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PROTECTING THE UNITED STATES FROM DRUG-RESISTANT TUBERCULOSIS: REINVESTING IN CONTROL AND NEW TOOLS RESEARCH

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED TENTH CONGRESS

FIRST SESSION

ON

EXAMINING WAYS TO PROTECT THE UNITED STATES FROM THE RISING THREAT OF DRUG-RESISTANT TUBERCULOSIS, FOCUSING ON REINVESTING IN CONTROL AND NEW TOOLS RESEARCH

OCTOBER 30, 2007

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C O N T E N T S

STATEMENTS

TUESDAY, OCTOBER 30, 2007

ADDITIONAL MATERIAL

PROTECTING THE UNITED STATES FROM DRUG-RESISTANT TUBERCULOSIS: REINVESTING IN CONTROL AND NEW TOOLS RESEARCH

TUESDAY, OCTOBER 30, 2007

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 10:04 a.m., in Room SD–430, Dirksen Senate Office Building, Hon. Sherrod Brown, presiding.

Present: Senators Brown, Enzi, Burr, Murkowski, Allard, and Coburn.

OPENING STATEMENT OF SENATOR BROWN

Senator BROWN. The Senate Committee on Health, Education, Labor, and Pensions comes to order.

I thank Senator Enzi for joining us today, and for his interest in tuberculosis. He and I had a discussion with some House members and the new president of the World Bank about tuberculosis and some other issues. And, I appreciate his interest.

I also appreciate Senator Coburn's interest in TB. In his brief respite between the House and Senate one day, on a TB amendment I had in the House, he lobbied his roommate on behalf of our tuberculosis amendment and got his vote for it. And I appreciate Senator Coburn's long-time interest in public health.

I just wanted to say first of all, I appreciate Dr. Castro being here, and others who have been so very involved in tuberculosis issues over the years, particularly Dr. Frieden, who's an old friend of mine and an old colleague and a long-time colleague in working on these issues. And, I also want to mention Lee Reishman, who has done so much to advance the cause of public health. Lee has been sick for a while but will be back at work fairly soon. He is here in spirit and would be here in person, I think, if he could be.

Some years ago, well, a long time ago, 30, almost 40 years, 35 years ago, my physician in general practice father and I were driving down the street in my hometown of Mansfield, Ohio, a town of about 50,000, and we drove by a clinic, a building that looked like it was about to close. And I said to my father, "What is that?" And he said, "It's a tuberculosis sanitorium. And we don't have TB in our town anymore. We used to have terribly difficult problems with TB and we don't need it anymore."

And I've obviously learned since then, that my father may have been correct in those days in Mansfield, Ohio, but it's a continuing worldwide problem to be sure, and a threat to public health in this country as we have learned. We know the toll that TB is taking on the health of people around the world. Globally, TB kills about 1.6 million people each year.

It's the leading cause of death, especially in Africa, for people with HIV/AIDS. It's estimated that one-third of the world's population is infected with the TB bacteria, and that some 2 billion people have that bacteria in their bodies. It's estimated that 10 to 15 million Americans may carry the TB bacteria also.

As our witnesses will describe, TB was never eradicated in our country and has emerged in a new and dangerous drug-resistant form. What's different now from the TB of my childhood, is that now we have the more dangerous drug-resistant forms of TB. Drug-resistant TB evolves when we fail to provide complete, consistent treatment regimens.

We know it's a problem created by humankind, this drug-resistant TB. It gained the spotlight earlier this year, as we all know, when Andrew Speaker boarded a plane and put his fellow passengers at risk. If any good came of that incident, and if any good is coming from the series of illnesses and a few deaths around the country now, with the public health problems that CDC is working so well and hard on, it's reminding us that in a globalized world, TB and other diseases like it are not only diseases of the poor and developing countries, but a risk to Americans, just sometimes a plane ride away. And once TB becomes drug-resistant, it becomes a tremendously costly and potentially deadly health threat, regardless of where you live.

Less than a year ago, last December, the Advisory Council for the Elimination of TB, the expert group that advises the Secretary of Health and Human Services on TB issues, warned,

> "If XDR, the excessively drug-resistant, the highest form, if you will, of drug-resistant TB, the most insidious form, is not addressed in the early stages before it becomes more prevalent in our country, it will become a Trojan Horse that will set back our country's ability to control TB for decades, and set back our whole public health system."

As Dr. Frieden knows from what happened in New York 15 or so years ago.

Because it's treatable and preventable, any new case of drug-resistant TB represents a failure of all of us in the public health system somewhere, either here or in another country. Today, while the overall rate of TB cases in the United States continues to fall, the significant slowing of the decline rate from 6 percent per year, in the period 1993 to 2002, to 3 percent per year in more recent, for 3-year period is of concern because of the history of TB in our country.

In the 1970s and 1980s, after making much progress toward eliminating TB, but never actually reaching that goal, we began cutting the Nation's TB control infrastructure. Our weakened domestic TB capacity at the time, coupled with the HIV/AIDS epidemic, caused an unprecedented surge in the Nation's TB rate between 1985 and 1992. We need to make sure history doesn't repeat itself.

Legislation I introduced with Senator Hutchison and Kennedy, the Comprehensive TB Elimination Act, would provide the resources necessary to respond to outbreaks of drug-resistant TB in the United States and put the Nation back on the path toward eradicating TB. The bill has key provisions for enhancing research and demonstration projects to eliminate tuberculosis in our country. It increases research funding for new diagnostic and treatment tools, new vaccines, studies of at-risk populations, and research into the relationship between TB and HIV/AIDS.

Our bill addresses a critical piece of the puzzle when it comes to combating TB domestically and globally, investment in new tools to diagnose, to treat, and to prevent TB. The reality is our TB diagnostic tests, drugs, and vaccines are all seriously outdated. And with the spread of drug-resistant TB, especially XDR TB, these tools are increasingly inadequate. The diagnostic tools that we have are more than 100 years old and aren't quick or sensitive enough to detect TB in all populations.

The TB vaccine is more than 85 years old and is only effective in children. The Comprehensive TB Elimination Act will expand CDC and NIH research efforts and new tools, so that we can develop the diagnostic tests and the drugs and the vaccines that we need to effectively control TB globally and domestically.

Today, we'll discuss how a combination of standard TB control, the directly observed treatment short-course and all that entails, and an investment in new diagnostic treatment and prevention tools can combat this disease.

I'll also want to briefly mention legislation Senator Hatch and I will introduce tomorrow that focuses specifically on antimicrobial resistance. Drug resistance sets the clock back on our ability to combat a host of infections, increasing the threat these infections pose to human health, and dramatically, dramatically increasing the cost of treatment. Our legislation's intended to ensure that the United States takes action now to prevent intractable problems later.

But today's hearing rightly focuses on a global killer with domestic implications. I look forward to our witnesses' testimony. And again, welcome Dr. Castro, and I'll call on Senator Enzi.

Thank you.

OPENING STATEMENT OF SENATOR ENZI

Senator ENZI. Thank you, Mr. Chairman. And I want to congratulate you on an outstanding summary. I do have a full statement that I'd like to be a part of the record, but I think you pretty well covered that. And, so I would just ask for unanimous consent to have it in the record.

Senator BROWN. Without objection, so ordered.

[The prepared statement of Senator Enzi follows:]

PREPARED STATEMENT OF SENATOR ENZI

Good morning, and thank you all for joining us today to address an extremely important and timely topic.

It is absolutely critical that we as a Congress and as a nation realize that the fight against TB is BOTH an urgent U.S. issue, but also a *GLOBAL* threat of immense proportions.

Hard as it may be to believe, each year approximately 9 million people worldwide contract active TB, and about 2 million of these die from the disease.

Because of increased mobility world-wide, up to one-third of the world's population are now TB carriers—most of whom are latent carriers who are unaware of their condition. In other words, fully one-third of the world's population—nearly 2 billion people—are infected with TB.

It is difficult to draw clear lines of distinction with regard to the spread of TB between domestic and international settings. In the United States, the problem is also very severe. Here at home, nearly 14,000 cases of active TB were reported in 2006, with an estimated 10 to 15 million more carrying latent versions of the infection. In 2006, the TB rate in foreign-born persons in the United States was 9.5 times greater than that of U.S.-born persons.

If these figures are not enough to wake us up and get us worried—we also face the emerging appearance of drug-resistant strains of tuberculosis—against which no current drug or combination of drugs can currently combat.

Although the need is clearly very great, both globally and nationally, neither we as a nation, nor we as a global community, currently have adequate mechanisms, either clinically or from a public health management perspective, to combat this threat.

Although it thankfully has not yet happened, the hazard posed by drug-resistant TB for a virtually unstoppable epidemic is a very real specter we must confront and combat—both nationally and globally.

The case last spring of the Atlanta lawyer Andrew Speaker made international headlines and drew needed attention to this danger. Mr. Speaker, allegedly with full knowledge of his infection both by himself and health authorities, nevertheless managed to travel to, from, and through several countries internationally.

Only very belatedly—and thankfully without tragic result—were authorities able to catch up to the problem and deploy needed intervention and effective containment mechanisms.

This case highlighted starkly not only our own shortcomings domestically, but the alarming absence of a global strategy to deal with this threat. As international travel becomes ever easier and greater in volume, so does the prospect of a horrendous disaster that could impact not only us here at home, but millions worldwide as well.

Amplifying this threat is the fact that drug-resistant TB is not a clinical problem that stands alone. Even as we face this threat, similar and intertwined hazards, such as drug-resistant AIDS strains and untreatable influenza viruses, challenge us as well.

A very serious hole in our ability to fight tuberculosis exists globally, nationally, and at the State and local levels. It is the current lack of systems for the containment, up to and including isolation of infected persons, should an outbreak occur.

I do realize that buzz words like "quarantine" and "isolation" raise controversy and concern—some of which I share, and I do

think we need to be careful in the terms we use—and the strategies we deploy.

As everyone here knows, I am certainly no advocate of heavy handed government policies. However, in the face of a problem as severe as this, I do believe we need to face squarely the reality that, sometimes, urgent hazard does require equally urgent and stern measures to fight it.

Although certainly not a direct answer to the problem of drug-resistant strains of TB, another TB-combating strategy worth close attention is the so-called DOTS approach. DOTS is short for "Directly Observed Treatment, Short-Course" action. The DOTS approach, which is gaining increasing international attention, focuses on a patient-centered strategy of closely supporting and monitoring the treatment of infected persons, both to assure they follow through on their own treatment and that the threat their infection poses to others is minimized.

Whether here at home or globally, my view is that the fight to control and prevent TB is one that should focus on marshalling and better coordinating the resources not only of government agencies, both United States and abroad—but also better deploying and coordinating State efforts, local efforts, and private sector innovation. Also of immeasurable potential are the skills and resources deployable through charitable and corporate collaborations.

The answer is not just more money—nor should it focus on top-down prescriptive legislative instructions, except where urgently and expressly needed.

Senator Brown, who is chairing this hearing, deserves tremendous credit for pushing hard for committee attention and action to help prevent, control, and manage tuberculosis—particularly drug-resistant strains of the disease.

The TB legislation he has authored, with Senator Clinton, which focuses principally on U.S. domestic strategies, has undergone considerable discussion and modification since its introduction earlier this year—and I am pleased by the forward steps he has taken to address serious concerns about his original bill, both by the Administration, many on this committee, and others.

We still have work to do on this bill, but I am hopeful—cautiously hopeful—a bipartisan resolution can be reached before the bill is taken up for markup. This committee's strong track record of bipartisan collaboration—particularly on public health bills—is, I believe, one of our committee's proudest features.

I think Senator Brown, Chairman Kennedy, and all of us on this committee, hope to avoid a repeat of what happened last summer, when this bill was rushed toward markup—only to be pulled when it became clear that outstanding concerns were too significant to be bridged in a collaborative, bipartisan manner.

Much progress has been made since then, but I think we need to keep last summer's experience very much in mind as we again proceed to markup—which the Chairman indicates may be scheduled very soon. This challenge may prove a tall order—but one I and others on this side will attempt in good faith to achieve.

One of the topmost concerns of many about the original Brown bill, including HHS, CDC, myself and others, was that it attempted to write a relatively detailed Federal prescription for fighting and

preventing TB. Much more preferable is greater flexibility for the Federal authorities on the ground, and better collaboration with our non-Federal partners, whether they be States, local entities, charities, or corporate innovators.

However, I do think most of us very much agree that the core directions of the Brown bill, both as introduced and as it has evolved, are ones of common concern and urgent need.

These include efforts to better develop diagnostic and treatment tools, better testing of the safety and effectiveness of new treatments and vaccines, and a need for special attention to at-risk populations, and closer examination of improved public health intervention strategies. This last point—better intervention strategies—is of particular importance.

This committee as we speak is aggressively engaged in examining the Andrew Speaker case of last spring.

This investigation, which is being conducted on a fully bipartisan basis, is not yet complete. But its work is already making very clear that greater authority may be needed—coordinated at both the Federal and State level—for rapid and firm containment of drug-resistant TB cases.

One of our witnesses today, Dr. Frieden, from New York, will speak to the work his city and State have been doing to put in place such systems.

I am hopeful that our committee's continuing investigation into the Speaker case and effective control of drug resistant outbreaks will give us useful guidance in this area.

I regret that the anticipated markup schedule planned by the Majority does not better accommodate incorporation of this work in a coordinated manner. I hope that we work to ensure that all our legislative activity is adequately informed by investigative efforts.

I do understand the importance of moving forward. This hearing, Senator Brown's legislation, and our HELP investigation are all steps toward a common goal of better attacking the challenge of TB—one I share.

Senator BROWN. Senator Coburn.

