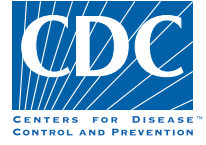




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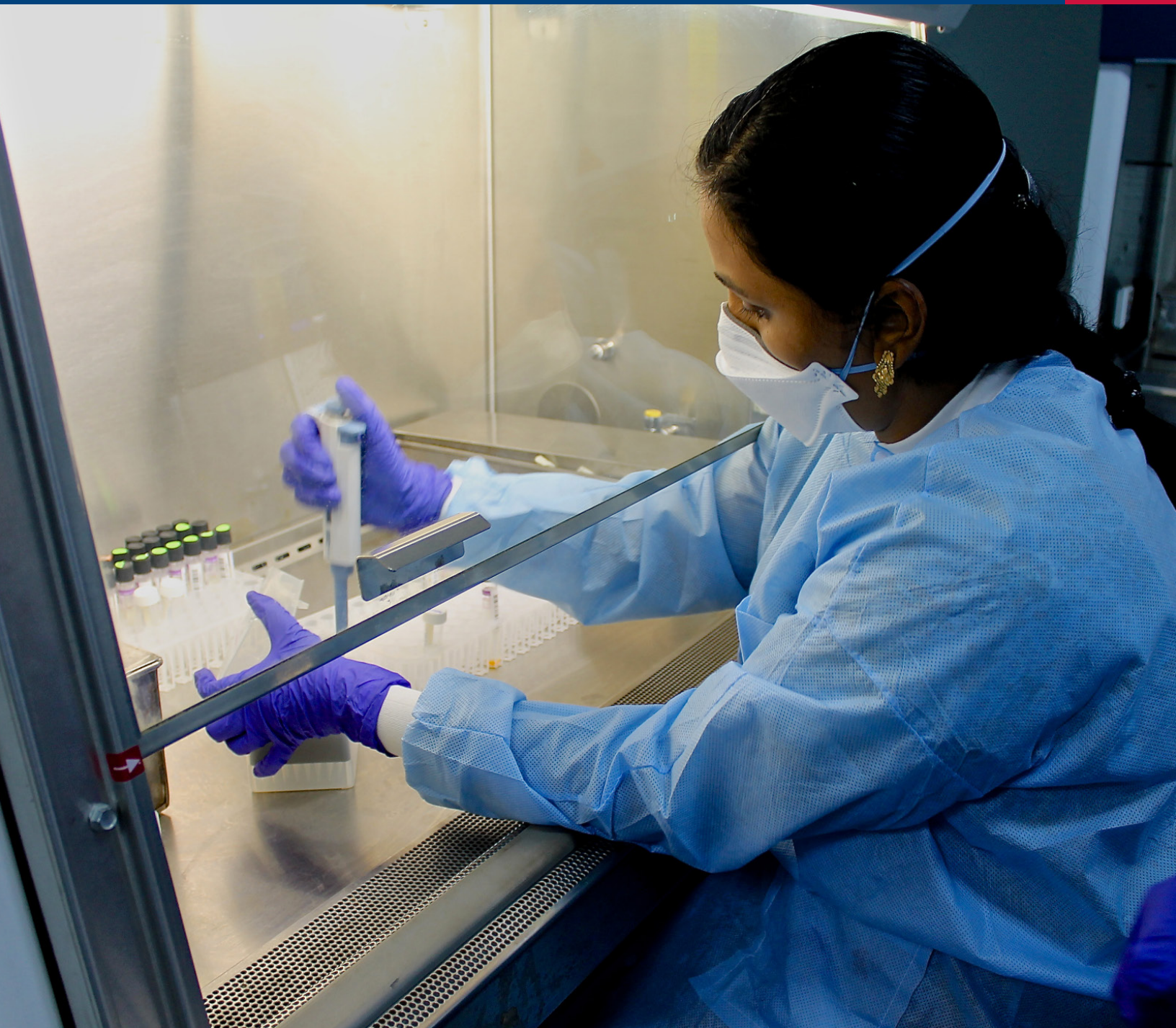


National Institute of
Allergy and
Infectious Diseases



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

YEAR THREE
REPORT
OCTOBER 2019



COMBATING MULTIDRUG-RESISTANT TUBERCULOSIS: **YEAR THREE OF THE NATIONAL ACTION PLAN REPORT**

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The U.S. Agency for International Development (USAID) submits this report pursuant to Section 7019(e) of Division F of Public Law (P.L.) 116-6, the Department of State, Foreign Operations, and Related Programs Appropriations Act, 2019, which incorporates by reference the requirements of Senate Report 115-282:

The Committee recognizes that Multidrug-Resistant Tuberculosis (MDR-TB) is a national security threat. Not later than 180 days after enactment of the act, the USAID Administrator shall submit a report to the Committee on implementation of Goals 2 and 3 of the National Action Plan for Combating Multidrug-Resistant Tuberculosis, issued on December 22, 2015, including a description of: (1) efforts to increase case discovery; (2) the approximate number of people receiving treatment for MDR-TB; and (3) an estimate of the resources required to achieve stated objectives.

On the Cover: USAID Uses Technology and Innovation to Fight TB in India. Photo by Bonnie Carlson, USAID/India, February 26, 2015

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ACRONYMS AND ABBREVIATIONS

ACTG	AIDS Clinical Trials Group	MDSTR	Molecular Drug Susceptibility Testing Reporting
aDSM	Active Drug Safety Management and Monitoring	MTB	Mycobacterium Tuberculosis
BDQ	Bedaquiline	NIAID	National Institute of Allergy and Infectious Diseases
CDC	Centers for Disease Control and Prevention	NIH	National Institutes of Health
DLM	Delamanid	NTP	National Tuberculosis Program
DOT	Directly Observed Therapy	PATRIC	Pathosystems Resource-Integration Center
DR-TB	Drug-Resistant Tuberculosis	PLHIV	People Living with HIV
DS-TB	Drug-Sensitive Tuberculosis	R&D	Research and development
eDOT	Electronic Directly Observed Therapy	RePORT	Observational International Research Cohorts
ELR	Electronic Laboratory Reporting	RIF	Rifampicin
FAST	Find cases Actively, Separate temporarily and Treat effectively	RR-TB	Rifampicin-Resistant Tuberculosis
FDA	U.S. Food and Drug Administration	SRS	Strategic Rotating Stockpile
GDF	Global Drug Facility	STR	Shorter treatment regimen
GeneXpert	Xpert® MTB/RIF	TB	Tuberculosis
H3Africa	Human Heredity and Health in Africa	TBRU-N	Tuberculosis Research Unit Network
HHS	U.S. Department of Health and Human Services	UNGA	United Nations General Assembly
HIV	Human Immunodeficiency Virus	UNHLM	United Nations High-Level Meeting
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network	USAID	United States Agency for International Development
IMPAC-TB	Immune Mechanisms of Protection Against Mycobacterium Tuberculosis	WGS	Whole-Genome Sequencing
IPC	Infection prevention and control	WHIP3TB	Weekly High Dose Isoniazid and Rifapentine Periodic Prophylaxis for Tuberculosis
LTI	Lilly TB Drug Discovery Initiative	WHO	World Health Organization
MDR-TB	Multidrug-Resistant Tuberculosis	XDR-TB	Extensively Drug-Resistant Tuberculosis

INTRODUCTION

Tuberculosis (TB) kills more people than any other infectious disease. In 2017, ten million people developed this deadly disease, and 1.6 million lost their lives as a result. *Mycobacterium tuberculosis* (MTB), transmitted through the air from person to person, causes TB. It is present in every country in the world, including the United States, which reported more than 9,000 cases of the disease in 2017. Although TB is both treatable and preventable, treatment requires multiple drugs for at least six months; failure to treat the disease appropriately can lead to drug-resistant TB (DR-TB).

DR-TB, as defined in this *Report*, encompasses TB that is resistant to at least rifampicin (RR-TB), the most-effective drug in the regimen required to treat TB. Multidrug-resistant TB (MDR-TB) is resistant to isoniazid (the second-most-vital drug in the regimen), as well as to rifampicin, and extensively drug-resistant TB (XDR-TB) is resistant to both rifampicin and isoniazid, as well as to drugs used to treat MDR-TB. Developing any type of DR-TB often has devastating effects on the individuals who develop the disease, as well as on their families. They endure long, toxic, and complicated regimens; the anxiety of potentially transmitting the disease to loved ones; and the loss of income because of illness, isolation, and stigma. In addition to the impact on individuals, families, and communities, any type of DR-TB is a significant global health-security threat. Outbreaks of DR-TB have serious consequences for health care and economies, not only because of the very high cost of treatment, but also because of the burden the disease places on providers, institutions, and national health budgets.

In 2017, an estimated 558,000 people developed DR-TB globally. Of these individuals, it is estimated that more than 441,000 had MDR-TB, and almost 41,000 had XDR-TB. However, only 160,684 cases (29 percent) of DR-TB were diagnosed and notified to National TB Programs (NTPs), of which 119,114 (87 percent) were enrolled on treatment—only 25 percent of the estimated RR-TB cases in 2017. While increasing numbers of individuals with RR-TB have been diagnosed, and have initiated and completed

treatment, progress has been slow. Greater efforts are required to ensure the development and rapid uptake of better diagnostic methods and treatment regimens, as well as person-centered care-delivery modalities.

In 2017 in the United States, 870 people developed drug resistance to at least one of the first-line drugs, and among these, 124 people were diagnosed with MDR-TB and four with XDR-TB. Of those treated for DR-TB, 73 percent require hospitalization, 37 percent require home isolation, 27 percent stop working, and nine percent die during treatment. 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). The cost to treat the disease in the United States is extremely high: more than \$164,000 per case for MDR-TB, and even more for XDR-TB. Preventing, diagnosing, and treating TB in the United States, as in the rest of the world, requires better options to diagnose and treat, accurately, rapidly, and successfully, every case of TB.

In December 2015, the U.S. Government released a plan to address the growing TB crisis domestically and internationally, and to advance research on this critical public health issue. The *National Action Plan for Combating Multidrug-Resistant Tuberculosis* (*National Action Plan*) is a five-year plan that builds on, and contributes to, the U.S. Government's domestic and global TB strategies, as well as the *END TB Strategy* of the World Health Organization (WHO) and the Stop TB Partnership *Global Plan to End TB*.

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

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

From 2000 to 2017, global efforts to ensure TB diagnosis, treatment, and care saved an estimated 54 million lives. The U.S. Government is a leader in these efforts, working through its Departments and Agencies to support the implementation of high-quality diagnosis and care. The *National Action Plan* builds on these efforts to support the appropriate treatment of more than 16 million TB patients, ensure a 90-percent cure rate, and prevent the further development of DR-TB. In addition to increased efforts to diagnose, cure, and prevent MDR-TB, the *National Action Plan* is designed to increase the number of MDR-TB treatment initiatives in countries with the highest burden of DR-TB, with a target of a 25-percent increase by Year One, a 35-percent increase by Year Three, and a 50-percent increase by Year Five, as well as many milestones in each of the three goals.

This report outlines how the Federal Departments and Agencies have successfully met the global target and all of the milestones for Year Three. By Year Three, the U.S. Government increased case discovery by 36 percent from baseline in *National Action Plan* countries, as outlined in Goal 2 below. Furthermore, there were 100,919 individuals enrolled on DR-TB treatment in Year Three, which met the Goal 2 target. An estimated 15 billion U.S. dollars a year is required to meet the commitment of the 2018 United Nations High-Level Meeting (UNHLM) on Tuberculosis of the United Nations General Assembly (UNGA). The U.S. Government's activities under the *National Action Plan* are critical to these efforts.

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

Following an increase that coincided with both the onset of the HIV epidemic and decreasing support and resources for programs to prevent and control TB, the incidence of the disease in the United States declined from 1993 through 2017. However, the U.S. TB case rate remains well above the elimination threshold of less than one case per million persons. The percentage of MDR-TB cases in the United States has remained steady for more than 20 years, at approximately one percent of U.S. TB cases; the majority of these (greater than 90 percent) occur among non-U.S.-born persons. The proportion of cases with reported mono-resistance to isoniazid has remained approximately nine percent in the last several years.

DR-TB cases complicate efforts to treat and prevent TB, and are extremely expensive for State and local TB programs to manage. Because drug resistance can develop when a patient does not complete a full TB-treatment regimen, TB programs must ensure continuity of care among persons who lack access to consistent health care. This includes the provision of wraparound services such as patient education. The TB programs of State and local health departments are responsible for the coordination and oversight of activities to ensure the achievement of objectives related to the prevention and control of TB. The U.S. Centers for Disease Control and Prevention (CDC) within the U.S. Department of Health and Human Services (HHS) provides funding and technical assistance to help TB programs address the burden of DR-TB in each State. A single case of MDR-TB costs far more to treat (\$164,000) than a drug-sensitive case (DS-TB) (approximately \$19,000); thus, support for better treatment options, rapid diagnosis, and expert management are essential to prevent and control DR-TB in the United States.

