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CDC
Centers for Disease Control and Prevention

NATIONAL ACTION PLAN
FOR COMBATING MULTIDRUG-RESISTANT TUBERCULOSIS

YEAR TWO REPORT
MAY 2018

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Cover: USAID Trains Aeta Community Volunteers in TB Prevention. Jennifer belongs to the Aeta community - thought to be among the earliest inhabitants of the Philippines - in the mountains of Porac and Floridablanca, Pampanga. With limited access to health services, the 10,000 Aetas who live here are vulnerable to contracting TB. USAID trained Jennifer and other health volunteers to teach their community about TB and to serve as treatment partners for people with the disease. Photo by: Kdador/PBSP. Courtesy USAID Philippines.

ACRONYMS AND ABBREVIATIONS

aDSM	Active Drug Safety Management And Monitoring
AIC	Airborne infection control
BASICS	Building and Strengthening Infection Control Strategies for Tuberculosis Prevention
BDQ	Bedaquiline
CDC	Centers for Disease Control and Prevention
CTB2	Consortium for Tuberculosis Biomarkers
DLM	Delamanid
DOT	Directly Observed Therapy
DR-TB	Drug-Resistant Tuberculosis
DS-TB	Drug-Sensitive Tuberculosis
eDOT	Electronic Directly Observed Therapy
ELR	Electronic Laboratory Reporting
ETTi	End TB Transmission Initiative
FAST	Find cases Actively, Separate temporarily and Treat effectively
GDF	Global Drug Facility
GeneXpert	Xpert® MTB/RIF
GLI	Global Laboratory Initiative
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GUV	Germicidal ultraviolet
H3Africa	Human Heredity and Health in Africa
HCW	Healthcare worker
HHS	U.S. Department of Health and Human Services
HIV	Human Immunodeficiency Virus
IC	Infection control
IPC	Infection prevention and control
JNJ	Johnson and Johnson
LPA	Line probe assay
MDR-TB	Multidrug-Resistant Tuberculosis
MDSTR	Molecular Drug Susceptibility Testing Reporting
MTB	Mycobacterium tuberculosis
NCTB	China National Center for Tuberculosis
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NITRD	National Institute of Tuberculosis and Respiratory Disease
NLSP	National Laboratory Strategic Plan
NSP	National Strategic Plan
NTP	National Tuberculosis Program
NTRL	National Tuberculosis Reference Laboratory
PEPFAR	President's Emergency Plan for AIDS Relief
PRDH	Puerto Rico Department of Health
PMDT	Programmatic Management of Drug-Resistant Tuberculosis
R&D	Research and development
RePORT	Observational International Research Cohorts
RIF	Rifampicin
RVCT	Report of Verified Case of Tuberculosis
STR	Shorter treatment regimen
STREAM	Standardized Treatment Regimen of Anti-Tuberculosis Drugs for Patients With Multidrug-Resistant Tuberculosis
TB	Tuberculosis
TBRU-N	Tuberculosis Research Unit Network
USAID	United States Agency for International Development
WHIP$_3$TB	Weekly High dose Isoniazid and Rifapentine Periodic Prophylaxis for Tuberculosis
WHO	World Health Organization
Xpert	Xpert® MTB/RIF

INTRODUCTION

Tuberculosis (TB) is the leading infectious disease killer globally, and in 2016 it claimed the lives of 1.7 million people. This deadly disease caused by *Mycobacterium tuberculosis* (MTB) is transmitted through the air from person to person, and occurs in the United States and around the world. TB is curable, but inappropriate treatment can lead to drug-resistant TB (DR-TB).[1] Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are both increasing global health security threats. An outbreak of MDR-TB would have serious consequences for individuals, because of the long, difficult and toxic treatment regimen required. Health systems and economies will also suffer, because of the very high cost of treatment, as well as the burden DR-TB places on providers, institutions and health systems.

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's Global Plan.

The goals of the National Action Plan are to accomplish the following:

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 2016, global efforts to ensure TB diagnosis, treatment and care saved an estimated 53 million lives. The U.S. Government is a leader in these efforts, working through its Departments and Agencies, to support implementation of high-quality services. The National Action Plan builds on these efforts to support the appropriate treatment of more than 16 million TB patients, ensure that 90 percent of them are cured, and prevent further development of MDR-TB. In addition to increased efforts to diagnose, cure and prevent MDR-TB, the National Action Plan proposes to increase the number of MDR-TB treatment initiatives in countries with the highest MDR-TB burden.

The National Action Plan is intended to promote greater coordination of U.S. Government resources—including domestic, bilateral and multilateral funding—to reduce the domestic and global risk of MDR-TB; increase the American public's awareness of the threats posed by the disease; and serve as a call to action to encourage bilateral and multilateral donors, the private sector and affected countries to increase investments in this critical area of worldwide concern. Additional investments in research and development will continue to contribute to improved treatment outcomes for individuals with MDR-TB through the discovery of new tools that are easy to implement in existing health systems; the increased availability of rapid diagnosis; the better use of new TB drugs; an enhanced drug-development pipeline; effective vaccines and other preventative interventions; and improved disease surveillance. These actions help prevent the emergence of further resistance to TB drugs, and significantly reduce the global spread of MDR-TB.

1 For the purposes of this report, DR-TB is defined as resistance to at least isoniazid and rifampicin, to include MDR-TB and XDR-TB.

GOAL 1: 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 TB control and prevention programs, the incidence of TB in the United States steadily declined from 1993 through 2014. After substantial progress during the past two decades, the rate of TB cases in the United States each year has now levelled off and remains well above the elimination threshold of less than one case per million persons. Although rates of MDR-TB have declined since 1993, annually, approximately 1 percent of U.S. TB cases are MDR-TB; the majority (greater than 90 percent) occur among non U.S.-born persons. DR-TB cases complicate treatment and prevention efforts and are extremely expensive for state and local TB programs to manage. TB programs ensure continuity of care so that drug-resistance does not develop among persons with lack of access to consistent healthcare services. This includes provision of wraparound services such as patient education. The TB program in the state health department is responsible for coordination and oversight of activities to ensure that objectives related to TB prevention and control are achieved. 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 MDR-TB in each state. A single case of MDR-TB costs 10 times more to treat (approximately $160,000) compared to a drug-sensitive case (DS-TB) (approximately $18,000); thus support for better treatment options, rapid diagnosis and expert management are essential to prevent and control MDR-TB in the United States.

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

CDC is upgrading surveillance systems for tracking DR-TB cases in the United States 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. CDC is working with state TB programs to identify common language and protocols for reporting drug-resistance to anti-TB drugs. A molecular drug susceptibility testing reporting (MDSTR) form has been successfully developed and tested within the National TB Surveillance System to provide standardization. Implementation of electronic links between clinical laboratories and TB surveillance programs at the federal, State, and local levels are also underway; CDC is in the beginning stages of developing and implementing 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 the National TB Surveillance System Case Reporting MDSTR data collection system.[2]

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

CDC has also expanded data collection for drug susceptibility testing results to be included in the new version of Report of Verified Case of Tuberculosis

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

(RVCT). This will enable epidemiologists to identify related cases of DR-TB and DS-TB that have been recently transmitted to facilitate targeted interventions to prevent additional transmission. State and local TB programs will also be able to use this improved data to more effectively define their burden of DR-TB.

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

Completion of treatment for those with MDR-TB is challenging on many levels. The activities supported by CDC to meet this objective encompass a broad range of interventions implemented by state and local health departments with funding and assistance from CDC headquarters. Electronic directly observed therapy (eDOT) is the use of electronic technologies to remotely monitor TB patients ingesting their medication, either in real-time or recorded. Because eDOT is an alternative method of delivering medication in which a patient is remotely observed (e.g., over a smartphone), it may improve adherence and be more cost-efficient than traditional in-person directly observed therapy (DOT). The benefits to having an eDOT program include, convenience for patients and staff, in addition to reduced staff travel cost and time. A form of eDOT was used successfully in 2016 by the Puerto Rico Department of Health (PRDH). Due to staffing shortages PRDH TB field personnel were not available to administer daily DOT. Use of video DOT saved PRDH approximately 240 hours in DOT-related activities, equivalent to 25 percent of the workload for a full-time epidemiology technician/case manager over six months of treatment. A randomized control trial is now underway to assess the efficacy of eDOT for treating TB disease as well as an economic evaluation. Results will help inform the needs that MDR-TB patients require in order to successfully complete their long, and often debilitating, treatment regimen. CDC, in collaboration with the HHS Supply Service Center, is successfully managing and maintaining a stockpile of TB drugs to have on hand in the event of manufacturer shortages that could result in interruption of treatment. The stockpile is composed of a small supply of drugs that would be necessary to protect TB patients and communities in the event of a time-limited manufacturing shortage. CDC has also developed a U.S.-Mexico binational case definition for the national TB surveillance system that can be measured using current performance indicators, including Completion of Therapy. This new definition will be published in 2018.

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

As the lead U.S. Government agency for global TB-control efforts, the U.S. Agency for International Development (USAID) works with CDC and other Departments and Agencies to reach every person with TB, cure those in need of treatment and prevent new TB infections. Progress towards detection and treatment of patients with DR-TB remains a challenge, primarily because of health-system constraints related to diagnostic and care services. In 2016, the most recent year for which complete data are available, there were an estimated 600,000 new cases of DR-TB globally. Because of the timing of the collection and data analysis and in the interest of providing the most recent data, the National Action Plan Annual Report presents preliminary national TB program data.

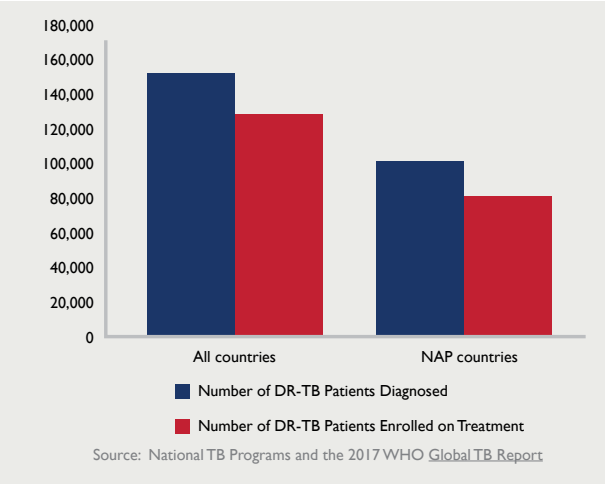
This Year Two report provides an update on the final 2016 data as well as the preliminary 2017 data. Finalized 2016 data for the first year of the National Action Plan's implementation appear below:
Globally:

- 153,119 DR-TB cases detected, which reflects slightly more than 25 percent of the estimated total DR-TB cases; and
- 129,689 DR-TB patients enrolled on treatment, which reflects almost 22 percent of the estimated total DR-TB cases.

In National Action Plan countries[3]:

- 101,702 DR-TB cases detected, which reflects 66 percent of the total DR-TB cases detected globally; and
- 81,876 DR-TB patients enrolled on treatment, which reflects 63 percent of the total DR-TB patients enrolled globally:
  - 4,277 DR-TB patients enrolled on a regimen that contains bedaquline (BDQ);[4] the majority of these patients were treated for XDR-TB; and
  - 272 DR-TB patients enrolled on a shorter treatment regimen (STR).[5]

Figure 1: DR-TB Detection and Treatment, Year One



Source: National TB Programs and the 2017 WHO Global TB Report

The data reported in this Year Two Report for 2017 should be considered preliminary, as they are based on nine months of validated data, and project the outcomes for the full 12 months of 2017. The Year Three report will reflect the finalized 2017 data, as well as preliminary 2018 data. Compared to Year One

3 National Action Pllan countries: Burma, the People's Republic of China, India, Indonesia, Kazakhstan, Nigeria, Pakistan, the Philippines, South Africa and Ukraine.

4 Bedaquiline (BDQ) is a recently developed anti-TB medication which is prescribed for patients with advanced forms of MDR-TB and XDR-TB. Treatment success rates using BDQ-inclusive treatment regimens show results greater than 80 percent vs. 25 percent in non-BDQ-inclusive treatment regimens.

5 STR is a novel approach to DR-TB treatment that utilizes treatment regimens designed for up to 11 months of use instead of the conventional standard of care, which can last up to 24 months.

results, the National Action Plan countries saw a slight increase in the number of DR-TB cases detected and enrolled on treatment in Year Two. However, the number of XDR-TB patients who initiated the most-appropriate treatment (with new TB medications), is projected to increase significantly to more than 8,020, an estimated 88 percent increase over Year One.

Estimates for the implementation of the Year Two National Action Plan, implementation based on preliminary 2017 data and our projections are as follows:

- 104,500 DR-TB cases detected; and
- 84,500 DR-TB patients enrolled on treatment;
  - 8,020 DR-TB patients enrolled on a regimen that contains BDQ; and
  - 5,600 patients enrolled on STR.

While no additional funds were provided for the implementation of the National Action Plan in Year Two, USAID and CDC prioritized resources to implement the MDR-TB activities in the National Action Plan. The table following is an estimate of the funding made available for these activities using USAID and CDC programmatic data.

Table 1: Estimated U.S. Government Funding for Implementation of Goal 2 National Action Plan Country Investments, Year Two

U.S. Government Department or Agency	Funding Total
USAID*	$24,034,000
CDC	$3,523,000

*Includes $1.2 million USAID funding provided to CDC for implementation of the National Action Plan.

