestones	Year Five Progress
<p>USAID will evaluate the programmatic impact of newly developed diagnostic tools.</p>	<p>USAID has been involved in evaluating the TrueNat technology (Molbio Diagnostic, India), a rapid point-of-care molecular diagnostic test included into the new WHO Rapid Communication for TB diagnostics in 2020. With proven ability to work in primary health care centers and with wireless data transfer capability, the technology can significantly bolster national capacity for detection, control, and management of TB, specifically at peripheral levels. The evaluation projects will generate evidence to inform national policy formulation in expanding rapid TB diagnostic technology for increasing case detection.</p>
<p>NIH, USAID, and CDC will support studies to understand the development of drug resistance to newly licensed or repurposed drugs.</p>	<p>USAID-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ In India, USAID has been supporting the Yaathum Biotech Private Limited (India) in the standardization and validation process of a rapid/affordable diagnostic kit for MDR/XDR TB.</li> <li>▪ USAID is planning to evaluate the TrueNat, a rapid molecular diagnostic test (currently being used in India). USAID will support studies to evaluate the accuracy of the test in diagnosing TB and DR-TB.</li> </ul> <p>NIH-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ Supports South African investigators to elucidate the mechanisms of Bedaquiline (BDQ)/ Clofazimine (CFZ) drug resistance that arise in clinical strains of Mtb (R01AI152110).</li> <li>▪ Supports study of de facto monotherapy during multidrug TB treatment and emergence of resistance (R01AI11967).</li> <li>▪ Supports U.S. and South African investigators studying emergence of bedaquiline and clofazimine resistance after interruption of drug-resistant TB therapy in a high HIV prevalence setting (R01AI145679).</li> <li>▪ Supports strengthening evidence on optimal MDR-TB treatment regimens through improved epidemiologic methods in Peru, Lesotho, and Kazakhstan (R01AI146095).</li> <li>▪ Supports study of evolutionary and functional significance of novel mutations in MDR-XDR TB in South Africa (R01AI105185).</li> <li>▪ Supports study of poor treatment response and outcomes in bedaquiline-based treatment regimens for drug-resistant tuberculosis in South Africa (R01AI158605).</li> <li>▪ Supports translational modeling of individual- and population-level outcomes of novel TB drug regimens in Uganda (K08AI127908).</li> </ul>



	<ul style="list-style-type: none"> <li>Supports investigating a critical issue of TB therapy, a rapid development of drug resistance. This project proposes a systems pharmacology approach that integrates state-of-the-art computational modeling and experimental data from humans, primates and rabbits to identify optimal antibiotics and regimens to improve treatment (U01HL131072).</li> </ul>
<p>CDC will use novel mobile health (m-health) and electronic health (e-health) systems to develop, pilot, and evaluate integrated models for real-time monitoring and evaluation of point-of-care and near point-of-care TB diagnostics to inform evidence-based laboratory and treatment program improvements.</p>	<ul style="list-style-type: none"> <li>HHS/CDC is working with Ministry of Health in Nigeria to implement differentiated service delivery models including multi-month scripting and community based as well as digital adherence technologies to ensure continuity and monitoring of TB treatment in an effort to mitigate the impact of COVID-19 on continuity of TB care. Adoption of differentiated service delivery models will allow TB programs to make TB service patient centric and patient-friendly.</li> </ul>
<p>NIH, USAID, and CDC will support evaluations of new diagnostic tests and their impact on patient care.</p>	<p>NIH-led Achievements:</p> <ul style="list-style-type: none"> <li>Supporting three awards funded under RFA-AI-19-030 (<a href="#">FEND for TB</a>), to conduct clinical evaluations of early stage TB diagnostic for drug-sensitive and drug-resistant TB in 12 TB endemic countries, including the evaluation of diagnostic performance in adult and pediatric populations with and without HIV co-infection. The three centers include R2D2 TB network (<a href="#">www.r2d2tbnetwork.org</a>, U01AI152087), FEND for TB (<a href="#">www.fend-tb.org</a>, U01AI152084), and ENDx TB (<a href="#">www.endxtb.com</a>, U01AI152075). These centers accept requests from diagnostic developers to evaluate early stage TB diagnostic technologies. The sites will evaluate many different assays and biomarkers, including diagnostics for triage testing and rapid point-of-care diagnosis and drug susceptibility testing, and will include testing for different patient populations, such as children and people living with HIV.</li> <li>Supports an extensive grant portfolio for the development of novel non-sputum based diagnostics for tuberculosis, including the use of urine, blood, serum, stool, breath volatile compounds, oral swabs and extracellular vesicles.</li> <li>Serum-Based Diagnosis of Pediatric Tuberculosis by Assay of Mycobacterium tuberculosis Factors: a Retrospective Cohort Study (J Clin Microbiol., <a href="https://pubmed.ncbi.nlm.nih.gov/33239373/">https://pubmed.ncbi.nlm.nih.gov/33239373/</a>).</li> <li>Supports evaluation of a novel breath sensor for rapid low-cost diagnosis of TB in children (R01HL139717).</li> <li>Funded four awards under RFA-AI-19-036, Advancing Biomarker Discovery and Novel Point-of-Care Diagnostics for Active TB Disease Detection in HIV-1 Infected and Exposed Children (R01AI152159, R01AI152158, R01AI152161, R01AI152157).</li> </ul>

- PA-18-574: One project awarded as a small business award to support development of a diagnostic technique that can concentrate a cell wall glycolipid from mycobacteria from several mL of urine into ~100 µL, which is then assayed by the lateral flow assay and specifically optimized for pediatric patients for analytical sensitivity (R44HD101201).
- PA-18-242: One project supporting an exploratory award investigating use of extracellular vesicles derived from host cells infected with TB that can be rapidly quantitated using a nanoparticle based end-point assay for diagnostics (R21EB026347).
- PA-15-269: One project awarded as a small business award to support the development of a point of care assay in children using the isothermal chain reaction to target TB genetic sequences in exhaled breath condensation, saliva and urine samples (R43HD090822).
- Conducted a retrospective cohort study to evaluate the serum-based diagnosis of pediatric TB by assay of Mtb virulence factors (J Clin Microbiol, <https://pubmed.ncbi.nlm.nih.gov/33239373/>).
- PA-19-126: One project supporting a mentoring award to measure the prevalence of undiagnosed TB and characteristics of TB among Brazilian prisoners who are unable to provide sputum samples, to optimize Mark Aerosol Sampling and to identify algorithms for TB screening in prisons (K01AI156022).
- Supporting a study of computer-aided detection using artificial intelligence to automatically read pediatric chest X-rays for radiologic manifestations consistent with pulmonary/ intrathoracic TB in children (HHSN272201000008C, Project #:WA-04).
- Supported research to validate methyl nicotinate and methyl p-anisate in exhaled breath as biomarkers for diagnosis of intra-thoracic TB in children when detected using a novel, low-cost, handheld device to generate high quality data for future non-invasive diagnosis of TB in children (R01HL139717).
- Urine TB diagnostic by amplicon reconstruction for PCR detection of DNA fragments (R21AI152497).
- Supporting evaluation of a novel breath sensor for rapid low-cost diagnosis of tuberculosis in children (R01HL139717).

