NATIONAL ACTION PLAN FOR COMBATING MULTIDRUG-RESISTANT TUBERCULOSIS

Vision: The United States will work domestically and internationally to contribute to the prevention, detection, and control of multidrug-resistant tuberculosis in an effort to avert tuberculosis-associated morbidity and mortality and support a shared global vision of a world free of tuberculosis.

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Executive Summary

Tuberculosis (TB) kills almost 30,000 people each week. The disease is caused by *Mycobacterium tuberculosis (Mtb)*, which is transmitted through the air from person to person. Currently, more than two billion people, nearly one-third of the world's population, are estimated to be infected with *Mtb* (latent TB) and are at risk of developing the disease. TB is curable, but inappropriate treatment can lead to multidrug-resistant TB (MDR-TB), which is resistant to the two most effective anti-TB drugs, and extensively drug-resistant TB (XDR-TB), which is resistant to many anti-TB drugs. This year alone, more than 480,000 people will develop MDR-TB (including XDR-TB).[1] Fewer than 20 percent of individuals with MDR-TB access treatment; of that small fraction, fewer than half are cured, due to health systems that are unable to appropriately diagnose and treat the disease.[2] If left unchecked, MDR-TB could erase decades of progress in global TB control, much of it achieved with U.S. leadership and support. Although the vast majority of individuals with TB and MDR-TB live outside the United States, it is critical that the Nation maintain and expand its global efforts to fight the disease, to save the lives of those afflicted with TB, and to prevent the spread of MDR-TB both in the United States and around the world. An MDR-TB outbreak in the United States could have serious consequences due to the costs associated with treating resistant TB. In the United States, the cost to treat and care for a patient with TB averages $17,000 for drug-susceptible TB, $150,000 for MDR-TB, and $482,000 for XDR-TB.[3] An increase in the number of patients with MDR-TB or XDR-TB could have a dramatic financial impact on State and local health-care systems.

Action taken now, while it is still possible to reverse the development and transmission of MDR-TB, will improve health and prosperity around the world. It will also ensure that the health and security benefits derived from decades of strategic U.S. investments in global health are maintained and continue to grow.

This *National Action Plan for Combating Multidrug-Resistant Tuberculosis* (hereafter referred to as the *National Action Plan*) identifies a set of targeted interventions that address the core domestic and global challenges posed by MDR-TB and XDR-TB. The recommended interventions represent the U.S. Government's contributions to reversing the worldwide spread of MDR-TB and should inform policy-development processes around the world. The *National Action Plan* is an effort to articulate a comprehensive strategy, mobilize political will, and spur additional financial and in-kind commitments from bilateral and multilateral donor partners, the private sector, and the governments of all affected countries.

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

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

Implementation of the *National Action Plan* will focus U.S. Government and partner efforts, to the extent permitted by law, on an ambitious set of targets by applying new and existing scientific and technological evidence and tools, and the expertise and experience gained from decades of fighting TB in the United States and elsewhere. Preventing the development of MDR-TB is paramount to this effort. The *National Action Plan*

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[1] *World Health Organization Global Tuberculosis Report 2015*: http://www.who.int/tb/publications/global_report/en/

[2] Ibid.

[3] CDC Factsheet on Tuberculosis: http://www.cdc.gov/tb/publications/infographic/pdf/take-on-tuberculosis-infographic.pdf updated to 2014 dollars from *Treatment Practices, Outcomes, and Costs of Multidrug-Resistant and Extensively drug-Resistant Tuberculosis, United States, 2005–2007,* S. M. Marks, et al., *Emerging Infectious Disease Journal* (2014)

builds on existing U.S. Government efforts to support the appropriate treatment of more than 16 million TB patients to prevent development of MDR-TB by achieving and maintaining a 90 percent TB treatment success rate.[4] In addition to increased MDR-TB prevention efforts, the *National Action Plan* proposes increasing the number of individuals initiating MDR-TB treatment in the 10 countries with the highest MDR-TB burden.[5] 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 MDR-TB, 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. Investments in research and development will contribute to improved treatment outcomes for individuals with MDR-TB through new tools that are easy to implement in existing health systems, better use of existing and newly licensed TB drugs, an enhanced drug-development pipeline, increased availability of rapid assays for TB diagnosis and drug-susceptibility testing, and improved disease surveillance. These actions will contribute to the prevention of further resistance to TB drugs and significantly reduce the global spread of MDR-TB.

The *National Action Plan for Combating Multidrug-Resistant Tuberculosis* is not intended to be a budget or commitment document. All activities included in the *National Action Plan* are subject to budgetary constraints and other approvals, including the weighing of priorities and available resources by the Administration in formulating its annual budget and by Congress in legislating appropriations.

[4] *United States Government Global Tuberculosis Strategy 2015–2019*: https://www.usaid.gov/sites/default/files/documents/1864/Reach-Cure-Prevent-2015-2019-TBStrategy.pdf

[5] Ibid.

Introduction

The emergence and spread of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) pose a significant global threat to health, economic development, and national security, undermining the significant progress made globally and domestically to achieve a world free of tuberculosis (TB).

Background

TB is among the most lethal infectious diseases in the world, killing one person every 3 minutes[6] (Box 1). TB disproportionately affects the poor, who are unlikely to have adequate nutrition and access to health care. It is also a danger to people with compromised immune systems due to human immunodeficiency virus (HIV), diabetes, or other conditions. The impact of the disease on individuals and families is often economically devastating. An average TB patient can lose up to 4 months of work and 30 percent of their annual income. The toll of TB on the global economy is estimated at $12 billion per year.[7] According to World Bank analyses, countries most affected by TB lose 4 to 7 percent of gross domestic product due to TB-related decreases in productivity.[8] Thus, combating TB will contribute to a strong and productive global workforce and to the U.S. Government's commitment to help end extreme poverty by 2030.[9]

Since 1993, when the World Health Organization (WHO) declared the TB epidemic a global health emergency, a renewed international commitment to expand access to care has reduced the incidence and prevalence of the disease. Intensified efforts to detect and treat TB have led to a nearly 50 percent decrease in global TB deaths, amounting to nearly 45 million lives saved in the last 15 years alone.[10] In the United States, TB diagnoses have declined annually over the past 20 years, falling below 10,000 for the first time in 2012.[11] This dramatic progress could, however, easily be eroded or reversed by the further development and spread of MDR-TB and XDR-TB.

Box 1: Health and Economic Impact of TB and MDR-TB

Over time, TB has caused more deaths worldwide than any other single infectious disease, and today is a leading cause of deaths by an infectious disease worldwide. Nearly one-third of the world's population is believed to be at risk of developing the disease as a consequence of being infected with *Mycobacterium tuberculosis* (*Mtb*), the causative agent of TB.[12]

Health Impact:

- Each year, about 9 million people develop active TB and 1.5 million die of the disease; 4,100 people die of TB every day.[13]
- TB is among the most frequent causes of death in females aged 15 to 44 and is responsible for one-third of all HIV-related deaths.[14]

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[6] *World Health Organization Global Tuberculosis Report 2015*: http://www.who.int/tb/publications/global_report/en/

[7] *The Economic Impacts of Tuberculosis*; World Health Organization Stop TB Initiative (2000): http://www.stoptb.org/assets/documents/events/meetings/amsterdam_conference/ahlburg.pdf

[8] *Health, Nutrition, and Population Development Goals: Measuring Progress Using the Poverty Reduction Strategy Framework*, World Bank (2002): http://web.worldbank.org/archive/website01213/WEB/IMAGES/MEASUREP.PDF

[9] *Ending Extreme Poverty by 2030*, USAID (2015): https://www.usaid.gov/endextremepoverty

[10] *World Health Organization Global Tuberculosis Report 2015*: http://www.who.int/tb/publications/global_report/en/

[11] *Reported Tuberculosis in the United States*, CDC (2014): http://www.cdc.gov/tb/statistics/reports/2014/default.htm

[12] *World Health Organization Global Tuberculosis Report 2015*: http://www.who.int/tb/publications/global_report/en/

[13] Ibid.

[14] Ibid.

- The risk of developing TB disease increases when individuals have other underlying health issues, such as HIV, diabetes, or malnourishment.[15]
- TB is the most common presenting illness among people living with HIV and the major cause of HIV-related death.[16]
- Although TB typically affects young adults in their most productive years, an estimated 550,000 children become ill with TB and 80,000 children die of TB annually.[17]
- Approximately 480,000 individuals develop MDR-TB each year.[18]
- Only about 20 percent of those with MDR-TB are diagnosed and appropriately treated and only 10 percent of those patients are successfully treated, leaving others to transmit the disease to others and probably die.[19]

Economic Impact:

- The economic impact of TB can devastate individuals and their families, many of whom are already living on the edge of poverty. The average TB patient can lose up to 4 months of work and up to 30 percent of his or her annual income.[20, 21]
- The toll of TB on the global economy is estimated to be $12 billion each year.[22, 23]
- In high-burden countries, TB is estimated to decrease gross domestic product by 4 to 7 percent.[24, 25]
- In the United States, it costs about $17,000 to treat a patient with drug-susceptible TB, $150,000 to treat a single patient with MDR-TB, and $482,000 to treat a single patient with XDR-TB.[26]
- According to projections from the United Kingdom's All Party Parliamentary Group on Global TB, 75 million people will lose their lives to MDR-TB over the next 35 years, and by 2050, this airborne infection could cost the global economy $16.7 trillion—the equivalent of the entire current economic output of the European Union.[27,]

Challenge

The impacts of TB are magnified by under-resourced health systems that are unable to ensure proper diagnosis and treatment of all forms of TB, whether drug-susceptible or drug-resistant. Inadequate treatment of TB is not only harmful to patients who, as a consequence, are likely to become severely ill or die of the disease, but also

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[15] Ibid.

[16] Ibid.

[17] Ibid.

[18] Ibid.

[19] Ibid.