OBJECTIVE I.1: UPGRADE TB SURVEILLANCE TO ENSURE COMPLETE AND ACCURATE DETECTION OF DRUG-RESISTANT TB

HHS/CDC is upgrading the U.S. domestic TB-surveillance system for tracking DR-TB cases to capture molecular test results and more-detailed clinical information about each case, which will enable better tracking of disease burdens, targeting of resources, and linkages to care and contact investigations. HHS/CDC is working with State and local TB programs to identify common language and protocols for reporting resistance to anti-TB drugs. HHS/CDC developed a form for reporting the results of molecular drug-susceptibility tests (MDSTR) to provide standardization within the National TB Surveillance System. HHS/CDC has pilot-tested the variables for use in its revised Report of Verified Tuberculosis (RVCT) form for 2020.

HHS/CDC has developed guidance for States to use in 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. HHS/CDC is pilot-testing HL7¹ standardized coding for Electronic Laboratory Reporting (ELR) into State surveillance systems, as well as standardized coding for electronic transmission from State surveillance systems and HHS/CDC labs into the National TB Surveillance System Case Reporting MDSTR data-collection system. Enhancing platforms for laboratory reporting and surveillance for data from molecular drug-susceptibility tests will allow HHS/CDC to capture drug-resistance results more quickly and completely.

¹ HL7 refers to the seventh level of the International Organization for Standardization (ISO) communications model for Open Systems.

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

HHS/CDC has also expanded the collection of data on the results of drug-susceptibility tests, which will be part of the new version of the RVCT. This will enable epidemiologists to identify related cases of DR-TB and DS-TB transmitted recently to facilitate targeted interventions to prevent additional transmission. State and local TB programs will also use these improved data to define the burden of DR-TB more effectively. The collection of data with the new RVCT will begin in 2020. In 2018, HHS/CDC began universal whole-genome sequencing (WGS) on isolates of MTB gathered from newly diagnosed patients. HHS/CDC will flag WGS results for identification of possible transmission by using outbreak-detection methods. HHS/CDC shares indications of possible transmission with State and local jurisdictions to support their response to identify and interrupt transmission in real time.

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

Completion of treatment for patients with DR-TB is challenging on many levels. The activities involved in meeting this objective encompass a broad range of interventions implemented by State and local health departments with funding and assistance from HHS/CDC. Electronic directly observed therapy (eDOT) is the use of electronic technologies to remotely monitor TB patients as they ingest their medication, either in real time or recorded. Because eDOT uses remote observation in lieu of clinic visits by the patient (e.g., over a smartphone), it could improve adherence and be more cost-efficient than traditional in-person directly observed therapy (DOT). The benefits of an eDOT program include convenience for patients and staff, in addition to reduced staff travel cost and time. A

randomized trial of eDOT led by HHS/CDC is currently underway in collaboration with partners at the New York City Department of Health and Mental Hygiene's Bureau of TB Control. The study will analyze both the economic benefit and the efficacy of treatment with eDOT.

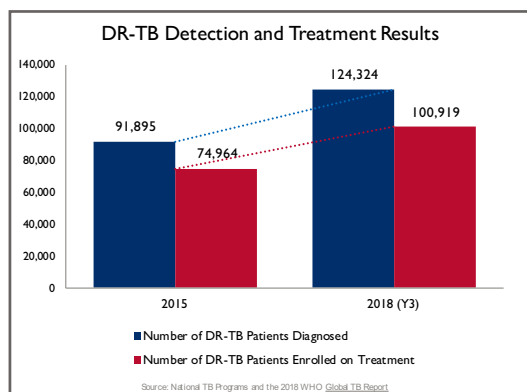
HHS/CDC, in collaboration with the HHS Supply Service Center, maintains a small supply of drugs that would be necessary to protect TB patients and communities during a time-limited manufacturing shortage. HHS activated the TB Emergency Drug Stockpile in 2018 in response to a shortage of rifapentine. HHS/CDC provided rifapentine to twelve States where more than 500 patients were at risk for interrupted treatment. HHS/CDC also developed and published a case definition for the national TB-surveillance system that can measure the performance indicators of TB programs, including completion of therapy for TB patients who are receiving treatment from both U.S. and Mexican TB programs.

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

As the lead U.S. Government Agency for global efforts to control TB, USAID works with HHS/CDC and other Federal Departments and Agencies to reach every person with TB, cure those in need of treatment, and prevent new TB infections. Discovering cases and treating patients with DR-TB remains a challenge, primarily because of diagnostic and health-care constraints.

This Report for Year Three provides a progress update with the finalized 2017 and validated 2018 data. With a concerted effort, the U.S. Government and partners achieved the target of Goal 2 of the *National Action Plan* successfully with a 35-percent enrollment of patients on DR-TB in Year Three (see Figure 1). However, the target for Year Five of enrolling 50 percent of people with DR-TB will be a significant challenge unless governments increase their domestic resources for TB and donors continue to increase their TB investments. USAID sees reducing the prevalence of DR-TB as an important component of the capacity and commitment that governments, civil society, and the private sector must show in our partner countries on their Journeys to Self-Reliance².

Figure 1: Detection and Treatment of DR-TB in Countries Covered by the *National Action Plan*, Baseline to Year Three



In 2018 alone, the countries covered by the *National Action Plan*³ recorded significant progress, with a 20-percent increase in the number of people diagnosed, and a 17-percent increase in the number of people enrolled in treatment for DR-TB. In addition, these countries saw a 28-percent increase in patients enrolled on a regimen that contains bedaquiline (BDQ), and a 360-percent increase in DR-TB patients enrolled on shorter treatment regimen (STR). India had the most significant increase in absolute numbers, with almost 50,000 people enrolled on DR-TB treatment in 2018.

Table 1: DR-TB Detection and Treatment from Year Two and Year Three

	DR-TB Detected	DR-TB Enrolled	Enrolled on BDQ Regimen	Enrolled on STR
Globally in 2017	160,684	139,114	14,517	10,079
10 NAP countries in 2017	104,340	86,272	9,754	6,500
10 NAP countries in 2018	124,324	100,919	12,500	30,000

The past several years have seen new advances in treatment for DR-TB. The most consequential thus far is BDQ, a recently developed anti-TB medication prescribed for MDR/XDR-TB patients. It is the first new drug approved for treating DR-TB in almost 50 years. Treatment-success rates with BDQ-inclusive treatment regimens show results greater than 80 percent, compared to 25 percent in regimens without BDQ. Delamanid, a new drug for treating DR-TB, was approved in 2014, and other new treatment regimens for DR-TB have emerged from recent studies. One such regimen includes a combination of BDQ, linezolid, and a novel TB drug, pretomanid, which has shown treatment success as high as 80 percent in patients with XDR-TB. In August 2019, pretomanid received U.S. Food and Drug Administration (FDA) approval to be used with BDQ

² USAID's Journey to Self-Reliance is an orientation of strategies, partnership models, and program practices to achieve greater development outcomes and work towards a time when foreign assistance is no longer necessary.

³ Countries covered by the *National Action Plan*: Burma; the People's Republic of China; the Republics of India, Indonesia, and Kazakhstan; the Federal Republic of Nigeria; the Islamic Republic of Pakistan; the Republics of The Philippines and South Africa; and Ukraine.

and linezolid for the treatment of XDR-TB. STR is a novel approach to DR-TB treatment that uses treatment regimens designed for up to 11 months of use instead of the conventional standard of care, which can last up to 24 months. Studies indicate that these shorter regimens are much more likely to lead to better treatment outcomes.

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

In Year Three, USAID and HHS/CDC increased case-discovery through screening for TB and DR-TB among close contacts of patients and high-risk populations, including people who are living with HIV (PLHIV). In addition, USAID placed greater emphasis on the early screening of people at risk, early detection with rapid molecular tests, and the early initiation of appropriate treatment. Increased focus on active case-finding and enhanced support to the diagnostic network also contributed to the better discovery of cases and enrollment of patients in treatment. To improve patients' experiences and outcomes, USAID's partners shifted to ensure "person-centered" care, which emphasizes greater control by individuals with the disease, greater attention to their needs and preferences, and a package of interventions designed to decrease the impact of the disease on individuals, families, and communities.

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

USAID funds national, regional, and Provincial TB laboratories to adopt new technology, broaden rapid-testing for TB and DR-TB, and improve the quality of their services. In 2018, USAID and HHS/CDC assisted seven governments (in Burma, China, India, Indonesia, Kazakhstan, Pakistan, and South Africa) to implement their National Laboratory Strategic Plans; national laboratories also are making progress in the three remaining countries covered by the *National*

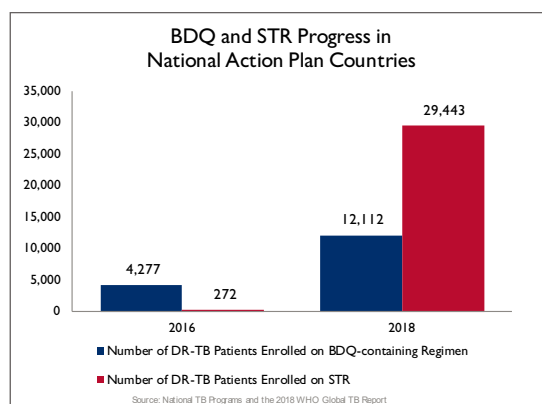
Action Plan. In addition, USAID worked with regional and Provincial laboratories to incorporate systems for quality-assurance.

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 2018, USAID and HHS/CDC worked with the WHO and other partners to update guidelines for the treatment of DR-TB. This work led to the WHO's new recommendations, which now include an all-oral treatment regimen that incorporates new and repurposed medications for TB, such as BDQ and linezolid. As a result, DR-TB patients do not have to endure six months of daily injections as an essential component of their treatment. Patients should tolerate this all-oral treatment regimen better, which will lead to better treatment outcomes. USAID, HHS/CDC and their partners worked diligently in countries covered by the *National Action Plan* to provide rapid education to Ministries of Health and providers on the updated recommendations and help ensure a rapid transition to the novel, improved regimens.

USAID's innovative BDQ-Donation Program partnership with Johnson & Johnson helped pave the way for the expanded treatment of DR-TB patients globally. What began in March 2015 as a donation program for a total of 30,000 treatments over four years grew to a program of 105,000 treatments in 72 countries by early 2019, which allowed three times as many people as originally conceptualized to benefit from the new medication.

Figure 2: Progress in Adopting BDQ and STR in Countries Covered by the *National Action Plan*



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

Surveillance is a core component of the effort to end TB and DR-TB, as it enables governments, donors, and other partners to track the epidemic and make timely and informed decisions based on data. USAID has long funded the WHO's work to track the epidemic and analyze the information gathered to identify challenges, solutions, and successes, showcased in the annual *WHO Global TB Report* and the open-source WHO Global TB database, both of which USAID has financed for the past 20 years. In countries covered by the *National Action Plan*, USAID and HHS/CDC strengthen TB-surveillance systems and the responsiveness of National TB Programs by supporting the scale-up of electronic TB databases and performing drug-resistant surveys that provide essential information to target activities to the most-vulnerable regions and populations.

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

Access to safe and affordable TB drugs is a priority for USAID. In 2018, USAID continued to provide substantial funding to the Stop TB Partnership's Global Drug Facility (GDF) to consolidate the market for TB medicines, reduce prices, and attract new quality-assured suppliers.

In 2018 alone, the GDF provided support for supply-chain procurement and management systems for TB and DR-TB through technical assistance in 118 countries, which allowed more than 33,000 patients to gain access to treatment for DR-TB. In addition, GDF helped governments and their partners introduce new products, including the new WHO-recommended child-friendly drug formulations; reduce drug prices; and overcome country supply-chain security barriers.

The creation of the GDF's Strategic Rotating Stockpile (SRS) has played a crucial role in providing uninterrupted availability,

as well as rapid access to medications at short notice to avoid stockouts. The SRS has accomplished this by decreasing lead times and ensuring the fulfillment of "urgent" orders from countries in need and by closely monitoring and redistributing medicines in short supply because of problems with manufacturers. In addition to improving care for patients, the SRS also provides stability for manufacturers in this fragile market for TB drugs.

