

**MULTIDRUG-RESISTANT TUBERCULOSIS:
ASSESSING THE U.S. RESPONSE TO AN EMERGING
GLOBAL THREAT**

BRIEFING AND HEARING
BEFORE THE
SUBCOMMITTEE ON AFRICA AND GLOBAL HEALTH
OF THE
COMMITTEE ON FOREIGN AFFAIRS
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ONE HUNDRED TENTH CONGRESS

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MULTIDRUG-RESISTANT TUBERCULOSIS: ASSESSING THE U.S. RESPONSE TO AN EMERGING GLOBAL THREAT

WEDNESDAY, FEBRUARY 27, 2008

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON AFRICA AND GLOBAL HEALTH,
COMMITTEE ON FOREIGN AFFAIRS,
Washington, DC.

The subcommittee met, pursuant to notice, at 2:32 p.m. In Room 2255, Rayburn House Office Building, Hon. Donald Payne (chairman of the subcommittee) presiding.

Mr. PAYNE. Good afternoon. Thank you for joining us this afternoon. I call the hearing of the Subcommittee on Africa and Global Health to order. We are here this afternoon to discuss the global threat posed by the spread of multiple drug-resistant and extensively drug-resistant tuberculosis and the United States' policy response to this pandemic.

I held a similar hearing last year on World TB Day where we explored the spread of TB and what it might take to eradicate it. At the time, we focused on the tragic outbreak that occurred in KwaZulu-Natal in South Africa in 2006. Bishop Desmond Tutu sent a letter to my office highlighting this event and said that they were very concerned about setbacks to the treatment of HIV and AIDS with this new serious TB outbreak. In the particular area he was talking about at the hospital, he mentioned that 52 of 53 people who died from XDR-TB had contracted it. They died in less than 2 weeks. And that certainly set the alarm off, and we had the hearing to highlight that problem.

At that time I voiced my concern that both multidrug-resistant TB, which is commonly known as MDR-TB and the more deadly XDR-TB could undermine the gains that we are making in both TB and HIV/AIDS treatment programs. Nearly a year later, WHO's 2008 tuberculosis drug resistance report shows that we have true cause for concern and a report we will hear from today highlights some of the problems that we are seeing.

MDR-TB is on the rise, especially in Eastern Europe. In four countries in the region, the incidence of MDR-TB was 15 percent or higher among new TB cases. In Estonia, MDR-TB represents 13.3 percent of new infections; an astonishing 24 percent of those MDR-TB infections were the deadly XDR strain.

What I find even more troubling about the report is the lack of information about what is happening related to MDR-TB in Africa. Only six countries were able to provide data for the survey: Cote

D'Ivoire, Senegal, Rwanda, Ethiopia, Madagascar and Tanzania. While the infection rates in those countries are relatively low, Rwanda, which reported that 3.9 percent of new TB cases were MDR-TB, had the highest incidence—the absence of data is alarming. It is hard to prove an unknown. Therefore, we are very concerned about what we do not know. We know that there have been cases of MDR and XDR-TB in both Botswana and South Africa, as I mentioned previously. What this surveillance report does not tell us is the extent of the problem in the other parts of the sub-region.

Part of the challenge with collecting data which you pointed out last year in your testimony, Dr. Raviglione, is that in all of Africa there are only 25 labs which have the capacity to detect MDR-TB. And of those, 19 of the 25 are in South Africa; therefore, leaving most of sub-Saharan Africa without the capacity to detect this without labs, training personnel and equipment. An outbreak in any country in Africa could kill hundreds of people before containment.

It is imperative that we respond appropriately before that occurs. The cure for non-drug-resistant TB is less than \$20. The cost of treating MDR and XDR, or where it is available, can be tens of thousands of dollars; and this is a real case of one ounce of prevention is certainly worth more than a pound of cure.

Low- and middle-income countries simply do not have the resources to treat drug resistance TB. It is a virtual death sentence in the developing world. We must do our part to help reverse that terrible situation.

I have just come from a markup of the reauthorization of the President's Emergency Plan for AIDS Relief. To my dismay, one of my Republican colleagues suggested that spending \$50 billion over 5 years to fund AIDS, TB, and malaria programs abroad was a waste of money. I am so happy that that was just a very, very small minority of what we heard at the markup this morning, with the majority supporting this bold step forward in the legislation named in memory of two of our former outstanding chairmen, Mr. Henry Hyde, who was the chair when the initial PEPFAR program was authorized, and Mr. Tom Lantos, who we lost several weeks ago.

I think it is a fine tribute to both of them that this quantum leap that we are making in the whole war against AIDS, TB, and malaria is in their name. And as I have indicated, I think that President Bush can be very pleased that probably his greatest legacy will be his awareness. Once this issue was brought to his attention and explained carefully, there was a total reverse of attitude in his administration. I spoke to him yesterday personally and noted his overwhelming support for the program. I think that it will be one of the very positive things that we will remember from his tenure as President. And in Africa and around the world, there is a real appreciation for this.

The fact that painful evidence surfaced last May indicated that this disease was an international concern. Joe Lewis was a long-time world boxing champ. He said, "You can run, but you can't hide." He was talking about in the ring. But it is the same thing, I believe, in the world. You can run, but you can't hide. And the fact that an Atlanta resident, Andrew Speaker, made a tour

through Europe and returned to the United States through Canada while affected with MDR-TB really raised the eyebrows of Americans to say TB is not necessarily over there, it is over here too. So fortunately, no one was infected by Mr. Speaker; however, next time we may not be so lucky.

There are steps that we can and should take to address the threat of MDR-TB, such as, providing the equipment necessary to rapidly diagnose MDR-TB to the countries that cannot afford it themselves. And we can help improve drug supplies for treatment and improve the laboratory capacity in low- and middle-income countries to gather better data. And I am happy to report that the Foreign Affairs Committee approved the PEPFAR reauthorization program despite the misgivings of some of our colleagues at the fact that the bill contains an authorization for \$4 billion over 5 years to treat TB. If appropriated, these funds could provide a significant amount of the money for all of the aforementioned activities.

I hope in the limited time we have available today, our witnesses will address what we have accomplished relative to halting the spread of MDR-TB and XDR, especially in sub-Saharan Africa and what the administration plans to do to help stop TB over the coming fiscal year. If we fail to do so, we not only do so at the risk of the investments that we have already made in TB and AIDS overseas, we risk an epidemic here at home.

And with that, let me turn to my colleague, Mr. Smith, who was very instrumental in working with the White House and the majority on our full committee to help navigate the reauthorization of the PEPFAR program. And I appreciate his continued strong support for issues of human rights and health around the world and I yield to my colleague, Mr. Smith.

Mr. SMITH OF NEW JERSEY. I thank my good friend for yielding, and thank you for your leadership on all of these issues, including PEPFAR. My sense is that as of this morning, the PEPFAR consensus of 2003 is not only alive and well, but it has been given a major advance this morning, with the reauthorization vote in committee. And it was a very spirited, but I think a good-faith give-and-take between a number of players, and for that I am so grateful.

The \$50 billion is an enormous amount of money that can do an enormous amount of good. And as we have seen, and even some of the questions today that both you and I answered about the capacity and whether or not there is an absorption capacity, clearly there is. There is a buildup of capacity in Africa, especially by indigenous, faith-based organizations. The incentive is there, the money now flows to an ever-growing network that will literally save the lives of people who will not contract the disease, children who will not get it—as they traverse the birth canal—because of mother-to-child transmission prevention initiatives.

And I really think—and as Mark Dybul who will be one of our witnesses has indicated so clearly, and as OGAC has indicated so clearly—that the evidence is showing that behavioral change remains the key to mitigating and hopefully ending this pandemic. Multistrategies for sure, but clearly and obviously it is all linked to the reason for this hearing, because it does get a boost of about

\$4 billion over about 5 years. So thank you, Mr. Chairman, for your leadership. It has been great.

I also want to thank you for calling this hearing on a timely global health issue of multidrug-resistant tuberculosis with a focus on how the United States is responding to this serious concern. It is shocking that this disease, which is curable, continues to kill over 1.6 million people each year. Perhaps the reason for this apparent contradiction is that the vast majority of those who die from TB, 98 percent, live in the developing world and are from the poorest and most marginalized segments of society. TB is particularly pernicious in that it targets young adults who are just starting to form their families and who are the producers and sustainers of their societies.

The emergence in recent years of drug-resistant TB has raised the specter of higher death rates, more children who will lose their parents, and communities that will fall deeper into poverty and despair. Combined with the fact that TB is the leading cause of death of persons with HIV/AIDS, this disease is having a particularly devastating impact on Africa. However, it is important to note that no region, indeed no country including our own, is immune from the effects of tuberculosis. We should all be alarmed. The strains that are resistant to a single drug have been documented in every country surveyed by the World Health Organization. Given the ease with which TB can be spread, TB is truly a disease without borders, and it is in our national but above all our humanitarian interest to seek its eradication.

The 2008 Tuberculosis MDR-TB and XDR-TB Report that was released by the World Health Organization just yesterday contained some very disturbing conclusions. It informs us that we have the highest rates of multidrug-resistant TB ever recorded. At the same time, as we are making insufficient efforts in many areas of the world to treat and control it, our access to data in Africa is limited to gross inadequacies and lab capacity. And extraordinary measures are urgently needed in Eastern Europe for rapid detection, effective care and access to drugs.

Therefore, we are fortunate to have some of the top experts in the World Health Organization and the administration with us today to provide us with a better understanding of the challenges we are facing and perhaps how we should be better responding.

I agree with my colleagues here in Congress who are advocating for significantly more resources to be directed toward TB. As I mentioned earlier, we are talking about an additional \$4 billion over 5 years as part of the Tom Lantos-Henry Hyde U.S. Global Leadership HIV/AIDS, Tuberculosis and Malaria reauthorization. I do believe that will make a significant impact on our goals.

This hearing provides us with an opportunity to examine the best means for directing these anticipated resources. And again I want to thank the chairman.

I would like to also just point out that we have with us today a member of the DR Congo Parliament, Mr. Albert Puello who is here, if you wouldn't mind being acknowledged. Thank you for being with us.

And I would also note, Mr. Chairman, that I have to run off just for a moment. I am also ranking member of the China Commission,

and we have a very important hearing simultaneously being held on the impact of the Olympics and human rights in China. As ranking member, I am going to give my opening statement and come right back. So I apologize for my brief absence, but I will be right back.

Mr. PAYNE. Thank you very much. And thank you for picking us first.

We have with us Dr. Boozman. Would you like to make an opening comment?

Mr. BOOZMAN. No, I really don't have a comment except to thank you and the ranking member for going forward with such an important hearing. I am an optometrist, an eye doctor. So I am not—we didn't deal with a lot of tuberculosis and some of these other things, fortunately. But I am anxious to hear the testimony.

Mr. PAYNE. Great. Thank you very much.

And I would also like to acknowledge Ambassador Girma from Eritrea who happens to be in our audience. Welcome.

We will call up our briefer. I am very pleased to have him with us. We had the opportunity to be with him yesterday when the WHO's report on the tuberculosis question was given at a press conference with many other interested groups. So we will—since he is technically from an international organization, our committees are unable to have them as witnesses. So we call him a briefer.

So our briefer today on this panel is Dr. Raviglione who was appointed director of Stop TB in 2003. Dr. Raviglione joined the World Health Organization in 1991 as an associate professional officer, sponsored by the Italian Government to work on TB-HIV and tuberculosis in Europe. Later, he became responsible for setting up the Global Drug Resistance Surveillance Project and the new TB Surveillance and Monitoring System in 1999 to 2003.

He was coordinator for tuberculosis strategy and operations globally, taking charge particularly of surveillance and program monitoring; operational research on community and private practitioner involvement in TB control; TB-HIV interaction; multidrug-resistance TB management in developing countries; and DOTS expansion worldwide. Currently, as director of the Stop TB Department of WHO, he is responsible for strategies and policies and works through a network of TB experts at all levels of the organization.

It is good to have you with us and we look forward to your testimony.

**STATEMENT OF MARIO RAVIGLIONE, M.D., DIRECTOR, STOP
TB DEPARTMENT, WORLD HEALTH ORGANIZATION**

Dr. RAVIGLIONE. Good afternoon. Mr. Chairman, it is an honor to join you and your colleagues today and to represent the World Health Organization in providing this briefing on drug-resistant tuberculosis.

I would like to begin by expressing my gratitude to Chairman Donald Payne, Ranking Member Chris Smith, Congressman Boozman and other distinguished members, and the committee staff organizing today's hearing.

I also would like to offer my condolences and to salute the distinguished career of Congressman Tom Lantos. Congressman Lantos

was an unwavering advocate on behalf of some of the world's poorest and most vulnerable, and his efforts will have lasting impact.

I will summarize the four key points of the report and would like to request that the statement in its entirety be entered in the congressional records of today's hearing.

Mr. PAYNE. Without objection.

Dr. RAVIGLIONE. I also want to acknowledge our staff, Ms. Abigail Wright, who is the lead author of the report, who is here in the audience.

Today, as requested, I will present the results from the just-released fourth report of the WHO Global Report on Anti-TB Drug Resistance Surveillance. The first report seems to document the emergence of extensively drug-resistant TB, which is also called XDR-TB; which is, in short, a highly lethal form of multidrug-resistant TB.

I will also discuss the global response underway, the urgent scaled-up need to face the scope of the MDR and XDR-TB challenge. Here I would like to gratefully acknowledge the ongoing support to WHO TB control efforts from the three agencies, the leaders of which are also speaking today: USAID, USCDC and PEPFAR. WHO and these agencies are all members of the Stop TB Partnership, which is a network of many organizations, many agencies, committed to halving TB deaths and prevalence by 2015 and eventually to eliminate TB by 2050.

What are the four key messages in this new report? First, we show the highest MDR-TB rates ever recorded since the history of TB control began. We are seeing the highest rates of MDR-TB recorded during the last 13 years. They are particularly in Eastern Europe, Central Asia and parts of China. We consider this an emergency, which requires an emergency response from the countries themselves and from the international community.

The second message, we understand better now MDR-TB and XDR-TB burdens. WHO warned in 1997 of a global MDR-TB epidemic at the time of the release of the first report. Today's report confirms that drug resistance is widespread, especially in the former Soviet Union and in China. The overwhelming majority of the estimated half a million new MDR-TB cases every year are occurring, in fact, in these countries. We have also seen the emergence of extensively drug-resistant, or XTR-TB, with now 45 countries reporting cases, and they actually increase by the day.

In the last week after we published the report in 2008, we have heard of an additional three countries, two of them in Africa. On average in the former Soviet Union, 10 percent of MDR-TB cases are now already XDR-TB. Untreatable XDR-TB could derail the important progress that has been made in controlling the global TB epidemic and in protecting the health of people living with HIV/AIDS who are highly vulnerable to TB as well as to MDR-TB, of course.

The third message of the report, trend analysis, shows both bad and good news for the countries where we have enough data to look at trends. The bad news comes again from the former USSR, and specifically from Russia, where MDR-TB trends are on the increase.

The good news is that MDR-TB cases have stabilized, instead, in Latvia and in Estonia. This stems from serious investment and commitment to tackling the problem. In fact, governments confronted with uncontrolled MDR-TB should look at these two countries as role models and seek to duplicate their success. I just want to emphasize that 10 years ago, we called Latvia and Estonia the hotspots of the world.

The fourth message is about Africa, the region—I call it the “region of uncertainty.” As you already mentioned, Mr. Chair, on this continent, many countries are unprepared to detect and to manage MDR-TB. In fact, only six countries were able to provide the MDR-TB surveillance data for this report. As a result, we do not know precisely what the real burden is. But we suspect that the MDR-TB and XDR-TB are more widespread than anybody today can think. The most critical factor in addressing MDR-TB in Africa, as well as elsewhere, is the lack of laboratories equipped to diagnose MDR-TB and XDR-TB.

My one-sentence conclusion out of this report and based on the four main messages is that much investment and urgent action are necessary if we are to tackle MDR and XDR-TB effectively and successfully, like in the case of the Baltic countries I mentioned. In particular, the situation of the former Soviet Union, parts of China and Africa, in my view, are true public health emergencies.

So what is the global response at this point, or what has been the global response? Last year, following the principles laid out by the WHO Global Task Force on XDR-TB that we convened in October 2006, WHO developed with a number of partners, a Global MDR/XDR-TB Response Plan, which is this one here, to deal with MDR and XDR-TB for 2007 and 2008. It laid out a vast scale-up needed to begin to more quickly diagnose and treat patients with these lethal forms of tuberculosis, especially in the countries with the highest estimated MDR-TB burdens.

While there has been increased action in some affected countries and from some donors, we are still just beyond the starting blocks, due to the lack of funds and human resources for implementation in countries, or for the necessary technical assistance which comes normally from international organizations, for surveillance, for research.

However, there are examples of steps forward, including the establishment of initiatives to help support diagnostic capacity, infection control and care in several of the poorest countries, in southern Africa particularly, and major plans and increased budgets laid out by several large affected countries.

By the end of 2007, through the Green Light Committee Initiative, 51 countries had approved projects to initiate treatment for over 30,000 MDR-TB patients with assured financing for their supply. The Green Light Committee’s technical advisory board, convened by WHO, reviews, evaluates and monitors technical aspects of approved MDR-TB treatment programs. The Green Light Committee is highly supported by USAID, US OGAC and the Global Fund among other donors. MDR-TB treatment program sites are financed, however, in countries by the governments and by a number of other mechanisms, including bilateral and multilateral agencies, the Global Fund grants, UNITAID and other mechanisms.

Despite these steps, the numbers to be served immediately are dwarfed by those in need. We estimate at WHO that nearly 490,000 new MDR-TB patients need treatment each year and we have only a very small fraction of those that are effectively diagnosed and treated.

Our first line of attack against MDR/XDR-TB is in ramping up the quality of basic TB control. TB control financing has more than doubled since 2001, in good part due to the Global Fund to Fight AIDS, TB and Malaria that provides today somewhere around 70 percent of donor grants for tuberculosis control. In the \$300 million approved financing for TB control in the last two rounds of the Global Fund grant making, an impressive 26 percent actually went to MDR-TB response.

Here I also want to commend Chairman Payne and the ranking member for their successful amendment to increase tuberculosis funding by \$50 million for Fiscal Year 2008. WHO estimates that \$4.8 billion is needed for TB control in general in low- and middle-income countries in this year, in 2008, including among these \$4.8 billion, \$1 billion for MDR-TB and the XDR-TB response.