STATEMENT OF SENATOR COBURN

Senator COBURN. First of all, let me thank you for your work on this subject and many others, on infectious disease. This is an important area that Congress needs to become more learned on. I appreciate those that are going to testify today and their efforts in resolving this.

There is something Congress can do and we ought to be doing it. And I look forward to our testimonies today. I will be leaving probably before we have time for questioning, and would like unanimous consent to submit my questions to the record for later.

Senator BROWN. Of course. Without objection, so ordered. Thank you.

Senator Allard.

STATEMENT OF SENATOR ALLARD

Senator ALLARD. Mr. Chairman, I'll also be brief. I don't have any organized comments here that I will be making, or formal com-

ments I'll be making, just would like to commend the committee for taking an interest in this particular subject area. It is important. And thank the panelists for taking time to be here to testify before this committee. We certainly appreciate you, Dr. Castro, being here from the Center for Disease Control and Prevention, Tuberculosis Research Facility at Colorado State University in Colorado.

We also have testifying before us here, Dr. Randall Reves, Professor of Medicine and Infectious Disease, University of Colorado. I want to welcome him personally. He's the Medical Director of the Denver Metro Tuberculosis Clinic and Chairman of the Stop TB, USA. We are certainly pleased to see so much interest in Colorado on this emerging disease, partly because we've had an incident, involving an individual who traveled internationally with tuberculosis and raised a lot of issues, I think, with that particular incident.

This is a very timely hearing and I want to thank all of you for being here, for your testimony. It's not always easy to get away from your daily jobs to be here and to give us your expertise. And we're looking forward to that. I have the same problem that Dr. Coburn has, which is that I have other events going on right now, so I may not be able to stay for the entire testimony, but I do have some questions I want to submit for the record.

Thank you.

Senator BROWN. Thank you, Senator Allard.

Since January 1993, Dr. Castro has served as the Director of the Division of Tuberculosis Elimination in the National Center for HIV, STD, and TB prevention in the Center for Disease Control and Prevention. In this role, Dr. Castro leads the team of technical experts devoted to TB elimination efforts in the United States. His division sponsors TB prevention control and research activities throughout the Nation. Dr. Castro has advanced the involvement by the United States international tuberculosis control efforts, serving as an expert advisor to the World Health Organization. He was promoted to the flag rank of Assistant Surgeon General in May 2000. Dr. Castro will provide an overview of TB in the United States. Dr. Castro, thank you for your fine work over the last decade and a half, and welcome.

STATEMENT OF DR. KENNETH G. CASTRO, M.D., ASSISTANT SURGEON GENERAL, USPHS, DIRECTOR, DIVISION OF TUBERCULOSIS ELIMINATION, CENTERS FOR DISEASE CONTROL AND PREVENTION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, ATLANTA, GA

Dr. CASTRO. Thank you very much. Good morning, Chairman Brown, Ranking Member Enzi, and other distinguished members of the committee.

It is my pleasure to be here today to discuss whether 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 United States to work toward eliminating tuberculosis domestically, and to assist in global tuberculosis control.

As the committee is already well-informed about the definitions of multidrug-resistant tuberculosis and extensively-drug resistant TB, I will go directly to my discussion of TB in the United States.

For starters, I would like to observe that Senator Brown's father's comment is a very commonly held misconception. When you interview persons throughout this country, many think TB is a disease of the past, and we still have 40 new cases being diagnosed every day. So, by the end of today, there will have been another 40 new persons diagnosed with TB in this country.

In 2006, States reported to see the lowest incidents of tuberculosis, with 13,779 persons diagnosed with tuberculosis in that year. Since the unprecedented tuberculosis resurgence in our country which peaked in 1992, the number of U.S.-TB cases reported on a yearly basis has decreased by 48 percent.

However, this remarkable accomplishment is tempered by a slowing of the rate of decrease, as you've already observed, Senator, from 7.3 percent, annual percent decrease from 1993 through 2000, to a slowing now to 3.8 percent between 2000 and 2006.

This may be a harbinger of the stagnation we're starting to see in our progress toward elimination, and several challenges to tuberculosis elimination remain, including: No. 1, the health disparities associated with tuberculosis. Racial and ethnic minorities continue to suffer from TB more than the majority of populations in the country. The rate of tuberculosis in U.S.-born blacks is 8 times higher than for U.S.-born whites.

Second, foreign-born persons are adversely impacted. In fact, 57 percent of cases last year were in persons born outside this country, reflecting the global reality.

Third, we continue to see sporadic outbreaks and clusters of tuberculosis which outstrip the local health departments' capacity to respond to these.

Fourth, cases with consistent patterns of drug-resistance threaten our ability to control tuberculosis.

And, fifth, there's a continued need to invest in the development of new tools—as you've already heard—to rapidly and reliably diagnose tuberculosis, provide safe and effective treatment, and ideally, vaccines.

In the United States, cases of multidrug-resistant TB accounted for less than 1 percent of all persons reported in 2006, and there were 48 persons with extensively drug-resistant TB identified between 1993 and 2006.

While the total number of these persons is relatively small, their impact on U.S.-TB control programs can be devastating in terms of human capital and financial resources. For example, the average hospitalization cost of one person with XDR TB is averaging about $500,000.

To eliminate tuberculosis, CDC and its partners must continue to ensure the United States has the essential elements of a strong TB control program. These include, No. 1, ensuring a strong Federal leadership, we have a Federal TB taskforce that coordinates activities between Federal agencies.

Second, ensuing that State and local TV programs are adequately prepared to identify and treat patients, and in treating them, prevent the manufacturer of drug resistance.

Third, invest in the research and development for improved drug treatment regimes, vaccines and diagnostics.

Fourth, training of healthcare professionals to identify and treat this complex disease. And that's becoming an increasing challenge, there are fewer cases of tuberculosis, the proficiency in the medical profession keeps going down, and one of those things that CDC is doing is sponsoring four regional training and medical consultation centers, to make sure that there is access to the repository of expertise somewhere in the country.

And last, we need to work with partners globally, to reduce the introduction of tuberculosis in the United States, and reduce the burden of the disease globally.

Thank you for your time, and for your interest. And I will be happy to answer any questions. I have provided written testimony that has additional details, for the record.

[The prepared statement of Dr. Castro follows:]

PREPARED STATEMENT OF RADM KENNETH G. CASTRO, M.D.

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 United States 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 1940s, 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 6 to 9 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 5 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 United States, ever, at 13,779 new cases diagnosed during 2006. This represents a 2.1 percent 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 percent. Since the 1992 TB resurgence peak in the United States, the number of TB cases reported annually has decreased by 48 percent. 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 percent for 1993 through 2000 to an annual decline of 3.8 percent 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 the 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 percent of report cases in 1986 to 57 percent 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 percent 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 percent of MDR TB cases in 1993 to approximately 76 percent 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 United States 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 United States. However, the majority of XDR TB cases that occurred from 2000–2006 were among foreign-born persons (75 percent 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 1 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 (6 months) 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 1960s. 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 United States-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 3 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 percent and the number of persons suffering from TB by 50 percent.

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.

Senator BROWN. Thank you, Dr. Castro.

You had said it's $500,000 average cost for an excessively drug-resistant TB patient, could be $500,00 in a hospital. What is it for MDR TB, what is it for the most common forms of TB?

Dr. CASTRO. Hospitalization costs, pardon me—alone. It excludes indirect costs, lost wages, that also contributes to the added cost.

Senator BROWN. When you said a few hundred times about MDR, can you give me something a little more specific in a range of 20,000 to 50,000, or whatever the range is?

Dr. CASTRO. Well, in the case of MDR, you could go up to about $2,500 for the treatment of someone, especially if they can be treated as outpatients, and don't require hospitalizations. Once they require hospitalization, and potential for surgery, the cost goes up.

Senator BROWN. So, MDR TB often is treated outpatient in our country, in the United States.

Dr. CASTRO. Yes, if we can rely on the workforce of outreach workers that many Health Departments have, working with private physicians. You could do that—it is difficult, though. Some patients will require hospitalization, because of the extent of the disease, some may also require surgical intervention as a more extreme measure for their type of disease.

Senator BROWN. And there's not a quarantine issue on the MDR TB patients?

Dr. CASTRO. No, what we do throughout the country is we rely on a system that facilitates the provision of treatment, the direct observation of treatment to ensure adherence, and in an experience that was published by New York City after following thousands of these persons, they showed that in 96 percent of the cases, you can successfully treat tuberculosis by relying on these systems. In about 4 percent, you needed to resort to the more restrictive measures, because in spite of all attempts to provide treatment, persons were defaulting, and that's when you'd then need to resort to the

judicial system, or restrict individuals. And those measures are available to us.

But, fortunately, we don't need to rely on them often, because most people want to get better, and if you provide the patient-centered approaches that would facilitate access to treatment, take care of the side effects that they will encounter with these medications, we will likely succeed.

Senator BROWN. Since the 1960s, I understand CDC has had the responsibility for TB, drug and diagnostic research. Describe, if you would, your role in what CDC does for research—drug and diagnostic research—and contrast that, so I can be a little clearer on what NIH's role is on all of this.

Dr. CASTRO. Yes, thank you. In the 1960s a clinical trial for tuberculosis of the public health service was transferred to CDC. For years that was done on a shoestring budget.

In the nineties when there were additional resources devoted to tuberculosis, we reconstituted the capacity to conduct clinical research. So, CDC sponsors a multicenter clinical-trials consortium that includes a few countries outside of the United States, but there are about 26 members of this consortium, most of them in the United States, and it enables us to implement the kind of clinical trials that you would have traditionally seen with NIH.

The way we conduct this, however, is by working closely with NIH to avoid any duplication of effort. NIH continues to support the basic research that is going to be required for the field trials that we would then be engaged in, and we have Memorandums of Understanding between our agencies to make sure that we can conduct it in this fashion.

Most recently, all of the evidence-based guidelines for TB treatment, have incorporated the findings of these type of research done over the last few years.

Senator BROWN. When we talk about TB diagnostic drugs, the diagnostic tests are pretty much 100 years old, the TB vaccine—which seems to be effective only in children—is 85 years old; are we likely to see NIH come up with the basic science, and the basic scientific breakthrough separate from what the private sector is doing—which is pretty huge—and then CDC would be more likely to do the clinical trials of that? Is that the way it will work?

Dr. CASTRO. That would be pretty much the way that you would see it operating, NIH supporting a lot of the basic science, and then we would come in and try to do the field trials to evaluate, how do these tests behave in the hands of clinicians in different parts of the country, and in the world?

Senator BROWN. Clinical trials also were conducted internationally, I assume?

Dr. CASTRO. Yes, we have a site in Brazil, another one in Durbin, Uganda and in Spain. But those are all done through collaborations with U.S.-based academic institutions.

Senator BROWN. Thank you, Dr. Castro.

Senator Coburn.

Senator COBURN. Thank you.

Dr. Castro, what is the total budget that the CDC is applying toward TB research, diagnosis and treatment?

Dr. CASTRO. Our total budget for the clinical trials is hovering about $9 million, it used to be a little bit more, we've had to cut back on that.

There's also another consortium to conduct epidemiologic and behavioral studies, and that is funded around $7 to $8 million. So, put together, I'd say about $15 million out of the total budget is used for applied research, or the more programmatically-relevant research.

Senator COBURN. OK. And outside of the research, how about treatment and coordination with State health departments and everything? In other words, I'm trying to look for a global number, what do we spend, CDC now, everything combined——

Dr. CASTRO. Oh, everything combined?

Senator COBURN. Treatment, research, trials, the whole works?

Dr. CASTRO. One hundred and thirty-eight million.

Senator COBURN. A hundred and thirty-eight million dollars.

All right.

I will submit the rest of my questions, I do want to enter into the record a statement that I have made recently, and it's going to be published in the Congressional Record, as well, just on disease-specific bills that we do, the Chairman knows that I'm supportive of efforts in this, but I have a great deal of problems when we start picking the disease and the amount of money, and take those decisions away from scientists and peer-reviewed studies to tell us where we should do it.

So, I'd just like unanimous consent to enter this into the record. My pledge is to work with the Chairman to accomplish his goals, and also my goal, of keeping decisionmaking on where we spend money, with the scientists and the professionals and not the politicians.

[Editor's Note: The statement referenced above was not available at time of print.]

Senator BROWN. Thank you, Dr. Coburn. Since you are both, especially. So, thank you. Dr. Coburn—and Senator Coburn, Senator Burr and I—on the Energy and Commerce Committee in the House would hear people, particularly from NIH come in and lobby for their disease, if you will, and we pretty much agreed over the years, bipartisanly, that we shouldn't direct NIH to put this much money in this disease control, and this much money in this research and this much money in this research, but really letting those decisions be made there.

In terms of the treatment, it's a bit of a different story. Certainly on the research, there's close to unanimity on that.

Senator Allard is recognized.

Senator ALLARD. Just briefly, would you describe the current tuberculosis research and development at CDC labs as it relates to clinical trials to evaluate safety and effectiveness of new drugs, diagnostics and vaccines for late-tuberculosis infections?

Dr. CASTRO. Let me see if I understand—you want me to describe——?

Senator ALLARD. The research that you're doing.

Dr. CASTRO. Yes, we're now evaluating a new drug, for example, Moxifloxicillin is a drug that looks very promising in the mouse model, so much so that we might be able to reduce the total dura-

tion of treatment for persons with tuberculosis, and we're evaluating that for its safety and efficacy.

We're also evaluating some of the newer tests that have been FDA licensed, yet need to be field-tested to see how well they behave in other settings at state-based laboratories. One of them is a Quanti-Feron gold test.