USAID has also been in the forefront of the introduction and scale-up of TB drug-safety monitoring through an active approach to the monitoring of drug safety (Active Drug Safety Management and Monitoring [aDSM]). In 2018, approximately 200 representatives from 20 countries, including all ten covered by the *National Action Plan*, participated in aDSM-focused workshops to help governments develop or strengthen existing aDSM plans. These monitoring plans are vital to identify quickly and rectify medicine-related adverse events experienced by patients, prevent others from similar experiences, and ensure patients that these life-saving medications are safe.

USAID's funding continues to be instrumental in helping manufacturers obtain WHO pre-qualification for their products. For example, in 2018, USAID assisted two new manufacturers of clofazimine, an essential component of the STR regimen for DR-TB treatment, in their submission of dossiers to the WHO's pre-qualification program. Approval of these dossiers will help ensure a safe and regular supply of clofazimine, as well as a 45-percent reduction in the cost of the drug; both outcomes are necessary to expand the use of this preferred regimen. USAID also works with drug manufacturers to submit dossiers for WHO-recommended formulations for the treatment of latent TB. This intervention will be crucial to meeting the UNHLM prevention targets, given the limited number of suppliers currently.

OBJECTIVE 2.2: PREVENT MDR-TB TRANSMISSION

Improving the quality of care for DR-TB, particularly early and accurate diagnosis, the rapid initiation of treatment, and support to ensure completion, will reduce the transmission of TB and lead to fewer cases of DR-TB, as well as higher

cure rates. In 2018, USAID and HHS/CDC supported partners to scale up patient-centered care; link communities to the detection and treatment of DR-TB; and provide increased support to patients and their families, including the introduction of innovative digital tools in eight countries covered by the *National Action Plan* to improve support and counseling for the treatment of DR-TB via the Internet.

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

In 2018, all countries covered by the *National Action Plan* expanded activities to monitor the quality of care provided to individuals with DR-TB. As part of regular site supervision and cohort-monitoring, the NTPs in these countries now track progress on both the detection of DR-TB cases and the quality of care for all DR-TB patients.

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

Introduced by USAID in 2016, the DR-TB Care Package, which focuses on providing holistic support for DR-TB patients who are receiving care, is now being introduced in eight countries covered by the *National Action Plan*. Evaluation of the package in pilot countries, demonstrated marked decreases in both initial loss-to-follow-up and adherence once on therapy, which has resulted in substantial increases in treatment-success rates.

USAID has introduced and scaled up digital solutions, including video directly observed therapy (DOT), SMS reminders (i.e. text messages), pill boxes, phone applications, and other tools to improve adherence and treatment success, in all countries covered by the *National Action Plan*. In 2018, the Government of India worked with USAID to host a Digital Health Conference, which brought together more than 130 TB specialists from ten countries. Participants learned about the wide field of digital technologies for health, presented on their own experiences, and gained the necessary tools and information to create national agendas for digital-health technology. Each country team selected the top three digital innovations to pilot.

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

Keeping TB health facilities safe for both patients and providers is a priority of the *National Action Plan*; implementing and expanding improved infection-control measures at hospitals and outpatient facilities are the keys to achieving this goal. In 2018, USAID worked with HHS/CDC to reduce the transmission of TB in diagnostic and treatment health-care facilities by updating national and facility-based guidelines for infection-control, developing tools for measuring transmission, monitoring the effect of interventions to prevent and control infections (IPC), and creating programs to help health-care workers determine risk and remediation. One of the tools developed for this purpose, called Find Cases and Actively Separate Them for Appropriate Treatment (FAST), has proven to be a successful approach to improve facility-level infection-control practices. In 2018, countries covered by the *National Action Plan* received technical support to adapt FAST to the local context and expand from pilot sites to cover regional and Provincial levels.

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

The National Institutes of Health (NIH) within HHS has a mission to finance and conduct domestic and international biomedical research on TB. Within NIH, the National Institute of Allergy and Infectious Diseases (NIAID) is the lead institute for TB research, complemented by programs financed by other NIH Institutes and Centers. This comprehensive research portfolio provides opportunities to contribute strategically to key areas of basic science that can lead to the discovery, development, and evaluation of new vaccines, drugs, and diagnostics.

In September 2018, HHS/NIH/NIAID released the *NIAID Strategic Plan For Tuberculosis Research*, which prioritizes expanding the fundamental knowledge of TB by using modern tools, such as state-of-the-art imaging and systems-biology methods, to better understand how TB remains latent in some individuals and then progresses to active disease, as well as the host and microbial factors that affect the transmission and epidemiology of TB. Many of these research projects highlight the synergy among the TB activities financed by U.S. Government Departments and Agencies. Programs managed by USAID and HHS/CDC continue to evaluate strategies and tools for the diagnosis, treatment, and care of TB developed with financing from HHS/NIH.

Many countermeasures developed with financing from HHS/NIH, such as the diagnostic tool GeneXpert MTB/RIF and the recently FDA-approved antibacterial drug pretomanid, are undergoing testing in clinical trials with support from HHS/NIH and HHS/CDC or are being implemented in TB-endemic countries with financing from HHS/CDC and USAID. HHS/NIH is currently evaluating pretomanid's safety for patients with renal or hepatic impairment. Observational international research cohorts, such as the Regional Prospective Observational Research for Tuberculosis Cohorts (RePORT) International (<http://www.reportinternational.org>), a cooperative strategy between HHS/NIH and interested foreign governments, benefit from

investments made by USAID, HHS/CDC, and other U.S. Government Departments and Agencies and help initiate country-based biomedical research. HHS/NIH contributes to research on diagnostics, vaccines, and therapeutics for TB research conducted by HHS/NIH scientists as well as through multiple funding mechanisms available to the greater scientific community. Since many global funders support research and development (R&D) for TB, HHS/NIH-supported scientists ensure the optimal application of the U.S. Government's investments so they complement other international programs. To facilitate coordination, HHS/NIH, USAID, and HHS/CDC continue to participate in the WHO-led Funder's Forum for TB R&D and the WHO Global TB Research Task Force.

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

Because of the complexity of the host/pathogen interactions that underlie the transmission of TB and the 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 financing for critical product-development and clinical-testing activities. Strategies for prevention and treatment that target the people at the highest risk of developing transmissible forms of the disease are expected to have a significant impact on individual and public health.

SUB-OBJECTIVE 3.1.1: ADVANCE R&D FOR NOVEL VACCINES

Building on a robust and comprehensive portfolio of TB research, HHS/NIH continues to finance multiple grants and contracts to expand its immunology TB research program, including the development of novel vaccines. HHS/NIH supports clinical trials that evaluate investigational vaccines against TB, including a Phase I trial of a thermostable vaccine and a Phase Ib/2a trial of the MTBVAC vaccine candidate in adults. In addition, HHS/NIH's Vaccine Research Center has established a Tuberculosis Vaccine Unit dedicated to the scientific investigation and clinical development of new vaccine strategies to prevent TB infection and disease.

HHS/NIH continues to provide resources to the academic community and industry to facilitate the translation of the findings from basic biomedical research into vaccine candidates. These resources include microbial, biochemical, and immunological reagents, bioinformatics tools and technologies to support data-integration, and animal-testing services and clinical-trials capacity. HHS/NIH's resources also contribute to the development of better predictive animal models and clinical trials to study the safety and efficacy of vaccine candidates. Through the U.S. Government's investments in vaccine-development and clinical-research activities, researchers are exploring novel approaches for preventing TB and evaluating innovative vaccine concepts. The continued, iterative development and testing of vaccine candidates is critical for advancing approaches developed in the laboratory and in animal models to strategies that will prevent TB in humans.

Among many collaborative working relationships, HHS/NIH participates in the [Stop TB Partnership Working Group on New TB Vaccines](#), the mission of which is to facilitate R&D for 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.

A new milestone for this sub-objective addresses the evaluation of new adjuvants and preventive drugs. HHS/

NIH finances research, including clinical trials, on protective and novel immune responses and the development of novel drugs. HHS/NIH also participates in the TB Drug Accelerator, an international collaborative effort among governments, companies, academia, hospitals, and non-government organizations to accelerate the discovery and development of novel drugs to treat TB.

In September 2019, HHS/NIH established three Immune Mechanisms of Protection Against Mycobacterium Tuberculosis (IMPAC-TB) Centers for immunology research to accelerate progress in TB vaccine development. The IMPAC-TB program aims to develop a comprehensive understanding of the immune responses required to prevent initial infection with MTB, establishment of latent infection, and transition to active TB disease. Other aims of the IMPAC-TB program include understanding the effects of co-infections such as HIV on immune responses to MTB infection or TB vaccination and improving the value of animal models in predicting MTB vaccine efficacy in humans.

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

In addition to the basic research necessary for new diagnostics, therapeutics, and vaccines, HHS/CDC, HHS/NIH, and USAID financed clinical research to inform the prevention, treatment, and management of TB. Clinical investigators financed by HHS/NIH recently reported a successful shortened regimen for the prevention of TB in HIV-infected adults in the Republic of South Africa (AIDS Clinical Trials Group [ACTG] 5279 BRIEF TB). This ultrashort regime of rifapentine/isoniazid daily for one month was non-inferior to nine months of isoniazid, produced fewer adverse events, and could offer improved adherence.

The HHS/NIH-financed AIDS Clinical Trials Group (ACTG) and the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) is conducting the "Protecting Households on Exposure to Newly Diagnosed Index Multidrug-Resistant (MDR) Tuberculosis Patients (PHOENIX)" clinical trial. PHOENIX is a Phase III 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 MDR-TB patients. HHS/NIH/NIAID supports and conducts research to improve the understanding of where, when, and how the transmission of TB occurs, including the factors that influence transmission. In addition, HHS/NIH/NIAID also finances research to develop more-efficacious approaches for preventing MTB infections and subsequent disease. The USAID-funded Weekly High-Dose Isoniazid and Rifapentine Periodic Prophylaxis for TB (WHIP3TB) study that evaluates two different approaches to the treatment of latent MTB infection [3HP and periodic (p3HP)] in HIV co-infected individuals (adults and children) has completed enrollment, and will continue to follow participants through the last quarter of calendar year 2019. Preliminary data are expected in the second quarter of calendar year 2020.

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

The rapid and accurate diagnosis of acute and latent MTB infection, MDR-TB, and XDR-TB is the cornerstone of programs to control and care for TB in the United States and worldwide. A variety of technologies are under development to confirm or rule out active TB, and to determine quickly which antibiotics will constitute the most-effective treatment regimen. Clinical studies to evaluate these technologies are underway in countries where TB is endemic. The diagnosis of latent MTB infection offers the opportunity to provide patients with preventive therapy to lower their immediate risk of developing active disease. The development of diagnostics for TB involves research to detect drug-sensitive and drug-resistant forms of TB or biomarkers identifiable in sputum, blood, or other body fluids or excretions and pairing those with novel, rapid technologies useable in health-care settings where they are most urgently needed. Unique collaborations among multiple partners, including health-care providers, and TB-control programs, are required to determine that a diagnostic test improves the accuracy and speed at which doctors can identify TB patients of all ages and offer them effective treatment.

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

HHS/NIH currently finances research that uses a broad and diverse range of technologies and approaches aimed at improving the identification of drug-susceptible 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 might have the highest risk for developing active disease. A continued area of focus is the creation of comprehensive datasets that give insight into the diversity of the biology and drug-resistance profiles of MTB strains and how they affect patients. The HHS/NIH-financed Pathosystems Resource-Integration Center (PATRIC), which has more than 10,000 MTB genomes and associated clinical data, provides tools to analyze genomic data. The HHS/CDC TB Trials Consortium is contributing specimens to a collaborative registry as part of the search for the 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 the developers of medical diagnostics provide opportunities for developing and strengthening reference laboratories in TB-endemic countries to evaluate promising new diagnostic tests.

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's Tuberculosis Research Units Network (TBRU-N) and other ongoing projects are identifying biomarkers that could be useful in differentiating between latency and persistence of TB in individuals in endemic countries. To enable coordinated and comparable research in TB-endemic countries, the RePORT Consortium, co-financed by HHS/NIH, uses standardized protocols and is contributing critical resources to HHS/NIH-financed studies, including the development of diagnostic tools specifically for diagnosing TB in children. In addition, HHS/NIH is financing the development of a novel, stool-based assay to diagnose

pediatric TB, as well as the validation of novel potential pediatric biomarkers.

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

Improving treatment options for TB also requires the full spectrum of TB research, from basic science to implementation. U.S. Government Departments and Agencies are contributing multiple kinds of resources and expertise to support preclinical and clinical research to enable the short-, medium- and long-term improvement of care for TB. 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. U.S. Government financing is allowing the optimization of the use of key drugs within regimens; the study of new drugs for their ability to shorten therapy and provide safer treatment options; and the development of completely new, innovative regimens and treatment approaches that could dramatically affect patient care.