Yet there is a financing gap overall of \$2.5 billion, of which about \$.5 billion is for MDR and XDR-TB. High-burden countries are generally not proposing large enough budgets when we ask them to make budgets, especially in the areas of MDR-TB and TB-HIV response. These responses are more complex normally than the usual way of dealing with TB, and this is likely due to lack of capacity and the underfunding of technical support from international agencies.

The strong leadership is also evident in the Congress' work to expand programs for the diseases of poverty. But my frustration, as expressed also to the press yesterday, is to see support growing for AIDS and malaria worldwide, and yet I see too little response worldwide to the tragedy of tuberculosis.

Mr. Chairman, in conclusion, urgent action is needed to build strong TB control programs with mainstream integral part MDR-TB treatment elements and rapid scale-up of HIV-TB collaborative intervention. Strength in laboratories for TB diagnosis, for surveillance, are essential, along with infection control and more health providers and communities prepared and motivated to ensure effective and safe treatment for patients in need.

The challenge we face today in TB control provides a prime example of why disease-specific efforts and the health system more generically need immediate and simultaneous strengthening and not gradual or sequential improvement, for we cannot afford to wait and let people die. And we need large-scale research for tomorrow's better tools to prevent, to detect, and to treat this evolving disease. Without such an acceleration, the poorest of this world will be further imperiled, as will public health and security for us all, including the richest.

We look forward to facing this challenge through a close collaboration with all of the relevant U.S. Government agencies and other partners.

Many thanks for the opportunity to brief you, Mr. Chairman, honorable members and colleagues.

[The prepared statement of Dr. Raviglione follows:]

PREPARED STATEMENT OF MARIO RAVIGLIONE, M.D., DIRECTOR, STOP TB
DEPARTMENT, WORLD HEALTH ORGANIZATION

Good afternoon, Mr Chairman. It is an honor to join you and your colleagues today, and to represent the World Health Organization (WHO) in providing this briefing on drug-resistant tuberculosis (TB). I would like to begin by expressing my gratitude to Chairman Donald Payne, Ranking Member Chris Smith, other distinguished Members and the committee staff for organizing today's hearing. I also would like to offer my condolences and to salute the distinguished career of Congressman Tom Lantos. Congressman Lantos was an unwavering advocate on behalf of some of the world's most poor and vulnerable, and his efforts will have lasting impact.

Today, as requested, I will present results from the just-released fourth report of the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance, the first report since the documented emergence of extensively drug-resistant TB (XDR-TB for short, and a highly lethal form of MDR-TB). I will also discuss the global response under way, and dramatic scale-up needed, to face the scope of the MDR/XDR-TB challenge. Here, I would like to gratefully acknowledge the ongoing support to WHO TB control efforts from the three agencies, the leaders of which are also speaking today: the US Agency for International Development (USAID), the U.S. Centers for Disease Control (CDC), and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). WHO and these agencies/initiatives are members of the Stop TB Partnership, a network of many organizations committed to halving TB deaths and prevalence by 2015, and to eventually eliminating TB.

I. AN OVERVIEW OF THE TB EPIDEMIC

Mr. Chairman, let me begin by reviewing the status of the TB epidemic globally. As noted to this Committee in my briefing last March, each year about 9 million people fall ill and over 1.6 million people die due to TB. TB is a top killer of those living with HIV. The disease thrives with poverty, malnutrition and strife, and with global travel and migration. In five regions, incidence is declining, albeit too slowly, and it is stagnating in Eastern Europe/Central Asia. In 2006, WHO launched the Stop TB Strategy, which builds on the successes of TB treatment scale up globally. It also explicitly addresses the outstanding challenges of responding to HIV-associated TB, multidrug-resistant TB, and reaching the most vulnerable, through new delivery approaches, like the engagement of the non-state sector and of affected communities, and it promotes research for better diagnostics, drugs and vaccines. The Stop TB Strategy underpins the Stop TB Partnership's Global Plan to Stop TB, which lays out regional scenarios for achieving the 2015 targets. A World Bank-sponsored analysis estimated that the economic benefits of pursuing the Plan are ten times the costs of investments.

II. A CLEARER VIEW OF THE LANDSCAPE OF DRUG-RESISTANT TB

Mr. Chairman, while the global situation gives us hope that we could face a future with far less TB, surveillance of drug-resistant TB suggests to us just how bad the alternative global scenario might be if we don't act now. Multidrug-resistant TB (MDR-TB) is a form of TB that is resistant to, at least, the two most powerful first-line, essential drugs used for TB treatment—it emerges where drugs are not properly supplied, prescribed and consumed. Extensively drug-resistant TB (XDR-TB) is MDR-TB plus resistance to the most effective "reserve" drugs, which are called "second-line drugs." Normal TB can be cured in six months, with drugs costing only US\$20. MDR-TB treatment is more complex and costly, but still effective. XDR-TB treatment, however, is far more complex and far less effective. XDR is therefore a virtual death sentence in most settings world-wide, as seen in the outbreak documented in 2005-6 in health facilities with high numbers of HIV-infected people in a South African Kwa Zulu Natal community.

Our new report gives a clearer view of the landscape of drug-resistant TB than we have had before. Included in this report are drug susceptibility test (DST) results from over 90,000 patients within 81 countries over the period 2002-2006. This represents the largest collection of quality-assured surveys ever compiled and includes information from areas representing one third of infectious TB patients worldwide over that period. Survey data were included if there was accurate sampling of the population under evaluation, and external quality assurance conducted by our internationally-recognized network of reference laboratories. Of the 81 countries, 32 had never previously reported data.

What is disturbing to me, and all those involved, is that we are now seeing the highest rates of MDR-TB ever recorded in the history of TB control. The highest

rates of MDR-TB among new cases were reported, in order, from Azerbaijan (22.3%), Moldova (19.4%), Ukraine (16%) and Russia's Tomsk Oblast (15%). In China, data from surveys in 8 of 31 provinces, and two municipalities, over a ten-year period indicate that drug resistance is widespread. Data from India, the country with the highest number of TB cases in the world, suggest that drug resistance is moderate, but with a large underlying TB burden—this translates to many cases or a high absolute number.

MDR-TB trends over time, from at least three different years, were assessed in 45 countries. In the two oblasts that reported trend data from Russia, the proportion of MDR-TB among new TB cases was increasing at 13%–32% per year.

In the U.S. and Hong Kong SAR, there were significant reductions in reported MDR-TB levels. In both countries, both TB case notifications and MDR-TB levels are declining, but MDR-TB is declining at a faster rate. Countries in the Baltic region are showing a stabilization in the proportion of MDR-TB among new TB cases, but they are experiencing a promising 5–8% decreases in TB case notifications per year. This is a significant change, as these Baltic nations in the past had reported dramatic increases in TB notification rates and the highest levels of MDR-TB. In these countries, political and financial commitment to the essentials of TB control and proper management of all cases, susceptible and drug-resistant, has resulted in a clear amelioration in the MDR-TB situation.

Included in the report are data from only six African countries. Only one African country, Botswana, has trend data. In this region, there is little capacity to diagnose MDR-TB, due to lack of well-equipped and good-quality laboratories. Countries—especially those with high HIV burdens—are simply not capable to design and implement appropriate plans to prevent and treat MDR-TB—let alone XDR-TB. Fortunately, for the time being, four of the five countries reported relatively low-levels of MDR-TB—the fifth, Rwanda, reported a high level of MDR-TB, 3.9 % among new TB cases. However, our suspicion is that MDR-TB is more widespread than we know and remains, simply put, hidden.

From another region, this survey demonstrated a link between HIV infection and MDR-TB. Surveys in Latvia and Donetsk, Ukraine found nearly twice the level of MDR-TB among HIV-positive TB patients compared with HIV-negative TB patients. These findings suggest how essential it is to accelerate the scale up of both TB/HIV interventions and MDR-TB prevention and treatment.

This report includes the first compilation of representative survey data and routine surveillance on XDR-TB levels among TB patients. A total of 46 countries have reported at least one case of XDR-TB to-date. In some countries like Estonia, over 20% of MDR-TB cases are XDR-TB, thus becoming virtually untreatable, as if we were in the pre-antibiotic era.

Based on data collected over the full 13 years of the global surveillance project, WHO has made global estimates of the MDR-TB burden. WHO estimates that nearly half a million MDR-TB cases occurred worldwide in 2006, and that well over 110,000 deaths were due to MDR-TB.

III. THE GLOBAL RESPONSE

Now, the global response. Last year, following the principles laid out by the WHO Global Task Force on XDR-TB, WHO developed with partners a Global MDR/XDR-TB Response Plan for 2007–2008. It laid out the vast scale-up needed to begin to more quickly diagnose and treat persons ill with lethal forms of disease, especially in the countries with the highest estimated MDR-TB burdens. While there has been increased action in some affected countries and from some donors, we are still just beyond the starting blocks, due to lack of funds and human resources for implementation in countries, or for global technical assistance, surveillance and research.

However, there are examples of steps forward including partnerships to help support diagnostic capacity, infection control and care in several of the most resource-poor countries in Southern Africa, and major plans and increased budgets laid out by several large affected countries. By the end of 2007, through the Green Light Committee Initiative (GLC), 51 countries had approved projects to initiate treatment for over 30,000 MDR-TB patients, with assured financing for drug supply. The GLC is a technical advisory body convened by WHO that reviews, evaluates and monitors technical aspects of approved MDR-TB treatment programmes. The GLC is supported by USAID, US OGAC and The Global Fund among other donors. MDR-TB treatment programmes are financed by governments, bilateral and multilateral agencies, Global Fund grants, UNITAID, and other mechanisms. Despite these steps, the numbers to be served immediately are dwarfed by those in need—WHO estimates that nearly 490,000 new MDR-TB patients need treatment each year.

Our first line of attack against MDR/XDR-TB is in ramping up the quality of basic TB control. TB control financing has more than doubled since 2001, in good part due to the Global Fund to fight AIDS, TB and Malaria that provides over 70% of donor grants for TB control. In the \$300 million approved financing for TB control in the last two rounds of Global Fund grant-making, an impressive 26% went to MDR-TB response.

WHO estimates that US\$4.8 billion is needed for TB control in low- and middle-income countries in 2008, including US\$1 billion for MDR-TB and XDR-TB response. Yet, there is a financing gap of \$2.5 billion, of which US\$ 500 million is for MDR-TB and XDR-TB.

High-burden countries are generally not proposing large enough budgets especially for MDR-TB and TB-HIV response, likely due to lack of capacity and the under-funding of technical support from international agencies.

U.S. agencies, the leaders of which will now speak, have all made strong contributions to fighting TB and MDR-TB as well as to expanding the joint response to HIV/AIDS and TB. Thanks also to the work of many Congressional champions, U.S. appropriations for TB control increased this fiscal year and the U.S. National Institutes of Health has outlined areas where expanded research is needed in light of MDR/XDR-TB.

Mr. Chairman, in conclusion, urgent action is needed to build strong TB control programs with mainstreamed MDR-TB treatment elements and rapid scale-up of HIV/TB interventions. Strengthened laboratories for TB diagnosis and surveillance are essential, along with infection control and more health providers and communities prepared and motivated to ensure effective and safe treatment for patients in need. The challenge we face today in TB control provides a prime example of why disease-specific efforts, and health systems more generally, need immediate and simultaneous strengthening, not gradual or sequential improvement for we cannot afford to wait and let people die. And, we need large-scale research for tomorrow's better tools to prevent, detect and treat this evolving disease. Without such an acceleration, the poorest of this world will be further imperiled, as will public health and security for us all, including the richest. We look forward to facing this challenge through even closer collaboration with all relevant U.S. Government agencies and other partners.

Many thanks for the opportunity to brief you, Mr Chairman, Honorable Members, and colleagues.

Mr. PAYNE. Let me thank you very much for that very thorough testimony.

Let me start the questioning by asking—you mentioned in your briefing the WHO report, which was just released, had data from only six African countries. I understand that that is because there is little to no capacity to diagnose MDR and XDR-TB in sub-Saharan Africa.

My question is: What do we need to do to build the capacity of African countries to detect the disease MDR and XDR?

And, secondly, how much cost would it be, in your opinion, to build that capacity in Africa? Are capacity-building activities included in the \$1 billion that WHO has said it needs to respond to MDR and XDR-TB?

If you could answer that, I would appreciate it.

Dr. RAVIGLIONE. Okay. So what do we need to do to build capacity in Africa? I think Africa is far behind the rest of the world in terms of their capacity to deal with diseases in general, TB being a good example.

In the specific case of tuberculosis, first of all, what Africa lacks—and I think you mentioned that in your intervention at the beginning—is in fact laboratories. Without laboratories, you have no diagnosis of MDR or XDR-TB. You can have, without a culture capacity and only with the microscope, you can actually diagnose tuberculosis. But you need to culture the bacillus in the sputum of the patient in order then to be able to do the antibiogram that tells us if we are dealing with an MDR or XDR-TB case. So that is ab-

solutely an essential need in the continent. But this is not all. Because once you diagnose the case, you have to deal with the case.

So what we need there is an infrastructure that allows these patients, especially those with MDR or XDR-TB, to be treated, to be supported during treatment, to be counseled, to be educated and supported for a period of time that is much longer than the usual 6 months. It may go up to 18 to 24 months. So it is a major effort that has to be undertaken at all levels of the health system of African countries.

Now, what is the cost? Well, we estimate, as you mention and as I mention, something around \$.5 billion gap at the moment for the work which includes Africa. Of this, I don't have the figure with me, but I would guess we are talking of \$100 million to \$200 million specifically for Africa, because there is where the need of building laboratories and the basic infrastructure is major.

I can tell you that in my own personal experience, it is quite actually possible to deal with the issue. I have been in Lesotho in November of last year to just inaugurate the new laboratory. A year ago, Lesotho was completely unable to detect MDR or XDR-TB. Now they are perfectly able to detect at least MDR-TB and, I hope, in the near future also XDR-TB. So it is possible and it is possible without a major investment of money. In this case, there were a number of relatively small donations that allowed a country like Lesotho, which is still a small country, but yet is a very poor country, to build the capacity that is necessary.

Mr. PAYNE. About how long do you think it would take—a several-year project, a year project—if immediate action was taken?

Dr. RAVIGLIONE. If the plan is really considered as an urgent plan and there is a massive investment as we have seen, say, in Latvia or in Estonia, in the case of Africa, actually to build the basic capacity in Lesotho, it was done in less than a year.

Now, I am not saying that they have solved all their problems. They are starting now, diagnosing cases and treating them. But I would say that a quick response could be built with intensive effort country by country, at least focusing on those that are the major priorities within a matter of a year or 2 literally. And then it is a matter of following what is going on and ensuring that the quality, for instance, of the laboratory is maintained over the years. And we still have to see what will happen in a country like Lesotho, for instance.

Mr. PAYNE. Thank you. We are going to have votes. Let me just ask one last question, and then we will hear from Mr. Boozman and Mr. Smith.

You pointed out in your briefing that surveys in Latvia and the Ukraine found nearly twice the level of MDR-TB among HIV-positive TB patients compared with HIV-negative patients. And I wonder, were the patients on ARVs and does being on an ARV regimen protect people from regular TB?

Dr. RAVIGLIONE. Yeah. I mean, part of the patients might have been on ARV; but I think that the main reason for this finding, which we were after for a number of years now to try to demonstrate there is an association between being HIV-infected and being more prone to multidrug-resistant TB, I think that this in my view means more specifically that these patients have been ex-

posed somehow, perhaps through congregate settings, to the risk of transmission of MDR-TB, more than any other biological factor. I mean, in the past we used to think that MDR-TB was just limited to the HIV-positive population and other immunosuppressed people because the general feeling was that these organisms, having acquired resistance, lost their virulence, like it has been detected in other bacteria. But in reality we see that this is not the case and the virulence depends on the virulence of the bacterium in a way, regardless of the fact that they have acquired resistance through the evolution, if you like.

ARV protecting against tuberculosis, yes, that has been proven. But there is also evidence now from recent studies that in some settings, it is not exactly so. And even being on anti-retrovirals does not protect completely against tuberculosis to the point that we are saying that if we don't manage to prevent tuberculosis more effectively, then the gains that we have with anti-retrovirals may be actually offset by the presence of a high level of transmission of tuberculosis in a society.

Mr. PAYNE. Thank you. Representative Boozman.

Mr. BOOZMAN. Why Latvia and Estonia, why did they have such a high incidence?

Dr. RAVIGLIONE. Latvia and Estonia, like all the former Soviet Union countries, were subject to a major—I would say a major problem of the public health infrastructure immediately after the collapse of the former Soviet Union.

Mr. BOOZMAN. But the other countries didn't have the outbreak, and they were all the same that way.

Dr. RAVIGLIONE. Do you mean the other countries of the former Soviet Union?

Mr. BOOZMAN. Yes.

Dr. RAVIGLIONE. No, no. They all had the same problem. If you look now at the list of the countries that have the highest levels—actually shown in that map—you find that in red, you have most of them—

Mr. BOOZMAN. Why Latvia and Estonia compared to East Germany?

Dr. RAVIGLIONE. Latvia and Estonia both responded better.

Mr. BOOZMAN. I guess what I am saying is, why were they the hotspots to begin with?

Dr. RAVIGLIONE. 10 years ago?

Mr. BOOZMAN. Yes.

Dr. RAVIGLIONE. Because they were the ones where we could do the study and they were the very first that could organize a proper survey. However, also 10 years ago, we found equally high levels in other parts of the former Soviet Union, in some other regions of Russia. But the top were in those two countries. My guess is that because they had availability of drugs that the other countries might not have had at the time, and therefore they developed more resistance.

Mr. BOOZMAN. Do healthy people get MDR and XDR tuberculosis?

Dr. RAVIGLIONE. Sure. I mean, the determinants of tuberculosis are many. People tend to get tuberculosis more if they are HIV-positive, if they are diabetics, if they are in renal failure, if they

are malnourished. But anyone can get tuberculosis and anyone can get multiresistant tuberculosis. I think it has shown actually—if you want just a dramatic example, there was the American lawyer last year who had no particular risk factor that you would consider for tuberculosis. So it shows that it is absolutely possible.

Mr. BOOZMAN. Thank you.

Mr. PAYNE. Thank you very much. Mr. Smith of Washington.