USAID-led Achievements:

USAID/India has been supporting the Yaathum Biotech Private Limited (India) in standardization and validation process of a rapid/affordable diagnostic kit for Multidrug resistant (MDR) and Extensively drug resistant (XDR) Tuberculosis. The test can rapidly provide information on susceptibility to antimicrobials (Platform 1 can be used to diagnose MDR-TB with susceptibility testing for rifampicin and isoniazid, and Platform 2 to test for the second line anti-TB drugs), it is more affordable, able to detect full range of drug resistance in TB, and can be used at the microscopy-center level of the health-care system.

**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 Five Milestones	Year Five Progress
<p>NIH and CDC will support clinical studies to validate biologic correlates of disease activation.</p>	<p>NIH-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ RePORT international consortium is conducting studies to identify and validate specific biomarkers that indicate TB disease activation in latently infected individuals in HIV endemic and non-endemic settings; continues to support studies in India to identify and validate specific biomarkers that indicate TB disease activation and treatment failure and relapse.</li> <li>▪ In collaboration with the Bill and Melinda Gates Foundation, continues to support and analyze biomarkers to predict TB treatment duration in the Predict TB trial in China (<a href="https://clinicaltrials.gov/ct2/show/NCT02821832">https://clinicaltrials.gov/ct2/show/NCT02821832</a>).</li> <li>▪ Supports the newly recompeted Tuberculosis Research Units (U19); the scope of this consortium is to understand 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.</li> <li>▪ Supported studies to evaluate the predictive performance of a 29-gene signature for distinguishing progressors from non-progressors (PREDICT29) in a Brazilian cohort of household contacts of pulmonary TB (U19A1111276, U01AI065663, and T32A1125185) (Tuberculosis, <a href="https://www.sciencedirect.com/science/article/pii/S1472979219303907">https://www.sciencedirect.com/science/article/pii/S1472979219303907</a>).</li> <li>▪ NIAID and the NIH Clinical Center launched a study to identify biomarkers, clinical signs, and molecular explanations for paradoxical reactions to TB treatment (<a href="https://clinicaltrials.gov/ct2/show/NCT04052022">https://clinicaltrials.gov/ct2/show/NCT04052022</a>).</li> <li>▪ Host Biomarkers for M. Tuberculosis Infection Activity in HIV-Infected Persons (R01A117927).</li> <li>▪ Identifying Individuals at Risk of Progression to Active Tuberculosis (R01A1137681).</li> <li>▪ Biomarkers and Mechanisms of Paucibacillary and Latent Tuberculosis (U19A1111276).</li> <li>▪ Pre- and Post-Treatment Lung Microbiota, Metabolome and Immune Signatures at the Site of Disease in Patients with Active Pulmonary Tuberculosis (R01A1136894).</li> <li>▪ Supports predicting TB outcomes using genotypic and biomarker signatures (R01HL145411).</li> <li>▪ PA-20-195: One project awarded to study cholesterol oxidation products in TB pathogenesis and as biomarkers of disease (R21A1160386).</li> <li>▪ PA-18-357: One mentored project awarded to study high resolution plasma metabolomics to identify biomarkers of TB (K23A1144040).</li> <li>▪ Support under grants to understand biomarkers for risk of progression, including:             <ul style="list-style-type: none"> <li>• Host blood biomarkers for the diagnosis, prognosis, and treatment response of childhood TB (R01A1143636).</li> <li>• Characterizing infectiousness of subclinical TB and identifying novel early diagnostic strategies for preventing transmission (R01A1149620).</li> <li>• "Identifying individuals at risk of progression to active tuberculosis" (R01A1137681).</li> </ul> </li> <li>▪ Supports studies aimed at discriminating active pulmonary TB from latent TB infection using genotypic and biomarker signatures. Research has already resulted in the design of a machine deep learning model to automatic discover clinically interpretable imaging biomarkers for Mtb supersusceptibility (R01HL145411), (EBioMedicine, <a href="https://pubmed.ncbi.nlm.nih.gov/33166789/">https://pubmed.ncbi.nlm.nih.gov/33166789/</a>).</li> </ul>

- Scientists at NIH revealed the role of mucosal-associated invariant T (MAIT) cells during tuberculosis infection. They showed during early infection MAIT cells directly contribute to the notoriously slow priming of CD4 T cells, but later during infection MAIT cell stimulation may be an effective host-directed therapy for tuberculosis (Mucosal Immunol, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7790750/>).
- Transcriptomic Signatures Predict Regulators of Drug Synergy and Clinical Regimen Efficacy against Tuberculosis (mBio, <https://pubmed.ncbi.nlm.nih.gov/31719182/>).

CDC-led Achievements:

- TBTC publication: Colangeli R, Jedrey H, Kim S, Connell R, Ma S, Chippada Venkata UD, Chakravorty S, Gupta A, Sizemore EE, Diem L, Sherman DR, Okwera A, Dietze R, Boom WH, Johnson JL, Mac Kenzie WR, Alland D; DMID 01-009/Tuberculosis Trials Consortium Study 22 Teams. Bacterial Factors That Predict Relapse after Tuberculosis Therapy. N Engl J Med. 2018 Aug 30;379(9):823-833.
- Working to standardize assay for assessment of RNA signatures for differentiation of clinical stages of M. tuberculosis infection in low incidence settings (ongoing).

**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 Five Milestones	Year Five Achievements
<p>USAID will use data from successful pilot interventions to work with partners to create guidelines and support expansion to all targeted priority countries.</p>	<p>USAID-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ USAID: Nix-TB, phase 3 clinical trial assessing the safety and efficacy of Bedaquiline Plus Pretomanid Plus Linezolid (BPaL regimen) for treatment of XDR, pre-XDR and hard-to-treat tuberculosis (<a href="https://clinicaltrials.gov/ct2/show/NCT02333799">https://clinicaltrials.gov/ct2/show/NCT02333799</a>) has been completed. The study is published in the New England Journal of Medicine: <a href="https://doi.org/10.1056/nejmoa1901814">https://doi.org/10.1056/nejmoa1901814</a></li> <li>▪ USAID: Zenix-TB, phase 3 clinical trial evaluating the efficacy, safety and tolerability of various doses and durations of linezolid plus bedaquiline and pretomanid after 26 weeks of treatment in participants with either pulmonary XDR-TB, pre-XDR-TB, or treatment intolerant or non-responsive MDR-TB is completing follow up of patients. (<a href="https://clinicaltrials.gov/ct2/show/NCT03086486">https://clinicaltrials.gov/ct2/show/NCT03086486</a>).</li> <li>▪ USAID/South Africa has been supporting the National TB Program in implementing BPaL Clinical Access Program (BPaL-CAP) to expand access to the novel regimen and provide evidence for national and international guidelines.</li> </ul>
<p>USAID and CDC will evaluate shorter regimens for MDR-TB in children using existing drugs.</p>	<p>USAID-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ Under the STREAM trial, Otsuka is enrolling HIV-negative infants, children, and adolescents with MDR-TB (0–17 years old); the pharmacology and safety of Delamanid will be assessed in children ≤5 years old to (results expected in 2022) - <a href="https://clinicaltrials.gov/ct2/show/NCT02409290">https://clinicaltrials.gov/ct2/show/NCT02409290</a>.</li> <li>▪ BEAT Tuberculosis, South Africa has been enrolling participants, regardless of HIV status, starting from 12 years old - <a href="https://clinicaltrials.gov/ct2/show/NCT04062201">https://clinicaltrials.gov/ct2/show/NCT04062201</a>.</li> </ul>

