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DRUG-RESISTANT TUBERCULOSIS: THE NEXT GLOBAL HEALTH CRISIS?

BRIEFING AND HEARING

BEFORE THE

SUBCOMMITTEE ON AFRICA, GLOBAL HEALTH, GLOBAL HUMAN RIGHTS, AND INTERNATIONAL ORGANIZATIONS

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DRUG-RESISTANT TUBERCULOSIS: THE NEXT GLOBAL HEALTH CRISIS?

TUESDAY, DECEMBER 8, 2015

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

The subcommittee met, pursuant to notice, at 2:01 p.m., in room 2200 Rayburn House Office Building, Hon. Christopher H. Smith (chairman of the subcommittee) presiding.

Mr. SMITH. Our briefing and hearing today is extremely urgent, focused on addressing what may very well be the next global health crisis: drug-resistant tuberculosis.

Just as Ebola surprised many at the ferocity with which it spread, all of us must be concerned that the world is not currently prepared to meet the threat from this highly contagious airborne disease which killed 1½ million people last year and that translates to about 4,000 people a day—4,000 lives that ended prematurely including many young children.

The World Health Organization released its global tuberculosis report just over a month ago and appealed to the world to beef up efforts to combat TB, and yesterday in Cape Town, South Africa the International Union Against Tuberculosis and Lung Disease concluded its annual meeting as they gathered experts in fighting TB through all of the world.

There are positive signs showing—these are positive signs showing that the global community continuous to surge toward ending TB by 2035 or sooner.

While most TB is curable if diagnosed patients strictly adhere to a treatment regimen, some 6 million new cases of TB were reported to the WHO in 2014.

However, it is likely the number is far higher. Some put it at approximately 9.6 million people. These individuals need to be diagnosed with a diagnostic that is fast and reliable and able to detect drug resistance and treated so that they can lead healthy and productive lives.

On a myriad of the fronts there is reason for hope. For example, the Xpert MTB/RIF can diagnose TB and resistance to rifampicin within 2 hours and Dr. Frieden, in his testimony, elaborates on that—which is an amazing breakthrough.

As Dr. Frieden will testify today, this new diagnostic holds great promise, enabling rapid detection of drug resistance and the U.S. Government has led the global effort to scale up access to this test.

The increase in the proportion of drug-resistant TB cases diagnosed and started on treatment over the past several years is largely attributable to this kind of test.

Yet, the tragic fact remains that some 480,000 new cases—of hard to treat cases of multi-drug resistant TB, a disease which often—far too often—hits the poorest of the poor—are estimated to have occurred in 2014.

Yet, only about 25 percent of those cases, or 123,000 individuals, were detected and reported, leaving a whopping 75 percent undetected and untreated.

Given the means at which TB can spread through the air, especially through coughing, and the fact that people with weakened immune systems are more susceptible, one can see how left untreated MDR–TB and its even more pernicious cousin, XDR—or extensively drug-resistant TB—can be absolutely catastrophic to individuals and wreak havoc on public health and public health systems.

To illustrate how fragile health systems can be overrun, a course of treatment for normal drug-susceptible TB costs, roughly, between $100 and $500, depending on the country. For MDR–TB, the cost is roughly $5,000 to $100,000 and some put the numbers at far, far higher than that.

To respond fully to the TB crisis, WHO estimates that some $8 billion per year is needed. Unfortunately, there is a global budget shortfall of about $1.4 billion.

We need to lead not only in terms of providing funding but also in terms of encouraging others—other countries but also the private sector and foundations in meeting this need by closing that gap.

Now is the time for a significantly enhanced response to build on the tremendous work that people like Dr. Goosby and others have been doing.

A sustained focus on tuberculosis prevention today will save lives and many tomorrow, helping people the world over as well as protecting their homelands from what otherwise could be a global pandemic.

Our briefer and two witnesses today are extraordinary leaders in the health field and experts on TB. They, like many others on the subcommittee, believe we can at least mitigate TB in the short term and eliminate this deadly infectious disease by 2035, just as the global community successfully fought polio and other debilitating and deadly diseases.

It takes political will, however, and an investment of resources that will pay dividends for healthier people in the long run.

The subcommittee will continue to work hard in combating TB along with members of the House Tuberculosis Elimination Caucus, whose co-chair, Eliot Engel, will be here shortly to join us. I would like to now yield to Dr. Bera for any comments he might have.

Mr. BERA. Thank you, Mr. Chairman, and thanks for convening this briefing and hearing and I want to thank the witnesses as

well—a great panel. I will keep my comments short so we can hear from the witnesses.

But as a physician and public health expert, the scourge of tuberculosis is one that we constantly have to be vigilant on and, certainly, I do worry that we are falling behind, given our arsenal and what medications we have and, certainly, having multi-drug resistant tuberculosis emerging and extremely multi-drug resistant tuberculosis is a global challenge.

It is not just limited to developing countries. As we think about the interconnected nature of the world, we clearly have to be concerned about it, combating extremely drug-resistant tuberculosis in the countries where it is starting to become endemic but then also knowing that we have got to invest the money and the dollars in research and coming up with those next therapies and so forth and I think we are falling behind there.

So with that, I am excited about the topic and look forward to hearing from the witnesses.

Mr. SMITH. Thank you, Dr. Bera.

I would like to now introduce our briefer, Dr. Eric Goosby, who currently serves as U.N. Special Envoy on Tuberculosis, a position he was appointed to in January by Secretary General Ban Ki-moon.

In this capacity as Special Envoy, Dr. Goosby works toward raising the profile in the fight against TB and promoting the adoption, financing and implementation of the World Health Organization's global End TB Strategy while pursuing tuberculosis 2015 targets described in the Millennium Development Goals, which soon will be supplanted by the post-2015 goals, beginning January 1st.

He previously served 4 years in U.S. State Department as Ambassador-at-Large and U.S. Global AIDS Coordinator and is no stranger to this subcommittee. I want to thank him for his availability as well as his exemplary work over the years.

But in that position he oversaw the implementation of the President's Emergency Plan for AIDS Relief. Ambassador Goosby returned to the University of California, San Francisco where he is Professor of Medicine and Director of Global Health Delivery and Diplomacy, Global Health Sciences.

Dr. Goosby, the floor is yours.

STATEMENT OF THE HONORABLE ERIC P. GOOSBY, M.D., SPECIAL ENVOY ON TUBERCULOSIS, UNITED NATIONS

Dr. GOOSBY. Well, thank you, Mr. Chairman, acting Ranking Member Bera.

It is a privilege to be with you today at this important briefing and hearing on drug-resistant tuberculosis and its potential to turn into the next global health crisis.

TB is now the number-one infectious disease killer in the world, surpassing HIV/AIDS, according to the latest World Health Organization report on TB.

We have a visual here to help you understand that. In this case, being number one is not an achievement. There is no trophy for taking more lives than any other disease.

As Chairman Smith said, 4,100 people a day die from TB. Of the estimated 9 million annual deaths from all infectious causes, 1½ million are attributed to tuberculosis.

That translates into one out of six deaths of all infectious diseases. An estimated 1 million children became ill with TB and 140,000 children died in 2014.

Today, we can prevent, treat, and cure tuberculosis. The world has joined together to set the goal to end TB by 2035. But we will not do so without radically changing the path we are on.

At the current rate, reducing incidence by 1½ percent per year, it will take nearly 200 years to achieve this goal. Putting in place universal health coverage for an essential set of healthcare interventions including TB diagnosis and treatment will be of great importance if we want to successfully combat TB and other infectious and noncommunicable diseases.

The problem of TB is not evenly distributed around the world. Today, there are 22 high-burden countries that account for 83 percent of the cases.

That said, the problem we have to come to discuss, namely, multi-drug resistant TB, varies dramatically by geography in terms of the concentration of cases and the severity of resistance.

While major strides have been made in the effort to reduce the burden of TB, the emergence of drug-resistant organisms presents a major challenge to patients and doctors.

Of the 480,000 cases of multi-drug resistant TB (MDR–TB) estimated to have occurred in 2014, only about a quarter of these, as the chairman said, were detected and reported.

In addition, treatment success rates are very low at less than 50 percent. Most cases come from previously treated TB patients who developed resistance but this year the WHO reported a 50-percent increase in the percentage of patients who contract the disease directly from infected individuals.

Remember, this is as an airborne disease. Many countries that bear the largest burden of MDR–TB are important strategic partners to the United States.

More than half of the global burden of MDR–TB is carried by the BRICS countries and other emerging economies. The Russian Federation and Ukraine have the highest proportions among all new MDR cases.

India, China, and the Russian Federation consist of over 45 percent of all the globally estimated numbers of MDR cases. An estimated 9.7 percent of people with MDR–TB have XDR–TB and countries like India, Ukraine, and South Africa reported the highest number of XDR–TB cases.

With our current drug regimens we only succeed in treating 20 percent successfully of XDR patients. Chairman Smith rightly warned last month that we must not allow multi-drug resistance to develop further as the climb to successfully combatting TB becomes much steeper.

Left unchecked, drug-resistant TB alone could account for one in four deaths from antibiotic infections by 2050. Drug-resistant TB services for addressing drug-resistant TB in the U.S. and abroad must be scaled up immediately.

Serious detection and treatment gaps for drug-resistant TB remain. Of the $13 billion in TB funding required in 2015, about two-thirds are for the detection and treatment of drug-susceptible TB and one-third for MDR–TB treatment.

Today, only $6 million is funded and recent plans indicate that greater funding is required for MDR–TB globally as well for the capacity-building for healthcare workers to provide high-quality care.

We need to find new resources to not only prevent this disease from shattering lives but also invest in research that will enable us to save more lives.

It is imperative that we focus our efforts on calling out the tragedy which often strikes the voiceless. Those who suffer do so in silence. We need to be their voice.

We need to unleash the outrage. We need to accelerate the political backing and momentum to make the bold strides needed to drive down the epidemic.

While the call is urgent, there are signs of hope. Death rates from tuberculosis have dropped by nearly one-half since 1990 and the MDG target calling for halting and reversing TB incidents by 2015 has been achieved globally.

I applaud these achievements. It took many governments worldwide that have large-scale and sustainable programs providing basic TB care in their primary health services, and many countries with high TB/HIV burdens are mounting a solid response to the joint epidemics with prevention and care being scaled up but not yet with full coverage.

It is also critical to note that TB interventions are cost effective and save lives. TB is the most effective health, intervention bearing a $43 return for every $1 invested.

I know firsthand the experience of having to tuberculosis. When I was a young doctor I was diagnosed with latent TB. I was fortunate.

I was diagnosed, active disease was ruled out and treatment with INH for 6 months was initiated, which successfully rid my body of the disease.

Unfortunately, as you know, this is not the case for everyone. Some people remain undiagnosed. Some find the regimen too difficult to follow, particularly in the developing world, too expensive for active TB, and others become resistant to the drugs they are using.

It is these people who drive me to work on this issue just as I am sure they drive you. The world owes a great deal of thanks to Congress and to the Obama administration for making global health a priority.

I want to personally thank the subcommittee for its efforts to provide generous resources in the fight against TB. But this fight must also be a shared responsibility among all partners.

Last week at a global summit on TB in Cape Town, mentioned by the chairman, I challenged all of the global health players involved with TB to take a hard look at their resources and how they are being used.

We need to better understand what is being spent on TB and match our funding against the unmet needs. By doing this, we not only can fill in the gaps, we can eliminate duplication and parallel

systems and identify and engage synergies that ensure resources are truly additive.

In other words, let us ensure that low-income and the most vulnerable communities worldwide are first, not last, in our efforts to fight TB.

Let us also ensure that we are not pitting one disease against another. It does not do any good to rob Peter to pay Paul. We can't save children from malaria and have them die from TB.

We need investments across the board in global health. Investments bent the incidence curve on HIV. It was dramatic and we saw this, and we can do the same for tuberculosis.

Mr. Chairman, I would like to leave you with a story. In last month's Tampa Bay Times, Dr. Jennifer Furin, a senior lecturer at Harvard Medical School, wrote an op-ed about her firsthand experience in dealing with children with TB in Lesotho.

She writes,

> "I cannot forget seeing an 8-year-old boy as he crawled across to play with his friends. Being on all fours was not part of the fun but his only means of mobility. An infection in his knees caused by multi-drug resistant TB left him unable to walk or to stand. Resilient in the face of his illness, he looked to the sky with a shy grin as the other children shouted, 'Crab, crab, come and get us, crab.' But the playful laughter was soon replaced by silence. The young boy was killed by MDR–TB, and his sister and mother are also ill with the disease now."

Sadly, this story is heard all too often. We can prevent, diagnose, and cure drug-sensitive TB. But MDR–TB increasingly presents a serious challenge. We can and must do better.

I thank you for your time.

[The prepared statement of Dr. Goosby follows:]

Testimony of UN Special Envoy on TB Dr. Eric P. Goosby
Subcommittee on Africa, Global Health, Global Human Rights and International Organizations
"Drug Resistant TB: The Next Global Health Crisis"
December 8, 2015

Mr. Chairman, Ranking Member Bass and members of the Subcommittee, it is a privilege to be with you today at this important hearing on drug resistant tuberculosis and its potential to turn into the next global health crisis.

TB is now the number one infectious disease killer in the world, surpassing HIV/AIDS according to the latest World Health Organization (WHO) report on TB. In this case, being number one is not an achievement – there is no trophy for taking more lives than any other disease. While major strides have been made in the effort to reduce the burden of TB the emergence of drug resistant organisms presents a major challenge to patients and doctors.

4,100 people a day die from TB. Of the estimated 9 million annual deaths from all infectious causes, 1.5 million are attributed to tuberculosis. That translates into one out of six deaths of all infectious diseases. An estimated 1 million children became ill with TB and 140,000 children died of TB in 2014.

Today, we can prevent, treat and cure TB. The world has joined together to set the goal to End TB by 2035 but we will not do so without radically changing the path we are on. At the current rate – reducing incidence by 1.5% per year it will take nearly 200 years to achieve this goal. Putting in place universal health coverage for an essential set of health-care interventions, including TB diagnosis and treatment, will be of great importance if we want to successfully combat TB.

TB is also the most common cause of death among people living with HIV in sub-Saharan Africa. More than 1,000 people infected with HIV die every day from TB. Tuberculosis and HIV/AIDS constitute a deadly combination that speeds the progression of illness and death. As the former US Global AIDS Coordinator and the current UN Special Envoy on TB, I can attest to the fact that HIV/AIDS and TB are true partners in crime.

The problem of TB is not evenly distributed around the world. Today there are 22 high burden countries that account for 83% percent of the cases. That said – the problem we have come to discuss, namely Multi Drug Resistant Tuberculosis (MDR-TB) varies dramatically by geography in terms of the concentration of cases and the severity of resistance.