[20] *The Economic Impacts of Tuberculosis*; World Health Organization Stop TB Initiative (2000): http://www.stoptb.org/assets/documents/events/meetings/amsterdam_conference/ahlburg.pdf

[21] *Health, Nutrition, and Population Development Goals: Measuring Progress Using the Poverty Reduction Strategy Framework*, World Bank (2002): http://web.worldbank.org/archive/website01213/WEB/IMAGES/MEASUREP.PDF

[22] *The Economic Impacts of Tuberculosis*; World Health Organization Stop TB Initiative (2000): http://www.stoptb.org/assets/documents/events/meetings/amsterdam_conference/ahlburg.pdf

[23] *Health, Nutrition, and Population Development Goals: Measuring Progress Using the Poverty Reduction Strategy Framework*, World Bank (2002): http://web.worldbank.org/archive/website01213/WEB/IMAGES/MEASUREP.PDF

[24] *The Economic Impacts of Tuberculosis*; World Health Organization Stop TB Initiative (2000): http://www.stoptb.org/assets/documents/events/meetings/amsterdam_conference/ahlburg.pdf

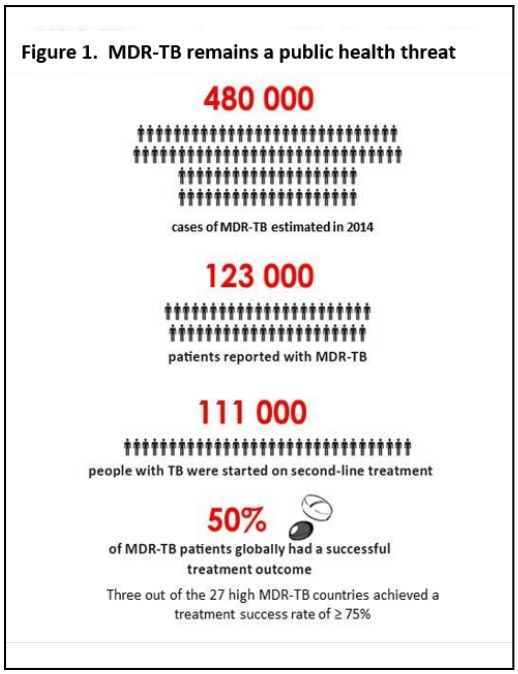
[25] *Health, Nutrition, and Population Development Goals: Measuring Progress Using the Poverty Reduction Strategy Framework*, World Bank (2002): http://web.worldbank.org/archive/website01213/WEB/IMAGES/MEASUREP.PDF

[26] CDC Factsheet on Tuberculosis: http://www.cdc.gov/tb/publications/infographic/pdf/take-on-tuberculosis-infographic.pdf updated to 2014 dollars from *Treatment Practices, Outcomes, and Costs of Multidrug-Resistant and Extensively drug-Resistant Tuberculosis, United States, 2005–2007,* S. M. Marks, et al., *Emerging Infectious Disease Journal* (2014)

[27] *The Price of a Pandemic: Counting the Cost of MDR-TB,* All Party Parliamentary Group of Tuberculosis: http://www.pdpfundersgroup.org/ewExternalFiles/APPG%20MDR-TB%20Report%20-%20Final%20Version.pdf

dangerous for the community; one person with active TB may infect 10 to 15 other persons each year.[28] Each patient ineffectively treated for TB provides a new opportunity for resistant strains of *Mtb* to multiply and overwhelm *Mtb* strains that are susceptible to antibiotics. Individuals exposed to these patients are at increased risk for infection with the drug-resistant forms of *Mtb*. If left unchecked, MDR-TB could erase decades of progress in global TB control and undermine long-term efforts to eliminate TB internationally and in the United States.

The identification and effective treatment of all individuals with active TB is the cornerstone of TB prevention, control, and eventual elimination. Treatment of drug-susceptible TB requires a 6-month, four-drug regimen; the disease is curable and relatively inexpensive to treat.[29] MDR-TB treatment is more complex and expensive. Regimens are not only less effective than treatment regimens for drug-susceptible TB, but are also more toxic (leading to grave potential side effects, such as deafness and liver damage) and of longer duration (often in excess of 2 years).[30] Many patients find it difficult to adhere to treatment that causes such severe physical side effects. Drug resistance is most likely to occur when patients do not complete a full course of treatment, or when health-care providers prescribe an incorrect regimen or miscalculate the length of therapy. It may also occur when drugs are of poor quality or not consistently available.



Only about two-thirds of all patients with TB are diagnosed and reported to national TB programs annually.[31] In 2013, of the estimated 480,000 individuals with MDR-TB, only 136,000 were properly diagnosed, 97,000 were started on therapy, and 47,000 were successfully treated (Figure 1). In addition, more than 100 countries have reported at least one individual with XDR-TB, which is resistant to all or nearly all first- and second-line TB drugs.[32] In many countries, XDR-TB is often incurable. Like all types of TB, XDR-TB is an airborne disease that spreads to others through coughing, sneezing, or talking. The spread of all forms of TB is exacerbated by poor infection-control practices in health-care facilities that put patients, visitors, and health-care workers at increased risk. Disease transmission is also facilitated by global travel, which can lead to the rapid dissemination of pathogens throughout the world.

The global challenge of eliminating TB in all its forms can be overcome with increased investments in innovative health technologies and patient-centered approaches to care; broader involvement of health-care providers from both the public and private sectors in the most affected communities; and better preventive, diagnostic, and treatment options. Strengthening basic TB control programs to improve access to diagnosis and care and to ensure successful treatment of patients with drug-susceptible TB is critical to preventing the development of drug-resistant TB. Early and accurate diagnosis and effective treatment of MDR-TB will reduce the spread of MDR-TB and prevent the development of XDR-TB. Ultimately, an effective vaccine to prevent all forms of TB will be required to eliminate TB globally.

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[28] *Treatment of Tuberculosis*; Morbidity and Mortality Weekly Report (2003): http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf

[29] *Tuberculosis Guidelines, Multidrug-Resistant Tuberculosis*; CDC (2013): http://www.cdc.gov/tb/publications/guidelines/mdr_tb.htm

[30] *World Health Organization Global Tuberculosis Report 2015*: http://www.who.int/tb/publications/global_report/en/

[31] Ibid.

[32] Ibid.

Opportunity

The Nation has a window of opportunity to ensure that accelerating progress towards a TB-free world is not imperiled by MDR-TB. The global community must come together to implement the targeted interventions outlined in the *National Action Plan* that will preserve, augment, and build on the momentum of the ongoing global effort to eliminate TB. These interventions are designed to take advantage of existing global and domestic partnerships as well as build new ones. The implementation of current validated tools and evidence-based strategies to eliminate MDR-TB in the world should be accelerated. Achieving the targets and goals of the *National Action Plan* will advance the use of scientific discoveries and technical innovations to help create game-changing medical products, including point-of-care molecular diagnostics for TB diagnosis and drug-susceptibility testing, novel therapies and better drug regimens, and new vaccines that can prevent TB and MDR-TB.

The scope of the *National Action Plan* (Box 2) includes a set of targeted interventions that address the core domestic and global challenges to effectively control MDR-TB. The interventions will increase rapid detection, investigation, and treatment of MDR-TB in the United States; strengthen national TB control programs in countries with high burdens of MDR-TB; and contribute to the discovery and development of innovative and effective ways to diagnose, treat, and prevent MDR-TB disease. Implementation of the MDR-TB goals set forth in this plan will also:

- Augment and accelerate achievement of the WHO's *End TB Strategy,*[33] the U.S. Government's *Global TB Strategy 2015–2019*,[34] U.S. President's Emergency Plan for AIDS Relief (PEPFAR) 3.0 – *Controlling the Epidemic: Delivering on the Promise of an AIDS-free Generation*,[35] and the WHO/Stop TB Partnership's *International Roadmap for Tuberculosis Research;*[36] and
- Advance broader efforts to address antimicrobial resistance under the *National Action Plan for Combating Antibiotic-Resistant Bacteria,*[37][38] the Global Health Security Agenda,[39] and the *WHO Global Action Plan on Antimicrobial Resistance.*[40]

[33] *End TB Strategy*, World Health Organization (2014): http://www.who.int/tb/post2015_strategy/en/

[34] *United States Government Global Tuberculosis Strategy 2015–2019*: https://www.usaid.gov/sites/default/files/documents/1864/Reach-Cure-Prevent-2015-2019-TBStrategy.pdf

[35] *U.S. President's Emergency Plan for AIDS Relief (PEPFAR) 3.0 – Controlling the Epidemic: Delivering on the Promise of an AIDS-free Generation* (2015): http://www.pepfar.gov/documents/organization/234744.pdf

[36] *International Roadmap for Tuberculosis Research*, World Health Organization/Stop TB Partnership (2011): http://www.stoptb.org/assets/documents/resources/publications/technical/tbresearchroadmap.pdf

[37] *National Action Plan for Combating Antibiotic-Resistant Bacteria* (2014): https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

[38] The decision to augment the *National Action Plan for Combating Antibiotic-Resistant Bacteria* with a companion plan on MDR-TB reflects the growing recognition that drug-resistant TB presents a unique risk to U.S. and global health.

[39] *The Global Health Security Agenda* (2014): http://www.globalhealth.gov/global-health-topics/global-health-security/ghsagenda.html

[40] *Global action plan on antimicrobial resistance*, World Health Organization (2015): http://www.who.int/drugresistance/global_action_plan/en/

Box 2: Scope of the *National Action Plan*

The *National Action Plan* identifies critical immediate actions the U.S. Government will take over a 3- to 5-year period to contribute to the global fight against MDR-TB. It is designed to achieve an impact within that timeframe. It builds on existing mandates of U.S. Government departments and agencies to advance efforts such as those identified in the WHO's *End TB Strategy*[41] and the U.S. Government's *Global TB Strategy 2015–2019*[42] that may not be included in this *National Action Plan*. It also builds on existing efforts to emphasize patient outcomes and program results, while encouraging innovative approaches. The *National Action Plan* guides U.S. Government activities tailored to key domestic, international, and research and development needs and serves as a call to action for other bilateral and multilateral donors, private sector organizations, and affected countries to further their investments in this critical area of worldwide concern.

Targets of the *National Action Plan*

Actions taken in alignment with this *National Action Plan* will contribute to meeting the following domestic and global targets:

- By 2016
  - Initiate appropriate treatment in 25 percent of patients with MDR-TB in 10 countries[43] with the highest burdens of MDR-TB.
- By 2018
  - Initiate appropriate treatment in 35 percent of patients with MDR-TB in 10 countries[44] with the highest burdens of MDR-TB.
- By 2020
  - Reduce by 15 percent the number of cases of MDR-TB disease in the United States.[45]
  - Initiate appropriate treatment in 50 percent of patients with MDR-TB in 10 countries[46] with the highest burdens of MDR-TB.
  - Reduce global TB incidence by 25 percent compared to 2015 levels.
  - Successfully treat at least 16 million TB patients in high-burden countries.[47]
  - Achieve and maintain treatment success rates of 90 percent for individuals in high-burden countries[48] with drug-susceptible TB.

[41] *End TB Strategy*, World Health Organization (2014): http://www.who.int/tb/post2015_strategy/en/

[42] *United States Government Global Tuberculosis Strategy 2015 – 2019*: https://www.usaid.gov/sites/default/files/documents/1864/Reach-Cure-Prevent-2015-2019-TBStrategy.pdf

[43] Hereafter within the *National Action Plan*, where appropriate, the identification of countries supported through *National Action Plan* objectives and sub-objectives will be in alignment with the *World Health Organization Global Tuberculosis Report 2015*: http://www.who.int/tb/publications/global_report/en/. The specific countries to be identified and supported will be dependent on resources and updates to disease burden and public health availability to support capability development.

[44] *World Health Organization Global Tuberculosis Report 2015*: http://www.who.int/tb/publications/global_report/en/

[45] This target reflects the domestic TB target in the CDC report *Antimicrobial Resistance Threats in the United States, 2013* and the *National Action Plan to Combat Antibiotic-Resistant Bacteria.*

[46] *World Health Organization Global Tuberculosis Report 2015*: http://www.who.int/tb/publications/global_report/en/

[47] Ibid.

[48] Ibid.