Mr. SMITH OF WASHINGTON. Thank you, Mr. Chairman. I do think we have a vote on and just a few minutes left.

I just wanted to follow up on that question. Do you have percentages on what percentage of the people who get MDR tuberculosis did not have a preexisting immune disorder? Do you have percentages on healthy people, if you want to refer to them as that, what percentage they get versus what HIV or people with other diseases get it?

Dr. RAVIGLIONE. No, no. We don't have precise estimates because there are many factors that can produce or facilitate the activation to active tuberculosis of a person that has been exposed and infected in the past. But outside of Africa, the association between TB and HIV is not that strong. I mean, still 92 percent of the global TB cases are nonHIV-related.

Mr. SMITH OF WASHINGTON. I guess I was referring specifically to the drug-resistant TB.

Dr. RAVIGLIONE. We don't have the precise statistics, but it can occur in the absence of any risk factor or immunosuppressing conditions—there is no specific statistic about that.

Mr. SMITH OF WASHINGTON. I think getting the specific statistics on that might shed, at least a little bit of light, on what causes the drug-resistant TB, if it is a vulnerability within the immune system or if there are other factors involved there.

The only other thing I want to ask, when you have a spread of the drug-resistant TB, what brings it under control? What stops it from spreading further? What is the best response that brings it to the quickest conclusion? Because I know that there have been some examples where as many as over 50 people have died in an outbreak, but at some point it was contained. What are the most critical steps in containing it?

Dr. RAVIGLIONE. Yeah. I mean in the case of KwaZulu-Natal—I think you are alluding to that case—it has not really been contained. I mean, we still know that there are cases emerging. South Africa's report that officially at the end of last year, something around 990-nearly-thousand, cases of XDR-TB all over South Africa. And even in KwaZulu-Natal, the outbreak is ongoing if you want to call it that way.

But the measures to control MDR and XDR-TB are those that we have outlined in the main outcomes of the XDR task force meeting. They start with basic strengthening of TB control measures. You basically stop producing MDR-TB by diagnosing cases very rapidly and putting them on adequate treatment very rapidly. And by following, of course, for the 6 months of treatment in such a way—with supervision and counseling and everything—in such a way that these patients get their treatment until the end. That is the best way to prevent it. So you start stopping the production.

At the same time, when you have already MDR-TB widespread or existing in a certain community in a certain country, then automatically you have to manage these cases; otherwise if you don't, then they keep spreading and the MDR-TB spreads to others. And so, to do that, what is necessary is obviously to have access to good level facilities that can make the diagnosis possibly rapidly, and there are methods today to diagnose MDR-TB within a matter of 2 weeks from the appearance of the patient in the health system. Therefore, you have all the underlying things to be done: Laboratories, availability of drugs, assuring the quality of drugs and ensuring that the patients are supervised until the end.

An additional measure is that of infection control. That refers particularly where you have a situation like in KwaZulu-Natal, where a good part of the epidemic was probably due to infection spreading within congregate settings, small hospitals where HIV-positive people were admitted with multidrug-resistant TB and therefore spreading it to others.

Mr. SMITH OF WASHINGTON. Thank you.

Mr. PAYNE. Thank you very much.

We have 2 minutes left on a vote. We are going to go vote. The committee will stand in recess. There are a series of three votes. Two of them are 5-minute votes. We should be able to be back here within 15 minutes.

[Recess.]

Mr. PAYNE. We will resume our meeting. Let me certainly offer our apologies for the 15 minutes I talked about we would be gone. One thing that is predictable on the House floor is that unpredictable things occur. There was a big unpredictable action taken. As a result, we had to wait until it was concluded. So I apologize.

We will have our second panel, please, come forward. I am very pleased to have you with us, our second panel. We will begin with Dr. Kent Hill, sworn in as Assistant Administrator for the Bureau of Global Health for the U.S. Agency for International Development, a position he has served in since November 2005. Prior to November 2005, Dr. Hill served as Assistant Administrator for the Bureau of Europe and Eurasia at USAID. As Assistant Administrator for the Bureau for Global Health, Dr. Hill was responsible for a bureau that in Fiscal Year 2006 managed or co-managed health programs all over the world.

Our second witness is Dr. Julie Gerberding. She became the Director of the Centers for Disease Control and Prevention (CDC) and the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) on July 3, 2002. Before becoming CDC's Director and ATSDR's Administrator, Dr. Gerberding was Acting Deputy Director at the National Center for Infectious Diseases, where she played a major role in leading CDC's response to the anthrax bioterrorism events in 2001.

Dr. Gerberding joined CDC in 1998 as Director of the Division of Health Care Quality Promotion. She developed CDC's patient safety initiatives and other programs to prevent infections, medical errors in health settings, and antimicrobial resistance. Prior to coming to CDC, Dr. Gerberding was a University of California-San Francisco faculty member. She is a clinical professor of medicine at

Emory College, and has a very distinguished background. We are so pleased to have her with us.

Our final witness, Ambassador Mark R. Dybul, is no stranger to us, and as we all know, is the United States Global AIDS Coordinator, leading President Bush's Emergency Plan for AIDS Relief. Prior to becoming the AIDS Coordinator, he served as Deputy Director U.S. Global AIDS Coordinator. Before coming to the Coordinator's office, Ambassador Dybul served on the planning Task Force for the Emergency Plan, was the lead for the Department of Health and Human Services (HHS) for President Bush's International Prevention of Mother-to-Child HIV Initiative at HHS. He also served as Assistant Director for Medical Affairs for the National Institute of Allergy and Infectious Diseases, the National Institute of Health, as well as co-executive secretary of the HHS HIV therapy guidance for adult and adolescents.

Dr. Dybul received his B.A. and M.D. from Georgetown University for completing his residency in internal medicine at the University of Chicago Hospital in 1995, and a fellowship in infectious diseases at the National Institute of Allergy and Infectious Diseases.

We are very pleased to have such qualified witnesses, and we will begin with Dr. Hill.

STATEMENT OF THE HONORABLE KENT R. HILL, ASSISTANT ADMINISTRATOR, BUREAU FOR GLOBAL HEALTH, U.S. AGENCY FOR INTERNATIONAL DEVELOPMENT

Mr. HILL. Mr. Chairman, Congressman Smith, it is a real privilege to be here, and thank you for holding this important hearing. I will try to abbreviate even further my oral comments since what I have said is mainly in the written record.

However, I would like to take a moment of personal privilege if I might and just express a personal tribute in the memory of Congressman Tom Lantos. In the 1980s, when my resume focused on human rights and religious freedom, Congressman Lantos and Chris Smith were both key members of a bipartisan coalition that I headed that did tremendous work, and the two of them have taught me much about how bipartisanship can work in the cause of something that is more important than our political differences.

The U.S. is on the front lines in the fight against TB and against MDR. I want to acknowledge at the very first my colleagues here because this is a good example of interagency cooperation. We have a clear division of labor. USAID takes the lead on international TB control; the Office of Global AIDS Coordinator and the President's Emergency Plan for AIDS Relief takes the lead on TB-HIV, and of course, Julie Gerberding at the CDC takes the lead on domestic TB, but also works closely with both USAID and OGAC abroad. I am pleased to say that the relationship is very close, both personally and professionally, and it means that USG dollars are used to their maximum best.

I also want to note that the core of USAID's work in TB is focused on developing the capacity of countries affected by TB to implement effective programs to combat and control TB. The Congress has been good enough through 2007 to invest over \$600 million in USAID to do this work worldwide, and you would be inter-

ested to know perhaps that \$166 million of that has gone to programs in Africa. Our work is done in 37 countries, but we focus particularly on 19 of these countries, many of which are high burden countries that have a lot of problems with respect to MDR and XDR TB.

I want to just say a word about the work we did in South Africa. I am not going to repeat any information about the problem per se, and just talk about what we are doing with the money to try to make a difference. When the XDR outbreak report was reported in KwaZulu-Natal, the USAID stepped up technical assistance to South Africa's national TB program to address both MDR and XDR. We worked with our South African counterparts and we enhanced national surveillance. We worked on the DOTS program, we worked on capacity of the labs, et cetera, and that is the kind of thing you have to do in these kinds of situations.

I must say something about Russia. You probably noticed in your press conference that you did yesterday that there are several hotspots in Russia. Actually, as was said earlier, throughout the former Soviet Union there are very dangerous places, precisely because there is a lethal combination of two factors—the collapse of the health system infrastructure and the availability of drugs. That is of course why TB resistance develops, because there is not regimen control and discipline. When that is absent, you have the kind of problems we have right now.

You mentioned in your opening statement, Mr. Chairman, the importance of laboratory capacity. If you were to look at the way USAID spends its money in Africa, particularly where the problem is particularly acute, it is particular laboratory capacity that we are going after. We are trying to do this in East Africa, West Africa, and southern Africa—and much of the money is going there.

I want to thank you and the Congress for the support that you have given to us because you raised our amounts from \$93 million in 2007 to \$153 million in 2008. I think that indicates that you have trust that what we can do with the money can make a difference, and I think that is exactly right. We are already thinking about how to spend the money, trying to work on the ways that will have maximum impact on MDR and XDR. We know which countries we want to try to work in.

I should add that a lot of our work is to support the international efforts. The report that was issued yesterday and which you gave a press conference about was funded through USAID primarily and through money given to us from the Congress.

Here is perhaps one of the most important points I want to make during my brief statement. In the press release yesterday, or that came out today but the press conference was yesterday, reporting on the WHO 2008 MDR–XDR report, there was a recommendation there of eight top WHO proposals to effectively deal with XDR and MDR. The very first proposal was this, and I quote: “We must strengthen TB control through the Stop TB strategy.” The very best way to stop MDR and XDR is to have a robust TB program generally; this is in affect what we are trying to do, and thus a lot of the money we are going to spend in high population countries is to make sure it doesn't break out there.

I want to conclude by simply noting this. We know what needs to be done. This is not one of those problems where we have to have a huge amount of research to figure out what needs to be done. We know exactly what needs to be done. Although we want to see research that will bring in the drugs that will make a difference, we know what to do most of the time. We have a good international strategy, and we have good interagency cooperation here. We know the challenges are enormous, but there has been progress, and there can continue to be progress, and we are thankful for the support that you have given to us to allow us to play a part in making a difference.

Thank you, Mr. Chairman.

[The prepared statement of Mr. Hill follows:]

PREPARED STATEMENT OF THE HONORABLE KENT R. HILL, ASSISTANT ADMINISTRATOR, BUREAU FOR GLOBAL HEALTH, U.S. AGENCY FOR INTERNATIONAL DEVELOPMENT

Chairman Payne, Representative Smith, distinguished members, thank you for convening this important hearing and for inviting me to testify. Thank you for putting the spotlight on multi-drug resistant (MDR) tuberculosis (TB). The timing of this hearing is particularly relevant since the Fourth Global Drug-resistance Report was released today and less than a month from now, the U.S. Agency for International Development (USAID) will join its partners in commemorating World TB Day. The World TB Day theme of "I am stopping TB" reminds us that we all have a role to play in controlling TB.

The U.S. is on the frontlines of the battle against TB. USAID, the Centers for Disease Control and Prevention (CDC), the Office of the Global AIDS Coordinator, and the National Institutes of Health (NIH) have been working closely together over many years on combating TB and have extraordinarily good working relationships that take advantage of our respective strengths and ensure that USG resources for TB and for TB/HIV are used in the most effective and efficient manner possible. We all work closely with our international and in-country partners, and the USG is recognized not only as the leading bilateral donor for TB, but also for our technical leadership and very supportive engagement. USAID and CDC represent the U.S. Government on the international Stop TB Partnership Coordinating Board, and a USAID staff member is currently serving as Chair of the Coordinating Board.

I will speak briefly about the problem and challenges of TB, particularly as related to MDR TB and extensively drug resistant (XDR) TB. I will also outline USAID's efforts to battle the disease, particularly MDR and XDR TB, and to build local capacity to control TB and deal with the threat of MDR TB; and describe our plan to accelerate programs with the additional funds in FY 2008. I will also talk about why I believe there is reason to be optimistic about the future.

CHALLENGES OF TUBERCULOSIS

In six years as an Assistant Administrator with USAID, first in the Europe and Eurasia Bureau and now in Global Health, I have visited hospitals, TB clinics and prison infirmaries in Russia, Moldova and other countries. I have seen the personal toll TB takes. TB kills about 1.6 million people each year, and each year, nine million people develop TB. With HIV/AIDS claiming over 2 million lives each year, and malaria killing more than 1 million, TB is one of the three leading causes of deaths worldwide due to infectious diseases. About 10 percent of TB patients are also co-infected with HIV, and TB is the leading cause of death for AIDS patients.

TB not only takes an enormous personal toll, it also places a tremendous economic burden on families, communities, and countries. While TB treatment is often free, diagnosis, laboratory charges, transport, food, and other costs can account for 8–20% of annual household income for TB patients, according to a study recently released by the World Bank.

Dr. Raviglione's testimony describes one of the more significant challenges we face—that of MDR TB and XDR TB. The occurrence of MDR and XDR TB is a growing problem. In every country that has conducted a survey for anti-TB drug-resistance, drug resistance has been found. The challenge we face is that in many countries, we do not know if we have a problem, especially in Africa where surveillance capacity is particularly weak. Many of the countries most affected by drug-resistant TB are the least able to confront the problem of drug resistance. Health system in-

frastructure and laboratory capacity are often inadequate. Anti-TB drugs are sold over-the-counter in many countries and untrained providers fail to follow appropriate standards for TB treatment. Crowded health facilities and the mixing of HIV-positive persons with persons with active TB disease put both patients and health workers at risk of contracting the disease.

The *2008 Global MDR TB and XDR TB Report* is the fourth in a series. As Dr. Raviglione noted, it gives us the most data we have to date on the status of MDR and XDR TB. Since USAID began working on TB in 1998, we have supported country-level drug-resistance surveys and this biannual Global Report on TB drug-resistance. We are very proud that we have helped make this vital data available, and we will continue to support this important work. We must know where the problem is to address it, and these data provide us with critically important information for targeting our collective response.

Globally, we have a strategy to fight TB and a clear plan for what is to be done. That plan, articulated in the Stop TB Partnership's *Global Plan to Stop TB, 2006–2015* clearly identifies actions that need to be taken to reduce the burden of TB. It also includes clear benchmarks for the critically needed new tools and weapons in the fight against TB. We must have new and more effective diagnostics, drugs, and vaccines. The most commonly used diagnostic—a microscope for detecting TB through a sputum smear—is over 100 years old. Today's treatment consists of a four-drug cocktail that is more than 40 years old, and to ensure cure, these drugs must be taken for six to nine months.

USAID'S SUPPORT FOR TB

The core of USAID's work on TB is focused on developing the capacity of countries affected by TB to put in place effective programs to combat and control TB. As part of that work, USAID has been working closely with in-country partners, WHO, CDC, PEPFAR, and others to implement the priorities identified by the *Global MDR and XDR TB Response Plan* issued by WHO. Like the global response plan, USAID's first priority is building strong TB programs to prevent future MDR cases—the most important action to stop the spread of MDR and XDR.

USAID programs support the priorities of the national TB control programs and are coordinated with resources from other international donors including the Global Fund to Fight HIV/AIDS, TB and Malaria and the World Bank. CDC and PEPFAR are core partners for USAID, and we are working closely together in many countries.

Between 2000 and 2007, USAID provided nearly \$600 million for TB programs worldwide, including about \$166 million directed specifically for Africa. This is in addition to funding for TB/HIV provided under PEPFAR. USAID supports TB programs in 37 countries, focusing particularly on 19 of these countries, which are primarily high burden TB countries, or high priorities for MDR TB or TB/HIV. Our programs support the expansion and strengthening of basic TB programs or DOTS (Directly Observed Therapy, Short Course) as the key intervention for preventing the emergence of drug-resistant TB.

USAID also supports high priority late stage research, currently focusing on evaluating promising new TB drugs and testing new diagnostics in high burden countries. Our investments in research are coordinated closely and complement those of the NIH and CDC.

USAID also supports the scale up of MDR treatment, procurement of laboratory equipment and supplies, quality assurance for laboratories, community-based DOTS, and information and communication activities to raise awareness of TB and to stimulate demand for services. USAID-assisted programs in countries such as India, the Philippines, and Afghanistan are leaders in engaging private providers and NGOs to provide DOTS services. To help ensure synergies between USG investments in TB and HIV/AIDS, many of our TB focus countries overlap with focus countries of the President's Emergency Plan for AIDS Relief (PEPFAR). These countries are Ethiopia, Kenya, Mozambique, Namibia, Nigeria, South Africa, Tanzania, Uganda, and Zambia. In these countries, USAID resources strengthen TB control services for the general population whereas PEPFAR resources generally focus on TB–HIV/AIDS collaborative activities targeting persons co-infected with both TB and HIV.

Despite the magnitude of the problem, we are making progress in controlling the epidemic. In 2005, the World Health Organization (WHO) reported that the rate of new TB cases—or the TB incidence rate—leveled off for the first time since the WHO began collecting data about the disease. The rate at which TB cases were detected has doubled since 2000. Globally the target of successfully treating 85% of TB cases has nearly been met, and we continue to make steady progress toward the

target of 70% case detection. Our efforts are having an impact and this is good news.

USAID'S MDR/XDR RESPONSE

Specifically with regard to MDR/XDR TB, USAID is deeply concerned about the magnitude of the drug-resistance problem and we are committed to addressing it. In addition to our work to help countries strengthen their basic TB programs, USAID has also been a global leader in addressing MDR TB. In the last year and a half, we have moved quickly to help countries and our international partners respond to the latest data on MDR and XDR TB. This has included support for drug-resistance surveys and the building of laboratory capacity to detect resistant strains, expanding country level programs to treat MDR TB patients, and support for the Green Light Committee, which helps ensure that countries have effective programs to manage MDR TB patients and second line anti-TB drugs.

Our efforts have particularly focused on countries that have the greatest burden of MDR TB, including Russia, South Africa, Namibia, the Baltic States, Ukraine, India, and Indonesia. Given the deadly combination of MDR/XDR TB and HIV, we have also focused attention on other parts of Africa, where laboratory capacity is particularly weak and there is very limited data on the scale of MDR TB. Let me give you a few specific examples of the kind of work USAID has done in the last year.