Nineteen-year-old Siba Senapati was diagnosed with pulmonary drug-resistant TB in October 2017. Photo by Muktai Panchal

CONTROL OF DR-TB BY THE PRIVATE AND PUBLIC SECTORS IN MUMBAI, INDIA

While most DR-TB patients in India present for evaluation and diagnosis in the private sector, quality DR-TB care is primarily available only in the public sector. USAID and CDC jointly support linking the private and public health sectors to improve access for patients to DR-TB care. DR-TB patients in private health settings first receive pre-treatment evaluation and testing, and then a referral in 23 additional cities for fast-tracked treatment initiation at DR-TB centers in the public sector. Treatment coordinators accompany the patients throughout the transfer process and ensure patient-centered support. This unique patient-support system has boosted the trust and confidence in the public-sector DR-TB care, and ensures more private-sector patients receive the appropriate treatment. This model is now being scaled-up across the country through funding from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) support.

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

In 2017, National Action Plan countries expanded services and activities initiated during the first year. TB detection expanded through the scale-up of diagnostic tools, which resulted in more people screened and tested. India underwent comprehensive international reviews of its diagnostic networks. Recommendations from these reviews will further strengthen and improve TB-detection capacity in the future.

Significant progress also occurred in scaling up the use of appropriate regimens for people diagnosed with XDR-TB, which is resistant to even more drugs than MDR-TB. Clinicians are now treating both XDR-TB and MDR-TB with BDQ; the number of patients who have access to this new drug has doubled because of the USAID- Johnson and Johnson (JNJ) Bedaquiline Donation Program. Rapid scale-up of STR, newly recommended by the WHO, was also observed, with a projected 5,600 patients in 2017, an estimated 2000-percent increase over 2016.

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

In 2017, USAID, with assistance from the Government of India, led a comprehensive review of its national TB diagnostic networks, and revision of its National TB Strategic Plan. In addition, USAID, CDC and the Global Fund supported Nigeria to conduct a comprehensive assessment of its national sample-transportation systems to identify network modifications that could reduce the time and distance between patients and TB diagnostic services. Lastly, USAID and CDC worked to improve the quality of TB laboratory services by assisting multiple TB-reference laboratories in National Action Plan countries, including China

NTRL AWARDED ACCREDITATION BY THE INTERNATIONAL ORGANIZATION FOR STANDARDIZATION (ISO)

USAID provides vital technical support to both achieve National Action Plan milestones and to improve and sustain national TB diagnostic services. In late 2017, the Philippines Department of Health's NTRL received ISO 15189 accreditation, an international standard that specifies the quality-management requirements for medical laboratories, with technical assistance from USAID. USAID assisted in documenting technical and management Standard Operating Procedures, including NTRL's Quality Manual.

Issued by the Accreditation Bureau of the Philippine Department of Trade and Industry, the accreditation places a quality seal on all laboratory procedures provided by the NTRL and guarantees end-users of the safety, reliability and quality of its procedures.

A NTRL medical technologist demonstrates her skill in preparing a TB culture required by ISO 15189. Photo by T. Bernas/PBSP.

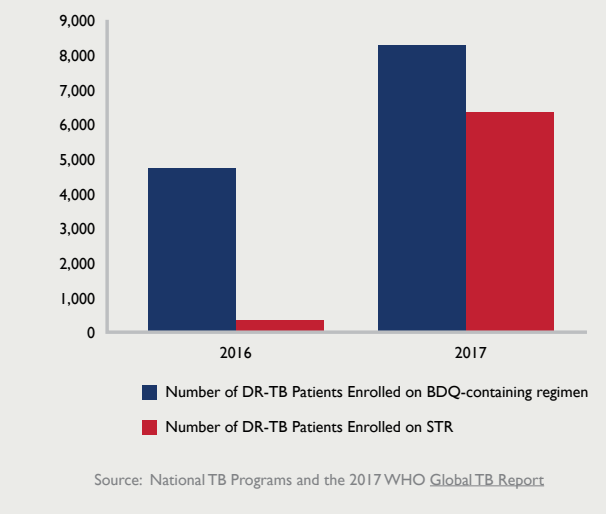
and the Philippines, to work towards international accreditation (see box below), and trained National TB Reference Laboratory (NTRL) staff in India. All 10 National Action Plan countries should have National Laboratory Strategic Plans (NLSPs) developed and approved by the end of Year Three. These plans will incorporate new diagnostic technologies, WHO-approved rapid TB-detection tools, and evidence-based strategies to strengthen detection of TB and DR-TB cases. In addition to improving patients' access to TB and DR-TB laboratories for enhanced diagnosis and treatment, USAID and CDC are working with Ministries of Health, National TB Programs (NTPs) and local partners across National Action Plan countries to optimize the use of TB testing services and improve access to testing throughout all levels of healthcare.[6]

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

Novel drugs, such as BDQ and delamanid (DLM), have recently been introduced in countries with high burdens of DR-TB. Introduction of new drugs and STRs to manage DR-TB offers patients and healthcare providers hope for improved treatment outcomes. These drugs are frequently the only chance to cure XDR-TB patients. During the first year of the implementation of the National Action Plan, USAID initiated work in seven countries to bring these new lifesaving drugs and regimens rapidly to patients. In 2017, assistance provided by USAID resulted in a projected 8,020 DR-TB patients in BDQ-containing regimens, and a projected 200 patients enrolling in DLM-containing regimens, a significant increase over the preceding year.

In 2017, the Bedaquiline Donation Program led to a five-fold increase in global access to BDQ in more than 60 countries. As a result, approximately 8,020 patients are projected to receive treatment, free of cost, in National Action Plan countries.

Figure 2: BDQ and STR Progress in National Action Plan Countries



Source: National TB Programs and the 2017 WHO Global TB Report

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

Monitoring and tracking TB and DR-TB is a critical component in the management of TB, because it allows the identification of trends, challenges and successes, and technical and programmatic areas that require additional attention. In 2017, USAID supported the WHO's TB disease surveillance and progress monitoring. In October 2017, the WHO updated its Global TB Report and the global TB public database, which contain comprehensive global and national TB data used by partners involved in national and global efforts to eliminate TB.

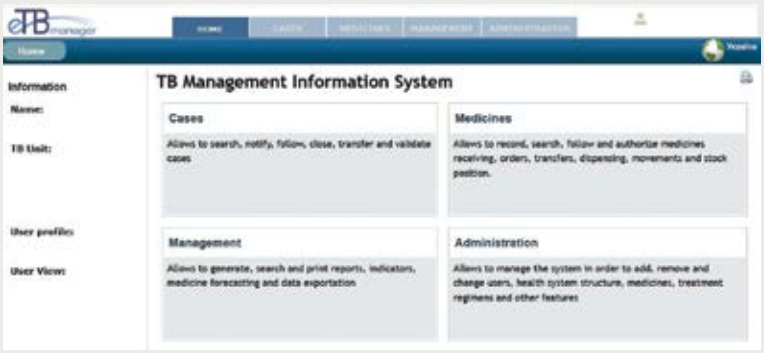
In National Action Plan countries, USAID and CDC work to strengthen TB surveillance systems, support the scale-up of electronic TB databases, and conduct drug-resistance surveys. In China, CDC performed a pilot TB-inventory study, the results of which led the National Center for TB Control to realize the need for routine record linkages between the results of the national TB-surveillance system, health facilities and insurance systems. In India, USAID funded the first-ever drug-resistance survey to understand drug-resistance levels and patterns, and inform treatment policies.

6 Country national TB laboratory systems consist of a National Reference Laboratory, regional/Provincial laboratories, District-level laboratories and sub-District laboratories.

The U.S. Government and the Global Fund to Fight AIDS, Tuberculosis and Malaria

The United States was the founding donor to the Global Fund in 2001 and is still the largest donor to the organization. The U.S. Government's TB lead serves at the Global Fund Board meeting as part of the U.S. Delegation. Seventeen years of collaboration means U.S. bilateral TB programs and those financed by the Global Fund now have a symbiotic relationship, and their success is mutually dependent in many countries. The Global Fund's TB investments are focused on improving quality programs including the purchase and delivery of drugs and diagnostics—and U.S. bilateral programs complement them in planning and execution. The U.S. Government invested $1.35 billion in the Global Fund in FY 2017; based on the Fund's portfolio, 18 percent of which is devoted to TB, the U.S. share of those grants was approximately $243 million.

WEB-BASED PLATFORM TRANSFORMS NATIONAL TB REGISTRY IN UKRAINE



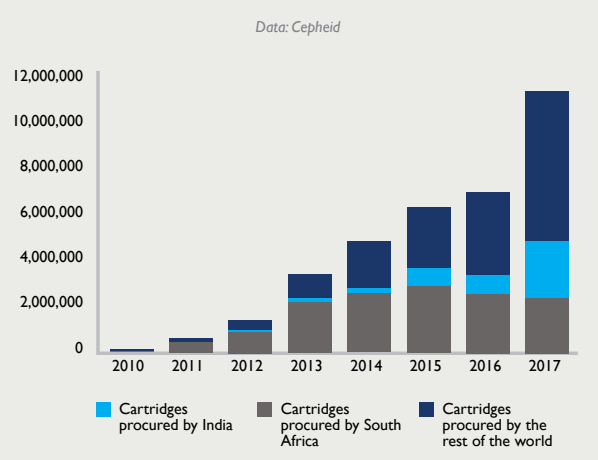
Snapshot of the e-TB Manager module used in Ukraine.

The eTB Manager is a web-based platform that integrates data across all components of TB monitoring and control, which makes it a key tool in the implementation of the National Action Plan. With USAID support, since 2016 the e-TB Manager has been the official national TB registry used by the Ukraine National TB Institute, the Ministries of Health and Defense, as well as the penitentiary system. By the end of 2017, the system linked 1,123 facilities with 2,332 active users who had already entered 247,940 TB cases and 53,804 DR-TB cases, or 92 percent of all cases that year. The e-TB Manager software has been helpful in reducing the time doctors spend on recording and reporting data, which allows them to spend more time on patient care, and increases their participation in the monitoring-and-evaluation system. The e-TB Manager also has halved the time needed to switch patients from DS-TB treatment to MDR-TB treatment when they receive a diagnosis of DR-TB. Moreover, the e-TB Manager helps to improve the quality of care by providing a system to track the medications prescribed for each patient, which increases the rational use of medicines, and ensures more-effective treatment. To date, three of the National Action Plan countries use e-TB manager.

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 second-line medications is essential for appropriate DR-TB care. USAID has therefore identified ensuring access to quality-assured second-line TB medications, traditionally a small and fragmented market, as one of its priority activities to achieve the goals of the National Action Plan. In 2017, USAID continued its funding of the Global Drug Facility (GDF), which aids countries to secure quality-assured medications via a pooled-procurement mechanism. In 2017, the GDF ensured that quality TB and DR-TB medications were available in 111 countries, decreased turnaround time from drug order to shipment to fewer than 60 days, and prevented drug stock-outs in 47 countries through its strategic rotating-stockpile mechanism.

Figure 3: Actual number of Xpert MTB/RIF cartridges procured under concessional pricing



As the world's leading supplier of TB diagnostics, GDF has played a key role in making new tools available to detect DR-TB. Since 2010, GDF has supplied GeneXpert commodities to 84 countries,[7] and in 2017 supplied 41 percent of the 11.3 million Xpert MTB/RIF cartridges procured globally. GDF currently serves as the main supplier of Xpert MTB/RIF cartridges for India and Pakistan's NTPs. In 2017 alone, India procured 97 percent of its 2.5 million cartridges, as well as 507 new GeneXpert modules through GDF.

GDF also supplies countries with line probe assays (LPA) for the rapid detection of first-and second-line drug resistance,[8] which allows providers to screen patients with additional confidence that patients will be enrolled on the appropriate regimens. Given its large and increasing share of the TB-diagnostics market, GDF plays a vital role as market coordinator, by leading stakeholders and governments in negotiations with manufacturers for better pricing and servicing of diagnostics to improve patient access and ensure the efficiency and sustainability of laboratory networks.

To improve the quality and safety of DR-TB treatment in patients who receive novel medications and regimens, USAID piloted the implementation of active drug safety management and monitoring (aDSM) systems in five of the National Action Plan countries. In 2018, USAID will provide technical assistance with aDSM to improve management approaches and the safe use of DR-TB drugs to all 10 of the National Action Plan countries, as well as an additional 20 high-burden TB countries.

7 GeneXpert is a diagnostic tool that tests sputum samples for the presence of TB. It is highly accurate, and detects difficult-to-diagnose forms of TB, such as DR-TB and HIV-associated TB, in less than two hours, at more-accessible decentralized facilities.

8 LPA is a molecular TB test used to detect resistance to two anti-TB medications(fluoroquinolones and injectables), within 24 hours

OBJECTIVE 2.2: PREVENT MDR-TB TRANSMISSION

In 2017, USAID worked with Ministries of Heath, NTPs, and local partners to prioritize TB and DR-TB activities to screen for high-risk patients; develop enhanced adherence programs; and support associated services in an effort to initiate treatment of individuals with DR-TB rapidly, not only to ensure they received appropriate care, but also to minimize the period during which they might transmit the disease to others.

In four of the National Action Plan countries, USAID and CDC worked together to improve guidance for infection control and assist NTPs in addressing gaps and bottlenecks in healthcare facilities.

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

The WHO recognizes active TB and DR-TB case finding among high-risk populations as a TB "best practice," which USAID has initiated in several National Action Plan countries in 2017 to adapt a screening tool and to target TB-detection activities.

Quality assessments of facility-and-community level DR-TB services, initiated in 2016 in National Action Plan countries, expanded in 2017. Regular site-monitoring and treatment-cohort reviews assisted TB programs in optimizing the management of services and the delivery of care.