Goals of the *National Action Plan*

The *National Action Plan* is organized around three goals that aim to strengthen health-care services, public health, and academic and industrial research through collaborative action by the U.S. Government in partnership with other nations, organizations, and individuals. The goals are:

- **Goal 1: Strengthen Domestic Capacity to Combat MDR-TB.** Although there are fewer than 100 individuals with MDR-TB diagnosed in the United States each year,[49] health authorities must follow up with every patient to ensure appropriate treatment and to determine if others have been infected and require treatment or preventive services. Goal 1 activities will help prevent TB drug resistance by ensuring that all patients with TB disease are promptly detected and treated, and that people who have been in close contact with infectious TB patients are identified, monitored, and, if necessary, treated. Although any transmission of TB is of public health importance, an outbreak sparked by an undiagnosed patient with MDR-TB or XDR-TB could have serious consequences due to the difficulty and costs associated with treating patients infected with these resistant strains.
- **Goal 2: Improve International Capacity and Collaboration to Combat MDR-TB.** The emergence of MDR-TB and XDR-TB not only results in significant loss of human life and economic damage, but has the potential to impede continued progress in mitigating the devastating effects of TB. Goal 2 describes efforts the United States will take to address the global threat of MDR-TB through strategic investments to broaden access to diagnosis and treatment by engaging providers from both the public and private sectors in the most affected communities, improving innovative health technologies and patient-centered approaches to care, and advancing diagnostic and treatment options.
- **Goal 3: Accelerate Basic and Applied Research and Development to Combat MDR-TB.** New products and innovations for the diagnosis, treatment, and prevention of TB are urgently needed to accelerate control of TB and MDR-TB at home and abroad. Goal 3 activities will help with the development of rapid tests to diagnose TB and determine susceptibility to available drugs; novel therapies and drug regimens that could cure TB and MDR-TB within weeks, making it easier for patients to complete therapy and decreasing opportunities for the emergence of drug resistance; and new vaccines with the potential to prevent all forms of TB.

[49] *Reported Tuberculosis in the United States*, CDC (2014): http://www.cdc.gov/tb/statistics/reports/2014/default.htm

Implementation of the *National Action Plan*

The *National Action Plan* was developed in response to the recommendations outlined in the *National Action Plan for Combating Antibiotic Resistant Bacteria* (CARB) released on March 27, 2015, and created by the CARB Federal Task Force established by Executive Order No. 13676 issued by President Barack Obama on September 18, 2014. The *National Action Plan* was drafted by an interagency TB Working Group with representation from the United States Agency for International Development (USAID); the National Institutes of Health (NIH); the Centers for Disease Control and Prevention (CDC); the Departments of State, Defense, Veterans Affairs, Homeland Security, and Health and Human Services (HHS); the Office of Science and Technology Policy (OSTP); the Office of Management and Budget; and the National Security Council.

Monitoring and Evaluation

No later than September 30, 2016 and each year thereafter until 2020, the Secretaries of State and HHS, the Administrator of USAID, and heads of other relevant Departments will submit a joint report on progress in implementation of the *National Action Plan.* Each year, the reports will be made available to the public and be submitted to the Assistant to the President for Science and Technology and Director of OSTP, the Assistant to the President for Homeland Security and Counterterrorism, and the Director of the Office for Management and Budget to inform program planning and the annual budget cycle.

Partnerships and Implementation

Implementation of the *National Action Plan* and achievement of its goals and objectives will depend not only on sustained coordination among U.S. agencies to ensure a strategic, whole-of-government approach but also on close collaboration with other Nation's ministries of health, the WHO, the Stop TB Partnership, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and other domestic and global partners in the fight against TB, which include:

- *U.S. and global front-line health-care providers* who detect, diagnose, and treat MDR-TB;
- *State and local public-health departments in the United States and regional health departments and TB control programs around the world,* which have primary responsibility for preventing and controlling TB in their jurisdictions;
- *Non-governmental organizations* that help build health-care capacity and expand quality treatment services for MDR-TB in TB-endemic countries;[50]
- *Private-sector organizations* who advance the development of innovative tools for the detection, treatment, and prevention of MDR-TB, including academic and industrial researchers; pharmaceutical, biotech and not-for-profit product developers; and manufacturers of vaccines, drugs, and diagnostics;
- *Community leaders, patient engagement organizations, and other community-based groups* that provide health literacy and social support to patients undergoing treatment for TB and MDR-TB;
- *Civil society organizations* that promote civic engagement and advance the development of national health policies for control of TB and MDR-TB;
- *TB survivors and other private citizens* who serve as patient advocates and raise awareness related to the danger posed by MDR-TB; and

[50] An "endemic country" is any country in which TB is regularly found among particular people or in a certain area. High-burden countries are a subset of those in which TB is endemic.

- *Governments, foundations, and other donor organizations* that support disease-control activities and innovative research to develop new tools for detection, treatment, and prevention of MDR-TB.

Goal 1: Strengthen Domestic Capacity to Combat Multidrug-Resistant Tuberculosis

Challenge of Domestic MDR-TB Control

Once believed to be "conquered" by antibiotics such as isoniazid and rifampin, TB rebounded in the United States in the 1980s, and more than 25,000 cases were diagnosed each year through the early 1990s.[51] The rise in the number of TB patients was related to the loss of funding of TB programs. Subsequently, the ability to prevent, detect, and cure TB disease and to respond to TB transmission was significantly diminished. Other factors, such as the emerging HIV/acquired immune deficiency syndrome (AIDS) epidemic and increases in travel between the United States and high-TB-burden countries, also contributed to the resurgence of TB. That resurgence, which included patients with drug-resistant TB, was brought under control by strengthening State and local capacity to provide essential TB services, including contact investigations to reduce disease spread and directly-observed therapy to ensure completion of TB treatment. Today, fewer than 10,000 patients are diagnosed with TB in the United States annually. About 9 percent of these patients have TB disease that is resistant to isoniazid, one of the key drugs in treating TB, and about 1 percent have TB that is resistant to both isoniazid and rifampin, which is categorized as MDR-TB. [52]

The United States, with its strong public health system, currently reports 100 percent of its diagnosed TB patients annually to the Centers for Disease Control and Prevention.[53] Public-health authorities follow each patient diagnosed with TB closely to ensure appropriate treatment is administered, and about 90 percent of all TB patients in the United States are cured.[54] Still, any gap in this system can allow TB to spread. For example, some people who are in close contact with an infectious TB patient will develop latent TB infection, which has no symptoms and cannot be transmitted but can progress to disease if left untreated. The major domestic challenge, therefore, is to remain active and vigilant to eliminate TB in the United States and to maintain a strong public health system for rapid identification and treatment of newly diagnosed patients and contacts. There have also been periodic shortages of TB drugs and diagnostic supplies due to declining manufacturing capacity and complex procurement processes in the United States. Because interruptions in availability of anti-TB drugs can contribute to development of drug resistance, shortages in the United States must be directly addressed to ensure local and State public health authorities have stable access to quality-assured anti-TB drugs. When shortages do occur, CDC has developed mechanisms to reduce usage so that those patients with the most urgent need receive treatment (Box 3).

[51] *Reported Tuberculosis in the United States*, CDC (2014): http://www.cdc.gov/tb/statistics/reports/2014/default.htm

[52] Ibid.

[53] Ibid.

[54] Ibid.

Box 3: Shortages of TB Drugs and Diagnostic Supplies in the United States

- Isoniazid is one of the first-line drugs used as part of a regimen to treat active TB disease and latent TB infection. In 2013, 79 percent of State and local TB programs reported difficulties in procuring isoniazid.[55]
- Second-line drugs are used for treatment of MDR-TB. In 2013, the National TB Controllers Association reported that 81 percent of U.S. TB programs that managed patients with MDR-TB had difficulty procuring second-line drugs. Ninety percent of these programs report that drug supply problems delayed treatment for patients, caused a lapse in treatment, or forced them to use a suboptimal regimen.[56]
- Purified-protein-derivative tuberculin products are diagnostic reagents used in TB skin tests. CDC used the Health Alert Network to provide health-care providers with emergency guidance on the use of alternative methods of TB-susceptibility testing to prioritize allocation of TB treatment until the shortage was remedied.[57]

Opportunity

Goal 1 includes activities that would help the United States meet its domestic TB challenges—and reduce health-care costs—by strengthening surveillance and outbreak response at the State and local levels, addressing drug shortages that hinder treatment, and ensuring optimal treatment (including hospitalization and isolation, as needed) for patients with MDR-TB or XDR-TB. The domestic opportunities are twofold:

- First, ensure that patients with TB are adequately and completely treated, so that resistance—whether to one drug, multiple drugs, or most drugs—does not develop.
- Second, prevent further transmission by ensuring that all patients with TB—including TB patients within vulnerable populations (e.g., persons who are homeless or incarcerated)—are promptly detected and treated and by identifying and treating persons at highest risk for latent TB infection prior to confirmed diagnosis. Although any transmission of TB disease is of public health importance, outbreaks sparked by an undiagnosed patient with MDR-TB or XDR TB, in which contacts to infectious patients are not located, evaluated, and treated, could have serious consequences because of the difficulty and costs associated with treating these individuals.

Taken together, these activities will help achieve the National Target of reducing by 15 percent the number of newly diagnosed MDR-TB cases by 2020, as specified in the *National Action Plan for Combating Antibiotic Resistant Bacteria.*[58]

Significant outcomes of Goal 1 will include:

- Creation of a National TB Stockpile to prevent shortages of TB medicines and diagnostic tests;
- Rapid detection of emerging patterns of TB drug resistance;
- Increased surge capacity nationwide for investigation and control of TB disease and latent TB infection; and
- Improved capacity for treating patients with MDR-TB.

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[55] *Impact of a Shortage of First-Line Anti-tuberculosis Medication on Tuberculosis Control — United States, 2012–2013*, Morbidity and Mortality Weekly Report (2013): http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6220a2.htm

[56] Ibid.

[57] *Recommendations for Drug Allocation, Tuberculosis Prevention, and Patient Care during Isoniazid Shortages*, CDC Health Alert Network (2013): http://emergency.cdc.gov/han/han00340.asp

[58] *National Action Plan for Combating Antibiotic-Resistant Bacteria* (2014): https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

Objectives

1.1. Upgrade TB surveillance to ensure complete and accurate detection of drug-resistant TB

Strengthened TB surveillance in U.S. States and localities is essential to identify and track emerging patterns of TB drug resistance. Achieving this objective will require upgraded capacity to gather, store, analyze, and report electronic data on drug-resistant TB. Improvements are also needed to support electronic capture of TB test results as clinical laboratories transition from culture-based to molecular testing for TB drug resistance.

As part of this effort, CDC will increase its capacity to use whole-genome sequencing to elucidate paths of transmission, identify recent transmission, and identify emerging patterns of resistance. This topic is addressed in the *National Action Plan for Combating Antibiotic-Resistant Bacteria.*[59]

MILESTONES

Within 1 to 3 years:

- CDC will work with its partners to lay the groundwork for an updated TB surveillance system by:
  - Identifying common language and protocols for reporting drug resistance to anti-TB drugs; and
  - Identifying requirements for creating electronic links between clinical laboratories and TB surveillance programs at the Federal, State, and local levels.

Within 5 years:

- CDC will work with its partners to establish an updated electronic surveillance system for collecting, analyzing, and storing national and State-level TB clinical data. The updated system will:
  - Capture molecular test results from clinical laboratories;
  - Record information on treatment of cases of MDR-TB and XDR-TB; and
  - Store de-identified case information that allows health authorities to distinguish between primary resistance (involving person-to-person transmission of drug-resistant TB) and secondary resistance (involving drug resistance that developed during the course of treatment).