In Russia, the USAID-supported Orel Center of Excellence for MDR TB was officially opened in August of 2007. The Center is conducting training of 300 technical personnel involved in the Global Fund MDR TB activities, an essential input to ensuring the success of the program. The USAID-supported MDR TB treatment program in Orel achieved a treatment success rate of 76%, compared to the national average of 59%. Of the sixteen provincial TB control programs in Russia that have been approved by the GLC—which is an indication of a strong TB and MDR TB program—six are currently supported by USAID. Infection-control measures have been implemented in all facilities in the USAID-supported sites.

In South Africa, following the XDR outbreak reported in KwaZulu Natal, USAID stepped up technical assistance to address MDR and XDR TB. USAID provided assistance to conduct an in-depth investigation into the KwaZulu Natal outbreak. We helped enhance national surveillance of MDR and XDR TB. USAID provided assistance to improve the quality of DOTS and TB/HIV care to two of the three TB crisis provinces (in line with the national TB emergency plan). USAID also assisted the MDR-TB Units in all provinces to establish teams to trace contacts of all confirmed XDR-TB cases.

In eastern, western, and southern Africa, USAID has provided substantial support to enhance regional laboratory capacity to undertake culture and drug-sensitivity testing. USAID supported the establishment of a supranational reference lab in Benin. Strengthening of national reference laboratories in Uganda and Tanzania is underway. The goal of this assistance is to create at least one laboratory that will have adequate capacity to serve as a supranational reference laboratory for East Africa, joining the USAID-supported laboratory in Benin and a lab in South Africa, to enable quality assurance and drug sensitivity testing for the continent.

In addition, PEPFAR funds through USAID, support the Green Light Committee to provide technical assistance to Global Fund grants with MDR TB components; this assistance includes preparation of GLC country applications, strengthening national laboratory capacity, strengthening country teams to manage MDR TB programs, and monitoring of GLC-approved projects. GLC has been able to substantially increase the number of patients approved for MDR-TB treatment through Global Fund grants with this USG support, and continued support ensures that the important work will continue.

Building strong human resource capacity and detailed strategic planning are crucial components of the response to MDR and XDR TB. USAID has supported regional training courses on MDR/XDR TB management in East and West Africa, India, South East Asia, and Latin America. With USAID support, WHO has carried out technical assistance visits to southern Africa countries at high risk for MDR and XDR TB—Lesotho, Malawi, South Africa, Swaziland, and Zambia—and helped prepare plans for accelerating MDR/XDR TB control activities in each country.

Confronting the challenge of MDR TB and the looming threat of XDR TB has galvanized the global TB community. The urgent need to bring this threat under control forces renewed focus on improving the quality of basic TB-control services to prevent the emergence of drug-resistance in the first place. Along with our colleagues from CDC, USAID is an active participant on the Global XDR TB Task

Force, and we supported the preparation of *Global MDR TB and XDR TB Response Plan 2007–2008*.

USAID TB programs have also advanced TB–HIV/AIDS collaborative activities. Working closely with PEPFAR, for example, the USAID program in Ethiopia increased HIV testing among TB patients from 30% in 2006 to 60% in 2007, and in Uganda, testing increased from 70% to 82% over the same time period.

These efforts are having an impact. The target for successfully treating TB cases of 85% of detected cases has been met or surpassed in Afghanistan, Bangladesh, Cambodia, the Democratic Republic of Congo, India, Indonesia, and Pakistan. Case detection rates are also improving, with substantial increases reported by countries such as Afghanistan, Bangladesh, Pakistan, the Russian Federation, and Ukraine. Indonesia, Kenya, Philippines, and South Africa have all surpassed the case detection target of 70% of estimated cases, and several other countries are closing in on this global target.

USAID’S PLAN FOR SCALING-UP IN FY 2008

The generous funding increase for USAID for TB from \$93 million in FY 2007 to \$153 million in FY 2008 demonstrates the ongoing commitment of the United States Government to do its part to stop TB. We are grateful for the confidence that the Congress has in our programs, and we believe your confidence is based on the success of our programs.

USAID’s FY 2008 TB funding will be used to scale up significantly interventions to respond effectively to and prevent MDR and XDR TB. Work is already underway. USAID’s response supports the *Global MDR TB and XDR TB Response Plan*, the targets set forth in the Stop TB Partnership’s *Global Plan to Stop TB 2006–2015* and the interventions recommended in the Stop TB Strategy.

USAID is focusing its program on scaling up interventions in priority countries that either already have or are threatened by MDR or XDR TB and in countries with weak performance in case detection and treatment outcomes. Our scale-up program will assist seventeen of the twenty-five priority countries identified in the WHO’s *Global MDR TB and XDR TB Response Plan*. In Africa, these include: Ethiopia, Democratic Republic of Congo, Nigeria, and South Africa. In Asia, increased funding will be targeted to Bangladesh, India, Indonesia, Pakistan, Philippines, and the Central Asian Republics. Finally, in the Europe and Eurasia region, increased funding will go to Russia, Ukraine, and Azerbaijan.

USAID’s technical team is working with our USAID missions to prepare plans for scaled-up country programs to support the national TB programs in our priority countries. The plans will focus on several key areas. First and foremost, country programs will improve the quality of basic DOTS services to slow the emergence of drug-resistant TB. This includes laboratory strengthening, improved management of TB programs, and involvement of private providers and communities. USAID will expand the capacity to treat MDR TB to ensure that more patients with MDR or XDR TB are put on appropriate treatment. Since surveillance information is lacking in many countries, USAID will support studies to determine the prevalence of MDR/XDR TB in all priority countries where the data is not currently available. To improve diagnostic capacity, USAID will support country-level laboratory infrastructure, including capacity for culturing samples for a definitive diagnosis of TB and drug-sensitivity testing. Working closely with PEPFAR, USAID will also support improved case management of patients co-infected with HIV and TB, particularly MDR TB. Finally, USAID will continue to support infection-control measures to protect health workers and patients from disease transmission. The county plans will include clear benchmarks and targets, and will describe how USAID’s resources will be coordinated with resources available from other sources such as the Global Fund and PEPFAR.

While the majority of our effort will focus on the country level, USAID will fund critical global and regional activities. These activities include providing technical support for two or three supranational reference laboratories for MDR/XDR referral in Africa, Asia, and Eurasia where they are desperately needed. USAID will also increase our support to the Green Light Committee and for technical assistance and training related to laboratory and infection control issues. We will provide \$15 million to the Global TB Drug Facility to support grants for TB drugs to countries in need. In order to expand the supply of quality-assured second line anti-TB drugs, USAID will provide technical assistance to manufacturers of second-line anti-TB drugs in order to help them achieve Good Manufacturing Practices. We will also invest in the future. Approximately 8–10% of our funding will be used for research for evaluating promising new TB drugs and drug combination regimens that could be used for treating and preventing MDR TB. This includes an increase in our fund-

ing for the evaluation of new diagnostics, including technologies for the rapid detection of TB and MDR/XDR TB, and research into the most cost-effective approaches to infection control.

U.S. COMMITMENT

We know what needs to be done. The *Global Plan to STOP TB 2006–2015* and the *Global MDR–TB and XDR–TB Response Plan 2007–2008* provide us the road map and key interventions. The challenges are enormous, but we have seen steady progress in TB control in recent years. Our strategy and approach are clear, and we are beginning to see the fruits of recent investments in research. In the coming year, we expect to see improved tools to help better diagnose patients, including patients with MDR TB. The international partnership is strong, global commitment is high, and the strong endorsement from this body reflects the unwavering commitment from the U.S. government. Your support is crucial, and I thank you very much for your strong commitment. With this engagement and political will, we can stop TB.

Mr. PAYNE. Thank you, very much.
Dr. Gerberding.

STATEMENT OF JULIE L. GERBERDING, M.D., M.P.H., DIRECTOR, CENTERS FOR DISEASE CONTROL AND PREVENTION, ALSO ADMINISTRATOR OF THE AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

Dr. GERBERDING. I am very, very honored to be part of this really important hearing, and I too want to begin my remarks with just a reflection on Congressman Lantos, who is someone who not only championed this issue, but also from time to time would call me directly for other health concerns in his district, and never failed to reach out to get the facts and was really one of the kindest and most respectful people I have interacted with. So we are very sad by his loss.

I think my colleagues have done a beautiful job of summarizing the issues. If I can paraphrase words that are more eloquent than mine, I would simply say that we have heard that MDR is an urgent global health threat and that urgent global action is required. We know what to do, but we need to do it in a comprehensive program. Any weak link in our system of interventions creates vulnerability for

everyone. Any weak location or any weak country in that network also creates vulnerability for everyone. So we do have to look at this in a partnership and in a way that really embraces the entire global health community.

I have a couple of graphics I wanted to share with you because I think one of the important sobering reminders here is this just isn't a problem somewhere else, it is a problem that exists here, and could become a much bigger problem in the United States. In this community that we are working in today, there were 72 cases of tuberculosis diagnosed last year. That is about three times the rate of tuberculosis in the United States. So this city has a special risk for tuberculosis. Yes, there were MDR TB cases diagnosed here in the District last year. So it is a problem in communities across America.

These graphs tell something very important here. First of all, in the United States, fortunately, the proportion of TB that is drug-resistant is very low, and getting lower, thanks in large part to the excellent tuberculosis control programs that are present in many of our cities and States. But also it shows that over time much of the

drug-resistant TB in the United States is from people who were born elsewhere. So they are bringing it into the country when they immigrate, and the major source or force of MDR TB now is from people who acquired their infection in parts of the world where it is much more common than it currently is here. That is very important. Any source can potentially present a threat to others.

I trained at San Francisco General Hospital at the very beginning of the HIV epidemic, and soon after that there was an epidemic of drug-resistant tuberculosis, much bigger in New York than it was in San Francisco, but nevertheless, when you put the fuel of AIDS on top of a smoldering ember of TB, you end up with a concentration that can move very quickly through populations. It only takes a few systems that aren't detecting and diagnosing and treating properly for that process to take off.

I think our colleague from the WHO made the point earlier, but I want to really emphasize how important infection control is. When you have someone with tuberculosis, it is critical the person be isolated until they are no longer infectious, and that applies in prisons and hospitals and aircraft and any other environment where tuberculosis can spread.

I will share just one other important graphic, which is a different picture than what we see in the United States. This is the proportion of drug-resistant tuberculosis in Botswana, comparing two populations. One are the people who have never, ever been treated with drugs before, so they have kind of the native tuberculosis, and then the people who were exposed to tuberculosis drugs for a previous episode or previous treatment. Obviously, there are big differences here. The reason for that is the same reason that we see drug resistance emerging for staph aureus or for influenza or any of the problematic germs that we are dealing with these days. When you present a drug treatment to any organism, it has an opportunity to develop resistance, and a few survivors can stick around and then outlive the sensitive bugs and become the dominant bug in the environment.

What happened in this environment with tuberculosis is that as the country was improving its economic status, drug treatments became available for tuberculosis, and then as those treatments began to be used, the infrastructure wasn't quite able to assure that they were used properly in all conditions. There wasn't testing available to know that you were using the right drug combinations. And so the exposure to the common drugs resulted in a subset of TB that has this resistant characteristic, and now they are beginning to spread, fueled of course by the HIV epidemic.

I am sure this pattern would be repeated in country after country in Africa. Unfortunately, Botswana is the only country we have data over time in to really make that direct comparison. The reason for that is because CDC has been working there in a program called BOTUSA, and I would certainly encourage you to visit if you every have a chance, because it is a perfect demonstration of the kind of innovative and creative clinical research that can go on as you are also improving a country's program to diagnosis, detect and properly treat TB in the context of a very serious HIV epidemic.

Some of the most important information we have learned on how to improve our drug treatment approaches to make them simpler

and more effective and shorter for tuberculosis have been done in places like this program in Botswana, and any of the 26 other program sites that we sponsor for clinical trials so that we have the science to tell us how can we use what we have in the most effective way possible.

I will just end with a perspective that while we know what to do with what we have, we also need some new tools. We definitely need news diagnostics that are quick and at the point of care for tuberculosis and also for drug resistance. We need new drugs. Yes, we have some in the pipeline, and I reference them in my testimony. We are a long way from having a full and robust pipeline of anti-tuberculosis drugs coming down the pike, and we need to incentivize and get the best and brightest working on new drug regimens and better ways to use the new drugs.

Of course, ultimately we need a vaccine. It is important to put the effort on the line to really focus on getting a TB vaccine. For a problem that affects a third of the people in the world, it is time to have a vaccine that takes this disease off the table.

It is a huge threat to families and children everywhere, but also a huge economic burden. We have referenced the testimony from the World Bank that really has developed a perspective on the economic impact of TB. I would be happy to submit that for the record if you would like to have it. It is a critical global health challenge, and we certainly look forward to doing our part in conjunction with our colleagues and sister agencies, as well as our colleagues in ministries of health around the country and all of the other organizations that support their work.

Just ending with thank you so much for letting us tell you how important we think this problem really is.

[The prepared statement of Dr. Gerberding follows:]

PREPARED STATEMENT OF JULIE L. GERBERDING, M.D., M.P.H., DIRECTOR, CENTERS FOR DISEASE CONTROL AND PREVENTION, ALSO ADMINISTRATOR OF THE AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

DRUG RESISTANT TB: CDC'S PUBLIC HEALTH RESPONSE

Good afternoon, I am Dr. Julie Louise Gerberding, Director of the Centers for Disease Control and Prevention within the Department of Health and Human Services (HHS). It is my pleasure to be here to discuss with you CDC's role in the response to drug resistant TB, globally and in the United States.

DEFINITION

Tuberculosis (TB) is an airborne infectious disease that is spread from person to person, usually through coughing. In the late 19th and early 20th centuries, until the introduction of streptomycin in the 1940s, TB was one of the leading causes of death in the United States. Currently, the World Health Organization (WHO) reports that one in three people in the world is infected with dormant TB bacteria (latent TB infection). Only when the bacteria become active do people become ill with TB. Bacteria become active as a result of anything that can reduce the person's immunity, such as HIV, advancing age, or some underlying medical conditions such as cancer or diabetes. Currently TB that is not resistant to drugs can be treated with six to nine months of "first-line drugs" (the most effective), including isoniazid and rifampin; this treatment cures over 95 percent of patients. Nearly nine million people in the world develop TB disease each year, and since people in many resource-poor countries lack access to appropriate treatment, about 1.6 million die.

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 much less effective, usually poorly tolerated by the patient, and far more costly. There are currently only six categories of second-line drugs, of which

two—fluoroquinolones and injectable aminoglycosides—are the most important. The cure rate is 70–80 percent under optimal conditions and, in most settings, is closer to 50 percent. Many countries with a high TB burden find it impossible to treat MDR TB patients because of the cost of drugs, and the more sophisticated laboratory services, technical expertise, and intensive programmatic support activities that are required. 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.

CAUSES

Drug resistance develops when patients receive incomplete or inadequate treatment. Treatment of drug-resistant TB requires at least six months of treatment with four different antibiotics. If this complex regimen is interrupted, drug susceptible bacilli are killed, but more resistant strains persist and form larger colonies. Persons with these resistant strains in their lungs can then pass these resistant bacteria to other susceptible individuals through coughing. We have also learned that weaknesses in a TB program create opportunities for drug resistance to develop: either through the interruption of drug supply, the inappropriate prescription of treatment regimens administered by medical providers, the failure to support patients on therapy, the non-adherence to treatment by patients, and the lack of implementation of infection-control precautions.

SCOPE OF THE PROBLEM

In response to anecdotal reports from physicians who were finding cases of TB that were unresponsive to the first-line and second-line TB drugs, in 2005 CDC and WHO jointly conducted the first survey, with support from the U.S. Agency for International Development, for resistance to both first and second line TB drugs. The survey examined almost 18,000 patient sputum samples, or isolates, collected during 2000 to 2004 by WHO's network of Supranational Reference Laboratories. Researchers examined the drug-resistant isolates, and found that, of those isolates meeting the definition of MDR TB, 10 percent met the definition for XDR TB. XDR TB was identified in 17 countries from all regions of the world, most frequently in the former Soviet Union and Asia. Data from sub-Saharan Africa were very limited. Most laboratories in this region use culture methods for diagnosis, which are unable to detect drug resistant organisms. This report, published in CDC's *Morbidity and Mortality Weekly Report* in March 2006, was the first widely circulated publication to use the term "extensively drug resistant TB." WHO is releasing the fourth global drug susceptibility test data today, which show worrisome trends in several countries. Dr. Raviglione will describe these in more detail in his testimony.

Because many countries do not routinely test all isolates for resistance to second line drugs, the precise global incidence of XDR TB remains uncertain. However, because of the ease with which drug resistance can occur (because of the use of second-line drugs in suboptimal conditions, funding shortages, changes in program focus away from TB case management, interruptions in drug availability, high HIV prevalence), XDR TB could be much more widespread than the WHO survey shows.

MORBIDITY AND MORTALITY FROM XDR TB

Reported mortality rates among persons with XDR-TB are extremely high. In the U.S., 25% of XDR-TB patients die within 1 year and 32% die during treatment (compared with 19% and 23%, respectively, for MDR-TB). Only 38% of XDR-TB patients complete treatment successfully compared to 53% of MDR-TB patients. Among HIV-infected persons, illness is more severe, mortality rates are higher, and death occurs within a shorter time, either because the disease itself is more severe, or whether at presentation, the patient is suffering with more advanced disease and more severe comorbidities, or a combination of factors. As Dr. Raviglione explained in his testimony, the world saw evidence of this in the alarmingly high mortality rates resulting from the 2006 outbreak of XDR-TB in an HIV-positive population in KwaZulu-Natal in South Africa. Of the 53 XDR-TB patients, 52 died—and they died within an average of 25 days, including those benefiting from antiretroviral drugs.

WHAT IS THE THREAT IN THE UNITED STATES?

The TB resurgence that occurred from 1985 to 1992 in our country provides a poignant example of how outbreaks of drug-resistant TB can develop. From 1953 (the establishment of national U.S. surveillance) through the mid 1980s, TB cases in the United States declined steadily, from approximately 83,000 to 22,000 new

cases per year. But in 1985, CDC began documenting increases in TB incidence. A key factor associated with this increase was the dismantling of TB programs, which occurred when health departments stopped receiving TB categorical funds, and shifted resources to other public-health activities. Other factors included the burgeoning HIV epidemic, increased immigration from countries with high TB incidence rates, lack of infection-control precautions in healthcare settings, and the widespread occurrence of MDR TB at a time when the laboratory capacity to readily identify these strains was inadequate. The Congress then appropriated an increase in funds, and the situation was remedied after programs were again able to prescribe appropriate drug regimens for patients, have adequate laboratory capacity to diagnose and manage patients, provide appropriate programmatic support for patients, assure adherence with prescribed regimens, and conduct effective contact investigations.