There are a couple of other diagnostic tests that are being evaluated for FDA approval, and we're looking to evaluate them as they get used to test healthcare workers, who get routinely screened for tuberculosis.

The relative advantage to some of these tests is that they would rely on a blood draw, rather than insert a needle in the forearm, have the person come back 48 to 72 hours later, we find that you lose many persons in this process who don't come back, you never have an accurate result. And there are other aspects that can yield false positive results, so those are some of the elements we're looking at.

We're also looking at the program environment, how to better enhance—especially with PEPFAR—joint activities with HIV. How do we make sure that every person with TB gets routinely offered a test for HIV, since it will make a difference to them in their treatment, and vice versa. Every person with HIV ought to be screened for the presence of tuberculosis, because throughout the world, it's going to be the most common HIV-associated disease.

This work is done by funding different sites that compete for those resources, and we developed the research protocols jointly with the investigators, subjected to external peer review processes, to make sure that there's a rigor applied to the type of research we do.

CDC oversees this umbrella structure for the multisite trials, but we get people together, agree on a common protocol, that gets implemented in different parts of the country.

Senator ALLARD. We've got a number of drugs that are immunosuppressive, we have a number of diseases that are immunosuppressive, and have you focused much on therapies, and what not, that may increase susceptibility to tuberculosis? HIV is one disease—are there other diseases, like leukemia, perhaps, is that immunosuppressive?

Dr. CASTRO. Absolutely, thank you, Senator, this is an excellent question.

What we have seen is that, with the advent of a lot of the new drugs that are being used, for example, for rheumatoid arthritis, we're seeing the occurrence of tuberculosis, because these drugs do immunosuppress some individuals. That has resulted in some policy guidelines to ensure that persons are routinely screened for the presence of tuberculosis, latent tuberculosis, before they get started on these drugs.

The questions becomes, are you getting to them before they get so immune suppressed that the test becomes meaningless and could we rely on other, better and more reliable tests to get to those results.

But, the bottom line is, as a result of these drugs being more commonly used, we've seen the need to issue policy guidelines, and in fact if you have listened to the adds on tuberculosis, they say

be careful if you have had TB, make sure you see your physician before you use these drugs, it's a very well-recognized phenomenon.

Other conditions that will facilitate progression from latent to active TB, in addition to HIV and these forms of drugs, as you pointed out, persons of cancer, immunosuppressive therapy for cancer—people who get placed on steroids for a long period of time could become immunosuppressed, also. Diabetes have been notoriously linked to tuberculosis—the low-body weight and malnutrition could also contribute to disease progression.

So, these are a variety of the underlying medical problems that will facilitate disease progression for someone who is latently infected with TB.

I will remind you, Senator, of the figures cited by Senator Brown earlier—a third of the world's population is thought to be latently infected with the bacterium that causes tuberculosis.

Senator ALLARD. Is there a high incidence of TB in new immigrants to the United States?

Dr. CASTRO. Yes, sir. There is a relatively high incidence of tuberculosis in immigrants and what we have in place is a system to screen—we provide a medical evaluation before entry for every person who applies for an immigrant or refugee visa. That includes screening for tuberculosis.

Most recently, we've updated those technical guidelines with another group at CDC, the Division of Global Migration and Quarantine, and are implementing some pilot projects to evaluate this enhanced screening process in a group of Burmese refugees that are slated for resettlement in the United States, a decision by the Department of State, so we're trying to make sure that we reduce the implication.

Senator ALLARD. Can the statement be made that we're seeing a decrease in tuberculosis in domestic populations, but an increase caused by new immigrants coming to this country? Or sustaining, I mean it's sustaining our levels, with new immigrants.

Dr. CASTRO. That would be an accurate statement. We are making progress against tuberculosis in the U.S.-born population, however, we don't see that yet in racial and ethnic minorities, there's still a gap where they have 8 times the risk of tuberculosis when you compare them with U.S.-born whites.

And the problem there is that, as long as you have TB in the community and someone transmitting TB, TB won't pick who it infects. So, that's going to be part of our challenge.

Senator ALLARD. It's also a zone overseas.

Dr. CASTRO. Yes, there is microbacteria in bovis associated with unpasteurized milk, but at least in this country, you have—with the U.S. Department of Agriculture—a fairly effective bovine eradication program, where they test cattle, and will kill or sacrifice any cattle known to be infected. We also pasteurize all dairy products as a way to reduce the possibility of tuberculosis.

Senator ALLARD. Thank you.

Thank you, Mr. Chairman.

Senator BROWN. So, it's more a function of—are you implying, or suggesting, or saying it's more a function of poverty than it is any of those other factors?

Dr. CASTRO. TB has notoriously preyed on the down and out in this very country, around the turn of the 20th Century, TB was a leading killer in the densely-populated urban environments. And, as we've made progress against it and improved those conditions, you're seeing less of it.

But, throughout the world, the World Health Organization and the Stop TB Partnership have linked tuberculosis to poverty and to sustainable development, because it is the young adult of these populations who are succumbing to tuberculosis and that's the most productive part, unfortunately often, the down and out.

Senator BROWN. Senator Burr is recognized.

Senator BURR. Thank you, Mr. Chairman.

STATEMENT OF SENATOR BURR

Dr. Castro, welcome, thank you for the work you do.

The current guidelines for air travel for persons affected by TB, as I understand it, are based on limited studies that were done over 10 years ago. What have we changed?

Dr. CASTRO. Thank you. Those guidelines are based on studies that I was personally involved in where what we have seen is, during short commercial air travel, we have not documented evidence of transmission. The total number of such studies amount to about 7. There's not that many situations, and CDC often gets called upon to do these investigations. It's a big challenge to identify all of the passengers once they've dissipated, and get them tested.

What we have learned through those studies is that transmission has been documented in long flights over 8 hours. That's the basis for the existing recommendations by WHO and by CDC, where we unequivocally State, No. 1, any person with active TB should not board a commercial aircraft; No. 2, if you have MDR TB, we want to see evidence that your cultures are negative, and what we're trying to do is improve the level of awareness.

It is a challenge. All of us travel on a daily basis, and it would be unrealistic to expect that we would all be screened before boarding the aircraft by an x-ray, which is what you would almost need to have a foolproof system.

So, we have the policy guidance in place, WHO, I understand, is going to try to update it to take into consideration the presence of XDR TB, because they were last printed in 2006 before the recognition of Extensively Drug Resistant Tuberculosis.

Senator BURR. Dr. Castro, after the Speaker TB incident, Senator Gregg and I sent an extensive letter to Julie Gerberding at the CDC. We asked, specifically, what changes would need to be made in current Federal isolation and quarantine laws and regulations. This was precipitated by the revisions that were sought by CDC in the public comment period that ended in March 2006. What's the status of that effort, and more importantly, has anything changed since Senator Gregg and I wrote to the CDC?

Dr. CASTRO. Yes, changes have been made, for example, we have improved the lines of communication between our Department and the Department of Homeland Security——

Senator BURR. But, have any of the new regulations actually been put in place?

Dr. CASTRO. Well, all States have State-specific laws for the prevention of tuberculosis transmission, as well as the implementation of worldwide agreed-upon standards for international health regulations which are a set of principles that not only try to reduce the importation of disease, but also plays upon our role as citizens of the world to reduce the exportation of disease.

We can certainly get back to you with details about what's being done, because some of it is work in progress, but we——

Senator BURR. Let me just say this—when I see an effort that was completed in 2006—March 1, 2006, CDC answer was, "Is working to respond to more than 500 pages of comments from approximately 50 organizations and individuals regarding the proposed rule," but the proposed rule has not been finalized. We're a year and a half from then, we've had a major incident since then.

Dr. Gerberding went on in the letter to say, "CDC is working to clarify its quarantine authority to expressly address the movement of patients out of the country. Historically the use of quarantine has been devoted to keep people out of the United States and containing them from outside the country. This case represents the first time the CDC has had to address the issue of preventing a person from leaving the United States. Public health statutes were not designed to deal with this."

My only question is, have we changed anything that enables us to address these challenges any better than what was expressed to me in that letter earlier this year?

Dr. CASTRO. I understand that the changes are being made, I don't have the specifics, but would be glad to provide them to you.

Senator BURR. I would appreciate you doing that, because my concern is, if you wait as long to do that as you have to propose the final rule, which has not been proposed since March 2006, this committee has something to worry about.

Senator BURR. Let me switch, if I could, just very briefly, to the Speaker case. Testing was done in Atlanta that showed Mr. Speaker to be multi-drug resistant—excuse me, extensively drug-resistant. He was tested in Denver, and was determined to be multi-drug resistant. We had asked that CDC send the original samples to Denver to be tested, to see if, in fact, there was a different result. My understanding is that a sample went to Denver, and it was tested as multi-drug resistant. How much time, if any, are we spending looking at the testing side of it, to see if we've got some discrepancies in our methods and technologies, and is that something the committee should be concerned with?

Dr. CASTRO. This is an area that is of concern to all of us. The testing for second-line drug resistance lacks the standardization—there are some national guidelines, CDC is a reference lab, and in fact, we follow those procedures.

Unfortunately, you're looking at samples obtained in different States, and the discrepancy is based on two drugs. What you find is, whenever you read any chapter that describes MDR TB or now XDR TB, there's always a segment devoted to how to interpret, or what are the causes that could lead to discrepant lab results? It happens constantly, and it is a problem that we need to resolve, by having the research developed, the newer methods to test these.

It takes 21 to 28 days to use the recommended measures to identify resistance to second line drugs——

Senator BURR. Let me go back to my point. CDC was asked to take the original sample, the sample that they tested and found to be extensively drug resistant, send it to Denver, and have Denver re-test it. Was that ever done?

Dr. CASTRO. Yes, I believe it was.

And, now keep in mind that there are some technical challenges to this, because in a bacterial population, when you take a wire loop and you take a sample of that, you're taking a subpopulation, you usually don't take a swab of the whole petri dish, so to speak, with all of the bacteria growing. So, you could be sampling subpopulations that could have rise to discrepant results that are bona fide discrepancies, because you may be testing a subpopulation of bacteria.

So, one has to be careful with over-interpreting those discrepancies, which happen all of the time. And, in fact if you were to ask any series of experts throughout the country, they would say, "This is not news to us, this is what we deal with, every time we have a case of MDR TB," and I bring us back to, what that highlights is the existing and prevailing deficiencies in testing, that is relatively antiquated and needs to be updated. And, we need to make sure that we invest in the research to get us those tools that we can rely upon.

Senator BURR. I thank the Chairman for his indulgence. And, what I think, as a member of the committee, I'm trying to get a better handle on, is what those tools are. And there's a point in time where CDC has to make a call based on where we are, where science is, and what we should change, versus continuing to use something that, I believe, Mr. Chairman, most people have expressed probably needs to be changed, based upon what we know today.

My message back to CDC is, tell us what needs to be changed. But tell us now. Let's not wait 6 months, another year, another year and a half from the study, let's get the final rules out.

Thank you, Mr. Chairman.

Senator BROWN. Thank you for your comments and your comments, Senator Burr.

Senator Murkowski.

STATEMENT OF SENATOR MURKOWSKI

Senator MURKOWSKI. Thank you, Mr. Chairman.

Dr. Castro, I'm trying to figure out what's going on in Alaska. In 1945, about 20 percent of the deaths in the State were attributable to tuberculosis; we'd like to think that being 1 of the 50 States that our statistics, too, are improving. But, in fact, we had a higher number of those afflicted with tuberculosis in 2006 than we had in 2005. With our reported cases of TB in 2006, we're looking at 10.4 cases per 100,000, and when you compare this to the national average, which is 4.6 cases per 100,000, our statistics are terrible.

In fact, in a newspaper article just this April in Anchorage, our largest city, the headline is "TB Outbreak Again Amongst our Homeless Population."

Now, I understand the difficulties in, particularly with a homeless population, trying to track and provide for treatment, recognizing that the treatment can be a lengthy one, and you have a population that may or may not be checking in for the continued treatment.

Can you give me some idea as to why in Alaska, we are not making better progress? Can you also speak to whether or not our numbers within our Alaska Native population are higher than our Caucasian numbers, or is it primarily with our homeless population? I understand that over 50 percent of all of the TB cases were among our homeless population, so I'm trying to understand what I'm dealing with in my State.

Dr. CASTRO. Thank you, Senator. I'll need to get back and run some of the analyses of the information shared with us by the State of Alaska, but you're absolutely right—the rate of tuberculosis has been disturbingly higher in Alaska than in the rest of the country, and then—in fact, for that matter there are many other States that are above the average.

One of the problems is, as you have pointed out, the occurrence of tuberculosis in the relatively marginalized populations. And, if you don't have the warm bodies to reach out and get them to complete therapy, you will have ongoing, unmitigated transmission.

You will be hearing from Dr. Frieden in New York later, but New York implemented a very successful approach when we had the resurgence of tuberculosis, with outreach workers who were meeting homeless individuals under bridges in Queens and the city and the various boroughs, and getting them successfully to complete treatment. But that requires the infrastructure that—what I was alluding to earlier, it is my understanding that the investment and infrastructure in Alaska has remained stable, not kept up with the cost of living increase, based on the information we get from our program consultants who interact.

Also, the rates have been traditionally higher in the Native Americans, and it's an area of concern, and it relates back to the health disparities that I was alluding to earlier.

Senator MURKOWSKI. Is there any specific research going on within CDC as to this sub-population?

Dr. CASTRO. No specific research, however CDC is ready to and has responded to requests by States for support during—the need to investigate clusters, unusual clusters or outbreaks in helpless populations.