1.2 Strengthen State and local capacity to prevent transmission of drug-resistant TB

Reducing the transmission of drug-resistant TB in U.S. States and localities requires:

- Surge capacity for rapid response to individual patients, patient clusters, and larger outbreaks of drug-resistant TB; and
- Contact investigations and treatment of latent TB infection and TB disease among vulnerable populations, including members of racial or ethnic minorities and homeless, incarcerated, or foreign-born individuals.

Some State and local health departments are facing limitations in staffing[60] and technical resources for investigating and controlling TB. TB contact investigations involve identifying, diagnosing, and, as needed, treating exposed persons ("contacts") because TB is transmitted from person to person.

CDC will work with the National TB Controllers Association—which represents TB control programs in all U.S. States and territories—to develop a plan to create surge capacity for TB contact investigations. CDC and State and local health departments will also strengthen relationships with clinicians, institutions, and community leaders to ensure rapid detection and complete treatment of drug-resistant TB among vulnerable populations and medically underserved groups.

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[59] *National Action Plan for Combating Antibiotic-Resistant Bacteria* (2014): https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

[60] *Budget Cuts Continue to Affect the Health of Americans*; Association of State and Territorial Health Organizations (2014): http://www.astho.org/budget-cuts-Sept-2014/

MILESTONES

Within 1 to 3 years:

- CDC will work with the National TB Controllers Association to develop a surge-capacity plan for rapid response to control cases, clusters, and outbreaks of drug-resistant TB. The surge-capacity plan will include procedures and protocols for:
  - Responding to reports of suspected drug-resistant TB;
  - Adopting improved tests for TB diagnosis, including rapid molecular tests and TB blood tests;
  - Providing diagnostic testing and, if applicable, treatment for patient contacts with suspected latent drug-resistant TB;
  - Ensuring that patients with TB disease are treated until cured; and
  - Maintaining ongoing technical capacity and resources.
- As part of these efforts, CDC will explore ways to increase staffing at State and local health departments during TB contact investigations.
  - CDC will assist State and local health departments in creating health-care liaisons with institutions that serve hard-to-reach groups at risk for TB, such as individuals who are homeless, incarcerated, or suffering from addiction. Those institutions may include Federally-qualified health centers, correctional institutions, detention facilities, emergency departments, community health centers, food pantries and food banks, and homeless shelters.

Within 3 to 5 years:

- CDC will work with its partners to develop new tools to facilitate contact investigations, including:
  - Databases to help track the contacts of drug-resistant TB patients and ensure that they receive diagnostic testing for latent or active TB and treatment, as needed;
  - Metrics for tracking TB transmission; and
  - Indicators for measuring the impact of contact investigations (e.g., numbers of persons identified and screened for exposure to TB).

1.3. Ensure that patients with drug-resistant TB receive treatment until cured

Complete and effective treatment of every patient with TB disease is essential. In the United States, the standard of care for TB disease is to use directly-observed therapy to ensure that the treatment is effective and that no drug doses are missed. Failure to cure a person with TB disease harms the patient but also exposes the patient's family, co-workers, and community to TB. In the United States, more than 90 percent of patients with TB disease are cured, including drug-resistant cases.[61] However, treatment of drug-resistant TB disease is difficult, as well as expensive (Box 4). The average cost to treat MDR-TB is $150,000; the average cost of treating a patient with XDR-TB is $482,000.[62] Many communities that have limited budgets for public health are unable to pay for the treatment, laboratory services, and drugs required to care for one patient with drug-resistant TB.

Ensuring that all patients with drug-resistant TB receive treatment requires:

- Adequate and stable supplies of TB medicines and screening tests;
- Education and clinical guidance for clinicians on identification, treatment, and management of drug-resistant TB; and
- Improved mechanisms for ensuring patients who travel between countries complete TB therapy.

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[61] *Reported Tuberculosis in the United States*, CDC (2014): http://www.cdc.gov/tb/statistics/reports/2014/default.htm

[62] CDC Factsheet on Tuberculosis: http://www.cdc.gov/tb/publications/infographic/pdf/take-on-tuberculosis-infographic.pdf, updated to 2014 dollars from *Treatment Practices, Outcomes, and Costs of Multidrug-Resistant and Extensively drug-Resistant Tuberculosis, United States, 2005–2007,* S. M. Marks, et al., *Emerging Infectious Disease Journal* (2014)

1.3.1. Explore the potential use of a national TB stockpile to ensure the availability of TB medicines and screening tests

Shortages of antibiotics—including first-line drugs to treat drug-susceptible TB and second-line drugs to treat drug-resistant TB—may result in inadequate treatment. Of the 15 Food and Drug Administration (FDA) - approved drugs used in TB regimens, 9 are produced by a single manufacturer. Any disruption in the supply chain for these drugs could have significant repercussions for TB control programs throughout the United States.

Establishment of a stockpile could create a buffer supply of TB drugs and screening tests that could be accessible in the event of a shortage.

Box 4: A Patient's Story

Liliana, a young woman in Texas, was diagnosed with MDR-TB in 2009. She does not recall ever being exposed to anyone with TB disease as a child or as an adult.

Liliana developed a bad cough shortly before her wedding. Not wanting to be sick for her big event, she went to see a doctor and was told she had bronchitis. The doctor gave Liliana a shot of antibiotics and prescribed an inhaler. Liliana's symptoms went away and she quickly felt better. But after her honeymoon, her cough came back even worse. Deciding it was time to see a specialist, she went to a pulmonologist. He sent Liliana to get a chest x-ray and prescribed an inhaler and antibiotics.

Liliana was better for a while, and she did not hear back from the doctor. However, when her cough returned, a few months later, she scheduled another appointment with the same pulmonologist. The doctor, alarmed by Liliana's x-ray results, sent her for blood work and sputum tests. Once the TB diagnosis was confirmed, she was referred to the county health department for directly observed therapy, which requires that every drug dose is taken and documented by a health-care worker.

Because TB disease is so serious—not taking the medication as directed can lead to the development of drug resistance—directly-observed therapy is recommended for all persons diagnosed with TB disease. However, in this case, the treatment was not effective because the *Mtb* strain causing Liliana's illness turned out to be resistant to most of the medications she was taking. As a result, she spent 2 months at an infectious disease hospital in San Antonio, followed by 16 additional months of MDR-TB treatment at home, aided by a local TB control program.

The source of the young woman's infection has not been determined.[63]

MILESTONES

Within 1 to 3 years:

- 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.

Within 3 to 5 years:

- CDC will work with public and private sector organizations to maintain a supply of TB drugs that provides:
  - An alternative source of procurement of drugs and screening tests for providers who care for persons with TB infection and disease; and
  - A steady market for off-patent drugs used in TB regimens.

1.3.2. Explore options for providing care for persons with MDR-TB or XDR-TB who do not have a medical home

The cost of treating a patient with XDR-TB exceeds the public health budgets of many States and localities. However, failure to complete treatment for a person with TB disease puts the patient at risk for relapse or death. Moreover, an untreated patient could expose a community, travelers, and people in other jurisdictions to infectious XDR-TB.

The responsibility and costs of isolating and treating a case of MDR-TB or XDR-TB in a person without financial resources or a home conducive to medical treatment—as could be the case for homeless individuals or travelers from TB-endemic countries—are addressed on an ad hoc basis.

[63] *Tuberculosis Personal Stories*; CDC (2014): http://www.cdc.gov/tb/topic/basics/lilianastory.htm

MILESTONES

Within 1 to 3 years:

- 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.

Within 3 to 5 years:

- CDC and other State and Federal agencies will identify mechanisms for providing resources to or care for patients with MDR-TB or XDR-TB. For example, recent cases of Ebola hemorrhagic fever in fall 2014 illustrated the potential value of identifying regional hospitals with special expertise in caring for patients with dangerous communicable disease The United States needs capacity, as well as resources, to treat patients with drug-resistant TB.

1.3.3. Improve completion of therapy for persons who travel in or out of the United States while on treatment for TB disease

The duration of therapy to cure TB patients can range from 6 months for drug-susceptible TB to more than 2 years for XDR-TB.[64] During treatment, some patients may travel or move to another country without plans for continuing their treatment in their destination. For example, between 2010 and 2013, 747 (9 percent) of patients undergoing treatment for TB in California moved to a different reporting jurisdiction prior to completing their treatment. Of those, 342 (46 percent) moved out of the country and 224 (65 percent) had unknown treatment outcome. Of patients that moved out-of-country, 208 (93 percent) were started on treatment prior to moving (median treatment duration before moving was 87 days).[65] Nationwide, CDC estimates that 500 to 1,000 patients a year leave the United States before finishing treatment.[66]

Each patient who does not complete the full treatment course for TB disease provides additional opportunities for the development of drug resistance, relapse, and further TB transmission. Over the next 5 years, CDC will work with domestic and international organizations to improve treatment-completion rate for transnational TB cases.

U.S.-bound immigrants and refugees with TB disease must receive curative treatment before they are allowed to enter the United States.[67] As stated in the *National Action Plan for Combating Antibiotic-Resistant Bacteria,* CDC plans to expand TB screening from 500,000 immigrants and refugees each year to include an additional 500,000 other visa holders, such as long-term visitors, workers, and students from high-burden countries.[68]

MILESTONES

Within 1 to 3 years:

CDC will explore ways to strengthen medical management of transnational cases of TB disease, working with outside organizations.

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[64] *Tuberculosis Guidelines, Multidrug-Resistant Tuberculosis*; CDC (2013): http://www.cdc.gov/tb/publications/guidelines/mdr_tb.htm

[65] *Tuberculosis Patients Who Move Out of the United States: Characteristics and Updated Surveillance Protocol in California*, T. K. Mochizuki, et al., California Department of Public Health, Tuberculosis Control Branch (2015): http://www.tbcontrollers.org/docs/conference/2015posters/Mochizuki_TB_Patients_Who_Move_Out_of_the_US_June2015NTC.pdf

[66] *Reported Tuberculosis in the United States*, CDC (2014): http://www.cdc.gov/tb/statistics/reports/2014/default.htm

[67] *Technical Instructions for Panel Physicians and Civil Surgeons*, CDC (2008): http://www.cdc.gov/immigrantrefugeehealth/exams/ti/civil/tuberculosis-civil-technical-instructions.html

[68] *National Action Plan for Combating Antibiotic-Resistant Bacteria* (2014): https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

Within 3 to 5 years:

- CDC will work with the State and local programs and other partners to identify mechanisms for improving U.S. management for transnational cases of TB disease;
- CDC will work with State and local programs and other partners to develop a case definition for transnational (or binational) TB disease cases;
- CDC will work with State and local programs and other partners to establish indicators to measure treatment completion rate for transnational TB cases;
- CDC will establish national baseline data to measure improvements in treatment completion rates; and
- CDC will explore the possibility of extending medical exams and treatment overseas to persons who are likely to remain in the United States for 6 months or longer, such as students and temporary workers who receive targeted screening only if a consular officer has reason to believe that they may have TB and would therefore be medically ineligible for a visa under Immigration and Nationality Act 2011 (INA) § 212(a)(1)(A)(i) prior to entry to the United States.[69] If such a program is determined to be medically efficacious, CDC will consult with State and the Department of Homeland Security as to how such a program could be implemented in a way that is consistent with applicable laws.