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

During the first year of the implementation of the National Action Plan, USAID developed Delivering Comprehensive Supportive Care to People with Drug-Resistant TB Guide to help improve adherence in patients who receive DR-TB treatment and services. The goal was not only to improve individual patient outcomes, but to render individuals non-infectious so they cannot transmit the disease to others. In 2017, the care package pilot launched in China, Pakistan, South Africa and Ukraine to provide enhanced care and support services to 600 patients. Lessons learned through analysis of these pilots will lead to a modified package that will better serve patients, beginning in 2018.

The treatment of DR-TB is challenging and complex for both patients and their families, and it can be difficult for patients to continue taking their medication for the very long period of time required. To minimize the burden of DOT on both patients and health systems, and to improve outcomes, USAID and CDC have introduced electronic technologies to assist daily adherence and treatment-monitoring. Video DOT, SMS reminders and other tools are currently being piloted, and USAID and CDC will adapt and expand them, if successful, in all National Action Plan countries in 2018.

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

Because TB, regardless of resistance pattern, is spread through the air, healthcare professionals who care for infectious TB patients are at particularly high risk of contracting the disease. The U.S. Government has introduced preventive strategies in National Action Plan countries that prioritize the well-being of healthcare workers through regular health assessments and active surveillance for TB. Building on the Year One successes of improving national infection control (IC) guidelines and curricula for healthcare workers, USAID and CDC provided technical assistance in Year Two to develop manuals and toolkits on specific IC technical areas, including IC administrative control and personal protection. USAID and CDC assisted countries with the implementation of national IC plans by using these tools, including the CDC TB BASICS program, a four-phase TB IC initiative developed to assess and improve IC practice, in healthcare facilities through, a continuous quality improvement methodology.[9]

9 The Building and Strengthening Infection Control Strategies (TB BASICS) is a four-phase initiative, developed by CDC, includes 1) training of healthcare workers in TB infection control; 2) baseline health-facility assessments and development of intervention plans; 3) implementation; and 4) monitoring and evaluation through, the engagement of local health officials and healthcare workers to encourage commitment to the initiative.

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

The National Institutes of Health (NIH) within HHS has a mission to fund and conduct domestic and international biomedical research on TB. Within NIH, the National Institute of Allergy and Infectious Diseases (NIAID) is the lead institute for TB research, complemented by programs supported through other NIH Institutes and Centers. This broad engagement provides opportunities to contribute strategically to key areas of science underpinning the discovery of new vaccines, drugs and diagnostics, as well as to conduct and support studies to identify product candidates and prepare them for clinical evaluation. Many research projects highlight the synergy between U.S. Government Agencies' TB activities. Care strategies and tools developed with NIH support continue to be evaluated or implemented through USAID and CDC programs. For example, many products, such as the investigational anti-bacterial drug Pretomanid and diagnostic tool GeneXpert MTB/RIF, that are being tested in clinical trials or are implemented in TB endemic countries with CDC and USAID support, were developed with NIH funding. Observational international research cohorts, such as the Observational International Research Cohorts (RePORT) Network (http://www.reportinternational.org), which is a cooperative strategy between NIH and interested governments, benefit from investments made by USAID, CDC and other U.S. Government agencies and are being used to initiate country-based biomedical research. NIH contributes to TB product development thro ugh a variety of funding mechanisms. Since many global funders support TB research and development (R&D), NIH officials and scientists ensure that U.S. Government investments are optimally applied and complement other international programs. To facilitate coordination, NIH, USAID and 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 TB TRANSMISSION

Due to the complexity of the host/pathogen interactions underlying the progression of latent MTB infection to active TB disease, developing new preventive strategies requires a thorough understanding of the biological mechanisms and dynamics of TB, and strategic support of critical product development and clinical testing activities. While products and care strategies that target persons at highest risk of developing transmissible forms of the disease are expected to have a significant impact on personal and public health, biomedical research and product development efforts are seeking to ensure that TB is preventable.

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

Building on a robust and broad TB portfolio of grants awarded to external institutions, and intramural projects conducted by NIH scientists, NIH continued and newly issued funding opportunity announcements in 2017 to expand its immunology and TB vaccine research portfolio. Critical topics remain: immune studies to identify markers that signal immune protection against infection or TB disease; exploration of the pathogen's immune-evasive strategies as targets against which new vaccines can be directed; elucidation of mechanisms underlying the transition to active disease; and translational studies for the development of novel TB vaccine candidates. These

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

U.S. Government-supported research has contributed to product development and clinical research to explore novel approaches for the prevention of TB and to evaluate innovative vaccine concepts. Continued, iterative development and testing of candidate products is critical for advancing approaches developed in the laboratory and in animal models to those that will prevent human TB. U.S. Government interactions and collaborations with product developers and academic institutions will help ensure that best practices in TB R&D and product development can be leveraged by the research community when new vaccine, host-directed therapeutics and other adjunct approaches are investigated and will continue beyond the current reporting year.

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

In addition to basic, clinical, and translational biomedical R&D activities necessary for new product development, U.S. Government agencies (USAID, CDC and NIH) engage in patient-oriented research to inform prevention, treatment and management of TB. Strategies that were under investigation and included shorter courses of more effective therapies and treatment schedules for persons latently infected with MTB and effectiveness of prophylactic treatment to protect contacts of patients with MDR-TB. CDC, USAID and the President's Emergency Plan for AIDS Relief (PEPFAR) supported a study of an enhanced infection control package on reducing TB transmission in healthcare facilities and communities in Vietnam and Thailand (EnTIC). This study has been completed with results expected in 2018. USAID began planning several collaborative projects to characterize transmission of MDR-TB in Kyrgyzstan and Moldova, countries with high rates of DR-TB, and continues its study evaluating a three-month, once-a-week treatment intended to prevent the development of drug-resistant TB in HIV-infected individuals ($WHIP_3TB$). NIH-supported a Phase III clinical trial of an ultra-short-course of rifapentine and isoniazid for HIV-infected individuals with latent TB in order to prevent the development of active TB disease. This trial has been completed, and highly promising data were presented at the March 2018 Conference on Retroviruses and Opportunistic Infections.

Each country and community affected by TB presents unique challenges and opportunities for intervention. U.S. Government support is helping to meet the needs of individual countries by developing and implementing targeted strategies to effectively prevent transmission. Evaluating strategies, candidates and approaches in a broader range of diverse high-burden countries will require additional studies and continued investment at the local, national and global levels.

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

Rapid and accurate diagnosis of acute and latent MTB infection, MDR-TB and XDR-TB is the cornerstone of TB care and control programs in the U.S. and worldwide. A variety of technologies are being developed and evaluated in countries where TB is endemic to confirm or rule out active TB and to quickly determine which antibiotics will constitute the most effective treatment regimen. Diagnosis of latent MTB infection offers the opportunity to provide patients with preventive therapy to lower their immediate risk of developing active – and often transmissible – TB. Diagnostic development involves research to identify what bacterial or biomarkers can be identified in sputum, blood or other body fluids or excretions and pairing those with novel, rapid technologies that can be utilized in healthcare settings where they are most urgently needed. Unique collaborations among multiple partners, including healthcare providers and TB control programs, are required to determine that a diagnostic test improves the accuracy and speed at which TB patients of all ages can be identified and offered effective treatment.

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

NIH currently supports research on a broad and diverse range of technologies and approaches aimed at improving the identification of DS-TB and MDR-TB/XDR-TB, as well as the identification of human biomarkers suitable to determine whether a person has MTB infection and may be at risk for developing active TB disease. A continued area of focus is the creation of comprehensive datasets that give insight into the diversity of the biology and drug resistance profiles of MTB strains and how they affect patients. One example is the NIH-supported "TB Portals" Program (https://tbportals.niaid.nih.gov), which is a web-based, open-access repository of socioeconomic/geographic, clinical, laboratory, radiological and genomic data from patients with DR-TB to facilitate multi-national collaboration for data sharing and analysis. NIH and CDC continue to support and participate in collaborations among international researchers to sequence and process genomes of MTB isolated from patients in Africa, Asia, Europe, Latin America and the Middle East. Data from several thousand bacterial isolates are being integrated into global databases benefiting the development of molecular diagnostic technologies. To facilitate integration of promising new diagnostics at the most critical stage of patient care, U.S. Government Agencies (NIH, USAID and CDC) also support clinical evaluations of and feasibility testing of new diagnostic tools. These biomedical and clinical programs are complemented by studies to strengthen the existing approaches to TB diagnosis in high-burden countries. This ensures that barriers to effective diagnosis are identified and best practices are in place to identify and refer patients for effective therapy. A program of stepwise activities leading to the confirmed diagnosis of TB is the platform on which new tools and approaches will be evaluated and is a cornerstone to successful rollout of new diagnostics. With the emergence of new diagnostic platforms, strong collaborations among clinicians, public health scientists, bioinformatics specialists and medical diagnostic developers provide opportunities for development and strengthening of reference laboratories in TB endemic countries to evaluate promising new diagnostic tests.

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

NIH's Tuberculosis Research Unit Network (TBRU-N) and other ongoing projects are identifying blood-based biomarkers that may 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 NIH co-funded RePORT Networks operate under standardized protocols and are contributing critical resources to NIH-funded projects that are studying TB in endemic countries. In collaboration with NIH, CDC continues to contribute TB samples to the Consortium for Tuberculosis Biomarkers (CTB2), which may speed the clinical trials of new drugs and facilitate the search for biomarkers in adults and children that will help predict or identify progression from MTB infection to TB disease.

The establishment of longitudinal cohorts and increased research capacity in endemic countries created platforms for collaborative research in human TB in the context of country specific co-infections, such as HIV and co-morbidities such as diabetes. To maximize the potential of international collaborative research, continued dialogue among specialists from all scientific disciplines – from basic to clinical to implementation/operational research – needs to be encouraged and facilitated.

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

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

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

U.S. Government agencies (USAID, CDC, and NIH) are conducting studies to assess the utility and effectiveness of several therapeutic regimens comprised of licensed and novel drugs that may result in fewer serious side effects and/or shorter treatment durations for patients with MDR-TB. NIH-funded studies designed to evaluate higher doses of key drugs for first and second line TB therapy are nearing completion and publication of data. The USAID-supported Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB (STREAM) randomized clinical trial suggests that the efficacy of a nine-month MDR-TB treatment regimen composed of existing TB drugs is similar to the efficacy of the current 20-24 month regimen. These studies also contribute to capacity building with other nations' TB programs and help ensure that the most recent scientific findings are integrated into treatment policies. Furthermore, to facilitate implementation of novel regimens, USAID is also supporting the development and introduction of ancillary packages of care that support MDR-TB patients during treatment and help them complete therapy. NIH collaborated on several workshops designed to identify new targets against which TB drugs can be directed and to develop best practices for preclinical development of all new treatment regimens.

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

In 2012 and 2014, biomedical R&D on TB resulted in the licensure of the first two new drugs, BDQ and DLM, in decades. The integration of these new

drugs into existing regimens to replace or improve therapy requires efficacy and safety studies to ensure that treatment is effective and that patients benefit from new drugs. During 2017, USAID continued to contribute to the second phase of the STREAM trial, which includes BDQ, a newly registered drug, and will recruit patients in 10 countries. The USAID co-sponsored Nix-TB trial also delivered promising results and is being followed by additional co-sponsored trials to further optimize this promising approach of immediately testing regimens including novel drug candidates, rather than licensing individual drugs that are then combined with or added to existing therapies. An NIH-sponsored trial will commence in 2018 to evaluate safety and tolerability of BDQ in infants, children, and adolescents who may or may not be co-infected with HIV, contributing data for the safe use of this drug in these important populations. As new drugs licensed for TB become available, clinical trials need to be conducted to evaluate how they perform in combination and determine what side effects may occur. If these new drugs are to be used for TB/HIV co-infected individuals, then clinical studies are needed to determine whether there are drug-drug interactions with antiretrovirals. The USAID-co-sponsored BDQ donation program also prioritizes support for pharmacovigilance and facilitates scale-up of the use of this drug in TB control programs.

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

Development of new chemical entities requires a thorough understanding of the biology of MTB, where it resides in organs, and how best to target drugs to these locations for maximum effectiveness. Anti-infective strategies are being complemented by therapies that enhance the ability of the patient's immune system to limit the destructive effects of TB on organs, and NIH is supporting several programs in host-directed therapy. NIH is also continuing to support preclinical studies in animals and the laboratory in order to select the most promising new chemicals for further advancement. NIH-sponsored scientists continue to make advances in drug discovery through participation in global drug development consortia, which are emerging as effective models for academic-pharmaceutical collaborations. These research partnerships are increasingly utilizing rational, pharmacologically-driven approaches to drug discovery, development of animal models, regimen selection and clinical trial design to improve the state of the science of TB drug discovery and lower risks for product developers.

Significant innovation has occurred, and important research discoveries are now being applied to the preclinical assessment of new chemicals and regimens. To help ensure that these approaches will contribute in a meaningful way to the best practices for drug development, long-term investment and sustained research partnerships among U.S. Government agencies, academia, not-for-profit and for-profit organizations will be important.

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

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

CONCLUSION

The U.S. Government Departments and Agencies charged with implementing the National Action Plan continue to make notable progress towards achieving the Plan's established milestones. Overall, results from improving care and strengthening programs as part of the implementation of the National Action Plan in Year Two showed slower progress than Year One, with the exception of the treatment of XDR-TB, which increased sizably. While National Action Plan countries achieved significant progress in updating their DR-TB treatment plans to include BDQ, or transitioned to the use of the STR as appropriate, observed rates in the areas of detection and treatment remained relatively unchanged, in line with the global trends observed in 2017. Increased political will within the target countries and access to additional resources will be required for the rapid scale-up needed in 2018, and through the rest of the Plan to achieve the milestones laid out for Year Three.