I can't recall having been, over the last couple of years, to Alaska, but certainly in Seattle we had last year a cluster of individuals who were homeless, mostly Native Americans also, several of whom who were also HIV-infected substance abusers, posing incredible challenges to getting them to get through the testing procedures that would diagnose them with TB, and subsequently to take the drugs for the time period that's required.

Senator MURKOWSKI. Is part of the problem the ethnicity, the genetic makeup of an Alaskan Native or, American Indian that makes them more susceptible? Or are you suggesting that they were not being as thorough with the treatment in these individuals because of certain issues like poverty and remoteness?

Dr. CASTRO. I would have to agree with the second part of your statement, which is that I don't think that there is anything inherent to the Native populations, although we do know that over years, TB was rampant in the Inuit population, however, Dr. George Comstock who died just a few months ago demonstrated that in that very population, if you were able to implement widespread isoniazid preventive therapy after testing and screening out for active disease, you could actually reduce the rates quite significantly.

I think what has happened is, you're dealing now with more remote populations where their contacts are not being promptly identified and screened, and you have unmitigated, ongoing transmission in these circles. And that's where we need to go back to the infrastructure of services that are going to be needed to get that done.

With the added challenge in the case of Alaska that you have remote populations where you can only get to by propeller, you know, single-engine aircraft, and I'm aware that that poses a formidable challenge.

Senator MURKOWSKI. It kind of goes to what my colleague Senator Burr was saying, about not being allowed to fly if you've been diagnosed. If you can't fly to get out of one of our villages, you can't get to where the treatment is. So, we've got kind of a Catch-22 there.

Mr. Chairman, this is an interesting discussion this morning, when you recognize that in this country—it's the poor, it's the homeless, it's those that are isolated for many different reasons, that we see this spread of this drug-resistant tuberculosis, and they certainly are the ones with the least ability to advocate for their cause.

So, thanks for having this hearing this morning.

Senator BROWN. Thank you, Senator Murkowski, thank you for your insights.

I've got a couple of questions and comments about Senator Murkowski's questions, too—the 10-point—she had said it's 4.6 nationally per 100,000, 10.4 in Alaska. And I appreciate your pointing out—as she did—the difficulty of doing the directly observed treatment in remote areas. You said something about Isoniazid protective therapy—is that different from the actual treatment of TB with Isoniazid?

Dr. CASTRO. Thank you, Senator.

Senator BROWN. Or did I hear that right?

Dr. CASTRO. It is different. Basically, what we have, in the tools to deal with tuberculosis is first and foremost, you have to find people who have TB in their respiratory system, because they're the ones who are, No. 1, sick, and No. 2, who are transmitting the disease in the community. By getting them cured, that's your best preventive measure.

Then you have a second group that you need to target, those are the persons who have latent tuberculosis infection. We estimate that in the United States, we have anywhere from 9 to 14 million such individuals. And these persons—if you target your approach to those of highest risk of developing TB, you give them isoniazid preventive therapy or treatment for latent tuberculosis with Iso-

niazid. That's a single drug, given for 9 months, and it will prevent them, quite effectively, from developing active tuberculosis. That was the intervention that I was alluding to, used by Dr. Comstock in Alaska.

Senator BROWN. So, these patients, if you will, they're not really sick, but these patients will have—they will take a skin test, or whatever, and you will find that they have the tuberculosis bacterium in their bodies, you will then give them only one drug, instead of four, and for 9 months, instead of a different period, it will only be Isoniazid, and they then will, two things supposedly will happen—one they will not be sick themselves and they will not be able to transmit TB then, correct? That's the idea?

Dr. CASTRO. That is correct, and in fact——

Senator BROWN. You're doing that in populations around the United States?

Dr. CASTRO. Pardon me?

Senator BROWN. You're doing that in places around the United States?

Dr. CASTRO. We try to, except that it's——

Senator BROWN. How do you decide on which of the 9 to 14 million to do the isoniazid preventive therapy?

Dr. CASTRO. Well, what we try to do is we go for the populations that are epidemiologically identified to be at highest risk for tuberculosis and promote what we call targeted screening. And, in fact, if you read our policy guidelines, decision to test should be accompanied by a decision to treat for every person that you find positive.

What often happens is we have these relatively archaic testing systems of schoolchildren who don't necessarily carry a high risk for tuberculosis, and no one is doing anything about the results, not starting them on preventative therapy. And I'm pretty sure you're going to hear additional testimony by people in the States about the challenges that we confront. Because, what we're able to do with the resources now is control TB, but not go for that next layer to accelerate the rate of decline that would be required to achieve elimination over time. And that's a very important distinction.

Let me also use this opportunity to state that one of the ongoing trials that CDC is sponsoring is looking at the potential use of two drugs, once weekly, because these drugs are longer-lasting, for a 3-month interval, and that would facilitate things, if they prove to be safe and effective in this particular setting. But it would be quite a promising finding if it turned out to be the case.

Senator BROWN. How many of the 9 to 14 million people carrying the bacteria in our country can you name? Can the public health system actually name by personal identity? Ten thousand, one hundred thousand, a million? How many do you actually know?

Dr. CASTRO. We don't do surveillance for persons——

Senator BROWN. Well, I know you don't do general surveillance, but does the public health system know the answer to that? So, those are the ones, I would guess, that would be the prime candidates for Isoniazid protective therapy.

Dr. CASTRO. Right.

Senator BROWN. I mean, you test school kids when they come in, you test people when they come to Doctor's offices, you don't screen everybody, you don't—I mean, I've been screened for TB, but only because I've been to a prison in Siberia, but you don't test people who typically look like me and dress like me, I understand, when you go into a doctor's office. But, you test people that are in higher risk populations, I assume. Is there a data bank that collects them, so you can—I mean, I'm not even suggesting the privacy issues around that—but so that you can look to them, perhaps, to do the isoniazid preventive therapy?

Dr. CASTRO. Well, in local, our State-based health department, some have been able to conduct the targeted screening of particular foreign-born populations, for example, refugee groups that are seeking medical care, substance abusers known to have a high risk of TB—I've left out of the list, at the very top, the HIV-infected, they are at the top of the list, because if they happen to have latent TB, they have the extraordinary risk of progressing.

But we don't have a data bank. And, now at the local State Department, I do believe that some will have those data, that they don't get reported to CDC, and you may want to ask the folks from the local State Department about how they handle that information.

Senator BROWN. Let me ask you another question about the isoniazid preventive therapy—if I go to the doctor, if I'm an immigrant, or I'm particularly from Asia, I would point out, in response to Senator Allard's question earlier, I would point out in your testimony which you—I don't believe you mention that, actually, in your testimony—rates among nonHispanic Asians are 25 per 100,000, Latinos are 9 per 100,000—so the immigrant population is almost three times Asians versus Latinos. I don't know if that's the assumption that everybody would make. African-Americans 10 per 100,000, and nonHispanic whites 1.2 per 100,000, as contrasted to the 10, as Senator Murkowski mentioned.

If I'm one of those and I'm tested and I have the latent bacteria TB bacillus in my body, and you decide to prescribe Isoniazid protective therapy to me, and I'm not really very cooperative, I mean, I start taking it and I just don't take the treatment the way that I should, can I develop a drug resistance that, when I might get TB later, I all of a sudden have MDR TB, just from—my question suggests if we're not doing the Isoniazid, and I don't have any idea if we are, I didn't know about it before—but if we're not doing the isoniazid preventive therapy, well, does that create another avenue for a man-made MDR TB?

Dr. CASTRO. Fortunately for us, the information shows that in persons who have latest tuberculosis, the bacterium are so dormant that you don't induce the selection of drug resistance by using Isoniazid.

Now, the caveat here is that you need to have ruled out active tuberculosis in these persons. And once you've successfully accomplished that, and you're satisfied that they have latent TB, No. 1, they pose no threat to anyone else around them. And that's a common misconception, people call us all the time and say, "Someone tested positive in their skin test, should I keep them out of work?" The answer is no, they are not a threat to anyone else.

Now, they should, ideally, take their drugs, if they don't take their drugs, or they interrupt treatment, they're not likely to result in drug resistance, based on studies that were published about four decades ago. And, it's obviously predicated on what I started out saying, you must have ruled out TB disease. Because once you have TB disease, using a single drug will, indeed, promote the selection of drug-resistant strains.

But, it's a different environment, set of bacteria being dormant, they're replicating in the body, and that's where you're going to be selecting for those mutants that occur sporadically.

Senator BROWN. And my last question, you had—in response to a question, I believe from Senator Coburn or Allard, I'm not sure, you said that diabetes is linked to tuberculosis, I had never heard that before, what does that mean?

Dr. CASTRO. Persons with diabetes who are latently infected carry a higher risk of disease progression——

Senator BROWN. Never happens the other way?

Dr. CASTRO. No.

Senator BROWN. Not people that—I, that's what I misunderstood.

Dr. CASTRO. No.

Senator BROWN. All right. Thank you very much, Dr. Castro, for your testimony. I urge you to get back with Senator Burr on his concerns and questions and I know that Senator Allard and Senator Coburn were submitting questions for the record, too. I thank them, and I thank you very much for your service.

Dr. CASTRO. Thank you, sir.

Senator BROWN. I'd like to call up the second panel, and as you get situated, I will introduce all three of you at once, and then begin with Dr. Frieden.

Dr. Frieden has served as Commissioner of New York City Health Department since January 2002. One of the world's leading experts on TB control, Dr. Frieden was appointed NYC Health Commissioner after working in India for 5 years, where he assisted with national TB control efforts.

Prior to his tenure in the Republic of India, Dr. Frieden was instrumental in stopping the tuberculosis epidemic in New York City. His investigations helped document and stop hospital spread of tuberculosis, and documented for the first time, the extent of drug-resistant TB. During his time as Director of the Bureau of Tuberculosis Control and Assistant Commissioner, from 1992 to 1996, New York City reduced cases of multidrug-resistant tuberculosis by 80 percent.

Jerald Sadoff is President, Chief Executive Officer of the AERAS Global TB Vaccine Foundation. Prior to working at AERAS, Dr. Sadoff was at Merck where he was Executive Director of Clinical Development of Vaccines. Prior to Merck, he worked at Walter Reed Army Institute of Research, which has done some of the best medical research in world history that Walter Reed has. He attained the rank of Colonel in the U.S. Medical Corps. Well, Dr. Enzi's office had wanted Dr. Sadoff to provide the perspective of private companies in TB efforts.

And Dr. Randall Reves is the Chairman of Stop TB USA, formerly the National Coalition for the Elimination of Tuberculosis. He's a Professor of Medicine at the Division of Infectious Diseases

at the University of Colorado Health Sciences Center. Dr. Reves is Medical Director of the Denver Metro Tuberculosis Clinic of the Denver Public Health Department, he's a member of the National TB Control Association, of which he was President some 4 years ago. He will provide stories of his TB patients, as well as discuss all of the States perspective on TB control.

Welcome all three of you—Dr. Frieden, if you would begin?

STATEMENT OF THOMAS R. FRIEDEN, MD., MPH, COMMISSIONER, NEW YORK CITY DEPARTMENT OF HEALTH AND MENTAL HYGIENE, NEW YORK, NY

Dr. FRIEDEN. Thank you very much. Good morning Senator Brown, and thank you for your long-term commitment to the issue of tuberculosis control.

Senator Enzi, members of the committee, Senator Burr, Murkowski, and Allard, I'm Tom Frieden. I'm Health Commissioner from New York City. Thank you for the opportunity to discuss TB control, an issue on which I've spent most or much of my career.

In the 1990s, I ran the New York City Tuberculosis Control Program, and I took care of a man from India. He had extensively drug-resistant TBR XDR TB. I was his physician and it took about 2 years and well over $100,000. He nearly died, but we did cure him. It took medications, surgery, experimental drugs. The cost again, over $100,000.

By chance, several years later, when I was working in India, I traveled to his home town where I helped start a DOTS or Directly Observed Treatment Shortcourse program. That program now is one of the most effective in the world. It has cared for more than 8 million patients, or nearly 8 million patients and prevented more than 1 million deaths. The cost to prevent a single case of drug-resistant TB is about $10 there.

It's an indictment of all of us, I think, that more than 1.5 million people will die from a disease this year, that is almost completely curable. TB isn't just a New York City problem or a U.S. problem, it's a global problem that can only be solved with a global approach. TB reminds us that we're all connected by the air we breathe. Until TB is controlled worldwide, it's continuing to cause avoidable suffering and death in developing countries, and an ongoing threat in developed countries like here in the United States.

Fighting TB requires persistence on the part of patients, programs, and policymakers. TB control is a winnable battle. Drug-resistant TB results from failure to implement effective TB control programs, programs that cost only a small fraction of what it costs to treat drug-resistant TB once it occurs. Protecting the United States from drug-resistant TB means developing and ensuring effective and continued implementation of both domestic and international programs. We'll never be able to build a moat around this country. We are connected to the world.

Just as TB patients are tempted to stop medicines when symptoms are gone, governments are also tempted to de-fund TB control when it's no longer in the headlines. Doing so, unfortunately, will lead, both in the individual and in the governmental case, to interruption of treatment, development and spread of drug resistance, and to death.

Rates go up, funding goes up, rates come down, funding comes down. I've got figures to show that in my chart. What you'll see is the control of TB in New York City with attention, and then a major decline in funding, both at the national and New York City level, our funding is down by 70 percent from the Federal Government compared to 10 years ago.

New York City's TB epidemic of the 1980s was in large part the result of Federal funding cuts, but TB control in 1990s led to declines of TB overall by 75 percent, U.S.-born cases by more than 90 percent, and multidrug-resistant TB by 95 percent. Our success wouldn't have been possible without CDC cooperative agreement, which provided financial and technical support. Incidentally, I'd note that the cooperative agreement process of CDC is a very successful model, and I hope Congress will consider expanding it to areas such as diabetes, cancer, tobacco, and heart disease, which are now the leading killers in this country.