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

Investigators from the HHS/NIH-financed TBRU-N collaborated with researchers from the HHS/CDC Tuberculosis-Trials Consortium to compare mycobacterial isolates before treatment and after treatment. Higher 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 supports research focused on treatments for DR-TB patients, including standard-of-care and second-line drugs, to optimize treatment regimens even further. HHS/NIH finances pharmacokinetic studies on TB drugs, and studies

to identify optimal regimens *in vitro* and in animal models that fulfill the requirements of shortening therapy. The HHS/NIH-financed ACTG conducts clinical trials of existing drugs, including the comparison of standard treatments, drug interactions, and pharmacokinetics. In collaboration with HHS/CDC, HHS/NIH finances the re-evaluation of existing drugs, such as rifapentine, linezolid, and moxifloxacin, for drug-susceptible TB. ACTG 5362 also will study combination therapy including high-dose rifapentine and clofazimine with PZA, INH, and ethambutol as a 3-month regimen for DS-TB. ACTG 5384 will evaluate a new combination of drugs, including linezolid and high-dose rifampin, to improve therapy for the most devastating form of TB – tuberculous meningitis. Finally, HHS/NIH finances studies to evaluate single and combination therapies of new and repurposed drugs, and the development of new models to guide the development of optimal combinations of TB drugs.

For its part, USAID is financing studies to determine the impact of introducing a predetermined package of care on the treatment outcomes of patients with DR-TB.

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 studies for efficacy and safety that ensure treatment is safe and effective, and that patients benefit from new drugs. An HHS/NIH-financed clinical trial is evaluating the safety and tolerability of BDQ in infants, children, and adolescents who might or might not be co-infected with HIV, which will contribute data for the safe and effective use of this drug in these important populations. Another clinical trial is evaluating the safety and tolerability of DLM in HIV-infected and uninfected children with DR-TB. HHS/NIH is conducting a pharmacokinetic and safety study of BDQ and DLM in patients with DR-TB.

USAID continues to finance efforts to strengthen national capacity for pharmacovigilance. Following up on activities started in Year One and Two of the *National Action Plan*,

in Quarters Two and Three of 2018, USAID supported two workshops (one in South Africa for the African Region and one in Kazakhstan for the Eastern Europe/Central Asia Regions) that focused on strengthening the capacity of Ministries of Health in pharmacovigilance and gathering best practices in the field.

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 continues to finance preclinical studies to select the most-promising new compounds for further advancement, including the preclinical development of new beta-lactam-class, rifamycin-class, and diarylquinoline-class antibiotics. HHS/NIH staff participate in the [STOP TB Partnership Working Group on New TB Drugs](#), which tracks progress in the global landscape of the development of medicines to treat the disease.

HHS/NIH is financing the development of new *in silico* models and pharmacokinetic studies to guide the development of treatment-shortening combinations of drugs. HHS/NIH is financing research into formulations, especially in the area of inhaled pulmonary-delivery methods for drugs, as well as longer-acting delivery approaches and pediatric-friendly formulations of existing drugs. HHS/NIH has funded studies to investigate further the mechanism of action of TB drugs like pyrazinamide that could inform the development of new TB-treatment regimens. HHS/NIH has provided preclinical and clinical support for the development of novel classes of antibiotics, including spectinomycin- and capreomycin-class antibiotics. HHS/NIH funds clinical trials on a shortened treatment regimen for MDR-TB (PREDICT-TB) and pharmacokinetics during pregnancy and the post-partum period. Finally, HHS/NIH provides financial support to the Structural Genomics Center for Infectious Diseases, which uses a structure-guided approach to evaluate drug targets and candidate drugs against TB and has established an expanded facility for the imaging of MTB infection in animal models.

HHS/NIH-funded scientists continue to make advances in

drug-discovery by participating in global drug-development consortia, such as the Lilly TB Drug Discovery Initiative (LTI), which are emerging as effective models for academic-pharmaceutical collaborations. These research partnerships are increasingly using rational, pharmacologically driven approaches to drug-discovery, the development of animal models, the selection of regimens, and the design of clinical trials to improve the state of the science for the discovery of TB drugs and lower risks for industry.

Separately, USAID funds Phase III clinical trials to evaluate the efficacy, safety, and tolerability of multiple shorter-treatment regimens for adult patients with DS- and DR-TB, including studies to evaluate a treatment regimen that contains pretomanid and studies to evaluate a combination regimen of BDQ and DLM.

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, 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. NIH has issued multiple funding opportunities targeted at TB research in endemic countries. As general infectious disease training benefits scientists who conduct TB research by improving their research and clinical skills, numerous NIH funding opportunities for training were issued during the reporting period that are not specifically directed toward TB but will have positive benefits for TB programs. To help facilitate applications for NIH funding opportunities, NIH continues to provide training in grant writing, financial administration, bioethics and implementation research, particularly through its ongoing Human Heredity and Health in Africa (H3Africa) program and similar initiatives.

CONCLUSION

U.S. Government Departments and Agencies charged with implementing the *National Action Plan* have reported significant progress in meeting the *Plan's* milestones in the fight against DR-TB: a 36-percent increase in the detection of cases and a 35-percent increase in the enrollment of patients in treatment since the launch of the *Plan*, including a 17-percent increase in the enrollment of patients in treatment in 2018 alone. These advancements occurred, in large part, because of work done by the national governments in countries covered by the *National Action Plan* and their partners to strengthen surveillance and laboratory capacity; introduce national aDSM systems; expand access to new and shorter DR-TB treatment regimens, including those that contain BDQ; and develop person-centered care packages to support patients from diagnosis to the completion of treatment. However, overall progress has been slower than required to meet the ambitious goals set for the last two years of the *Plan*. Success in achieving the milestones for Year Five will require additional resources and collaborative efforts.

The UNHLM on TB in September 2018 brought together Heads of State and other government representatives to affirm their commitment to a Declaration to end TB. The Declaration sets a specific and ambitious target of successfully treating 1.5 million people with DR-TB by 2022, including 115,000 children, and dovetails with the targets set out in the *National Action Plan*. In addition, all UN Member States, including the United States, committed to “mobilize sufficient and sustainable financing for universal access to quality prevention, diagnosis, treatment and care of TB, from all sources, with the aim of increasing overall global investments for ending TB and reaching at least 13 billion U.S. dollars a year by 2022,”⁴ which would eliminate the estimated annual shortfall of \$3.5 billion, and to “mobilize sufficient and sustainable [funding] for R&D with the aim of increasing overall global investments to 2 billion U.S. dollars, in order to close the estimated 1.3 billion U.S. dollar gap in funding annually for TB research, ensuring that all countries contribute appropriately to research and development...”⁵

The *National Action Plan* has demonstrated that increased commitment and financial and technical resources can lead to significant improvements in the diagnosis and care of DR-TB and, subsequently, outcomes for patients. However, only by supporting the resolve of national governments, other implementers, and donors to increase their investments in TB and DR-TB will it be possible to achieve the life-saving targets laid out in Year Five of the *Plan* and the UNHLM Declaration. The U.S. Government Departments and Agencies that are implementing the *National Action Plan* remain committed to working together to help governments, civil society, and the private sector reach these goals, and ultimately, end TB.

⁴ United Nations. UNGA HLM Political Declaration 2018. <https://undocs.org/en/A/RES/73/3>

⁵ Ibid.

APPENDIX: MILESTONES AND ADVANCES

GOAL I

Objective 1.1 Upgrade TB surveillance to ensure complete and accurate detection of drug-resistant TB		
Year One to Three Milestones	Year One Achievements (previously reported)	Year Three Achievements
CDC will work with its partners to lay the groundwork for an updated TB surveillance system.	<ul style="list-style-type: none"> Development of standardized reporting underway. 	<ul style="list-style-type: none"> CDC is upgrading 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. 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 and CDC labs into MDSTR data collection system. Nationwide standardized coding will improve the validity of all data on drug resistance.
Objective 1.2 Strengthen State and local capacity to prevent transmission of drug-resistant TB		
Year One to Three Milestones	Year One Achievements (previously reported)	Year Three Achievements
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"> Finalizing new metrics for tracking TB transmission that can be applied to drug resistant TB as well as drug-sensitive TB. 	<ul style="list-style-type: none"> Finalized new metrics for tracking TB transmission that can be applied to drug resistant TB as well as drug-sensitive TB. Expanded data collection for drug susceptibility testing results to be included in the new version of Report of Verified Case of Tuberculosis (RVCT) beginning in 2020.
As part of these efforts, CDC will explore ways to increase staffing at State and local health departments during TB contact investigations.	<ul style="list-style-type: none"> Unable to address surge capacity, increased staffing, or development of other new tools without additional funding. 	<ul style="list-style-type: none"> Unable to address surge capacity, increased staffing, or development of other new tools without additional funding.

Year Three to Five Milestones	Year Three Progress	
<p>CDC will work with its partners to develop new tools to facilitate contact investigations.</p>	<ul style="list-style-type: none"> ▪ CDC began universal whole genome sequencing on isolates of Mycobacterium tuberculosis gathered from newly diagnosed patients. Results will be flagged by CDC for identification of possible transmission using outbreak detection methods. Indication of possible transmission will be shared with state and local jurisdictions to support response to identify and interrupt transmission in real-time. 	
<p>Objective 1.3 Ensure that patients with drug-resistant TB receive treatment until cured</p>		
<p>Sub-objective 1.3.1 Explore the potential use of a national TB stockpile to ensure the availability of TB medicines and screening tests</p>		
Year One to Three Milestones	Year One Achievements (previously reported)	Year Three Achievements
<p>CDC will explore the development of a National TB Stockpile that could store and rotate TB supplies that can be ordered by State and local TB programs.</p>	<ul style="list-style-type: none"> ▪ Stockpile, managed by the DHHS Supply Service Center, is operational in the event of a national shortage of drugs used in treating and preventing TB. 	<ul style="list-style-type: none"> ▪ The TB Emergency Drug Stockpile was activated in response to a rifampentine shortage. CDC provided rifampentine to twelve states where more than 500 patients were at risk for interrupted treatment.
<p>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.</p>		
Year One to Three Milestones	Year One Achievements (previously reported)	Year Three Achievements
<p>CDC and State and local TB programs will work together on plans for completion of therapy once MDR-TB or XDR-TB patients are released from a hospital.</p>	<ul style="list-style-type: none"> ▪ Clinical trial design to evaluate electronic directly observed therapy (eDOT) for treating TB disease 	<ul style="list-style-type: none"> ▪ A randomized trial of Electronic Directly Observed Treatment (eDOT) is underway. Informed consent forms and study-specific data collection forms were created in collaboration with partners at the New York City Department of Health and Mental Hygiene's Bureau of TB Control. The study specific database is under development. The non-inferiority study is currently recruiting study participants. Data collection forms for the economic evaluation were finalized and data collection in the selected sites has begun.
<p>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</p>		
Year One to Three Milestones	Year One Achievements (previously reported)	Year Three Achievements
<p>CDC will explore ways to strengthen medical management of transnational cases of TB disease, working with outside organizations.</p>	<ul style="list-style-type: none"> ▪ Evaluation of binational (U.S.-Mexico) case definition for surveillance system in progress. 	<ul style="list-style-type: none"> ▪ CDC has developed a case definition for the national TB surveillance system that can be used to measure TB programs' performance indicators, including Completion of Therapy for TB patients receiving treatment from both US and Mexican TB programs. The Surveillance Definition for Binational TB Cases Workgroup published the new definition in 2018.

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 Three Milestones	Year Three Achievements
<p>USAID and CDC will work with up to ten countries to implement each country's laboratory strategic plan to improve diagnostic capacity from the central to the peripheral level as part of each country's National TB Strategic Plan.</p>	<p>USAID-led achievements:</p> <ul style="list-style-type: none"> ▪ Development of National Laboratory Strategic Plans (NLSPs) is the first step toward improvement of TB laboratory capacity in a country. NLSPs provide technical and administrative directives to government facilities and local partners on addressing the gaps and limitations in current laboratory capacity. ▪ USAID has supported NLSP development in all ten priority countries by guiding strategic discussion on implementation and facilitating appropriate approval of the plan. Seven countries (Burma, China, India, Indonesia, Kazakhstan, Pakistan and South Africa) have an NLSP in place, and the remaining three countries are in the final stages of an approved NLSP. ▪ USAID is supporting implementation of NLSPs, as well as providing support to sub-national laboratories, improving local staff capacity and quality assurance programs, and strengthening specimen transport systems. ▪ Eight countries (Burma, China, India, Indonesia, Kazakhstan, Nigeria, Pakistan, and South Africa) are already implementing the NLSP at the sub-national level. ▪ USAID will continue to support implementation of NLSPs at all levels to improve DR-TB screening at early stages and ensure quality laboratory practices are in place at all levels (national, regional, provincial). <p>CDC-led achievements:</p> <ul style="list-style-type: none"> ▪ CDC completed TB GeneXpert instrument inventories for 25 PEPFAR-supported countries in Africa and Asia as a first step towards optimizing testing networks and improving patient access to rapid diagnostic and resistance to rifampin (RIF) testing services. ▪ In China, CDC and USAID collaborated with China CDC to develop a NLSP that aligns with the Chinese National TB Program Strategic Plan and is supported by an Operational Plan with clear indicators for progress monitoring. ▪ In India, CDC is: <ul style="list-style-type: none"> • Supporting implementation of the whole genome sequencing technology at a national TB reference laboratory for enhanced, prospective characterization of DR-TB cases and national DR-TB surveillance. • Nationally scaling-up the CDC-transferred Xpert MTB/RIF external quality assurance program to more than 1,200 testing sites across the country.

