NATIONAL ACTION PLAN FOR COMBATING MULTIDRUG-RESISTANT TUBERCULOSIS:
Six–Month Progress Report and Future Direction

INTRODUCTION

On December 22, 2015, the White House officially released a plan to address multidrug-resistant tuberculosis (MDR-TB) domestically and internationally and to advance research on this critical public health issue through a **National Action Plan for Combating MDR-TB** (hereafter referred to as the NAP). The release was followed by a launch event on January 7, 2016, which was open to the general public. The NAP, which will build on the World Health Organization's (WHO) END TB Strategy and the U.S. Government's (USG) domestic and global tuberculosis (TB) strategies, will contribute to the success of these existing strategies.

Since January 2016, the USG agencies charged with implementing the NAP have made progress toward achieving its three goals and corresponding objectives. During this short period of time, the urgency of addressing MDR-TB as a global public health emergency has grown and the international landscape for action has begun to shift. "In May 2016, the highly anticipated Review on AntiMicrobial Resistance (AMR) was released by Lord Jim O'Neill, Commercial Secretary to Her Majesty's Treasury in the UK and Chair of the AMR Review, setting a global blueprint for action, including specific recommendations to counter MDR-TB. Following on this report, AMR will be the priority health topic highlighted at the United Nation's General Assembly (UNGA) in September 2016. During Prime Minister Narendra Modi's visit to Washington, D.C., in early June 2016, he discussed the MDR-TB situation in India with President Obama. In both India and South Africa,

National TB Programs have begun to expand access to new diagnostic tools and treatments. Notably, both countries are mobilizing domestic resources that will contribute to the NAP milestones.

Improvement of MDR-TB diagnosis and treatment is a key objective of the NAP. On May 12, 2016, WHO announced a new policy on shortened drug regimens for MDR-TB that will greatly reduce the length of time patients must stay on treatment. The USG supported the development of this policy, and introduction of these regimens is a key milestone in the NAP. Affected countries are starting to adopt these regimens with technical assistance from USG agencies. These new regimens are considerably less expensive than the current standard 24-month course of treatment. On the same day, WHO announced a new diagnostic tool that will identify resistance to second-line drugs in 24 to 48 hours, another promising development. And on July 7, 2016, *The Lancet* published results from the first multi-country survey on resistance to fluoroquinolones and pyrazinamide, an important contribution to the evidence base for action. Additionally, basic and applied TB research previously supported by the USG has laid the foundation for many promising new diagnostic, prevention and therapeutic tools that are now becoming available for testing in humans.

The US Centers for Disease Control and Prevention (CDC), the United States Agency for International Development (USAID) and the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes for Health (NIH)

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In 2014, the most recent year for which complete data are available, an estimated 480,000 people around the world developed MDR-TB; more than half of them live in India, China and the Russian Federation. A total of 111,000 people started second-line treatment for MDR-TB globally, an increase of 14% from 2013. Only 50% of MDR-TB patients who received treatment were successfully treated, demonstrating the need for improved quality of treatment programs and more timely diagnosis.

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have worked together over the past six months to coordinate plans for achieving the objectives of the NAP, including agreement on roles and responsibilities and pathways for implementation of the NAP, and sharing lessons learned on NAP activities. In May 2016, the highly anticipated Review on AntiMicrobial Resistance (AMR) was released by Lord Jim O'Neill, Commercial Secretary to Her Majesty's Treasury in the UK and Chair of the AMR Review, setting a global blueprint for action, including specific recommendations to counter MDR-TB. In addition, USG agencies are also leveraging the investments of the Global Fund and domestic resources by providing technical assistance aimed at ensuring access to high-quality MDR-TB diagnosis, treatment and prevention services, and utilizing existing biomedical research funding mechanisms to advance product development and to drive innovation. The interagency group has met several times in person and maintains communication through monthly coordination calls and email updates. In May 2016, the Federal TB Task Force had an in-person meeting focused on research to highlight existing work and coordinate future activities that will contribute to achieving the NAP goals. One key result of this collaboration has been finalization of the monitoring and evaluation framework and initiation of baseline data collection for milestones. This six-month progress report summarizes activities undertaken in support of the NAP from January through June 2016 by Goal and Objective.

The scope and objectives of each Goal are aligned to current needs and also take into account the resources, capabilities, and expertise of each agency involved in achieving the objectives. As such, each Goal varies in scope, approach, and timeline for implementation of major milestones. Across all goals, Year One Milestones were more narrowly drawn to reflect activities that could be achieved with currently available resources.

"We need to see a global commitment and collaboration across sectors. We need to enhance detection capabilities, improve diagnostics, and develop less toxic drugs. And we need to make sure these efforts get the funding they need. This Action Plan will help get all these gears in motion."