Today, the city again faces Federal funding cuts that threaten to undo this support and this success. This year, CDC's grant is worth less than one-third, in real terms, what it was 10 years ago. And yet, we still have far to go. New York City's rate is about 12 times the national goal for TB of one case per 100,000 people.

Globally, we have to greatly improve lab capacity. New tools are needed, but we also have to make better use of existing tools, which are very accurate, inexpensive, and unavailable in most of the world. Treatment can cure more than 95 percent of patients, and I urge you to support the global anti-TB drug facility with at least $15 million annually, and to provide funding for expanded assistance as outlined in the Stop TB Now Act.

Good TB control is basically good management. It includes a standardized reporting system that documents the outcomes of every patient treated, and I think it's a model of effective care management. We need to build and maintain these systems nationally and globally.

Currently, we do not have the tools to control TB in Sub-Saharan Africa, but DOTS can prolong lives, prevent drug-resistance, and blunt the increasing cases, and simple measures can prevent spread of TB in hospitals. Efforts to develop a more effective TB vaccine deserve support, but even if an effective vaccine is identified, effective treatment systems will be required for several decades.

Substantial increases in funding are needed to strengthen State and local TB control programs. I urge you to enact and fully fund the Comprehensive TB Elimination Act, which would provide essential support to domestic TB control efforts and for needed research. There is an urgent need for substantially increased support for global TB control and I urge enactment and full funding of the Stop TB Now Act. Preventing TB and drug-resistant TB abroad will not only save millions of lives, but it is the only way to protect this country from the disease.

Thank you.

[The prepared statement of Dr. Frieden follows:]

PREPARED STATEMENT OF THOMAS R. FRIEDEN, M.D., MPH

Good morning Senator Brown, Senator Enzi, and members of the committee. I am Dr. Tom Frieden, Health Commissioner for New York City. Thank you for this opportunity to discuss the important issue of TB control, a problem on which I have spent much of my career.

When I ran the New York City TB control program, I spent mornings in our clinics caring for TB patients. For nearly 2 years in the mid-1990s, I cared for a man from India with extensively drug-resistant (XDR) TB. He nearly died. But with intensive treatment, surgery, and experimental medicines, he was cured. The cost was well over $100,000. Several years later, I helped start a Directly Observed Treatment Shortcourse (DOTS) program in his hometown in India, along with programs that now cover all of India. The cost to prevent a case of drug-resistant TB there: about $10.

As a Centers for Disease Control and Prevention (CDC) employee detailed to New York City in the 1990s, I documented and helped stop both hospital and community spread of multidrug-resistant TB (MDR TB). Cases had nearly tripled in a decade, and 1 in 5 patients had MDR TB. The attached chart (Attachment 1) illustrates the decline of new TB and MDR TB cases as the DOTS strategy was implemented in the city. After TB declined rapidly in New York City as a result of our efforts, I spent 5 years in India on loan from the CDC to work with the World Health Organization helping India develop what is now one of the world's most effective TB control programs. India has now treated nearly 8 million patients and saved more than a million lives.

Tuberculosis remains a serious disease that will be with us for a long time. It is an indictment of all of us that more than 1.5 million people will die this year from a disease that is nearly 100 percent curable. TB is not just a New York City problem, or a national problem, but a global problem that can only be solved with a global approach. TB reminds us that we all live in the same world community and we are all connected by the air we breathe. Until tuberculosis is controlled worldwide, it will continue to cause avoidable suffering and death in developing countries and will be a continuing threat in developed countries.

The greatest enemy to TB control is complacency. Fighting TB is hard work that doesn't end. Our biggest need is persistence and energy, not only on the part of patients and our programs, but also policymakers. This is a winnable battle. We need sustained national and global political commitment to fight TB. The three critical issues for the future of tuberculosis control are sustained funding, technical rigor, and good management

MDR and XDR TB are the result of failure to implement effective TB control programs—programs that cost a small fraction of the medical care and treatment costs for patients with MDR or XDR TB. No program can treat MDR/XDR TB faster than a bad program can create it, no matter how many resources are available. Protecting the United States from drug-resistant tuberculosis means developing and ensuring effective and continued implementation of both domestic and international TB control programs.

As the overall caseload has fallen dramatically in New York City, non-U.S.-born patients now are more than 70 percent cases, compared to only 18 percent in 1992; nationally, as you have heard, the proportion is only slightly lower, and is growing. And increasingly, TB cases are found in the workplace and among business travelers, Wall Street executives, sales personnel, teachers, lawyers, and others.

The story of the fall and rise and fall of TB in the United States provides valuable lessons for how to control a serious communicable disease—and how not to. Just as patients with tuberculosis are tempted to stop medicines when the symptoms are gone, so also governments are tempted to neglect tuberculosis control programs when TB is no longer in the headlines. But doing so will lead, both in the individual and in the governmental case, to interruption of treatment, development and spread of drug-resistant TB, and death.

When TB is in the headlines, resources increase. Once those resources succeed in reducing the disease, we neglect the modest investment that needs to be maintained to prevent future epidemics—epidemics that will cost lives and money. Rates go up, funding goes up; rates come down, funding comes down. The attached chart shows that CDC's tuberculosis control funding has declined steadily, in real dollars, over the past 15 years. New York City's funding has declined even faster.

The TB and drug-resistant TB epidemic that began in the 1980s in New York City was in large part a result of the funding cuts to TB programs in the previous decade, further fueled by the rise in HIV/AIDS in the city. The TB epidemic ultimately cost the city's medical care system $1 billion. Today, New York City again faces Federal funding cuts that threaten to undermine the public health infrastructure that

can maintain this success. In 2007, the city's CDC grant of about $13.8 million is less than *half* its 1996 funding level of almost $30 million, and, after adjustment for inflation, is worth less than *one third* of that year's support. (Attachment 2) Although we successfully contained the epidemic, we still have far to go. The Healthy People 2010 objective for tuberculosis is less than 1 case per 100,000 people; New York City had 12 cases per 100,000 people in 2006.

New York City's success in controlling tuberculosis would not have been possible without the financial support from the Federal, State and local governments, and without the partnership with the CDC. Through a cooperative agreement with CDC, we not only received essential financial support but also important technical expertise. I would add that the cooperative agreement approach is a successful model, and I hope that Congress will expand its implementation to areas such as diabetes prevention and control, colon cancer prevention, tobacco control, and heart disease prevention, which are now the leading killers in this country.

The key to the NYC TB program's success was using policies that had been rigorously proven to work, strong program management, and a focus on supporting the front lines—patients, laboratory workers, TB control and other health staff, and program managers. Support from public officials, hospital staff, and the academic community was also important

Diagnosis: Rapid diagnosis of infectious tuberculosis by simple sputum smear for acid-fast bacilli remains an important tool, and more rapid molecular techniques hold promise. New techniques for diagnosing latent infection may be useful, but they are expensive: in New York City we have not applied these tests widely solely because we do not have sufficient funds. Globally, we need to greatly improve basic laboratory capacity, as part of a general health systems strengthening approach. It is key to start with simple smears, which diagnose the most seriously ill and infectious patients, and proceed to cultures, which are important to diagnose some patients, especially children and HIV-infected people, and then on to high-quality drug-susceptibility testing. While new tools are needed, it is unethical not to ensure effective use of existing tools—which are highly accurate, relatively inexpensive, but unavailable in most of the world.

Treatment: Treatment can cure more than 95 percent of patients; direct observation of treatment, a component of the recommended five-element DOTS strategy, is the standard of care. In the United States and globally, we need to strengthen our health care system, including TB care systems such as chest clinics. This means investing in education and training to improve the quality of laboratory and primary care services, building State and local public health laboratory capacity, and assuring that all drug-resistant patient isolates are tested for second-line drug susceptibility and isolates genotyped to identify outbreak patterns. We need new drugs, but we also need to ensure effective use of existing drugs worldwide. One of the highest priorities for global TB programs is an adequate supply of high quality drugs, as well as trained personnel to ensure an effective DOTS strategy. Hence I urge you to support the Global Anti-Tuberculosis Drug Facility with at least an annual allocation of $15 million and to provide funding for expanded technical assistance for TB control, as outlined in the "Stop TB Now Act" (S. 968/H.R. 1567.)

Monitoring: Systematic monitoring of case detection and treatment outcomes is essential to effective service delivery. The proportion of patients diagnosed and treated effectively has increased greatly over the past decade but is still far short of global targets. New York City's program had a system of accountability that enabled us to tell policymakers the number of people we could—and did—cure for the dollars provided. Effective TB control includes a standardized reporting system which documents the outcomes of every patient and which is a model for effective care management.

Good TB control is basically good management. That means supporting well-trained personnel for direct service and supervision, from those who provide or supervise DOT to lab technicians, to national program managers. Programs must have the ability to hire staff, purchase supplies, and contract for services efficiently without unnecessary administrative constraints.

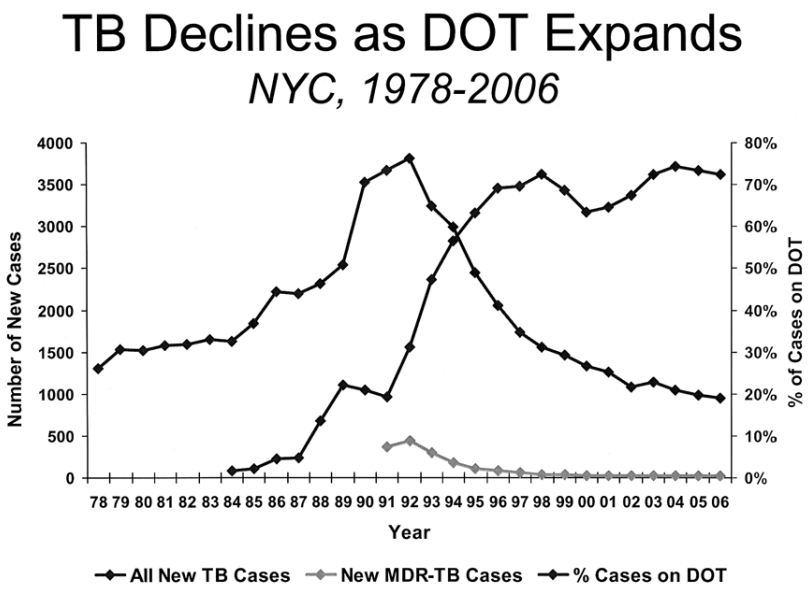
Strengthen Health Systems: We need to build and maintain a strong health care and public health infrastructure in order to implement good tuberculosis control. The global HIV epidemic has created increasing challenges for TB control, especially in sub-Saharan Africa. HIV exposes any weaknesses in TB control programs. We don't currently have the tools to control the epidemic of TB in high-HIV prevalence regions of sub-Saharan Africa, but we can prevent deaths and drug resistance by ensuring prompt and accurate diagnosis and treatment, including use of directly observed therapy. DOTS can prolong lives, prevent drug resistance, and blunt the increase in cases.

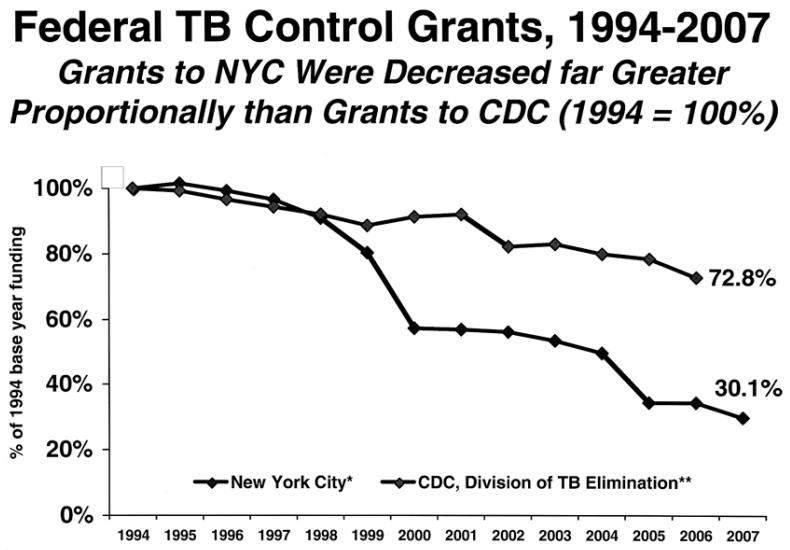
Research: Efforts to develop more effective tuberculosis vaccines are underway, and deserve support. But even if a vaccine is identified, more effective treatment systems are likely to be required for decades. Other modes of tuberculosis control, such as treatment of latent infection, have a potentially important role in some contexts, such as infectious TB patients and patients co-infected with HIV. And we must face the tragic fact that at present we cannot control tuberculosis in sub-Saharan Africa with current technologies. We must explore ways to make improved care and control possible and prevent the spread of TB in hospitals.

The current funding level for CDC's domestic TB activities is inadequate and represents a 27-percent decrease over the past decade when adjusted for inflation. Substantial increases in funding are needed to strengthen State and local TB control programs. I urge you to enact and fully fund S. 1551/H.R. 1532, the Comprehensive TB Elimination Act, which would provide essential support to domestic TB control efforts and for needed research for new diagnostic tools, drugs, and vaccines.

Importantly, there is an urgent need for substantially increased support of global TB control programs. I also urge the enactment and full funding of the Stop TB Now Act, S. 968/H.R. 1567. Preventing TB and drug-resistant TB abroad will not only save millions of lives, but it is the *only* effective way to protect this country from the disease.