NIH, CDC, and USAID will contribute clinical evidence related to optimal use of existing first- and second-line treatment regimens in adults and children to improve future treatment recommendation.

#### NIH-led Achievements:

- Supported a landmark Phase 3 clinical trial (Study 31/A5349) that demonstrated that a four-month daily treatment regimen containing high-dose rifapentine and moxifloxacin is as safe and effective as the existing standard six-month daily regimen at curing drug-susceptible pulmonary TB disease. The trial, conducted at 13 clinical sites in 34 countries, was led by the CDC's Tuberculosis Trials Consortium and supported by the NIAID AIDS Clinical Trials Group with sites enrolling two-thirds of participants (N=1617). This regimen is the first successful short-course treatment regimen for drug-susceptible TB disease in more than 40 years (N Eng J Med, <https://www.nejm.org/doi/full/10.1056/NEJMoa2033400>) (<https://www.clinicaltrials.gov/ct2/show/NCT02410772>).
- Clinical trial A5312 (<https://www.clinicaltrials.gov/ct2/show/NCT01936831>): Early Bactericidal Activity of high-dose INH in individuals with INH resistance mutations (InhA or KatG) compared with standard dose INH (Am J Clin Respir Med, <https://www.atsjournals.org/doi/10.1164/rccm.201910-1960OC>).
- Supports South African investigators studying improvements in treatment outcomes of pericardial TB with high dose rifampicin and analysis of drug exposure (U01AI152103). (<https://clinicaltrials.gov/show/NCT04521803>).
- Pharmacokinetics and Safety of Three Months of Weekly Rifapentine and Isoniazid for Tuberculosis Prevention in Pregnant Women (Clin Infect Dis, <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab665/6330598>).
- CDC and NIH: Tuberculosis Research Unit Network (TBRU-N) investigators collaborated with the CDC Tuberculosis Trials Consortium (TBTC) staff and TBTC Study 22 investigators to compare mycobacterial isolates before treatment and after treatment. Higher pretreatment minimal inhibitory concentrations (MICs) values for isoniazid and rifampin were associated with increased risk of later relapse. These data suggest that regimens that include higher-potency drugs at higher doses could be beneficial (U01AI065663, U19AI11276, NO1-AI95383, and HHSN266200700022C/NO1-AI-70022).

#### CDC-led Achievements:

- Goswami ND, Mase S, Griffith D, Bhavaraju R, Lardizabal A, Lauzardo M, Chen L, Wilson J, Chappelle C, Haley CA. Tuberculosis in the United States: Medical Consultation Services Provided by Five TB Regional Training and Medical Consultation Centers, 2013-2017. Open Forum Infectious Diseases, 6(6):1-3; April 4, 2019. <https://doi.org/10.1093/ofid/ofz167>.
- Imada EK, MPH, Roberson EK, PhD, Moser K, Goswami ND, Tardivel K. "Notes from the Field: Meningeal and Pulmonary TB on a Commercial Fishing Vessel — Hawaii, 2017. MMWR Weekly, June 21, 2019.
- Gobaud A, Haley CA, Wilson JW, Bhavaraju R, Lardizabal A, Seaworth B, Goswami ND. "Multidrug-Resistant Tuberculosis Care in the United States: A Summary of Medical Consultations." International Journal of Tuberculosis and Lung Disease (IJTLD), April 1, 2020.
- Fernando R, Bhavaraju R, Fraimow H, Wilson JW, Armitage L, Haley C, and Goswami ND. "A Model for Bringing TB Expertise to HIV Providers: Medical Consultations to the CDC-Funded Regional Tuberculosis Training and Medical Consultation Centers, 2013-2017." PLOS One, 2020.

	<ul style="list-style-type: none"> <li>▪ McDowell A, Haas M, Seaworth B, Wilson JW, Haley C, Patrawalla A, Lauzardo M, and Goswami ND. "Linezolid Use for the Treatment of Multidrug-Resistant Tuberculosis, TB Centers of Excellence, United States, 2013-2018." Journal of Clinical Tuberculosis and Other Mycobacterial Diseases, 2020.</li> <li>▪ Tsang CA, Langer AJ, Kammerer JS, Navin TR. <a href="#">US Tuberculosis Rates among Persons Born Outside the United States Compared with Rates in Their Countries of Birth, 2012-2016<sup>1</sup>. external icon</a> Emerg Infect Dis. 2020 Mar;26(3):533-540. doi: 10.3201/eid2603.190974. Emerg Infect Dis. 2020. PMID: 32091367. Tsang CA, Patel NN, Stout, JE, Fernando R, Pratt R, Goswami ND. Treatment Duration Among Tuberculosis Patients Possibly Eligible for 4-Month Therapy. Abstract accepted for presentation at International Union Against Tuberculosis and Lung Disease (IUATLD), 2021.</li> </ul>
<p>USAID and CDC will evaluate innovative methods and approaches to support patients on treatment to enhance adherence and treatment success.</p>	<p>USAID-led Achievements:</p> <p>BEAT Tuberculosis, South Africa:</p> <ul style="list-style-type: none"> <li>▪ Dried Blood Spot (DBS) validation sub-study: there are no published data on DBS for the drugs used to treat MDR-TB. Considering that treatment completion rates in MDR-TB have historically been recorded at approximately 50%, a simple validated adherence measure will provide critical adherence information to assist in the management of those with MDR-TB. The pharmacokinetic study nested in BEAT Tuberculosis is a unique opportunity to validate DBS for bedaquiline, levofloxacin, linezolid and clofazimine.</li> <li>▪ ECG sub-study: multi-lead mobile technology for monitoring cardiac repolarization. This sub-study will establish the accuracy and precision of an FDA-approved smartphone enabled device (AliveCor Triangle) for serial monitoring of electrocardiographic QT intervals compared with standard 12-lead ECGs. Assess as well as acceptability, barriers to and facilitators of Triangle among nurses and participants.</li> </ul> <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ Tsang CA, Langer AJ, Kammerer JS, Navin TR. <a href="#">US Tuberculosis Rates among Persons Born Outside the United States Compared with Rates in Their Countries of Birth, 2012-2016<sup>1</sup>. external icon</a> Emerg Infect Dis. 2020 Mar;26(3):533-540. doi: 10.3201/eid2603.190974. Emerg Infect Dis. 2020. PMID: 32091367 (also, as stated above).</li> <li>▪ Tsang CA, Patel NN, Stout, JE, Fernando R, Pratt R, Goswami ND. Treatment Duration Among Tuberculosis Patients Possibly Eligible for 4-Month Therapy. Abstract accepted for presentation at International Union Against Tuberculosis and Lung Disease (IUATLD), 2021.</li> </ul>