Of the 480 000 cases of multidrug-resistant TB (MDR-TB) estimated to have occurred in 2014, only about a quarter of these – 123,000 – were detected and reported. In addition, treatment success rates are very low at less than 50%. Most cases come from previously treated TB patients who develop resistance, but this year the WHO reported a 50% increase in the percentage of patients that contract the disease directly from infected individuals. Remember this is an airborne disease.

Many countries that bear the largest burden of MDR-TB are important strategic partners to the U.S. More than half of the global burden of MDR-TB is borne by the BRICS countries and other emerging economies. The Russian Federation and Ukraine have the highest proportions among all new MDR-TB cases. India, China and the Russian Federation consist of over 45% of all the globally estimated numbers of MDR-TB cases. An estimated 9.7% of people with MDR-TB have XDR-TB and countries like India, Ukraine and South Africa reported the highest number of XDR-TB cases. With our current drugs regimens we only succeed in treating 20% of XDR patients.

Chairman Smith rightly warned in a press release last month that we must not allow multidrug-resistance to develop further, as the climb to successfully combatting TB becomes much steeper. Left unchecked, drug resistant TB alone could account for one in four deaths from antibiotic infections by 2050. Drug resistant TB services for addressing drug resistant TB in the U.S. and abroad must be scaled up immediately.

As one of the wealthiest countries in the world and the third most populous, we have a moral obligation to commit financial resources to this global health security threat. Serious detection and treatment gaps for drug resistant TB remain. Of the $13 billion in TB funding required in 2015, about two- thirds are for the detection and treatment of drug-susceptible TB and one-third for MDR-TB treatment. Today, only $6 million is funded and recent plans indicate that greater funding is required for MDR-TB globally as well as for capacity building for health care workers to provide high quality care. We need to find new resources to not only prevent this disease from shattering lives, but also invest in research that will enable us to save more lives.

It is imperative that we focus our efforts on calling out the tragedy which often strikes the voiceless. Those who suffer, do so in silence. We need to be their voice. We need to unleash the outrage. We need to accelerate the political backing and momentum to make the bold strides needed to drive down the epidemic.

While the call is urgent, there are signs of hope. Death rates from tuberculosis have dropped by nearly one half since 1990, with most of the improvement coming since 2000 and the establishment of the UN Millennium Development Goals. The MDG target calling for halting and reversing TB incidence by 2015 has been achieved globally. 43 million lives were saved between 2000 and 2014, thanks to effective TB diagnosis and treatment. In comparison – ART averted over 9 million deaths from AIDS between 1995 and 2014. Over 6.2 million malaria deaths have been averted between 2000 and 2015. In terms of lives saved, TB has had a tremendous impact – more than other current public health interventions have achieved.

I applaud the achievements of many governments worldwide that have large-scale and sustainable programs providing basic TB care in their primary health services, which are saving millions of lives each year. These programs provide solid foundations and models for others struggling to get ahead of this epidemic. But I must emphasize that the risks of not intensifying our TB efforts are real, with so many people needlessly missing out on care, and with truly menacing hot spots for drug-resistance.

Countries with high TB-HIV burdens are also mounting a solid response to the joint epidemics with prevention and care being scaled-up, but not yet with full coverage. Many countries have shown they can adopt new tools, innovate delivery, reach more patients, and contain drug-resistant TB at low levels.

TB interventions are cost effective and save lives. TB is the most effective health intervention bearing a $43 return for every $1 invested. We need revolutionary new technology and improved ways of delivering services. This will require intensifying basic and implementation research with innovation. This will be possible only through increased investments and effective engagements of both the public and private sectors.
I plan to continue conversations over the coming months with leaders on how we can truly activate that commitment. If we want to achieve an end to TB deaths and to the epidemic altogether, we'll need more investments. We'll also need progress on universal health coverage and poverty alleviation.

Some people remain undiagnosed. Some find the regimen too difficult to follow or, particularly in the developing world, too expensive. And others become resistant to the drugs they are using.

It is these people who drive me to work on this issue. Just as I'm sure they drive you.
The world owes a great deal of thanks to Congress and the Obama Administration for making global health a priority. I want to personally thank this Subcommittee for its efforts to provide generous resources in the fight against TB.

But this fight must also be a shared responsibility among all partners. Last week, at a Global Summit on TB in Cape Town, I challenged all of the global health players involved with TB to take a hard look at their resources and how they are being used. We need to better understand what is being spent on TB and match our funding against the unmet needs. By doing this, we not only can fill in the gaps, we can eliminate duplication and parallel systems and identify and engage synergies that ensure resources are truly additive.

We need a country-by-country analysis that does a deep dive on resources and on needs. When I was overseeing PEPFAR, we did exactly what I am calling upon the TB community to do. And the results speak for themselves. I was able to find millions of dollars that I could then strategically invest in countries with the greatest need. I was able to make decisions based on impact.

In other words, let's ensure that low-income and the most vulnerable communities worldwide are first, not last, in our efforts to fight TB.

Let's also ensure that we are not pitting one disease against another. It does not do any good to rob Peter to pay Paul. We can't save children from malaria and have them die from TB. We need investments across the board in global health. Investments bent the incidence curve on HIV. We can do the same for TB.

Finally, it is important to note that the United States is not immune to TB. According to the Centers for Disease Control and Prevention (CDC), a total of 9,421 TB cases were reported in

the U.S. in 2014, 66% of reported TB cases occurred among foreign-born persons. Furthermore, there were 96 cases of MDR-TB diagnosed in 2014.

Mr. Chairman, I'd like to leave you with a story. In last month's *Tampa Bay Times*, Dr. Jennifer Furin, a senior lecturer at Harvard Medical School, wrote an op-ed about her first-hand experience in dealing with children with TB in Lesotho. She writes, "I cannot forget seeing an 8-year-old boy as he crawled outside to play with his friends. Being on all fours was not part of the fun, but his only means of mobility. An infection in his knees, cause by multidrug-resistant TB, left him unable to walk or stand.

Resilient in the face of his illness, he looked to the sky with a shy grin as the other children shouted 'crab, crab, come and get us, crab.' But the playful laughter was soon replaced by silence: The young boy was killed by MDR-TB and his sister and mother are also ill with the disease."

Sadly, this story is heard all too often.

We can prevent, diagnose and cure drug sensitive TB, but MDR-TB increasingly presents a serious challenge.

We can do better. We must do better, but we need to act now.

Thank you.

Mr. SMITH. Dr. Goosby, thank you so much for your very powerful insights and, again, your tremendous leadership over the years.

With regards to new drugs and new diagnostics, I would note that bedaquiline is new yet it has a high toxicity, particularly toward the liver.

And my question is, what can be done to incentivize pharmaceuticals here and anywhere else in the world, particularly in Europe where there is a highly sophisticated pharmaceutical industry, given this explosion of cases?

Are there many ideas in the pipeline or compounds that are being looked at? And secondly, in the diagnostics—the Xpert MTB/RIF—I know that the U.S. Government, and Dr. Frieden speaks about this in his testimony—and is being exported but waiting weeks or months for a diagnosis could lead to more drug resistance and a false diagnosis because that might be missed, the resistance part.

For instance, an example at your meeting you just had in South Africa, was there an emphasis on new drugs and diagnostics and getting some of these very important new initiatives out?

Dr. GOOSBY. Well, Chairman, I think you really hit one of the sensitive areas in the response to global TB burden, having adequate drug treatment is critical.

As we have said, you can diagnose and treat tuberculosis for drug-sensitive TB. Eighty-seven percent of the time, people who take these medications correctly are cured with that engagement.

It requires a 6-month treatment course but it requires, to do it safely, that the person be in care, linked to a monitoring and delivery system that can monitor the effects of the drugs on especially the liver and kidney, and have been part of the problem in identifying, entering and retaining people effectively in care for the duration of the need.

That has been aided by two new drugs that, again, require continued monitoring, that have been approved by our FDA for drug treatment for multi-drug and XDR resistance.

Interestingly, they are also effective in drug-sensitive treatment but are being reserved for the multi-drug XDR moment.

The ability to get people in delivery systems that can diagnose, resist an organism, and not inappropriately start drug-sensitive medications at the first initiation of treatment is the critical piece that must be focused on.

The pressure to generate multi-drug resistant and XDR–TB comes out of individuals who take the medication inappropriately, go on and off of one or two of the drugs and put an environmental pressure on the organism to favor the resistant outbreak.

That can be changed by better retention and better education continuously throughout their treatment period and the strategies for that have been identified but have not been brought to scale or sustained in the manner that is needed to prevent MDR/XDR development.

The Gene Xpert is a remarkable thing. Tom will speak to this. It has allowed us not to have to grow and culture an organism that grows very slowly and takes up to 6 to 8 weeks for us to actually get it to grow out of culture so we can identify it and then identify

whether or not it contains resistance to the effective microbactericidal drugs, INH and rifampin.

The ability to do that with the Gene Xpert is in about 2 hours what had been 6 weeks routinely, plus the patient stays in front of you. You don't have them go off, have to find them to bring them back, to interpret the results and initiate the appropriate treatment.

So Gene Xpert is a sea change in our ability to minimize the pressures in the system that favored the development of resistance.

Mr. SMITH. In terms of the sea change, how many diagnostic kits do you think can be supplied worldwide? What is the capability?

Dr. GOOSBY. I think some of my colleagues may have an answer to that. They are at a fraction of what they are needed in any given country.

Many of the U.S. systems—PEPFAR, the USAID systems on tuberculosis—have invested early on in the Gene Xpert machine to make their availability wider. But it is a fraction of what the total amount is.

Mr. SMITH. And does it detect for other antibiotics as well or just the one?

Dr. GOOSBY. It looks for resistance to rifampin, one of the bactericidal antibiotics, and in the new formulations it will look for INH, rifampin and they have formulations now, cassettes that are being set up to look for other forms of antibiotic resistance that would give you a diagnosis for multi-drug and XDR–TB.

Mr. SMITH. You mentioned that more than half of the global burden of MDR–TB is borne by the BRICS countries and other emerging economies. You didn't mention Brazil. Do you have some insights on Brazil?

Dr. GOOSBY. Brazil is a country that is heavily burdened with the response to tuberculosis, again, something that is known but has not moved to scale yet in the country.

They are struggling with the knowledge of how to diagnose and treat but not having it available to all of those in the population that need it.

Their economic wobble that they are on now has created an interval in their ability to invest in it as a country and they are now in need of support globally to try to get over this period of economic decline.

Mr. SMITH. Let me just ask you with regards to so many people with compromised immune systems which seems to be in ascendancy——

Dr. GOOSBY. Yes.

Mr. SMITH [continuing]. My wife has an autoimmune disease and it seems it is—there are growing numbers of those cases, which makes, obviously, she and so many others more susceptible.

Do you see—as Dr. Frieden points out, there—92, I think it was, was the point where we hit—you know, that we have gone down ever since here in the United States.

If you could speak to this trend, it seems to be, of autoimmune diseases that are throughout the country, and secondly, the—if you could answer that and then I will do my final question and then go to Dr. Bera.

Dr. GOOSBY. Sure.

Well, Mr. Chairman, I think you are right to point out that the susceptibility to tuberculosis goes across a spectrum of diseases that engage or diminish your immune system's ability to respond to an infectious agent, identify the organism and clear it.

The identification often is not the difficult part but having the ability for your white cells and so-called cell-mediated response to come in and clear that organism from the body, to sterilize it, has been a big part of why individuals who are immunochallenged, immunocompromised like with HIV, those with collagen vascular diseases, those who have had chemotherapy, the third trimester of pregnancy, and just aging as your immune system wanes, increases your vulnerability to developing active disease with the same exposure.

The defect in cell-mediated response is especially bad for those who are HIV positive. The susceptibility to gaining an active disease from the same exposure in an HIV-infected person has been estimated to be over 100 times that of the HIV negative individual and explains why tuberculosis remains the leading killer for HIV-infected people on the planet.

Mr. SMITH. I have a question. Excuse me.

Dr. GOOSBY. I was just going to say the ability to identify those aspects of the immune response that makes them susceptible to active TB is a critical target for research and our ability to understand this is well within our realm of our understanding of immunology.

But we have not applied our immunologic tools to characterize the more subtle responses that individuals have when exposed to TB in their immune system.

NIH is now primed, as is CDC, to take those studies through to completion because in many ways they follow the same path that was used to characterize the immunologic response description of the natural history pathophysiology for HIV. So those labs are set up and ready to turn to TB.

Mr. SMITH. Last question. Since 2007, we, in the United States, as you know so well, have been doing very aggressive screening among the immigrant population—legal immigrants this is—and the refugees, the 450,000 immigrants and 70,000 refugees annually, and as a matter of fact, it is so stringent that if somebody has TB they have to come in without it or they are inadmissible to the United States.

Seven weeks ago, I held a hearing on Syrian refugees and we had the regional representative for the UNHCR as one of our witnesses, Pitterman, who did a wonderful job and he talked about the fact that the gross underfunding of the refugees including the appeals—we have more people who are displaced—IDPs or genuine refugees—than ever before, and yet the appeals go out for the UNHCR and 41, 44, 43 percent comes back so we are underfunding it, and that the trigger for this mass exodus into Europe and someday to the United States was, frankly, the World Food Programme cut of 30 percent, which put a number of people to flight, thinking that they were hopeless.

Huge migrations of people across borders. Many people are sick, compromised immunity, I would think, as a result. Since we are doing such robust screening on at least legal immigrants, what is

the U.N. looking to do with all of these mass flows of individuals who could be carrying these horrific diseases, putting themselves, their families and then anyone else with whom they have come in contact with at risk of getting TB?

Dr. GOOSBY. Well, Chairman, you bring a terrific point forward. Our colleagues in the European sector as this immigration occurs are scrambling to try to mount a humane and responsive screening mechanism that allows those individuals who are suffering from underlying diseases that can be diagnosed and treated, those that indeed may afford a risk to their new population that they are entering but also afford a risk to themselves and their families, need to be screened for, identified, diagnosed, and treated.

Mr. SMITH. Are any countries doing that, particularly European countries, Germany, for example? Are they screening for TB?

Dr. GOOSBY. They are doing it once people get to the country but are not doing it in a refugee status to the degree that they need to. They are at a very early stage in mounting that response.

On the down side, they need to do more. On the up side is they realize that and are really working to gain a global awareness that results in, hopefully, investment by the global community in trying to put a screening capability in place.