[69] *Technical Instructions for Panel Physicians and Civil Surgeons*, CDC (2008): http://www.cdc.gov/immigrantrefugeehealth/exams/ti/civil/tuberculosis-civil-technical-instructions.html

Goal 2: Improve International Capacity and Collaboration to Combat Multidrug-Resistant Tuberculosis

Challenge to Global TB Control

The WHO estimates that approximately 480,000 people develop MDR-TB each year. Those who are treated face long, difficult, and expensive treatment that is often unsuccessful; only about 10 percent of the 480,000 are cured.[70] In addition, more resistant forms of TB, such as XDR-TB, are becoming more common.[71] XDR-TB is often incurable and frequently deadly, especially in countries where access to quality health-care services is limited.[72]

Changes in global health and population dynamics present additional challenges to controlling TB. Large segments of poor populations, where the economic and human impact of TB are greatest, lack access to health services and suffer from conditions such as diabetes, HIV, and smoking, which greatly increase their risk of developing TB and can complicate management. Individuals with diabetes are two to three times more likely to develop TB and have a higher risk of death. Currently, 9 percent of the adult population has diabetes (450 million people), and the WHO predicts the prevalence of diabetes will increase dramatically by 2030. Similarly, the 35 million people living with HIV are about 25-30 times more likely to develop TB and are at higher risk of mortality due to delayed diagnosis and co-morbidities than are individuals without HIV; TB is a major cause of HIV-related death. Finally, nearly 80 percent of the world's one billion smokers live in low- and middle-income countries, many of which have high MDR-TB burdens.[73, 74] Because one-third of the world's population is thought to be already infected with *Mtb*, there is a large reservoir of individuals at risk of active TB. Given the conditions described above that predispose individuals to progress from *Mtb* infection to TB disease, it is likely that the number of patients with TB and MDR-TB will significantly increase in the next several decades.

Current treatments are often ineffective even if used appropriately. Contrary to popular belief, there is no effective vaccine against TB in adults; the BCG vaccine available in some countries (but not the United States) only partially protects children in the first years of life. Treatment of drug-susceptible TB requires taking several drugs, usually for 6 to 9 months. The regimens available to treat MDR-TB are much less effective than those used for drug-susceptible TB even when taken as prescribed, and are toxic (leading to grave side effects such as deafness and liver toxicity), expensive, and of very long (often more than two years) duration. New therapeutics—and new approaches to delivering existing therapeutics – are urgently needed to reduce the duration, cost, and side effects of treating TB, MDR-TB, and XDR-TB. Enhanced basic and applied research and product development, including improvements in our understanding of the disease and the pathogen that causes it, are prerequisites for the discovery of improved drugs, vaccines, and diagnostics for TB, MDR-TB, and XDR-TB (see Goal 3).

In many countries, essential TB services are often unavailable, quality control and standards for medications are inadequate, and insufficient support is provided to patients during therapy. While current efforts have helped reduce the prevalence and mortality of TB, much more work is needed as TB and MDR-TB continue to pose a significant global health threat. The great majority of MDR-TB is likely generated by under-resourced health systems that are unable to ensure the proper diagnosis and treatment of any type of TB, whether drug-

[70] *World Health Organization Global Tuberculosis Report 2015*: http://www.who.int/tb/publications/global_report/en/

[71] Ibid.

[72] Ibid.

[73] *Tuberculosis and Diabetes Factsheet*, World Health Organization (2011): http://www.who.int/tb/publications/diabetes_tb.pdf

[74] *Tobacco Factsheet*, World Health Organization (2015): http://www.who.int/mediacentre/factsheets/fs339/en/

susceptible or resistant. At the facility level, laboratories often lack the equipment and staff to perform appropriate tests, diagnostic tools are outdated and of poor quality, and results are slow to reach providers. Providers are overwhelmed by patient responsibilities and frequently unable to offer adequate support and care to patients, resulting in low treatment completion rates and poor outcomes, including the generation of MDR-TB. The difficulties in caring for those who develop MDR-TB are even more challenging. In addition to resources shortages in laboratories and provider constraints, the complexity of diagnosis and treatment, and the need to use drugs of high toxicity and low effectiveness leads to very low cure rates and high death rates, particularly in those who are immune compromised. Finally, poor infection control practices further exacerbate the problem by fostering transmission among patients, families, and co-workers.

Opportunity

The U.S. Government and its global partners are currently working to address the challenges posed by TB and MDR-TB (Box 5). The U.S. Government works closely with national TB Programs in countries most affected by TB to develop and support the implementation of their national TB strategic plans. This support consists of critical technical assistance, from development of key innovations to scale-up of proven interventions aimed at decreasing the impact of TB and MDR-TB on both individuals and health-care systems and, ultimately, saving lives. The U.S. Government builds capacity at all levels of the service delivery system and supports multiple organizations to ensure a coordinated and sustained effort. In addition, U.S. Government efforts contribute to achieving the outcomes identified in the WHO's *End TB Strategy* and the U.S. Government's *Global TB Strategy*.

Box 5: Global Partnerships

The U.S. Government's international TB activities are implemented in collaboration with global partners, from national governments and multinational organizations to affected individuals and communities. Close coordination with the WHO helps ensure global alignment of TB-related policy and programmatic issues. As the largest donor to the Global Fund, the United States also contributes to the largest multilateral funding effort for TB and MDR-TB. The U.S. Government works directly with other Nation's ministries of health to support their national TB strategic plans. Furthermore, the involvement of numerous constituencies is essential to ensure access to communities beyond the reach of governmental and multilateral agencies to address medical, social, and economic aspects of the disease. Through its close alliance with these organizations, the U.S. Government has helped shape and strengthen collaborative efforts across the globe to expand access to TB and MDR-TB diagnosis and treatment and to increase political commitment and engagement in the fight against the disease. Through existing and expanded partnerships, the United States will continue to work with its global organizations to strengthen international capacities to reach individuals with MDR-TB, cure those in need of treatment, and prevent further development and transmission of the disease. Goal 2 of the *National Action Plan* identifies targeted near-term actions to complement ongoing activities of the U.S. Government's *Global TB Strategy* and accelerate the global response to the epidemic, focusing on improving access to high-quality, patient-centered MDR-TB diagnostic, treatment, and prevention services.

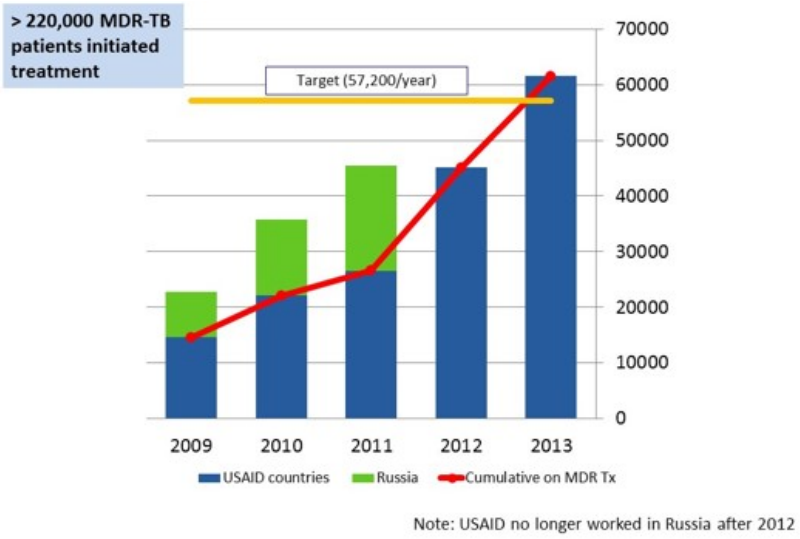
The U. S. Government's international TB work is conducted by several agencies. USAID leads the U.S. Government's international care and treatment efforts, working closely with PEPFAR, CDC, the Department of Defense (DOD), NIH, State, and other relevant departments and agencies to ensure a coordinated U.S. Government response to the global epidemic.

Sustained and focused investments to fight TB have already made a significant difference in the trajectory of the global epidemic. Since 1990, the collective efforts of the global community have reduced the number of deaths due to TB by 45 percent and reduced TB prevalence (the number of persons with active TB) by 41 percent. In USAID-supported countries, including those with high disease burdens, deaths due to TB decreased 44 percent and the prevalence of TB was reduced by 42 percent since 1990. Furthermore, in 2013 (the last year for which data are available), more than 2.7 million people with TB were successfully treated, and more than 60,000 people with MDR-TB began treatment in countries where USAID works (Figure 2).[75] The U.S. Government has also been working with country partners to maximize the impact of Global Fund to Fight AIDS, Tuberculosis and Malaria TB grants by providing technical assistance to support grant development, implementation, and

[75] *World Health Organization Global Tuberculosis Report 2015*: http://www.who.int/tb/publications/global_report/en/

evaluation. The U.S. Government has also been working with global organizations to increase access to new diagnostics and quality medications to identify and treat TB and MDR-TB. The U.S. Government was instrumental in working with the manufacturer of a new TB diagnostic and MDR-TB screening test called GeneXpert *Mtb*/RIF to reduce the price of the diagnostic by more than 40 percent, resulting in more than $50 million in savings after only 2 years.[76] The availability of the new screening test has significantly increased the medical community's ability to diagnose both TB and MDR-TB. In addition, the U.S. Government has worked with global organizations to increase the availability and affordability of quality-assured TB medicines. For example, in 2014, USAID supported the Global Drug Facility (GDF) to reduce the price of second-line TB drugs by 32 percent, increasing the availability and accessibility of quality medicines to treat MDR-TB worldwide.[77]

Figure 2. Trends in MDR-TB Treatment Initiated in USAID-Supported Countries, 2009–2013



Note: USAID no longer worked in Russia after 2012

While these efforts have enabled significant progress in many countries, more work is needed to raise the profile of TB and MDR-TB and to secure greater involvement of national governments and international organizations. Diplomatic and foreign policy engagement is necessary to expand the effect of U.S. global health investments on MDR-TB. The U.S. Government will address this need by developing tools and resources for diplomats to increase political awareness of the health, economic, and security risks of MDR-TB. The U.S. Government will also increase diplomatic efforts in bilateral and multilateral engagements to mobilize international financial, political, and operational support to combat MDR-TB by strengthening health systems, leveraging investments, and aligning TB efforts with broader U.S. foreign policy objectives.[78, 79]

Objectives

The strategies and tools currently used to address the global MDR-TB crisis are insufficient. Additional efforts are required to reach the Sustainable Development Goals and the WHO's *End TB Strategy*.[80,81] The U.S. Government will work with the Global Fund, WHO, Stop TB Partnership and other partners to support countries to develop new approaches to address MDR-TB and to improve the quality of existing MDR-TB programs. The best available

[76] *TB XPERT Project - Rolling Out Innovative MDR-TB Diagnostics*; UNITAID: http://www.unitaid.eu/en/mdr-tb-diagnostics

[77] *Improving Access for Quality-Assured TB Medicines and Diagnostics*; Stop TB Partnership (2015): http://www.stoptb.org/assets/documents/about/cb/meetings/26/26-00%20Presentations/GDF%20Board%20Presentation%20.pdf

[78] *Accelerating Progress in the Global Effort Against Tuberculosis, Fiscal Year 2014*; USAID (2014): https://www.usaid.gov/sites/default/files/documents/1864/USAID-AnnualReport-2014.pdf

[79] *Tuberculosis*; USAID (2015): https://www.usaid.gov/what-we-do/global-health/tuberculosis

[80] *Governments agree to new Sustainable Development Goals to Replace Millennium Development Goals - Online Consultation on Indicators Now Open*; Stop TB Partnership (2015): http://www.stoptb.org/news/stories/2015/ns15_035.asp

[81] *Sustainable Development Goals*; United Nations (2015): https://sustainabledevelopment.un.org/topics

approaches for diagnosis, treatment, and prevention will be employed by the global TB community to achieve these objectives in up to 10 of the highest-burden MDR-TB countries. The implementation of the *National Action Plan* will accelerate access to life-saving MDR-TB diagnosis and treatment, while improving the quality of these countries' TB and MDR-TB programs to enhance both prevention and care.