**Sub-Objective 3.3.2. Enhance Knowledge to enable optimal and safe use of newly registered TB drugs**

Year Five Milestones	Year Five Progress
<p>NIH and CDC will support clinical trials to assess the safety and drug interactions of bedaquiline, delamanid, or both.</p>	<p>NIH-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ A Phase II trial, Evaluating the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, For Drug-Resistant Pulmonary Tuberculosis (<a href="https://clinicaltrials.gov/show/NCT02583048">https://clinicaltrials.gov/show/NCT02583048</a>; <a href="http://www.croiconference.org/sessions/qt-effects-bedaquiline-delamanid-or-both-mdr-tb-patients-deliberate-trial">http://www.croiconference.org/sessions/qt-effects-bedaquiline-delamanid-or-both-mdr-tb-patients-deliberate-trial</a>).</li> <li>▪ A Phase I/II trial to Evaluate the Pharmacokinetics, Safety, and Tolerability of Bedaquiline in HIV-Infected and HIV-Uninfected Infants, Children, and Adolescents with Multidrug-Resistant Tuberculosis (<a href="https://clinicaltrials.gov/ct2/show/NCT02906007">https://clinicaltrials.gov/ct2/show/NCT02906007</a>).</li> </ul> <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ TBTC Publication: Moro RN, Scott NA, Vernon A, Tepper NK, Goldberg SV, Schwartzman K, Leung CC, Schluger NW, Belknap RW, Chaisson RE, Narita M, Machado ES, Lopez M, Sanchez J, Villarino ME, Sterling TR. Exposure to Latent Tuberculosis Treatment during Pregnancy: The PREVENT TB and the iAdhere Trials. Ann Am Thorac Soc. 2018 Feb 2.</li> <li>▪ TBTC Publication: Weiner M, Gelfond J, Johnson-Pais TL, Engle M, Peloquin CA, Johnson JL, Sizemore EE, MacKenzie WR, for the Pharmacokinetics Pharmacodynamics Group of the Tuberculosis Trials Consortium. Elevated Plasma Moxifloxacin Concentrations and SLCO1B1 g.-11187G&gt;A Polymorphism in Adults with Pulmonary Tuberculosis. Antimicrob Agents Chemother. 2018 Feb 20. pii: AAC.01802-17. PMID: 29463526.</li> <li>▪ TBTC Publication: Rifat D, Prideaux B, Savic RM, Urbanowski ME, Parsons TL, Luna B, Marzinke MA, Ordonez AA, DeMarco VP, Jain SK, Dartois V, Bishai WR, Dooley KE. Pharmacokinetics of rifapentine and rifampin in a rabbit model of tuberculosis and correlation with clinical trial data. Sci Transl Med. 2018 Apr 4;10(435). pii: eaai7786.</li> </ul>
<p>NIH, CDC, and USAID will support clinical trials to evaluate clinical evidence for the integration of bedaquiline, delamanid, or both into currently approved regimens to inform new guidelines for the management of drug-resistant TB.</p>	<p>NIH-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ ACTG 5343 Phase II trial, Evaluating the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, For Drug-Resistant Pulmonary Tuberculosis (<a href="https://clinicaltrials.gov/show/NCT02583048">https://clinicaltrials.gov/show/NCT02583048</a>; <a href="http://www.croiconference.org/sessions/qt-effects-bedaquiline-delamanid-or-both-mdr-tb-patients-deliberate-trial">http://www.croiconference.org/sessions/qt-effects-bedaquiline-delamanid-or-both-mdr-tb-patients-deliberate-trial</a>).</li> <li>▪ A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease (<a href="https://impaactnetwork.org/studies/PI108.asp">https://impaactnetwork.org/studies/PI108.asp</a>).</li> <li>▪ A Phase I/II Open-label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in HIV-infected and HIV-uninfected Children with MDR-TB (<a href="https://impaactnetwork.org/studies/IMPAACT2005.asp">https://impaactnetwork.org/studies/IMPAACT2005.asp</a>).</li> <li>▪ Pharmacokinetics, safety and acceptability of Pretomanid in children with Rifampicin-Resistant TB (IMPAACT 2034, <a href="https://www.impaactnetwork.org/studies/impaact2034">https://www.impaactnetwork.org/studies/impaact2034</a>).</li> <li>▪ IMPAACT 2020: Shortened Oral Treatment for Multidrug-Resistant Tuberculosis in Infants, Children and Adolescents (SMaRT Kids): A Phase III Randomized Multi-center Trial (<a href="https://www.impaactnetwork.org/studies/impaact2020">https://www.impaactnetwork.org/studies/impaact2020</a>).</li> </ul>