Mr. SMITH. Is there any preliminary data from, like, Germany or any of the other countries that suggest that——

Dr. GOOSBY. You know, I am not aware of any, Mr. Chairman, that I would be willing to give to you at this point. But I will look into that and come back to you with it.

Mr. SMITH. Appreciate that.

Dr. Bera.

Mr. BERA. Thank you, Mr. Chairman, and again, thank you for your testimony, Dr. Goosby.

As one of those young interns who started my residency negative on my skin tests and turned positive, I was grateful for that surveillance program.

I was grateful that I was able to have the latent TB infection treated and it does talk about the importance of surveillance.

In my public health career as chief medical officer to the programs that I directed for Sacramento County was the refugee screening program, which was exactly that.

We have a large Eastern European refugee population in the Sacramento area. You would have rudimentary screening in their country of origin so we would certainly do much more robust screening on arrival and, obviously, tuberculosis was one of the entities that we were looking for.

A second program that we treated, that we had under my jurisdiction, was the chest clinic, which was our TB surveillance program in Sacramento County.

And as you have rightfully pointed out, a key component of treating tuberculosis is not just making the diagnosis of active TB, getting the patient on the right therapy, but then making sure, and our program was a directly observed therapy program where you were sending public health nurses out there on a regular basis, observing them take their medications, because that is the risk that we run—folks starting the medications, not completing therapy, and then we run into this issue of a limited arsenal.

A couple questions. You talked about Gene Xpert and the ability to better sort out susceptibility and sensitivity to the arsenal. I may have missed it. I think Chairman Smith asked the cost of Gene Xpert.

Dr. GOOSBY. So there were the research and development costs and then there was the initial kind of formulation of the machinery, all of that now being tucked and settled.

The cartridge costs started at about $24 for each sputum examined to determine whether it was resistant, had microbacterium, and whether or not there was rifampin resistance.

That now went down to $10 with investments from USAID and PEPFAR back in 2013 and now it is down to below $8 and with kind of unit price, scale-up will actually drop below that.

Mr. BERA. And the actual machinery is of a size that you can have out in the field with you so if you were to take this to a refugee camp, let's say.

Dr. GOOSBY. It is of the size that you could take out in the field. It is the size of a small computer about this high down there, about that wide.

The cartridges, you stick them into the machine and literally it won't evaluate sputum only, but spit will be good enough because it is a PCR-generated test.

So you don't have to induce sputum like you do for a normal smear positivity and staining exercise and that advantage alone makes it hugely impactful. It can run on solar power and we have many examples of that and doesn't require a cold chain to keep specimens and store specimens.

There is also a whole technology trying to look at how to preserve specimens without a cold chain for days that will allow for a pooling and aggregation of specimens so you can run batches.

All of that technology has been worked out but has not been brought to scale.

Mr. BERA. So there is a urgency of getting this to scale and getting this out to the field as quick as possible. If we think about the 1½ million cases of tuberculosis, what percentage would you say are INH- and rifampin-sensitive versus not sensitive?

Dr. GOOSBY. So of the initial cases of tuberculosis, less than 3 percent actually are carrying MDR in the whole pool of TB and of the 3 percent that develop MDR about 10 percent of those cases can develop XDR–TB.

Mr. BERA. Well, again, if we are thinking about a global strategy here, it is incredibly important that we don't overuse our arsenal.

Dr. GOOSBY. Yes.

Mr. BERA [continuing]. Our superantibiotics here and that we actually—again, if what you are saying is 97 percent are still sensitive to INH and rifampin, the danger we run into is that we just treat everything with our most effective medications and then we start losing those.

And so the starting point is really getting to scale, getting this Gene Xpert out there into the field and recognizing that, you know, here is the 97 percent of folks that we can treat with our usual medications so we just save our latest medications for those that are multi-drug resistant or extremely multi-drug resistant.

We have seen what has happened in general as antibiotic use over time where we go to the next latest and greatest antibiotic therapy and we start to develop this drug resistance whereas we have got to be vigilant so, certainly, is where investing in those next therapies and so forth.

We still got a good arsenal in INH and rifampin. Doesn't mean we shouldn't be investing in the next generation and the next arsenal and staying ahead of this but we should make sure we are using the appropriate medications.

Dr. GOOSBY. Your background speaks to your wisdom with that. You are absolutely right.

Part of our task is to be excellent in making the diagnosis and identifying those who are carrying a resistant organism and then putting them on the appropriate medication, not inappropriately or unnecessarily using the medication that we want to reserve for those who, indeed, hold a resistant organism.

I think that your time in Sacramento showed you how easy and with all the well meaning in the world you can do that and I believe that the widely available ability to diagnose MDR or XDR–TB will preempt that evolution.

Right now, we have a moment to prevent that evolution from going is your point. I completely agree with you, and the urgent need for drugs in the pipeline and for other diagnostics to continue to be on the working table is also evident to all of us who have done this a long time and that we see how fragilely we are standing on a precipice that we could go over and never be able to recover from.

Mr. BERA. Chairman Smith alluded to the fact that we have gotten ahead of this in the United States. But would you articulate why folks here domestically have to be concerned with, you know, the emergence and escalation of TB around the world?

Dr. GOOSBY. Well, I think the next two speakers are expert in this threat. Our ability to move people in hours from one area of the world to another is well established—airplanes—and an airborne disease such as tuberculosis is in its ability to spread affords a real threat in that regard.

It is shortsighted to think that we need to wait until a person, a patient, comes in from a foreign life where TB is endemic and they are infected and then manifest with symptoms here in this country.

We have to be vigilant but compassionate in our ability to identify, enter and retain these patients and people in care and services.

Our country has open arms in the immigration sense. This is a threat that makes us question if we are doing this correctly. But we are smart enough to figure out how to do it safely.

Mr. BERA. Great. And, again, just for the domestic audience, while we may think of tuberculosis as a disease that infects lower-income immigrant populations, et cetera, what we know, since it is an airborne disease, having done some of these epidemiologic surveys, when you get these outbreaks it is not limited to those populations.

It spreads, and it is much better to prevent and get ahead of this. It can affect anyone.

Dr. GOOSBY. Absolutely right. Absolutely right.

Mr. BERA. Well, thank you for being here.

Mr. SMITH. Mr. Engel.

Mr. ENGEL. Thank you. Okay. That is better.

Thank you. Thank you, Mr. Chairman, and I also want to thank our ranking member, Congresswoman Bass, and our witnesses for appearing here today.

I am the ranking member of the entire committee of the House Committee on Foreign Affairs but also have done a lot of work on the fight against tuberculosis. It has been a priority for me for a long time.

So many people around the world needlessly suffer from this disease and investing in diagnosis and treatment helps build healthier communities in the developing world, something I tried to achieve through the Stop TB Now Act, much of which became law in 2008.

We know that healthier communities are stronger and more prosperous, so for me this is a foreign policy priority as well as a global health priority.

We like to think of tuberculosis as a disease quickly becoming part of the past and, after all, we have made wonderful strides in the fight against TB. But between 2000 and 2014, effective diagnosis and treatment accounted for 43 million lives saved. That is great.

Since I came to Congress nearly 27 years ago, the worldwide TB death rate has dropped by nearly 50 percent and here in the U.S., the number of annual deaths due to TB has dropped by two-thirds just since 1992.

And we know how to diagnose this disease. We know how to cure it. So in some ways we seem to be headed in the right direction when it comes to wiping out tuberculosis.

But the reality, however, is that TB has become the number one infectious killer worldwide. One and a half million people, including 140,000 children, died from TB last year, and during that same period, nearly 10 million people became infected with the disease, and nearly ½ million developed multi-drug resistant TB, and we know people fighting HIV/AIDS also are very prone to getting TB as well.

So while we have made real progress fighting tuberculosis, we need to stay focused and finish the job. So I thank you, Doctor, for all the good work that you do.

Obviously, we need to be clear-eyed about the challenge that remains, set ambitious goals and do what it takes to reach these aims. For example, I am glad that the U.N. included the fight against TB in its sustainable development goals.

Ending the global TB epidemic by 2030 won't be easy but it is a good first step that the U.N. is prioritizing this effort. And let me just say finally as the co-chair of the TB Elimination Caucus, I will continue talking about this issue and pushing for robust investment in TB research and treatment.

I am pleased that this subcommittee is taking the time to examine this problem. I look forward to a good discussion. I thank you for your partnership.

Doctor, thank you and all the other people, even in the audience, who have worked so hard and made this a priority in their lives.

I yield back. Thank you for giving me the opportunity today.

Mr. SMITH. Thank you very much, Ranking Member Engel, and another example where there is just close bipartisanship, cooperation and support, the way it ought to be, and I want to thank my good friend for his leadership for these many, many years.

I would like to ask you just finally, and maybe you can get back to us on this, but as you come across members of Parliament, executive branch members that you think we might liaison with and talk to and try to get a stronger concerted effort, please let us know.

I chair the delegation to the Organization for Security and Cooperation in Europe Parliamentary Assembly. I work on trafficking and a whole host of issues, and I often find when you bring up an issue like this they say oh, Joe or Jim or Mary, they work on this too—you ought to talk to them.

And since you are in contact with them all the time it would be an open door invitation for us to work with like-minded parliamentarians.

Thank you again.

Dr. GOOSBY. It was a pleasure, Chairman. Thank you so much.

Mr. SMITH. Thank you, Dr. Goosby.

The briefing now comes to an end and pursuant to notice now call to order the hearing. Let me now invite to the witness table our second panel, beginning with Dr. Tom Frieden, who has been the Director of the Centers for Disease Control and Prevention since June 2009 and has dedicated his career to fighting infectious and chronic diseases both here in the United States and abroad.

He led New York City's program that controlled tuberculosis and reduced multi-drug resistant cases by 80 percent. He worked in India as well for 5 years helping to build a tuberculosis control program that has saved nearly 3 million lives.

As the commissioner of New York City's Health Department Dr. Frieden led programs that reduced illness and death and increased life expectancy substantially.

He is a recipient of numerous awards and honors, has published more than 200 scientific articles, has previously testified before this subcommittee and we welcome him back.

And then we will go to the Honorable Ariel Pablos-Mendez, who is the Assistant Administrator for Global Health in USAID, a position he assumed in August 2011.

Dr. Pablos-Mendez joined USAID's leadership team with a vision to shape the Bureau for Global Health's efforts to accomplish a measurable and sustainable impact on the lives of people in developing countries, and he has been doing that and doing it extremely well.

Prior to joining USAID, he worked on global health strategy and the transformation of health systems in Africa and Asia.

He has also served as the Director of Knowledge Management at the World Health Organization. Dr. Pablos-Mendez is a board-certified internist and until recently was a professor of clinical medicine and epidemiology at Columbia University.

Dr. Frieden, the floor is yours.

STATEMENT OF TOM FRIEDEN, M.D., DIRECTOR, CENTERS FOR DISEASE CONTROL AND PREVENTION

Dr. FRIEDEN. Thank you very much, Chairman Smith and Congressman Engel, for your interest and leadership addressing this and other critically important global health issues.

I am here as CDC Director but I have spent much of my career working on the issue of tuberculosis and support for tuberculosis patients. I would like to tell you about one of them.

In the early 1990s, while I was working as an epidemic intelligence service officer and then director of the Bureau of Tuberculosis Control program in New York City, I treated a young man from Kerala, India.

He had what we would now call extensively drug-resistant tuberculosis, or XDR–TB. I treated him for close to 2 years. He required the resection of part of his lung, experimental treatment, and treatment with injectable antibiotics, which his wife, fortunately a nurse, was able to provide for him for a period of well over 18 months.

Fortunately, he was able to be cured of his disease. At that time many years ago it cost over $100,000 for his care. Years later, while working on secondment from CDC to the World Health Organization in India, I was able to go to his home village in Kerala where we were able to establish a program that would have prevented his case of multi-drug resistant tuberculosis for $10.

In New York City, we documented the largest outbreak of multidrug resistant tuberculosis to have ever occurred in this country and we also documented its very rapid control, and that brings me to the three key points I would like to make about tuberculosis.

First, it is a big problem, second, we can stop it, and third, the CDC plays a pivotal role in that global effort. It is a big problem, as you know. Last year, 1½ million people died from a disease that is virtually 100 percent curable.

In addition, we are seeing increase in drug-resistant strains of the organism and this is a reflection not only of a failure of effective programs but also of a failure of a investment and coordination.

Tuberculosis affects society and increases poverty. It is also a reflection of challenges that countries have to support patients and effective health systems.

If you look at the countries where tuberculosis is spreading most widely, they have the combination of poverty, HIV, in some cases a government system that is not providing as effective care as it can, in some cases a private healthcare system that is providing chaotic and irrational treatments for tuberculosis.

And as a result of that, you are seeing lots of spread in communities in the healthcare systems. And one thing to really emphasize is the risk of spread within healthcare facilities.

Both Dr. Bera and Dr. Goosby commented on having become infected with tuberculosis during their training. I have too, I mentioned that I am a member of that club as well, having become infected working in a tuberculosis clinic in New York City. Again, preventive treatment has greatly reduced my risk of ever developing the disease in the future.

But that is just an example of what happens. Around the world, people with HIV get infected in hospitals and go on to develop disease.

In New York City in the early 1990s, we were able to show with one of the first molecular epidemiological studies ever done of tuberculosis that a large proportion of cases—in fact, perhaps even more than half of all of the multi-drug resistant cases in New York City at that time, were picked up in the hospital.

So the first point is it is a big problem. The second point is that we can stop TB. We need political will. We need to build on momentum. We need investment. We need commitments that are matched by resources, both from within countries multilaterally and bilaterally.

We also have better diagnostics now and as I, and as you mentioned, Mr. Chairman, we have gone from 2 months to 2 days to the diagnosis of multi-drug resistant tuberculosis and there are many different technologies.

Gene Xpert is one very strong one that is being used for TB and other pathogens. There are others as well and there will be others coming down the pike.

In the U.S., we are using forms of sequencing large parts of the TB genome to be able to get resistance testing to first- and second-line drugs, at least on a preliminary basis, in real-time throughout the U.S. and that has been a very successful pilot.

We also need to improve the treatment and the treatment of patients as the VIP of the program. TB patients all over the world don't get the services they need to complete treatment and that is not just bad for them and their families.

That is bad for all of us. That is why the TB patient has to be the VIP of the program and effectively manage programs to treat them as such.

We also need to ensure that there is effective supervision and the core technical excellence continues. We continue to hear all too often about medications not being available, diagnostics not being available, patients not being supported through the course of their treatment.

And, of course, we need continuous innovation. We have the tools we have today because of innovations. We will have better tools if we continue to innovate.