Sub-Objective 2.1.2 Expand and strengthen national MDR-TB care and treatment capacity to optimize the use of current and novel regimens	
Year Three Milestones	Year Three Achievements
USAID will work with up to ten countries to introduce new MDR-TB drugs (BDQ, DLM, or both).	<ul style="list-style-type: none"> ▪ In Year Two (previously reported), USAID expanded access to BDQ and DLM to seven countries; ninety percent of <i>National Action Plan</i> countries expanded their BDQ treatment sites; with USAID support, GDF, through the Bedaquiline Donation Program, increased the global supply of BDQ from 1,487 packs to 8,000 packs; and more than thirty percent of the global DLM procurement was shipped to <i>National Action Plan</i> countries. ▪ In Year Three, in partnership with Johnson & Johnson, USAID has successfully implemented the Bedaquiline Donation Program in nine <i>National Action Plan</i> countries (all priority countries except China). With USAID technical assistance, the Bedaquiline Donation Program was rapidly scaled-up and increased access to TB medicines. ▪ To date, more than 12,000 DR-TB patients, across our ten priority countries, are enrolled on a BDQ regimen - a 25 percent increase from 2017. Due to the high cost of DLM, significantly fewer patients have been enrolled in DLM treatments.
USAID will work with at least seven countries to introduce shortened MDR-TB regimens (STR).	<ul style="list-style-type: none"> ▪ STR for patients with DR-TB is a novel approach to treatment. Patients receiving STR are treated for a shorter duration, experience fewer side effects and have better treatment success rate than observed with conventional regimens. STR is also approximately 3-4 times cheaper than the conventional regimen. ▪ In 2016, WHO approved a nine-month STR for MDR-TB patients. USAID has been supporting rapid scale-up of the approved STR in its priority countries. ▪ In 2018, USAID has provided technical assistance for the scale-up of STR to eligible patients across all ten <i>National Action Plan</i> countries. There has been a significant uptake of STR in all priority countries with the exception of China. ▪ Across the ten <i>National Action Plan</i> countries, almost 30,000 patients are enrolled on this shorter, cheaper, and safer regimen, an almost five-fold increase from 2017.
USAID will work with up to ten countries to develop quality facility and community-based MDR-TB care and treatment services.	<ul style="list-style-type: none"> ▪ In 2017, USAID convened a workshop for 68 participants from the 10 <i>National Action Plan</i> countries. The workshop presented current best practices in DR-TB community care and support with the goal of developing national roll-out plans for each of the ten <i>National Action Plan</i> countries. Through a collaborative approach, workshop attendees were empowered to create context-specific action plans for implementing aspects of community-based DR-TB care within their country, including relevant timelines, quality improvement strategies, and monitoring and evaluation strategies. ▪ In 2018, USAID continues to provide technical assistance for quality facility and community-based MDR-TB care and treatment services across all ten <i>National Action Plan</i> countries. ▪ In 2018, eight countries (Burma, China, India, Kazakhstan, Nigeria, Philippines, South Africa and Ukraine) successfully introduced or scaled-up community-based and home care services for DR-TB patients. Indonesia and Pakistan have initiated community-based programs targeting DR-TB patients and their families, and are expected to achieve national scale-up by 2020.

Sub-Objective 2.1.3 Strengthen TB and MDR-TB surveillance

Year Three Milestones	Year Three Achievements
<p>USAID and CDC will work with up to ten countries to implement standards and benchmarks to improve surveillance and vital registration systems to directly measure TB burden.</p>	<ul style="list-style-type: none"> Standards and benchmarks (S&B) were introduced by WHO to help countries improve monitoring and evaluation (M&E) systems for TB data collection and analysis. USAID and CDC continue to provide technical assistance to NTPs and local partners to improve M&E systems at all levels (national, regional, district). As of December 2018, the following countries have completed the S&B checklist and implemented the S&B benchmarks: Burma (2016), Indonesia (2017), Kazakhstan (2017), Nigeria (2017), Pakistan (2016), Philippines (2017), South Africa (2015), Ukraine (2014). China is currently undertaking the checklist (estimated completion in 2019); India has postponed the checklist.
<p>CDC will develop and implement, in at least one country, an approach to link laboratory and TB and MDR-TB program surveillance systems.</p>	<ul style="list-style-type: none"> CDC began piloting an interim, web-based laboratory information system database at one National TB Reference Laboratory in India to collect, collate and quality-check clinical and laboratory data for patients receiving next generation sequencing to improve indicator monitoring for a national sample of MDR-TB patients.
<p>USAID will work with up to five countries to introduce patient-based electronic recording and reporting systems.</p>	<ul style="list-style-type: none"> <i>National Action Plan</i> countries have various approaches for electronic data collection and analysis. In several countries, an e-TB Manager tool, which was developed several years ago by USAID and partners, has been fully implemented and received government support for scale up e.g. Ukraine. In other countries, local government has been investing in developing electronic tools to track several diseases, including TB. USAID continues to support all ten <i>National Action Plan</i> countries in improving the patient-based electronic systems under the larger umbrella of improving M&E systems. In 2018, all ten priority countries have introduced electronic recording and reporting systems for TB. In Ukraine, the NTP, with USAID support, developed a personalized electronic medical record system for DR-TB patients that is now the accepted main national registry system. USAID will continue to support the scale-up of patient-based electronic recording and reporting systems at sub-national levels to include patients treated not only at TB facilities but also at primary health care and private facilities and by partner organizations.

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 Three Milestones	Year Three Achievements
<p>USAID will work with up to ten countries to develop and implement pharmacovigilance systems to monitor adverse drug reactions to all second-line drugs in conjunction with the roll-out of the bedaquiline donation program and ongoing drug management support.</p>	<ul style="list-style-type: none"> Active drug safety management and monitoring system (aDSM) is a pharmacovigilance approach which is used in the TB and DR-TB communities. aDSM was first introduced by the WHO in 2015. USAID technical assistance to countries to adopt and pilot the approach started in 2016 and continues. USAID continues to train TB specialist globally, through aDSM workshops, to initiate implementation of pharmacovigilance systems with a particular focus on new TB drugs and new regimens. Since 2016, 161 participants across 20 countries have attended an aDSM workshop. In 2018, all <i>National Action Plan</i> countries have introduced aDSM at the national level. In 2019 and beyond, USAID will continue supporting aDSM expansion across priority countries regardless of whether or not they receive new TB medications.

<p>USAID will work with up to seven countries to introduce an MDR-TB early warning drug procurement and management system to prevent stock-outs.</p>	<ul style="list-style-type: none"> ▪ USAID continues to work closely with NTPs, national drug regulators and local partners to help improve and strengthen TB drug supply chain systems. ▪ In 2018, eight countries (Burma, India, Indonesia, Kazakhstan, Nigeria, Pakistan, Philippines and Ukraine) have introduced early warning systems. South Africa is on track to introduce an early warning in 2019. ▪ USAID, with support from GDF and other local partners, continues to assist national governments in the introduction and/or further scale up QuantTB, an electronic tool that acts as an early warning system to equips countries with the ability to track the drug stock of second line medications in real time.
Objective 2.2 Prevent MDR-TB Transmission	
Sub-Objective 2.2.1 Improve access to high-quality, patient-centered MDR-TB services	
Year Three Milestones	Year Three Achievements
<p>USAID will work with up to ten countries to scale-up enhanced patient identification and medical screening of individuals at high risk for MDR-TB, based on data gathered using the risk-prioritization screening tool results.</p>	<ul style="list-style-type: none"> ▪ USAID provides continuous support to countries for active case finding, early TB diagnosis, and early treatment initiations and adherence. USAID also invests in developing innovative strategies and effective tools for this purpose. ▪ USAID and its partners have launched a number of activities and campaigns aimed at TB screening among high-risk populations (e.g. children, people living with HIV). ▪ In 2018, five <i>National Action Plan</i> countries (Burma, India, Indonesia, Nigeria, Philippines) have scaled-up DR-TB screening activities among close contacts of index cases and other high-risk populations. Kazakhstan and South Africa have introduced pilots and will further scale-up activities in 2019.
<p>USAID will work with up to ten countries to introduce patient-centered TB and MDR-TB quality service delivery site monitoring.</p>	<ul style="list-style-type: none"> ▪ USAID is supporting country implementation of proactive quality monitoring system through regular cohort reviews and assessment. Because DR-TB treatment is complicated and lengthy, these regular evaluations help TB specialists more quickly identify and address gaps and issues before individuals are lost to follow-up. ▪ USAID continues to provide support to all ten priority countries to scale up person-centered TB and MDR-TB quality service delivery by enhancing treatment adherence and monitoring systems. ▪ In 2018, all ten <i>National Action Plan</i> countries, with the exception of Kazakhstan, introduced regular cohort monitoring in pilot facilities; by 2020 the approach will be implemented nationwide.
Sub-Objective 2.2.2 Enhance adherence to TB and MDR-TB treatment	
Year Three Milestones	Year Three Achievements
<p>USAID will work with up to ten countries to implement ancillary care packages to improve MDR-TB patient treatment outcomes.</p>	<ul style="list-style-type: none"> ▪ USAID developed a DR-TB care package tool and piloted the tool in four <i>National Action Plan</i> countries. In 2018, 811 DR-TB patients were enrolled in, and later completed, the pilot. ▪ In 2018, USAID convened a group of TB experts from across the ten <i>National Action Plan</i> countries to share knowledge of, and best practices on, effective implementation of the DR-TB care package. ▪ Eight countries (Burma, China, India, Indonesia, Nigeria, Pakistan, South Africa and Ukraine) have introduced or implemented DR-TB care packages nationally or across multiple sites in country.

<p>USAID will work with up to ten countries to implement a TB treatment adherence assessment tool.</p>	<ul style="list-style-type: none"> ▪ USAID and its partners have implemented a number of activities (e.g. regular cohort monitoring, expansion of social support and education, scaling up community-based care) to improve treatment success rates by improving patients' treatment adherence. ▪ Efforts have focused on developing electronic tools (e.g. smartphone apps, computer software) to provide remote support to TB patients and monitor adherence to TB treatment. ▪ In 2018, USAID convened experts across the ten <i>National Action Plan</i> countries in India to present on the new digital tools available. Countries decided on the top three innovations to pilot and later scale-up.
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Sub-Objective 2.2.3 Prevent the transmission of TB and MDR-TB within health care facilities