APPENDIX: MILESTONES AND ADVANCES

GOAL 1

Objective 1.1 Upgrade TB surveillance to ensure complete and accurate detection of drug-resistant TB		
Year One Milestones	**Year One Achievements (previously reported)**	**Additional Progress Made in Year Two**
Identify common language and protocols for reporting drug resistance to anti-TB drugs.	▪ Development of standardized reporting underway.	▪ The U.S. domestic TB surveillance system is being upgraded to be able to collect and report the results of new methods for the identification of resistance. The molecular drug susceptibility testing reporting (MDSTR) form has been successfully developed and tested within the National TB Surveillance System Case Reporting (NTSSCR) system. CDC is in the beginning stages of adding pilot users to the system for beta testing the MDSTR form.
Identify requirements for creating electronic links between clinical laboratories and TB surveillance programs at the Federal, State and local levels.		▪ CDC is in the beginning stages of developing and implementing 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 the NTSSCR MDSTR data collection system.
Objective 1.2 Strengthen State and local capacity to prevent transmission of drug-resistant TB		
Year One Milestones	**Year One Achievements (previously reported)**	**Additional Progress Made in Year Two**
Work with the National TB Controllers Association to develop surge capacity for controlling transmission of drug-resistant TB.	▪ Finalizing new metrics for tracking TB transmission that can be applied to drug resistant TB as well as drug-sensitive TB.	▪ Expanded data collection for drug susceptibility testing results to be included in new version of Report of Verified Case of Tuberculosis (RVCT).
Explore ways to increase staffing at State and local health departments during TB contact investigations.		▪ Unable to address surge capacity, increased staffing, or development of other new tools without additional funding.
Objective 1.3 Ensure that patients with drug-resistant TB receive treatment until cured		
Sub-objective 1.3.1 Explore the potential use of a national TB stockpile to ensure the availability of TB medicines and screening tests		
Year One Milestones	**Year One Achievements (previously reported)**	**Additional Progress Made in Year Two**
CDC will explore the development of a National TB Stockpile that could store and rotate TB supplies that can be ordered by State and local TB programs.	▪ Stockpile, managed by the DHHS Supply Service Center, is operational in the event of a national drug shortage.	▪ The TB Emergency Drug Stockpile has been successfully maintained. There has been no national shortage of TB drugs, so the stockpile was not utilized in Year Two.

Sub-objective 1.3.2 Explore options for providing care for persons with MDR-TB or XDR-TB who do not have a medical home		
Year One Milestones	**Year One Achievements (previously reported)**	**Additional Progress Made in Year Two**
CDC and State and local TB programs will work together on plans for completion of therapy once MDR-TB or XDR-TB patients are released from a hospital.	▪ Clinical trial design to evaluate electronic directly observed therapy (eDOT) for treating TB disease.	▪ 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 NYC 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.
Sub-objective 1.3.3 Improve completion of therapy for persons who travel in or out of the United States while on treatment for TB disease		
Year One Milestones	**Year One Achievements (previously reported)**	**Additional Progress Made in Year Two**
CDC and others will explore ways to strengthen medical management of transnational TB disease cases.	▪ Evaluation of binational (U.S.-Mexico) case definition for surveillance system in progress.	▪ The Surveillance Definition for Binational TB Cases Workgroup has developed a revised definition for binational TB cases that will be published 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 One Milestones	**Year One Achievements (previously reported)**	**Additional Progress Made in Year Two**
USAID and CDC will work with up to 10 countries to develop comprehensive national TB/MDR-TB laboratory strategic plans addressing provision and placement of services at each level, as part of each country's National TB Strategic Plan.	▪ The NTPs of Burma, India, Indonesia, Kazakhstan, Pakistan, Philippines, South Africa, and Ukraine have NLSPs that address TB and MDR-TB. ▪ USAID developed a framework for assessing TB laboratory and diagnostic networks in multiple countries using tools adapted through a USAID-led comprehensive international review of Nigeria's TB diagnostic network in March 2016. This framework is a key step towards prioritizing and planning laboratory strengthening and monitoring. ▪ In Nigeria, USAID and CDC developed an operational plan/work plan in response to the TB diagnostic network assessment, including revisions to the DR TB diagnostic algorithm. ▪ Mapping of diagnostic networks is also underway in several countries in sub-Saharan Africa, and the U.S. Government is working with the Global Laboratory Initiative (GLI) and GLI Africa to promote best practices and accelerate scale up of MDR-TB diagnostics in priority countries.	▪ USAID and CDC supported sub-Saharan African and Asian countries to complete national inventories of their GeneXpert instruments as a first step toward optimizing testing networks and improving patient access to rapid diagnostic and resistance-testing services for rifampicin (RIF). USAID-led achievements: ▪ Worked with NTPs and bilateral partners to create NSLPs during Year Two of the implementation of the National Action Plan. By the end of Year Three, we expect nine out of the 10 National Action Plan countries will have national lab plans developed and approved for implementation. ▪ A comprehensive assessment of the TB-diagnostic network in India was conducted to review the diagnostic network, current practices and algorithms holistically; identify challenges that prevent the overall diagnostic network from performing efficiently and effectively; and propose evidence-based interventions to improve the overall ability of the TB-diagnostic network to meet the goals and targets of India's ambitious new National Strategic Plan (NSP). As a result of the assessment, India is revising its NLSP and developing operational plans at national and State levels, with a focus on strengthening the diagnosis of MDR-TB. ▪ In Ukraine, a team of domestic and international experts worked together to create a NSLP, based on recent recommendations of the WHO. In-depth assessment and country visits have helped to shape the document and set ambitious targets and goals for the next five years. ▪ In the Philippines, USAID worked with the NTRL to introduce new technology for the rapid detection of TB and develop a plan for country scale-up by leveraging both national and funding and resources from the Global Fund. ▪ USAID financed the development of a specimen-referral toolkit to help countries identify gaps within their networks and solutions for an efficient and integrated specimen-referral system. ▪ India leveraged Global Fund and USAID funding to complete a trial of a domestically-developed diagnostic, Truenat that was endorsed as a molecular-test replacement for smear microscopy. A second-step assay to detect resistance to RIF) is currently undergoing optimization studies.

		CDC-led achievements:
		▪ CDC began work in countries in Africa and Asia that are part of PEPFAR, to complete national inventories of their GeneXpert instruments as a first step towards optimizing testing networks and improving patient access to rapid diagnostic and RIF resistance testing services.
		▪ CDC is strengthening the capacity of national and intermediate TB reference laboratories to provide quality testing and supervisory services in India and China through:
		  ▪ Successful transfer and ongoing national scale-up of the agency-developed Xpert MTB/RIF external quality assurance program to one national reference laboratory in India.
		  ▪ Implementation of a structured, mentorship-based quality management system improvement program to support national (India) and intermediate (India and China) reference laboratories work toward international accreditation.
		▪ CDC supported the establishment and validation of whole genome sequencing technology at a NTRL in India for enhanced characterization of DR-TB cases and DR-TB surveillance.

Year Three Milestones	**Progress towards Year Three to Five Milestones**	
USAID and CDC will work with up to 10 countries to implement laboratory strategic plans to improve diagnostic capacity from the central to the peripheral level as part of each country's National TB Strategic Plan.	▪ Development of national laboratory strategic plans is the first step towards improvement of TB laboratory capacity in a country. As TB diagnostic networks consist of national, regional, provincial and district-level laboratories, appropriate decentralization and support to all levels of the network is needed. USAID worked in Year Two with NTPs and local partners to optimize diagnostics throughout the network, especially peripheral-level laboratories, to ensure that TB diagnostic instruments are running, have the necessary commodities, and are delivering real-time results to inform appropriate patient management. An example of USAID's approach to optimizing diagnostics throughout the network can be seen through the introduction of "connectivity" solutions whereby instruments that produce electronic results are connected with the TB program to monitor instrument utilization and commodity stock, analyze performance of diagnostic tests, and receive timely results about new TB and DR-TB patients. USAID works with the national partners to further scale up laboratory plans, follow-up with national and international standards and demonstrate progress towards five-year goals. ▪ USAID and CDC are working with the GLI and GLI Africa partnerships to develop and implement guidance on key diagnostic network strengthening components, inventory country NSLPs and develop best practices on plan development.	
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 One Milestones	**Year One Achievements (previously reported)**	**Additional Progress Made in Year Two**
USAID will work with up to five countries to introduce a new MDR-TB drug (BDQ, DLM or both).	▪ USAID supported NTPs in Burma, India, Indonesia, Kazakhstan, Pakistan, Philippines and South Africa to introduce BDQ for treatment of MDR-TB. This support encompassed a wide variety of activities; for example, revision of NTP treatment guidelines to include BDQ, training of clinicians on the appropriate use of BDQ, coordination with pharmaceutical regulatory agencies to facilitate importation and development of systems to monitor adverse events. ▪ Additionally, Burma and South Africa introduced DLM in limited research conditions.	▪ USAID further expanded access to BDQ and DLM, building upon the introduction of the drugs into seven of the 10 National Action Plan countries during Year One. ▪ Collaboration between South Africa's Department of Health, Johnson & Johnson and USAID resulted in National Action Plan countries enrolling 4,277 DR-TB patients on BDQ and on DLM. The majority of the patients enrolled on BDQ. More than 85 percent of the patients enrolled on BDQ were enrolled in South Africa.

USAID will work with up to 10 countries to introduce and scale-up new DR-TB drugs.	▪ South Africa was an early adopter of BDQ for treatment of DR-TB. Since the inception of the Bedaquiline Donation Program, almost 4,000 patients received the drug as part of their treatment regimen. Technical assistance provided by USAID to the NTP greatly increased access to the drug.	▪ Significant progress was made by USAID during Year Two in all of the National Action Plan countries. Ninety percent of National Action Plan countries expanded their BDQ treatment sites. In Burma, India, Indonesia, Nigeria and Ukraine, the number of BDQ treatment sites is estimated to have tripled. ▪ With USAID support, GDF, through the Bedaquiline Donation Program, increased the global supply of BDQ from 1,487 packs in 2016 to more than 8,000 packs in 2017, a five-fold increase. In 2017, 2,689 packs of DLM were shipped globally; more than 30 percent of these packs were shipped to National Action Plan countries.
Year Three Milestones	**Progress towards Year Three to Five Milestones**	
USAID will work with up to 10 countries to introduce shortened MDR-TB regimens	▪ 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, during the Year One of the National Action Plan implementation, the Philippines was the only country that had introduced STR with 272 DR-TB patients enrolled on treatment. In 2017, USAID worked with NTPs and local partners to bring this novel regimen to all National Action Plan countries. As a result, three additional National Action Plan countries (South Africa, Nigeria and Indonesia) have introduced STR and approximately 5,600 patients have been enrolled on treatment. ▪ In 2018, as many as nine out of 10 National Action Plan countries are expected to introduce STR, and more than 10,000 will be enrolled on treatment.	
USAID will develop quality facility and community-based MDR-TB care and treatment services	▪ In September 2017, USAID convened a workshop for 68 participants from the 10 National Action Plan 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 10 National Action Plan priority 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. ▪ CDC supported a counseling program in Mumbai to improve adherence and retention of DR-TB patients on treatment. Over 2,000 patients have received adherence counseling, as well as repeated home visits through this program. ▪ CDC led a demonstration project of the ECHO platform for DR-TB treatment at one national treatment facility in New Delhi. ▪ It is expected that by the end of Year Three of the National Action Plan, all 10 countries will initiate or scale up community-based programs targeting DR-TB patients and their families. As a result, significant numbers of people globally will have access to patient-centered service.	
Sub-objective 2.1.3 Strengthen TB and MDR-TB surveillance		
Year One Milestones	**Year One Achievements (previously reported)**	**Additional Progress Made in Year Two**
USAID will enhance tracking of MDR-TB disease burden and surveillance data for dissemination.	▪ USAID developed and provides ongoing financial and technical support to the WHO's Tuberculosis Monitoring and Evaluation (TME) Unit to perform annual collection and analysis of TB data, including routine data on MDR-TB in over 200 countries.	▪ USAID continues to develop and provide ongoing financial and technical support to the WHO's Tuberculosis Monitoring and Evaluation (TME) Unit to perform annual collection and analysis of TB data, including routine data on MDR-TB in over 200 countries.