At CDC within this country we coordinate a network of experts in the treatment of multi-drug resistant tuberculosis with extensive experience. This includes physicians, laboratory workers, public health outreach workers, public health nurses, implementation experts, and others.

We have a very successful program, as you mentioned, Mr. Chairman, on refugee and immigrant screening. It is really a triple win.

What we have done is to strengthen the diagnostic and treatment capacity in countries all over the world. That means that not just for immigrants and refugees but for other people in those countries there is the better opportunity to be accurately diagnosed and effectively treated.

It is a win for these individuals because they are more likely to be cured and it is a win for the U.S. because we have been able

to treat just over the last 2 years close to 3,000 patients around the world who didn't come here with tuberculosis. This is a very successful and cost-effective program.

We also have at CDC unique expertise in areas such as infection control where we are hoping to reduce the risk that people will pick up tuberculosis in clinics and hospitals all around the world and a unique opportunity to advance research.

We have been in our laboratory validating and extending and creating some new tools for diagnostics. Some of the drugs that are currently being used were first studied in our own laboratory and, of course, we all hope that at some point in the future there will be a vaccine for tuberculosis, although at present we have nothing to offer beyond a vaccine that protects children against some forms of TB.

Also, with support from Congress we are expanding the Global Health Security Agenda and in this regard expanding programs to track and stop drug-resistant bacteria, including tuberculosis.

And, of course, the PEPFAR program, which Dr. Goosby ran for many years, is critically important in providing treatment for HIV, which will reduce the rate of TB, and for TB, which is the most deadly opportunistic infection among people living with HIV, killing nearly one-third of the people with HIV who die each year.

In conclusion, there is one core fact I would like us always to remember about multi-drug resistant tuberculosis and drug-resistant tuberculosis in general, and it is this: No program can treat drug-resistant tuberculosis faster than a poorly organized program can spread and create drug-resistant tuberculosis.

Therefore, it is essential that we focus on the core aspects of providing high-quality diagnosis and treatment to all patients with tuberculosis, those susceptible to tuberculosis, and those with drug-resistant tuberculosis.

TB is nearly 100 percent curable, but the biggest challenge to tuberculosis control and prevention and elimination efforts is the challenge of persistence—that individual patients, when their symptoms resolve, programs when it is no longer on the headlines, physicians when they are no longer thinking of it, will not sustain the programs needed to sustain the progress which we can achieve to stop tuberculosis.

And we look forward at CDC to continuing to work with Congress, with our agency partners from throughput the U.S. Government, and with partners from affected countries and around the world to accelerate the cure and eventual elimination of tuberculosis.

Thank you.

[The prepared statement of Dr. Frieden follows:]

House Foreign Affairs Committee,

Subcommittee on Africa, Global Health, Global Human Rights, and International Organizations

December 8, 2015

Statement of Dr. Thomas R. Frieden, M.D., M.P.H.

Director, Centers for Disease Control and Prevention

I. Introduction

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

III. Causes

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

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

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

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

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

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

IV. Complexities of Diagnosing and Treating Drug-Resistant TB

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

VI. Conclusion

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

Mr. SMITH. Dr. Frieden, thank you so very much.

Dr. Pablos-Mendez.

STATEMENT OF THE HONORABLE ARIEL PABLOS-MENDEZ, M.D., ASSISTANT ADMINISTRATOR, BUREAU FOR GLOBAL HEALTH, U.S. AGENCY FOR INTERNATIONAL DEVELOPMENT

Dr. PABLOS-MENDEZ. Thank you very much, Chairman Smith, Congressman Bera, and Engel, my own Representative.

Thank you for being champions for global health for tuberculosis and for allowing us into this room to testify on our work in tuberculosis and MDR–TB work that USAID has been doing for many, many years.

I also want to thank Dr. Eric Goosby for his leadership and passionate comments. I guess all the four doctors in the room with Dr. Bera have been infected with tuberculosis so we all have personal experience.

But also we go back a long way. When I was training in New York in the 1980s, we began to notice MDR–TB among the homeless, and it was through tuberculosis that I think many of us got into the global health space.

I worked with Tom Frieden turning the tide of what at the time was a big outbreak of MDR–TB accelerated by HIV.

You will recall that people have forgotten tuberculosis in the United States by the 1980s and now we had an incredible flare. We did turn the tide in New York and we feel confident we can also beat the disease globally.

Since that situation in New York, the World Health Organization declared a global emergency and a lot of effort has been going on in the international community that we didn't have in the 1980s. So the 1990s began to have a transformation.

The U.S. Government stepped up to the plate; all of the agencies began to work. In the last 20 years, plenty has been happening. Plenty has been accomplished.

I was in 1997, I went to WHO for the first time where we produced the first global report on MDR–TB. I came to testify on what was the first piece of evidence on MDR–TB around the world. We showed a big, big problem, of course, in Eastern Europe, hot spots also in other parts of the world.

When I joined the Rockefeller Foundation, I was very engaged in public-private partnerships, working with the NIH and the pharmaceutical companies to create a new partnership, the Global Alliance for TB Drug Development, to begin the development of new drugs.

None had been developed over 50 years and we needed new drugs to fight the disease, not only to have new drugs against MDR–TB but also to shorten—to make the treatment of tuberculosis shorter and simpler, because as Tom has stated, if we can control TB in the right way we can prevent the emergence and spread of MDR–TB.

We also worked together in the year 2000, a pivotal year for global TB control, in the establishment of the Global TB Drug Facility which the U.S. Government supported.

USAID supported the first global surveillance report and since has supported the Alliance for TB Drug Development, has sup-

ported now the Global TB Drug Facility, which is a platform that allow us to procure prequalified drugs and make it available to expand international TB programs around the world.

A lot has been done. I am very proud of the work of the USAID and the U.S. Government, but we need to do more and in new ways, no doubt.

The problem that we are addressing—MDR–TB—is a big, big challenge. Tuberculosis is now, as you heard, the leading infectious killer in the world and I think that that is a very important signal. This year's report is an important piece of evidence that will help us rally attention and support in the fight against tuberculosis.

In those 20 years where, thanks to your support, the commitments of the U.S. Government have increased. We started with about $10 million 20 years ago to fight tuberculosis.

We now, of course, have far more than that. That period of time, in that 20 years, tuberculosis was growing and then was stopped and has begun to decline at a 10-percent decline in the incidence of tuberculosis worldwide.

Tuberculosis mortality, as we heard from the introductory commentary, has been nearly halved in these 20 years. So about 43 million lives have been saved by treating tuberculosis—quite an impressive accomplishment in these 20 years—and there is no doubt the U.S. Government in particular to all of our agencies and USAID, as the lead international agency for TB control, has been truly the champions in this campaign.

We think we are doing okay, but not on MDR–TB. We need to do a lot more. We have put together the U.S. Government across the agencies a new strategy for the U.S. Government Global TB strategy, which aims to reach, cure, and prevent tuberculosis.

As we know, there are many patients who cannot, at present, be detected and we have to decrease that; our goals by 2019 are to reduce the incidence further by 25 percent, maintain the success rate of those patients who are now being detected at 90 percent, successfully treat 13 million patients directly by our efforts, and initiate the treatment of 360,000 MDR–TB patients as well as reaching all of the people who have HIV and TB with antiretroviral treatment.

Our work is focused in about 54 countries but we also extend the reach of the U.S. Government commitment through the Global Fund, which reaches about 100 countries, providing more focused technical assistance to ensure that those resources are matched by others in the fight against tuberculosis.

MDR–TB itself is, of course, the big challenge and we heard before about the Xpert DNA testing system. It has been really a transformation in this decade and it is the fruit of research, the fruit of the cooperation with the private sector.

In the year 2011, there were about ½ million cartridges distributed around the world; in the last year, 5 million, so a tenfold increase in the spread of the Xpert system reached around the world.

Quite significant, not only for the MDR–TB detection and treatment, but also for the regular TB among children that have more difficulty in being diagnosed with the traditional methodologies.

Likewise, just since 2010 the treatment of MDR–TB has been tripled. There were about 20,000 patients put on MDR–TB treatment

in the year 2010. Now we have tripled that and with the Global Fund we are doubling that. Still, it is not enough.

We have many more patients that we need to diagnose and treat. But it gives you a sense of the great progress that we have had recently thanks, again, to the bipartisan support of Congress and the work of the interagency in the United States but also working with many partners.

Our work is, clearly, leveraging the World Health Organization guidance to countries and the countries' own ability to pay for tuberculosis control.

Scaling up the treatment of MDR–TB will require more resources than we have at the moment. There is no doubt about that. But it also requires better ways to do what we do with the resources we do have.

We have been working on investing in new diagnosis and new drugs, and new drugs are finally coming online though they are not great yet.

Indeed, we are working with bedaquiline, for example—a drug Congressman Smith noted is, indeed, not a perfect drug it is a drug that has been approved by the FDA, the first such approved TB drug in 50 years, and is part of the development of new drugs coming in the pipeline.

We are working on bedaquiline with Johnson & Johnson and Janssen Pharmaceuticals to begin to introduce. More than 4,000 patients have now been treated. We are learning. We are following the research guidance carefully to learn further as we expand donation programs and others.

It is a new drug. We have to be careful. We don't want to lose it. As Congressman Bera said, we have to be careful with those drugs both in monitoring and toxicity.

There are two things that many of the drugs we use today in tuberculosis had they gone through the FDA approval today may not have gone through. But they have been quite successful over the last 50 years and we have to still do better in this regard.

And as I said, MDR–TB will be important. We have been working and I am very proud of the work the team has been doing. As someone who has been quite involved in drugs for tuberculosis—the development, purchasing, and so on—there have been clever ways to work with the manufacturers because we need to have drugs.

And I remember in New York, Tom, that the manufacturers were not there. So working with the manufacturers to ensure that we have prequalified MDR–TB drugs has been very important. There were not many in 1993.

We have been working with many of them. Now we have over 30 manufacturers capable of producing the drugs that we are using and also working with them and exchanging technical assistance for price reductions that have led to a 50-percent reduction in the cost of MDR–TB regimes in the last 10 years.

We need to do more. We need to do better. USAID is also working on the cutting edge of research. The NIH invests significantly. It is the leading organization investing in research for the U.S. Government and we are working on the implementation side in the later phases of randomized clinical trials, working also on how we

implement and expand treatment and diagnosis, and working to support most of the guidance that the WHO has put out have been the result of the support that we are doing, working with them technically and financially.

We are in the midst now of the STREAM clinical trial, which is the first randomized clinical trial of MDR–TB long term. We have been doing lots of pieces of that but this is going to be a very significant effort for us going forward. However, we agree we need to do more.

I think that the cost of TB control will run from $8 billion cited by Chairman Smith to about $13 billion by 2030 and so we need to almost double the commitments that we have today.

But most of the high-burden countries in tuberculosis pay for 80 percent of the cost. So we have been quite focused. We are working on domestic resource mobilization.

We want to make sure those governments supplement the taxpayers' money that we are bringing in with technical assistance with international partnerships and so on for them to take more ownership of that and they are doing very well.

I think South Africa, with the Xpert system for diagnosis, has been a great example—India doubling their budgets for TB control, many others—like Indonesia, where we have been working to expand a nationwide MDR–TB diagnostic and treatment. So, clearly, we need to continue to do that.

In conclusion, tuberculosis has been around for awhile. We have done a lot of good work recently but it is now the leading infectious killer in the world.

And MDR–TB is like Ebola with wings. Indeed, it is something that can be as easy to acquire in a way as Ebola—as a percentage over time—and has equivalent mortality untreated and it can be transmitted—it is airborne. So we are—you are right to be calling this attention to this important program.

The U.S. Government, the USAID efforts in the fight will be maintained with the strategy that we have right now for 2019 as well as a part of the global effort for TB.

I think, importantly, we have stopped TB from growing. It is now declining. We need to do the same thing with MDR–TB. We can do it.

Thank you.

[The prepared statement of Dr. Pablos-Mendez follows:]

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Assistant Administrator for Global Health
U.S. Agency for International Development

House Committee on Foreign Affairs
Subcommittee on Africa, Global Health, Global Human Rights, and International Organizations
December 8, 2015

Introduction

Chairman Smith, Ranking Member Bass, and members of the Subcommittee, thank you for inviting me here today to testify on the U.S. Agency for International Development's (USAID) response to the global Tuberculosis and Multi-Drug Resistant Tuberculosis (MDR-TB) epidemic. I would like to express my appreciation for your steadfast support for USAID's TB program and our other global health programs, which have improved and saved lives around the globe and are vital to President Obama's call for ending extreme poverty.

For the past 20 years, the U.S. Government, through USAID, has led the global effort to increase access to TB diagnosis, treatment and care, particularly among those who are most impoverished. The USAID TB program has been a major catalyst in decreasing the TB burden in many countries. Our efforts to build partnerships with National TB Programs, Ministries of Health, multilateral organizations, and departments and agencies across the U.S. Government have developed and strengthened country capacity to control the TB epidemic. These efforts have also contributed to sustainable health systems and made substantial contributions to building the coordinated global community for TB. Since USAID's TB program began almost 20 years ago, together with the critical assistance of its partners 43 million lives have been saved—a tremendous accomplishment for which we should all be proud. Further, investments in TB diagnosis, care and treatment have had a significant impact on the lives of the most impoverished individuals and communities globally. As a result of the united global effort, the world is on track to meet the Millennium Development target of a 50 percent reduction in TB incidence by the end of 2015. This is a remarkable achievement.

Throughout my career, combating TB and MDR-TB has been a personal priority. While living in New York in the 1990s and on faculty at Columbia University, I worked with Dr. Tom Frieden and others on combating the MDR-TB outbreak in New York City. The challenges we faced in New York were in some ways similar to the challenges we face globally: Re-emergence of TB and MDR-TB was due to the decline in attention and resources dedicated to controlling and treating TB. With USAID's support, I led WHO's first global MDR-TB report in 1997 and a second one in 2000. While at The Rockefeller Foundation, I was instrumental in the creation of the Global Alliance for TB Drug Development, the Global TB Drug Facility and the Stop TB Partnership. I care deeply for the fight against TB and I am proud of the work being done today by the U.S. Government. But we need to do more and in new ways.

Global TB Situation

New data released this fall by the WHO shows that tuberculosis is now the leading infectious killer in the world. Each day, more than 4,100 individuals die, each week, more than 28,000—more than twice the total number of deaths from Ebola in West Africa since the outbreak began—and each year, 1.5 million succumb to this preventable disease. In 2014, approximately 9.6 million people developed TB, including 3.2 million women and 1 million children. TB affects individuals in the most economically productive age groups and is one of the top five causes of death among women of reproductive age. TB predominantly affects the poorest and most vulnerable, and approximately 95 percent of TB deaths occur in low- and middle-income countries.