Year Three Milestones	Year Three Achievements
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<p>USAID and CDC will develop guidance on best practices for TB infection control within health-care facilities based on evidence-based policy recommendations.</p>	<p>USAID-led achievements:</p> <ul style="list-style-type: none"> ▪ Through the End TB Transmission Initiative (ETTi), USAID supported the development of the global infection, prevention and control (IPC) implementation guidelines that will provide practical recommendations and operationalize the WHO policy guidelines on IPC. The draft of the document is currently under review by experts and stakeholders. ▪ In 2018, USAID TB experts supported the process of updating the WHO IPC policy recommendations, which included an extensive review of the current state of IPC implementation <p>CDC-led achievements:</p> <ul style="list-style-type: none"> ▪ CDC expanded the use of TB BASICS to identify and address TB infection control gaps, implement routine monitoring and evaluation, and ensure continuous program improvement in healthcare facilities in India, China, Nigeria, and multiple other countries in Asia and Africa. ▪ In Nigeria, CDC and USAID provided support to improve infection control practices, including incorporation of TB BASICS into national guidelines and curricula for healthcare workers, which has been scaled-up nationwide. ▪ In India, CDC supported the establishment of a novel AIC unit linked to the local TB program to assess, implement and evaluate infection control interventions in healthcare facilities treating TB using the TB BASICS toolkit; this is now being scaled up across numerous states in India.
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<p>USAID and CDC will work with up to ten countries to improve the implementation of infection-control practices 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"> ▪ In 2018, USAID and its partners conducted landscape analyses on infection-control practices to assess whether existing tools (e.g. guidelines, standard operating procedures) are evidence-based and align with NSPs. A gap analysis on IPC strategic plan implementation was also conducted. This analysis led to the development of a scorecard system to identify the level of implementation and existing gaps in IPC practices. ▪ USAID worked with countries to help identify gaps in data collection, analysis, and completeness of IPC indicators to better define an effective approach to collect data for these indicators. ▪ USAID supported the development of country-level implementation plans for IPC practices, adopted from the internationally-accepted IPC practices, in all ten <i>National Action Plan</i>
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	<ul style="list-style-type: none"> ▪ In 2018, with support from USAID, all NAP priority countries, with the exception of China, have developed national infection-control strategic plans and roadmaps. <p>CDC-led achievements:</p> <ul style="list-style-type: none"> ▪ CDC is working with the NCTB in China to implement TB BASICS in six counties (nine TB-designated health facilities) to improve infection control practices and to understand the feasibility and acceptability of TB BASICS in China. Training-of-trainers was conducted for the provincial China CDC staff who then trained local China CDC and health facility staff during regional TB BASICS training. ▪ Participating TB-designated health facilities have completed 12 months of the program with the final assessments to be completed in July 2019. Results will be reviewed and discussions of integration into national strategic plans will commence in September 2019. ▪ Two additional sites in China were incorporated into TB BASICS in July 2018 for a 12-month TB BASICS program at MDR-TB-designated facilities. ▪ CDC has continued to support the AIC unit in India and has expanded the AIC unit work with Municipal Corporation of Greater Mumbai (MCGM) to include baseline and follow-up assessments on all outpatient, secondary hospital healthcare facilities, and ART treatment centers in 10 wards. Improvements in almost all facilities has been documented through a 41-indicator instrument.
<p>USAID and CDC will work with up to ten countries to introduce or improve health-care worker surveillance and screening in facilities responsible for the 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"> ▪ Healthcare workers (HCWs) surveillance is a key component of the country IPC roadmaps. Situational analysis revealed that although data on TB in HCWs is being collected in almost all priority countries, the data are not aggregated systematically or reported nationally. ▪ Country IPC roadmaps identify specific steps to implementing disease surveillance among HCWs. ▪ In South Africa, a pilot is currently underway to determine the feasibility of using Interferon Gamma Release Assay (IGRA), to detect TB infection (LTBI) in HCWs. A key objective of this study is to understand and provide a baseline of the prevalence of LTBI, active TB and progression from latent to active TB among HCWs. ▪ In 2018, six <i>National Action Plan</i> countries (Burma, Indonesia, Kazakhstan, Nigeria, South Africa, Ukraine) introduced or improved healthcare surveillance systems for early detection and diagnosis of TB. In 2019 and 2020, USAID will continue supporting all ten priority countries in the scale-up of surveillance systems. <p>CDC-led achievements:</p> <ul style="list-style-type: none"> ▪ In India, CDC is working with MCGM to establish a health-screening program for healthcare workers. More than 1,100 HCWs have been screened for TB, hypertension and diabetes annually by the AIC unit of the city and quarterly by the medical officer of the respective health institution. The model will be scaled-up across the city and shared with the national program as a best practice for national scale-up.

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 Three to Five Milestones	Year Three 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>	<ul style="list-style-type: none"> ■ NIH: Recent funding opportunities: <ul style="list-style-type: none"> • NIH: PAR-18-923: Characterization of Mycobacterial Induced Immunity in HIV-infected and Uninfected Individuals (R2I Clinical Trial Not Allowed); • NIH: PAR-16-254: Mechanisms of Mycobacterial-Induced Immunity in HIV-Infected and Uninfected Individuals to Inform Innovative Tuberculosis Vaccine Design (R01); • NIH: RFA-AI-17-039: Understanding Immunopathogenesis of Tuberculosis in HIV-1 Infected and Exposed Children (R0I Clinical Trial Not Allowed). ■ NIH: Supporting three awards made in response to NIAID-DAIT-NIH AI-201700104: Immune Mechanisms of Protection Against Mycobacterium tuberculosis Center (IMPACTB). ■ NIH: 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). ■ NIH: Supporting five investigator-initiated awards focusing on the preclinical development of novel TB vaccine candidates (R01AI143788; R01AI138587; R2IAI141090; R2IAI131035; R01AI125160). ■ NIH: 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 (https://impaactnetwork.org/studies/IMPAACT2001.asp). ■ NIH: Protecting Households on Exposure to Newly Diagnosed Index Multidrug-Resistant TB Patients (https://impaactnetwork.org/studies/IMPAACT2003B.asp). ■ NIH: Phase I Clinical Trial of Single-Vial ID93 + GLA-SE in Healthy Adults (https://clinicaltrials.gov/ct2/show/NCT03722472). ■ NIH: Co-sponsoring through U01 AI131861 the MTBVAC Study in Adults With and Without Latent Tuberculosis Infection in South Africa (A-050) (https://clinicaltrials.gov/ct2/show/NCT02933281). ■ NIH: The Vaccine Research Center has established a Tuberculosis Vaccine Unit dedicated to the scientific investigation and clinical development of new vaccine strategies for preventing TB infection and disease. ■ NIH intramural: Continues to support research on new drugs as part of the Bill and Melinda Gates Foundation's Drug Accelerator Program. ■ NIH intramural: Conducting research on novel host-directed therapies for TB. ■ NIH intramural: Tuberculosis following PD-1 blockade for cancer immunotherapy (Sci Transl Med, https://stm.sciencemag.org/content/11/475/eaat2702.short).

<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"> NIH: 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 (http://www.newtbvaccines.org/). NIH: 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. <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> Developing novel physiological 3-D tuberculoma model to study host-directed therapy; ongoing 2019.
<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>	<ul style="list-style-type: none"> In February 2018, USAID supported participation of researchers from selected countries at the 5th Global Forum on TB Vaccines in India. This Forum is the world's largest gathering of stakeholders striving to develop new vaccines to prevent TB. It provides a unique opportunity to review the state of the field; share the latest research and findings; and identify new and innovative approaches to TB vaccine research and development, with the end goal of developing and deploying new TB vaccines as quickly as possible. USAID also continued to support the work of the Global TB Vaccine Working group of the STOP TB Partnership.
<p>Department of State (State) and the Department of Defense (DOD) will explore a proof-of-concept randomized controlled study to assess whether 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"> Developed and funded a 2,000-person clinical trial to assess whether BCG vaccine (compared to placebo) can protect higher risk travelers from acquiring latent tuberculosis. We anticipate initiating enrollment by November 1, 2019.
<p>Sub-Objective: 3.1.2. Support the development of methodologies to prevent transmission and development of TB and MDR-TB</p>	
<p>Year Three to Five Milestones</p>	<p>Year Three Progress</p>
<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"> USAID is supporting the implementation of two projects that are aiming at characterizing the transmission of MDR-TB using MTB genome sequencing. The projects study 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 hospital 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 community based and nosocomial TB transmission to guide effective risk management of TB and MDR-TB, and to strengthen and monitor infection control measures in hospitals.

	<ul style="list-style-type: none"> The two studies are in Kyrgyzstan and Moldova; both are currently recruiting patients and collecting specimen. In Moldova, 3,921 sputum specimens from newly diagnosed TB patients were collected. 1,396 have thus far been culture-positive. The project is on track for reaching its goal of sending 1,800 culture positive specimen for whole genome sequencing. <p>NIH-led achievements:</p> <ul style="list-style-type: none"> NIH: Supporting six awards made in response to RFA-AI-18-037: Halting TB Transmission in HIV-Endemic and Other High-Transmission Settings.
<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"> Weekly High-dose Isoniazid and Rifapentine © Periodic Prophylaxis for TB (WHIP3TB) (https://www.clinicaltrials.gov/ct2/show/NCT02980016) is continuing to evaluate two different approaches to treatment of latent TB infection [3HP and periodic (p3HP)) prevention treatment regimens in HIV co-infected individuals (adults and children)]. The co-funded STREAM-1 trial is completed. The final results were reported in September 2018 and showed that a 9-month treatment regimen for MDR-TB was non-inferior to the 20- to 24-month regimen recommended by WHO at the time when the trial started enrolling patients. <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> Authored updated guidelines for the Treatment of Drug-Resistant Tuberculosis. Publication expected in 2020. TBTC publication: Peloquin CA, Phillips PJ, Mitnick CD, Eisenach K, Patientia RF, Lecca L, Gotuzzo E, Gandhi NR, Butler D, Diacon AH, Martel B, Santillan J, Hunt KR, Vargas D, von Groote-Bidlingmaier F, Seas C, Dianis N, Moreno-Martinez A, Kaur P, Horsburgh CR Jr. Increased Doses Lead to Higher Drug Exposures of Levofloxacin for Treatment of Tuberculosis. Antimicrob Agents Chemother. 2018 Sep 24;62(10). TBTC Study 31/ACTG A5349 study: Completed enrollment of 2,516 patients into Phase 3 clinical trial of Rifapentine-containing Treatment Shortening Regimens for Pulmonary Tuberculosis. (https://clinicaltrials.gov/ct2/show/NCT02410772). 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). <p>NIH-led Achievements:</p> <ul style="list-style-type: none"> NIH: Protecting Households on Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIX) (http://www.impaactnetwork.org/studies/IMPAACT2003B.asp). NIH: Brief Rifapentine-Isoniazid Evaluation for TB Prevention (BRIEF TB) (https://clinicaltrials.gov/ct2/show/NCT01404312; http://www.croiconference.org/sessions/one-month-rifapentineisoniazid-prevent-tb-people-hiv-brief-tba5279).

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 Three Milestones	Year Three Achievements
<p>USAID will complete evaluation of at least one promising (preferably a point-of-care) TB and MDR-TB diagnostic tool in adults and children with and without HIV.</p>	<ul style="list-style-type: none"> ▪ 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. ▪ 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.
<p>NIH will expand collaborations across the U.S. Government and with researchers and product developers to facilitate the integration of bacterial and host markers into diagnostic platforms.</p>	<ul style="list-style-type: none"> ▪ NIH: Released the NIAID Strategic Plan to Address Tuberculosis (TB) Research that identified the need to integrate biomarkers and biosignatures derived from fundamental TB research into technology platforms to facilitate the development of diagnostics as a high priority (https://www.niaid.nih.gov/sites/default/files/TBStrategicPlan2018.pdf). ▪ NIH: The Pathosystems Resource Integration Center (PATRIC) (https://www.patricbrc.org/view/Taxonomy/1773) provides a variety of tools to study AMR and its genetic determinants. As of Dec 2018, PATRIC has over 10,000 MTB genomes consistently annotated using PATRIC's annotation services. Plans are to include additional genomes and associated data such as AMR phenotypes where available from specialized consortia, such as the Comprehensive Resistance Prediction for Tuberculosis: an International Consortium (CRyPTIC). This is expected to increase the accuracy of data-driven AMR predicting tools for clinical diagnostics. ▪ NIH: Supporting several studies to discover and validate biomarkers and biosignatures that may be adapted to diagnostic platforms for different applications, including distinguishing latent TB from active or incipient disease, response to treatment and pediatric TB disease. ▪ CDC and NIH: CDC's TB Trials Consortium and the NIH AIDS Clinical Trials Group (ACTG) are contributing specimens to a collaborative repository, CTB2 (http://www.tbbiorepository.org/about-ctb2), as part of the search for markers of progression from latent TB infection to active TB disease and to monitor treatment response.
<p>NIH will encourage and support evaluations of tests suitable for use in young children where diagnosis of TB is more difficult.</p>	<ul style="list-style-type: none"> ▪ NIH: Released the NIAID Strategic Plan to Address Tuberculosis (TB) Research that identified development of non-sputum-based diagnostics, particularly for application to pediatric patients, as a high priority (https://www.niaid.nih.gov/sites/default/files/TBStrategicPlan2018.pdf). ▪ NIH: Solicited grant applications under RFA-AI-19-030, Feasibility of Novel Diagnostics for TB in Endemic Countries (FEND for TB) to support evaluation of novel TB diagnostics in TB endemic countries, with an emphasis on diagnostics that target special populations, including pediatric populations and people living with HIV. ▪ NIH: Solicited grant applications 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. ▪ NIH: RePORT platform cross-consortium studies (2 projects) are conducting studies towards the development of diagnostic tools specifically for TB diagnosis in children.