CDC will assist one country in the completion of an inventory study to determine gaps in the TB surveillance system.	▪ CDC supported China's National Center for TB (NCTB) to conduct a pilot inventory study. ▪ In nine provinces, lessons learned were reviewed, and a standardized process for routinely matching laboratory, hospital, and surveillance records to identify TB cases that were not reported to the national system was developed. In 2016, CDC assisted the NTP in the Philippines in planning its national inventory study to measure the level of under-reporting of diagnosed TB cases to the surveillance system. ▪ USAID also provided technical assistance to the State TB program in Lagos, Nigeria, to plan an inventory study.	▪ The CDC supported the China National Center for TB's (NCTB) pilot inventory study which was completed in Fall 2016. Overall, 19 percent of cases were not registered within six months, with a variation of 3-37 percent across counties. These findings helped the NCTB realize the need for routine record linkage between the national TB surveillance system and health facility and insurance systems. Using the lessons learned from this project, a set of tools including a computer program to match cases have been developed and shared with six counties. ▪ USAID is providing ongoing support for an inventory study in Lagos, Nigeria, to assess the level of underreporting by private sector providers. Fieldwork is complete, with 680 facilities and 511 providers assessed, and data analysis is ongoing. Results and recommendations are expected to be available by the end of 2018.
Year Three Milestones	**Progress towards Year Three to Five Milestones**	
USAID and CDC will work with up to 10 countries to implement standards and benchmarks to improve surveillance and vital registration systems to directly measure TB burden.	▪ Standards and benchmarks (S&B) have been used as a part of the NTP review process as well as during prevalence surveys. It is expected that at least eight countries will have S&B benchmarks implemented by the end of December 2018. As of December 2017, the following countries have completed the S&B checklist: Burma (2016), Indonesia (2017), Kazakhstan (2017), Nigeria (2017), Pakistan (2016), Philippines (2017), South African (2015) and Ukraine (2014). China is currently undertaking this with support from WHO/TME and CDC; India will complete their checklist in 2018.	
USAID will work with up to five countries to introduce and scale up patient-based electronic recording and reporting systems.	▪ National Action Plan 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. ▪ India continues to develop its e-Nikshay case-based notification system. USAID is planning to support e-Nikshay's expansion to include Programmatic Management of Drug-Resistant Tuberculosis (PMDT) and direct connectivity to Xpert. ▪ By the end of Year Three, it is expected that all 10 National Action Plan countries will either introduce or fully scale up electronic recording and reporting systems for TB.	
Sub-objective 2.1.4 Improve the global availability and affordability of quality-assured, second-line drugs and improve country-level procurement and supply chain management		
Year One Milestones	**Year One Achievements (previously reported)**	**Additional Progress Made in Year Two**
USAID will support the continued development and maintenance of a global supply of affordable, quality-assured, second-line drugs to ensure access to life-saving drugs.	▪ USAID has provided ongoing support to the GDF to maintain a strategic rotating stockpile (SRS) of second-line medications that NTPs can access to ensure timely and affordable supply of second-line drugs at all times. The SRS is also available for emergency orders. The GDF is able to turn around requests to the SRS very quickly to ensure that patients can stay on life saving treatment. Additionally, USAID works with the GDF to improve procurement and distribution systems in countries.	▪ USAID continues to support GDF, an organization responsible for procurement and delivery of anti-TB medicines globally. ▪ In 2017, 111 countries were served by the GDF. ▪ GDF delivered nearly $304 million of TB products (first-line drugs, second-line drugs and diagnostics) to 119 countries in 2017 an almost 50 percent increase compared to 2016. ▪ Additionally, the turnaround time from request to shipment decreased from four to six months to less than 60 days, and in coming years, GDF will work to reduce the lead time even further. ▪ Thanks to price negotiation by GDF, the price of clofazimine has been reduced by 11 percent in the first quarter of 2017, and an additional price reduction is expected in 2018.

Year Three Milestones	Progress towards Years Three to Five Milestones
USAID will work with up to 10 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.	▪ 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. ▪ In April 2017, USAID convened key stakeholders from Burma, China, India, Indonesia, Pakistan, Papua New Guinea, Philippines, South Korea, Thailand and Vietnam for the Asia Regional Pharmacovigilance Workshop to initiate implementation of aDSM activities with the focus on new TB drugs and new regimens. Following the workshop, countries initiated aDSM pilots and planning for further scale-up will continue through 2018. ▪ In 2018 USAID will continue working with the National Action Plan countries to plan two additional aDSM workshops.
USAID will work with up to seven countries to introduce and scale up an MDR-TB early warning drug procurement and management systems to prevent stock-outs.	▪ QuanTB is the electronic tool developed by USAID and partners to support countries as they track drug stock at national and regional levels. The tool allows for accurate quantification of drug orders and provides easy visualization of the system. As of December 2017, four countries have implemented QuanTB at the national level: Nigeria, Pakistan, Philippines and Ukraine. ▪ In 2018, USAID will provide technical assistance to additional countries to launch the tool.

Objective 2.2 Prevent MDR-TB Transmission

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

Year One Milestones	Year One Achievements (previously reported)	Additional Progress Made in Year Two
USAID will work with up to 10 countries to validate and introduce a risk prioritization screening tool.	▪ In Burma, Indonesia, Kazakhstan, Nigeria and South Africa, USAID implemented a risk prioritization tool to identify the important populations and screening strategies to maximize detection of additional TB cases that might not otherwise be found.	▪ Additional National Action Plan countries have implemented a similar prioritization exercise and USAID expects to review these alternative tools and corresponding results by the end of Year Three.

Year Three Milestones	Progress towards Years Three to Five Milestones
USAID will work with up to 10 countries to introduce and/or scale up patient-centered TB and MDR-TB quality service delivery site monitoring.	▪ Site monitoring for the quality of DR-TB care delivery is one of the tools at the NTPs used to assess and improve the quality of care provided. USAID will start implementation of intensified quality assurance DR-TB programs in early 2018 and expect to cover at least nine countries by the end of Year Three.

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

Year One Milestones	Year One Achievements (previously reported)	Additional Progress Made in Year Two
USAID will develop generic ancillary care packages (e.g., services and supplies not directly related to treatment, but which enable patients to continue therapy, such as pain or nausea medicine, food rations and supportive services) for MDR-TB patients.	▪ USAID developed an ancillary care package to identify key services and interventions needed to support MDR-TB patients throughout the diagnosis and treatment processes. During Year One, USAID undertook a survey of patients, providers and technical partners to identify the key barriers to successful MDR-TB diagnosis and treatment.	▪ During Year Two of National Action Plan implementation, USAID launched the pilot program of DR-TB care package in four countries: China, Pakistan, South Africa and Ukraine. Seven hundred DR-TB patients were enrolled on comprehensive, patient-centered care support.

Year Three Milestones	Progress towards Years Three to Five Milestones
USAID will work with up to 10 countries to implement and scale up ancillary care packages to improve MDR-TB patient treatment outcomes.	▪ By July 2018 the pilot activity will be finalized and results will be assessed. USAID will report on efficacy, feasibility and cost-benefits of the DR-TB care package provided and collect lessons learned. ▪ Based on the results and experience of the DR-TB care package pilot in China, Pakistan, South Africa and Ukraine, USAID will further expand the approach into six additional countries. ▪ A workshop is planned for September 2018 in Kazakhstan and will target NTP staff, civil society and patient groups from Burma, India, Indonesia, Kazakhstan, Nigeria and the Philippines.

USAID will work with up to 10 countries to implement and scale up a TB adherence assessment tool.	▪ USAID has been consulting with the WHO on the methods to better track the adherence of TB and DR-TB patients and to improve quality of treatment overall. In early January 2018, the WHO released the Handbook for the use of digital technologies to support tuberculosis medication adherence. ▪ During 2018, USAID will work with five countries and pilot novel electronic tools to monitor adherence to TB treatment and remote support to TB patients. ▪ CDC has supported the Mumbai-based SAKSHAM counseling program in India, which provides counselors to follow-up MDR-TB patients to encourage adherence, improve retention and provide guidance for referrals in the case of adverse events. Over 2,700 patients have been provided counseling through SAKSHAM. The first cohort, approximately 700 patients, showed a retention rate of 70 percent at the end of 12 months of MDR-TB treatment.

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

Year One Milestones	Year One Achievements (previously reported)	Additional Progress Made in Year Two
USAID will work with up to 10 countries to develop quality national infection control guidelines.	▪ Building on the existing TB portfolio, USAID has supported the development of quality national infection control guidelines in Burma, India, Indonesia, Kazakhstan, Nigeria, Pakistan, South Africa and Ukraine. All infection control guidelines are based on the WHO-recommended standards and guidelines, a subset of which is integrated into the USAID supported FAST strategy, as requested by NTPs.	▪ Through the End TB Transmission Initiative (ETTi) USAID and CDC are supporting the National Institute of Tuberculosis and Respiratory Disease (NITRD) in New Delhi, India, in applying the principles of airborne infection control (AIC). A facility-wide risk assessment identified enhancements to NITRD's infection prevention and control (IPC) plan starting with administrative controls. After the successful implementation of the administrative controls, the next phase will be to enhance the facility's AIC included environmental controls to supplement natural ventilation. The NITRD demonstration project results will be used to refine guidelines for monitoring safety and output performance of the fixtures. ▪ USAID supported biosafety cabinet testing and maintenance training, through the WHO, with participants from Ukraine and helped with the development of TB laboratory maintenance guidance. ▪ USAID supported the building of capacity in TB IPC consultants through the AIC Summer Course on *Building Design and Engineering Approaches to Airborne Infection Control*, mentoring visits for selective would-be consultants, and the TB Design Roster to connect projects in need of consultants with individuals who have undergone special training. Together, these three interrelated activities address the inability of projects to identify consultants in IPC with both training and some field experience. ▪ USAID in Indonesia developed a self-assessment tool for PMDT sites which includes IPC. The tool has been used in 10 PMDT sites and will be expanded to PMDT sites nationwide. ▪ CDC provided extensive training of healthcare workers in AIC measures in India and China. CDC also supported facility assessments and oversaw facility renovations for developing and supporting model programs at apex institutes in India, NITRD (New Delhi) and Sewri TB Hospital (Mumbai).

Year Three Milestones	Progress towards Years Three to Five Milestones
Develop guidance on evidence-based best practices for TB infection control within healthcare facilities based on evidence-based policy recommendations.	▪ USAID supported the development of a maintenance manual for germicidal ultraviolet fixtures and upper-room germicidal ultraviolet (GUV) air disinfection systems for TB transmission control. Based on lessons learned from South Africa and India, the guidelines implementation will be expanded in additional National Action Plan countries. ▪ Through the WHO, USAID is supporting the update of the global TB IC guidelines ▪ CDC designed an intervention package and toolkit to identify and address TB infection control gaps, implement routine monitoring and evaluation, and ensure continuous program improvement, TB BASICS in healthcare facilities. ▪ In Nigeria, CDC and USAID provided support to improve infection control practices, including incorporating TB BASICS into national guidelines and curricula for healthcare workers, which is being scaled-up nationwide. ▪ In Mumbai, India, CDC is supporting the establishment of a novel AIC unit to assess, implement and evaluate infection control interventions in healthcare facilities treating TB using the TB BASICS tool.
USAID and CDC will work in up to 10 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.	▪ As of December 2017, seven countries have strengthened their IC practices for sites and facilities involved in management of DR-TB patients: India, Indonesia, Kazakhstan, Nigeria, Pakistan, South Africa and Ukraine. ▪ In 2018, USAID will continue to work with the pilot countries to scale up activities initiated in 2017 and engage the additional National Action Plan countries. ▪ USAID continues to work with countries to implement evidence-based practices for TB infection control in National Action Plan countries. In addition, to further implementation of the GUV guidelines, USAID will continue to expand the implementation of the FAST strategy, provide highly specialized training for IC consultants, build national IC capacities through support for Centers of Excellence (to include IC) and support innovative approaches to improved disease transmission measurements. ▪ CDC is working with 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.
USAID and CDC will work in up to 10 priority countries to introduce and/or improve healthcare worker surveillance and screening in facilities responsible for diagnosis and treatment of individuals with, and at high risk for, MDR-TB.	▪ With USAID support, as of December 2017, eight National Action Plan countries have initiated activities focused on screening of healthcare workers. ▪ In South Africa, USAID supported the development of TB screening modules for healthcare workers (HCWs) including implementation of relatively new infection diagnostics such as Interferon-Gamma Release Assays (IGRAs). ▪ In most of the National Action Plan countries, there are surveillance systems in place to capture incidence of TB among HCWs. Due largely to prevailing stigma, however, these data remain at sub-national level and often do not get reported to national authorities. ▪ The number of HCWs diagnosed with TB, however, is increasing, reflecting the improved efforts in these countries on screening and detecting cases. ▪ CDC is working with Mumbai Municipal Corporation of Greater Mumbai to establish a health-screening program for healthcare workers in Mumbai. HCWs will be 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 One Milestones	**Year One Achievements (previously reported)**	**Additional Progress Made in Year Two**
NIH will expand its dialogue among basic scientists, funders, and vaccine developers to identify novel strategies for vaccine development, encourage research related to vaccine design, and educate partners about resources available to contribute to vaccine development.	▪ NIH: Workshop on March 7/8, 2016 on "The Impact of Mycobacterial Immune Evasion on Protective Immunity: Implications for TB Vaccine Design." ▪ NIH: Poster presentation on clinical resources for TB at the June 21/23, 2016 TB Summit in London, and on preclinical R&D resources at the EMBO Conference on Tuberculosis in September 2016 in Paris. ▪ NIH: Established the Intramural TB Research Initiative (NITBRI) and held kick-off symposium on June 27, 2016 "New Approaches to Combating Tuberculosis. Leveraging NIH Intramural TB Research for the Global Effort." ▪ NIH: Participated in the 2nd "Collaboration for TB Vaccine Discovery" (CTVD) meeting in July 2016, hosted by the Bill and Melinda Gates Foundation in Seattle, WA ▪ NIH: Workshop on September 28/29, 2016 on "Developing Functional Assays for TB Vaccine R&D: An Aeras/NIAID Workshop." ▪ NIH: Ongoing participation in R&D discussions/leverages resources with TB vaccine development product development partnerships and for profit organization.	▪ NIH: Annual Meeting of the NIAID supported Vaccine Adjuvant Discovery Contract in November 2017. Novel adjuvants with potential utility in TB vaccines are being evaluated. ▪ NIH: Participated in the 3rd annual "Collaboration for TB Vaccine Discovery" (CTVD) meeting in July 2017, hosted by the Bill and Melinda Gates Foundation in Seattle, WA. ▪ NIH: Workshop in September 2017 on "Molecular Mechanisms and Immune Consequences of Pathogen Reservoirs: Battling unseen enemies" in Rockville, MD. ▪ NIH: Ongoing participation in R&D discussions with product development partnerships and for-profit organization to assure NIAID resources are appropriately leveraged for TB vaccine development. ▪ NIH: Workshop in June 2017 on "Halting TB Transmission in HIV Endemic Settings", in Cape Town, South Africa. Co-organized with the South Africa Medical Research Council (SAMRC), and the Bill & Melinda Gates Foundation (BMGF). ▪ NIH: Workshop in September 2017 on "TB Infection: Building a Framework for Eradication" in Dubai, United Arab Emirates. Co-organized with the Harvard Medical School Center for Global Health Delivery formulations. ▪ NIH: Poster presentation on preclinical and clinical resources for TB at the January 2017 Keystone Symposia in Canada and the April 2017 ASM TB Conference in New York.