These intensive control efforts also resulted in a decrease in MDR TB cases in the United States, which fell from 483 reported cases in 1993 to 111 in 2006. However, the epidemiology of these cases also changed. In 1993, 31 percent of MDR TB cases in the United States occurred in foreign-born persons; whereas in 2005, 81 percent of MDR TB cases occurred in foreign-born persons. Between 1993 and 2006, a retrospective analysis of 47 cases of XDR TB were reported in the United States to CDC. As with MDR TB, the epidemiology for XDR has changed. In the years 1993–1999, 62 percent of XDR TB cases occurred in U.S.-born persons and most of these cases occurred in persons with HIV infection. While from 2000–2006, 73 percent of XDR TB cases occurred in foreign-born persons, and only 18 percent of the U.S. XDR TB cases occurred in HIV-infected persons.

While the total number of MDR and XDR TB cases in the U.S. is relatively small, their impact on U.S. TB control programs can be significant in terms of human capital and financial resources. One patient with MDR or XDR TB requires a minimum of 18–24 months of treatment. Recently collected data from California show that inpatient costs alone for someone with XDR TB may exceed \$600,000 per case.¹ The treatment of some individual cases has cost as much as \$1 million. The cost of a potential resurgence, however, is far higher. In New York City alone, the estimated cost to control the MDR TB epidemic of the late 1980's exceeded one billion dollars (in 1991 dollars).²

CDC also works to prevent the introduction of TB cases into the United States and the movement of infected individuals between states. The required overseas medical screening of immigrants and refugees is an important activity to prevent importation of TB into the United States. In 2007, CDC updated its Technical Instructions for Tuberculosis Screening and Treatment, which are used by the physicians who perform overseas medical examinations, to be consistent with modern diagnostic technologies and international standards for treatment. With the cooperation of the U.S. Department of State and international partners, HHS/CDC is in the process of implementing these improved screening procedures. These procedures include routine screening procedures for children; cultures for persons whose x-ray suggests TB, and drug susceptibility testing if cultures are positive. Patients are required to complete treatment overseas before embarking for the United States, under directly observed therapy and using established drug regimens. According to preliminary studies, these revised procedures are three times as sensitive at detecting TB. We have clear evidence of the new procedures' efficacy. For example, during 2004–2006, CDC responded to an outbreak of MDR TB in a refugee group in Thailand that was resulting in cases being imported into the United States. CDC and international partners implemented comprehensive measures in Thailand that allowed the Hmong refugees to receive treatment according to international standards, and TB importations to the U.S. were greatly reduced. Evaluation and monitoring of this activity are ongoing.

When necessary, CDC can use isolation and quarantine strategies to restrict the movement of individuals who are traveling with TB. 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. However, CDC maintains a close partnership with DHS and its

¹ Inpatient care has been estimated for California XDR TB patients from 1993–2006 at an average of approximately \$600,000 per patient. These estimates do not include outpatient costs or productivity losses, which are likely to be substantial for those treated for many years, or for the 25 percent of whom died from XDR TB. Jenny Flood, MD, TB Controller, State of California, personal communication.

² (Tuberculosis in New York City—Turning the Tide. Thomas R. Frieden, M.D., M.P.H., Paula I. Fujiwara, M.D., M.P.H., Rita M. Washko, M.D., and Margaret A. Hamburg, M.D. *New England Journal of Medicine*, July 27, 1995).

agencies, and coordinates with DHS when asked by states for assistance to restrict travel. CDC 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 provides situational awareness that allows for an effective response to public health threats.

MDR AND XDR IN HIV HIGH-PREVALENCE AREAS

In areas such as sub-Saharan Africa, TB rates have substantially increased over the past decade, which parallels the rising number of HIV/AIDS patients. HIV co-infection makes it more difficult to diagnose and treat TB. More than 50 percent of persons with TB in sub-Saharan Africa are HIV-infected. In countries with a high HIV burden, weak and underfunded TB control programs become strained by the influx of new HIV-TB patients. In most of these countries, the government does not regulate second-line TB drugs and they are not widely available. In Botswana, for example, TB incidence was declining until about 1987, when it began to rise sharply as HIV prevalence increased, tripling by 2002. A significant increase in the prevalence of overall drug resistance among the TB cases followed this jump in the burden of TB patients. The WHO and its partners anticipate that drug resistance will continue to increase because of weaknesses in national TB programs in many countries.

MDR AND XDR TB IN COUNTRIES WITH LOW HIV PREVALENCE

XDR TB is also a potentially dangerous problem for countries with low HIV prevalence if they lack adequate national TB programs. One of the conditions that contribute to the development of drug-resistant TB is when physicians prescribe drug regimens without the benefit of timely drug-susceptibility testing. Available data indicate the highest MDR TB and XDR TB prevalence rates occur in the former Soviet Union and Asia in low-HIV-prevalence populations. Persons in these countries who are treated effectively are cured of non-resistant TB. However, if conditions exist in which second line drugs prescribed for MDR TB are misused, development of XDR TB will result.

RESPONSE TO XDR TB GLOBALLY

CDC works closely with other agencies to prevent TB globally, including the National Institutes of Health (NIH), the U.S. Agency for International Development (USAID), WHO and non-governmental agencies through a variety of programs, including the Emergency Plan and the Global Fund for AIDS, TB and Malaria. In September 2006, HHS/CDC, WHO, and other partners from the Stop TB partnership developed an action plan to address XDR TB. This includes taking the first, all-important step of addressing TB program deficiencies as quickly as possible to "turn off the faucet" of drug resistance. The action plan recommended the following:

1. Conduct rapid surveys of XDR TB to determine the burden of disease;
2. Enhance laboratory capacity to support surveillance and diagnosis, with emphasis on drug-susceptibility testing;
3. Improve the technical capacity of practitioners to respond to XDR TB outbreaks and manage patients;
4. Implement infection-control precautions;
5. Increase research support to develop new anti-TB drugs;
6. Increase research support to create rapid diagnostics for TB and for MDR and XDR TB; and
7. Promote universal access to antiretrovirals under joint TB/HIV activities.

The U.S. Federal TB Task Force, which was established in 1991 by then CDC Director Dr. William Roper to coordinate federal efforts to address TB, has written a domestic and international response plan to address XDR TB for U.S. Government agencies. The U.S. Government also participated in the development of WHO's Global MDR/XDR TB Plan.

HHS/CDC also supports WHO and the Stop TB Partnership on a number of important activities, including providing technical assistance to the Global Drug Facility, which works to supply quality medications for TB programs. HHS/CDC also is a member of the Green Light Committee, which supports efforts to procure high-quality, low-cost medications linked to appropriate, managed treatment for MDR TB. During the period 2000-2007, the Green Light Committee evaluated 126 applications for access to reduced-cost TB drugs, and approved 93 applications for access to drugs for drug-resistant TB treatment project sites in 51 countries.

In addition, HHS/CDC's TB Trials Consortium has a leading role in clinical tuberculosis research that forms the basis for the Treatment Guidelines developed by HHS/CDC with the American Thoracic Society and the Infectious Diseases Society of America, and in updating TB treatment regimens for both HIV and non-HIV infected patients. The complementary research efforts of CDC and NIH play a key role in the development of new drugs and new regimens for drug-resistant TB. In FY 2007, CDC funded the consortium to initiate a pilot study to identify a treatment regimen for patients with drug-resistant strains of TB.

In collaboration with USAID and others, CDC technical experts are also working directly with host country governments and partners to implement improved infection control, rapid case detection, effective treatment, surveillance for drug resistance, and expanded program capacity, on an urgent basis. For example, currently CDC staff is assisting with an XDR TB outbreak in Botswana. CDC has also assembled teams of experts, including epidemiologists, microbiologists, and infection control specialists who are prepared for rapid deployment to respond to XDR TB outbreaks throughout the world.

RESPONSE TO XDR IN PEOPLE LIVING WITH HIV/AIDS

With the support of the Office of the Global AIDS Coordinator (OGAC) and PEPFAR funding, CDC has been providing technical assistance to host governments in PEPFAR-supported countries. This funding has been used to strengthen collaboration between National TB and AIDS Control Programs and to work with National Public Health Laboratories to strengthen TB diagnostic services. This technical assistance supports a variety of activities, including (1) decreasing the pool of severely immunocompromised patients through ARV treatment, (2) reducing TB morbidity and mortality through early identification of TB suspects and patients in HIV prevention and care settings, (3) integrating TB and HIV services to assure uninterrupted treatment of HIV-infected TB patients, and (4) providing isoniazid preventive therapy as part of a package of care for HIV-infected patients. In addition, CDC is helping to strengthen TB laboratory capacity, especially at points of service to promote rapid diagnosis of TB; conduct TB drug resistance surveillance; and strengthen TB infection control practices in HIV care settings. In FY 2007, a portion of PEPFAR funds were used to address prevention and control of XDR TB in HIV-infected persons. In FY 2008, this funding will be continued.

GAPS

Globally, HHS/CDC, WHO, and USAID have taken critical steps toward characterizing and controlling the threat of XDR TB. The importance of the role of infection control in high-burden HIV settings is becoming increasingly apparent. In the FY 2008 Conference on Retroviruses and Opportunistic Infections, data were presented that suggest a large proportion of persons with HIV in South Africa recently became infected with these highly resistant strains. We know that considerable improvement in TB infection-control practices in healthcare settings, achieved through relatively simple and inexpensive practices (for example, having waiting rooms outside in covered but open areas, installing fans, separating coughing patients, etc.), can achieve considerable improvements in TB infection-control practices in healthcare settings. To provide guidance on TB infection control, CDC, in collaboration with the WHO, OGAC, and the International Union Against TB and Lung Disease recently published a guidance document titled "TB Infection Control in the Era of Expanding HIV Care and Treatment."

There is room for improvement in other areas, especially diagnostic services, treatment, and program management. Research on new tools for prevention, treatment, and diagnosis is needed both domestically and internationally to modernize and accelerate TB elimination. Importantly, the international community lacks new, effective drug regimens to replace drugs that have become ineffective against TB, or that interact unfavorably with anti-retrovirals and other HIV medications. According to the Advisory Council for the Elimination of Tuberculosis, TB drug development is at an unprecedented point. For the first time in 50 years at least four new anti-TB compounds entered human clinical trials, and several others are ready for advanced pre-clinical testing. These new compounds represent new drug classes that are not cross-resistant with existing agents, and can offer promise for resistant cases. CDC is working with WHO and other partners to develop the laboratory capacities and services required to meet the goals of the Global Plan for Tuberculosis Control and the Millennium Development goals, as well as to build integrated sustainable laboratory networks capable of providing the laboratory services needed to combat TB, HIV, and malaria.

New diagnostic tests in TB control are beginning to appear on the horizon and could provide beneficial results. Currently diagnosis of TB disease relies on the sputum smear examination, which has been in use for 125 years and is poorly sensitive and imperfect, especially in HIV infected persons. New blood tests have entered the market recently, and appear to offer improved performance, although they are more costly and have yet to undergo extensive field testing. Field evaluation of optimal, efficient diagnostic tests, as well as rapid tests for the detection of TB drug resistance, is critical. CDC is working with WHO and other partners to determine how best to integrate the use of these tests into routine TB diagnostic and control activities. For example, in Peru, CDC decentralized drug susceptibility testing to two district laboratories including a rapid low-cost test for MDR TB. In this project, the turn-around-time for testing for drug susceptibility was cut from nearly 3 months to 1 month at \$5 per patient. In Latvia, CDC helped implement molecular screening for rifampentine resistance with about a 2-day turn-around-time. In Russia, Nepal, and the Philippines and Uzbekistan, CDC is implementing a modern laboratory standard for rapid culture and drug susceptibility testing. All of these projects include cost-effectiveness evaluations.

The presence of XDR TB globally has highlighted the need for laboratories to make services for TB, MDR TB and XDR TB more rapid and reliable. TB patients in developing countries frequently lack access to reliable, quality-assured, and prompt TB laboratory services. As a result, clinicians are unable to make timely, correct patient management decisions. Many laboratory techniques used in these countries to confirm a diagnosis of TB and to identify drug resistance were developed in the 1950's, 60's, and 70's. To combat resistance to anti-TB drugs, clinicians must have the most current methods, applied to their fullest capacity. Increasing the availability of genotyping also would allow programs to identify links between patients.

Given that TB is still a major threat to HIV-infected persons, partners such as the President's Emergency Plan, the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria, national governments, and others must ensure programs to prevent and control TB work closely together to protect vulnerable populations from acquiring this virtually untreatable form of TB.

In addition, given the increasing proportion of the burden of TB in the United States among foreign-born persons, there is a strong need to improve the quality of overseas medical screening of U.S. bound immigrants, including the ability to detect and treat XDR TB in this population.

Equally important will be the strengthening of program infrastructures, both domestically and abroad, through training and sustained support. While we are working to improve methods to diagnose and treat TB, we should continue to work to assist countries in improving their detection of new cases of TB and of successfully treating those that are detected. Strong program infrastructure, utilizing proven effective methods, such as Directly Observed Therapy Short-Course (DOTS), capable of meeting targets for detection of new cases and successful treatment, will prevent new agents from becoming drug-resistant in the first place.

Thank you for the opportunity to present CDC's findings and activities on drug resistant TB to date. I would be happy to answer any questions.

Mr. PAYNE. Thank you very much. Thank you for all that you do.
Ambassador Dybul.

STATEMENT OF THE HONORABLE MARK R. DYBUL, COORDINATOR, OFFICE OF THE U.S. GLOBAL AIDS COORDINATOR, U.S. DEPARTMENT OF STATE

Dr. DYBUL. Mr. Chairman, Ranking Member Smith, it is a particular pleasure to be with you both today. It is always a pleasure to be with you. You both have been extraordinary champions for those less fortunate, for those who aren't protected otherwise, and this morning you led and championed an extension of the President's Emergency Plan for AIDS Relief that will serve and save the lives of millions and millions of people, and we thank you for that leadership and for that extraordinary act this morning, an act of bipartisanship. I certainly share the tribute to Chairman Lantos of my two colleagues, but no greater tribute could be done for Chair-

man Lantos and Chairman Hyde than the work that was done this morning. Thank you. It is a pleasure to be with you this afternoon.

It has been noted the clear link between HIV and tuberculosis. We don't need to go into the details on that any further. As Dr. Gerberding noted, the two fuel each other. So our office is very engaged with this, working with USAID and CDC.

I am pleased to report that resources for HIV TB have increased more than six-fold, from \$26 million in 2005, to a plan level of \$150 million in 2008. We do work with that money by supporting government, nongovernment, faith and community-based organizations, as we have talked about often before your committees. Faith-based organizations provide 30 percent of health care in Africa. So they are an important component of all the work we do.

By the end of September, 2007, PEPFAR supported care for approximately 367,000 TB HIV co-infected patients in 15 focus countries. That has been done through a collaboration of these in-country organizations but also within the U.S. Government, as Dr. Hill noted, with USAID, Department of Health and Human Services, CDC, and with our multilateral partners. The results have been impressive. PEPFAR-supported WHO collaboration in these countries is producing compelling results. In Kenya, 84 percent of TB patients were tested for HIV by the second quarter of 2007. That is up from 41 percent. In Rwanda, 88 percent of TB patients were tested, up from 45 percent. Data from Namibia indicate an increase in testing from 16 percent in 2005, to 47 percent in the first half of 2007. Data from Botswana that Dr. Gerberding was talking about suggests that in national TB programs, 68 percent of all registered TB patients now undergone HIV tests. In some districts in Tanzania with provider-initiated HIV counseling and testing, more than 80 percent of all TB patients opt for HIV testing, and learn their results. So results are being achieved.

Another important goal is to ensure that TB HIV patients have access to anti-retroviral therapy. Anti-retroviral therapy is an important component of anti-TB measures. In Kenya, 42 percent of HIV-positive patients identify TB positive and began anti-retroviral therapy. In Ethiopia, 28 percent of HIV-positive TV patients received anti-retroviral therapy by mid-2007. That was up from 19 percent shortly before that. In Rwanda, 36 percent of HIV-positive TB patients received ART by the end of 2007, up from 13 percent. Almost a three-fold increase. So we have a lot of work left to do, a lot has been done.

As was mentioned, there is an important investment in infrastructure that is required for HIV/TB programs, and funds for PEPFAR increasing host countries' capacity to respond to TB, including diagnosis and laboratory work, and our work is really the work of USAID and CDC because these are the agencies that we support to do the work.

An example of that is in South Africa. We are supporting an integrated HIV lab supporting the WHO global lab initiative, which will provide regional support, which is an important thing when you have limited infrastructure, to have regional support so you can support the programs.

We also support the Stop TB and HIV Departments of WHO, the Green Light Committee. We support the Global Fund in their work. All of this work together is making a tremendous difference.

It is a clear priority for the emergency plan to increase cooperation and effective linkages between HIV and TB. It is a clear priority of ours to make sure the executive branch is working together. We appreciate the work of this committee in the multiple hearings you have had and the multiple promptings from you and your staff to make sure we are addressing HIV TB. We appreciate deeply our partnership with this committee and our partnership with those around the world.

Again, thank you, Mr. Chairman, Ranking Member, for your work not on only TB HIV, but for your broader work to defend those who are defenseless without you.

[The prepared statement of Dr. Dybul follows:]

PREPARED STATEMENT OF THE HONORABLE MARK R. DYBUL, COORDINATOR, OFFICE OF THE U.S. GLOBAL AIDS COORDINATOR, U.S. DEPARTMENT OF STATE

Mr. Chairman, Ranking Member Smith, and Members of the Subcommittee:

Thank you for this opportunity to discuss the President's Emergency Plan for AIDS Relief and our efforts to combat the spread of multi-drug resistant tuberculosis (MDR-TB) globally. The partnership between PEPFAR and the Committee on Foreign Affairs over the years is one for which I am very grateful. Chairman Payne, Ranking Member Smith and Members of the Subcommittee, thank you for your commitment to the U.S. leadership in the fight against HIV/AIDS. Bipartisan support for this historic initiative has been a key to its success.