Worldwide, more than two billion people are infected with the bacterium that causes TB *(Mycobacterium tuberculosis)* and are at risk of developing TB disease. While most people infected with the bacterium will not develop TB disease, conditions that suppress an individual's immune system increase the person's risk of progressing from TB infection to TB disease. The most significant among these include medical conditions, such as HIV infection, diabetes, and cancer. In addition, malnutrition, smoking, and immunosuppressive medications are associated with the development of active TB.

Despite the continuing and devastating impact of TB around the globe, considerable progress has been made in the past 25 years. Since 1990, TB deaths have declined by 47 percent and TB prevalence has declined by 42 percent globally. Recent innovations have dramatically expanded our ability to rapidly diagnose all forms of TB and provide appropriate, life-saving treatment and care to those in need. This includes the GeneXpert diagnostic tool that has revolutionized diagnosis of TB drug resistance, shortening the time for laboratory confirmation from a month or more to less than two hours. And new and improved drugs, diagnostic tools, and programmatic approaches are in the pipeline and are expected to be rolled out over the next few years.

The global community has recently developed a new WHO END TB strategy and Stop TB Partnership Global Plan to End TB to accelerate progress and end the TB epidemic by 2030. The strategy identifies intermediate targets for 2025, 2030, and 2035 to stimulate the rate of decline in TB incidence from the current 1.5 percent to 10 percent each year. This acceleration will require all partners to work closely together to optimize the use of existing tools and approaches as well as increase investment in the development and implementation of new and better methods to diagnose, treat, and prevent tuberculosis (including vaccines).

Every year, more than 3.5 million individuals with active TB are not properly diagnosed or reported to national TB programs. A majority of these "missing" 3.5 million people do not have access to or do not receive appropriate services, resulting in poor outcomes. Many die of TB, and many of those who survive endure long illnesses and significant morbidity. They frequently infect those in close contact in their families and communities. Every person with active TB disease who is not on treatment can infect between 10-15 other people each year. As such, "missing" people with TB is not only a clinical and humanitarian issue, it is a serious public health issue. Most of the individuals who comprise the "missing" cases are from 10 countries: Indonesia, India, Nigeria, Pakistan, Bangladesh, South Africa, Democratic Republic of the Congo, China, Tanzania and Mozambique. USAID is partnering with almost all of these nations to help accelerate TB detection and scale up treatment programs. Intensified efforts to reach and treat every person with active TB are vital to curbing the global TB epidemic. USAID has supported countries to find the TB cases earlier through community based approaches, engaging

all care providers, introducing new tools, and expanding diagnostic networks. This past year, for example, USAID supported countries to improve their community-based TB interventions, ranging from TB education and awareness campaigns, to community-level sputum collection and treatment support.

The recently released Stop TB Partnership's Global Plan estimated that to end TB by 2030 the world collectively will need to invest about $13 billion a year to implement TB control activities and research and development. In 2015, a total of about $6.6 billion was invested in TB worldwide. Yet, despite donor support and domestic resources, there is a major funding gap in reaching the WHO END TB 2030 target. In the future, most resources for implementation will continue to come from domestic country budgets, with additional support from other donors and the private sector. Providing technical support to host country governments to increase and maximize their resources for TB and working with local and international private sector resources to expand private sector commitments for TB are important areas of work for USAID. It is critical to maximize existing U.S. Government investments. As such, USAID will continue to work with other USG agencies to leverage all U.S. Government resources and encourage partner countries and other key stakeholders to increase their country level and research support for TB.

Drug-resistant Tuberculosis

Despite recent gains in combating TB globally, the increase in drug-resistant TB threatens to reverse the progress made. Inadequate TB diagnosis and treatment contribute to the development and spread of MDR-TB, a form of TB that is resistant to two of the most important first-line drugs, and extensively drug-resistant TB (XDR-TB), which is resistant to first-line and some second-line TB drugs.

In October 2015, the G-7 Health Ministers signed the Berlin Declaration for Antimicrobial Resistance (AMR) to address this serious and growing public health issue. In December 2014, the O'Neill Commission AMR Review determined that by 2050, 10 million people will die each year from drug-resistant infections. There is also the potential to devastate economies, with an estimated output loss of $100 trillion from now to 2050. MDR-TB is one of the most common drug resistant diseases. More than half a million people develop MDR-TB each year. If the MDR-TB problem is not rapidly addressed, it will continue to grow, exacting a huge toll in terms of morbidity and mortality and potentially threatening national economies, particularly those of low income countries.

I had the privilege of working with WHO on the first MDR-TB survey nearly 18 years ago. Since then, WHO has updated this data every two years, providing critically important data for countries and the global community. MDR-TB now occurs worldwide, with an estimated 480,000 cases in 2014, making up about 3.3 percent of all new TB cases. XDR-TB has been reported in more than 100 countries. HIV and MDR-TB is a particularly deadly combination—people living with HIV are more likely to develop TB and those with MDR-TB are more likely to die, even if they are diagnosed and receive treatment.

MDR-TB is harder to cure and takes much longer. While more than 85 percent of TB patients who are diagnosed and notified are successfully treated, the WHO reports that globally only 48 percent of individuals diagnosed with and treated for drug-resistant TB (both MDR and XDR-TB) are treated successfully. If the spread of drug-resistant TB is not quickly prevented and controlled, TB-related deaths and treatment costs will increase dramatically. It will reverse the past twenty years of progress. The Obama Administration recognized the urgent need to address antimicrobial resistance, directing the U.S. Government to "work domestically and internationally to reduce the emergence and spread of antibiotic-resistant bacteria," under the Presidential Executive Order *Combating Antibiotic-Resistant Bacteria*.

The focus of our precious global TB resources has always been to develop strong TB diagnosis, treatment, and care programs to "turn off the tap" or stop the transmission of new cases, as well as prevent the development of MDR-TB. Countries have started to address their MDR-TB programs only after their national TB programs were established and achieved high TB treatment success rates. Countries that were successful in developing strong national TB programs have been able to keep their MDR-TB rates low. In many countries throughout the world, however, the breakdown in health service delivery systems, the poor quality of services in the private sector, and a lack of regulations on TB drugs has created MDR-TB.

Unfortunately, the tools to address MDR-TB diagnosis and treatment have been sub-optimal. It was only a few years ago that quality diagnosis of MDR-TB in high burden countries was even possible and even then it took months to diagnosis. Recently, new diagnostic techniques have given us the ability to diagnose MDR-TB within hours, such as Xpert MTB/RIF. USAID has made a significant investment in the scale-up of Xpert. In collaboration with CDC and PEPFAR, USAID provides a comprehensive technical approach to help countries successfully utilize Xpert. USAID partnered with PEPFAR, the Bill and Melinda Gates Foundation, and the manufacturer Cepheid to lower the price of Xpert cartridges for the developing world.

While significant gains have been made in rolling out this new technology, it is not fully available at the point of care—that is, it is not readily available at the clinics where individuals at risk seek care. Due to funding constraints, the test, despite being cost-effective, is still thought to be relatively expensive, and often "saved" for special circumstances rather than used as intended. As a result, many who might have been diagnosed are still missed. As seen in the global report released a few weeks ago, however, substantial progress has occurred in the diagnosis of MDR-TB, largely attributable to new molecular diagnostics. In 2014, 58 percent of previously treated patients (and therefore at highest risk of having MDR-TB), and 12 percent of new cases were tested, compared to just 17 percent and 8.5 percent, respectively, in 2013, an increase of 300 percent and 50 percent, respectively. Of the 123,000 cases detected globally, 111,000 started on MDR-TB treatment in 2014, an increase of almost 15 percent over the previous year. While MDR-TB treatment success remains unacceptably low at 50 percent, 43 of the 127 countries and territories that report treatment outcomes to WHO successfully treated more than 75 percent of patients.

I am very proud to note that USAID's support has been a key factor in much of this progress. In many of our priority countries, including Indonesia, Kenya, DR Congo, India and others, our partnership and technical support to National TB Programs has helped establish effective MDR-TB diagnosis and treatment capacities, including scaling up of the use of the GeneXpert

diagnostic tool. In Indonesia, for example, USAID worked in partnership with the Ministry of Health and the Global Fund to stand up MDR-TB diagnosis and treatment centers. There are now more than 30 in-patient MDR-TB treatment facilities and 900 MDR-TB treatment satellite sites across the country.

While the number of patients on treatment has doubled and tripled over the past several years, treatment scale-up is still much slower than desired for several reasons. First, until recently, diagnosis was lengthy and complicated, and individuals were lost to follow-up. Second, many programs felt ill-equipped to address a complicated disease that required toxic drugs for long periods of time. Initially, many countries believed that adequate treatment could only be delivered in clinic or hospital settings that had limited capacity. Great strides have been made in the past couple of years. Treatment is now being brought to the community level to provide patient-centered care. Community health workers and volunteers are being trained and are delivering care, and quality of care by private practitioners has improved. Progress has occurred in locally adapted treatment guidelines, and with the procurement of appropriate supplies of quality drugs. New, shorter and less toxic regimens are now being tested widely. The prospect is for a much more rapid scale-up in the near future.

TB and poverty

People living in poverty are more likely to develop TB and individuals with TB are more likely to be driven further into poverty. This year was a historic moment when world leaders adopted the 2030 Agenda for Sustainable Development, which provided the path to poverty elimination. Today, roughly 1 billion people live in extreme poverty. While that is still an overwhelming number of people—great progress has been made. Compared to 1990, today nearly one billion fewer people live in extreme poverty. By 2012, the poverty rate in the developing world had fallen to 15 percent from 44 percent in 1990. Together with our partners, President Obama has called for Ending Extreme Poverty and USAID has incorporated it into its overall mission of partnering to end extreme poverty and promote resilient, democratic societies while advancing our security and prosperity. USAID's TB program is critically important to achieving the SDGs for eliminating poverty and ending the TB epidemic.

TB disproportionately affects people living in poverty and imposes further financial hardships on TB patients and their families. Even when TB diagnosis and treatment are available free of charge, the cost of accessing care can be difficult for families to bear. On average, TB patients in low- and middle-income countries lose three to four months of work and up to 30 percent of their annual income. This financial burden is greater for persons with MDR-TB and for the extreme poor. Households affected by TB often resort to coping mechanisms that can cause further hardship. Children may be taken out of school to help an ailing parent or to seek paid work to support the family. Patients themselves may take out a loan, sell household items, or seek financial help from relatives. This healthcare-related impoverishment increases the future risk of TB for the entire affected family, thus continuing or worsening the cycle of poverty.

TB resource mobilization

TB is one of the key priorities of the Global Health Bureau at USAID. In FY2015, USAID's planned contribution was over $240 million towards the effort to combat TB. In fact, the U.S. Government is the single largest donor to TB programs globally through the TB portion of our contribution to the Global Fund to Fight AIDS, TB and Malaria (Global Fund), USAID bilateral funds, and PEPFAR TB/HIV funds. Further, the NIH, led by NIAID, supports a comprehensive biomedical research program in TB. These complementary efforts ensure the maximum impact to save countless lives and prevent the further development of MDR-TB.

The majority of the TB burden is in the BRICS countries (Brazil, Russia, India, China, and South Africa), consisting of almost 50 percent of all TB cases and 60 percent of the MDR-TB cases. While domestic resources make up 80 percent of all the funding in high burden countries, it is important for these countries to continue to devote resources to addressing this problem within their borders so that we can collectively achieve the global targets in TB. Over the past eight years, China has tripled and India has doubled its domestic TB budget. Many of the high burden TB countries are expected to continue on an economic growth trajectory of up to 9 percent per year. However, out of pocket health expenditures are above 30 percent for most of the high burden countries. As can be expected, government health spending improves with income level. Of the 22 high burden TB countries, there are 10 countries that have doubled their domestic TB investments over the past eight years, including Ethiopia with an eight fold increase over this time period. USAID will continue to work with countries to mobilize domestic resources for TB through a multi-pronged approach, as well as reduce out-of-pocket costs for those individuals that can't afford to pay.

USAID's TB Vision

Preventing the spread of TB and the development of resistant strains globally is vital to safeguarding U.S. national interests. Reducing TB morbidity and mortality is an important element of the USAID's efforts to improve global health and reduce poverty. The USAID's investments in combating TB have yielded impressive health dividends. Working in the highest burden countries that often provide limited access to quality healthcare, we have played a pivotal role in achieving global targets on TB prevalence and mortality. Since 2000, our contributions have helped these countries achieve a 43 percent decrease in TB-related mortality and a 42 percent decrease in TB prevalence.

USAID's efforts focus on: preventing the spread of TB through earlier detection of individuals with TB; support to develop high-quality TB treatment and care programs; creation and development of MDR-TB diagnostic and treatment services; and expansion of research and innovation capacity. USAID provides significant support for strengthening and expanding high quality TB programs in 23 priority countries. We provide focused assistance to an additional 31 countries to implement their national TB programs and Global Fund grants. Across its programs, USAID works closely with government, private sector, academia, and community partners to increase the impact and sustainability of USAID investments. With FY 2014 funding, USAID helped provide high-quality TB treatment for over 2.7 million TB patients, including 60,000 multidrug-resistant TB (MDR-TB) patients. USAID also worked closely with global country partners to improve TB surveillance and estimates of TB burden. USAID and CDC worked with WHO to support TB prevalence surveys in high priority countries, which resulted in a better

understanding of the TB burden. USAID also partners with the Global Fund, international donors, and affected countries to maximize the impact of the Global Fund's TB and TB/HIV grant portfolio of almost $4.5 billion disbursed across 100 countries since 2002.

Research has been a key part of USAID's portfolio since the program's creation. New treatment regimens that are safer and shorter are urgently needed. USAID supports projects designed specifically to explore ways to improve the diagnosis and treatment of MDR-TB. One example of a USAID-supported activity is the Standardized Treatment REgimen of Anti-tuberculosis drugs for patients with Multi-drug resistant Tuberculosis (STREAM) study, the first randomized clinical trial to evaluate standardized MDR-TB treatment regimens. STREAM was developed to determine whether a nine-month treatment regimen as opposed to a 20-month or longer regimen for MDR-TB is both better for patients and more cost effective for health systems. The Phase II of STREAM study will determine whether two standardized regimens for 6 and 9 month containing bedaquiline, with and without injectables are better than the current WHO recommended 20 month or longer regimen. In addition, in several countries, CDC and USAID have worked side by side on select TB research projects.