NIH will continue to support studies to map the diversity of immune responses required for vaccine efficacy.	▪ NIH: TB Research Portfolio (https://report.nih.gov/categorical_spending.aspx)
	▪ NIH: Recent funding opportunities:
	  ▪ PAR-15-360: Characterization of Mycobacterial Induced Immunity in HIV-infected and Uninfected Individuals (R21)
	  ▪ PAR-16-254: Mechanisms of Mycobacterial-Induced Immunity in HIV-Infected and Uninfected Individuals to Inform Innovative Tuberculosis Vaccine Design (R01)
	  ▪ RFA-AI-16-079: Partnerships for Development of Vaccines to Prevent Mycobacterium tuberculosis Infection and/or Tuberculosis Disease (R01)
	  ▪ RFA-AI-16-047: Partnerships for Structure-Based Design of Novel Immunogens for Vaccine Development (R01) RFA-AI-16-034: Partnerships for Countermeasures Against Select Pathogens (R01)
		▪ NIH: TB Research Portfolio can be accessed here: https://report.nih.gov/categorical_spending.aspx
		▪ NIH: RFA-AI-17-039: Understanding Immuno-pathogenesis of Tuberculosis in HIV-1 Infected and Exposed Children (R01 Clinical Trial Not Allowed)
		▪ NIH: PAR-15-360: Characterization of Mycobacterial Induced Immunity in HIV-infected and Uninfected Individuals (R21). Two awards were made in 2017. Progress from awards made in 2016 includes safety evaluation of an attenuated combination *Mycobacterium tuberculosis* vaccine strain that also co-expresses SIV antigens in SIV infected non-human primates; The vaccine is immunogenic but appears to facilitate oral SIV infection in infant macaques. (Clin Vaccine Immunol. 2017 Jan 5;24(1). pii: e00360-16. doi: 10.1128/CVI.00360-16. Print 2017 Jan.)

	▪ NIH: Clinical Challenge Model for Assessment of Human TB Immunity (https://clinicaltrials.gov/ct2/show/NCT01868464)	▪ NIH: PAR-16-254: Mechanisms of Mycobacterial-Induced Immunity in HIV-Infected and Uninfected Individuals to Inform Innovative Tuberculosis Vaccine Design (R01). Five awards were made in 2017.
Years Three to Five Milestones	**Progress towards Years Three to Five Milestones**	
NIH will continue to support research, pre-clinical studies, and clinical trials and studies for the evaluation of new vaccines, adjuvants, and preventive drugs.	▪ NIH: Continues to support the development of a thermostable preparation of the Infectious Disease Research Institute (IDRI) ID93 GLA-SE TB vaccine under contract HHS N272201400041C. ▪ NIH: 4 awards were made in response to RFA-AI-16-079: Partnerships for Development of Vaccines to Prevent *Mycobacterium tuberculosis* Infection and/or Tuberculosis Disease (R01). ▪ NIH: Awarded Co-funding for the Phase 1/IIa Trial: MTBVAC Study in Adults with and without Latent Tuberculosis Infection in South Africa (A-050, NCT02933281) under grant 1U01AI131861. ▪ NIH: Received Council approval for a 2019 grant initiative on "Halting TB Transmission in HIV Endemic Settings" (https://www.niaid.nih.gov/grants-contracts/june-2017-daids-council-approved-concepts). ▪ NIH: Received Council approval for a 2018 contract initiative on "Immune Mechanisms of Protection Against Mycobacterium tuberculosis Center (IMPAc-TB) https://www.niaid.nih.gov/grants-contracts/september-2017-dait-council-approved-concepts#04	
NIH and CDC will intensify collaborations with domestic and international vaccine developers to leverage pre-clinical and clinical resources for vaccine development.	▪ NIH: Continues to make its vaccine evaluation services available to vaccine developers and the academic community and will continue to support preclinical and clinical vaccine evaluations through its various clinical networks and targeted funding opportunities.	
USAID will support platforms for TB vaccine researchers and key stakeholders in countries to facilitate collaboration and increase knowledge on TB vaccine research.	USAID: Planning to support participation of researchers from selected countries at the 5th Global Forum on TB Vaccines on February 20-23, 2018, in New Delhi, 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 R&D, with the end goal of developing and deploying new TB vaccines as quickly as possible.	
Department of State and the Department of Defense 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 (for example, U.S. active military personnel and U.S. diplomatic corps); the published risk of infection is 4–8 percent for such travelers.		
Sub-objective: 3.1.2. Support the development of methodologies to prevent transmission and development of TB and MDR-TB		
Year One Milestones	**Year One Achievements (previously reported)**	**Additional Progress Made in Year Two**
USAID will initiate at least one study to evaluate the impact and cost-effectiveness of at least one TB prevention measure on TB and MDR-TB transmission in different care settings in high-burden TB countries.	▪ USAID: Weekly High dose Isoniazid and Rifapentine® Periodic Prophylaxis for TB ($WHIP_3TB$) https://www.clinicaltrials.gov/ct2/show/NCT02980016). ▪ Other U.S. Government supported ongoing or planned clinical trials/studies ▪ NIH: Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx) (http://www.impaactnetwork.org/studies/IMPAACT2003B.asp)	▪ USAID: Weekly High-dose Isoniazid and Rifapentine® Periodic Prophylaxis for TB ($WHIP_3TB$). Eight study sites (South Africa (RSA): 5; Ethiopia: 2; Mozambique 1) are involved and have completed targeted enrollment (n=4000). 90% of participants attended their 3-month follow-up visit, no safety issues identified. Patient centered practices are being implemented to maintain volunteer retention. Participants in the Periodic Prophylaxis (p3HP) arm will be offered another round of 3 months of Isoniazid + Rifapentine (3HP) in 2018 and 2019. https://www.clinicaltrials.gov/ct2/show/NCT02980016).

	▪ CDC/PEPFAR: Evaluation of an Enhanced Tuberculosis Infection Control Intervention in Healthcare Facilities in Vietnam and Thailand (EnTIC) (www.clinicaltrials.gov/ct2/show/NCT02073240) ▪ NIH: Evaluating the Pharmacokinetics, Tolerability, and Safety of Once-Weekly Rifapentine and Isoniazid in HIV-1-Infected and HIV-1-Uninfected Pregnant and Postpartum Women with Latent Tuberculosis Infection (www.clinicaltrials.gov/ct2/show/NCT02651259) ▪ NIH: Finding and Treating Unsuspected and Resistant TB to Reduce Hospital Transmission (R01-AI112748) ▪ NIH: Cell Phone Video Directly Observed Therapy to Monitor Short Course LTBI Treatment (https://www.clinicaltrials.gov/ct2/show/NCT02641106) ▪ NIH: Innovative Interdisciplinary Approaches to Sustainable Airborne Infection Control (D43-TW9379) ▪ NIH: Impact of Effective Chemotherapy on Transmission of Drug Resistant Tuberculosis (R01-AI099603)	▪ CDC/USAID/PEPFAR: Evaluation of an Enhanced Tuberculosis Infection Control Intervention in Healthcare Facilities in Vietnam and Thailand (EnTIC) (www.clinicaltrials.gov/ct2/show/NCT02073240). The study has been completed and data are expected in 2018. ▪ NIH: Protecting Households on Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx). Enrollment expected to begin 2Q2018. CDC is participating in protocol development, leading regional trainings, and providing technical assistance to the Philippines site. ▪ NIH: The Phase I/II trial "Evaluating the Pharmacokinetics, Tolerability, and Safety of Once-Weekly Rifapentine and Isoniazid in HIV-1-Infected and HIV-1-Uninfected Pregnant and Postpartum Women with Latent Tuberculosis Infection" continues enrollment. (www.clinicaltrials.gov/ct2/show/NCT02651259). ▪ NIH: Expecting results in 1Q2018 from the Phase III Clinical Trial of Ultra-Short-Course (one month) Rifapentine/Isoniazid for the Prevention of Active Tuberculosis in HIV-Infected Individuals with Latent Tuberculosis Infection www.clinicaltrials.gov/ct2/show/NCT01404312).
	▪ NIH: Development and Clinical Evaluation of a Lyophilized, Thermostable Tuberculosis Vaccine (HHSN272201400041C). ▪ DoD: Planning a randomized clinical trial of proof-of-concept of BCG immunization to prevent MTB infection in healthy adults.	▪ NIH: Cell Phone Video Directly Observed Therapy to Monitor Short Course LTBI Treatment (https://www.clinicaltrials.gov/ct2/show/NCT02641106) continues enrollment. ▪ CDC: Piloting with the Municipal Corporation of Greater Mumbai an innovative approach to TB prevention by establishing a local, city-wide air-borne infection (AIC) control unit to assess health facilities for infection control practices and implement AIC interventions to prevent transmission of MDR TB in Mumbai.
Years Three to Five Milestones	**Progress towards Years Three to Five Milestones**	
USAID will evaluate at least one intervention to prevent the spread of MDR-TB based on assessments of probable transmission routes.	▪ USAID: Planning several collaborative projects to characterize transmission of MDR-TB: Kyrgyzstan:- Study of nosocomial and community transmission of MDR-TB through combined analysis of whole genome sequencing data with spatial, epidemiological, 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. Moldova: Characterize TB transmission and identify and evaluate strategic new interventions for its reduction that could also be of value to global TB programs. The study will combine whole genome sequence analysis with spatial, epidemiological and laboratory information to: 1) characterize existing TB transmission patterns; 2) estimate the impact of TB interventions; and 3) better understand the relative contribution of acquired and transmitted resistance to the MDR TB epidemic in Moldova.	
USAID and CDC will evaluate at least one new TB treatment regimen to prevent TB and MDR-TB in adults and children.	▪ USAID: Weekly High-dose Isoniazid and Rifapentine® Periodic Prophylaxis for TB (WHIP$_3$TB) https://www.clinicaltrials.gov/ct2/show/NCT02980016) ▪ Will continue to evaluate two approaches to treatment of latent TB infection [3HP and periodic (p3HP) prevention treatment regimens in HIV co-infected individuals (adults and children)].	

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 One Milestones	**Year One Achievements (previously reported)**	**Additional Progress Made in Year Two**
NIH will continue to support large-scale sequencing efforts to map the global genetic diversity of drug resistance in Mtb to define genetic markers that can be included in diagnostic tests to improve the identification of MDR-TB and XDR-TB.	▪ NIH: TB portal at "Pathosystems Resource Integration System" (PATRIC) (https://www.legacy.patricbrc.org/portal/portal/patric/TB) ▪ NIH: Center of Excellence for Translational Research – Integrated discovery and development of innovative TB Diagnostics (U19-AI109755)	▪ NIH: The *Mycobacterium tuberculosis* portal at PATRIC is established as a public resource for researchers https://www.patricbrc.org/view/Taxonomy/1773. PATRIC currently hosts more than 9300 Mycobacterium *tuberculosis* genomes and associated metadata that are consistently annotated to support comparative genomic analysis. Annotation services also include prediction of microbial resistance phenotypes which can aid in the design of novel diagnostics to identify MDR- and XDR-TB (NCBI GenBank Bioproject Accession number PRJNA343736). PATRIC also hosts data from the Omics4TB Disease Progression Program (www.omics4tb.org/, U19AI106761). ▪ NIH: Continue support of a large-scale international *Mycobacterium tuberculosis* genome sequencing project at the Broad Institute Genomic Center for Infectious Diseases (U19AI110818). To date, the project has sequenced genomes of approximately 2,900 strains from South Africa, Uganda, Korea, Belarus, Moldova, Taiwan, Mali, India, Iran, Sweden, Romania, Peru, Thailand, Democratic Republic of Congo, Tanzania, Côte d'Ivoire, Georgia, and Azerbaijan, which includes contribution by the NIH supported IdEA consortium (https://www.iedea.org/, to understand genetic diversity and patterns of drug resistance. Genomic data and associated metadata are publicly available (See PATRIC). ▪ NIH: The TB Portals Program (https://tbportals.niaid.nih.gov) is a web-based, open-access repository of socioeconomic/geographic, clinical, laboratory, radiological and genomic data from drug-resistant TB patient cases to facilitate multi-national collaboration for data sharing and analysis. ▪ NIH: Genomic analysis of globally diverse Mycobacterium tuberculosis strains provides insights into the emergence and spread of multidrug resistance (Nature Genetics, http://www.nature.com/articles/ng.3767).
NIH will continue to support non-clinical and clinical studies to evaluate early-stage diagnostic tests and will educate partners about resources available to contribute to diagnostic development.	▪ NIH: RFA-AI-16-034: Partnerships for Countermeasures Against Select Pathogens (R01)	▪ NIH: Supported a prospective multicenter diagnostic accuracy study of the GeneXpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance (HHSN2722000900050C and K24AI104830) www.sciencedirect.com/science/article/pii/S1473309917306916. ▪ NIH: Supported a prospective diagnostic accuracy for an experimental new Xpert (Cepheid) cartridge for detection of resistance to Isoniazid, fluoroquinolones and aminoglycosides (HHSN2722000900050C, https://clinicaltrials.gov/ct2/show/NCT02251327) www.nejm.org/doi/full/10.1056/NEJMoa1614915.