	<ul style="list-style-type: none"> <li>▪ A Phase II trial evaluating the efficacy and tolerability of duration randomized treatment of multidrug resistant pulmonary TB in the Philippines and Vietnam (U01AI152980) (<a href="https://clinicaltrials.gov/show/NCT03828201">https://clinicaltrials.gov/show/NCT03828201</a>).</li> <li>▪ Supporting study of the emergence of bedaquiline and clofazimine resistance after interruption of drug-resistant TB therapy in a high HIV prevalence setting in South Africa (R01AI145679).</li> <li>▪ Clinical Outcomes among Patients with Drug-resistant Tuberculosis receiving Bedaquiline or Delamanid containing regimens (K23AI103044 and R21AI122001) (Clin Infect Dis, <a href="https://pubmed.ncbi.nlm.nih.gov/31712809/">https://pubmed.ncbi.nlm.nih.gov/31712809/</a>).</li> </ul> <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ TBTC planning and pre-clinical activities in 2019, including modeling, EKG, and management of clinical trials' drug supply.</li> </ul> <p>USAID-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ USAID continues to support the TB Alliance's phase 3 clinical trial to Evaluate the Efficacy, Safety and Tolerability of BPamZ in Drug-Sensitive (DS-TB) Adult Patients and DR-TB Adult Patients (SimpliciTB, <a href="https://clinicaltrials.gov/ct2/show/NCT03338621">https://clinicaltrials.gov/ct2/show/NCT03338621</a>).</li> <li>▪ USAID continues to support the TB Alliance on a Phase III trial to evaluate the Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants with Pulmonary TB, XDR-TB, Pre- XDR-TB or Non-responsive/ Intolerant MDR-TB (ZeNiX, <a href="https://clinicaltrials.gov/ct2/show/NCT03086486">https://clinicaltrials.gov/ct2/show/NCT03086486</a>). The study has completed the recruitment of participants expecting the final results by the end of 2021.</li> <li>▪ USAID, in collaboration with Janssen and Otsuka, is supporting an open label phase 3 randomized clinical trial to evaluate the Efficacy and Safety of a Combination regimen of Bedaquiline, Delamanid, Linezolid and Clofazimine in MDR patients with additional resistance to fluoroquinolones in South Africa. Recruitment has been ongoing (<a href="https://clinicaltrials.gov/ct2/show/NCT04062201">https://clinicaltrials.gov/ct2/show/NCT04062201</a>).</li> <li>▪ USAID, in collaboration with Janssen and Otsuka, is supporting an open label Phase 3 clinical trial to evaluate the Efficacy and Safety of a Combination regimen of Bedaquiline, Delamanid, Linezolid and Clofazimine in pre-XDR and XDR-TB patients in India (5 clinical sites). Recruitment has been completed with expectation of the final results by the end of 2021.</li> </ul>
<p>CDC and USAID will identify best practices for the use of new drugs in novel MDR-TB treatment regimens based on pharmacovigilance data.</p>	<p>CDC-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ Notes from the Field: Acquisition of Delamanid Under a Compassionate Use Program for Extensively Drug-Resistant Tuberculosis — United States, 2017 Weekly / September 7, 2018 / 67(35);996–997.</li> </ul> <p>USAID-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ All clinical trials (BEAT TB, India; BEAT Tuberculosis, South Africa) that include novel therapeutics also assess the safety for these drugs. Furthermore, technical support for all programs that are focused on the introduction of shortened regimens and new drugs (STR/ND) for treatment of DR-TB prioritizes pharmacovigilance. The studies' protocols have included Pharmacokinetic evaluation including pharmacogenetics and pregnancy PK.</li> </ul>

<p>USAID and CDC will expand the evaluation of new drug regimens to treat children, including novel TB drugs for both TB and MDR-TB.</p>	<p>USAID/CDC-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ The STEP-TB Project (Janssen, UNITAID/TB Alliance) is currently enrolling HIV-negative infants, children, and adolescents with MDR-TB (0-18 years old); children <math>\leq</math> 12 years old (n=60) will receive pediatric formulations to characterize the pharmacology of Bedaquiline for four age groups: i) 0 months to &lt; 2 years; ii) &gt; 2 to &lt; 5 years; iii) &lt; 5 to &lt; 12; and iv) &lt; 12 to &lt; 18 years) to help determine dosage guidelines for pediatric use.</li> <li>▪ Under the STREAM trial, Otsuka is enrolling HIV-negative infants, children, and adolescents with MDR-TB (0–17 years old); the pharmacology and safety of Delamanid will be assessed in children <math>\leq</math> 5 years old to (results expected in 2018). USAID plans to participate in further Phase IIb and III trials, pending the final assessment of these studies.</li> <li>▪ BEAT Tuberculosis, South Africa has been enrolling participants, regardless of HIV status, starting from 12 years old.</li> </ul> <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ TBTC Study 35: CDC is supporting a Phase I/II, open-label, single arm, exposure-controlled study to determine appropriate dosing of a novel water-dispersible, child-friendly formulation of rifapentine with isoniazid in children aged 0-12 years. The trial aims also to assess safety of this formulation in HIV-infected and HIV-uninfected children. If successful, the trial will contribute to global availability of a pediatric formulation that can be used to treat latent TB infection in young children. Recruitment has been ongoing with expectation of the final results in February 2022 (<a href="https://clinicaltrials.gov/ct2/show/study/NCT02011111">Tuberculosis Clinical Trials Consortium Study 35 - Full Text View - ClinicalTrials.gov</a>).</li> <li>▪ Goswami ND, Oxtoby M, Moore M, Westenhouse J, Barry PB, Shah S. Introduction and Evaluation of Multidrug-Resistant Tuberculosis Supplemental Surveillance in the United States. <i>Journal of Clinical Tuberculosis and Other Mycobacterial Diseases</i>, Vol 15, May 2019. (<a href="https://doi.org/10.1016/j.jctube.2019.01.005">https://doi.org/10.1016/j.jctube.2019.01.005</a>).</li> <li>▪ Haley CA, Macias P, Jasuja S, Jones BA, Rowlinson MC, Jaimon R, Onderko P, Darnall E, Gomez ME, Peloquin C, Ashkin D, Goswami ND. "First U.S. Patient Treated with a Novel Six-month Treatment Regimen including Bedaquiline, Linezolid, and Pretomanid ("BPaL") for Drug-Resistant Tuberculosis — United States, 2019-2020." <i>Emerg Infect Dis</i>. 2020.</li> <li>▪ Goswami ND, Peddareddy LP, Jereb J, Semidey AC, MD, Darnall E, Macias P, Jasuja S, Landers K, Dasgupta S, Oxtoby M, MD, MPH, Spitters C, Dov L, Narita M, DeSilva M, MD, MPH, Cropper T, Gullickson C, Ashkin D, Haley CA. Pretomanid in the Treatment of Patients with Tuberculosis in the United States: the Bedaquiline, Pretomanid and Linezolid (BPaL) Accelerated Monitoring (BAM) Project. Submitted to IDWeek, June 2021.</li> <li>▪ Bedaquiline, Pretomanid and Linezolid (BPaL) Accelerated Monitoring Project: CDC-led effort to work with TB programs and the TB Centers of Excellence to identify and monitor patients on BPaL regimen.</li> <li>▪ Goswami ND, Peddareddy LP, Jereb J, Semidey AC, MD, Darnall E, Macias P, Jasuja S, Landers K, Dasgupta S, Oxtoby M, MD, MPH, Spitters C, Dov L, Narita M, DeSilva M, MD, MPH, Cropper T, Gullickson C, Ashkin D, Haley CA. Pretomanid in the Treatment of Patients with Tuberculosis in the United States: the Bedaquiline, Pretomanid and Linezolid (BPaL) Accelerated Monitoring (BAM) Project. Submitted to IDWeek, June 2021.</li> </ul>
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**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 Five Milestones	Year Five Progress
<p>NIH will expand and strengthen support for the pre-clinical evaluation of new drug candidates and regimens for the treatment of drug-susceptible and drug-resistant TB.</p>	<p>NIH-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ NIH continues to support the early stage basic science to support repurposing of drugs as well as development of new classes of antibiotics for TB. Examples include:</li> <li>▪ Triazolothiadiazoles, a narrow spectrum antibiotic class with a novel mechanism of action (R43AI148228).</li> <li>▪ Artemisian natural products being developed/repurposed for TB (R21AI151481).</li> <li>▪ A new class of antibiotics that target a novel enzyme in bacterial cell wall biosynthesis is being (MTb KasA, R01AI153145).</li> <li>▪ Spectinomycin analogs represent a novel class of antibiotics with commercial development actively underway for TB with support from NIAID (R44AI098271, R01AI120670, R01AI090810).</li> <li>▪ With the recent clinical data showing that newer, synthetic rifamycin analogs can substantially shorten TB treatment, NIH continues to support the rational design of newer analogs in this important TB drug class (ex. R01AI110780).</li> <li>▪ Mycobacterial Transpeptidases and the beta lactam antibiotics that target these, some with clinical data others with even more promising preclinical data, are a highly promising area for new TB treatments and an area that NIAID is continuing to fund a substantial amount of work in (ex. R01AI137329, R01AI149737, R21AI144501, R01AI141805 and many others).</li> <li>▪ Awards to identify new nucleoside antibiotics (R01AI128862, Co-Funded by U.S.-China Program for Biomedical Collaborative Research RFA-AI-16-006 and R21AI142210).</li> <li>▪ Supported the development of the preclinical candidate indole-2-carboxamide to improve immune responses to Mtb infection in healthy subjects and individuals with type 2 diabetes (Int Microbiol, <a href="https://pubmed.ncbi.nlm.nih.gov/31218537/">https://pubmed.ncbi.nlm.nih.gov/31218537/</a>).</li> <li>▪ Assisted in the collaborative preclinical development of new diarylquinolines by providing evaluations and administrative assistance in Investigational New Drug applications (R01AI132374) (Antimicrob Ag Chemother, <a href="https://pubmed.ncbi.nlm.nih.gov/31712198/">https://pubmed.ncbi.nlm.nih.gov/31712198/</a>).</li> <li>▪ Continues to support the advanced development of novel drugs to treat TB such as the nucleoside CPZEN-45 antibiotic with the goal of an IND filing for MDR-TB as soon as 2023.</li> <li>▪ Award to investigate the potential of an inhalation formulation for the semisynthetic nucleoside antibiotic CPZEN-45 to treat MDR/XDR TB (R01AI141082).</li> <li>▪ Supporting development of a data-driven pipeline to rapidly prioritize drug combination regimens by combining in vitro and in vivo measurements of drug action within lesions with mathematical modeling (R01AI150684).</li> <li>▪ Continues to support the re-evaluation of traditional TB drugs like pyrazinamide (R01AI123146).</li> <li>▪ Supporting the development of a Phase 2 study (ACTG 5409) with an adaptive design to evaluate the safety and efficacy of multidrug regimens for the treatment of adults with pulmonary TB.</li> </ul>