	<ul style="list-style-type: none"> ▪ NIH: Real-time Detection of Active TB in HIV Exposed Children on Customized Nanotrap (R01AI113725-04). ▪ NIH: Quantification of Circulating Antigens for Pediatric TB Diagnosis and Treatment Monitoring (R01AI122932-04) ▪ NIH: Supporting the development of a novel stool-based Xpert assay to diagnosis pediatric TB (R01AI131617). ▪ NIH: Supporting the validation of potential pediatric TB biomarkers for further diagnostic development (R01AI128765).
<p>CDC will pilot and evaluate a training program for measurable continuous quality improvement across the entire MDR-TB diagnostic cascade to shorten time to treatment initiation.</p>	<ul style="list-style-type: none"> ▪ Expanded understanding of the molecular basis of drug resistance through applied research and clinical testing (CDC's Molecular Detection of Drug Resistance service) through rapid detection of mutations associated with drug resistance. Ongoing 2019. ▪ Administered Model Performance Evaluation Program for drug susceptibility testing (DST) of Mycobacterium tuberculosis as a voluntary performance assessment program for public health, clinical, and commercial laboratories performing DST in the United States. The program was evaluated and expanded to include evaluation of both phenotypic and genotypic methods. ▪ Implemented rifampin-resistance alert for U.S. TB Programs using whole genome sequencing data generated at the National TB Molecular Surveillance Center. Ongoing 2019. ▪ Contributed to: <ul style="list-style-type: none"> • https://www.nejm.org/doi/10.1056/NEJMoa1800474?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov; • https://aac.asm.org/content/62/10/e00974-18; • https://www.nature.com/articles/s41598-018-33731-1
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 Three to Five Milestones	Year Three Achievements
<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"> ▪ NIH intramural: NIAID scientists identified CD153 as major immune mediator of host protection against pulmonary Mtb infection (Nat Microbiol, https://www.nature.com/articles/s41564-018-0231-6). ▪ NIH: 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 ▪ NIH: 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 (https://clinicaltrials.gov/ct2/show/NCT02821832). ▪ NIH: Host Blood Biomarkers for the Diagnosis Prognosis and Treatment Response of Childhood TB (R01AI143636).

<p>NIH and CDC will support clinical studies to validate biologic correlates of disease activation.</p>	<p>CDC-led Achievements:</p> <ul style="list-style-type: none"> ▪ 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. <i>N Engl J Med.</i> 2018 Aug 30;379(9):823-833. • Working to standardize assay for assessment of RNA signatures for differentiation of clinical stages of <i>M. tuberculosis</i> infection in low incidence settings. Ongoing 2019.
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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 Three Milestones	Year Three Achievements
<p>USAID will evaluate pilots of innovative strategies to improve treatment outcomes in at least five countries.</p>	<ul style="list-style-type: none"> ▪ All countries implementing pilot studies to contribute evidence to the MDR-TB Package of Care (South Africa, Ukraine, Pakistan, and China) are expected to finish patient enrollment, data analysis and dissemination of findings to all ten countries included in the <i>National Action Plan</i> in 2018. Findings from these pilot studies will inform implementation of the Package of Care in the remaining six countries.
<p>NIH will support research to improve knowledge about the pharmacology of first- and second-line TB drugs in various patient populations to optimize therapy for the largest number of patients, including children.</p>	<ul style="list-style-type: none"> ▪ NIH: Several ongoing trials through the AIDS Clinical Trials Group (ACTG): <ul style="list-style-type: none"> • Early Bactericidal Activity of high-dose INH in patients with INH resistance mutations (InhA or KatG) compared with standard dose INH; • In collaboration with CDC/TBTC - Phase 3 trial of rifapentine with/without moxifloxacin to shorten TB therapy to four months; • Pharmacokinetic interactions among DMPA, RIF, and EFV in women co-infected with HIV and TB; • Six months of high-dose RIF, high-dose INH, and LNZ vs. standard 9-month treatment of adults and adolescents with TB meningitis. ▪ NIH: 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 (https://impaactnetwork.org/studies/IMPAACT2001.asp). ▪ NIH: Shortened Oral Treatment for Multidrug-Resistant Tuberculosis in Infants, Children and Adolescents (SMaRT Kids): A Phase III Randomized Multi-center Trial (https://impaactnetwork.org/studies/IMPAACT2020.asp). ▪ NIH: Pharmacokinetic Properties of Antiretroviral, Contraceptive and Related Drugs During Pregnancy and Postpartum (https://impaactnetwork.org/studies/PI026s.asp). ▪ NIH: Pharmacokinetic Properties of Antiretroviral, Anti-Tuberculosis, Contraceptive and Related Drugs During Pregnancy and Postpartum (https://impaactnetwork.org/studies/IMPAACT2026.asp). ▪ NIH: Pharmacokinetic and Programmatic Evaluations to Optimize HIV/TB Co-Treatment Regimens in Children (K23AI125122). ▪ NIH intramural: Continuing the PREDICT-TB trial, which studies treatment shortening in low-risk PTB in China and South Africa (https://clinicaltrials.gov/ct2/show/NCT02821832; Gates Open Res, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5841574/).

	<ul style="list-style-type: none"> ▪ NIH: Pharmacometric Optimization of Second Line Drugs for MDR (R01AI116155). ▪ NIH: Novel Structure-Based Rifamycins for Drug-Resistant TB and HIV Co-Infection (R01AI110780). ▪ NIH: Diagnostics and Pharmacotherapy for Severe Forms of TB (U01AI115594). ▪ NIH: Intra Cavitory Pharmacokinetics and Drug Resistance in Pulmonary Tuberculosis (K23AI103044). ▪ NIH: An Exploratory Study of Anti-Tuberculosis Drug Penetration into Cerebrospinal Fluid (R03AI139871). ▪ NIH: Supporting studies to identify optimal regimens in vitro and in animal models that fulfill the requirements of shortening therapy: most rapid cell kill, resistance suppression, and activity against different metabolic states in MTB, including log-phase growth, acid-phase growth and Non-Replicative Persistent Phenotype-phase (P01AI123036). ▪ NIH: Supporting the Development of Point of Care Assays to Quantify anti-Tuberculosis Antibiotics in Blood through SBIR contract solicitation PHS-2019-1. Three awards were made in August 2019. ▪ 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).
<p>NIH will contribute to the development of pediatric formulations for new and existing TB drugs.</p>	<ul style="list-style-type: none"> ▪ NIH: Supporting the development of pediatric formulations of fixed dose combinations of first line TB drugs through HHSN272201800051C.
Sub-Objective 3.3.2. Enhance knowledge to enable optimal and safe use of newly registered TB drugs	
Year Three to Five Milestones	Year Three Progress
<p>IH 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"> ▪ NIH: A Phase II trial, Evaluating the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, For Drug-Resistant Pulmonary Tuberculosis (https://clinicaltrials.gov/show/NCT02583048; http://www.croiconference.org/sessions/qt-effects-bedaquiline-delamanid-or-both-mdr-tb-patients-deliberate-trial). ▪ NIH 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 (https://impaactnetwork.org/studies/PI1108.asp). ▪ NIH: 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 (https://impaactnetwork.org/studies/IMPAACT2005.asp).

- NIH: 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 (<https://clinicaltrials.gov/ct2/show/NCT02906007>).

CDC-led Achievements:

- 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.
- 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.
- 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.

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.

NIH-led Achievements:

- NIH: A Phase II trial, Evaluating the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, For Drug-Resistant Pulmonary Tuberculosis (<https://clinicaltrials.gov/show/NCT02583048>; <http://www.croiconference.org/sessions/qt-effects-bedaquiline-delamanid-or-both-mdr-tb-patients-deliberate-trial>).
- NIH 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 (<https://impaactnetwork.org/studies/PI108.asp>).
- NIH: 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 (<https://impaactnetwork.org/studies/IMPAACT2005.asp>).

CDC-led Achievements:

- TBTC planning and pre-clinical activities in 2019, including modeling, EKG, and management of clinical trials’ drug supply.

USAID-led Achievements:

- 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, <https://clinicaltrials.gov/ct2/show/NCT03338621>). The study is currently recruiting in 10 sites.

	<ul style="list-style-type: none"> ▪ 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, https://clinicaltrials.gov/ct2/show/NCT03086486). The study is recruiting patients in South Africa and Georgia, with plans to enroll in other countries. ▪ 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 for the study will start in quarter three of 2019. ▪ 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 for the study will start in quarter two of 2019.
<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"> ▪ 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. <p>USAID-led Achievements:</p> <ul style="list-style-type: none"> ▪ All clinical trials 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 MDR-TB prioritizes pharmacovigilance. The USAID/Janssen Bedaquiline donation program also prioritizes pharmacovigilance via the USAID-funded project, Systems for Improved Access to Pharmaceuticals and Services (SIAPs). ▪ The “Control and Prevention of Tuberculosis Project” (CAP-TB) convened key stakeholders from Asia – Thailand, Burma, China, India, Indonesia, Pakistan, Papua New Guinea, Philippines, South Korea, Thailand and Vietnam – for a Regional Pharmacovigilance Workshop in April 2017 in Thailand. ▪ Following-up on activities started in year 1 and 2, USAID has supported two workshops focusing on gathering best practices and strengthening country pharmacovigilance capacity. Workshops were held in South Africa for the African Region and in Kazakhstan for the Eastern Europe/Central Asia Regions (quarter two and three of 2018). ▪ As a result of these workshops countries developed pharmacovigilance roadmaps to guide planned and ongoing activities, establish and/or strengthen reporting structures and enhance coordination and partnership for the introduction and scale-up of ND and STR for MDR-TB patient care. The aDSM roadmap will be used to assess potential technical assistance may be required by a country and to measure progress through 2019. The key components of these aDSM road maps are adapted from the WHO aDSM framework and include i) national coordination and policy guidelines and implementation plan; ii) recording and reporting structures; iii) development of health care workers capacity; iv) clinical management; and v) data management and analysis.

<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"> ▪ 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 ≤12 years old (n=60) will receive pediatric formulations to characterize the pharmacology of Bedaquiline for four age groups: i) 0 months to < 2 years; ii) > 2 to < 5 years; iii) < 5 to <12; and iv) <12 to <18 years) to help determine dosage guidelines for pediatric use. ▪ 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 2018). USAID plans to participate in further Phase IIb and III trials, pending the final assessment of these studies. <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> ▪ TBTC Study 35: Evaluation of rifapentine pharmacokinetics in HIV-uninfected children 0-23 years of age to begin fall 2019.
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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 One to Three Milestones	Year One Achievements (previously reported)	Year Three Achievements
<p>NIH will support novel therapeutic approaches for the treatment of TB, such as host-directed therapeutics.</p>	<ul style="list-style-type: none"> ▪ NIH: RFA-AI-16-034: Partnerships for Countermeasures Against Select Pathogens (R01). ▪ NIH: Supporting 4 awards under the Initiative “Host Directed TB Therapy: New Approaches (UH2/UH3). ▪ NIH: Preclinical TB drug discovery services are currently accessed by over 100 research groups annually in more than 30 countries. ▪ NIH intramural: Exploratory research in immune targeted adjuncts to TB chemotherapy. ▪ NIH intramural: Collaborating agency in the Bill and Melinda Gates Foundation’s Drug Accelerator Program. ▪ NIH: Optimizing Combination Therapy to Accelerate Clinical Cure of Tuberculosis (P01 AI123036). 	<ul style="list-style-type: none"> ▪ NIH: NIH has assisted in the development of the new TB drug pretomanid, approved by the FDA in August 2019 as part of a three-drug oral regimen for the treatment of XDR-TB. NIH is currently evaluating pretomanid’s safety for patients with renal or hepatic impairment. ▪ NIH: Awarded a Center for Excellence in Translational Research grant to the Global Alliance for TB Drug Development entitled “Modulation of Protein Production and Degradation as an Integrated Approach to Rapid Sterilization of Drug Sensitive and Resistant Mtb.” under RFA-AI-17-042. ▪ NIH: Awarded A07 75N93019D00005 / 75N93019F00132 A07, Anti-mycobacterial Target or Mechanism Identification Contract that will focus on testing preclinical therapeutic candidates from >40 countries and >100 research groups to develop leads, understand mechanism of action and prioritize best combinations with other antibiotics. ▪ NIH: RFA-AI-16-034: Partnerships for Countermeasures Against Select Pathogens. One award was made in 2017 that will focus on new drug targets against TB (R01AI132300). NIH: At the Gordon Research Conference on Tuberculosis Drug Discovery & Development in July 2019, presented a poster on “The Global TB Drug Development Pipeline” and organized a satellite workshop on “Drug Targets for Tuberculosis Drug Discovery.”

NIH will support novel therapeutic approaches for the treatment of TB, such as host-directed therapeutics.