		▪ NIH: Centers of Excellence in Translational Research (CETR) grant U19 AI109755 is developing sensitive diagnostic tests that are using minimally invasive and low volume samples to detect TB and drug resistance in adults and children. (JCM Accepted Manuscript Posted Online 5 January 2018 J. Clin. Microbiol. doi:10.1128/JCM.01652-17). A low cost, lateral flow cell is also being evaluated which has the potential to be used at the point of care. ▪ NIH: RFA-AI-17-042: Centers of Excellence for Translational Research (CETR) (U19 Clinical Trial Not Allowed)
USAID will initiate an evaluation of at least one promising (preferably point-of-care) TB and MDR-TB diagnostic tool in adults and children.	▪ USAID: Planning an evaluation of the Cepheid "OMNI" point of contact diagnostic platform in low resource settings.	▪ USAID: Evaluation of the Cepheid "OMNI" point of contact diagnostic platform in low resource settings is delayed pending release of the GeneXpert OMNI system by the manufacturing company (Cepheid).
CDC will initiate baseline assessments of the entire diagnostic and treatment cascade for MDR-TB to identify factors that affect the time between first patient contact, diagnosis, and treatment initiation.	▪ CDC: Led an assessment of diagnostic and treatment cascade for MDR-TB in Mumbai to identify factors affecting time between first patient contact, diagnosis and treatment initiation. CDC in collaboration with the Government of India has initiated interventions to address barriers to diagnosis and improve treatment initiation and adherence.	▪ CDC: Collaborative demonstration project with the national and local TB program, as well as with private providers in Mumbai, India. This project is to develop a multi-pronged approach to address barriers to diagnosis and treatment of MDR-TB, provide adherence counseling and assure efficient communication between public and private TB care providers to help identify TB patients. ▪ CDC: Supported early adoption of national guidelines for universal culture and drug susceptibility testing to fast track the diagnosis of drug resistance and modification of MDR-TB treatment based on the resistance patterns, thus ensuring appropriate and effective MDR-TB treatment. Early results demonstrate improved retention and potentially improved treatment outcomes.
Year Three Milestones	**Progress towards Years Three to Five Milestones**	
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.	▪ USAID: Evaluation of the Cepheid "OMNI" point of contact diagnostic platform in low resource settings is delayed pending release of the GeneXpert OMNI system by the manufacturing company (Cepheid).	
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.	▪ NIH: Continues to develop funding opportunities and support structures to facilitate the development and feasibility evaluation of the most promising diagnostic candidates. See also ongoing studies listed under Additional Progress made during Year Two.	
NIH will encourage and support evaluations of tests suitable for use in young children where diagnosis of TB is more difficult.	▪ NIH: Continues to encourage research on predictive genomic and biological markers facilitating diagnosis of TB in children and their integration into suitable platforms. See also ongoing studies listed under Progress Made in Year Two.	
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.	▪ CDC: Continues to support continuous quality improvement of Xpert testing in India by transferring and piloting an agency-developed proficiency testing program to TB centers to help assure presumptive RR/ MDR-TB patients receive accurate, reliable and timely diagnostic test results for early and appropriate TB treatment. Scale up of the proficiency testing program is supported in collaboration with the government of India and CDC partner stakeholders.	

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 One Milestones	**Year One Achievements (previously reported)**	**Additional Progress Made in Year Two**
NIH will continue to support biomedical research studies to identify novel biological markers and signatures to detect the likelihood of progression from infection to active TB.	▪ NIH: A blood RNA signature for tuberculosis disease risk: a prospective cohort study (Lancet, http://dx.doi.org/10.1016/S0140-6736(15)01316-1) ▪ NIH: Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis (Lancet Respir Med, http://www.sciencedirect.com/science/article/pii/S2213260016000485) ▪ NIH: PET CT Identifies Reactivation Risk in Cynomolgus Macaques with Latent M. tuberculosis (PLoS Pathogen, http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1005739)	▪ NIH: Grant R01 AI128765 is focused on validation of potential serum and plasma-based diagnostic biomarker signatures of pediatric TB for further use in diagnosis utilizing five well-defined and volunteer independent cohorts. ▪ NIH: Grant U01AI115940, "Inflammatory determinants of disease severity and treatment outcome in TB patients" continues to deliver insights into biological markers that may be indicative of a person's risk to develop active TB from latent Mycobacterium tuberculosis infection. ▪ Frontiers in immunology. 2017;8:968 (https://www.frontiersin.org/articles/10.3389/fimmu.2017.00968/full) ▪ Frontiers in immunology. 2017;8:542. https://www.frontiersin.org/articles/10.3389/fimmu.2017.00542/full ▪ Journal of immunology 2017:199(7):2440. http://www.jimmunol.org/content/199/7/2440
NIH, CDC, and USAID will expand clinical cohorts in TB endemic countries to study correlates of progression from TB infection to active disease.	▪ NIH: TBRU-N (https://www.niaid.nih.gov/research/tuberculosis-research-units-network). The CDC-supported Kenya Medical Research Institute (KEMRI) in Kisumu is a clinical site for a Tuberculosis Research Unit that is enrolling a clinical cohort to identify immune markers that predict progression from latent TB infection to active disease. ▪ NIH: RePORT network (http://reportcohort.org/) ▪ CDC: The TB Trials Consortium, in collaboration with NIH, is contributing specimens to a collaborative repository (CTB2 http://www.tbbiorepository.org/about-ctb2) to contribute to the search for markers of progression from latent TB infection to active TB disease and to monitor treatment response.	▪ NIH: RePORT network (http://reportcohort.org/) has expanded to include cohorts in India, Brazil, South Africa, China, Indonesia and the Philippines and are continuing their studies to identify correlates of risk and progression of latent infection to active disease. Common protocols for sample and data collection are being implemented in all countries. The RePORT cohorts collaborated in the following recent grant awards: R01AI123310- ▪ "IFN-**γ** independent inhibition of MTB growth in human macrophages"; R21AI134129 ▪ "The role of innate immunity in the acquisition of sterile protection against TB infection". ▪ NIH: Continues to contribute TB samples through its AIDS Clinical Trials Consortium (ACTG) to the collaborative CTB2 consortium (http://www.tbbiorepository.org/about-ctb2).
Year Three Milestones	**Progress towards Years Three to Five Milestones**	
NIH and CDC will support clinical studies to validate biologic correlates of disease activation.	▪ NIH: Continues to encourage and support identification of predictive and genomic biological markers in relevant epidemiological studies and facilitate evaluation of these markers for their suitability as prognostic tests. See also ongoing studies listed under Additional Progress Made in Year Two.	

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 One Milestones	**Year One Achievements (previously reported)**	**Additional Progress Made in Year Two**
NIH will discuss innovative and pharmacologically-based strategies for the development of new, shorter regimens with the research and product development community and will educate partners about resources available to contribute to drug development.	▪ NIH: Co-hosted two workshops on "Optimization of Oxazolidinones for Use in TB Drug Regimens" with the Stop TB Partnership's Working Group on New Drugs (http://www.newtbdrugs.org/) in July and December 2016. ▪ NIH: Poster presentation on clinical resources for TB at the June 21/23, 2016 TB Summit in London, and on preclinical R&D resources at the EMBO Conference on Tuberculosis in September 2016 in Paris. ▪ NIH: Intramural TB Research Initiative (NITBRI) held kick-off symposium on June 27, 2016, "New Approaches to Combating Tuberculosis. Leveraging NIH Intramural TB Research for the Global Effort." ▪ NIH: provided preclinical resources to the Lilly TB Drug Discovery Initiative to study the antiparasitic drug Nitazoxanide for use against MTB.	▪ NIH: Poster presentation describing NIH extramural preclinical resources for TB product development at the January 2017 Keystone Symposium on "New Developments in our Basic Understanding of Tuberculosis" (Vancouver, Canada), the April 2017 ASM Conference on "Tuberculosis: Past, Present and Future" (New York) and the June 2017 Gordon Conference on "New Approaches, New Chemical Entities and New Targets for Tuberculosis Drug" (Lucca, Italy). ▪ NIH: Continues to provide preclinical resources to the Lilly TB Drug Discovery Initiative to help accelerate discovery and development of new drugs to treat TB. NIH supported early studies of CPZEN-45, an inhalable nucleoside antibiotic, that is now entering advanced development https://www.genengnews.com/gen-news-highlights/idri-hisun-to-partner-in-developing-tb-candidate-cpzen-45/81254853. Other chemical entities are emerging from this initiative that had been supported by NIAID (Oxaboroles, Imidazopyridines and Spectinamides). ▪ NIH: Co-hosted a workshop with the Critical Path to TB Regimens (CPTRinitiative.org) in September 2017 on "Evolution of a data driven preclinical roadmap for novel TB regimens: Emphasis on animal models and pharmacometrics for selection of efficient, rational sequential TB Treatment Regimens." ▪ NIH: Workshop in September 2017 on "Molecular Mechanisms and Immune Consequences of Pathogen Reservoirs: Battling unseen enemies" – general workshop of interest to the TB community. ▪ NIH/FDA: Public Workshop in July 2017 on "Bacteriophage Therapy: Scientific and Regulatory Issues" (https://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm544294.htm) ▪ NIH/FDA: The NIH Intramural TB Research Initiative (NITBRI) and FDA co-hosted in April 2017 a "World TB Day Mini-Symposium" in Washington, DC. ▪ NIH: Continues to co-chair the StopTB Partnership's Working Group on new Drugs (http://www.newtbdrugs.org/core-group) and presented the updated global TB drug development pipeline in July, 2017 at the annual meeting of the International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis (INTERTB) in London, UK. ▪ NIH: The Vaccine Research Center (VRC, https://www.niaid.nih.gov/about/vrc) continues studies into the effect of TB Therapy on immune responses against Mycobacterium tuberculosis. (https://www.ncbi.nlm.nih.gov/pubmed/27367521).

USAID will initiate an assessment of new methods or packages of care to enhance treatment success.	▪ USAID: USAID has developed and will soon pilot an ancillary care package to identify key services and interventions needed to support MDR-TB patients through the diagnosis and treatment processes. During the first year of the NAP, USAID undertook a survey of patients, providers and technical partners to identify the key barriers to successful MDR-TB diagnosis and treatment. The results of this survey were used to draft a simple tool that will allow providers to assess the needs of specific patients and prioritize support activities that best fit those needs, with the ultimate aim of improving treatment outcomes. In Year Two, this tool will be piloted in four NAP countries.	▪ USAID has been supporting the development and introduction of package of care that will contribute to the improvement in patient adherence to MDR-TB treatment. ▪ During the previous reporting period, USAID drafted a list of comprehensive ancillary services based on patient needs and a survey of the literature; developed a brief Practical Guide to Delivering Essential Supportive Care to Patients with Drug-resistant Tuberculosis and accompanying tools to ease implementation; and identified four pilot countries (China, Pakistan, South Africa, and Ukraine) in which to test the approach and materials and evaluate results. The pilot efforts will inform further refinement of the package of patient services and the guidance documents with the goal of scaling up the approach in 2018, focusing on 10 high-priority countries. ▪ ***Achievement***: During this reporting period the four countries participating in the pilot project started implementing activities. China has already completed the enrollment with 240 patients in the intervention arm and 270 patients in control group. China is expecting to finalize data analysis by May 2018. The South African pilot project has enrolled 85 patients and is on track for completing the enrollment by the end of December. Ukraine has so far enrolled 80 patients and is expect to complete enrollment during the first quarter of 2018. Pakistan has started enrollment in October 2017.
USAID and CDC will continue to support ongoing studies in adults to assess shorter MDR-TB regimens using existing TB drugs.	▪ CDC, USAID: Provided technical assistance to initiate a clinical protocol assessing feasibility, effectiveness, and safety of the newly recommended 9-month treatment regimen for MDR-TB in the National TB Control Program of the Philippines. ▪ CDC: Leading a multi-site clinical trial to assess the bactericidal activity of specific anti-TB drugs to guide treatment decisions when susceptibility test results differ between closely related drugs, which occurs in a large fraction of patients. This study should inform clinical and laboratory practice and guidelines and may expand options for treatment for certain patients. ▪ NIH: Efficacy and Safety of Levofloxacin for the Treatment of MDR-TB (Opti-Q) (https://www.clinicaltrials.gov/ct2/show/NCT01918397) ▪ NIH: Trial of High-Dose Rifampin in Patients With TB (HIRIF) (https://www.clinicaltrials.gov/ct2/show/NCT01408914)	▪ CDC/USAID: Based on a 2015-2016 pilot study to assess the feasibility, effectiveness, and safety of the newly recommended 9-month treatment regimen for MDR-TB in the National TB Control Program of the Philippines, the National TB Control program is now implementing a national scale up plan to introduce the standard short treatment regimen (SSTR) for all qualifying patients. ▪ USAID: Contributed to Stage 1 of the first randomized controlled trial to test the efficacy, safety and economic impact of a standardized shorter MDR-TB regimen (STREAM). Preliminary data were made public in 2017 and suggest that efficacy of the nine-month regimen will be closely related to the regimen recommended in the 2011 WHO guidelines, which has a duration of 20–24 months. (www.theunion.org/news-centre/news/stream-clinical-trial-results-provide-vital-insight-into-nine-month-treatment-regimen-for-multidrug-resistant-tuberculosis). Final Stage 1 data are expected in 2018. ▪ NIH: Phase II trial on the "Efficacy and Safety of Levofloxacin for the Treatment of MDR-TB (Opti-Q)" (https://www.clinicaltrials.gov/ct2/show/NCT01918397) has been completed and is in data analysis. ▪ NIH: Phase II Trial of "High-Dose Rifampin in Patients with TB (HIRIF)" (https://www.clinicaltrials.gov/ct2/show/NCT01408914) has been completed. Data are being published (Antimicrob Agents Chemother. 2017 Jul 25;61(8). pii: e00038-17. doi: 10.1128/AAC.00038-17. Print 2017 Aug.)

