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I. Introduction

Chairman Smith, Ranking Member Bass, and Members of the Subcommittee, thank you for inviting me to testify on drug-resistant tuberculosis (TB) prevention and control. I am Dr. Tom Frieden, Director of the Centers for Disease Control and Prevention (CDC) within the Department of Health and Human Services (HHS). It is my pleasure to be here to discuss with you CDC's role in the response to drug-resistant TB in the United States and globally.

As you know, I come before you today in my capacity as the Director of the Federal public-health agency charged with preventing and ending TB, working in partnership with other Federal, state and local agencies in the United States and around the world.

My career in public health has been shaped and defined to a large degree by a connection to TB. I have seen, first-hand, the emotional and financial toll drug-resistant TB can take on a community, and that TB respects no borders – TB anywhere is TB everywhere. I have edited a book on TB prevention and control and contributed to more than 120 journal articles, book chapters and other publications on this topic. I have overseen the treatment of more than 1,000 patients with multi-drug resistant (MDR) TB, and have personally investigated and helped to stop outbreaks of MDR TB affecting hundreds of patients in the United States – the largest MDR TB outbreaks this country has ever experienced.

The spread of MDR TB and extensively drug-resistant (XDR) TB is a global health security concern worldwide, threatening decades of progress in TB prevention and control. Even in countries with a low TB burden such as the United States, MDR TB cases strain the public health system. It is a struggle to fund and maintain a steady supply of the very expensive drugs needed for these cases that are rare in the United States. I know from first-hand experience how critical it is that we address the looming crisis of drug-resistant TB immediately by helping vulnerable nations build capacity in core public health competencies: tracking disease, building strong laboratory systems, setting up responsive Emergency Operations Centers, and training a public health workforce.

TB has been treated for decades by a combination antibiotic and anti-infective medicine, so-called first line drugs, isoniazid and rifampin. Drug-resistant TB occurs when the TB bacteria adapt to the drugs used to treat it, making them ineffective. TB caused by strains of the bacteria that are resistant to the two most effective, first-line drugs -- isoniazid and rifampin -- is called multidrug-resistant (MDR) TB. MDR TB strains that are also resistant to second-line drugs, including a fluoroquinolone and at least one of the three injectable medications (amikacin, kanamycin, or capreomycin) are called extensively drug-resistant TB (XDR TB). XDR TB is a less common type of MDR TB, making up about 10 percent of all MDR TB cases. XDR TB was identified by CDC epidemiologists who had been consulted on treatment plans for TB patients who were resistant to not only the traditional TB therapy, but also the regimen used to treat MDR TB in 2004-2005. Seeing a pattern, CDC and the

World Health Organization (WHO) surveyed leading international TB reference labs in search of this phenomenon, which they found on every continent except Antarctica.

Imagine for a moment you have MDR TB – one of the nearly 500,000 people each year who become sick with strains of TB resistant to our best drugs. You face two years of treatment, during which time you will see a health provider nearly every day and receive 250 injections and 15,000 pills. The drugs that are most likely to cure you can have long-term side effects such as hearing loss. Treatment will cost 8 times more than the treatment for drug-susceptible TB, while treatment for XDR TB can reach almost a half a million dollars (or nearly 30 times the cost of drug susceptible TB treatment) in the United States. Now consider that if you actually receive such treatment, you are one of the lucky ones. Globally today, only about 1 in 5 people with MDR TB receive appropriate treatment, and only half of those are cured.

I cared for a TB patient for almost two years. He came to the United States from a rural area in Kerala, India. He developed what we would now call extensively drug resistant TB, or XDR TB. His infection was very difficult to treat, although he was very willing to be treated. His disease was so bad that we had to remove part of one lung and try experimental treatments. He needed an intravenous medication given to him for about a year, which luckily his wife, a nurse, could administer.

Twenty years ago this treatment cost more than $100,000. Today, it would cost as much as five times that amount. Years later, I went to India where I helped the Government of India (GOI) and the state government of Kerala implement a program in his village that could have prevented his case of drug resistance for $10. If we fail to stop the emergence of drug resistance anywhere, all of us are at risk.