In another example, USAID and the Gates Foundation, through the Global Alliance for TB Drug Development, contributes to the development and testing of novel drug compounds and new drug combinations. One of these, the Nix-TB study, is the world's first clinical trial to study an XDR-TB drug regimen with only pills, no injections. The Nix-TB regimen consists of a combination of three drugs with the goal of curing XDR-TB in six to nine months. If successful, the injection-free regimen being tested in Nix-TB could transform XDR-TB treatment, with patients being cured by taking a relatively short, simple, and effective regimen. Importantly, the regimen being tested could reduce the complexity and cost of the treatment to a fraction of what it is today, facilitating the global implementation of XDR-TB treatment in resource-poor nations.

USAID also invests in strengthening TB diagnostic networks. Quality diagnostic networks enable health facilities to provide rapid, accurate diagnoses for individuals with all forms of TB. This in turn enables providers to initiate appropriate treatment for TB patients quickly, thereby improving patient outcomes and reducing the spread of TB. At the national level, USAID helps countries strengthen laboratory and diagnostic networks to increase access to services, such as culture, molecular testing, and drug susceptibility testing. USAID also works with ministries of health to help them map and develop clear plans to strengthen key diagnostic services, such as developing algorithms for introducing new diagnostic tools along with quality-assured smear microscopy. USAID and CDC have worked together in several countries to optimize new tools and strengthen national reference labs.

Conclusion

The U.S. Government is committed to directing its future investments in high-burden TB countries to achieve even greater global health progress. As laid out in the U.S. Government Global TB Strategy (2015 – 2019), the U.S. Government will work with affected countries and international partners in an effort to reach every person with TB, cure those in need of treatment, and prevent new infections and curb the spread of the disease. Under this strategy, the U.S. Government will work to reduce TB incidence by 25 percent from the 2015 levels, successfully treat at least 13 million TB patients, initiate appropriate treatment for at least 360,000 MDR-TB patients, and provide antiretroviral therapy (ART) to 100 percent of registered HIV-infected TB

patients by 2019. USAID will lead the implementation of this strategy, in close coordination with other U.S. Government agencies involved in global TB care.

Healthy, productive citizens are essential for global economic growth and regional security. USAID is committed to working with partners and high burden countries to combat this leading infectious killer. We will optimize our investments to make the most impact towards the objectives of the 2030 Agenda for Sustainable Development, WHO END TB Strategy and the Stop TB Partnership's Global Plan to end TB by 2030. Achieving these ambitious targets cannot be done by the U.S. government alone – even if we are a significant partner – but will require substantial domestic and private sector resource mobilization and increased global attention. Millions of lives have been saved from this terrible disease through concerted and coordinated effort. I am confident that together we can End TB by 2030.

Thank you very much for giving me the opportunity to share some perspectives on USAID's fight against TB. I look forward to your questions.

Mr. SMITH. Thank you so very much, Doctor.

Just let me begin the questioning. In talking about the diagnostics, if you are talking about Lyme disease or any other disease out there, the response is only as good as the diagnostics.

And so the Gene Xpert that has been talked about by all of you: How much does it cost, who manufactures it, and are orders coming in or requests coming in all over the world for it, to put it into this healthcare setting or that?

And what kind of infrastructure does that require? Is it adaptable to a very rural situation in a developing country?

Dr. FRIEDEN. Maybe I will start and then Dr. Pablos-Mendez will continue.

As you point out, Chairman Smith, the key is a laboratory network. A laboratory network includes a national lab. That might be a reference lab, sometimes a supranational lab.

At CDC, we have been able to support, for example, the African Society for Laboratory Medicine, which has strengthened laboratory systems in dozens of countries around Africa.

And then within countries, you need to have the diagnosis at the point of care or diagnosis at an intermediate level and then at referral levels.

Different tests are appropriate and effective for different levels of the healthcare system. We don't yet have the ideal test for tuberculosis.

Today in west Africa we are using point of care tests for Ebola that give us a preliminary result in 20 minutes. We don't have that for TB.

But the Gene Xpert is a major advance as are other rapid molecular diagnostic tools which allow us to get in a few hours at least a preliminary result or, in the case of Gene Xpert, a definitive result about the presence of resistance mutations or the presence of tuberculosis bacteria.

There are some requirements, some of them more fixed than others in terms of refrigeration and electrical supply, and I would emphasize that it doesn't replace the need to have and strengthen core diagnostic systems including microscopy, sputum collection, sputum referral, specimen transport, and follow-up.

But it is a very important new tool that has allowed us to greatly increase the diagnosis of drug-resistant TB which is a preliminary step to improving the treatment of drug-resistant TB.

Dr. PABLOS-MENDEZ. Thank you.

Indeed, I think the laboratory structure Tom alluded to and as we spoke of, the overall surveillance of MDR–TB, all this network of global reference—regional reference level to a national reference laboratory is, indeed, one of the best in class.

I think in bacterial it has been an incredible accomplishment. USAID has been a proud supporter of that global network of reference laboratories for surveillance.

As you go down, indeed, and as you go into the clinical phase it, indeed, depends on the network of laboratories on the ground.

On the Xpert system, I think that we feel it really has been a game changer and it is in the process of scaling up and, Chairman Smith, I noted that in the year 2011 there were 500,000 cartridges.

The cartridges are really straightforward and in 2 hours you can get a result that used to take 6 weeks or more in the regular laboratory.

Now, from 500,000 we have increased tenfold by as of last year to about close to 5 million cartridges, which is quite significant, and this is being driven now by the demand of countries themselves.

We are working with WHO, with CDC to provide us the technical guidance, technical assistance and the cartridges themselves are increasingly adopting these. India is now also working to develop even cheaper alternatives and maybe they will succeed.

But they have been good to do other things and I think that that will add. The price of the cartridge itself came down from over $20 apiece to less than $10 and that alone has helped us save over $50 million in the last year or so.

So I think that the economics of this system will allow us to continue the expansion and the demand because it is performing.

Mr. SMITH. Let me just ask, the—2035—and this is not, why—end TB by 2035. Alzheimer's is 2025. The post-2015 so, say, the Sustainable Development Goals are 2030. Was that arrived at with some realistic set of benchmarks that might be achievable or is it aspirational?

Dr. FRIEDEN. I would say it is aspirational. Fundamentally, we need to do two things in tuberculosis. First, implement what we know how to do but isn't getting well implemented everywhere, and there is still a big gap between what we could be doing and what we are doing.

Far too many patients are not getting promptly diagnosed, not getting effectively treated and far too much tuberculosis is spreading in healthcare facilities and elsewhere.

We also need to continue to innovate. We need better diagnostics. We need better treatment and, ideally, we would need a vaccine. So I don't see a clear pathway with the tools at hand to get to that goal.

It is aspirational, but I do see a real urgency of doing those two things now—implementing what we know, better, for more patients and continuing to learn more.

Dr. PABLOS-MENDEZ. Congressman, if I may add, TB is different than most other infectious diseases and you are really an expert because you have been looking to so many of them.

But in many other diseases, as the problem of the disease shrinks and the manifestations shrink, usually the problem, indeed, is smaller and over time it is ended.

With tuberculosis, because 2 billion people are estimated to be already infected, about 10 percent of which will activate the disease, as we heard earlier from Dr. Goosby, even if we could totally perfectly treat all cases of TB and MDR–TB today, you will still see TB coming up for decades to come.

So, indeed, I think while it is a fact that we have moved from the control to stop as we now begin to see the declining incidence and dramatic declines in mortality, we can now move to a vision of elimination and to end tuberculosis. The tail end is going to be longer than some of the other diseases we are fighting today.

Mr. SMITH. Bedaquiline, the first new drug in 40 years or 50 years, you mentioned some others are in the pipeline.

Now, is that just the U.S. pipeline or is it, as I suspect, the European pipeline as well and how less rigorous might their standards be vis-a-vis FDA that might get it onto the market sooner?

Dr. FRIEDEN. There is a global collaboration to develop new drugs, and Dr. Pablos-Mendez can speak more about this. At CDC, we have participated in clinical trials in many countries.

Tuberculosis control is interesting in that there really has been a global collaboration. The U.S. Public Health Service, the Medical Research Council of the United Kingdom, the Japanese, Hong Kong, many other countries have done some of the best studies of the drug efficacy for any disease ever over a period of decades. There is good global collaboration and there are definite standards for efficacy.

One of the challenges with some of the newer drugs is that there may not be a large number of patients with drug resistance to be tested and that the outcomes may not be as good as we would like.

But there are trials underway and there have been trials underway for some time to look at what may work better. The new drugs are encouraging, but exactly as was stated earlier, at this point their role is a reserve role for when the tried and true drugs that are so well documented to be both effective and safe are no longer, unfortunately, effective.

Dr. PABLOS-MENDEZ. Well, the modern era of antibiotic randomized clinical trial started with tuberculosis streptomycin back in 1948.

We had a period of a lot of products coming in the 1950s and 1960s and then we stopped and we have been using those which, when well deployed correctly can be very effective.

But resistance is natural when you use an antibiotic and, indeed, that was the wake-up call back in the year 2000.

In the last 15, indeed, the PPPs for tuberculosis: The NIH at the basic research levels, companies sharing their chemical libraries showing you companies who came with innovation.

So now we have a richer pipeline. Tuberculosis is slow. The nature of the disease means the clinical trials are more complicated, as Tom alluded, and so we have a tradition of that partnership to tackle this.

MDR–TB is particularly challenging but, nonetheless, so we are proud now we are entering an era of randomized clinical trials with new drugs for MDR–TB as well.

Mr. SMITH. Let me ask you, Dr. Frieden, in your testimony you spoke of the 450,000 immigrants and 70,000 refugees who are rigorously screened and before entry into the United States have to be cured prior to entry.

Since we do have a very sizeable number of people who are not legal, what can be done, what is being done to ensure that they are not carrying this disease?

Similar to that with war and conflict being ever present in so many parts of the world, especially in the Middle East and Syria and Iraq, I am always reminded that more people died of the misnamed Spanish Flu than from World War I, and who knows if that was the proximate cause, but a lot of experts have suggested it

probably was laying a groundwork for that terrible disease or that pandemic to occur.

Is there a risk of a huge exponential explosion because of what is happening in places like Syria and Iraq? That would be global I am talking about, but especially in the maleffected area.

Dr. FRIEDEN. In the United States currently, about two-thirds of all of our tuberculosis cases are among people who were born abroad.

Those cases include people from China, from India, from Vietnam, Philippines, from South Korea, and many of them occur in people in who have been here for many years because, as has been discussed earlier, tuberculosis resides in your body and can be there for many years before you develop active tuberculosis.

There are several things that we are doing to advance this and make further progress. You mentioned the program we have for immigrants and refugees. We think that is a highly successful program.

It has been great for the immigrants and refugees. It has been great for their host countries, which have better services, and great for us in this country.

One of the components of the antibiotic resistance proposal, which is now under consideration in Congress as part of the Fiscal Year 2016 budget, would expand some of that screening program for countries with very high rates of tuberculosis and high numbers of people coming into this country to long-term visitors such as people coming on certain kinds of work visas or student visas.

In addition, it is very important that the services for tuberculosis patients in this country are provided to all patients with tuberculosis because it is in everybody's interest that they get treated quickly and completely, and that is one of the things that we work very closely with health departments throughout the United States for.

Our budget in the U.S. for tuberculosis control is a little bit over $140 million a year and with that we make sure that funds are available to treat every patient from a public health standpoint—not just clinically, but to make sure that contacts are followed, that they are provided with support, that they receive directly their treatment to maximize the likelihood that they will be cured and not develop drug-resistant tuberculosis here because we know that if that were to happen it would cost us far more than the prevention costs us today.

Mr. SMITH. In terms of ensuring that U.S. personnel and other healthcare workers around the world are properly protected, two of you today have said you have TB only because you cared enough to deal with patients who had TB.

What could be done to protect our USAID people, our healthcare professionals, the NGO community? Is there enough being done along those lines?

Secondly, I was concerned that the administration's budget had a $45 million cut for TB. I am absolutely sure people in this room are no way a part of that.

I will never forget when I was chairman of the House Committee on Veterans Affairs I asked Tony Principi, who was then the Secretary, who came in with a budget that OMB had slashed to bits

and they said how much did you ask for that you didn't get and he said about $1 billion, and we immediately moved the goalpost to include that $1 billion and got it, and he was raked over the coals.

So I don't want any of you to get raked over the coals, but if you had additional resources, $236 million is what is likely to be in the 2016 budget.

Is it enough? Not taking to task the proposed cut of $45 million but, Congress, in a bipartisan way said no, not going to happen, we at least want to get up to $236 million.

How much more should be provided, in an ideal world where you really can say look, this is what we will do. We know, you know, Dr. Goosby, it is over $1 billion globally. If you could maybe speak to that.

Dr. FRIEDEN. Let me take your first question first, Mr. Chairman.

There are three things we can do to protect Americans working overseas from tuberculosis. The first is to improve the tuberculosis treatment programs in those countries because TB rates can actually come down quite rapidly.

The study that I was part of in India, funded by USAID, done at what is now called the National Institute for Research on Tuberculosis, showed that you could get a very rapid control of tuberculosis prevalence by treating effectively and if you have got half as many patients around in just 5 years you have half the risk of getting infected.

So the first thing is to help those countries have effective programs. The second is to improve infection and control in healthcare facilities. There is still far too much TB being spread in healthcare facilities all over the world and there are a series of things and at CDC we have launched a program called TB BASICS on infection control that has resulted in very rapid improvements in Nigeria, India and elsewhere in infection control in healthcare facilities so that it is less likely that any healthcare workers, U.S. or others, will get infected.

The third is on a matter of personal health. It is very important for healthcare workers to be tested periodically to see if they have become infected with either the tuberculosis skin test or another more sophisticated or separate test that would look at whether or not you are infected and if you are infected to get preventive treatment.

On your second question of resources, exactly 100 years ago in 1915 one of the great public health leaders in New York City wrote that public health is purchasable. Within natural limitations, a community can determine its own death rate.

That was Herman Biggs and he actually made his career on tuberculosis, establishing rapid diagnostic facilities throughout the city in the 1890s.

So some things never change and some things do. But, clearly, there is a need for more resources to expand programs that are effective and also to offer countries around the world matching funds so that they will increase their expenditure as well and to advance innovation so that we have new tools to fight tuberculosis in the coming years.

Dr. PABLOS-MENDEZ. Chairman Smith, thank you again, and you are right about our own staff facing risks and we do, of course, follow the guidance of those who interact with communities who are in difficult settings or who have themselves some vulnerabilities to follow guidance that exists to protect them against getting infected and against reactivating disease, and this is one of the many reasons you allow me.

I will also—on Saturday—just on Saturday a special service to one of the staff of our partners implementing work in Mali, Anita Datar, was killed in the terrorist attack at the Radisson Blu Hotel.