Thank you for your support for tuberculosis control and for the opportunity to comment.





SUMMARY

Tuberculosis remains a serious disease and it will be with us for a long time. It is a global problem that can only be solved with a global approach. Until tuberculosis is controlled worldwide, it will continue to cause avoidable suffering and death in developing countries and will be a continuing threat in developed countries.

Our greatest enemy is complacency. This is a winnable battle, but we need the political commitment and persistence for a sustained national and global approach to fighting TB. MDR and XDR TB result from failure to implement effective TB control programs—programs that cost a small fraction of the medical care and treatment costs for drug resistant TB patients. Protecting the United States from drug-resistant tuberculosis means developing and supporting—for the long-term—effective domestic and international TB control programs.

Government funding rises and falls with the rise and fall of TB rates; when government support falls, the public health infrastructure built to prevent TB is compromised, creating the potential for another epidemic.

New York City was able to reduce TB cases by 75 percent, U.S.-born cases by 90 percent, and MDR TB cases by 95 percent since the last epidemic's peak in 1992. The key to the TB program's success has been using policies that had been rigorously proven to work, strong program management, and a focus on supporting the front lines—patients, laboratory workers, TB control and other health staff, and program managers.

We need new diagnostic tools, but also wider use of effective existing tools—which are highly accurate, relatively inexpensive, but unavailable in most of the world. We need to:

- Develop new drugs, but we also need to assure an adequate supply of current high-quality drugs domestically and globally;
- Support directly observed treatment, which can save lives, reduce drug resistance, and save future health care treatment dollars;
- Ensure accountability for all programs and support the training and human resources necessary to get results;
- Support the public health infrastructure and strengthen the health care systems that these public health programs work with.

I urge enactment of and full funding for S. 1551/H.R. 1532, the Comprehensive TB Elimination Act and the Stop TB Now Act, S. 968/H.R. 1567 for a comprehensive approach to win the battle against TB. I also recommend at least $15 million for the Global Anti-Tuberculosis Drug Facility as well as substantially increased funding to

international tuberculosis control in general. Preventing TB and drug-resistant TB abroad will not only save millions of lives, but it is the *only* effective way to protect this country from the disease.

Senator BROWN. Thank you, Dr. Frieden.

Dr. Sadoff, welcome, nice to see you again. Thank you for being here.

STATEMENT OF JERALD C. SADOFF, M.D., PRESIDENT AND CEO, AERAS GLOBAL TB VACCINE FOUNDATION, ROCKVILLE, MD

Dr. SADOFF. Senator Brown and other committee members, thank you for this opportunity to appear before you to discuss the state of tuberculosis vaccine development and to describe the work of the AERAS Global TB Vaccine Foundation, which is a public/private partnership focused on product development.

We appreciate your interest in this critical matter and we look forward to working with you and other Senators in the future. Your role is crucial to ensuring adequate resources and incentives to accelerate vaccine development. We applaud your leadership in addressing the worldwide tuberculosis pandemic, which you point out infects 8 million people and kills 1.6 million people a year. And of course of particular concern, the rising threats of drug-resistant tuberculosis and especially co-infection with HIV/AIDS.

And in fact, tuberculosis, as you pointed out, is the cause of death of half the people with HIV/AIDS who die in Africa from HIV. New tools are urgently needed to diagnose, test, and prevent TB, including new and effective vaccine. And modeling studies show that without such vaccines, we can not eliminate TB from the world.

We thank Senator Brown and others for highlighting the needs for these new tools, and bipartisan Comprehensive Tuberculosis Elimination Act. And as this bill makes clear, more resources and strategic focus are needed to spur the creation of 21st Century technologies to curb the pandemic.

We also applaud Ranking Member Enzi and the full committee for the support of Senator Brown and Senator Brownback's creative, balanced, and forward-looking amendment to the FDA Revitalization Act. This measure holds promise of speeding the development of products to combat neglected diseases like TB.

As recent experience shows, tuberculosis, like any infectious disease, is a problem that knows no borders. And the United States needs to significantly strengthen the efforts to halt its spread. The tools used in most places around the world are outdated and inadequate. Diagnostic tools currently used were invented 100 years ago, as you pointed out, antibiotics used to fight TB are over 50 years old, and the vaccine currently in use in countries outside the United States was invented 85 years ago and had very limited effectiveness, even in children. Clearly we need new solutions.

One approach, important approach to developing these new tools is the product development partnership model, which bridges the gap between public sector's urgent need for these interventions and the private sector's technological expertise. Three such PDPs are engaged in the search for new tools to combat TB. The Global Alliance for TB Drug Development, the Foundation for Innovative New

Diagnostics, and my organization, the AERAS Global TB Vaccine Foundation.

AERAS's mission is to accelerate the development and delivery of safe, effective, affordable vaccines to prevent TB infection around the world. We are essentially a non-profit biotech company, guided by business principles, and seeking to be as efficient and flexible as a for-profit entity. I myself, am a hybrid of public and private experience, having spent more than 20 years, as you mentioned, creating vaccines at the Walter Reed Institute of Research, followed by over 7 years as Executive Director of Clinical Development of vaccines at Merck, before becoming the AERAS CEO in 2003.

During my career, I've had the opportunity to be involved in the development of nine vaccines that are currently on the market today. Based on that experience, we operate AERAS on an industrial model, making tough decisions, weighing risks, resources, and time. My staff, most of whom have biotech or pharma experience, have quarterly benchmarks they must reach, directly tied to their compensation.

However, unlike any individual pharmaceutical company, we are testing a portfolio of the world's most advanced TB vaccine candidates from a variety of sources, including several we have invented ourselves. AERAS collaborates with the best scientists around the world, whether in South Africa, India, Maryland, or Tennessee, whether with a small biotech, a large vaccine manufacturer, a leading academic researcher, or outstanding scientists in our own Government. This gives us an advantage over any single company and provides our funders with a central focus for TB vaccine development.

My own pharmaceutical companies do more of this research. The private sector, where most vaccine product development expertise resides, has generally stayed on the sidelines because of the scientific challenges in an unpredictable market. Vaccines are among the most cost-effective and medically effective health interventions, but inventing them presents technical challenges that require significant investment. For profitable products, the public and private sectors have collaborated in a model where public sector agencies, such as National Institute of Health, finance basic research that industry translates into products by clinical trials, process development, manufacture, licensure, and marketing.

This model breaks down for neglected diseases, such as TB. While the NIH continues to play a vital role in funding basic research and some early clinical development, its mandate does not generally include industrial-style product development. Biotech and pharmaceutical companies may have potential vaccine candidates or technologies that could help solve the TB problem, but they feel constrained by the need to maximize shareholder value.

By taking on the expense and effort of early to late stage product development, PDPs like AERAS minimize risk and offer the private sector an opportunity to develop products that they would otherwise not be commercially viable. At the same time, our agreements with industry contain provisions to ensure the vaccine that emerges will be affordable and produced in adequate quantities.

AERAS currently has six vaccine candidates in our pipeline, with clinical trials underway in the United States, Europe, Africa, Asia.

The best of these vaccines are scheduled to enter proof of concept efficacy trials in 2009, enabling us to rationally select vaccines for subsequent large-scale trials in field sites, which we're developing in South Africa, India, Kenya, Uganda, and Cambodia. These trials will be conducted under the highest ethical standards, with vaccines that meet all FDA quality and safety requirements.

I want to express appreciation for past financial support providing to AERAS by the CDC to develop field sites in India, and the cooperation we have received from the National Institute of Health. AERAS's programs have also attracted funding from the governments of the Netherlands and Denmark, as well as the Bill and Melinda Gates Foundation.

I ask your sustained and increased leadership and commitment to research, and designing and testing new tools to fight TB needs more funding. Supporting the NIH basic research and CDC programs and directing resources for product development partnerships is the most effective way to develop new tools to defeat this horrible disease.

I thank you for this opportunity to highlight the need for preventative TB vaccine and AERAS's efforts to develop such a vaccine. I look forward to answering any questions you may have.

Senator BROWN. Thank you, Dr. Sadoff, for your work.

Dr. Reves.

STATEMENT OF RANDALL REVES, M.D., PROFESSOR OF MEDICINE, INFECTIOUS DISEASES, UNIVERSITY OF COLORADO; MEDICAL DIRECTOR, DENVER METRO TUBERCULOSIS CLINIC; CHAIRMAN, STOP TB USA, DENVER, CO

Dr. REVES. My name is Randall Reves. I'm the Medical Director of the Denver Metro Tuberculosis Control Program, and a Professor in Infectious Diseases at the University of Colorado Health Sciences Center. I'm here representing the Stop TB USA Coalition, the American Thoracic Society, and importantly, my colleagues in the National TB Controllers Association.

I want to thank Chairman Kennedy, Senator Brown, and Ranking Member Enzi, and the other Senators here today, including Senator Allard from Colorado, for holding this important hearing and for their leadership in global and domestic tuberculosis control.

TB is an important issue, and I hope the hearing today will encourage the Senate to act favorably on legislation that will provide increased authority, resources, and coordination for TB control among Federal agencies.

There are three points I want to make today in my presentation. No. 1, tuberculosis is still a problem in the United States. No. 2, we have tools to combat tuberculosis. But No. 3, we will never defeat TB until we develop and apply a new generation of diagnostic tools, TB drugs, and an effective vaccine.

TB control, like all of public health, is ultimately delivered at the local health department level. This is the perspective that I bring to you today. To illustrate these points, I will tell you the story about a patient treated in our community. This is not someone you would recognize from news reports, but this patients' course would be familiar to many local health department staff in your own States.

This young man arrived from Denver after several years in a refugee camp in Egypt. He completed and passed the mandatory refugee TB screening program before departing Egypt, but became quite ill during travel to the United States. He was promptly admitted to the hospital in Denver, in fact, he was admitted directly from Denver International Airport to the hospital.

Preliminary tests were negative, but after 5 days, cultures grew tuberculosis. His doctors consulted with us at the Health Department and promptly initiated treatment for disseminated tuberculosis. He was brought to the TB clinic the day of hospital discharge by our outreach worker. We did this and we do this to ensure that the patient makes their first TB clinic visit and doesn't get lost in the transition.

Several weeks later, test results revealed we were dealing with MDR TB, a strain resistant to isoniazid, rifampin, and streptomycin. Our public health workers, in doing the contact investigation, identified several other family members who also had active multidrug-resistant tuberculosis.

This patient and his family members remained TB free after completing 2 years of daily multidrug-resistant treatment, each dose directly observed by our health department staff members. This was very expensive. But you see, we could not afford to have his treatment fail for him, for his family, or for our community. The man and his family members felt well within months, but we worked with them to ensure that they completed the necessary 18 months of treatment to prevent eventual relapse.

This man is now a productive member of our community, holding a job, going to school, and supporting his family. This story illustrates how a public health emergency can, and should be, managed. However, imagine what could have happened if his TB disease had become highly infectious during travel. We were just lucky.

If the hospital physicians had missed the diagnosis or delayed treatment, if the laboratory results had been inaccurate or slower in returning, if the patient was lost to follow up at discharge and never got into the clinic for treatment, if budget cuts meant we no longer had the staff to ensure curative treatment of the patient and his contacts, and if, even worse, the patient's treatment was inadequate his disease would then have become XDR TB.

The effectiveness of your local health department is the only thing standing between you and XDR TB. Why do I say that? Because every MDR TB case is a potential XDR TB case if treatment fails. With over 100 new MDR TB cases in the United States each year, that means there are two diagnosed every week in either your local health department in your State or in a health department in my State. And it's incredibly important that these be managed correctly.

We have a superb staff at the Denver TB Control Program, with expertise in clinical and public health management of TB. We have the experience of treating one MDR TB case each year, on average. I'm sure that you can imagine, however, that in a health department where MDR TB is not seen, that when one surfaces, it is a public health crisis.

I hope you can appreciate from my local perspective, that TB remains a problem in the United States and that our current tools can be effective if we have the necessary resources to apply them.

For the last point, I hope you're asking yourself, why we should have to treat this man's TB for 2 years. This is a throw-back to how we treated TB in the 1960s. In fact, we are now perfecting the obsolete treatments we abandoned over 30 years ago. But why? Part of the answer lies in the nature of the TB bacterium. It mutates when inadequately treated. More importantly, we knew this, but we failed to respond. Globally, we failed to ensure the completion of curative treatment to prevent drug resistance and we allowed research for new and better drugs to grind to a halt.

There is no scientific reason why we should not have a TB diagnosis confirmed or excluded within days. This can be done at selected places in the United States now, but nearly half of persons with culture-positive TB across the globe can not get a diagnosis because of reliance on ancient tests. Most patients with MDR TB and XDR TB, unlike the one who made it to Denver and survived, will die without a diagnosis ever being made.

In 1993, AIDS was a chronic, progressive, infectious disease, for which treatment only delayed eventual death. Our national investment in clinical research changed that, and HIV can now be diagnosed rapidly and treatment is highly successful. In fact, there's one single-dose, daily treatment that involves three drugs that is highly effective for treating AIDS. These new HIV tools are now being implemented with governmental funding around the globe. In contrast, we have largely ignored TB research needs and millions are now paying for it.

The good news is, that today, our existing tools can prevent the further development of drug-resistant strains if we apply them correctly. We have labor-intensive, but successful, public health strategies to prevent the spread of TB. We even know how to implement these in resource coordination's around the world. What is needed is the authority and resources to get the job done.

The American Thoracic Society is pleased to support the legislation, the Comprehensive TB Elimination Act sponsored by Senators Brown, Hutchison, and Kennedy. This legislation responds to the public health threat that TB poses today and it seeks to ensure that the CDC, State and local health departments, and all health care providers are ready for the future. It would expand the resources and the authority of the CDC to more effectively apply today's TB diagnostic and treatment tools in the United States. The bill also expands CDC's authority to conduct the research needed to bring effective diagnostic and treatment tools into practice.

