Testimony
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Protecting the U.S. From Drug-Resistant Tuberculosis: Reinvesting in Control and New Tools Research

Statement of

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Good morning, I am Dr. Kenneth Castro, Director of the Division of Tuberculosis (TB) Elimination, in the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, in the Coordinating Center for Infectious Diseases, in the Centers for Disease Control and Prevention (CDC) within the Department of Health and Human Services (HHS). Chairman Brown, Ranking Member Enzi and other distinguished members of the Committee, it is my pleasure to be here to discuss with you CDC's role in eliminating tuberculosis, including multidrug-resistant and extensively drug-resistant tuberculosis, in the United States. This statement highlights what is necessary for the US to work toward eliminating TB domestically and to assist in the Millennium Development goals for global TB control.

TB and Drug Resistant TB

Tuberculosis is an airborne infectious disease that is spread from infectious persons when lung or throat secretions become aerosolized. In the late 19th and early 20th centuries, until the introduction of the antibiotic streptomycin in the 1940's, TB was one of the leading causes of death in the United States. TB may also mimic many other diseases in its clinical state. Currently, the World Health Organization (WHO) reports that one in three people in the world are infected with dormant or latent *Mycobacterium tuberculosis*, the bacteria that cause TB and nearly 9 million people develop active disease each year.

The risk of transmitting any type of TB depends on several factors, including the extent of disease in the patient with TB, the duration of exposure, and ventilation. Most of the people who become infected with TB do so after prolonged, close contact with an infectious patient. People can also be infected, but remain healthy until the bacteria become active at a later time. This can happen when immunity is compromised, for example, by HIV, advancing age, immunosuppressive therapies and some medical conditions such as some autoimmune disorders and cancers.

TB that is not resistant to drugs can be treated with a six to nine month course of "first-line drugs" (the most effective and safe), including isoniazid and rifampin; this treatment cures over 95 percent of patients. However, since people in many resource-poor countries lack access to appropriate treatment, about 1.6 million people die each year from TB.

TB that is resistant to at least isoniazid and rifampin is called multidrug-resistant (MDR) TB. MDR TB requires treatment for 18-24 months with "second-line drugs" that are less effective, often poorly tolerated by the patient, and far more costly. The cure rate for MDR TB is 70-80 percent under optimal conditions, but is usually closer to 50 percent. Many countries with a high TB burden lack the laboratory capacity to test for MDR TB and, even when MDR-TB patients are identified, these countries often lack the resources to cover the cost of second-line drugs and the intensive support required to administer the drugs.

Extensively drug-resistant TB (XDR TB) is a subset of MDR TB caused by strains of bacteria that are resistant to the most effective first- and second-line drugs. Reported mortality rates among persons with XDR TB are extremely high. Among non-immunocompromised persons, reports indicate that approximately 30 percent of patients can be cured, and more than half of those with XDR TB die within five years of diagnosis. Among immunocompromised persons, the illness is more severe, the mortality rate is even higher and death occurs within a shorter time.

To date, 41 countries have confirmed cases of XDR TB; however, because many countries do not routinely test all isolates for resistance to second line drugs, the precise global incidence of XDR TB remains uncertain. Since drug resistance does occur, XDR TB could be much more widespread. Factors associated with development of drug resistant cases include the use of second-line drugs in suboptimal conditions, inconsistent TB case management, interruptions in drug availability due to supply management or resource limitations, patient non-adherence with drug treatments, and high HIV prevalence. The ability of the disease to develop resistance to therapies and for those infected with drug resistant strains to travel easily across borders makes worldwide TB control efforts critical. This is especially critical given the burden to the public health care system resulting from intense patient management and prolonged therapy.

TB in the United States:

CDC has reported the lowest number of TB cases in the US, ever, at 13,779 new cases diagnosed during 2006. This represents a 2.1% decrease from the previous year. The case rate also decreased from 4.7 to 4.6 cases per 100,000, a decline of 3.1%. Since the 1992 TB resurgence peak in the United States, the number of TB cases reported annually has decreased by 48%. The latest data show that deaths are also decreasing, from 657 deaths in 2004 to 646 deaths in 2005. Despite these successes, the decreasing trend has slowed from an annual average decline of 7.3% for 1993 through 2000 to an annual decline of 3.8% for 2000 through 2006. Challenges to TB control remain, including: (1) racial and ethnic minorities continue to suffer from TB more than majority populations; (2) foreign born persons are adversely impacted; (3) sporadic outbreaks/clusters which outstrip local capacity; (4) cases of drug resistance threaten our ability to control TB; and (5) need for new tools for rapid and reliable diagnosis, safe and effective treatments and vaccines.

The United States still faces disparities in TB rates between racial and ethnic groups in U.S.-born persons. Current rates among non-Hispanic Asians are 25.6 cases per 100,000; among Hispanics or Latinos, 9.2 cases per 100,000; among black or African-Americans, 10.2 cases per 100,000; and among non-Hispanic whites, 1.2 cases per 100,000. These case rates clearly indicate that additional efforts may be needed for these population groups.