II. Scope of TB: Burden of drug-resistant TB in the United States and Globally:

Before we can understand the problem before this Subcommittee today – the threat posed by drug-resistant TB – we need to understand tuberculosis in its broader context. TB is an airborne infectious disease that is spread from person to person, usually through coughing. A person exposed to TB is at risk of becoming infected with TB, a state known as latent TB infection, where the bacteria is dormant and does not immediately cause illness or infectiousness. WHO reports that one in every three people around the world is infected with dormant TB bacteria. I was infected with the tuberculosis bacteria while working in tuberculosis treatment centers in New York City before there was effective infection control. People infected with TB bacteria have an approximately 10 percent lifetime risk of developing active TB disease, developing symptoms, and potentially becoming infectious to others. The risk of developing active TB disease goes up dramatically for people with weakened immune systems, such as those with HIV, for example. Only when the bacteria become active do people become ill with TB. Appropriate treatment with effective drugs therapy will prevent the transition from latent TB infection to active TB disease. If not treated properly, TB disease can be fatal or develop resistance to the drugs used to treat it. Currently, drug susceptible TB, TB that is not resistant to first-line drugs, can be treated with six to nine months of therapy, including isoniazid and rifampin, a combination antibiotic and anti-infective medicine. This treatment cures more than 95 percent of patients.

In the late 19th and early 20th centuries, TB was one of the leading causes of death in the United States and Europe. Less crowded housing, improved nutrition, isolation of patients in sanatoria, development of effective TB drugs in the 1940s and other public health interventions led to a steady decline of TB in the United States and other industrialized countries; however, in much of the rest of the world TB remains a critical public health problem.

In 2014, 9.6 million people around the world developed TB disease. WHO recently announced that TB ranks alongside HIV as the leading cause of death from an infectious disease worldwide, claiming 1.5 million lives in 2014 alone, despite being nearly 100 percent curable. The disease is particularly deadly for people living with

HIV, whose weakened immune systems make them more susceptible to developing, and dying from, active TB. In 2014, 12 percent of all new TB cases were among people living with HIV, and 400,000 persons living with HIV died of TB – approximately one third of all deaths among people living with HIV.

In the United States last year there were 9,421 new TB cases, the 21st consecutive year of declining incidence due to intensive control efforts rigorously applied at the local, state, and national levels. Stewardship of antibiotics used against TB, completion of therapy among persons diagnosed with TB, contact investigations, and laboratory support have enabled us to prevent this problem from becoming widespread in the United States. However, any weaknesses in our public health system can easily be exploited by an airborne pathogen such as TB.

WHO estimates that globally last year there were nearly 500,000 MDR TB cases, approximately 50,000 cases of XDR TB, and 190,000 deaths from MDR TB and XDR TB. In contrast, intensive control efforts in the United States have resulted in a decrease in TB and MDR TB cases, which fell from approximately 400 per year in the early 1990s to fewer than 100 per year since 2012. The epidemiology of these cases also changed: of the total number of reported primary MDR TB cases, the proportion occurring in foreign-born persons increased from 25 percent (103 of 407) in 1993 to 85 percent (57 of 67) in 2014. Between 1993 and 2014, a total of 74 cases of XDR TB were reported in the United States to CDC.

While there were few cases of MDR TB in the United States, each case requires lengthy treatment regimens with drugs that are difficult to take and often have serious adverse effects, imposes high costs on the health care system and society, and has a mortality rate that is much higher than for drug susceptible TB cases. These drug-resistant strains are transmitted in the same manner as drug-susceptible TB, but they have lower cure rates.

III. Causes

How did we get here? The most important thing to understand about the cause of MDR TB is that it results from an ineffective treatment program, insufficient infection control, or both. Breakdowns in the clinical and public health care systems cascade lead to antibiotic resistance, and the same is true for TB. Antibiotic resistance is now recognized as a global priority.