NIH will increase collaborations with pharmaceutical and academic partners to broaden strategies for shortening treatment duration.

NIH-led Achievements:

- Supported a landmark Phase 3 clinical trial (Study 31/A5349) that demonstrated that a four-month daily treatment regimen containing high-dose rifapentine and moxifloxacin is as safe and effective as the existing standard six-month daily regimen at curing drug-susceptible pulmonary TB disease. The trial, conducted at 13 clinical sites in 34 countries, was led by the CDC's Tuberculosis Trials Consortium and supported in part by the NIAID AIDS Clinical Trials Group. This regimen is the first successful short-course treatment regimen for drug-susceptible TB disease in more than 40 years and involved NIH-supported academic investigators and the pharmaceutical company Sanofi (N Eng J Med, <https://www.nejm.org/doi/full/10.1056/NEJMoa2033400>) (<https://www.clinicaltrials.gov/ct2/show/NCT02410772>).
- OMICS For TB: Response to Infection and Treatment (U19AI135976).
- Supporting three awards with aims to identify new targets for host-directed therapy of TB through RFA-AI-17-010, Dysregulation of immune cell regulatory pathways by Mycobacterium tuberculosis (R61AI138328, R61AI138272, R61AI138280).
- Supporting research grant to evaluate treating TB with the diabetes drug metformin. This project is aimed to characterize the metformin pathways responsible for limiting inflammation, matrix destruction and fibrosis in TB, thereby preserve lung function in Mtb-infected hosts (HL152078).
- Assisted in the collaborative preclinical development of new diarylquinolines by providing evaluations and administrative assistance in Investigational New Drug applications with the TB Alliance (R01AI132374) (Antimicrob Ag Chemother, <https://pubmed.ncbi.nlm.nih.gov/31712198/>).
- Supports partnering through a Center of Excellence for Translational Research (CETR) cooperative agreement with the Global Alliance for TB Drug Development "Modulation of protein production and degradation as an integrated approach to rapid sterilization of drug sensitive and resistant Mtb." This multidisciplinary project supports product discovery and development with multiple institutions and experts in pharmaceutical research (U19AI142735).
- Continues to co-chair the Stop TB Partnership's Working Group on New TB Drugs (<http://www.newtbdrugs.org/core-group>) and updated the global TB drug development pipeline in October 2020 at the annual meeting of the Working Group on New TB Drugs in conjunction with the International Union Against Tuberculosis and Lung Disease (IUATLD) world conference. The annual TB drug pipeline landscape represents candidates being advanced by international research work groups and pharmaceutical companies (<http://www.newtbdrugs.org/pipeline/clinical/>).
- Supports research on new drugs as part of the Bill and Melinda Gates Foundation's Drug Accelerator Program. This program aims to speed up the discovery and development of novel compounds against TB. The TB Drug Accelerator (TBDA) is a ground-breaking partnership between NIH, pharmaceutical companies and research organizations with support from the Bill & Melinda Gates Foundation to develop new pre-clinical drug candidates with treatment-shortening potential and provide proof-of-concept for a one-month three-drug regime. The long-term goal of the TBDA is to create a TB drug regimen that cures patients in only one month, rather than the 6 months now needed for treatment.