Despite decreasing TB incidence in United States, the majority of reported TB cases are foreign-born. The percentage of TB cases in foreign-born persons in the United States increased from 22% of report cases in 1986 to 57% in 2006. Overall the number of TB cases among the foreign born remained stable, at about 7,000 to 8,000 a year from 1993 through 2006.

Cases of MDR TB accounted for less than 1% of TB cases reported in 2006 (91 primary MDR cases out of 13,779). The proportion of cases of MDR TB among foreign-born persons has increased dramatically since the early 1990s, increasing from approximately 26% of MDR TB cases in 1993 to approximately 76% of MDR TB cases from 1999 through 2006. And of the 48 cases of XDR TB identified from 1993 through 2006, more than half were among the foreign born. In addition, trends in XDR TB cases indicate that the problem in the US is shifting to reflect the global epidemic. XDR TB cases that occurred from 1993-1999 were more likely to be in patients who were HIV co-infected and born in the US. However, the majority of XDR TB cases that occurred from 2000-2006 were among foreign-born persons (75% of 11 cases).

While the total number of MDR and XDR TB cases is relatively small, their impact on U.S. TB control programs can be significant in terms of human capital and financial resources. For example, one patient with MDR or XDR TB requires a minimum of 18-24 months of treatment, and in-patient costs alone for XDR TB can average $500,000 per case. Small programs are vulnerable in the event that an MDR or XDR TB case is identified in their jurisdiction. For example, this year,

a case of MDR in Idaho nearly depleted the State's entire drug budget of approximately $40,000. States that are unable to carry out their TB programs could be more likely to face outbreaks. From 1999 to 2004 CDC investigated only one outbreak of MDR TB, involving three patients in a state jail. Since 2004, CDC has been called to investigate four state outbreaks of MDR TB, including one which involved international travel. The occurrence of MDR and XDR TB unveils longstanding limitations with available diagnostic tools.

Essential Elements of an Effective TB Program in the United States

Essential elements of an effective TB program in the United States include Federal leadership and policy guidelines development working in partnership with strong state and local TB control programs. Other elements include: research into new drugs, diagnostics and vaccines, prevention of the importation of disease, and work with other countries and organizations to control TB globally.

Strong Federal Leadership and Guideline Development

At the Federal level, CDC serves several critical roles in controlling TB. CDC provides leadership and scientific support for TB control efforts both nationally and internationally. CDC monitors TB at the national level and develops standards for monitoring TB at the state level. CDC also utilizes expert panels and internal technical expertise to develop TB guidelines to be implemented with the help of other U.S. government agencies and professional associations. These guidelines address factors such as core components of TB control

programs, TB control in healthcare settings, use of diagnostic tests and recommended treatment regimens. The Federal TB Task Force established in 1991 facilitates coordination of activities between federal agencies.

Strong State and Local TB Control Programs

The best defense against the development of drug resistant tuberculosis is a strong network of state and local public health programs and laboratories. If the United States does not protect its public health infrastructure, weaknesses in programs will enable additional MDR TB outbreaks – as seen in the 1980's and early 1990's. As with other infectious diseases, state, local, and territorial health departments support and augment the medical care system. These "front line" public health agencies are in direct contact with medical care providers and patients, providing important TB control services such as directly observed therapy (DOT, a proven method to improve adherence and thus prevent drug resistance), laboratory support, surveillance, contact tracing, and patient counseling. CDC provides about $100 million annually in support to state, local and territorial health departments to prevent and control TB. Federal funding levels for TB control have been relatively stable, but many state and local governments have faced budget challenges in recent years. To better match TB funding to the current TB disease burden across the United States, CDC uses a funding formula to distribute a portion of available funds to states with higher disease burden and more complex cases to manage.

Improved ability to diagnose and treat TB

Research to improve TB diagnostics and drug treatment regimens is critical to controlling TB worldwide. The most widely used diagnostic test for latent TB is over 100 years old. More rapid and sensitive tests are needed for the diagnosis of active TB and for MDR TB and XDR TB. The most common drugs used to treat TB are more than 40 years old. The global goals for a better TB treatment regimen include a shorter treatment length (2 months or less); high (99 percent) cure rate; and decreased side effects and fewer drug interactions, especially with HIV treatment medicines. In addition, development of a very short course (i.e., weeks), well tolerated treatment is greatly needed for latent TB infection.

Diagnostics

CDC has supported efforts to improve surveillance and diagnosis of TB in the United States. These include the TB Genotyping Program, now active in 50 states, research to evaluate the use of nucleic acid amplification testing, and development of guidelines for use of QuantiFERON-TB-Gold to diagnose infection.

However, new diagnostic tools are needed to identify TB infection and to determine the best course of action for treating both active and latent cases. Identification of rapid, highly accurate, point-of-care tests for TB diagnosis and identification of drug resistance would enable physicians to identify the correct regimen at the time of diagnosis. New point-of-contact tests have been

developed to identify TB infection. However, further evaluation of these tests is needed.