Drug resistance develops when patients receive incomplete or inadequate treatment. Treatment of drug susceptible TB requires at least six months of treatment with four different antibiotics. This regimen was developed to assure that all the bacteria in the person's system are killed. However, if this regimen is interrupted, only some of those TB bacteria are killed. Others are able to withstand the partial treatment and continue to grow, selecting for resistance to drugs in the incomplete regimen. Patients whose treatment is not completed can relapse, die, or develop drug-resistant strains of bacteria, which can then be passed to other individuals, generally through coughing.

These circumstances are more likely to arise in the context of under-resourced public health systems and ineffective national TB control programs, which are often unable to consistently apply the fundamentals of TB control. While the co-epidemic of TB and HIV has fueled the spread of TB in many parts of sub-Saharan Africa where drug resistance is a growing problem, MDR TB is also concentrated in countries with low HIV burdens where investment in TB control has been uneven in the past. In fact, more than half all cases of MDR TB occur in India, China, and the Russian Federation.

No program, no matter how well funded, can treat MDR TB faster than a poorly functioning program can create and spread MDR TB. We must never lose sight of the need to continue to improve treatment of the majority of patients, because, if they are not effectively treated today, they will have, and spread, MDR TB tomorrow. Gaps at any point in the public health system – from rapid and accurate diagnosis of resistance, to providing patients

with effective drugs under a regimen of patient-friendly directly observed therapy, to effective infection control to prevent transmission – contribute to the development and spread of drug-resistant TB. These gaps *can* be closed. Strong public health systems can address the barriers that fuel resistance if they have a well-functioning surveillance network, solid laboratory capacity, and a trained health workforce to implement the fundamentals of TB control.

The TB resurgence that occurred from 1985-1992 in our country provides a clear example of how outbreaks of drug-resistant TB can develop. From 1953, when the current U.S. TB surveillance system was established, through the mid-1980s, TB cases in the United States declined steadily, from approximately 83,000 to 22,000 new cases per year. However, in 1985 CDC began documenting increases in TB incidence. Factors associated with this increase include the dismantling of TB programs, which occurred when health departments stopped receiving TB-categorical funds and shifted resources to other public-health activities. Other factors included the burgeoning HIV epidemic, increased immigration from countries with high TB incidence rates, the spread among homeless people, lack of infection-control precautions in healthcare settings, and the occurrence of MDR TB at a time when the laboratory capacity to readily identify these strains was inadequate. After the resurgence of TB and spread of MDR TB in the early 1990s, Congress appropriated additional funding to CDC to support TB programs, laboratories, and research. CDC provides funding for state and local TB programs in all 50 states, 10 major cities, and eight territories. This funding supports the capacity to screen people who have been exposed to infectious disease, treat those with latent TB infection and TB disease, manage patient care, and carry out programs including effective contact investigations, surveillance, and outreach. Since the TB resurgence peaked in the United States in 1992, the number of TB cases reported annually has decreased by 65 percent.

IV. Complexities of Diagnosing and Treating Drug-Resistant TB

Detecting MDR TB is challenging primarily because traditional diagnostics used in much of the world – such as smear microscopy and drug-susceptibility testing from culture – are either unable to detect drug resistance or take weeks to months to provide an accurate diagnosis. This causes delays in diagnosis and treatment that undermine our ability to break the cycle of transmission. In many parts of the world, drug-resistant TB is only suspected when a patient fails to respond to therapy for drug-susceptible TB after months of treatment. Delay in testing leads to inappropriate therapy that itself can create increasingly drug resistant strains and substandard patient care.

There have been many advances in diagnostics in the past five years. CDC is working to increase the use of these new diagnostics and make them available to high-burden countries around the world. For example, Xpert MTB/RIF® is an automated molecular diagnostic that can diagnose TB and resistance to rifampicin - one of the first-line anti-TB drugs – within two hours. This new diagnostic holds great promise in enabling rapid detection of drug resistance, and the U.S. Government has led the global effort to scale up access to this test. The increase in the proportion of drug-resistant TB cases diagnosed and started on treatment over the past several years is largely attributable to the scale-up of this test. But it is expensive and still does not provide the cheap, point-of-care diagnosis of all forms of drug resistance that would be optimal to accelerate control of drug-resistance.