The U.S. Government, alongside groups such as the Global Fund, WHO, Stop TB Partnership, and others, will focus available resources and effort on achieving the global targets outlined in the *National Action Plan.* Subject to available resources and strong financial and technical commitment, this focus is expected to result in treatment being initiated for additional 200,000 MDR-TB patients (almost 60 percent more than the current target), compared with the current estimated number (360,000 MDR-TB patients) who will receive treatment under the U.S. Government's *Global TB Strategy 2015–2019*.[82] This *National Action Plan* will support activities in up to 10 countries that carry approximately 65 percent of the global MDR-TB burden.[83]

2.1. Improve access to high-quality, patient-centered diagnostic and treatment services

While many countries have developed MDR-TB diagnosis and treatment capacity in recent years, services are not at scale to meet the needs of the current epidemic, quality control and standards are inadequate, and insufficient support is provided to patients during treatment. Building on existing U.S. Government and other efforts, the activities for this objective, carried out by Federal Government and non-government partners as described in the milestones below, will increase availability and access to quality MDR-TB diagnosis and treatment. Laboratory networks and treatment services will be strengthened and expanded, new tools will be developed and implemented, and a stronger surveillance system to monitor progress and identify challenges will be supported. In addition, ensuring the quality and availability of existing and new drugs will be emphasized, and prices may be reduced to allow for treating more patients and faster scale-up of MDR-TB programs.

2.1.1. Strengthen the capacity of national TB laboratory networks to diagnose TB and MDR-TB

A strong laboratory network, capable of detecting and monitoring individuals with TB, is critical to providing quality care. Laboratory systems will be strengthened to ensure earlier and more accurate TB and MDR-TB diagnoses. Point-of-care (or near point-of-care) molecular diagnostic tools that detect TB and key drug resistance mutations should become the new standard of care. Diagnosing TB is the critical first step; without it, diagnosis of MDR-TB is not possible. Because only two-thirds of estimated TB cases are diagnosed and reported,[84] it is only possible to identify MDR-TB within this limited population. To address these issues, clear and comprehensive national plans for laboratory networks will be developed or enhanced, systems to ensure standardized reporting of TB and MDR-TB diagnoses from local to national TB laboratories will be developed, new approaches for improving quality will be implemented, and new tools will be scaled-up.

MILESTONES

Within 1 year:

- USAID and CDC will work with up to 10 countries[85] 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.

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[82] *United States Government Global Tuberculosis Strategy 2015 – 2019*: https://www.usaid.gov/sites/default/files/documents/1864/Reach-Cure-Prevent-2015-2019-TBStrategy.pdf

[83] *World Health Organization Global Tuberculosis Report 2015*: http://www.who.int/tb/publications/global_report/en/

[84] Ibid.

[85] U.S. Government work in nine countries will build upon existing funding during the first year of the *National Action Plan.*

Within 3 years:

- USAID and CDC will work with up to 10 countries[86] to implement each country's laboratory strategic plan to improve diagnostic capacity from the central to the peripheral level as part of each country's National TB Strategic Plan.

Within 5 years:

- USAID and CDC will work with up to 10 countries[87] to implement nationwide screening of TB patients for MDR-TB through drug-resistance testing; and
- USAID and CDC will work with up to 10 countries[88] to develop quality-assured laboratories capable of diagnosing and monitoring MDR-TB consistent with international standards using the latest tools and technology.

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

Current WHO-recommended MDR-TB regimens are extraordinarily difficult to manage for both providers and patients. Available regimens are toxic, complicated, of long duration, and expensive, leading to treatment failures and poor outcomes.[89] The implementation of novel regimens consisting of existing and new drugs is critical to improving treatment and survival rates among individuals with MDR-TB. There are several ongoing observational and clinical trials assessing the effectiveness of a shortened regimen for MDR-TB, including a USAID-funded study; preliminary data indicate favorable outcomes. New WHO MDR-TB treatment guidelines reflecting final results are anticipated in the first year of the Plan. A phased approach to the introduction of new regimens and drugs will build on existing U.S. Government programs. In addition, new approaches to the delivery of MDR-TB services will promote retention in care and highlight patient-centered practices that enable care closer to home and emphasize supportive services.

MILESTONES

Within 1 year:

- USAID will work with up to 5 countries[90] to introduce a new MDR-TB drug (bedaquiline, delamanid, or both); and
- USAID will work with 1 country[91] to scale-up use of bedaquiline or delamanid.

Within 3 years:

- USAID will work with up to 10 countries[92] to introduce new MDR-TB drugs (bedaquiline, delamanid, or both);
- USAID will work with at least 7 countries[93] to introduce shortened MDR-TB regimens; and
- USAID will work with up to 10 countries[94] to develop quality facility and community-based MDR-TB care and treatment services.

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[86] *World Health Organization Global Tuberculosis Report 2015*: http://www.who.int/tb/publications/global_report/en/

[87] Ibid.

[88] Ibid.

[89] Ibid.

[90] Ibid.

[91] Ibid.

[92] Ibid.

[93] Ibid.

[94] Ibid.

Within 5 years:

- USAID will work with up to 10 countries[95] to introduce shortened MDR-TB regimens; and
- USAID will work with up to 10 countries[96] to scale-up quality facility and community-based MDR-TB care and treatment services.

2.1.3. Strengthen TB/MDR-TB surveillance and monitoring systems

A strong surveillance and monitoring system is an essential tool of MDR-TB diagnosis and treatment programs. The data provided enable countries to better plan, implement, and evaluate their TB programs. Importantly, the system can also reveal weaknesses in the program, allowing for targeted operations research and interventions to improve outcomes. Building on current U.S. Government efforts, the *National Action Plan* will strengthen global and country activities through the introduction and implementation of new tools to better understand TB control issues in each country. In addition, new technologies will be used to modernize and enhance systems.

MILESTONES

Within 1 year:

- USAID will enhance tracking of MDR-TB disease burden and surveillance data for dissemination; and
- CDC will assist one country in the completion of an inventory study to determine gaps in the TB surveillance system.

Within 3 years:

- USAID and CDC will work with up to 10 countries[97] to implement standards and benchmarks to improve surveillance and vital registration systems to directly measure TB burden;
- CDC will develop and implement, in at least 1 country,[98] an approach to link laboratory and TB and MDR-TB program surveillance systems using novel approaches still being developed that enable more rapid diagnosis and initiation of treatment nationwide; and
- USAID will work with up to 5 countries[99] to introduce patient-based electronic recording and reporting systems.

Within 5 years:

- USAID and CDC will work with up to 10 countries[100] to implement standards and benchmarks to improve surveillance and vital registration systems to directly measure TB burden;
- USAID will work with up to 10 countries[101] to scale-up patient-based electronic recording and reporting systems;
- DOD will work with other U.S. departments and agencies to enhance collection and sharing of TB and MDR-TB data in strategically relevant areas where the U.S. military may be deployed; and
- USAID and CDC will work with up to 10 countries[102] to implement an approach to link laboratory and TB and MDR-TB program-surveillance systems using novel approaches that enable more rapid diagnosis and initiation of treatment nationwide.

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[95] Ibid.

[96] Ibid.

[97] Ibid.

[98] Ibid.

[99] Ibid.

[100] Ibid.

[101] Ibid.

[102] Ibid.

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

The global market for second-line drugs (i.e., drugs for treating MDR-TB) is fragile. In fact, until a few years ago, quality-assured second-line drugs were generally unavailable. Realizing this critical gap, the U.S. Government has provided the support necessary to ensure availability of quality-assured drugs globally. The inability to predict drug needs and variations in regimens at the country level, unique in-country procurement mechanisms, and the limited quantity of drugs procured through the global pooling mechanism, however, make it difficult to quantify global needs and provide drugs in a timely manner.

MILESTONES

Within 1 year:

- 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.

Within 3 years:

- USAID will work with up to 10 countries[103] 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; and
- USAID will work with up to 7 countries[104] to introduce an MDR-TB early warning drug procurement and management system to prevent stock-outs.

Within 5 years:

- USAID will work with up to 10 countries[105] to scale up an MDR-TB early warning drug procurement and management system; and
- USAID will work with up to 10 countries[106] to assist them with their in-country regulatory approval processes of first-line and second-line drugs.

2.2. Prevent MDR-TB Transmission

The most effective way to prevent MDR-TB is to implement quality TB programs. Availability of appropriate medications and adherence to TB treatment and care helps prevent the development of MDR-TB; availability of and adherence to MDR-TB treatment, in turn, helps prevent the development of XDR-TB. The U.S. Government must accelerate and strengthen its efforts to monitor the quality of medications and adherence to treatment and address other program weaknesses to prevent further development and spread of MDR-TB and XDR-TB. In addition, access to earlier treatment for MDR-TB will significantly reduce transmission because patients become non-infectious soon after starting treatment, thereby preventing the possibly of their spreading the disease to others.

Evidence has shown that a proactive approach that employs community outreach and involves health-care workers is more likely to result in earlier diagnosis and treatment of TB and MDR-TB than would be the case when relying on individuals to seek medical care for TB symptoms.[107] Targeted approaches in each country need to be developed and implemented to identify and address delays in diagnosis and to explore opportunities to access those at high risk who are less likely to use health facilities. Lastly, the prevention of TB and MDR-TB transmission in health-care facilities is of paramount importance. The U.S. Government must intensify efforts to help protect health-care workers, patients, and families that use facilities at risk of spreading TB.

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[103] Ibid.

[104] Ibid.

[105] Ibid.

[106] Ibid.

[107] *TB Reach, Finding and Treating People with TB in the World's Poorest Communities*; Stop TB Partnership (2015): http://www.stoptb.org/global/awards/tbreach/

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

Lack of access to services and facilities is a major barrier to earlier diagnosis and treatment. Many individuals are unable to get to health facilities and either do not seek care or receive substandard care due to a lack of resources. Outreach programs are essential to connect those at risk with appropriate services and to prevent further spread of disease. Country-specific approaches are required to identify the groups and individuals in both the public and private sectors that are most at risk and the best ways to reach them. The U.S. Government will build on existing efforts to reach more individuals with patient-centered services.