Thanks to the commitment of President Bush, Congress and the American people, PEPFAR is on track to meet its ambitious goals, and efforts are now underway to reauthorize PEPFAR for another five years. The majority of those resources are being invested directly into partnerships with host nations. By working with our host countries to build high-quality health care networks and increase capacity, we are laying the foundation for nations and communities to sustain their efforts against not just HIV/AIDS, but a wide range of other diseases, including MDR- and extensively drug-resistant (XDR)-TB—long after the initial five years of the Emergency Plan.

Because its effect on the immune system makes HIV-infected people more susceptible to infection, HIV is the greatest risk factor for developing tuberculosis. In Africa, TB is in lock step with the increase in HIV/AIDS. In fact, TB is the number one killer of people living with HIV—which is why PEPFAR is leading a unified U.S. Government (USG) global response to fully integrate HIV and TB services at the country level and build the capacity, particularly in Africa, to detect and treat MDR- and XDR-TB. Our goal is to ensure that people who are infected with HIV receive the best treatment and care possible, in order to reduce their risk of contracting or developing TB in the first place. This is critical to the long-term control of TB at the global level. Antiretroviral treatment (ART) is a powerful deterrent to the development of TB, because it restores immune function. A strong immune system means that an HIV-positive person on ART is much less likely to contract TB; and even if he or she already has been infected with tuberculosis, the bacteria are more likely to remain dormant.

PEPFAR also supports the full range of HIV treatment and care for people who already are co-infected with HIV and active TB. Appropriate and full treatment of TB is vital, not only to prevent HIV-positive people from dying but also to alleviate the risk of them developing drug-resistant TB. One study reported an 80 percent reduction in the incidence of TB among HIV-positive people who are on antiretroviral treatment, as compared to those who are not receiving anti-retroviral therapy. Thus, in a country where 60 percent of all TB patients also have HIV, if all those who needed antiretroviral therapy received it, it is possible that overall TB rates could drop by as much as 50 percent. HIV drug therapy is a powerful tool in the fight against TB.

PEPFAR ACTIVITIES TO THWART MDR-TB

Our most important work in combating TB and thwarting the development of MDR-TB takes place through partnerships at the country level to support national

health authorities, non-governmental organizations, and community- and faith-based organizations to implement more effective TB/HIV activities. PEPFAR increased its funding for HIV/TB five-fold, from \$26 million to \$131 million, from fiscal year 2005 to fiscal year 2007, and a planned level of \$150 million for fiscal year 2008. By the end of September 2007, PEPFAR had supported care for more than 367,000 TB/HIV co-infected people in the 15 PEPFAR focus countries.

Accelerated activities include supporting HIV services for people with TB and improving TB diagnosis and treatment for people with HIV. Within these categories, specific activities supported by PEPFAR include:

1. Providing HIV testing for TB patients;
2. Supporting cotrimoxazole and isoniazid preventive therapy to HIV-infected people in order to reduce their risk of developing TB;
3. Ensuring that routine TB screening is an integral part of PEPFAR-supported preventive care package for HIV-infected people;
4. Implementing effective TB infection control to reduce the risk of transmission of TB to people living with HIV/AIDS (PLWHA) in settings where they access HIV care as well as to healthcare workers, a scarce and valuable cadre that must be protected;
5. Implementing the World Health Organization (WHO)-recommended International Standards for TB Care, which build on Directly Observed Therapy-Short Course (DOTS) strategy, in PEPFAR HIV care settings, in order to ensure that patients complete their TB treatment;
6. Funding for drug resistance surveillance in six countries (Lesotho, Namibia, Nigeria, Swaziland, Russia, and Uganda);
7. Improving laboratory surveillance systems in order to detect outbreaks of MDR- and XDR-TB
8. Supporting the development of strong, tiered public health laboratory networks for diagnosing and managing drug-resistant TB and other opportunistic infections; we are strengthening capacity to diagnose both smear negative and extrapulmonary TB among PLWHA, which are critical elements in TB detection and control in the PLWHA population.

PEPFAR also supports expanding the capacity of the local health workforce to deal with these dual epidemics. Efforts include protecting healthcare workers—many of whom are also HIV-infected—from exposure to TB as an important aspect of TB infection control; supporting improvements to supply chain management systems for medications and other commodities; and establishing linkages between TB treatment and ART so that people who are co-infected receive the medical attention they need. We also work with partners to train health care providers in DOTS, the expansion and successful implementation of which helps prevent the development of drug resistance.

As an initial step in addressing MDR- and XDR-TB, the USG reconvened the U.S. Federal TB Task Force to develop a coordinated response by USG agencies to the looming threat of MDR- and XDR-TB. This Federal Task Force has formulated a comprehensive, coordinated USG response to both domestic and international aspects of MDR and XDR-TB. The USG also participates in the WHO Global XDR-TB Task Force, which has formulated the global plan to respond to XDR-TB, which Dr Raviglione can go into more detail about.

THE EVOLUTION OF DRUG-RESISTANT TB

In discussing XDR-TB, let me make two observations: (1) the development of drug resistant tuberculosis is of concern, but not surprising; and (2) it is not new. The combination of poverty, overcrowding, and HIV, particularly in high HIV prevalence countries in Africa, has led to dramatic increases in TB infection. Beginning in the 1990s, the number of TB cases exceeded the capacity of poorly-financed, understaffed TB control programs to deliver effective TB management. Drug-resistant TB is the direct result of improperly-implemented TB control programs. This is why there is a saying in TB circles that poor TB treatment is worse than no treatment at all.

On an individual patient level, drug resistance can develop when someone is infected with an already-resistant organism. [It also can develop if a person infected with TB and the disease progresses to active TB, which can happen very quickly among people who are immuno-compromised.] This is what has happened in the well-publicized outbreak in South Africa. Another way to develop drug-resistant TB is through inadequate TB treatment, or by not completing a full course of TB therapy. The more this happens, the more TB drug-resistance will develop. We have

seen the same problem with resistance to HIV medications when antiretroviral treatment is improperly prescribed or taken.

The implications of MDR- and XDR-TB, particularly for people with HIV, are serious. Most cases of TB are drug-sensitive and can be cured in someone with or without HIV infection after six months of treatment and for just a few hundred dollars. However, people with MDR-TB have a much poorer prognosis, requiring as much as 18 months of treatment, and costing many thousands of dollars. When the second-line drugs for MDR-TB are misused or mismanaged and therefore also become ineffective, XDR-TB can develop. Because XDR-TB is resistant to both first- and three of the six classes of second-line drugs, it is—for the time being at least—almost untreatable.

There has been growing concern recently about the incidence of drug-resistant TB, and we *should* be concerned. As cited in the new WHO Fourth Global Drug Resistance Report being launched yesterday in Washington and Brussels, there are an estimated 500,000 cases of MDR-TB per year globally resulting in 110,000 deaths. Data on the true extent to which XDR-TB in high-burden countries are generally unavailable due to inadequate lab capacity for diagnosis and surveillance. However, the fact that XDR-TB has now been detected in 45 countries is of particular concern to us because it is almost universally fatal to people who are HIV-positive.

DRUG-RESISTANT TB AND SUB-SAHARA AFRICA

The explosive potential of XDR-TB in settings of high HIV prevalence, such as sub-Saharan Africa, has been well documented. In the U.S. during the early 1990s, we saw numerous outbreaks of MDR-TB in people with HIV/AIDS, but drug-resistant TB has not been seen among HIV-positive people in sub-Saharan Africa until recently. To date, little surveillance data have been available from sub-Saharan Africa on MDR- and XDR-TB, but it appears that new cases may be rapidly increasing. The recently-reported outbreak of XDR-TB in South Africa is especially troubling. It appears that people with MDR-TB had received inadequate treatment and developed XDR-TB. They then subsequently spread their XDR-TB to people with HIV/AIDS in the community or in the local hospital. Because their immune systems were so weak, the people with HIV/AIDS rapidly developed XDR-TB and the consequences have been devastating—52 out of 53 XDR-TB patients in the original report have died. Of these, 44 patients had been tested for HIV, and all were positive. USG agencies, including HHS/CDC and USAID, along with the WHO and local authorities, took the lead in alerting the world to this potential threat.

ADDRESSING HIV AND DRUG-RESISTANT TB

PEPFAR-supported ARV programs have not reported a decline in the uptake of ART or changes in patient outcomes or non-attendance in care settings due to concerns about transmission of drug-resistant TB. However, given the importance of drug-resistant TB to HIV programs, guidance on TB/HIV activities supported by PEPFAR has been included in our technical guidance since 2004. In response to the XDR-TB outbreak in South Africa, PEPFAR has alerted all focus countries to the problem, and we have advised them to take it into account during the development of their Country Operational Plans, in partnership with national TB and HIV control programs. Teams of epidemiologists, laboratory scientists, and environmental engineers have been dispatched to a range of countries to develop response plans, conduct local assessments and training, and support implementation. Six teams of USG staff along with local staff from TB and HIV control programs in focus countries (Kenya, Rwanda, Ethiopia, Zambia, Namibia, and South Africa) were brought to Washington in March 2007, in collaboration with the WHO and the Bill and Melinda Gates Foundation, to develop accelerated TB/HIV plans. These plans helped define priority actions for integration into PEPFAR operational plans.

PEPFAR recognizes the significance of these dual epidemics and the danger they pose for societies worldwide, particularly in settings of high HIV prevalence, and as mentioned earlier, this is why our support for TB/HIV has increased *five-fold* in just three years—from \$26 million to \$131 million, from fiscal year 2005 to fiscal year 2007. As of September 2007, PEPFAR had supported care for approximately more than 367,000 TB/HIV co-infected people in the focus countries.

LEVERAGING MULTINATIONAL PARTNERS

Collaboration among USG agencies, including those working domestically, has been strengthened—as have PEPFAR's ties with our multilateral partners, including the WHO and the Global Fund to Fight AIDS, Tuberculosis and Malaria. Such collaborations are essential for mounting an effective response.

Our in-country partnerships include leveraging PEPFAR resources to amplify the effects of other global health initiatives, especially the Global Fund. The USG remains the largest contributor to the Global Fund. Of the approximately \$3.5 billion the USG has contributed to date 17% or \$595 million is being used to prevent and treat TB. Through PEPFAR, the USG has provided approximately one-third of the Fund's resources—and through 2007, the Global Fund will have committed \$1.4 billion to TB grants.

To date the Global Fund has approved *153 TB grants in 106 countries for a total of \$2.2 billion*. Moreover, the Global Fund reports remarkable results achieved from its financing of TB programs: *more than 3.3 million people with TB have been treated under DOTS with Global Fund support*. According to the Global Fund's primary recipients, approximately 9,700 of those people are being treated for MDR-TB.

Much of the Global Fund's success comes as a result of its focus on the expansion of DOTS programs, leveraging efforts of the TB community to develop a consistent and comprehensive strategy for TB control.

Global Fund TB grants also benefit from technical assistance from USAID as well as major partners like the Stop TB Partnership and WHO which provide in-country support to Global Fund grants.

The Global Fund has played a critical role in increasing the availability of MDR-TB drugs in resource-poor settings. In several countries, Global Fund TB financing has led to ground-breaking progress in the scale up of DOTS programs and the roll out of MDR-TB treatment. To date, Global Fund has committed approximately \$750 million dollars to fight MDR-TB.

In addition, many African countries can only now address the issue of MDR-TB thanks to funding for the expensive drugs needed through Global Fund grants.

The Emergency Plan also provides support for the WHO (both the STOP TB and HIV Departments) as well as the Green Light Committee for multi-drug resistant TB, which supports a variety of interventions aimed at strengthening TB control as well as preventing, detecting, and treating drug-resistant TB. Funding for technical assistance supports countries' ability to develop applications to the Green Light Committee and supports country programs to improve their capacity to provide treatment for MDR-TB. Some of the U.S. funding for the Green Light Committee specifically supports provision of technical assistance to Global Fund grants that treat MDR-TB. We also work with the World Bank, UNAIDS, the International Union Against TB and Lung Disease, and the private sector.

EFFICACY AND INVESTMENT OF PEPFAR PROGRAMMING

Addressing HIV/TB and drug-resistant TB is particularly challenging—especially in impoverished settings that are heavily impacted by HIV/AIDS. In sub-Saharan Africa and elsewhere, TB control programs are already overburdened and unable to deal with the emerging threat of drug-resistant TB.

The first step in accelerating TB/HIV collaborative activities and preventing the emergence of drug-resistant TB is to strengthen weak and struggling TB programs. For years, TB programs have been under-resourced and they now face incredible challenges in delivering care to thousands of TB patients, many of whom also have HIV. There are a number of essential components for a strong TB program. Through our focus on supporting and building host country capacity, PEPFAR is focusing on a few of the most important elements.

Laboratories are the most important but weakest link in the fight against TB/HIV. The diagnosis and the provision of high-quality care depend on an efficient public health lab network. International recommendations for diagnosing TB have changed and now include sophisticated investigations such as culture, and effective high-quality microscopy, including fluorescent microscopy. All this requires an effective and efficient laboratory system. The emergence of XDR-TB has further highlighted the need for strong lab systems. Finally, lab support is essential for the delivery of high-quality HIV testing and treatment services. PEPFAR is working closely with host country partners to ensure the establishment of well-functioning public health laboratory networks to diagnose and manage TB among people living with HIV/AIDS.

Despite being one of the 12 WHO-recommended collaborative TB/HIV activities, TB infection control has been heretofore neglected. Given the recent emergence of XDR-TB and increasing evidence of infection risk among not only HIV-infected people but also among health care workers, it is becoming clear that countries must develop the capacity to provide appropriate care and treatment for large numbers of co-infected people. Whether it is drug-resistant or not, TB is an airborne, potentially deadly disease. PEPFAR is mobilizing our resources to meet this challenge head-on, so that health care facilities do not become "amplifiers" of the TB epidemic.

An old public health axiom is “what is measured is done.” A strong HIV/TB program relies on a well-functioning monitoring and evaluation (M and E) system. M and E are critical activities, and building an effective M and E system is essential if we hope to capture what is going on in countries and use that information to inform and accelerate implementation of HIV/TB activities. PEPFAR is working closely with host countries and international partners to ensure that an effective M and E system for collaborative TB/HIV activities is central in program implementation.

In tackling the problem of HIV/TB and drug-resistant TB, a key entry point is HIV testing for TB patients. Estimates are that more than half of the people infected with TB in sub-Saharan Africa are co-infected with HIV. For example, in South Africa, 58 percent of all TB patients are HIV-positive—and in Botswana and Swaziland, 80 percent of all TB cases are co-infected. Unfortunately, by the end of 2005, only 10 percent of all TB patients throughout the African region had been tested for HIV.

However, progress is being made through PEPFAR partnerships. Through a PEPFAR-funded WHO collaboration in three countries, compelling results bear this out: in Kenya, 84 percent of TB patients were tested for HIV by the second quarter of 2007, up from 41 percent; and in Rwanda, 88 percent of TB patients were tested, up from 45 percent.

Similarly, data from Namibia indicate an increase in testing from 16 percent in 2005 to 47 percent in the first half of 2007. Data from Botswana’s national TB program suggest that 68 percent of all registered TB patients now undergo HIV testing. In some districts of Tanzania with provider-initiated HIV counseling and testing, more than 80 percent of all TB patients opt for HIV testing and learn their status.

Another goal is to ensure that eligible TB/HIV patients are placed on ART. The same PEPFAR–WHO collaboration demonstrated positive results: in Kenya, 42 percent of HIV-positive TB patients identified were started on ART by the end of 2007; in Ethiopia, 28 percent of HIV-positive TB patients received ART by mid-2007 from a baseline of 19 percent; and in Rwanda, 36 percent of HIV-positive TB patients received ART by the end 2007 from a baseline of 13 percent.

Important investments in the requisite infrastructure to scale-up HIV/TB activities are also being made. Funds have been made available for numerous PEPFAR host countries to increase access to rapid methods of diagnosing TB and detecting drug resistance. To facilitate this process, a Center for Integrated TB/HIV Lab Training has been launched in South Africa and the WHO’s Global Lab Initiative will be supported.

We know that the percentage of TB patients who are tested for HIV continues to vary widely. Often, this is a matter of logistics: even when referred, a TB patient may not go for HIV testing if the HIV counseling and testing center is not in close proximity to the TB clinic. Because of this, PEPFAR is working with partners in many countries—including Botswana, Ethiopia, Kenya, Rwanda, and Tanzania—to expand provider-initiated HIV counseling and testing services, either right in the TB clinics or nearby. We are also supporting efforts to integrate services for people living with HIV/AIDS (PLWHA). For instance, in Côte d’Ivoire, where ART programs are being decentralized, efforts are underway to co-locate TB and HIV care in the same facilities.

Diagnosing and managing TB in patients with HIV can be a challenge—but it is vital to prevent the high morbidity and mortality associated with TB.

NEXT STEPS: THE ROAD AHEAD

In partnership with host nations and the international community, PEPFAR has taken substantial steps toward combating global HIV/TB and drug resistant TB, and we will continue to do so. In 2007, we co-sponsored a meeting of the WHO’s Stop TB partnership, local Ministers of Health, and other key USG and international partners to accelerate the implementation of HIV/TB activities in Ethiopia, Kenya, Namibia, Rwanda, South Africa, and Zambia. One of our first tasks following the meeting was to work with PEPFAR missions to use additional HIV/TB resources to support host country HIV/AIDS and TB program managers to implement collaborative HIV and TB services.

Another exciting development with enormous potential for fighting TB is PEPFAR’s public-private partnership, the Phones for Health program. It joins African entrepreneurs with local NGOs and multi-national corporations to use cell phone technology to connect health systems in 10 PEPFAR-supported countries by 2010. Working closely with national Ministries of Health and global health organizations, the Phones for Health partnership develops an integrated set of standard information solutions that support the scale-up of HIV/AIDS, TB, malaria, and other infectious disease initiatives in a cost-effective manner that builds local capacity.

Moreover, PEPFAR will continue to maximize its resources with our international and country partners to support the global response in combating and ultimately conquering both HIV/AIDS and tuberculosis around the world.

PEPFAR takes the issue of MDR- and XDR-TB very seriously, and in response, have increased the Fiscal Year 2008 commitment for TB/HIV efforts to \$150 million. It is a clear priority of the Emergency Plan to increase cooperation and effective linkages between TB and HIV programs. In partnership with Congress and strong coordination within the Executive Branch, the U.S. Government and the American people are doing their part. Mr. Chairman and Ranking Member Smith, thank you again for your interest in this important issue. I look forward to your questions.