Improving testing for drug susceptibility is also critical. Current tests for drug susceptibility testing are conducted by growing colonies of TB bacilli and exposing them to various antibiotics. Since TB bacilli are notoriously slow-growing organisms, this process takes at least one month to complete. This process is also a difficult procedure to standardize, and maintaining the proficiency to perform these tests is challenging in laboratories that do not conduct them frequently.

Newer molecular tests for drug susceptibility testing hold great promise for reducing the time for detecting resistance from months to days. However, such tests are not standardized and are only performed at a handful of laboratories in the United States. Commercial test kits have been developed, but have not been adequately field tested and are not licensed for use in the United States by the Food and Drug Administration (FDA).

New Treatment Regimens

It has been over 30 years since the effectiveness of short-course (six month) TB therapy was first introduced. Since then, only one new anti-TB drug class has appeared, and the utility of that class of drugs may be limited by their widespread use for other common conditions. For the first time in over 40 years, four new

anti-TB drug candidates have entered clinical trials, and other candidate compounds are in earlier stages of development.

CDC's TB Trials Consortium has a leading role in clinical tuberculosis research. Results from these consortium trials have formed the basis for the treatment guidelines developed by CDC and the American Thoracic Society, and in updating regimens for both HIV and non-HIV infected patients. This research will be increasingly important for the development of new drugs and regimens for drug-resistant TB. CDC has had primary responsibility for programmatically relevant TB drug and diagnostics research since the early 1960's. CDC also works closely with the National Institute for Allergy and Infectious Diseases which has the lead basic research on TB drugs and vaccines.

Training of Health Care Workers

TB remains difficult to diagnose and treat, and because there are relatively few cases in the United States, many health care workers lack experience and proficiency in recognizing it. CDC supports Regional Training and Medical Consultation Centers to train health care workers in TB prevention and control, and to serve as consultants to community physicians and local and state TB programs. CDC also provides direct training and health communication tools for TB programs and health care workers.

Preventing the Importation of Disease

The United States works with partners worldwide in an effort to reduce the introduction of TB and drug-resistant TB into the United States. For example, CDC is involved with US-Mexico Border activities to protect against the development of drug resistance. CDC supports TB prevention and control activities in the four states that border Mexico to ensure uninterrupted access to treatment throughout the entire course of therapy.

In addition, the United States has strengthened the requirements for screening and treatment of refugees prior to their resettlement in the United States. These requirements are credited with a 14-fold reduction in reported TB cases in refugees from Thailand since 2005. CDC is also piloting a project to provide rapid notification to U.S. TB control programs on the TB status of newly-arriving immigrants and refugees.

Finally, CDC also works to prevent the introduction of TB cases into the United States and the movement of infected individuals between states. When necessary, CDC can use isolation and quarantine strategies to restrict the movement of individuals who are traveling with TB. To this end, CDC maintains a close partnership with DHS and its agencies, and has worked hard over the past months to strengthen the link between public health and homeland security. The partnership between Customs and Border Protection and CDC is particularly vital, as CBP officers act as CDC's "eyes and ears." It should be noted that state and local governments have primary responsibility for isolation and

quarantine within their borders and conduct these activities in accordance with their respective laws and policies.

Controlling TB Globally

Because we live in a global economy and because most cases of TB in the United States are among foreign-born persons, it is critical for the United States to assist in TB control globally. CDC provides leadership and technical assistance in infection control, epidemiology, surveillance (including drug resistance surveys), program and laboratory services development, monitoring and evaluation, operations research and training, improving diagnostic services, and identifying clinical factors important to TB outcomes. These efforts build upon CDC's successful program to control TB in the United States. CDC collaborates with U.S. partners to reduce TB in high-burden countries by developing guidelines, recommendations, and policies. Over the past three years, CDC has been supporting TB control efforts in more than 25 countries on 5 continents.

In addition to working closely with Ministries of Health in other countries, CDC works with multilateral organizations including the World Health Organization and the International Union for TB and Lung Disease, foundations (including the Bill and Melinda Gates Foundation funded collaboration, such as the Foundation for Innovative Diagnostics (FIND)), and non-governmental organizations. CDC is a founding member of the Stop TB Partnership, a global

effort of more than 500 governmental and non-governmental organizations, housed by the WHO. Members of the Stop TB Partnership work towards achieving the 2006-2015 Millennium Development Goals of reducing global TB deaths by 50% and the number of persons suffering from TB by 50%.

Finally, as an implementing partner of the President's Emergency Plan for AIDS Relief (PEPFAR), CDC plays a critical role in efforts to address TB in the context of PEPFAR's HIV/AIDS prevention and treatment programs. Funding under these activities is tracked and accounted for under PEPFAR country operation plans.

Conclusion

To control TB, CDC and its partners must continue to ensure the United States has the essential elements of a strong TB control program. These include: (1) ensuring strong Federal leadership; (2) ensuring that state and local TB programs are adequately prepared to identify and treat TB patients to prevent drug resistant cases; (3) developing improved drug treatment regimens and diagnostics, (4) training health care professionals to identify and treat this complex disease; and (5) working with partners globally to reduce the introduction of TB into the United States and reducing the burden of disease globally.