	<ul style="list-style-type: none"> <li>Continues to support research on new drugs as part of the Bill and Melinda Gates Foundation's Drug Accelerator Program. As part of the Drug Accelerator Program, intramural uncovered that Mtb uses a large family of repeated proteins, in place of a porin, to transport small molecules and drugs across the waxy cell wall. Understanding transport/selectivity of novel channels helps optimize new drug uptake properties (Science, <a href="https://pubmed.ncbi.nlm.nih.gov/32139546/">https://pubmed.ncbi.nlm.nih.gov/32139546/</a>).</li> </ul>
<p>NIH will contribute to establishing state-of-the-science pre-clinical approaches and strategies for the selection of the most promising drug candidates and regimens for clinical trials.</p>	<p>NIH-led Achievements:</p> <ul style="list-style-type: none"> <li>Supported several very innovative approaches to new TB treatments including the development of new in silico models to guide development of optimal TB drug combinations (R01AI125454) and innovative new delivery routes including research into inhaled pulmonary delivery methods for drugs and investigational agents (R01AI141082).</li> <li>Supports a study aimed at characterizing how regulating factors called sirtuins influence defense against TB, which could identify new treatments to hasten TB cure and improve lung health by restoring the proper balance of sirtuin activity during antibiotic treatment (HL153162).</li> <li>Supporting research to evaluate single and combination therapies of promising new drugs and repurposed antimicrobials with the newly validated hollow fiber methodology (P01AI123036).</li> <li>Supports research on the mechanisms of action and structural biology interactions of tuberculosis drugs. (Nature Commun., <a href="https://pubmed.ncbi.nlm.nih.gov/31953389/">https://pubmed.ncbi.nlm.nih.gov/31953389/</a>).</li> <li>Continuing to support research to characterize the underlying mechanisms by which GSH deficiency in the lung parenchyma leads to altered immune responses in the granulomas resulting in increased susceptibility to Mtb infection and tap the potential use of GSH as a possible immunomodulatory agent (R15HL143545).</li> <li>Supports research on the most promising new chemical entities (R41AI13456, R01NS102164) (J Med Chem, <a href="https://pubmed.ncbi.nlm.nih.gov/32259446/">https://pubmed.ncbi.nlm.nih.gov/32259446/</a>).</li> <li>Awarded a contract in 2020 (AToMIC, Anti-mycobacterial Target or Mechanism Identification Contract, 75N93019D00005 / 75N93019F00132) that provided a wide array of mechanism of action studies on new experimental antibiotics for TB. These studies helped to inform about individual new antibacterial agents and preclinically prioritize new TB drug regimens for further development. In 2020, 400 samples were received, and 60 reports generated for TB researchers around the world. Four of the new lead series were selected for further genomic analysis studies under this contract: <ul style="list-style-type: none"> <li>5-trifluoromethyl-1,2,4-oxadiazoles a new class of antibiotics with antiviral activity as well (Eur J Med Chem., <a href="https://www.ncbi.nlm.nih.gov/pubmed/31881489">https://www.ncbi.nlm.nih.gov/pubmed/31881489</a>).</li> <li>Benzo[d]thiazole 3-oxides: NIH-supported investigator is using the data in ongoing commercial technology transfer negotiations for therapeutic development.</li> <li>5-thio-1,2,4-triazoles: An early-stage investigator who is using the data to obtain additional grant funding to further study these compounds.</li> <li>non-fluoroquinolone-based bacterial topoisomerase inhibitors with new TB activity and related to an antibiotic, gepotidacin, which is already in late clinical trials for other indications. While the target was already known, the developers expressed that ruling out other targets would further help with development (ACS Infect. Dis., <a href="https://pubs.acs.org/doi/10.1021/acsinfecdis.8b00375">https://pubs.acs.org/doi/10.1021/acsinfecdis.8b00375</a>).</li> </ul> </li> </ul>



NIH, CDC, and USAID will increase inclusion of pharmacological evaluations in clinical and non-clinical studies to better understand the effectiveness of new drugs and regimens and to minimize side effects.

#### NIH-led Achievements:

- Pharmacokinetic Properties of Antiretroviral, Contraceptive and Related Drugs During Pregnancy and Postpartum (<https://impaactnetwork.org/studies/PI026s.asp>).
- Pharmacokinetic Properties of Antiretroviral, Anti-Tuberculosis, Contraceptive and Related Drugs During Pregnancy and Postpartum (<https://impaactnetwork.org/studies/IMPAACT2026.asp>).
- [Mycobacterium tuberculosis precursor rRNA as a measure of treatment-shortening activity of drugs and regimens](#) (R01AI127300 and ACTG supplement) (Nat Commun., <https://www.nature.com/articles/s41467-021-22833-6>).

#### CDC-led Achievements:

- TBTC publication: Weiner M, Gelfond J, Johnson-Pais TL, Engle M, Peloquin CA, Johnson JL, Sizemore EE, MacKenzie WR, for the Pharmacokinetics Pharmacodynamics Group of the Tuberculosis Trials Consortium. Elevated Plasma Moxifloxacin Concentrations and SLCO1B1 g.-11187G>A Polymorphism in Adults with Pulmonary Tuberculosis. Antimicrob Agents Chemother; 2018 Feb 20. pii: AAC.01802-17. PMID: 29463526. [Mycobacterium tuberculosis precursor rRNA as a measure of treatment-shortening activity of drugs and regimens](#). Nat Commun. 2021 May 18;12(1):2899. doi: 10.1038/s41467-021-22833-6
- [Comparing rates of mycobacterial clearance in sputum smear-negative and smear-positive adults living with HIV](#). BMC Infect Dis. 2021 May 22;21(1):466. doi: 10.1186/s12879-021-06133-4
- [Feasibility of Direct Sputum Molecular Testing for Drug Resistance as Part of Tuberculosis Clinical Trials Eligibility Screening](#). Diagnostics (Basel). 2019 May 30;9(2):56. doi: 10.3390/diagnostics9020056

#### CDC/NIH-led Achievements:

- CDC and NIH: Supported inclusion of pharmacological measures in clinical studies. For example, the CDC and NIH are collaborating in the Tuberculosis Trials Consortium (TBTC) phase 3 treatment trial, Pharmacokinetic and Pharmacodynamic Study of High-Dose Rifapentine and Moxifloxacin for Treatment of Tuberculosis, that is investigating the efficacy and safety of daily rifapentine with or without moxifloxacin as part of multidrug treatment regimens for drug-sensitive pulmonary TB (<https://clinicaltrials.gov/ct2/show/NCT02563327>).

#### USAID-led Achievements:

- USAID is supporting a number of clinical trials that are collecting blood specimens to estimate blood levels of all study drugs and their metabolites.
- USAID supported clinical trials that are evaluating blood levels of study drugs are:
  - Phase II of the STREAM study;
  - Phase 3 clinical trial to evaluate the Efficacy and Safety of a Combination regimen of Bedaquiline, Delamanid, Linezolid and Clofazimine in MDR patients with additional resistance to fluoroquinolones and/or aminoglycoside (BEAT TB, India); and
  - BEAT Tuberculosis, South Africa includes pharmacokinetic (PK) evaluation (children and adults from 12 years old), plus, pharmacogenetics (genetic determinants of variability in the pharmacokinetics of anti-TB drugs) and pregnancy PK

- The collaborative Phase III trial to evaluate the Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants with Pulmonary TB, XDR-TB, Pre- XDR-TB or Non-responsive/Intolerant MDR-TB (ZeNiX, <https://clinicaltrials.gov/ct2/show/NCT03086486>).