Mr. PAYNE. Let me thank all three of you for your testimony. It is encouraging when we can get our government agencies together. I know that you do cooperate so that the left hand knows what the right hand is doing.

I just wonder, Dr. Hill, the President's Fiscal Year 2009 budget justification requests \$84.5 million for TB within the global account, another \$12.5 million for TB in the Eastern European and former Soviet states account. This would actually be a significant cut from the 2008 levels of over \$160 million.

I just wonder, is there a rationale for the cut in the funding. In the light of the information provided by the WHO survey, do you think that the funds are adequate, or is there some other part of the budget perhaps that includes such funding that doesn't meet the eye in some other part of the budget? Because it does appear as though next year's budget will be requesting less.

Mr. HILL. I think if you look and compare the most recent President's request, the administration's request, it is about straight-lined with the last couple of years. In health interventions, it has often been the case that administration request levels by both Democrats and Republicans have been increased by the Congress. The Congress seems to have been for a number of years unusually sensitive with respect to health issues.

We were faced this year, as we often are, with some spending limitations that were very tough for us to negotiate through. A lot of parts of our health portfolio and other parts of the budget were going up. There were expenses elsewhere as well. We might have wanted more than we got.

I think, frankly, had the information come out from WHO a little earlier, we maybe would have been able to press for a little bit more from the administration, because it certainly justifies more money based on the recent data. It is often the case that we don't ask for as much as we need. We just have to make very difficult choices.

Mr. PAYNE. Thank you very much. Dr. Raviglione, perhaps next time you might do your budget a month earlier.

Let me just ask you again, Doctor, about the strengthening of labs in Uganda and Tanzania in order to create a lab that can serve the supranational reference lab in East Africa. I wonder what needs to happen to create such a capacity, and how long will it take, and is there any way to speed up the process?

Secondly, you mentioned that you were helping build such a lab in Benin, which of course is in West Africa, one of countries that the President recently visited, and was received very well there. We have a lab in South Africa; we are talking about developing this one in West Africa. Central Africa really is a place that has

so many problems, the CAR and Chad and all those places. Is there any thought of trying to create a lab in Central Africa also?

Mr. HILL. This is one of those areas where we coordinate quite closely with CDC and sometimes the funds go back and forth and we will transfer funds from CDC or work together very closely on where the greatest needs are. The very fact that you articulated so well that there were only six countries that reported or could report on the MDR-XDR TB indicates the more sophisticated nature of the labs that must be present to go beyond normal 48-hour sputum detection that you can do more easily.

We can, if we have the funds, get a lot of this up and going within a year. It doesn't take a long time to do. But you have to have enough money to do it, and you need to spread them out well enough. But in a way, I am a little frightened by what we will actually see when the labs are able to tell us what the situation is. I think it was mentioned earlier that we maybe knew a little bit more about Latvia and Estonia than we did other parts of the former Soviet Union. It is not necessarily the case that it was a lot worse there, but it might have been. This has clearly got to be a priority. We are going to work closely with CDC to pick the places to do it and do it in Central Africa, as well as East, West, and southern Africa.

Mr. PAYNE. At the news conference yesterday, we did mention that it was disturbing to hear from the few countries that had testing in Africa. But of course the more disturbing issue is the 45-48 countries in sub-Saharan Africa that have no way of testing and therefore the unknown is just anything you could imagine. So we really have to somehow be able to get effective testing.

Dr. GERBERDING, you mentioned that there were four new TB drugs which have entered into human clinical trials, and others that are ready for advanced pre-clinical testing. I wonder how long before the efficacy of these drugs are known. Do you know how effective they will be against MDR and XDR-TB and are there currently efforts underway to develop drugs specifically for MDR and XDR-TB?

I wonder, the old streptomycin, does that work? I know the world had run out of it just about when TB re-emerged, and once the disease was thought to be eliminated, there was therefore no business interest in developing something that wasn't going to be sold. I think they found a laboratory in a little village in France that was able to get some of the streptomycin back out.

How about the new drug? You did touch on it in your remarks. I think you said we are still far off. Could you give us a little more specifics on that?

Dr. GERBERDING. I will try to give a little bit more detail. The new drugs in the pipeline are from completely new families. And so we would expect, although we don't know yet, but we would expect these new drugs would be effective against the TB that we are concerned about today because those bacteria have never seen this class of drugs before and so presumably they will respond to it.

What we can't predict right now is, first of all, how effective will they actually be under real clinical situations. We can't know yet without doing more clinical trials how to do the new drugs because you can't just use one drug for tuberculosis, you need to use several

to reduce the chance of resistance. We don't know how they will interact with the old or other new drugs, and we don't know, very importantly, how they will interact with the AIDS drugs because a large proportion of people that we need to treat also need anti-retroviral therapy. If you have a patient with drug-resistant TB who is on anti-retroviral therapy, they may be taking 10 different medications a day, and that just creates a nightmare of drug-drug interaction. Sometimes some of the HIV drugs may interfere with absorption of the TB drugs. So you lose the effectiveness because it is not getting into the bloodstream, and so on and so forth.

So good promising drugs in the test tube and some early clinical trials that work, as I said, in the test tube. But they are really way premature in the clinical pipeline. I would like to be optimistic, but it is not something we really know right now. We would like to see lots more lanes open up for the tuberculosis so that we would have the broad set of choices that we do with other types of bacteria with less toxicity.

I could say similarly with respect to new approaches to vaccine, there are some promising ideas that are coming out of the lab, like Dr. Fouche, who is not here today, but I am sure he would be willing to say of course that would be a high area of interest for NIH. We just don't have anything that looks like a magic bullet in the short run. This problem is going faster than the drugs are developing, and the bacteria evolve much faster than our drug pipeline.

Mr. PAYNE. How about Mr. Speaker, what finally happened to him? What treatment did he get?

Dr. GERBERDING. In terms of Mr. Speaker's medical information, I really don't have it, and probably would not be privileged to report it in a public forum, given that he is a patient and that would be considered confidential medical information.

But my understanding from a public health perspective is that there is currently no indication that he is currently posing a threat to the public's health. He is not in quarantine at this point in time.

Mr. PAYNE. Thank you very much.

Finally, Ambassador Dybul, it is good to see you again. In your testimony you talk about a great deal of the activities supported by the Global Fund for AIDS, TB and malaria. As you point out, the Global Fund has approved 153 grants in 106 countries, totaling \$2.2 billion over a 5-year period. Congress approved over \$840 million to the Global Fund for this fiscal year. However, according to figures compiled by the Congressional Research Service, the administration's budget request for a contribution to the Global Fund for Fiscal Year 2009 is only \$500 million, even though we did \$840 million previously.

So I wonder once again, figures are tough when you get into the budget. Sometimes they say figures lie, but liars figure. I don't know how that works.

Dr. DYBUL. I will be careful how I answer.

Mr. PAYNE. See what category you're in. They accuse Congress of that. So we were talking about ourselves. Do you have any way to kind of give us a correct figure and in terms of support for Global Fund for providing TB treatment—we know it provides over two-thirds of the funding for TB—why would the administration advocate scaling back when we are talking about the need?

Dr. DYBUL. It is a very good question. As you know, each year we struggle together, the administration and Congress, with the correct level of funding for the Global Fund for that year. It is an increase from the President's request from last year, from \$300 million last year to \$500 million this year.

It really does come down to, as Dr. Hill pointed out, trying to decide what to do with the resources we have available. In our estimation, the bilateral program, we deal mostly with HIV/AIDS in the program I oversee, can use the money in a rapid way in this year, and we judge how much money can be used in this fiscal year by a different organization.

So in our estimation, \$500 million is the appropriate level for the Global Fund in 2009. But as in all years, we will have a back and forth and discussion with Congress and you all will come to a level. But in our estimation, that is the correct level based on our estimation of utilization of resources this year and what we can accomplish in the bilateral program, but we are very respectful and understand differing points of view.

Mr. PAYNE. I will just ask one more question because we will give our ranking member a chance to ask questions, and, believe it or not, there is supposed to be a reception here at 5:30. I am sure they don't mind waiting a little bit longer for something very important as this, because they are not going to be ready at 5:30. But we have got more important issues here.

You mentioned in your testimony about the ARVs as a powerful deterrent to the development of TB. So my question is: Is it a deterrent to MDR and XDR TB? Were the 44 patients with XDR-TB who were HIV positive in KwaZulu-Natal on the ARVs?

Dr. DYBUL. The answer unfortunately is yes and no. What drug therapies do is build a person's immune system. And one of the reasons people become more susceptible to TB is their immune system is weakened. So by boosting the immune system, as was pointed out by our WHO colleagues, there are data to show that anti-retroviral therapy does help avoid TB.

Where multidrug TB comes from is people who are insufficiently treated for their tuberculosis, for the most part, as Dr. Gerberding showed with the data from Botswana. As was pointed out, I am not aware of data that show an HIV person is necessarily more susceptible to that failure. However, as Dr. Gerberding pointed out, there are drug-to-drug interactions between HIV and TB therapies, and so we have to stage sometimes how we do the treatment.

So I don't know of data, and I would have to defer to Dr. Gerberding if she knows of data to show that MDR TB is more likely to occur in an HIV person than a negative person. But we do know TB is more likely to occur in an HIV-positive person. Anti-retroviral reduces that risk. So if you did a syllogism, you would guess that it would actually reduce the MDR TB as well. But I don't have the data to prove that to you, and I would be happy to look to see if such are available.

Dr. GERBERDING. One of the reasons there is clustering of drug-resistant TB and AIDS patients is because they are crowded together in places where they infect each other. So if you put someone in a closed hospital environment with MDR TB and you are not using the standard infection control to prevent them from infecting

others, the health care workers and the patients in that facility can pick up that drug-resistant infection even though they have never been treated with TB drugs before.

We fear that may be happening in some communities in Africa as well. Once somebody is there with drug resistance, they are not treated effectively but they are also either close to people in the health care environment or living in the same home, so they are transmitting the drug resistance to people who would not normally be at risk for it.

Mr. PAYNE. Thank you.

Mr. Smith.

Mr. SMITH. Thank you very much, Mr. Chairman. I want to thank our three very distinguished panelists for their extraordinary public service that you provide, the three of you, each and every day, not just to our own Americans but the world. It is extraordinary and very much appreciated by Members of Congress, and especially this committee and this subcommittee.

Ambassador Dybul, again I want to thank you for your role in helping craft the compromise. You talk about everyone else but you were very, very helpful and I think pivotal today and yesterday as the negotiations worked their way out in helping find solutions. So thank you for that.

You pointed out that estimates of more than half of the people infected with TB in sub-Saharan Africa are co-infected with HIV. You mentioned Botswana and Swaziland having 80 percent. You point out the good news that in Kenya 84 percent were tested, 88 percent in Rwanda, up from 45 percent. Then you point out in Kenya, again, where there has been significant new testing, 42 percent of the HIV-positive TB patients identified were started on ART by the end of 2007.

The first question is what about the other 58 percent, what are they getting, if you could?

Dr. DYBUL. The difficulty of course is all the programs are scaling up at once. So you can't manage all the problems at once. What you want to see are the trends going in the right direction. I can tell you from being in these countries, the gains in the last year are almost breathtaking. The opt-out approaches in TB clinics, I was in Tanzania 2 years ago, and people weren't really taking it seriously. I just was in Tanzania, fortunate enough to be there with President Bush and to see the incredible thanks the Africans have for what you have done and the American people have done, and it was extraordinary to me how much more people are taking seriously that opt-out testing. So the trajectory is the exact trajectory we want.

We will always be a little bit behind in terms of people who are tested and get on to treatment and also behind in our ability to track it. So some of them might be getting treatment. They might be referred to sites that we don't have monitoring capabilities. So it is going to take us time to catch up. Both those trajectories are going in the right direction. The intent is to have every person who is HIV- and TB-positive receive therapy.

Again, there is also a delay in the time frame that you begin anti-retroviral therapy. And some people are TB-positive. So you

will have an automatic delay of a couple of months when you start anti-TB therapy before you begin the anti-retroviral therapy.

Mr. SMITH. With regards to the whole issue of infection control, which you point out in your testimony, and the old adage is go to the hospital for a night and you might come out with a staph infection. The words you used, these health care facilities shouldn't become amplifiers of the TB epidemic. Could you speak to that issue?

Dr. DYBUL. I am certain you have seen them on your travels when you go into a hospital ward where you have got hundreds of people in a room and they are coughing. That is what Dr. Gerberding was talking about, one of our concerns, that when you have HIV-positive people who are immuno-compromised and in the vicinity of MDR TB, it may be more transmissible than we would see otherwise. Infection control is a high priority, but it is often the case that it is not the highest priority for a local health organization, the government or otherwise. So it actually is working through our implementers, and particularly CDC, who is very strong on infection control and also USAID, to build those capacities up. It is not just an issue for TB, it is for reusing needles that could transmit HIV/AIDS, using gloves so blood doesn't spill. These are all things that are being developed.

I have to say again, if you look at the trajectory and what has happened over the last couple years, it is rather exciting to see these technologies and things being adopted and being put into hospitals. We have the same thing in United States. When Dr. Gerberding and I were medical students and residents, we were doing the same thing. I wasn't wearing gloves and I bet Dr. Gerberding often wasn't, and we had different types of needles and we would recap them and do things that we would never do today.

So it is a learning curve but we have great implementing agencies that are focusing on it. But it will take some time.

Mr. SMITH. On the issue of laboratories, which you call the weakest link in the fight against TB-HIV/AIDS, how many laboratories are there and what is the estimated cost of the lab? Are there scaled-down versions, the Cadillac of laboratories? Could you give us the range on that?

Dr. DYBUL. I will defer to Dr. Gerberding on that because they are really the premier laboratory workers globally and much of the work we do in laboratories is to support the work that Dr. Gerberding's institution does. But also USAID. I was just in Lesotho, the lab that was just referenced. I think they told me it was a couple hundred-thousand dollars without equipment. When you added equipment, I am guessing here, but I think I remember them saying \$1 million, or something thereabouts. It was a small lab. They are building a bigger national labor.

But there is a big range here, and you can start smaller and grow larger. But to have the full capacity, we are going to need the full range. You can't do all small laboratories.

Mr. SMITH. Is there also the capacity of people?

Dr. DYBUL. Absolutely. Dr. Gerberding and Dr. Hill can probably give a much more intelligent answer than I could.

Dr. GERBERDING. First of all, this is a generic priority for our international health work, whether it is influenza or global disease detection, malaria, TB, or even HIV. One of the principles that we

are working toward is to have integrated labs so that we don't build a malaria lab and then build a TB lab. We want integrated at least HIV, TB and malaria work to be done in the same place since these diseases track together. Just as there are in the United States, there are levels of capability in the laboratory network.

So what we really want is at the point of care where actually the patient, where the doctors and the patients are interacting, that we have tests that can be done right there at the point of care. So rapid diagnostic tests that are easily kitted. There are some of those capabilities now beginning to come online with the support of some private partners. But to get the kind of lab that would be doing drug susceptibility testing, which is a more complicated procedure, is not a huge investment because there are ways to screen for resistance to one of the drugs that is a marker for all of the other potential resistances. So if a bacteria is INH-resistant, you want to get that particular bacteria some place where you can study it in a more reference laboratory in more detail. But if the bacteria tests negative for that resistance, the chance of it being resistant to anything else is slim to none, and therefore you can usually use the traditional treatment regimens.

So that is the approach that we are taking, inexpensive at the point of care but backing that up with regional and national capabilities that can do the kind of gold standard tests that we are talking about. We are very impressed with the success of the regional center for training where people are coming in from all over southern Africa to train in the ability to do these kind of tests in their own countries. So it is a huge, successful model.

Mr. HILL. The only thing I would add is that this is a place where the niches of the agencies really make a difference. I mean you look at the USAID pie chart of USAID TB money, you will see money there for research. It is not a lot of money. It is several million dollars. But the kind of research we fund tends to be the 3 to 5 years after the drugs are ready to be piloted out in the field and we will be there when it is pretty close to implementation. We may give some money for labs, et cetera, but the real strength of USAID is in primary health care, which often has to do with information and has to do with communication. It has to do with developing protocols and training health workers to do things. You do that out in the rural areas where there are not going to be in our lifetime the hospitals that you really want, but there are things you can do that make a difference. That is the strength that we try to bring to the table. Even though we will fund some of these other things, what we often focus on is how to hit the masses where those other interventions will not yet make much difference.

Mr. SMITH. Ambassador Dybul, you mentioned that to date little surveillance data has been available from sub-Saharan Africa on MDR and XDR TB, but it appears new cases may be rapidly increasing. In gathering that data, has there been any kind of a qualitative analysis about how hard it is to get from war-torn areas or areas, for example, DR Congo is not a PEPFAR-focus country. It has got a million or so HIV-positive individuals, a country of 80 million people. I mean the roads there are incredibly hard to navigate. I met with a farmer out of Kinshasa along with my colleague Mr. Puello who said he lives six miles out of Kinshasa and he can't

get his crops to market because of the roads. In Goma I thought I was on the Moon. I mean the roads were so despicable. Obviously it is war-torn with Tutsis, Hutus, you know, General Nukunda. But the whole problem of the peace conference, Darfur. How do you get data out of there? People could be rife with TB, and very little is being done by way of intervention.

Dr. DYBUL. There is no question about that. It is really not just for TB and it is not just for surveillance, it is surveillance, services, everything. I think one of the more exciting things is because we are supporting local capacity development, building the capacity of faith, community-based, government, nongovernmental organizations in-country, one of the more exciting things is not only the bad examples where we don't have good estimates for HIV rates because we can't do the surveillance, or TB rates, is you can do a lot if you build that local capacity, even when war and conflict come.

So in Cote D'Ivoire and Haiti, during the worst of the years, over the last couple of years, there has been a significant enhancement in services for HIV, a significant enhancement of our ability to monitor and evaluate, even though bad things were happening. So it is very hard, but it takes a lot of work. One of our priorities now is to focus on post-conflict steps so we can get in rapidly, do assessments of TB and HIV/AIDS, and see what services can be provided. Unfortunately, you put your finger on something which is a very difficult thing where there is conflict. You promote disease, including TB and HIV, and it is hard to measure, and then you don't have services. It is something we are all working on together to build that local capacity.