- NIH: New chemical entities are entering preclinical studies through the NIH supported Lilly TB Drug Discovery Partnership (<https://www.niaid.nih.gov/research/partnership-elililly>).
- NIH: Hosted workshop on “Tuberculosis Meningitis: Advancing Immuno-pathogenesis, Diagnosis, and Treatment” in May 2017.
- NIH: Two awards transitioned to the second phase of RFA-AI-14-058 “Host Directed TB Therapy: New Approaches (UH2/UH3)” to begin Phase II clinical trials in 2018.
- NIH: Issued PA-17-283 (R01) and PA-17-282 (R21): “Therapeutic Strategies for the Converging TB/T2DM/HIV Epidemics”.
- NIH: Issued RFA-AI-17-101 (R61/R33): “Dysregulation of Immune Cell Regulatory Pathways by Mycobacterium tuberculosis in the Context of HIV Infection”.
- NIH: Continues to provide preclinical assays and animal model services to assist in the discovery of new chemical entities against TB. Approximately 100 research groups in over 30 countries worldwide are being supported.
- NIH: Contributing to the preclinical development of a novel chemical institute for drug-resistant TB through the Lilly TB Drug Discovery Initiative. Safety and efficacy studies have supported CPZEN-45’s candidacy, and the Infectious Disease Research Institute has completed a co-development agreement with Hisun Pharmaceuticals.
- NIH intramural: Continues exploratory research in immune targeted adjuncts to TB chemotherapy and determined that pharmacologic inhibition of a newly discovered biochemical pathway inhibits growth of Mycobacterium tuberculosis in cells and in mice (manuscript in preparation).
- NIH intramural: Conducting an international trial “Using Biomarkers to Predict TB Treatment Duration” (<https://clinicaltrials.gov/ct2/show/NCT02821832>) in collaboration with the Bill and Melinda Gates Foundation, the European and Developing Countries Clinical Trials Partnership, the National Natural Science Foundation of China, and the China Ministry of Science and Technology, and the NIH.
- NIH intramural: Collaborating agency in the Bill and Melinda Gates Foundation’s Drug Accelerator Program.

Year Three to Five Milestones	Year Three 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>	<ul style="list-style-type: none"> ▪ NIH intramural: Established an expanded facility for PET/CT imaging of Mtb infection in animal models (AI001239). ▪ NIH: Brief Rifapentine-Isoniazid Evaluation for TB Prevention (BRIEF TB) (https://clinicaltrials.gov/ct2/show/NCT01404312; http://www.croiconference.org/sessions/one-month-rifapentineisoniazid-prevent-tb-people-hiv-brief-tba5279; N. Engl J Med, https://www.nejm.org/doi/10.1056/NEJMoal806808). ▪ NIH: The Structural Genomics Centers for Infectious Diseases (CSGID) (HHSN272201700060C) take a structure-guided approach to evaluate infectious disease pathogens, including MTB (Expanding Benzoxazole-Based Inosine 5'-Monophosphate Dehydrogenase (IMPDH) Inhibitor Structure–Activity as Potential Antituberculosis Agents, J Med Chem, https://pubs.acs.org/doi/pdf/10.1021/acs.jmedchem.7b01839. The Centers also are part of the Structure-guided Drug Discovery Coalition (SDDC), which is financed by the Bill and Melinda Gates Foundation to perform structure-based lead optimization of validated drug candidates against TB, Malaria and NTDs for delivery to preclinical development partners. ▪ NIH: Assisted the TB Alliance in the preclinical development of a new oxazolidinone by providing evaluations and administrative assistance in preparation for a safety study; Phase I trial to Evaluate the Safety, Tolerability, and PK of TBI-223 in Healthy Adults (https://clinicaltrials.gov/show/NCT03758612). ▪ NIH: Provided services to domestic and international researchers to test new drug candidates, including some advanced leads such as CPZEN-45 and spectinomides, in infectious models of disease (https://www.niaid.nih.gov/research/pre-clinical-models-infectious-disease). (HHSN272201100009I, HHSN272201000009I, HHSN27200005) ▪ NIH: Support research at the interface of preclinical and clinical evaluations of long-acting formulations and combinations of drugs for active and latent tuberculosis (R24AI118397, NIH intramural). ▪ NIH: Supporting re-evaluation of traditional TB drugs like pyrazinamide (R01AI123146) and beta-lactam/carbapenem class antibiotics for greater understanding of the mechanism of action (R33AI11739, R01AI137329) to help inform the development of TB regimens.
<p>NIH will increase collaborations with pharmaceutical and academic partners to broaden strategies for shortening treatment duration.</p>	<ul style="list-style-type: none"> ▪ NIH: OMICS For TB: Response to Infection and Treatment (1U19AI135976). ▪ NIH: 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). ▪ NIH: Planning to initiate two Phase II trials of innovative host-directed therapy agents (Imatinib and pravastatin) as adjunctive treatments for tuberculosis through the RFA-AI-14-058, Host Directed TB Therapy: New Approaches (UH2/UH3). ▪ NIH: Continues to co-chair the Stop TB Partnership's Working Group on New TB Drugs (http://www.newtbdrugs.org/core-group) and presented the updated global TB drug development pipeline in October 2018 at the annual meeting of the Working Group on New TB Drugs in The Hague in conjunction with the IUATLD world conference. ▪ NIH: Assisted in the collaborative preclinical development of a new diarylquinoline by providing evaluations and administrative assistance in preparation for an Investigational New Drug application planned for 2019.

	<ul style="list-style-type: none"> NIH continues to support and participate in The Lilly TB Drug Discovery Initiative, a non-profit public-private partnership with a mission to accelerate early-stage drug discovery and to develop clinical candidates (https://www.idri.org/products/drugs/lilly-tb-drug-discovery-initiative/).
<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>	<ul style="list-style-type: none"> NIH: Supporting research to evaluate single and combination therapies of promising new drugs and repurposed antimicrobials with the newly validated hollow fiber methodology (P01A1123036). NIH: Funding the development of new in silico models to guide development of optimal TB drug combinations (R01A1125454) and inhaled pulmonary delivery methods for drugs and investigational agents (R01A1141082; R21A1131241; R03A1144706). NIH: A Maldi LTQ Orbitrap XL Mass Spectrometer for Bioimaging (1S100D018072).
<p>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.</p>	<p>NIH-led Achievements:</p> <ul style="list-style-type: none"> NIH: Shortened Oral Treatment for Multidrug-Resistant Tuberculosis in Infants, Children and Adolescents (SMaRT Kids): A Phase III Randomized Multi-center Trial (https://impaactnetwork.org/studies/IMPAACT2020.asp). NIH: Pharmacokinetic Properties of Antiretroviral, Contraceptive and Related Drugs During Pregnancy and Postpartum (https://impaactnetwork.org/studies/P1026s.asp). NIH: Pharmacokinetic Properties of Antiretroviral, Anti-Tuberculosis, Contraceptive and Related Drugs During Pregnancy and Postpartum (https://impaactnetwork.org/studies/IMPAACT2026.asp). <p>CDC-led Achievements:</p> <ul style="list-style-type: none"> 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. <p>CDC/NIH-led Achievements:</p> <ul style="list-style-type: none"> 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). <p>USAID-led Achievements:</p> <ul style="list-style-type: none"> 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);
 - 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 One to Three Milestones	Year One Achievements (previously reported)	Year Three Achievements
USAID will create an inventory (map) of potential sites and initiate needs-based procurement of equipment to prepare study sites.	<ul style="list-style-type: none"> ▪ USAID has initiated discussion in South Africa to identify new research sites for upcoming clinical trials for the treatment of MDR TB. 	<ul style="list-style-type: none"> ▪ Following discussion with the South African Ministry of Health, USAID is supporting the capacity building of clinical trial sites in Eastern Cape. These new clinical trial sites will implement the BEAT TB study and contribute to equity for access to clinical research within the country.
NIH, CDC, and USAID will provide training in clinical research to high-burden TB countries with the capacity to conduct biomedical clinical research to facilitate their active participation in trials and studies.	<ul style="list-style-type: none"> ▪ CDC: Providing technical assistance to the Kenya Medical Research Institute (KEMRI) in Kisumu for oversight and conduct of therapeutic, preventative, diagnostic and implementation clinical trials for TB and TB/HIV. ▪ NIH: Through the Fogarty International Center, targeted training programs for TB and HIV/TB are supported under five framework programs in Global Research. <ul style="list-style-type: none"> • PAR-16-082 - International Bioethics Research Training Program (D43); 	<ul style="list-style-type: none"> ▪ NIH FIC: Through the Fogarty International Center, targeted research training grants for TB and HIV/TB are currently supported under programs in Global Research: ▪ PAR-18-840 – Global Infectious Disease Research Training Program (D43); 5 awards for TB training in Uganda, Ethiopia, Republic of Georgia, Thailand and Vietnam; <ul style="list-style-type: none"> • PAR-18-717 - Fogarty HIV Research Training Program for Low-and Middle-Income Country Institutions (D43); 12 awards for TB/HIV training in Uganda, Zimbabwe, Tanzania, Ghana, Mali, Mozambique, India and Peru; • RFA TW 14-003 - Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43); 3 awards in Uganda and Peru; • RFA-TW-18-002 Health-Professional Education Partnership Initiative 1 award in Uganda; • PAR-15-291 - International Research Scientist Development Award (IRSDA) (K01); 1 U.S. career development award in Peru; • PAR-15-292: Emerging Global Leader Award (K43); 5 LMIC career development awards in South Africa, Gambia, Uganda and Peru.

	<ul style="list-style-type: none"> • RFA-AI-16-082/083 – Revision Applications for U.S. South Africa Program for Collaborative Biomedical Research (various funding mechanisms); • PAR-14-193 - Fogarty Global Infectious Disease Research Training Program; • NIH: PAR-15-291 - International Research Scientist Development Award (IRSDA) (K01); • PAR-15-292: Emerging Global Leader Award (K43); • PAR-14-080 International research in Infectious Diseases, Including AIDS (IRIDA) (R01). ▪ NIH: Fogarty International Center held a “Tuberculosis Network Meeting” on June 21, 2016 to expand their dialog among international trainees supported through their training centers. 	<p>CDC: Hired 1.5 additional FTE (0.5 medical office, 1.0 administrative) to provide technical assistance for TB-related studies at KEMRI in Kisumu, Kenya. Provision of technical assistance has been hampered by political instability from national elections and resultant travel restrictions from July to December 2017.</p> <p>USAID-led Achievements:</p> <ul style="list-style-type: none"> ▪ In July 2018, USAID, through the TREAT TB project, launched a webinar series to strengthen capacity to conduct high quality clinical trials for MDR-TB. The first webinar brought together eight experts to discuss challenges faced when implementing MDR-TB clinical trials. The presentations provided an overview of ongoing and future trials and covered various aspects of MDR-TB clinical trial implementation, including patient recruitment, enrolment and retention, challenges encountered by sponsors and regulatory requirements like import and export permits. Over 65 participants including clinicians, donors, researchers, representatives from the pharmaceutical industry, and advocates from around the world joined the discussion. The second webinar in the series focused on supply chain management and drew upon experiences learned from STREAM Stage 2. ▪ In the Philippines, as part of the comprehensive technical assistance package offered to the NTP, USAID, through TREAT TB, is conducting an operational research course to build research capacity at the national and regional level.
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<p>NIH will expand opportunities for funding of biomedical clinical research in TB-endemic countries.</p>	<ul style="list-style-type: none"> ▪ NIH: Expanding Regional, Observational TB Cohorts (RePORT Network – FHI 360 website when available) in high burden TB countries to facilitate collaborative, clinical research. ▪ NIH: H3 Africa Program (http://www.h3africa.org/). 	<ul style="list-style-type: none"> ▪ NIH FIC: FIC currently supports tuberculosis research in low- and middle-income countries through the following programs: <ul style="list-style-type: none"> • PAR-18-242: Mobile Health: Technology and Outcomes in Low- and Middle-Income Countries; 2 awards in India and Cambodia; • PAR-18-732: Reducing Stigma to Improve HIV/ AIDS Prevention, Treatment and Care in Low- and Middle-Income Countries; 1 award in South Africa; • PAR -18-836: Global Brain and Nervous System Disorders Research Across the Lifespan; 1 award in Uganda. ▪ Additional NIH programs in low- and middle-income countries: <ul style="list-style-type: none"> • RFA-AI-18-054 U.S.-Brazil Collaborative Biomedical Research Program • RFA-AI-19-024 U.S.-South Africa Program for Collaborative Biomedical Research • PAR-17-142 International Research in Infectious Diseases, including AIDS (IRIDA) (R01) • PAR-18-335 Global Infectious Disease Research Administration Development Award for Low-and Middle-income Country Institutions
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