In the United States, state and local TB programs conduct culture-based tests for TB and drug susceptibility testing for positive isolates to determine whether they can be treated with isoniazid, rifampin, and other first-line drugs. Drug susceptibility results are reported each year to CDC. In 2014, the drug susceptibility testing rate in the United States was 96.2 percent, and this level of coverage allows CDC to track forms of resistance and ensure that patients with drug-resistant strains are detected and started on appropriate therapy. These laboratory technologies require six weeks to determine how the bacterial colony will react to various anti-TB drugs. In 2009, CDC began to provide molecular detection of drug resistance (MDDR) service to states. The molecular detection methods allow bacterial DNA to be examined for mutations associated with drug resistance,

producing actionable results in a few days. This enables clinicians to prescribe second-line drugs for a patient with MDR TB or XDR TB.

Thanks to new Advanced Molecular Detection (AMD) funding provided by the Congress in FYs 2014 and 2015, CDC is building capacity in State public health laboratory programs to conduct Whole Genome Sequencing of Mycobacterium tuberculosis, (Mtb). Whole Genome Sequencing is a powerful tool that examines the entire genome of Mtb and provides higher resolution as compared to conventional genotyping methods. This is useful in refining strains of Mtb that are circulating among populations experiencing large outbreaks.
But the challenges continue. Even after the disease has been found and confirmed, patients, physicians, nurses, and outreach workers face other daunting challenges.

MDR TB and XDR TB are far more difficult to cure than drug-susceptible TB. It generally requires 18–24 months of treatment with four to six drugs (*i.e.*, first-line drugs to which the patient is still susceptible plus an injectable agent, a fluoroquinolone, and other second-line drugs as needed). These drugs are less effective and more toxic, leading to a series of adverse side effects, some of which may be permanent, such as hearing loss. The first new drug that operates via a new mechanism of action for the treatment of TB approved in over 40 years is bedaquiline fumarate. As part of a combination minimum four-drug therapy, this new drug is used for the first 24 weeks of treatment for some MDR TB patients. Though it represents a new class of drugs, it still requires that patients complete an entire 18 to 24 month treatment regimen. Like other anti-TB drugs, this drug may be poorly tolerated and result in adverse side effects such as liver toxicity, or cardiac toxicity.[1]

Drug-resistant TB also takes an economic toll. The cost of treating MDR TB and XDR TB is significantly higher than the cost of the first-line regimen used for drug susceptible TB. More than 75 percent of patients with drug-resistant TB in the United States require hospitalization and isolation, at least during the initial phase of treatment. Also, anti-TB drugs are now off-patent and vulnerable to shortages caused by problems in manufacturing and distribution. Costs for these drugs can fluctuate wildly. Earlier this year, the price of cycloserine jumped 2,000 percent after its manufacturer and distributor sold the rights to another company. The rights were subsequently returned to the original owner and now it is $27 per tablet, double the original cost. Treatment costs in the United States average $150,000 per MDR TB patient and $482,000 per XDR TB patient. In comparison, costs are estimated at $17,000 per non-MDR TB patient. [2] The 373 MDR/XDR TB cases that occurred during 2005–2007 cost the U.S. health care system an estimated $53 million. The public sector incurred 80% of the MDR TB costs and 100 percent of the XDR TB costs.[3]

V. CDC's response to drug-resistant TB in the United States and around the world

The United States Government is a global leader in combatting TB. We are actively engaged in implementing international TB control plans, including the *Stop TB Partnership's Global Plan to End TB*[4] and the World Health

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[1] CDC. Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis. MMWR 2013; 62(RR09);1-12.

[2] Marks SM, Flood J, Seaworth, Hirsch-Moverman Y, Armstrong L, Mase S, Salcedo K, Oh P, Graviss EA, Colson PW, Armitige L, Revuelta M, Sheeran K, and the TB Epidemiologic Studies Consortium. Treatment Practices, Outcomes, and Costs of Multidrug-resistant and Extensively Drug-resistant Tuberculosis, United States, 2005-2007. Emerging Infectious Diseases. 2014;20(5):812-820.