Mr. SMITH OF NEW JERSEY. Three final questions.

First, Dr. Gerberding, on the incentivizing of the pharmaceuticals companies to undertake R&D to find breakthroughs for new drugs, what are your recommendations on incentivizing?

And secondly, because we are going to run out of time unfortunately, the WHO report indicates that 50 percent of the MDR-TB is present in China and India. Is there a breakout between those two countries? And what is being done there?

And thirdly, if you could, Dr. Hill, you mentioned that PEPFAR funds from USAID support the Green Light Committee to provide technical assistance to the Global Fund grants, which includes preparation for GLC country applications. Are faith-based organizations getting any tactical support so that they can—we know that it has been a dismal failure, and maybe it is turning around at the Global Fund, that faith-based organizations usually don't even get through the door. And are they getting technical assistance on the lab issue?

Dr. GERBERDING. I will start and try to be brief. The issue of incentivizing interest in drug development or vaccine development, if you will, for this is something that is really a government, private sector, and NGO partnership approach. And I think we need to really have some serious conversations, how far the government should go to have more input into this process.

And we have seen what happens with government taking on an issue like this through the barter process. And in the context of a global health threat, I think it is at least worth having that conversation here too.

With respect to India and China, even if the proportion of drug resistance is extremely low in India and China, the number of people there is so huge that a small percentage of 1 billion is still a lot of people. And so we recognize that both India and China are countries where the citizens have a very high rate of exposure to tuberculosis, but there are also countries where drug treatment is available. And one of the ironies about drug resistance is that if you have no drugs, you have no drug resistance. When you start to have drugs, but you don't have a program that really completely supports effective observed therapy, that is where resistance occurs, because you have got incomplete treatment. And in some parts of both of those countries, those are real challenges.

So I don't have the exact breakout, but I am sure our colleagues from WHO can get that information to you and we can provide some more specificity.

Mr. DYBUL. Very quickly, just to point out on the India point. I think you are right to mention countries with such a large population. You mentioned China, too. There are a variety of reasons we don't do much in China. They have their own resources, et cetera. We sometimes provide TA.

But the number one country for 2008 in terms of the total amount of money that we are likely to spend is actually India for U.S. Aid on TB. Now, there is such a large number of people, that if anything goes wrong there, it is going to have a huge impact. And you will often find that our top 11 list includes places like South Africa and Russia, Indonesia, Nigeria, Bangladesh, places with very dense populations. And so that is where you have to focus.

On the global front on technical assistance and who receives it, it is a specific policy of USAID in all things, both HIV and TB, to provide technical assistance to leverage the 30 percent of the Global Fund money that comes through the United States in the first place. So much of what the Global Fund does is because of the contribution of the United States. But we facilitate the effectiveness of those grants by helping them write good grants and then to perform on those grants.

With respect to USAID and the faith-based groups, we do bring to the table the community in faith-based groups, as you know. Global Fund did not have as good a record on that in the initial years, no question about it. That was brought to their attention for several years. And I see a turnaround in the last few months.

There was a big event here not so long ago where they brought the faith-based groups in themselves, they talked about they wanted to be more—they confessed that they hadn't done as well as they should have, they wanted to do better, and they had a handbook on how to do it. And so I think we can see progress there, partially because we have pushed on that front.

Mr. SMITH OF NEW JERSEY. Thank you for pushing. Thank you, Mr. Chairman.

Mr. PAYNE. Thank you very much.

Well, that will conclude our hearing.

Let me ask technical things. One, I ask unanimous consent that the following submissions be a part of this afternoon's hearing records: A statement from the Tuberculosis Legislative Coalition;

and a statement from the American Public Health Association. Hearing no objections, it will be in order.

Let me thank the witnesses again, and certainly Dr. Raviglione for coming all the way here. I think your press conference yesterday was very important.

This hearing is very important and it is just sort of a home run, I guess, that we were able to pass out of committee the PEPFAR program at a \$50 billion target. And it certainly would have been impossible without the cooperation from Ms. Ros-Lehtinen and Mr. Smith because, as you can imagine, there was one or two pieces of opposition to it. But my friend to the right, although he is to my left, really helped out to get this passed.

We will adjourn the meeting so Mr. Manzullo can have his reception. Thank you.

[Whereupon, at 5:20 p.m., the subcommittee was adjourned.]

A P P E N D I X



MATERIAL SUBMITTED FOR THE HEARING RECORD

**Statement for the Record for the House Africa & Global Health
Subcommittee Hearing:
Multidrug Resistant Tuberculosis: Assessing the U.S. Response to an
Emerging Global Threat**

February 27, 2008

On behalf of the undersigned organizations:
Aeras Global TB Vaccine Foundation
American Lung Association
American Public Health Association
American Thoracic Society
Association of Public Health Laboratories
Families USA Global Health Initiative
Global Alliance for TB Drug Development
Global Health Council
RESULTS
Treatment Action Group

We would like to thank Chairman Payne for holding this important hearing and we appreciate the opportunity to submit a statement for the record. We applaud the World Health Organization (WHO) for the release of its new analysis of the prevalence of drug resistant TB globally, *Anti-Tuberculosis Drug Resistance in the World*. This important report provides the data necessary to assess the scale of the drug resistant TB crisis and prepare an appropriate global response. Recent publicized cases of drug resistant TB in the U.S. have demonstrated the ease with which this disease travels across borders and serves as a timely warning of the public health preparedness challenges we face in controlling TB globally in all forms.

Introduction

Tuberculosis (TB) is the second-leading infectious disease killer in the world, taking 1.6 million lives per year. Currently, about a third of the world's population is infected with the TB bacterium.ⁱ The disease is predicted to kill millions more people in the next decade. TB is a leading global killer of women of reproductive age and the leading cause of death among people with HIV/AIDS.

The rise in HIV infection levels and the neglect of TB control programs have caused a global resurgence of TB. Drug-resistant strains of TB, including multi-drug resistant (MDR) TB and extensively drug-resistant, (XDR)TB, have emerged and are spreading. While most TB prevalent today is a preventable and curable disease when international prevention and treatment guidelines are used, many parts of the world, such as Africa, are struggling to implement them, giving rise to more drug resistant TB, and, increasingly, XDR-TB.

TB Has Not Been Controlled in the U.S.

In the U.S., many people think tuberculosis (TB) is a disease of the past. This is untrue. In the early 1990's New York City had a resurgence of TB that cost the city over \$1 billion. The 2000 Institute of Medicine (IOM) report, found that the resurgence of TB in the U.S. between 1985 and 1992 was due, in large part, to funding reductions and concluded that, with proper funding, organization of prevention and control activities, and research and development of new tools, TB could be eliminated as a public health problem in the U.S.

TB occurs among foreign-born individuals over nine times as frequently as among people born in the United States (according to the latest Centers for Disease Control and Prevention figures). Minorities are also disproportionately affected by TB. According to the CDC, although the overall rate of new TB cases is declining in the U.S., the annual rate of decrease in TB cases has slowed significantly, from about 6.6 percent (1993 to 2002) to 3.1 percent currently (2003 – 2006).ⁱⁱ

We support enactment of the Comprehensive TB Elimination Act, sponsored by Reps. Green (D-TX) and Wilson (R-NM) and Sens. Brown (D-OH) and Hutchison (R-TX), and the Stop TB Now Act, sponsored by Reps. Engel (D-NY), Wilson (R-NM) and Sens. Boxer (D-CA) and Smith (R-OR), to provide full funding for TB control as

recommended by the Institute of Medicine 2000 report, *Ending Neglect: The Elimination of Tuberculosis in the U.S.* To strengthen domestic TB control, including efforts to prevent the spread of XDR TB in the U.S., we recommend a funding level of \$300 million in Fiscal Year 2009 for the Centers for Disease Control's Division of Tuberculosis Elimination program.

Drug Resistant TB as a Global Health Crisis

MDR-TB is TB that is resistant to at least two of the best anti-TB drugs, isoniazid and rifampicin. These drugs are considered first-line drugs. MDR-TB has been identified in all regions of the world, including the U.S. XDR-TB is resistant to two main first-line drugs and to at least two of the six classes of second-line drugs. This makes the strain very difficult and costly to treat. Because it is resistant to many of the drugs used to treat TB, XDR-TB has an extremely high fatality rate. In an outbreak in South Africa from late 2005 until early 2006, XDR TB killed 52 out of 53 infected patients.ⁱⁱⁱ All of those who were tested were co-infected with HIV. The convergence of several factors threatens to result in XDR TB occurring on a much broader scale. The major factors include inadequate attention to and funding for basic TB control measures in high TB burden, resource-limited settings, which also have high HIV prevalence, and the lack of investment in new drugs, diagnostics and vaccines for TB.

Resources Needed to Address TB

Currently, the extent of the global drug resistant TB burden remains unknown. A global supranational laboratory capacity must be built to enable drug susceptibility testing in all parts of the world. Immediate interventions require outbreak and cluster investigations to identify and interrupt the chains of transmission, and implementation of infection control precautions to protect healthcare workers, other patients, and their families. New rapid diagnostic tests must be deployed and promising new drugs against TB must be promptly evaluated for efficacy and safety, especially in populations with virtually untreatable forms of XDR TB. Further investment must be made in developing new TB vaccines that will protect against all strains of TB, including those that are MDR and XDR. Drug resistant TB develops as a result of poor basic TB control. Thus one of the best ways to prevent outbreaks of drug resistant strains is to reinvest in basic TB control programs.

The following specific resources are required to address the current unmet domestic and global needs:

- 1) Build supranational TB reference laboratory capacity for rapid surveys to evaluate susceptibility to first- and second-line anti-TB drugs and genotype isolates to guide planning for the global response.
- 2) Improve the domestic and global preparedness and outbreak response capacity, and options for effective treatment of affected persons. This includes providing travel and technical support for subject-matter experts to identify and investigate outbreaks; building capacity to institute infection control measures in affected areas - with emphasis on healthcare settings where vulnerable HIV-infected persons congregate; and improving

the use of anti-TB drugs and adherence to measures that prevent the development of drug resistance.

3) Accelerate field-testing of new methods to screen for drug resistance and for real-time culture and drug-susceptibility testing of clinical isolates from TB patients.

4) Improve the capacity to conduct clinical research to evaluate the efficacy and safety of new promising compounds against drug-resistant forms of tuberculosis; and develop new drugs to target resistant microbes that can be safely used in conjunction with antiretroviral therapy.

Need for New TB Tools

New research on diagnostic, treatment and prevention tools is urgently needed. The standard method of diagnosing TB was developed 100 years ago and fails to adequately detect TB in children and those co-infected with HIV/AIDS. Moreover, the newest class of drugs to treat TB is over 40 years old. The current TB vaccine, BCG, provides some protection against severe forms of TB in children, but is unreliable against pulmonary TB, which accounts for most of the worldwide disease burden. We support enactment of the Comprehensive TB Elimination Act, S.1551/H.R. 1532, sponsored by Sens. Brown (D-OH) and Hutchison (R-TX) and Reps. Green (D-TX), Wilson (R-NM) and the Stop TB Now Act, S. 968/H.R. 1567, sponsored by Sens. Boxer (D-CA) and Smith (R-OR) and Reps. Engel (D-NY), Wilson (R-NM), which will both expand research efforts into new tools to combat TB. The bill includes authorization for research at the Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH) into new TB drugs, diagnostics and vaccines.

Global TB Control Efforts

The World Health Organization declared TB a global health emergency in 1993. The Stop TB Partnership released the Global Plan to Stop Tuberculosis 2006-2015 at the World Economic Forum in January 2006. If all elements of the plan are implemented, an estimated 14 million lives will be saved between 2006 and 2015. The Global Plan estimates that \$56 billion is needed over ten years to halve the TB deaths and disease burden by 2015. This includes \$47 billion for country needs and \$9 billion for research and development into new TB diagnostics, drugs and an effective vaccine.

The components of the plan and corresponding implementation strategies are as follows:

1. Pursue high-quality directly-observed treatment strategy (DOTS) expansion and enhancement through:

- a) Political commitment with increased and sustained financing
- b) Case detection through quality-assured bacteriology
- c) Standardized treatment, using internationally recommended drug regimens and quality-assured drugs with appropriate supervision and patient support
- d) Monitoring and evaluation system, and impact measurement

2. Address TB/HIV, MDR-TB and other challenges

- a) Implement collaborative TB/HIV activities
- b) Prevent and control MDR-TB
- c) Address prisoners, refugees and other high-risk groups and situations

3. Contribute to health system strengthening

- a) Actively participate in efforts to improve system-wide policy, human resources, financing, management, service delivery, and information systems.
- b) Share innovations that strengthen systems, including the Practical Approach to Lung Health (PAL)
- c) Adopt innovations from other fields

4. Engage all health care providers

- a) Public-public and public-private mix (PPM) approaches
- b) Implement the International Standards for Tuberculosis Care (ISTC)

5. Empower people with TB, and communities

- a) Advocacy, communication, and social mobilization
- b) Community participation in TB care
- c) Implement the Patient's Charter for Tuberculosis Care

6. Enable and promote research

- a) Program-based operational research
- b) Research to develop new diagnostic tools, drugs and vaccines

Recommendations

The best way to prevent the future development of drug-resistant strains of tuberculosis is through establishing and supporting effective tuberculosis control programs in the U.S. and globally. As we provide resources to respond specifically to the XDR TB emergency, we must keep in mind the ongoing need for consistent support of global TB control programs through the U.S. Agency for International Development (USAID) and the CDC.

To increase USAID's resources and authority to combat TB globally, we support enactment of the Stop TB Now Act, S. 968/H.R. 1567, sponsored by Sens. Boxer (D-CA) and Smith (R-OR), and Reps. Engel (D-NY) and Wilson (R-NM) and the House legislation sponsored by Rep. Lantos (D-CA), the United States Global Leadership Against HIV/AIDS, Tuberculosis and Malaria Act, that the Stop TB Now Act has been incorporated into. As authorized in the Stop TB Now Act, we recommend a funding level of \$450 million for USAID's global TB program and \$100 million for CDC's global TB activities in Fiscal Year 2009. We recommend an appropriation of \$400 million in Fiscal Year 2009 for the Global Fund to Fight AIDS, TB and Malaria. Enactment of the global TB control legislation, the Stop TB Now Act and the domestic TB control legislation, the Comprehensive TB Elimination Act, will provide researchers and public health officials the tools needed to help eliminate TB in the U.S. and around the world.

We appreciate the opportunity to submit this statement for the record.

ⁱ Tuberculosis. World Health Organization (WHO) Factsheet No. 104, March 2006.

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

ⁱⁱⁱ "Virulent TB in South Africa May Imperil Millions." New York Times. 28 Jan. 2007. 21 Mar. 2007.



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Statement of the American Public Health Association
 “Multidrug Resistant Tuberculosis:
 Assessing the U.S. Response to an Emerging Global Threat”
 House Committee on Foreign Affairs
 Subcommittee on Africa and Global Health
 Submitted for the Record
 February 27, 2008

The American Public Health Association (APHA) is the oldest and most diverse organization of public health professionals in the world. APHA represents a broad array of health officials, educators, environmentalists, policy-makers, and health providers at all levels working both within and outside government organizations and education institutions. We are pleased to submit our views on global control of tuberculosis (TB) and drug resistant TB.

Many countries have contributed to global TB control with positive results including noticeable economic benefits. However, greater support for global TB control is urgently needed for several reasons: the number of TB cases is growing dramatically, TB inflicts a considerable economic burden on families and government budgets, strains of multidrug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) are emerging and spreading internationally, and TB has become one of the leading causes of death among people living with HIV/AIDS.

In 2005, there were 8.8 million new cases and 1.6 million deaths attributable to TB. Without treatment, two-thirds of infected individuals die within five to eight years, most of which die within 18 months of being infected. The death rate is significantly higher for cases of MDR-TB and XDR-TB. Even though TB can usually be cured through a six-month antibiotics regimen, it remains the number two cause of adult deaths among infectious diseases worldwide, second only to HIV/AIDS.

TB is strongly linked to poverty. Most TB cases occur among working-age adults, killing them or making them unable to work. Children also are vulnerable and TB could force them out of school, limiting their future employment prospects. According to the World Bank, the economic cost of TB-related deaths in sub-Saharan Africa from 2006-2015 is expected to be about \$519 billion without effective TB control. If these countries are able to halve the prevalence and death rates by 2015 relative to 1990 figures, as prescribed in the World Health Organization’s Stop TB Strategy, they could obtain about a nine-fold return on investments in TB diagnosis, treatment and control. Countries like China and India, which together account for 36 percent of all estimated new TB cases each year, could reap even greater economic returns.

Drug resistant TB represents a serious challenge to global TB control and is associated with worse treatment outcomes. MDR-TB develops when anti-TB drugs are misused, become ineffective and must be treated with second-line drugs, which are more expensive and have more side-effects.

XDR-TB can develop when these second-line drugs are also misused and treatment options are seriously limited.

Today's global economy provides TB and drug resistant TB ample opportunities to spread among populations and across borders. Elimination of TB in the United States is dependent on control of the disease in developing countries. In addition, TB treatment and program costs abroad are significantly cheaper making investing in global TB control a cost-effective strategy to reduce TB cases domestically.

Finally, TB is among the leading killers of people living with HIV/AIDS causing 12 percent of deaths globally and up to half in some settings. According to the World Health Organization, about 630,000 new TB/HIV cases were diagnosed in 2005. However, TB in people living with HIV/AIDS is curable and treatment can prolong and improve their quality of life.

We support a strong U.S. commitment to international efforts to control TB including participation and support of the Stop TB Partnership and the Stop TB Strategy lead by the World Health Organization. The Stop TB Partnership is a network of over 500 international public and private organizations working to eliminate TB. The Stop TB Strategy builds on the Directly Observed Treatment Short-course (DOTS) program, which is one of the most cost-effective health interventions available today, and works to implement TB and HIV collaborative activities; prevent and control drug resistant TB; strengthen health systems; disseminate the International Standards for Tuberculosis Care; empower individuals with TB and communities; and support research.

In addition, we support programs at the Centers for Disease Control and Prevention that assist countries with a high burden of TB. These programs help implement the TB control strategies recommended by the World Health Organization and conduct clinical and operational research to identify and evaluate new diagnostics, treatments and strategies.

We thank the House Committee on Foreign Affairs, Subcommittee on African and Global Health for its commitment to the global effort to combat TB and the opportunity to present our views on this serious public health threat.