Our public health system must be prepared to respond to the mutating TB germ. I thank the committee for this opportunity to testify on this important subject.

[The prepared statement of Dr. Reves follows:]

PREPARED STATEMENT OF RANDALL REVES, M.D.

INTRODUCTION

My name is Randall Reves, M.D. and I am Director of the Denver Metro Tuberculosis Control Program and Associate Professor at the University of Colorado Health Sciences Center Department of Preventative Medicine and Biometrics. I am

representing the National Tuberculosis Controller's Association (NTCA), the national association representing State tuberculosis control programs, the Stop TB USA Coalition (formerly the National Coalition for the Elimination of Tuberculosis), the U.S. partner of the global Stop TB Partnership, and the American Thoracic Society (ATS), a medical professional society that was founded over 100 years ago to foster the prevention, detection, treatment and cure of tuberculosis. The NTCA/Stop TB USA/ATS would like to thank Chairman Kennedy, Senator Brown and Ranking Member Enzi for holding this important hearing and for their leadership on global and domestic tuberculosis control. Tuberculosis is an important global and domestic public health threat that deserves the attention of Congress. I hope the hearing today will encourage the Senate to act favorably on legislation that will provide increased authority, resources and coordination for TB control efforts among key Federal agencies.

There are three points I want to make. First, tuberculosis is a problem in the United States. Second, we have tools today to combat the spread of TB. Third, we will never defeat TB until we develop a new generation of diagnostic tools, a new generation of TB drugs and an effective vaccine.

THE SCOPE OF THE TB PROBLEM

What is tuberculosis? Tuberculosis is an airborne infection caused by a bacterium, *Mycobacterium tuberculosis*. It primarily affects the lungs but can also affect other parts of the body, such as the brain, kidneys or spine. Tuberculosis is spread through coughs, sneezes, speech and close proximity to someone with active tuberculosis. People with active tuberculosis are most likely to spread it to other people they spend a lot of time with, such as family members or co-workers. It cannot be spread by touch or sharing utensils used by an infected person. The statistics for TB are alarming. TB is the second leading infectious disease killer in the world, taking at least 1.6 million lives per year.[1]

Until the Andrew Speaker case emerged earlier this year, many Americans thought TB was a disease of the past. The number of persons with newly diagnosed TB in the United States appears to be leveling off at just under 14,000 new cases and over 600 deaths each year. Although the number of TB cases in the United States continues to fall, the slowing of the decline rate, from 6.6 percent per year in the period 1993–2002 to 3.1 percent per year in the period 2003–2006, is of concern because of the history of TB in the United States.[2] In the 1970s and early 1980s, the Nation let its guard down and began significantly reducing the TB control infrastructure. Consequently, the trend towards elimination was reversed and the Nation experienced an unprecedented resurgence of TB with a 20 percent increase in cases reported between 1985 and 1992.

That's the medical explanation and statistical background on TB in the United States. But what do we mean when we say TB is a domestic problem? It means that people in the United States are getting TB, including the drug resistant strains featured in the Andrew Speaker case earlier this year. It means even in the United States, where the TB incidence is much lower than the developing world, we are still vulnerable to outbreaks of multidrug-resistant (MDR) TB. As the Andrew Speaker story made clear, it only takes one infectious individual in close proximity to other people—in this case an intercontinental flight—to cause a public health alarm.

While the Andrew Speaker story is alarming, the truly alarming news is that TB is mutating. Poor control of TB has lead to the development of drug resistant strains of TB. There are even strains of extremely drug resistant TB that are resistant to four or more of the drugs commonly used to treat TB. Without immediate attention to this problem, we may soon see strains of TB that are infectious, lethal and essentially impossible to cure.

While the Andrew Speaker case got media attention, Mr. Speaker is far from the typical case of TB found in the United States. Let me share with you a more typical example of a TB case found in the United States. A couple of years ago, I treated a young man with tuberculosis from Egypt. The man most likely became infected with TB while living in a refugee camp. Despite completing and passing the mandatory TB screening program prior to entering the United States, he was hospitalized for pulmonary symptoms shortly after arriving in the United States. Based on his symptoms and case history, he was presumed to have TB and was put on antibiotic treatment. He responded well to treatment. A few weeks after treatment was initi-

[1] Tuberculosis, World Health Organization (WHO) Factsheet No. 104, March 2006.

[2] CDC. *Reported Tuberculosis in the United States, 2006.* Atlanta, GA.: U.S. Department of Health and Human Services, CDC, September 2007.

ated and he was discharged from the hospital, test results came back indicating the man had drug-resistant TB with resistance to isoniazid, rifampin and streptomycin—the three first line drugs used to treat TB. He survived because initial treatment included drugs with MDR TB activity.

The patient remained free of TB after completing 2 years of daily treatment with health care workers delivering and observing ingestion of each dose. Public health workers also did standard contact follow up and identified other members of his family that had MDR TB. They also were located and treated successfully. This man is now a productive member of our society holding a job and supporting a family.

This case illustrates many of the strengths and weaknesses of the current tools used to detect, treat and cure TB. And let me tell you that Denver is one of the best run TB programs in the United States. We are experts in both the medical and public health aspects of TB. Any potential flaws in how a case is handled in Denver are going to be magnified in programs with less expertise.

Refugee camps are well recognized as being hot beds for developing drug-resistant strains of TB. However, applying standard public health practices for TB in refugee camps could significantly reduce this problem. Identifying cases under a microscope, screening for HIV and providing the standard course of anti-TB drugs can be done cheaply and with a minimum financial investment. Instead, the lack of TB control measures in Egypt meant that my patient and several of his family members developed MDR TB, significantly increasing the cost of treating the disease and posing significantly higher health risks for everyone they came in contact with.

How this man passed the initial screening test prior to entering the United States, I don't know, but I would suspect the reason, in part, is due to the lack of fast, cheap tests capable of effectively screening for TB.

While my patient from Egypt responded well to the initial treatment, it was weeks after he was discharged from the hospital that we found out he had MDR TB. We were able to keep track of Mr. X and alter his treatment accordingly, and provide follow up for 2 years to ensure he completed his treatment. What if during that 2-week timeframe, he got "lost" and could not be followed up with? Then a super-germ would be circulating throughout the community potentially infecting others. Diagnostic tests that can detect TB in hours or days—not weeks—are needed to accurately detect TB and its level of drug susceptibility.

What if, due to cuts in public health funding, we did not have the staff to follow up with my patient's contacts? Then we would have failed to identify his family members who also had MDR TB, again putting the community at risk.

THE NEED FOR BETTER DIAGNOSTICS AND DRUGS

Why did it take 2 years to successfully treat his TB? While we should be pleased that the Denver public health system was able visit him daily for 2 years to ensure he completed his antibiotic treatment, think of the staff time and organizational effort involved in a 2-year treatment plan. Drugs with shorter treatment times and novel antibiotics to treat TB are desperately needed.

When the first highly successful treatment for TB with INH-streptomycin-PAS was introduced in the 1950s, we failed to ensure that all patients completed the 2-year course of treatment, allowing the bacteria to become resistant. Most experts at the time believed that drug-resistance was harmless since many patients improved clinically despite persistence of positive sputum cultures. The "mutant" bacteria were believed incapable of being transmitted to others. That theory held for 20 years until 1977 when I, as a new CDC trainee stationed in Mississippi, pursued the investigation of a high school outbreak of INH-streptomycin-PAS resistant TB in Alcorn County. These bacteria had spread to 150 students and faculty resulting in five active TB cases. The source was a smoldering community outbreak with a total of 22 active TB cases that began when the public health system failed to ensure treatment for patients diagnosed up to 12 years earlier.

We moved on to the next wonder drug and cured most of the drug-resistant TB cases in Alcorn County using the new wonder drug, rifampin, in combination with ethambutol. At least two patients lapsed from treatment and the bacilli added rifampin resistance to their existing repertoire of drug resistance genes, killing one previously healthy young woman. This shot across the bow by an organism, later named MDR TB, was largely ignored for the next two decades as we allowed local, State and national tuberculosis control capacity to deteriorate to the point that successful completion of the new 6-month TB treatment in many areas became the exception, rather than the rule.

The end result was extensive, deadly outbreaks of TB in New York City, Miami and other cities in the 1980s and 1990s and MDR strains resistant to more than six drugs were found to be readily transmitted. Patients with HIV/AIDS in New

York City died within weeks, usually before the drug resistance was detected. We had no new TB drugs to use but learned by experience, not by research, that new fluoroquinolone antibiotics could be used successfully in combination treatment lasting 18–24 months. For patients with MDR TB this meant going back to treatments we abandoned two decades ago, including lung surgery. We learned to stop complaining about patients who were not compliant, and became committed to ensuring curative treatment. Many programs adopted the approach touted decades earlier by John Sbabaro in Denver, insisting that a health care provider Directly Observe the ingestion of each dose of Treatment (DOT).

There is no scientific reason that we should not have a TB diagnosis confirmed or excluded within days. This can be done in selected places in the United States now, but nearly half of all persons with culture-positive TB across the globe cannot get a diagnosis because of reliance on the sputum AFB smear, a 100-year-old test. Most patients with MDR TB and XDR TB will die after treatment failure without a culture and/or drug susceptibility test ever being done. There are promising diagnostic tools that will need evaluation in field studies before successful implementation.

In 1993, AIDS was a chronic progressive infectious disease for which treatment only delayed the inevitable progress to death. Because of our national investment in clinical research, HIV infection can now be diagnosed within weeks of onset, and AIDS can now be successfully treated with one triple-drug pill taken daily. These new tools for HIV are also being implemented, with governmental funding, around the globe. We have largely ignored TB research and needs, and millions are now paying for it.

DOMESTIC TB CONTROL CHALLENGES

The fiscal year 2007 funding level of $137.4 million for the Centers for Disease Control and Prevention's Division of Tuberculosis Elimination actually represents a 27 percent decrease over the past decade when adjusted for inflation. To effectively address TB in the United States and appropriately develop both domestic and global preparedness and outbreak response capacity for drug-resistant TB, additional resources are urgently required.

In order to prevent the spread of drug resistant TB in the United States and to put the Nation back on the path to eliminating the disease in the United States, domestic TB control capacity, and treatment, and prevention systems must be strengthened to ensure diagnosis, and treatment. The following are some additional specific steps that must be taken:

- Improve strategies to identify and treat latent TB infection and reach at-risk populations.
- Intensify TB control activities among persons who regularly cross the United States-Mexico border.
- Intensify efforts to prevent, detect, and treat TB among foreign-born persons in the United States.
- Expand United States-provided leadership and intensify technical assistance activities to address the global TB crisis.

CONCLUSION

The slowing of the decline in the overall national TB rate and the inability to effectively address persistent disparities in TB rates between U.S.-born and foreign-born persons and between minority populations threatens progress toward the goal of eliminating TB in the United States.

The good news is that today, appropriately applying our existing tools can prevent the further development of drug resistant strains of TB. We have successful—but labor intensive—public health strategies to prevent the spread of TB. We even know how to make TB control programs work in the most resource-poor nations in the world. What is needed is the authority and resources to get the job done.

The American Thoracic Society is pleased to support the legislation—the Comprehensive TB Elimination Act—sponsored by Senator Sherrod Brown of Ohio, Senator Kay Bailey Hutchison of Texas, and Senator Edward Kennedy of Massachusetts. This legislation responds to both the real and immediate public health threat that TB poses today as well as looking to the future to ensure that the Centers for Disease Control and State and local public health departments and all health care providers are ready for the future.

It responds to today's needs by expanding the resources and authority of the CDC to more effectively apply today's diagnostic and treatment tools to identify and effectively treat TB in the United States. The legislation also gives CDC expanded authority to conduct research to develop more effective diagnostic and treatment tools

particularly a new generation of anti-TB drugs—to ensure that our public health system is prepared to effectively respond to a mutating TB germ.

I thank the committee for this opportunity to testify on this important subject.

Senator BROWN. Thank you, Dr. Reves.

Dr. Reves, earlier, I think Dr. Castro mentioned—and I really appreciate your comments about drug resistance and your statement that every TB case is potentially a multidrug-resistant case, and what that means to patients and doctors and the whole public health system and policymakers—Dr. Castro had talked about the difficulty of having people who really do know how to treat tuberculosis, how to recognize it, how to diagnose it, how to treat it—are you seeing as a representative here, in some sense, of the States and of public health authorities all over the States, all over the communities of this country, is it a significant long-term problem that we don't train doctors and nurses and other public health officials well enough to recognize TB? Talk about that as a problem, and what we need to do about it.

Dr. REVES. Well, it is a major problem, and the health department sector where I work, we really rely upon physicians in practice—whether that be the emergency room, the hospital, other clinics and so forth—to diagnose at least two-thirds of the cases that they then refer to us, report to us, and refer for treatment. So, it is a challenge, because you have physicians who haven't seen a case of TB in 5 or 10 years. And how do we provide them with some sort of an ongoing continuing education reminder, and a small enough piece that it doesn't consume their whole day? Nobody needs to go to the 3-day National Jewish course if they're not going to see a TB case in 5 years. But, they need to be reminded and to think about tuberculosis.

One of the things we've done in Denver is working with some of our community-based groups—there's an Asian-Pacific Islander Health Education Project involving a number of different community groups, and at their health fairs, they talk about TB, they've gotten past the stigma about it. And it's helpful, I think, if a patient goes into their doctor who hasn't seen TB in 5 years and say, "Well, you know, I'm from Thailand, I'm from India, I'm from Korea, I'm from Mexico—could these symptoms be due to tuberculosis?"