Year Three Milestones	Progress towards Years Three to Five Milestones
USAID will evaluate pilots of innovative strategies to improve treatment outcomes in at least five countries.	▪ USAID: 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 in 2018 to all ten countries included in the National Action Plan. Findings from these pilot studies will inform implementation of the Package of Care in the remaining six countries.
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.	▪ NIH: Supporting a Phase 1 trial to study the "Pharmacokinetics and safety of PA-824 in Subjects with mild, moderate and sever hepatic impairment compared with matched non-hepatically impaired subjects" (https://clinicaltrials.gov/ct2/show/NCT02422524). (Note: While PA-824 (Pretomanid) is not an approved drug, it is being studied as part of a new three-drug regimen in Phase III clinical trials with promising preliminary results (https://clinicaltrials.gov/ct2/show/NCT02333799, http://www.croiconference.org/sessions/nix-tb-trial-pretomanid-bedaquiline-and-linezolid-treat-xdr-tb).)
NIH will contribute to the development of pediatric formulations for new and existing TB drugs.	▪ NIH: Accepting applications under the SBIR Phase II program to continue work on the development of pediatric formulations. Results from SBIR Phase I awardees have been made public: https://globenewswire.com/news-release/2017/08/22/1091157/0/en/CURE-Pharmaceutical-Subsidiary-Oak-Therapeutics-Completes-Critical-Milestone-in-Phase-1-of-NIH-Grant-to-Develop-Oral-Dissolvable-Strip-for-Tuberculosis.html, http://lunainc.com/union-world-conference-lung-health/. ▪ NIH: Issued PAR-17-193: Development of Appropriate Pediatric Formulations and Pediatric Drug Delivery Systems (R01).

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

Year One Milestones	Year One Achievements (previously reported)	Additional Progress Made in Year Two
USAID will support the evaluation of new and shorter TB regimens containing novel anti-TB drugs in adults.	▪ USAID: Co-sponsoring "A Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 Plus Linezolid in Subjects With Drug Resistant Pulmonary Tuberculosis (NiX-TB, https://clinicaltrials.gov/ct2/show/NCT02333799) ▪ USAID is developing a package of care to support treatment adherence for MDR-TB patients: Several meetings held with Key stakeholders to inform the content of the package of care that will be evaluated Other U.S. Government supported ongoing or planned clinical trials/studies ▪ NIH: A Trial of the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, among Participants Taking Multidrug Treatment for Drug-Resistant Pulmonary Tuberculosis. (https://clinicaltrials.gov/show/NCT02583048). ▪ NIH: Evaluating the Pharmacokinetics, Safety, and Tolerability of Bedaquiline in HIV-Infected and HIV-Uninfected Infants, Children, and Adolescents With Multidrug-Resistant Tuberculosis (https://clinicaltrials.gov/ct2/show/NCT02906007) ▪ NIH: Planning a clinical trial to evaluate the Safety, Tolerability, and Initial Efficacy of Linezolid Combined with Delamanid and Optimized Background Therapy (OBT) for the Treatment of Multidrug Resistant Tuberculosis.	▪ USAID: Co-sponsored "Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 Plus Linezolid in Subjects with Drug Resistant Pulmonary Tuberculosis (NiX-TB, https://clinicaltrials.gov/ct2/show/NCT02333799) has ended recruitment. has officially ended for the Nix-TB trial. Preliminary results relapse-free cure 6 months after completion of the 6-month therapy for the first 45 patients with XDR-TB completing 6-month treatment and 6-month follow-up for relapse. Current cure rates for XDR-TB patients on prolonged therapy are only 16 percent. ▪ USAID: Contributing to Stage 2 of the first randomized controlled trial to test the efficacy, safety and economic impact of a standardized shorter MDR-TB regimen (STREAM, https://clinicaltrials.gov/ct2/show/NCT02409290). This trial will recruit patients in 10 countries. ▪ NIH: The 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" is expected to begin enrollment in 2Q2018 (https://clinicaltrials.gov/ct2/show/NCT02906007)

Years Three to Five Milestones	Progress towards Years Three to Five Milestones
NIH and CDC will support clinical trials to assess the safety and drug interactions of bedaquiline, delamanid, or both.	▪ See ongoing studies listed under Additional Progress Made in Year Two.
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.	▪ USAID: Collaborating with the TB Alliance on a Phase 2c trial to Evaluate the Efficacy, Safety and Tolerability of BPaMZ in Drug-Sensitive (DS-TB) Adult Patients and Drug-Resistant (DR-TB) Adult Patients (SimpliciTB, https://clinicaltrials.gov/ct2/show/NCT03338621). ▪ USAID: Collaborating with 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). ▪ USAID: Participating in the planning of a collaborative, public-private open label Phase 3 clinical trial to evaluate the Efficacy and Safety of a Combination regimen of Bedaquiline, Delamanid, Linezolid and Clofazimine in Multidrug resistant (MDR) patients with additional resistance to fluoroquinolones and/or aminoglycoside in South Africa and India (BEAT TB).
CDC and USAID will identify best practices for the use of new drugs in novel MDR-TB treatment regimens based on pharmacovigilance data.	▪ USAID: 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-Johnson and Johnson Bedaquiline Donation Program also prioritizes pharmacovigilance and 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 from 25 to 27 April 2017 in Bangkok. Thailand. Two more Workshops have been planned for the Spring of 2018 to cover the African Region (to be convened in South Africa) and the Eastern Europe/Central Asia Regions (to be convened in Kazakhstan and). The intended outcomes of these workshops are drug safety monitoring and management (aDSM) roadmaps, that are developed by each country 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 what technical assistant may be required by a country and to measure progress by the end of 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.
USAID and CDC will expand the evaluation of new drug regimens to treat children, including novel TB drugs for both TB and MDR-TB.	▪ CDC: The STEP-TB Project (Janssen, UNITAID/TB Alliance) is 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 aid in dose selection guidance for pediatric use. ▪ USAID: Under the STREAM trial, Janssen Pharmaceuticals is enrolling adolescents with MDR-TB.

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 Milestones	Year One Achievements (previously reported)	Additional Progress Made in Year Two
NIH will support novel therapeutic approaches for the treatment of TB, such as host-directed therapeutics (HDT).	▪ 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: 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 June 2017, presented a poster on "Host Directed Therapy for TB/HIV Co-Infection: Preclinical Studies and Early Clinical Plans at DAIDS" and a talk on "Preclinical Pathway to Host-Directed Therapy for TB/HIV Co-Infection" at a satellite workshop on "Strategic Discussion on Repurposing Drugs & Host Directed Therapies for TB".

	▪ 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) ▪ NIH: New chemical entities are entering preclinical studies through the NIH supported Lilly TB Drug Discovery Partnership (https://www.niaid.nih.gov/research/partnership-eli-lilly)	▪ 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 entity 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.
Years Three to Five Milestones	**Progress towards Years Three to Five Milestones**	
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.	▪ NIH: Continues its preclinical services to facilitate early stage evaluations of drug candidates for academic organizations and product developers. See also ongoing studies listed under Additional Progress Made in Year Two.	
NIH will increase collaborations with pharmaceutical and academic partners to broaden strategies for shortening treatment duration.	▪ NIH: Co-hosted a workshop with the Critical Path to TB Regimens (CPTRinitiative.org) in September 2017 on "Evolution of a data driven preclinical roadmap for novel TB regimens: Emphasis on animal models and pharmacometrics for selection of efficient, rational sequential TB Treatment Regimens".	

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.	▪ NIH: Researchers supported under U19-AI111143, Tri-Institutional TB Research Unit: Persistence and Latency developed a laboratory assay that detects viable but not culturable antibiotic tolerant Mycobacterium tuberculosis cells for eventual use as part of clinical trials (http://www.pnas.org/content/114/24/E4832.full.pdf)
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.	▪ USAID: The planned collaborative Phase 3 clinical trial to evaluate the Efficacy and Safety of a Combination regimen of Bedaquiline, Delamanid, Linezolid and Clofazimine in Multidrug resistant (MDR) patients with additional resistance to fluoroquinolones and/or aminoglycoside (BEAT TB) will include estimates of blood levels for all study drugs and their metabolites to help interpret safety and efficacy findings. ▪ USAID: 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) intends to optimize the dosing and duration of linezolid that was used in the NiX-TB regimen (https://clinicaltrials.gov/ct2/show/NCT02333799). The ZeNIX trial will include pharmacokinetics of six different dosing schedules of Linezolid in patients with drug sensitive TB.

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

Years One to Three Milestones	Year One Achievements (previously reported)	Additional Progress Made in Year Two
USAID will create an inventory (map) of potential sites and initiate needs-based procurement of equipment to prepare study sites.	▪ USAID has initiated discussion in South Africa to do identify new research sites for upcoming clinical trials for the treatment of MDR-TB.	▪ USAID: In discussions with the South African Ministry of health, the Eastern Cape, which has many MDR and XDR-TB patients but very poor cure rates, has been identified as benefiting from strengthening research capabilities and collaborations. The BEAT TB clinical trial will therefore be initiated at the Eastern Cape provinces in South Africa to increase 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.	▪ 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 NIH Supported Funding Opportunities: ▪ PAR-17-057 – Global Infectious Disease Research Training Program (D43) ▪ PAR-16-279 - Fogarty HIV Research Training Program for Low-and Middle-Income Country Institutions (D43) ▪ PAR-16-082 - International Bioethics Research Training Program (D43) ▪ PAR16-081 - International Research Ethics education and Curriculum Development Awards (R25) ▪ RFA-AI-16-082/083 – Revision Applications for U.S. South Africa Program for Collaborative Biomedical Research (various funding mechanisms)	▪ NIH: Funded one award under RFA-AI-16-082/083 – "Revision Applications for U.S. South Africa Program for Collaborative Biomedical Research" (various funding mechanisms) ▪ NIH: PAR-17-057 – Global Infectious Disease Research Training Program (D43) ▪ NIH: PAR-16-279 - Fogarty HIV Research Training Program for Low-and Middle-Income Country Institutions (D43) ▪ NIH: PAR16-081 - International Research Ethics education and Curriculum Development Awards (R25) ▪ NIH: PAR-17-057 - Global Infectious Disease Research Training Program (D43) ▪ NIH: PAR-17-001- Emerging Global Leader Award (K43) ▪ NIH: PAR-17-142 - International research in Infectious Diseases, Including AIDS (R01) ▪ NIH: PAR-17-474 – Reducing Stigma to Improve HIV/AIDS Prevention, Treatment and care in low and middle-Income Countries (R21) ▪ NIH: RFA-TW-17-001 – Health-Professional Education Partnership Initiative (HEPI) (R25 Clinical Trial Not Allowed) ▪ NIH: RFA-TW-18-001 – African Association for Health Professions Education and Research (R25 Clinical Trials Not Allowed)

	▪ 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	▪ USAID: Supported capacity building for operational research (OR) through the "TREAT TB" mechanism. In the Philippines, 16 participants from the national TB program and key partner organizations completed the first training module in May 2017. In Peru. 6 participants completed the OR course and prepared preliminary manuscripts for publication in peer-reviewed journals. Five abstracts were also accepted for presentation at the 48th Union World Conference on Lung Health. Course facilitators will continue to provide mentorship and guidance to course participants to finalize and publish their manuscripts. ▪ 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.
NIH will expand opportunities for funding of biomedical clinical research in TB-endemic countries.	▪ 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/)	▪ NIH: Continues to contribute to the expansion of the Regional, Observational TB Cohorts (RePORT Network) in high-burden TB countries to facilitate collaborative, clinical research (https://www.reportinternational.org/. The 6th RePORT India leadership meeting was held Feb 2-4, 2017, in Hyderabad, India. The 3rd RePORT International Symposium was held Sept 12-13, 2017, in Rio de Janeiro, Brazil. RePORT investigators continue their independent, in country-focused research studies. Cross consortium studies are active in India, Brazil and South Africa to assess the impact of diabetes on TB and studying biomarkers in children and persons with HIV/*M. tuberculosis* co-infection. ▪ NIH: Phase II of the H3 Africa Program (http://www.h3africa.org/ was published in 2016 (RFA-RM-16-016, Human heredity and Health in Africa (H3 Africa): Collaborative Centers (U54)) and awards made in 2017. Under the Collaborative African Genomics Network (CAfGEN), NIH continues to support projects to study host response to HIV/TB in pediatric populations. ▪ NIH, CDC, USAID, Department of State: Attended first ministerial conference on TB in Russia, presented (NIH) plenary talk on the importance of research for global TB elimination (http://www.ajtmh.org/content/journals/10.4269/ajtmh.17-0999).