– The Honorable Eliot L. Engel,
  US Representative from New York State
  and Chair, Congressional TB Caucus

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

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

CDC is upgrading surveillance systems for tracking drug-resistant TB (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 burden, targeting of resources, and linkages to care and

contact investigations. CDC is working with state TB programs to standardize reporting for DR-TB cases, improve methods for transitioning to next generation sequencing for molecular detection, and refining methods for culture-based drug susceptibility testing.

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

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

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

Completion of treatment for those with MDR-TB is challenging on many levels. The activities 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. These include the development and implementation of strategies to ensure the day-to-day support MDR-TB patients require in order to successfully complete the long, and often debilitating, treatment regimen, as well as strengthening the data collection and analysis needed to monitor treatment completion. CDC is also currently working with the Department of Health and Human Services Supply Service Center (HHS SSC) to create and manage a mini-stockpile of TB drugs to have on hand in the event of manufacturer shortages that could result in interruption of treatment. The stockpile is composed of a small supply of drugs that would be necessary to protect TB patients and communities in the event of a time-limited manufacturing shortage. Additionally, the CDC's Division of Tuberculosis Elimination (DTBE) is evaluating a U.S.-Mexico case definition for the national TB surveillance system that can be measured using current performance indicators, including Completion of Therapy. Finally, state and local TB programs continue to be responsible for caring for uninsured TB patients until they complete TB therapy for drug-susceptible and drug-resistant TB. Exploring options for providing care for persons with MDR-TB or extensively drug-resistant TB (XDR-TB) who do not have a medical home, remains an unmet need.

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

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

Since the launch of the NAP, USAID and CDC have developed a framework for assessing TB laboratory and diagnostic networks 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 that will be undertaken in contribution to the NAP. Mapping of diagnostic networks is underway, and USG agencies are 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. Continuous quality improvement of diagnostic networks is underway, and CDC is leading the development of tools to introduce Continuous Quality Improvement (CQI) for GeneXpert networks using diagnostic connectivity solutions. Through its flagship technical assistance project, USAID is supporting the piloting and scale up of shortened MDR-TB regimens and has released guidance to missions and projects on how to move forward. For example, USAID senior technical advisers and flagship technical assistance partners have already held a series of webinars and in-person briefings for mission and project staff on preparation for the introduction of these shorter regimens. USAID and CDC are also working with National TB Programs (NTPs) to strengthen surveillance, including support for in-depth

epidemiological assessments undertaken to identify strengths and weaknesses in TB surveillance, as well as specific studies aimed at quantifying under- and mis-reporting of TB.

Over the last six months, USAID has worked through implementing partners to lay the groundwork for achievement of this objective through development and finalization of tools such as the Expanded Cohort Review, which is critical for monitoring initiation and continuation of treatment and quality of care, and thus, interrupting ongoing transmission of MDR-TB. USAID and CDC are also strategically programming FY 2017 activities under existing technical assistance mechanisms to ensure that key milestones related to infection control and health care worker surveillance are undertaken in collaboration with NTPs. USAID and CDC are working with NTPs to assess, implement and evaluate infection control interventions in health facilities using standardized approaches that include administrative, environmental and personal protective measures to protect the health care workforce and prevent the spread of TB in health care settings. These activities involve training, supportive supervision, and monitoring infection rates among health care workers through routine screening. USAID and CDC will be evaluating these activities to identify the best models for scaling up infection control interventions, as well as identifying lessons learned from implementation of best practices for infection control in other countries. Finally, both agencies are facilitating the transfer of knowledge and competencies to NAP countries. With USAID and CDC support, the progress of implementation of these innovative approaches is being consolidated with development of guidelines and operational implementation in the NAP targeted countries. Building on this programming, the USG will continue to advocate for the interventions needed to accomplish the objective of preventing the ongoing transmission of MDR-TB.

Under the leadership of USAID, the USG will continue to support implementation and scale up of priority interventions to achieve Goal 2. The USG is already working with implementing partners to position NAP countries to adopt shortened treatment regimens for MDR-TB and anticipate major investment in this technical area in the coming six months leading up to the NAP annual report. Likewise, 38 countries now have access to bedaquiline (BDQ) with USAID support through a partnership with Janssen Pharmaceuticals (of parent company, Johnson & Johnson), with additional countries expected to finalize orders in the coming months.