[3] Marks SM, Flood J, Seaworth, Hirsch-Moverman Y, Armstrong L, Mase S, Salcedo K, Oh P, Graviss EA, Colson PW, Armitige L, Revuelta M, Sheeran K, and the TB Epidemiologic Studies Consortium. Treatment Practices, Outcomes, and Costs of Multidrug-resistant and Extensively Drug-resistant Tuberculosis, United States, 2005-2007. Emerging Infectious Diseases. 2014;20(5):812-820.

[4] http://www.stoptb.org/global/plan/plan2/

Organization's *End TB Strategy*,[5] which identifies key interventions and ambitious targets for the global community to End TB by 2035. CDC was a founding member of the "Green Light Committee," WHO's initiative to scale-up treatment for MDR TB in 2000. Additionally, CDC has been closely involved in the efforts of the WHO and the Global Fund to Fight AIDS, TB, and Malaria in the development of standards and policies to improve control of MDR TB. These partnerships are critical to translating evidence into action as we develop novel strategies and approaches to find, cure, and prevent TB and MDR TB.

For CDC, addressing the crisis of MDR TB is a frontline endeavor. Our goal is to find, cure, and prevent TB at home and abroad. CDC strongly believes that core public health capabilities – particularly improved disease surveillance, laboratory capacity, response capabilities, and a trained public health workforce – are critical to addressing drug-resistant TB and ensuring that the fundamentals of TB control are consistently and effectively applied.

The missions of the U.S. Federal agencies working on TB must be aligned and cover all aspects of biomedical, operational, domestic and international public health research, response, and program implementation. CDC is the lead agency for domestic TB prevention and control efforts. Domestically, CDC carries out TB prevention, control, and laboratory services in partnership with state and local health departments. In the area of research, clinical studies funded through the TB Trials Consortium (TBTC), CDC and international and domestic research partners are seeking to shorten TB treatment and address the significant limitations of current therapies—including harmful adverse effects—and improve therapy for children; people with HIV infection, diabetes, other co-morbidities; and people with drug-resistant TB. In 2011, CDC published results from a major TBTC study showing that once-weekly isoniazid and rifapentine for three months by directly observed therapy is safe and effective for treating latent TB infection and preventing the development of TB disease. In addition to clinical trials, CDC supports the TB Epidemiologic Studies Consortium (TBESC), which applies epidemiologic, behavioral, economic, laboratory, and operational research to improve programmatic efforts in TB elimination. TBESC focuses on approaches to diagnosing and treating people with latent TB infection to prevent future cases of TB disease.

CDC also works to prevent the importation of TB into the United States in multiple ways, including the administration of regulations that govern the health screening of approximately 450,000 immigrants and 70,000 refugees annually. Immigrants and refugees are subject to a medical examination overseas, which includes screening for active TB. Beginning in 2007, CDC rolled out new and more stringent TB screening requirements. Drug susceptibility testing is also required, so that applicants with drug resistant tuberculosis are identified. All U.S.-bound immigrant visa applicants and refugees diagnosed with tuberculosis overseas must complete treatment to cure their TB prior to entry into the country. These initiatives have been a win-win-win; resulting in improved tuberculosis diagnosis and treatment services in many countries, more rapid diagnosis and effective treatment of people with TB, and in California public health officials have documented a nearly threefold reduction in the percentage of prospective immigrants and refugees coming to the United States through California with active tuberculosis following implementation of these screening enhancements.

In combating TB globally, CDC partners with other U.S. Government agencies, multilateral institutions, and ministries of health to provide technical support and lead critical research to identify innovative strategies and approaches to control TB around the world. Globally, CDC, is on-the-ground to address TB in more than 30 countries, conducting research, assisting with policy development, and sharing technical expertise with our global partners. Through partnerships with USAID and other federal agencies, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Health Security Agenda platforms, CDC is addressing some of the critical gaps affecting TB control and antimicrobial resistance efforts around the world. A whole-of-Government approach is critical to the global fight against TB. Achieving maximum impact will require more effective

[5] http://www.who.int/tb/post2015_strategy/en/

interagency collaboration to promote synergies, avoid duplication of efforts, leverage specific agency expertise, and assure a comprehensive response to the TB epidemic.