She represents the best of an American hero and we have many American heroes who have faced the ultimate sacrifice. But when you face the ultimate sacrifice by helping save the lives and improve the lives of others it deserves our greatest respect and recognition.

On the budget question, you are right—and Tom has already made the point; the United States is right now the largest donor in the fight against tuberculosis and that is something we can feel very proud of not only through the bilateral line, the USAID budget, also through PEPFAR, through the NIH, through the Global Fund and I am going to talk to you next week when we will begin the replenishment conversation.

We need to make sure all the countries remain committed also to the fight against AIDS, TB, and malaria. And we have seen the results of that commitment. As we said before, almost cutting mortality by half.

Incidence was now reversed down and the diagnostic kits going fivefold, tenfold, and in treatment of MDR–TB threefold. We can and we need to do more. We need new tools. The current tools will get us into other trouble.

That is, you treat a patient with MDR–TB, you develop total resistance, et cetera. But more importantly, we will continue to work in domestic resource mobilization.

So we appreciate the support that you have entrusted in us. We are doing very well with those but we will need more. We will need more for the other countries to also come in.

Mr. BERA. This is great bipartisan teamwork, Democrats and Republicans working together. I think both of you in your testimony, and Dr. Goosby, certainly talked about this.

We can win this. We can eliminate tuberculosis, right. It does take a concerted effort and we just have to look at our own history. If we think about smallpox in the 20th century killed hundreds of millions of individuals just in the 20th century.

But we came together as a world, as multiple countries, to eliminate smallpox and the last natural occurring case of smallpox was 1977, I believe, in Somalia.

We are close on polio. Now, it's not apples to apples. We had a very effective vaccine for both polio and smallpox. But it took a focused worldwide effort to say we are going to eliminate this and we did it.

So it is going to take that effort because the downside of not doing it is going to cost us exponentially much more money in resources and lives lost in morbidity.

If—and maybe I will start with Dr. Frieden—if we are, you know, thinking about this, obviously, we don't have a vaccine similar to what we had as a tool to fight against smallpox and what we are using to fight against polio.

I do know that in Europe they use BCG a fair bit and, certainly, in endemic countries they use the tuberculosis vaccine for kids and others. Efficacy of that vaccine, you know, how does that fit into the arsenal?

Dr. FRIEDEN. BCG is the world's most widely used vaccine. It is used at birth in most of the world. It is effective at reducing two particular serious forms of tuberculosis in children—TB meningitis and miliary tuberculosis.

Unfortunately, it has a very little effectiveness at reducing tuberculosis overall in children or in adults. There have been many efforts to develop better vaccines but they are challenging, and as you point out, with smallpox and polio we have had the benefit of vaccines.

With tuberculosis, think of the world as those with healthy immune systems and those without healthy immune systems. Among those with healthy immune systems, tuberculosis control program can result in 95 percent cure rates and can cut the rate of tuberculosis in half in a decade or less.

In the context of HIV and other immunosuppressive conditions, we have many more challenges and we have seen, of course, exponential increases in Africa.

As we expand HIV treatment reconstituting the immune systems of whole communities, there is the documentation of a modulation and a reduction in the rate of tuberculosis.

But right now, the goal to eliminate tuberculosis globally is aspirational and relies on new technologies.

Dr. PABLOS-MENDEZ. Mr. Bera, first, I share the spirit that you alluded to and all our history. So I am thinking the big picture here and as you did with smallpox or now in the middle of polio.

We are in the midst of a historical transition in the traditional challenges of global health. We have to always keep our guard up. That has been one of the key lessons of tuberculosis.

But it is also beyond smallpox or now polio, which is close at hand, and thanks to Tom also for the leadership on that space. The reduction in measles over 80 percent, reduction in leprosy over 90 percent.

Many of the NTDs are now slotted for eradication as well. We are in a period of which it is possible. We have shown it is possible because we invested resources, the partnerships and the commitments.

We can indeed roll back many of these things. The idea to end tuberculosis, while aspirational at this point, is directionally correct.

As I said before, a few years ago we were still growing. Now we are going down and that is a very significant shift. We need to continue to make sure that we treat tuberculosis right. DOTs has been the most cost effective intervention that we have for 25 years.

In SDGs, the Copenhagen Consensus lists the no-brainers and DOTs remains one of the no-brainer investments for regular TB for

mortality among the poor and to prevent MDR–TB when done right.

So I think that even though it will have a longer tail to end for the reasons we explained earlier about the infections—the long termination of the infection—that, indeed, the vision is correct, the direction is correct and I think this generation will get us to a point we couldn't have imagined possible 20 years ago.

Mr. BERA. Absolutely. So again, there is not enough aspirational thinking in this town. So let us aspire to what we don't know exactly how to do today but we know that if we don't think about it, if we don't think about this in terms of elimination, we won't get there.

So if we are going to continue on this theme of kind of the aspirational goals, if we are laying out where we make our investments hypothetically, obviously, vaccine development, vaccine research is important, continuing to have therapies in our arsenal for the existing cases, et cetera.

Tom, you touched on the fact that we can't think about this in isolation because with healthy populations, you have got one approach. But as we saw in the 1980s and 1990s as HIV emerged, you saw this reemergence of tuberculosis.

How would you go about treating these co-morbid conditions?

Dr. FRIEDEN. If you go back 100 years, the TB social reformers talked about clearing out the crowded slums where there was no ventilation and people were together—the isolated people who were sick—and they went for better nutrition.

Ironically, we have kind of come full circle. We recognize that while TB can be cured, we also have to try to improve the social context in which it occurs because that will reduce the rates—something like expanding ARV—antiretroviral treatment—to all people who are HIV positive will dramatically reduce TB rates.

But in terms of your question about prioritization, I would think of, broadly, four categories—diagnosis, treatment of disease, treatment of latent TB infection, and then vaccines.

Vaccines are challenging since it is hard for us to do better with the vaccine than Mother Nature does and since we don't have great immunity from tuberculosis from infection that makes it challenging but still well worth doing. A TB vaccine would be worthy of a Nobel Prize.

For diagnosis we have lots of advances and the really exciting developments with molecular diagnosis are changing the way we do this.

We now can identify most of the mutations that lead to resistance to first- and second-line drugs within a couple of days in sequencing in the laboratory and that is getting less expensive, more accessible, quicker. The computing power is big but we are learning more about that.

In terms of treatment, we are looking at new regimens. One of the areas that I think is particularly exciting is the idea of improving the treatment of latent tuberculosis infection.

At CDC, our clinical trials consortium working with others has identified a 12-dose regimen of weekly isoniazid and rifapentine directly observed as equivalent to other preventive regimens.

So you have now got a 12-dose regimen completed in 3 months. If we could add that to studies that would help us identify which of the people with infection are most likely to progress the disease because currently it is 5 or 10 percent.

So you are treating 85, 90, 95 people to prevent those five cases. And if we could identify those individuals then we could target preventive or treatment of latent TB infection there we might be able to drive down future cases quite substantially.

So there are lots of really exciting areas for research in investigation and innovation and, of course, the way innovation works it may be something totally different from these that makes the difference.

Dr. PABLOS-MENDEZ. Thank you.

Indeed, the U.S. Government strategy on TB control that was released earlier this year that really brings all of the agencies together has clearly stated goals. It is to reach, to cure, to prevent.

And to reach means, indeed, to go for those who currently are not being diagnosed and so improving the diagnosis is very important and we are doing that.

Then to treat, cure is paramount. DOTs remains the basis, I think, for most of what we do in the TB control, but now MDR–TB is very important.

And then prevent—the vaccine, as you just heard the discussion on vaccines, but also infection control—very important. When we were in New York and the crisis that we had in Eastern Europe in prisons, New York hospitals, Eastern Europe prisons, if you don't isolate patients, you just spread the disease.

And so I will just stress that it is reaching, curing, and preventing disease is indeed where we are putting our money. It is working.

We need to do more and we need to do better and the investments in research remains significant. We couldn't be here without the research that we invested 10, 20 years ago.

Mr. BERA. Talk about those investments and have outlined the U.S. investments in terms of combating tuberculosis as well as on many other conditions.

Who are the big foundational players in philanthropy? Are Gates and others investing?

Dr. FRIEDEN. Gates has done quite a bit in tuberculosis control as they have in other areas and they have done the whole gamut of research from vaccines to diagnostics to treatments to programmatic initiatives in both India and China as well as elsewhere.

One of the challenges we have is that although we wish we had better tools and we hope we will have better tools soon, our currently existing tools are not being used for a large proportion of patients and that is something that we really need to urgently address. Other countries such as Japan also have traditionally invested substantially in tuberculosis control globally.

Mr. BERA. So, first making sure the tools that we have available are actually available to the countries that need them, right.

So, again, it brings us back to Gene Xpert, which really seems like—yes, try to get that out there as much as possible and get

folks using it while we are discovering the next generation of diagnostic and therapies.

Thank you.

Mr. SMITH. Let me just ask one final question.

The National Action Plan to Combat Drug-Resistant TB, is that soon going to be announced or has it? I might have missed it.

Dr. PABLOS-MENDEZ. It is a very important plan and it is under development. We don't have a date yet for the release. But you can see we are all champions and we have been working on it.

Mr. SMITH. Finally, I just want to say, again, I think it has been very clear that our efforts are bipartisan and very strong.

If there is a way this subcommittee could be of help, we are in constant contact with our friends on the appropriations side, Kay Granger and, of course, over on the Senate side as well.

If there is a way we can be helpful let me know, let us know so we can rally the troops, so to speak. And is there any authority, any legal authority that you are lacking or a push that in legislation that might be helpful?

Dr. Pablo-Mendez, you have been very helpful in helping us on our neglected tropical disease legislation, which I think will make a difference. You are doing a magnificent job on it but we always need to do more.

So many people are walking around with parasites and worms. So if we could be of help, this subcommittee will have your back as best we can to push this. And it is an open door, obviously, because you are leaving.

But I think the game changer, frankly, was in terms of getting people's attention in Congress was that report from about a month ago, which you really just put in neon lights that this is the leading killer of people by infectious disease in the world.

So if there is any specific authority you need or anything along those lines.

Dr. PABLOS-MENDEZ. I will say that, first of all, thank you again because I know that you have been great champions across our programs in global health and for tuberculosis in particular and bringing attention with this hearing also.

So it is part of what we need and it is very helpful. It has been helpful to our agencies. It is helpful in the U.S. Government as a whole.

We have a coordination effort across the USG. CDC, of course, has been a partner all along and we have worked with CDC for many years, even before I was at USAID.

We have a particular responsibility domestically but also great technical partners in the fights against TB globally.

The NIH is the lead for research in tuberculosis. The USAID has the lead when it comes to the international TB control efforts and funding us on. PEPFAR, very important when it comes to TB, HIV. And so I think we have, as you can see in the plan, a coordination platform for efforts and domestically I think Tom can speak to us to how much more we will need.

But I like the idea that you have for Dr. Goosby earlier of linking the parliamentarians to make sure that the voice of tuberculosis is heard across many other halls because we really need the support

not only for my own taxpayers, as we said before, but also from others.

Dr. FRIEDEN. Thank you, Mr. Chairman, for all of your support for issues to support people with tuberculosis as well as global health in general, and Dr. Bera, for your deep knowledge and experience with public health and your commitment to it.

To answer your specific question about authorities, I think this is something about which we will be having discussions over the coming months.

One of the things that we have thought about coming out of the Ebola response was are there things that would have allowed us to be even quicker in our response, even more effective than we were.

So that is one area that we will be looking at and possibly coming back to you on.

Mr. SMITH. Thank you. On that very thing, I recently met with a group that actually makes emergency vehicles that can carry Ebola patients. Turns out it is my district.

I have no financial connection whatsoever. But when I sat with a great deal of attention, which I will convey to you, but it certainly would have applicability here as well.

And we are told——

Dr. PABLOS-MENDEZ. I am happy to hear.

Mr. SMITH [continuing]. That Liberia is very interested in this. So if our witness wanted to——

Dr. PABLOS-MENDEZ. We're with you——

Mr. SMITH. Yes.

Dr. PABLOS-MENDEZ [continuing]. We were here together in August the year before when it was really depth of the fear of Ebola. But, really, safe transportation was a big, big issue. And so any technology, any innovations that help us in that is certainly welcome.

Mr. SMITH. Thank you.

Dr. Bera, thank you, and thank you, gentlemen, and Dr. Goosby, thank you.

Without objection, the hearing record will stay open for 5 legislative days. There are a number of people who would like to submit testimony and we have one from the American Thoracic Society.

Without objection, so ordered, and the hearing is adjourned and I thank you very much.

[Whereupon, at 3:39 p.m. the committee was adjourned.]

APPENDIX

Material Submitted for the Record

SUBCOMMITTEE BRIEFING & HEARING NOTICE
COMMITTEE ON FOREIGN AFFAIRS
U.S. HOUSE OF REPRESENTATIVES
WASHINGTON, DC 20515-6128

Subcommittee on Africa, Global Health, Global Human Rights, and International Organizations
Christopher H. Smith (R-NJ), Chairman

December 1, 2015

TO: MEMBERS OF THE COMMITTEE ON FOREIGN AFFAIRS

You are respectfully requested to attend an OPEN briefing and hearing of the Committee on Foreign Affairs, to be held by the Subcommittee on Africa, Global Health, Global Human Rights, and International Organizations in Room 2200 of the Rayburn House Office Building (and available live on the Committee website at http://www.ForeignAffairs.house.gov):

DATE: Tuesday, December 8, 2015

TIME: 2:00 p.m.

SUBJECT: Drug-Resistant Tuberculosis: The Next Global Health Crisis?

BRIEFER: The Honorable Eric P. Goosby, M.D.
Special Envoy on Tuberculosis
United Nations

WITNESSES: Tom Frieden, M.D.
Director
Centers for Disease Control and Prevention

The Honorable Ariel Pablos-Mendez, M.D.
Assistant Administrator
Bureau for Global Health
U.S. Agency for International Development

By Direction of the Chairman

The Committee on Foreign Affairs seeks to make its facilities accessible to persons with disabilities. If you are in need of special accommodations, please call 202/225-5021 at least four business days in advance of the event, whenever practicable. Questions with regard to special accommodations in general (including availability of Committee materials in alternative formats and assistive listening devices) may be directed to the Committee.