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

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

NIH maintains a broad TB research portfolio which currently includes more than 500 projects, including critical research on the human immune response to TB, which will lead to a better understanding of the progression from TB infection to TB disease. This type of research can be leveraged for the design of new vaccines and other prevention strategies. NIH also facilitates research with preclinical and clinical services, research tools and technologies that are available to investigators throughout the world. The agency has also hosted scientific meetings in support of vaccine development and recently released four new relevant funding opportunities. Additionally, USG agencies are engaged in the preparation and conduct of research to inform

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prevention, treatment, and management of TB. These include clinical trials to determine the feasibility and impact of a three-month regimen to prevent TB among exposed individuals (USAID) and to evaluate the potential use of the Bacillus Calmette–Guérin (BCG) vaccine in healthcare workers who travel to areas with a high burden of MDR-TB, as well as assessments of new case finding (NIH) and infection control (CDC) strategies to interrupt transmission within communities and health facilities.

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

NIH's current portfolio includes a number of projects aimed at developing and evaluating tools to aid TB diagnosis, including tests to characterize

the genetic diversity, evolution and patterns of drug resistance of the pathogen, and research on biomarkers that can facilitate TB diagnosis and monitoring for confirmed TB patients. NIH also supports testing of the clinical performance and feasibility of new TB diagnostic tests and recently announced a related funding opportunity under its Partnership Program. In March 2016, an international team partially supported by NIH published new data in *The Lancet*, describing biological markers in the blood of individuals with latent TB infection, an important accomplishment that may provide better ways to predict who is at risk of progressing to TB disease. CDC is working with the Government of India's Central TB Program to improve diagnosis and management of MDR-TB in Mumbai, while USAID is planning an evaluation of the Cepheid "OMNI" tool, a new point of care diagnostic tool that can be used in very low-resource settings.

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

Since the launch of the NAP, USG agencies continue to support numerous ongoing activities aimed at improving treatment options for all forms of TB. These activities fall under three main areas: 1) improving the use of existing TB drugs, 2) enhancing knowledge on the use of newly developed drugs such as BDQ and delamanid (DLM), and 3) developing novel drugs and shorter regimens to treat DR-TB and improve the selection of drug candidates for clinical trials. For example, CDC and USAID provided technical assistance to the Philippines' NTP to develop a clinical protocol to assess the feasibility, effectiveness, and safety of the newly recommended nine month treatment regimen for MDR-TB. In addition, NIH is now enrolling its first formal study to evaluate the safety, tolerability, and pharmacokinetics of BDQ and DLM, alone and in combination, among participants with or without HIV co-infection, who are also taking multidrug treatment for MDR-TB. NIH is currently planning a clinical trial to evaluate the safety, tolerability and initial efficacy of linezolid combined with DLM and optimized background therapy for the treatment of MDR-TB. NIH also continues to collaborate with partners engaged in global TB drug discovery efforts, such as the Stop TB New Drug Working Group (funded by USAID), the Lilly TB Drug Discovery Initiative, and the Bill and Melinda Gates Foundation's Drug Accelerator Program. And finally, USAID is supporting studies in several countries to evaluate the efficacy and safety of shorter regimens containing novel drugs for the treatment of MDR-TB and XDR-TB.

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

USG agencies are making progress on this objective through a combination of ongoing and newly planned activities. For example, USAID is creating an inventory of potential research sites in TB-endemic countries to support future needs-based procurement of equipment that is necessary to conduct TB research. NIH continues to support research capacity building in countries with high TB burden through collaboration and partnership with local scientists and universities, as well as bilateral programs with governments of these countries. The NIH Global Infectious Disease Training program is being leveraged to enhance TB research and includes training in grant writing, financial administration, bio-ethics and research methods. CDC is working with the Kenya Medical Research Institute to further research in the areas of pediatric TB and implementation of new TB diagnostics, as well as ongoing capacity building for clinical trials.

The USG, primarily through its lead biomedical research agency, NIH, will continue to support basic, translational, and clinical research to develop and evaluate new and more effective TB drugs, vaccines, and diagnostics. These efforts will engage multiple stakeholders, including strategic interactions across the USG and collaborations with other funders of biomedical research, relevant public/private partnerships and industry partners. The USG will build on its existing programs and apply available resources to advance the biomedical research goals and objectives of the NAP.

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CONCLUSION

Since its release in December 2015, the NAP has provided the global TB community and USG agencies with the opportunity to strengthen use of existing projects and platforms, better coordinate USG efforts to address MDR-TB and examine new strategies to accelerate progress. In the first six months, the important WHO policy changes and commitments to improve NTPs represent great promise for achievement of the goals and objectives of the NAP. The USG agencies implementing the NAP will continue working together to move priority activities forward over the next six months.

The evolving environment includes promising new tools, yet there is a need for even more innovation, particularly for point-of-care diagnosis of MDR-TB. USG agencies will address these challenges on two fronts – through accelerating implementation and scale up of existing tools and supporting the research needed to generate improved diagnosis and treatment options. The first annual report for the NAP will be released on World TB Day, March 24, 2017. This report will include a summary of milestones achieved under each goal.

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