Senator BROWN. Thank you, and continue to do some thinking about that, and all of you, really give this committee your input about how we can help to prepare the public health sector better.

Dr. Frieden, you mentioned the sort of analogy of when patients stop taking their medicine, it's not too far different from when government stops doing things, because the patient quits coughing in the second month, that they can now stop, and they feel better, or they feel worse when they're taking the medicine, feel better when it stops—the analogy that government stops funding when TB starts to look better. Do you see similarities between the current domestic TB situation and what you saw in New York a decade and a half ago?

Dr. FRIEDEN. A decade and a half ago, what was happening is that we had ignored warning signs in the poorer communities of New York City, where rates were quite high. Funding was reduced, and programs were reduced, and there was an inappropriate focus

on things that didn't make a big difference in TB control. We lost sight that the priority is to cure patients with infectious disease, and once you've got that underway, you can then start preventing TB in people who have infection but aren't sick. And there were simply insufficient resources.

What happened then, there was intense media interest, there was a crisis mentality, there was a big increase in funding at the local level, at the State level, at the Federal level, and TB is a very rewarding disease to treat as a physician or as a public health officer, because it responds to good management. You do the right things, and in just about everywhere in the world, it goes away. You can cure the vast majority of patients, you can bring rates down. That's what we saw. So, as I mentioned, our rate of multidrug-resistant tuberculosis is 95 percent less than it was at the peak of our epidemic.

U.S.-born cases are down by 91 percent, and overall cases are down by 75 percent. It used to be that only about 18 percent of our cases were among the foreign-born, now it's 70 percent among the foreign-born.

What we're seeing now is the erosion of the public health infrastructure. Funding for CDC has not kept up with inflation, it's down by 27 percent in constant dollars, funding in New York City is down by 70 percent from the Federal Government. We do our best to continue to control the disease, but we're ignoring warning signs that could be a serious problem.

At the same time, we have to recognize that there is a huge problem globally, and we can't just put our head in the sand. Unless we can address that problem, we're never going to control TB in this country. I can't stop those 70 percent of cases that are coming into New York City—they feel fine when they come in—but 1 year, 5 years, 10 years, 20 years later, they break down with active tuberculosis having been infected overseas.

We don't want to keep people out. These are people who, in the vast majority of cases are here legally, they're part of our society, they're contributing, they're working, they actually use fewer health services than many other people, but they may have a higher risk of having active tuberculosis.

One of the most effective ways we can protect our own country is by improving tuberculosis control globally, so that they don't have drug-resistant tuberculosis, they don't have multidrug, or XDR TB, they don't have TB at all, because the disease is controllable.

Senator BROWN. Thank you, thank you, Dr. Frieden.

Dr. Sadoff, unfair question perhaps, but predict when we're going to see a vaccine, when we're going to see a new, improved diagnostic tool. Share with us where the emphasis and the resources have been on those two—are we putting more public/private emphasis on vaccines, or on diagnostic tools and what do you predict in the next few years, if you could?

Dr. SADOFF. Thank you. Well, we think that others working on diagnostics are going to come up with better diagnostics, actually in the next 2 years, with something that might be very effective in the next 3 to 5 years. There's a couple of drugs that look very promising that could be available 3 to 5 years from now, and we

think that a new vaccine will be available at around 2015—late 2014, 2015. As I said in my testimony, we've got 6 candidates that we're narrowing down with small trials, so that we can pick the best to go into very large-scale trials, which should start mid-2010, and then we should have licensure of 2014, 2015.

I know it sounds like a long time, and I agree completely that we have to do everything we can to control TB with the tools we have now, but I also believe that if we're not forward-thinking on new tools, we'll really never get control of this disease worldwide and even in the United States.

And that's because the synergy between immunosuppression, that was brought up by one of the Senators, and TB is making TB go completely out of control worldwide. The synergy between the HIV epidemic and the TB epidemic is overwhelming our standard control measures around the world. And that doesn't mean we shouldn't do everything we can to use everything we can right now, but I really believe without new tools, we're going to be overwhelmed.

Senator BROWN. In 2 years, you said 2 years diagnostic—good diagnostic tool, 3 to 5 years really something good, and 2014 or 2015 vaccine. I've worked in this town a long time—I've never seen a witness give that specific a prediction on anything, especially on the Federal budget, but thank you for that. We will——

Dr. SADOFF. We work on timelines.

Senator BROWN. No, I appreciate the way you've thought about that, the way you laid that out, with the people, with the researchers working in your operation and all of that. Thank you.

Senator Burr.

Senator BURR. I also should say, I don't believe this Congress or any Congress can change the ebb and flow of what we throw at any given disease, Dr. Frieden—I think it's inherent in the institution. When there's pressure and concern and fear, the investment goes up. When that fear goes away, the investment goes down. Some of us don't like it, but that's the reality of the institution.

Dr. Reves, you talked about needing new tools and drugs, let me just ask you quite candidly—what, if anything, could the CDC be doing today that would improve our ability to better educate health professionals and the public, respond to TB outbreaks, prepare, all of the above?

Dr. REVES. Well, there's, in terms of training, there are these regional training centers and those are doing their best now. I think we—clearly we can expand that. We do our best to try to get out to our community to educate our physicians, but there's a limited amount of time that we have for that.

In terms of treatment tools, what's required is studies that enroll around 1,000 or maybe 1,500 patients during the course of treatment and follow up for a couple of years afterwards. We're at the phase now at the CDC clinical trial group of really looking at short-term treatment to find out, does this look like a promising drug to take into a long-term regimen? So, if we had more sites that we could enroll in those studies—we have sites in Uganda, South Africa, Brazil and Barcelona, that also contribute—if we could expand to some additional sites and enroll those studies more rapidly, get to the answers more quickly, then go onto the next study to find

out how these really work in combination with other drugs, we could get there a lot quicker. And, I think that's a key thing, if we could really expand that clinical trials network.

And, in terms of the diagnostics, there's a lot of promising things out there, but what you have to do is go out and put them in the clinic, and find out—how does this really work? When we have a group of refugees coming in from Burma. If we apply this test, compared to our previous test—how well does it actually pick up active tuberculosis in a timely fashion?

Senator BURR. Clearly we have an implementation problem. We have an aversion to the risk, because we're trying to do something different. I mean, we've been doing it for 100 years, there's a great comfort level.

Dr. Frieden, you talked about the need to educate healthcare providers and communities. What strategies would you suggest we consider to effectively do that education?

Dr. FRIEDEN. I think there are two different aspects of that question, in this country, and then a different issue globally.

In this country, as Dr. Reves pointed out, many physicians won't see a case of TB for the next 5 years, so——

Senator BURR. Some have never seen a case of TB.

Dr. FRIEDEN. That's right. And, so you basically need to keep it simple. If someone's coughing or has fever, think of the diagnosis, because we really rely on the general healthcare system to make the diagnosis.

Senator BURR. But let me ask you—who can effectively do that?

Dr. FRIEDEN. Who can give that education? I think there are a lot of possibilities. In New York City, we do quite a bit of outreach to physicians through actually office visits, patterned after the pharmaceutical detailing-type visit. We do continuing medical education——

Senator BURR. But New York City is a place where there are 12 or 13 now, per 100,000 so you—people in New York City are way more aware of it than they are in Charlotte, I would think, or in Asheville—in more rural areas.

Dr. FRIEDEN. Somewhat. Though, we also have challenges, for example, with some of our physicians who may have been trained elsewhere, and they have a different approach to diagnosing and treating TB. So, one of the things that we find very useful, is first off, we have to maintain the care system in the public health world. We run TB clinics, as do the public hospital system. Those clinics need support—they need support in the short-term and in the long-term, TB is going to be with us for a long time. They need to provide excellent care, so that doctors can refer the patients to us when they've found them, or we can do the follow up of those around the patient to see if there are people who have become infected, and make sure they get preventative treatment so they don't become tomorrow's case.

At the same time, there's a lot that we can do around each case. So, anytime a case is diagnosed, or even suspected, it's reported to us, we reach out to the doctor or the hospital or the health center, and we can use that as a teachable moment.

Senator BURR. Is there a Federal template that every community health agency in the country can easily access to learn how to educate the medical community on TB?

Dr. FRIEDEN. There are good Federal materials on education about tuberculosis and we work with our own partners on this. I think educating physicians, both in training and afterwards, is an area where we've worked hard, and I would have to say, frankly, we haven't always gotten the results we'd like to get.

Senator BURR. I guess the question I'm asking is, the CDC is connected to public health, I keep reminding everybody of the prevention side. Isn't that the best avenue for us to have some type of standardized educational process—not just limited to TB, but it might include other infectious disease areas that we've got concerns about down the road?

Dr. FRIEDEN. Absolutely, I think there are many ways in which Federal, State and local public health agencies can really enrich the quality of healthcare. We spend $2 trillion a year on health care in this country, and yet we don't prevent a lot of preventable diseases.

Senator BURR. Well, when you've got a system that only triggers when you get sick, you understand exactly how flawed our healthcare system is in this country.

We're going to get called out for votes, I just want to ask one more question and let the Chairman have the rest of the time.

Dr. Sadoff, we've created a new mechanism to try to help finance private companies in the advanced development of drugs, vaccines, and antivirals, as it relates to the threat of bioterrorism. It seems like what you've designed is extremely similar, you've just done it from the private side—private companies, private dollars, foundations, commitments to take products through, what I call, the Valley of Death—in between the initial funding from NIH, to the end where they're actually in the FDA approval process.

Is there anything that you'd like to expand on your model that would help us to better understand it?

Dr. SADOFF. Thank you for the question. Yes, that Valley of Death is a good description of it, because not only is it very difficult and requires tremendous levels of expertise and experience, but for scientists that are used to excitement, it's quite boring. And, it's something where you take a novel, exciting idea, and then make it into something that's routine, that works in millions of cases, where you can make millions of doses of something. That process is not something that is very well appreciated outside of industry, where that's what they actually do.

Our model, then, tries to capture that process, and those processes which take the novel ideas, and the creative spirit that scientists use to generate these novel concepts, and then make them into something practical. And that requires—as I said in my testimony—three things: a balance between resources, risk, and time. Time is critical because 1.7 million people are dying every day. And you can shorten time by taking more risk and using more resources. But you have to do that in a balanced way, because you can use too many resources—there's only limited resources, and there's limited risk. And that balance is what's absolutely critical to the industrial model.

We've tried to capture that by having people from industry that have that experience, including people like myself, work with industry to provide—or work with academics, or even work with the government—to try and provide whatever is necessary that they're missing—whether it be money and resources, experience, field sites, technical expertise. Biotechs don't have the same expertise as a big pharma does in manufacturing, but they may have more of an entrepreneurial spirit.

So, there's a balance for each one. That's what we try and create. And I think that this model, with funding from philanthropy and with funding from government, can help channel and help develop that type of expertise which really exists primarily currently in industry, but there's plenty of industry people very dedicated to doing good for the world in this type of a model, and that's what we're trying to capture.

Senator BURR. Well, let me thank all three of our doctors for, No. 1, your experience, and No. 2, your passion for this infectious disease, and the belief that it's unacceptable for us not to make progress, because this is achievable if we all head in the same direction.

I thank you, Mr. Chairman.

Senator BROWN. Thank you, Senator Burr.

And thank you all, Dr. Reves, Dr. Sadoff, Dr. Frieden, thank you for being here today, but especially thank you for your commitment, as Senator Burr said.

And, any of you that have thoughts—and that includes anybody in the audience, too, that has thoughts about improving the legislation we're working on, any of the bills we've talked about today—feel free to share those thoughts with Roberta Downey, who is sitting behind me, in our office, or anyone with committee staff on either side of the aisle. Because, I think this is an issue that we want to do it right and work on this long-term the way that we should.

So, I thank all of the witnesses, thank you Dr. Castro, too.

The committee is adjourned.

[Additional material follows.]

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ADDITIONAL MATERIAL

QUESTIONS OF SENATOR COBURN FOR DR. CASTRO, CDC

Question 1. Dr. Castro, Senator Brown's bill calls for a comprehensive plan to address TB prevention, control, and treatment. Does CDC have the authority to do that sort of planning today? Why have they not?

Question 2. Dr. Castro, what does Senator Brown's legislation include that you cannot already do?

Question 3. Can you comment on the effect that passing one disease-specific bill has on the other disease prevention efforts that are ongoing at CDC? Are resources and efforts diverted from some when we pass bills about our favorites?

Question 4. Dr. Castro, I understand that CDC provides $100 million to support local and State efforts to prevent TB. Can you outline for me the metrics that are used to evaluate how effectively these dollars are being used?

Question 5. How does CDC justify spending $1.7 million on Hollywood liaison programs, $10 million in furniture, $45 million in conferences, and syphilis prevention funds on a porn star's presentation (http://coburn.senate.gov/ffm/index.cfm?FuseAction=OversightAction.Home&ContentRecord—id=bf7e1789-802a-23ad-42e1-57d542e77901) when the threat of TB is very real and very imminent?

Question 6. The Federal deficit is estimated to be $163 billion this year. The national debt is $9.1 trillion. The CDC already provides $100 million to States and local entities. Dr. Castro, your testimony mentions that many State and local governments have faced budget challenges in recent years and that's why CDC needs more funding to help them. New York has a $3.2 billion budget surplus this year, and the Federal Government has a $163 billion deficit. If you were a CEO, which budget would you pull from to get both governments out of the red ink next year?

[Editor's Note: Responses to the above questions were not available at time of print.]

[Whereupon, at 11:43 a.m., the hearing was adjourned.]

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