MILESTONES

Within 1 year:

- USAID will work with up to 10 countries[108] to validate and introduce a risk-prioritization screening tool.

Within 3 years:

- USAID will work with up to 10 countries[109] to scale-up enhanced patient identification and medical screening of individuals at high risk for MDR-TB, based on data gathered using the risk-prioritization screening tool results.
- USAID will work with up to 10 countries[110] to introduce patient-centered TB and MDR-TB quality service delivery site monitoring.

Within 5 years:

- USAID will work with up to 10 countries[111] to further increase, beyond the 3-year milestones, enhanced patient identification and medical screening of individuals at high risk for MDR-TB; and
- USAID will work with up to 10 countries[112] to scale-up patient-centered MDR-TB quality service delivery site monitoring.

2.2.2. Enhance adherence to TB and MDR-TB treatment

TB and MDR-TB treatment is long and, often for those with resistant disease, toxic, costly, and stressful. In addition, TB affects the poorest and most marginalized individuals, populations that are among the hardest to reach with services. As a result, it is often difficult for TB-infected individuals to access and receive appropriate, quality treatment.

Effective adherence strategies and enhanced approaches to care are essential to avoid interruption of treatment and to prevent the development of drug-resistant TB disease. The U.S. Government will increase its support to high-burden countries to further promote strong adherence to treatment regimens in TB programs.

MILESTONES

Within 1 year:

- 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; and
- USAID will develop a quality-care-monitoring tool to improve the rates of adherence to TB programs of treatment.

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[108] *World Health Organization Global Tuberculosis Report 2015*: http://www.who.int/tb/publications/global_report/en/

[109] Ibid.

[110] Ibid.

[111] Ibid.

[112] Ibid.

Within 3 years:

- USAID will work with up to 10 countries[113] to implement ancillary care packages to improve MDR-TB patient treatment outcomes; and
- USAID will work with up to 10 countries[114] to implement a TB treatment adherence assessment tool

Within 5 years:

- USAID will work with up to 10 countries[115] to scale-up ancillary care packages to improve MDR-TB patient treatment outcomes; and
- USAID will work with up to 10 countries[116] to address gaps identified by the TB treatment adherence assessment tool.

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

Without the implementation of proven prevention practices, health-care facilities can accelerate the transmission of TB and MDR-TB. It is necessary to ensure that facilities are safe for both health-care providers and those they serve and that individuals are not put at risk when they perform their jobs or access care (Box 6). Building on existing U.S. Government work, the *National Action Plan* will focus on developing quality national infection control plans, ensuring proper equipment is available and procedures are followed in facilities that serve individuals with TB and MDR-TB, and monitoring and addressing TB and MDR-TB in health-care workers.

Box 6: MDR-TB Transmission to a Medical Worker

After qualifying as a doctor in South Africa, Dr. Dalene von Delft was working as a medical officer at a large State hospital when she developed a dry cough, which she attributed to allergies and sinusitis. However, because several of her colleagues had developed TB, she decided to get a chest x-ray. To her surprise, the x-ray showed significant lung abnormalities indicating TB. Because she knew that she had been in contact with MDR-TB patients, she was evaluated to determine if she might have resistant disease. Unfortunately, her hunch proved correct; laboratory testing led to a diagnosis of MDR-TB, resistant to four drugs. Dr. von Delft 's physician initiated a seven-drug regimen, consisting of 30 pills daily, as well as injections of amikacin, a drug known to cause hearing loss. Although Dr. von Delft started to improve after 2 months of therapy, her hearing began to deteriorate, which threatened the future of her medical career. Fortunately, in 2011, Dr. Von Delft was granted access to bedaquiline, a new drug that had not yet been approved by the U.S. Food and Drug Administration but was offered in South Africa through a compassionate-use program. Dr. von Delft was able to complete her new treatment regimen and considers herself fortunate, unlike the majority of individuals with MDR-TB, to have recovered from the disease, which she attributes to her access to this life-saving drug regimen and her care support system. Health-care workers in countries with high rates of TB and MDR-TB are at high risk of the disease. More than 15 of Dr. von Delft's colleagues have since been diagnosed with TB, including a colleague who recently became ill with XDR-TB. Dr. von Delft's story exemplifies just a few of the many hardships that individuals with MDR-TB have to endure, and it highlights the need for continued research to improve treatment options and optimize patient care.[117]

[113] Ibid.

[114] Ibid.

[115] Ibid.

[116] Ibid.

[117] *Physician heal thyself, Q&A with Dr. Dalene von Delft*; TB Proof (2015): http://www.tbproof.org/physician-heal-thyself-qa-dr-dalene-von-delft/

MILESTONES

Within 1 year:

- USAID will work with up to 10 countries[118] to develop quality national infection-control strategic plans; and
- CDC will develop a tool for assessing implementation and impact of TB infection-control interventions.

Within 3 years:

- USAID and CDC will develop guidance on best practices for TB infection control within health-care facilities based on evidence-based policy recommendations;
- USAID and CDC will work with up to 10 countries[119] 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; and
- USAID and CDC will work with up to 10 countries[120] to introduce or improve health-care worker surveillance and screening in facilities responsible for the diagnosis and treatment of individuals with, and at high risk for, MDR-TB.

Within 5 years:

- USAID and CDC will work with up to 10 countries[121] to ensure surveillance and screening of all health-care workers in facilities responsible for diagnosis and treatment of individuals with, and at high risk for, MDR-TB.

[118] Ibid.

[119] Ibid.

[120] Ibid.

[121] Ibid.

Goal 3: Accelerate Basic and Applied Research and Development to Combat Multidrug-Resistant Tuberculosis

Challenge to Developing Effective Diagnosis, Treatment, and Prevention of MDR-TB

New products for the diagnosis, treatment, and prevention of TB are urgently needed to accelerate control of drug-resistant and drug-susceptible TB. Faster and more accurate tests to diagnose TB and determine its susceptibility to available drugs would allow more timely and effective treatment of drug-resistant TB. Shorter regimens and new drugs that are effective against all forms of TB, including TB that is caused by strains of *Mtb* that are resistant to the currently available drugs and could cure TB within days or weeks—rather than months or years—would make it more likely for patients to complete therapy and decrease opportunities for the emergence of drug resistance. Finally, the development of an effective vaccine against TB could have a significant impact around the world by preventing all forms of drug-susceptible and drug-resistant TB.

Opportunity

Innovations in biomedical research, largely supported through NIH, have led to great strides in the understanding of TB and its causative pathogen *Mtb*. The U.S. Government and other major supporters of TB research and development globally have developed strategies and programs to support myriad scientific questions and approaches that need to be studied to improve scientific and medical understanding of TB; facilitate translation of basic research into development of new drugs, vaccines, and diagnostics; and provide medical evidence to allow for the safe and effective integration of new diagnostic, preventive, and therapeutic strategies into TB care programs in the United States and abroad.

While U.S. Government biomedical research programs have contributed significantly to the current pipeline of drug, vaccine and diagnostic candidates, more progress is critically needed in the development and introduction of new tools and infrastructure, and approaches to combat drug-resistant TB has been slow. Achievement of Goal 3 objectives will require close collaboration between the clinical and biomedical research communities and among many private and public sector groups, including pharmaceutical companies, patient and community engagement organizations, and U.S. Federal agencies (Box 7) to:

- Advance basic research to advance understanding of the interactions of host and pathogen and the human immune response to TB; and
- Ensure clinical findings are effectively translated into innovative tools and strategies for detecting, treating, and preventing drug-resistant TB.

Goal 3 activities will also build capacity to conduct clinical trials of TB drugs and vaccines in high-burden TB countries, including countries targeted by the U.S. Government TB efforts described in Goal 2.

The U.S. Government objectives summarized in Goal 3 represent selected high-priority activities that are already part of the established mission and programs of relevant U.S. Government agencies. In addition to these targeted efforts, the U.S. Government remains committed to continuing to support the full breadth of its existing TB research and development programs. Recognizing the value of domestic and international research and development collaborations, the U.S. Government will work to leverage and enhance the capacity of existing U.S. Government-supported research sites and programs, as well as those of its domestic and international partners, to combat the emergence and spread of drug-resistant TB (Box 7).

Significant outcomes of Goal 3 will include:

- Development of clinical and programmatic evidence to improve the use of current first- and second-line antibiotics and newly licensed drugs to improve treatment outcomes and prevent the development of drug resistance.
- Characterization of DNA sequences that confer resistance to antibiotics in *Mtb* strains isolated throughout the world. These sequences can be used to develop rapid assays for drug-susceptibility testing and for surveillance of drug-resistant TB.
- Development and validation of improved pre-clinical strategies for selecting the most promising drug and vaccine candidates for clinical trials, to contribute to a continuous supply of TB care products in the development pipeline.
- Focused research into the discovery of biological markers that indicate early response to therapy or protection against TB. These markers can be used in clinical trials to help expedite testing of new drugs, vaccines, and treatment regimens.

Box 7. Research and Development Partnerships

The U.S. Government's activities in TB research and development are coordinated with a wide range of global and domestic organizations. In particular, the development and licensure of new drugs, vaccines, and diagnostics requires the expertise and participation of pharmaceutical companies. The translation of research findings into implementable tools and strategies for global TB care and control depends on many constituencies, from academic scientists to health-care providers. Through its coordination among U.S. Government departments and agencies, and with other national and international funders, the U.S. Government has been able to contribute significantly to global biomedical and product development and implementation of TB research.

Through its existing and emerging collaborations, the U.S. Government will continue to support the generation of knowledge and its translation into new health-care interventions and strategies, while increasing the capacity of countries to contribute to global TB research. Milestones identified in the *National Action Plan* are dependent on the continued contributions from, and participation of:

- Academic scientists;
- Pharmaceutical and biotechnology companies;
- Not-for-profit product-development partnerships;
- Affected communities and their patient volunteers
- Research ethics oversight committees;
- Government and philanthropic supporters of TB research and development;
- Research advocates and professional societies; and
- Regulatory agencies.

Objectives

3.1. Increase options for preventing active TB, latent TB infection, and TB transmission

The development of a TB vaccine that prevents both latent infection and active TB disease—whether drug-susceptible or drug-resistant—would be a breakthrough in global health. Until such a vaccine becomes available, TB prevention can be advanced by optimizing other approaches (e.g., improved infection control in health-care settings and use of prophylactic treatments to prevent progression from latent to active drug-resistant TB).

3.1.1. Advance research and development of novel vaccines

Most high-burden TB countries employ the Bacille Calmette-Guerin (BCG) vaccine to protect infants and small children from severe complications of TB.[122] But the BCG vaccine is not considered to be effective against adult pulmonary TB and is not an effective tool for curbing the global TB epidemic.[123]

Development of a TB vaccine that can protect both adults and children requires multi-disciplinary approaches and close collaboration among public and private sector partners to ensure that scientific information is rapidly translated into new strategies and that vaccine candidates are rapidly evaluated.

MILESTONES

Within 1 year:

- NIH will:
  - Expand its dialog 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; and
  - Continue to support studies to map the diversity of immune responses required for vaccine efficacy.