In support of the PEPFAR 3.0 strategy – the right intervention, at the right place, at the right time – CDC is implementing innovative approaches for active case finding, rapid HIV and TB treatment, linkage and retention in care, and service integration. The strategy dovetails well with the UNAIDS 90-90-90 targets: people living with HIV need access to effective HIV treatment to survive MDR TB or XDR TB.

Through PEPFAR, CDC works directly with Ministries of Health to expand laboratory capacity to diagnose all forms of TB and drug-resistant TB quickly and accurately. CDC was involved in the initial field evaluations of Xpert MTB/RIF, a testing platform for the detection of TB and rifampicin-resistant TB - a proxy for multidrug resistant TB. CDC has supported implementation, quality assurance and monitoring and evaluation of this novel technology in more than 20 countries. CDC has worked with other technical leads in developing how to best deploy and optimally use Xpert MTB/RIF. Globally, approximately 20,000 GeneXpert machines have been deployed to countries and as of March 2015, the ten millionth test was completed.

CDC further strengthens the laboratory capacity of PEPFAR countries. Working together with WHO-AFRO and the African Society for Laboratory Medicine, CDC introduced systems for lab quality and accreditation via two important programs: Strengthening Laboratory Management Toward Accreditation, and Stepwise Laboratory Quality Improvement Process Towards Accreditation. Such processes assure clinicians and patients that their laboratory will be able to accurately and reliably detect drug resistant TB to guide treatment decisions. Currently, more than 600 TB, HIV, and other public health laboratories from 47 partner countries have implemented these accreditation programs, many making measurable progress towards accreditation.

TB control can also be advanced through the Global Health Security Agenda (GHSA). Health security is a global issue, yet less than a third of the world (65 countries) is currently able to rapidly detect, assess, report and respond to public health events from Ebola to emerging infections such as Middle East Respiratory Syndrome (MERS). To address these challenges, the Global Health Security Agenda serves as a unifying framework to improve global readiness to prevent, detect, and respond to disease outbreaks, so disease threats are stopped at the earliest possible opportunity. The same public health systems to be strengthened by GHSA will also help countries better respond to TB and other more common diseases.

Examples of CDC TB control activities that can be addressed by GHSA include:

- Strengthening laboratory diagnostics and increasing availability of point-of-care rapid testing for early diagnosis of MDR TB
- Strengthening surveillance systems and infection control (especially in clinical settings to prevent healthcare associated transmission of TB)
- Training public health workforces to deliver directly observed treatment
- Putting emergency management systems in place to direct resources during outbreaks and quickly mitigate them
- Encouraging countries to develop comprehensive plans to combat antimicrobial resistance and support responsible use of antibiotics
- Supporting development of new, shorter, and alternative treatments

As an example of Global Health Security Agenda activities rolling out this year, CDC and GOI clinical partners have identified TB and four other pathogens as the initial focus of drug resistance work. The clinical facility phase of the project will assess and strengthen both clinical antimicrobial use practices and infection control capacities for containment of antimicrobial resistant (AMR) pathogens. CDC and the GOI clinical partners are working to provide reliable drug resistance data to support successful patient care, address the public health

need to measure and track the magnitude of drug resistance threats affecting the country, and report on those data. To date, CDC and the GOI have successfully established the first 18 clinical sites with project collaborators and have identified a partner for a drug resistant TB treatment training center. CDC will be working with Indian partners to implement advanced, rapid molecular diagnostics to detect rapidly, better characterize, and support public health responses to drug-resistant TB. Through this effort, rapid molecular detection methods will be in place for screening patients at high-risk of drug-resistant TB, coupled with drug susceptibility testing, in targeted facilities. Coming full circle, I hope this will prevent more cases such as the patient I treated from Kerala, India at the source.

VI. **Conclusion**

Each year, 1.5 million people die from a disease that is nearly 100% preventable. But to prevent these deaths, we must greatly improve the application of currently proven tools and also innovate to end TB as a global public health threat. CDC is at the forefront of these innovations. Our goal is to find, cure, and prevent TB at home and abroad. No single agency or government can succeed in isolation. To win the fight against this disease, we need greater resolve and action from the entire global community.