COMMITTEE ON FOREIGN AFFAIRS

MINUTES OF SUBCOMMITTEE ON *Africa, Global Health, Global Human Rights, and International Organizations* HEARING

Day *Tuesday* **Date** *December 8, 2015* **Room** *2200 Rayburn HOB*

Starting Time *2:01 p.m.* **Ending Time** *3:39 p.m.*

Recesses [*0*] (____to ____) (____to ____) (____to ____) (____to ____) (____to ____) (____to ____)

Presiding Member(s)

Rep. Chris Smith

Check all of the following that apply:

Open Session [✓]
Executive (closed) Session [ ]
Televised [✓]
Electronically Recorded (taped) [✓]
Stenographic Record [✓]

TITLE OF HEARING:

Drug-Resistant Tuberculosis: The Next Global Health Crisis?

SUBCOMMITTEE MEMBERS PRESENT:

Rep. Ami Bera

NON-SUBCOMMITTEE MEMBERS PRESENT: *(Mark with an * if they are not members of full committee.)*

Rep. Eliot Engel

HEARING WITNESSES: Same as meeting notice attached? Yes [✓] **No** [ ]
(If "no", please list below and include title, agency, department, or organization.)

STATEMENTS FOR THE RECORD: *(List any statements submitted for the record.)*

Statement of the American Thoracic Society, submitted by Rep. Chris Smith
Statement of Aeras, submitted by Rep. Chris Smith

TIME SCHEDULED TO RECONVENE _____
or
TIME ADJOURNED *3:39 p.m.*

Gregory B. Simpkins
Subcommittee Staff Director

MATERIAL SUBMITTED FOR THE RECORD BY THE HONORABLE CHRISTOPHER H. SMITH, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY, AND CHAIRMAN, SUBCOMMITTEE ON AFRICA, GLOBAL HEALTH, GLOBAL HUMAN RIGHTS, AND INTERNATIONAL ORGANIZATIONS

Subcommittee on Africa, Global Health, Global Human Rights, and International Organizations Hearing

Drug Resistant Tuberculosis: The Next Global Health Crisis?

Statement of the American Thoracic Society

December 8, 2015

Contact:
Nuala Moore, Assoc. Director of Government Relations
American Thoracic Society
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The American Thoracic Society is a 15,000 member international scientific society representing pulmonary, critical care and sleep medicine. Founded in 1905 as the American Sanatorium Association, the ATS maintains a strong focus on global and domestic TB control and research. The ATS thanks Chairman Smith and Ranking member Bass for holding this hearing into one of the leading global health threats, drug resistant tuberculosis (TB). We also thank the subcommittee for this opportunity to submit a statement for the record.

Tuberculosis (TB) is now the leading infectious disease killer in the world, with 1.5 million deaths from the disease reported in 2014.[i] It is the third leading cause of death in women of reproductive age. In sub-saharan Africa, TB is the leading killer of people with HIV/AIDS. The rise in HIV infection levels and the neglect of TB control programs have caused a global resurgence of TB. 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 drug resistant TB. The continued TB pandemic threatens to undo much of the progress made by the U.S. investment in the fight against HIV/AIDS through PEPFAR, particularly in sub-Saharan Africa.

Drug Resistant TB

Multi-drug resistant (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. MDR-TB is very complex and expensive to treat and as a result of these factors, fatality rates from MDR-TB in developing countries are high. XDR-TB, extensively drug resistant TB, which has been identified in most countries, including the U.S., is even deadlier. The WHO estimates that there about 480,000 cases of multi-drug resistant globally but less than 25% of MDR-TB patients are being identified and treated.[ii] The convergence of several factors threatens to result in drug resistant 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. 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.

Drug Resistant TB in the U.S.

In its 2013 report on antibiotic resistance, the CDC identified drug resistant TB as a serious health threat to the U.S.[iii] In 2014, the U.S. had 91 cases of multi-drug resistant (MDR) TB.[iv] California has an estimated 15 – 25 cases of MDR-TB each year. Additionally, between 1993 and 2011, the U.S. had 63 cases of XDR-TB and in 2015, there are at least 2 cases of XDR-TB in the U.S. [v] MDR-TB is extremely expensive to treat in the U.S., costing between $300,000 - $500,000 to treat per case, costs which can completely outstrip state TB control program budgets and XDR-TB is even more expensive to treat, with costs that can exceed $1 million.

Drug Resistant TB Treatment

Treatment for MDR- TB is an 18 – 24 month regimen of old antibiotic drugs including injectables that have severe side effects including hearing loss and psychosis, making the

regimen very difficult for patients to tolerate. Patients compare MDR-TB treatment to cancer chemotherapy. A recent CDC study found that nearly three-quarters of U.S. MDR and XDR patients had to be hospitalized for at least one month.[vi] The long and arduous treatment regimen is a key reason why only a quarter of people globally are being identified and placed on treatment for drug resistant TB and only 50 % are successfully treated.[vii]

TB Research and Development

Only one new MDR-TB drug, bedaquiline, has been developed and FDA-approved in the last 45 years. In order to halt the global spread of drug resistant TB, new drugs and shorter, more tolerable treatment regimens must be developed. A shorter drug regimen with new classes of drugs active against susceptible and drug-resistant strains would increase compliance, prevent development of more extensive drug resistance, and save program costs by reducing the time required to directly observe therapy for patients.

The Xpert Mtb/RIF diagnostic, rolled out in 2012, has significantly improved and speeded up TB diagnosis around the world. But current diagnostic tests to detect drug resistance take at least one month to complete. Faster drug susceptibility tests and a point of care TB diagnostic test must be developed to stop the spread of drug resistant TB and there is also a need to develop an easier, more accurate TB diagnostic for children. The TB vaccine, BCG, provides some protection to children, but it has little or no efficacy in preventing pulmonary TB in adults. The National Institutes of Health (NIH), specifically, the National Institute of Allergy and Infectious Disease (NIAID), is the leading global funder of TB research and development, from basic science to clinical drug trials.

New End TB Strategy

The END TB Strategy, 2016 – 2035, developed by the WHO, Stop TB Partnership and global partners, was passed by the World Health Assembly in May 2014. The strategy aims to end the global TB epidemic, with targets to reduce TB deaths by 95% and to cut new cases by 90% between 2015 and 2035, and to ensure that no family is burdened with catastrophic expenses due to TB.

USAID TB Program

The U.S. Agency for International Development (USAID) is the largest bilateral donor supporting global TB prevention and control in the 23 most highly-burdened countries, such as India, South Africa, Indonesia and Uganda. USAID's overall goal is to contribute to the global reduction of morbidity and mortality associated with TB. USAID supports the implementation of the WHO END TB strategy in priority countries. USAID provides financial and technical support to five main areas including DOTS (directly-observed treatment short course therapy) expansion and enhancement, scaling up management of MDR/XDR, addressing HIV/TB co-infection, strengthening health systems and human resource capacity and developing new tools and improved approaches. The program has had notable success in scaling-up drug resistant TB programs and this work must be expanded to stop the spread of drug resistant TB. The USAID also supports critical research and development efforts, including late stage clinical drug trials. The agency was a key supporter of the first-ever TB drug formulation for children, introduced by the TB Alliance in December 2015.

CDC Global TB Activities

CDC is recognized globally for providing leadership and technical assistance in infection control, epidemiology, surveillance (including drug resistance surveys), program and laboratory services development, monitoring and evaluation, operations research and training, improving diagnostic services, and identifying clinical factors important to TB outcomes. The CDC provides technical assistance under the President's Emergency Plan for AIDS Relief (PEPFAR) initiative, and to the United States Agency for International Development (USAID) in over 20 countries.

Recommendations

Although TB is now the leading global infectious killer, TB control and research and development remain chronically underfunded. The ATS urges the Administration to release the National Action Plan to Combat Drug Resistant TB and to propose robust funding for its implementation in the President's FY2017 budget in recognition that TB is now the leading global infectious disease killer. We urge the Congress to allocate robust funding for the National Action Plan's (NAP) implementation through FY2017 appropriations. Specifically, we recommend $400 million in FY2017 for USAID's global TB program, $70 million for the CDC's Division of Global HIV/AIDS and Tuberculosis and $243 million for the CDC's Division of TB Elimination, in order to combat drug resistant TB in the U.S., and increased funding through the NIH for the accelerated development and introduction of new TB diagnostic, treatment and prevention tools, as outlined in the NAP. Over two-thirds of international funding for global TB control is provided through the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), so it is critical that the U.S. provide an appropriate investment for the Fund.

The ATS thanks the subcommittee for the opportunity to provide a statement for the record.

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[i] World Health Organization, Global TB Report, 2015. http://www.who.int/tb/publications/global_report/en/

[ii] Ibid.

[iii] Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2013. http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf

[iv] Centers for Disease Control and prevention. http://www.cdc.gov/tb/statistics/reports/2014/pdfs/tb-surveillance-2014-report.pdf,

[v] Centers for Disease Control and Prevention, 2015. Factsheet. http://www.cdc.gov/tb/publications/factsheets/drtb/xdrtb.htm.

[vi] Marks SM, Flood J, Seaworth B, Hirsch-Moverman Y, Armstrong L, Mase S, et al. Treatment practices, outcomes, and costs of multidrug-resistant and extensively drug-resistant tuberculosis, United States, 2005–2007. Emerg Infect Dis. 2014 May.

[vii] WHO. Multi-drug Resistant Tuberculosis, 2015 Update. http://www.who.int/tb/challenges/mdr/mdr_tb_factsheet.pdf

MATERIAL SUBMITTED FOR THE RECORD BY THE HONORABLE CHRISTOPHER H. SMITH, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY, AND CHAIRMAN, SUBCOMMITTEE ON AFRICA, GLOBAL HEALTH, GLOBAL HUMAN RIGHTS, AND INTERNATIONAL ORGANIZATIONS

AERAS

December 15, 2015

The Honorable Christopher Smith
Subcommittee on Africa, Global Health, Global Human Rights & International Organizations
The House of Representatives
2200 Rayburn House Office Building
Washington, D.C. 20515

Chairman Smith,

I am submitting this letter of testimony to the Subcommittee regarding the recent hearing on the global threat of multidrug resistant tuberculosis (MDR-TB), as CEO of Aeras, a non-profit biotechnology organization working to develop new tuberculosis (TB) vaccines for the world. I appreciate the Subcommittee's work on this important global health and security issue. As the leading nonprofit organization in TB vaccine research and development, Aeras is a partner on 6 of the 13 TB vaccine candidates currently in the global pipeline. Aeras's global headquarters is in Rockville, Maryland, and we have offices in Africa and Asia.

The World Health Organization's (WHO) announcement that TB was responsible for 1.5 million deaths worldwide in 2014 while HIV/AIDS was responsible for 1.2 million deaths might come as a surprise to some[1]. The news from the WHO confirms, however, what clinicians, researchers, and advocates working in the TB field already knew: TB is a neglected disease that continues to thrive in the more impoverished parts of the world.

The threat of the TB epidemic is growing, in part because of the spread of dangerous strains of MDR-TB and extensively drug-resistant TB (XDR-TB) around the world. While MDR-TB is resistant to at least two of the key front-line drugs used to treat TB, XDR-TB is resistant to nearly all current drug options. The costs to treat MDR- and XDR-TB are enormous. In the U.S., a case of MDR-TB costs about 15 times the amount to treat drug sensitive TB[2]. Treating a single case of XDR-TB could cost more than half a million dollars – enough to wipe out a city's total public health budget for a year[2].

The WHO's announcement illustrates that the TB epidemic is far from being controlled, as people in poverty throughout the world are still suffering from and dying of TB in great numbers. About one-third of the world's population is latently infected with the bacteria that cause TB, and approximately 10 percent of them will develop active TB infection. According to the WHO, an estimated 9.6 million people became ill with this debilitating disease in 2014. The world desperately needs new technologies—vaccines, drugs and diagnostics—to control and eventually eliminate TB.

The U.S. is not immune to cases of drug-resistant TB. Last year, a woman with XDR-TB was treated at the National Institutes of Health after she travelled to and through the U.S. She took a long flight from India to Chicago, and then drove through Illinois, Tennessee, and Missouri, visiting friends and relatives, while contagious with a potentially deadly disease that is spread through the air. She ended up being airlifted to the NIH and placed in isolation in the same room previously used to isolate Ebola patients. This demonstrates the potential for fear and disruption that even one case of XDR-TB can cause in the U.S. The true scope of the problem comes into focus when one considers that XDR-TB has been reported in 105 countries, and represents almost 10 percent of all MDR-TB cases[3]. This further illustrates the critical need to develop better drugs capable of treating drug-resistant strains, better diagnostics to improve detection of such cases, and, critically, new vaccines, given that a vaccine effective at preventing TB caused by drug-sensitive strains will protect against MDR- and XDR-strains as well.

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Building on the End TB Strategy adopted by the World Health Assembly in 2014, this September the United Nations endorsed a set of development goals to guide international efforts to fight poverty (known as the Sustainable Development Goals). A core component of these goals was a target to end the TB epidemic by 2030, yet without new approaches we have no clear path to achieve this.

Improvements in diagnostics and outreach have led to a better understanding of the epidemic, but we remain too far away from developing solutions. The current front-line TB drugs were developed in the 1950s and 60s. The current vaccine is even older, dating back to the 1920s, and is ineffective in adolescents and adults. Research and development are urgently needed to discover new tools but TB research and development is woefully underfunded. The new WHO report points to an estimated $1.3 billion a year funding gap[3].

The U.S. government can do more to fund research and development for new products that can combat MDR-TB. U.S. government agencies like the Centers for Disease Control and Prevention (CDC) and the U.S. Agency for International Development (USAID) already perform great work in providing domestic and overseas programming to prevent, treat and cure TB. The National Institute of Allergy and Infectious Diseases, likewise, strongly supports basic research into the bacteria that cause TB. Yet there is relatively little support for product development and no financial support for the new vaccine product development that will ultimately prevent TB. This is extremely important to address because, without new tools, we are not likely to reach the goal of eliminating TB by 2030.

Our mindset about TB must change. We have so many promising scientific avenues worthy of exploration, but they cannot be progressed without sufficient resources. And with these tools left undeveloped, the disease continues to take a tremendous personal and economic toll around the world. TB needs to become rare and then nonexistent: here and everywhere. Again, your time and attention to this matter is appreciated by the entire TB stakeholder community.

Respectfully submitted,

Jacqueline E. Shea, Ph.D.
Chief Executive Officer
Aears Global Headquarters

1. The Global Tuberculosis Report 2015 also notes that an estimated 0.4 million TB deaths are among HIV-positive people

2. CDC, 2014. The Costly Burden of Drug-Resistant TB in the U.S. http://www.cdc.gov/nchhstp/newsroom/2014/TB-Infographic2014.html?s_cid=nchhstp-nr-wtbd-003

3. WHO, 2015. Global Tuberculosis Report 2015