Within 3 to 5 years:

- 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 and CDC will intensify collaborations with domestic and international vaccine developers to leverage pre-clinical and clinical resources for vaccine development;
- USAID will support platforms for TB vaccine researchers and key stakeholders in countries to facilitate collaboration and increase knowledge on TB vaccine research; and
- State and DOD will explore a proof-of-concept randomized controlled study to assess whether BCG can provide short term protection to adults for prevention of TB infection during extended travel to high-risk countries (for example, U.S. active military personnel and U.S. diplomatic corps); the published risk of infection is 4–8 percent for such travelers.[124,125,126]

3.1.2. Support the development of methodologies to prevent transmission and development of TB and MDR-TB

Each person with untreated latent TB or infection with drug-resistant *Mtb* has an about 10-percent chance of developing active (and infectious) disease, and each person with untreated disease can infect 10 to 15 persons within the course of a year.[127] In the absence of an effective vaccine, chemotherapeutic strategies to prevent development of active disease in adolescents and adults already infected with *Mtb* remain the mainstay of available preventive approaches in TB control programs. Prophylactic treatment approaches to protect persons who may already be infected with drug-resistant *Mtb* from developing active MDR-TB, however, have not been

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[122] *Revised BCG Vaccination Guidelines for Infants at Risk for HIV Infection*, *Weekly Epidemiological Record* 21; World Health Organization (2007): http://www.who.int/immunization/wer8221bcg_May07_position_paper.pdf?ua=1

[123] *BCG Vaccine Factsheet*; CDC (2011): http://www.cdc.gov/tb/publications/factsheets/prevention/bcg.htm

[124] *Tuberculosis Among Participants in an Academic Global Health Medical Exchange Program,* A. Gardner, et al*., Journal of General Internal Medicine* (2011)

[125] *Tuberculin skin test conversion rate among short-term health-care workers returning from Gaborone, Botswana*, Z. Szep, et al., *Travel Medicine and Infectious Diseases* 12 (2013)

[126] *Risk of infection with Mycobacterium tuberculosis in travellers to areas of high tuberculosis endemicity*. F. G. Cobelens et al., Lancet 2000 (August 5): 461–5

[127] *The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection*, E Vynnycky, et al., *Epidemiology & Infection* (1997)

well established. Intensified efforts are needed to evaluate and optimize the impact and cost-effectiveness of prevention strategies, including:

- Strategies to ensure completion of TB treatment regimens to decrease opportunities for the emergence of TB drug resistance; and
- Infection control strategies to prevent person-to-person transmission of MDR-TB in health-care settings (see Goal 2, Objective 2.2).

MILESTONES

Within 1 year:

- 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.

Within 3 to 5 years:

- USAID will evaluate at least one intervention to prevent the spread of MDR-TB based on assessments of probable transmission routes; and
- USAID and CDC will evaluate at least one new TB treatment regimen to prevent TB and MDR-TB in adults and children.

3.2. Improve the diagnosis of drug-resistant and drug-susceptible latent and active TB

Timely treatment of drug-resistant TB requires diagnostic tests that can rapidly detect disease and identify drug resistance. New diagnostic tools and drug-susceptibility tests are also needed to:

- Detect latent early-stage TB, which can develop into active TB; and
- Improve diagnosis of TB in children.

Childhood TB is particularly difficult to diagnose in resource-poor settings and often goes undetected or unreported.

Other diagnostic tools that could have a major impact on detection and treatment include TB biomarkers—measureable substances that provide information about disease progression, such as whether latent infections are progressing to active disease.

3.2.1. Support the development of new tools and approaches for detection of drug-resistant TB

The development of simple, inexpensive, and rapid tests that can distinguish among different types of drug-resistant TB will help ensure that patients receive timely and effective treatment.

MILESTONES

Within 1 year:

- 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 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;
- USAID will initiate an evaluation of at least one promising (preferably point-of-care) TB and MDR-TB diagnostic tool in adults and children; and
- 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.

Within 3 years:

- 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;

- 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 will encourage and support evaluations of tests suitable for use in young children where diagnosis of TB is more difficult; and
- 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.

Within 5 years:

- USAID will evaluate the programmatic impact of newly developed diagnostic tools.
- NIH, USAID, and CDC will support studies to understand the development of drug resistance to newly licensed or re-purposed drugs.
- CDC will use novel mobile health (m-health) and electronic health (e-health) systems to develop, pilot, and evaluate integrated models for real-time monitoring and evaluation of point-of-care and near point-of-care TB diagnostics to inform evidence-based laboratory and treatment program improvements; and
- NIH, USAID, and CDC will support evaluations of new diagnostic tests and their impact on patient care.

3.2.2. Support research to identify biological markers to help detect latent TB and progression to active TB in children and adults

One-third of the world's population is thought to be infected with latent (asymptomatic) TB, and each infected person has a 10-percent likelihood of progressing to active disease.[128] The identification of biomarkers that indicate which persons are mostly likely to develop active (and infectious) disease would allow national TB control programs to target treatment resources to persons who would benefit from therapy. TB biomarkers would also help simplify and expedite clinical trials by indicating, at an early stage, whether a patient is responding to a vaccine or drug regimen.

MILESTONES

Within 1 year:

- 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; and
- NIH, CDC, and USAID will expand clinical cohorts in TB endemic countries to study correlates of progression from TB infection to active disease.

Within 3 to 5 years:

- NIH and CDC will support clinical studies to validate biologic correlates of disease activation.

3.3. Improve treatment options for drug-susceptible and drug-resistant TB

Treatments for TB and drug-resistant TB are lengthy and difficult to complete. Priorities for improving TB treatment include:

- Using existing drugs as effectively as possible (the short-term solution);
- Integrating newly registered drugs into current treatment regimens (the medium-term solution); and
- Developing novel TB drugs and shorter regimens (the long-term solution).

3.3.1. Improve the use of existing TB drugs for treatment of drug-susceptible and drug-resistant TB

Improved uses of existing TB drugs may include:

- Dose adjustments or new drug combinations that improve safety and lead to faster cures; and

[128] *The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection*, E Vynnycky, et al., *Epidemiology & Infection* (1997)

- New drug formulations and treatment regimens that address the needs of young children and other special populations.

MILESTONES

Within 1 year:

- 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 vaccine development;
- USAID will initiate an assessment of new methods or packages of care to enhance treatment success; and
- USAID and CDC will continue to support ongoing studies in adults to assess shorter MDR-TB regimens using existing TB drugs.

Within 3 years:

- USAID will evaluate pilots of innovative strategies to improve treatment outcomes in at least five 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; and
- NIH will contribute to the development of pediatric formulations for new and existing TB drugs.

Within 5 years:

- USAID will use data from successful pilot interventions to work with partners to create guidelines and support expansion to all targeted priority countries;
- USAID and CDC will evaluate shorter regimens for MDR-TB in children using existing drugs;
- NIH, CDC, and USAID will contribute clinical evidence related to optimal use of existing first- and second-line treatment regimens in adults and children to improve future treatment recommendation; and
- USAID and CDC will evaluate innovative methods and approaches to support patients on treatment to enhance adherence and treatment success.

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

Two new drugs, bedaquiline and delamanid, have received recent approvals by regulatory authorities in the United States, FDA, and in Europe, European Medicines Agency (EMA), respectively, for treatment of drug-resistant TB when no other treatment options are available. Intensified efforts are needed to determine:

- How to integrate these new drugs into existing regimens in ways that allow safe and efficacious use; and
- Whether these two drugs can be administered at the same time without increasing the likelihood of adverse effects or adverse drug interactions.

MILESTONES

Within 1 year:

- USAID will support the evaluation of new and shorter TB regimens containing novel anti-TB drugs in adults.

Within 3 to 5 years:

- NIH and CDC will support clinical trials to assess the safety and drug interactions of bedaquiline, delamanid, or both;
- 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;
- CDC and USAID will identify best practices for the use of new drugs in novel MDR-TB treatment regimens based on pharmacovigilance data; and
- USAID and CDC will expand the evaluation of new drug regimens to treat children, including novel TB drugs for both TB and MDR-TB.

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

With the increased emergence of drug-resistant TB, new drugs, with novel mechanisms of action against which drug-resistant *Mtb* strains are not resistant, are urgently needed. Furthermore, new science underlying the rational combination of drugs into new regimens, as well as their pre-clinical characterization and clinical evaluation, is now emerging.[129] Innovative new strategies are being leveraged to ensure only the most promising new drugs and regimens advance to clinical trials. The development of these drugs and their assembly into new regimens also has the potential to provide shorter treatment options for all forms of TB.

MILESTONES

Within 1 to 3 years:

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

Within 3 to 5 years:

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

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

Research conducted in TB-endemic countries is essential to:

- Optimize strategies to improve diagnosis, clinical management, and prevention of TB;
- Conduct clinical trials of new drugs, drug regimens, and vaccines; and
- Evaluate the impact of local co-factors that may affect TB severity or increase susceptibility to TB (e.g., HIV/AIDS, diabetes, and use of tobacco).

U.S. agencies will provide research training, technical assistance, and guidance to help academic organizations and national TB programs build capacity to participate in clinical trials and conduct research to answer key questions and develop solutions to local TB control issues. The provision of technical assistance and research training will also help universities in high-burden countries compete for global research grants.

MILESTONES

Within 1 to 3 years:

- USAID will create an inventory (map) of potential sites and initiate needs-based procurement of equipment to prepare study sites;
- 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; and
- NIH will expand opportunities for funding of biomedical clinical research in TB-endemic countries.

Within 5 years:

- USAID and CDC will establish research training centers in up to 10 priority targeted countries; and
- NIH and CDC will increase the number of clinical trials and studies conducted in TB-endemic countries.

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[129] *Advances in the development of new tuberculosis drugs and treatment regimens,* A. Zumla, et al., *Nature Reviews Drug Discovery* (2013)

Next Steps

Over the next 5 years, the U.S. Government will work with members of the public and private sector, affected countries, non-government organizations, and global partners to meet the goals identified in the *National Action Plan* for the purpose stated in Box 8. These activities will be coordinated by the White House Office of Science and Technology Policy, National Security Council, and Office of Management and Budget. This initiative will require a sustained effort, thus, through 2020, the interagency leads responsible for executing the actions identified in the *National Action Plan* will report on an annual basis to the public and the White House on progress made. Federal departments and agencies are expected to take steps beyond what is explicitly included in the *National Action Plan* to combat MDR-TB; these efforts will also be summarized and included in the annual progress report. Industry, non-governmental organizations, and international partners will play key roles in accelerating progress in combating MDR-TB. This *National Action Plan* will solidify an ongoing collaboration among these entities that will ensure resources are leveraged effectively to address this urgent global threat to public health and prosperity. A healthy global population makes for stronger, more prosperous, and more stable nations; enhances international security and trade; and ensures a safer, more resilient America.

Box 8. Intended Purpose of the *National Action Plan*

The *National Action Plan* is intended to promote greater investment and coordination of U.S. Government resources to reduce the domestic and global risk of MDR-TB and to encourage other bilateral and multilateral donors, the private sector, and affected countries to invest additional resources in these important actions. The *National Action Plan* will inform the Federal budget and regulatory development processes within the context of the goals articulated in the President's Budget. All activities included in the *National Action Plan* are subject to budgetary constraints and other approvals, including the weighing of priorities and available resources by the Administration in formulating its annual budget and by Congress in legislating appropriations.