**Objective 3.4: Increase capacity to conduct biomedical and clinical research on TB in TB-endemic countries**

Year Five Milestones	Year Five Progress
<p>USAID and CDC will establish research training centers in up to 10 priority targeted countries.</p>	<p>USAID-led Achievements:</p> <p>Supporting capacity building of clinical trial sites in Eastern Cape through the BEAT TB Study and Eastern Europe through the WHO/TDR grant. The BEAT Study sites are newly developed clinical trial sites in Eastern Cape province, a province that doesn't have many research sites. The new sites will contribute to equity for access to clinical research within the country.</p> <p>Through the TREAT TB project launched a webinar series to strengthen capacity to conduct high quality clinical trials for MDR-TB. As a part of the comprehensive technical assistance package to the NTP, funded by the USAID Mission in the Philippines, TREAT TB is conducting an operational research course to build research capacity at the national and regional level <a href="https://treattb.org">TREAT TB – Technology, Research, Education, and Technical Assistance for Tuberculosis</a> (<a href="https://treattb.org">https://treattb.org</a>).</p> <p>Supported by USAID, TDR and the Global TB Program (GTB) at the World Health Organization has launched ShORRT (Short, all-Oral Regimens For Rifampicin-resistant Tuberculosis), an operational research package to assess the effectiveness, safety, feasibility, acceptability, cost and impact (including on health-related quality of life) of the use of all-oral shorter treatment regimens for adults and children with multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB)</p> <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ None to report.</li> </ul>
<p>NIH and CDC will increase the number of clinical trials and studies conducted in TB-endemic countries.</p>	<p>NIH-led Achievements:</p> <ul style="list-style-type: none"> <li>▪ Recompeted and awarded in 2020 (UM1AI068636) the AIDS Clinical Trials Group (ACTG) Leadership and Operations Center that has prioritized tuberculosis research in its agenda for international clinical trials. The Tuberculosis Transformative Science Group oversees protocol development, implementation, and training at TB endemic sites worldwide including India, Philippines, Thailand, Kenya, Tanzania, Botswana, Zimbabwe, South Africa, Brazil, Peru, Argentina, Haiti. Included formally in the ACTG research agenda is the specific aim to improve the treatment and prevention of drug sensitive and drug resistant tuberculosis in people with and without HIV.</li> <li>▪ Supported the engagement of the AIDS Clinical Trials Group (ACTG) in TB research by contributing the majority of cases to the Study 31/A5349 trial led by the CDC Tuberculosis Trials Consortium (TBTC). This study was a Phase 3, open label, randomized controlled clinical trial that demonstrated that durable cure of TB was possible with 4 months of treatment. It took place in 13 countries and included more than 2,500 participants ages 12 and older, including 193 people living with HIV. ACTG sites enrolled two-thirds of participants (N=1617).</li> </ul>

- Supported the Phase 3 Brief Rifapentine-Isoniazid Evaluation for TB Prevention (BRIEF TB) trial, which demonstrated that a one-month regimen of daily rifapentine and INH was as effective, safe and tolerated as standard 9-month INH and with better adherence. BRIEF TB enrolled 3000 adults and adolescents with HIV infection in 10 countries who were followed for at least 3 years (N. Engl J Med, <https://www.nejm.org/doi/10.1056/NEJMoa1806808>).
- Recently awarded investigator-initiated clinical trials and studies of TB drug interventions in Vietnam, Philippines, Uganda, South Africa, Tanzania, Brazil, Peru, Kazakhstan (U01AI152103, U01AI152961, U01AI152980, U01AI150508, R01AI146095, R01AI160434).
- Awarded grant applications from South African investigators under RFA AI-024 U.S.-South Africa Program for Collaborative Biomedical Research (U01AI152103, R01AI152110).
- Issued RFA-AI-21-001, "Tuberculosis Research Advancement Centers (P30 Clinical Trials Not Allowed)." The main goal of these TRAC centers is to provide facilities and services to foster and elevate multidisciplinary TB research at US institutions. Centers can support cores offering services in TB endemic countries and provide exceptional mentorship to new investigators including those in TB-endemic countries through the Development Core.
- Supports increased capacity for TB diagnostics research under the FEND for TB initiative (RFA-AI-19-030). NIH is supporting three centers in the network to evaluate early-stage TB. These three centers will provide clinical site capacity in 12 TB-endemic countries and will evaluate many different assays and biomarkers, including diagnostics for triage testing and rapid point-of-care diagnosis and drug susceptibility testing.
- Through the Fogarty International Center (FIC), targeted research training and career development grants for TB and HIV/TB are currently supported:
  - PAR-18-840: Global Infectious Disease Research Training Program (D43); 6 awards for TB training in Kenya, Tanzania, Ethiopia, Republic of Georgia, Thailand, Myanmar, Indonesia, Bolivia, Peru and Vietnam.
  - PAR-18-717: Fogarty HIV Research Training Program for Low-and Middle-Income Country Institutions (D43); 13 awards for TB/HIV training in Uganda, Zimbabwe, Tanzania, Ghana, Mali, Mozambique, South Africa, Haiti, India and Peru.
  - PAR-18-539/PAR-18-540: International Research Scientist Development Award (IRSDA) (K01); 3 U.S. career development awards in Peru, Eswatini, Lesotho, South Africa and Tanzania.
  - PAR-19-051, PAR-19-098: Emerging Global Leader Award (K43); 9 LMIC career development awards in South Africa, Gambia, Uganda, Malawi, Mali and Peru.
- FIC currently supports tuberculosis research in low- and middle-income countries through the following programs:
  - PAR-18-242: Mobile Health: Technology and Outcomes in Low- and Middle-Income Countries; 3 awards in Cambodia, Lesotho & Uganda.
  - PAR-18-732: Reducing Stigma to Improve HIV/AIDS Prevention, Treatment and Care in Low- and Middle-Income Countries; 2 awards in South Africa and Uganda.
  - PAR-18-836: Global Brain and Nervous System Disorders Research Across the Lifespan; 2 awards in Uganda and South Africa.
  - PAR-19-059: Global Noncommunicable Diseases and Injury Across the Lifespan: 2 awards in South Africa and Georgia.

CDC-led Achievements:

- TB Clinical Trials Consortium: CDC awarded contracts to six institutions and an interagency agreement with the Veterans Administration for the Tuberculosis Trials Consortium (TBTC) for the 2021-2030 research cycle, initiating the 28th year of this collaborative effort. CDC's domestic tuberculosis TB program conducts vital, unparalleled clinical trials and epidemiologic research through the TBTC, which advances the TB elimination strategy in the United States and globally TBTC sites are located in Australia, Benin, Canada, Haiti, South Africa, Uganda, the United States, and Vietnam.

