

Death by Drug-Resistant TB and How to Stop it



Center for Global Health Policy

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About the Center for Global Health Policy

The Center for Global Health Policy, established by the Infectious Diseases Society of America and the HIV Medicine Association in 2008, supports and promotes U.S. efforts to combat HIV/AIDS and tuberculosis around the world. The center provides scientific and policy information to U.S. policymakers, federal agencies, nongovernmental organizations and the news media, linking decision makers to the latest evidence-based input and guidance from physician/scientists and other professionals from both developing and developed countries.

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Introduction

"Tuberculosis Germ Resurging as Risk to Public Health" blared a headline in the *New York Times* in July 1990. The *Times* story detailed a sudden, unexpected rise in TB rates in New York and other U.S. cities and highlighted a new threat—a virulent new strain of the disease that was resistant to standard TB medicines.¹

"We thought we had the problem licked, so we let a number of tuberculosis programs lapse. We're obviously having to rethink that," Dr. Dixie Snider, then-director of the Division of Tuberculosis Control at the U.S. Centers for Disease Control and Prevention, told the newspaper.

To be sure, in the 1970s and 1980s, many believed the battle against TB had essentially been won. Prevention programs were neglected, federal grants to states for TB were eliminated, research funding virtually evaporated, and the capacity to treat patients in the U.S. began to erode. The CDC even stopped looking for drug-resistant strains in 1980 because it was not considered a significant threat.

But in 1985, the decades-long decline in U.S. TB rates reversed, and a new epidemic of drug-resistant TB emerged, threatening to overwhelm public health agencies. Between 1985 and 1992, TB increased by 20% in the U.S., and there were dangerous outbreaks of drug resistant tuberculosis in New York, Florida and other states.² MDR-TB epidemics

were reported in other countries across the world.³ In New York City, dramatic reductions in staff and infrastructure to respond to TB, coupled with a burgeoning HIV epidemic, created a perfect storm of multidrug-resistant tuberculosis (MDR-TB).⁴ In 1989, only half of the patients treated for TB in New York City were effectively cured.⁵ Drug resistance among patients who had never been treated increased from 10 percent in 1983 to 23 percent in 1991.⁶ Some hospital programs were overwhelmed and health care workers were getting sick and dying of TB. By the early 1990s, the number of TB cases had nearly tripled over a 15-year period.⁷ In 1993, Congress responded to this public health crisis through emergency funding.⁸ New York City alone spent more than \$1 billion to get tuberculosis under control.⁹

The moral of this story: we ignore tuberculosis at our peril. And yet here we are in 2010, facing a global epidemic of drug-resistant TB that's getting inadequate funding and suffering political neglect.

"There is more tuberculosis today than ever before in history, but it is truly a forgotten disease."

—Mel Spigelman, MD, the President of the Global Alliance for TB Drug Development, February 2010



Drug-Resistant TB 101

Unless we act quickly and aggressively, this emerging global health threat will spiral, threatening a return to the pre-antibiotic era in which our medical arsenal is no match for the advancing disease.^{10, 11}

“Tuberculosis has again placed the world in a precarious situation,” Margaret Chan, director-general of the World Health Organization (WHO), warned in an April 2009 speech. Resistant strains of TB “are now circulating in the general population, spreading widely and largely silently in a growing pool of latent infection.”

The WHO recently reported that drug-resistant TB is at record levels in some regions of the world. Right now, there are drug-resistant disease hotspots, where one in four people who become sick with TB have a form of the illness that does not respond to standard anti-TB drugs.¹² Other places could be even worse, but there little to no reliable data providing an accurate picture of the epidemic’s scope in much of the world.

Drug-resistant TB—like regular TB—spreads when a person ill with TB caused by a drug-resistant strain coughs, sneezes, or even sings. These new strains of TB, known as multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), are, at best, very difficult to cure—involving expensive, toxic, and lengthy drug regimens. Failure to develop programs to diagnose and treat such patients now will be more costly in the future, leading to increased incidence, greater resistance, and more deaths.¹³ Already, strains of TB that are resistant to all drugs are emerging.¹⁴ The longer we wait, the harder it will be to get a handle on this deadly scourge.

Three major interventions are urgently needed to address this crisis:

- First, improved and expanded diagnostic tests that can rapidly detect both standard TB and drug resistant TB
- Second, the development of new drugs that work against resistant strains of TB, as well as wider use of existing drugs for resistant TB (although these are limited by low potency and toxicity)
- Third, aggressive attention to treatment of existing patients and preventing transmission of MDR and XDR-TB in hospitals, clinics, and communities.

Aggressive early case detection for disease coupled with accurate, speedy diagnosis and effective treatment will go a long way to solving this global health threat. That means more and better laboratories and improved easy-to-use diagnostic tools available at the point where care is delivered. It also means faster and wider access to existing technologies and to high-quality treatment managed by health care providers who understand TB. These are, of course, not the only steps we need to take to combat the global TB epidemic. Infection control, new drugs, and a more effective TB vaccine, delivered through a strong and effective health care system, are all key ingredients to ending this epidemic. But new TB drugs and expanded treatment will not help much if infected patients are never properly screened and diagnosed in the first place.

Without rapid, reliable diagnosis and vastly improved laboratories, TB will continue to spread and become more resistant. Right now, the most widely used method to diagnose TB in developing countries is sputum microscopy, a tool that is more than a century old and fails to detect as many as 70 to 80 percent of the world’s TB cases.¹⁵ Another diagnostic, TB culture, is more accurate, but not commonly available in resource-poor countries. Plus, getting results from a culture test can take up to 6 weeks.

Greater access to current tools, enhanced labs, and new diagnostics are vital starting points toward reversing the tide of drug-resistant TB. It can be done. In places like Ethiopia and Lesotho, scientists and technicians went from no capacity for diagnosing TB to high-quality, sophisticated laboratory systems that now stand out as islands of excellence in the developing world.¹⁶ The benefits of better laboratory systems do not stop with TB; improved laboratory capacity can also provide more effective surveillance of a range of diseases of great concern to the U.S., including H1N1 influenza. And in the field of diagnostics, researchers are on the cusp of exciting innovations that could revolutionize TB screening in resource-limited settings, bringing this archaic process into the 21st Century.¹⁷

This global health threat cannot be confronted with incremental steps and tiny funding boosts. Improving labs and diagnostics is fundamental and feasible, but it will require robust new resources and committed, visionary leadership. If there's anything we've learned about combating TB, it's that half-measures do not work and, indeed, only lead to a more virulent threat.

The Global TB Epidemic

Tuberculosis is the second leading infectious disease killer of adults in the world, exceeded only by HIV/AIDS. TB is also the No. 1 killer of people with HIV in the developing world. One in three people in the world is infected with the organism that causes TB, known as *Mycobacterium tuberculosis*. Most of these people have latent, non-transmissible infection, not active TB disease. An estimated 5 to 10 percent of those with latent TB and normal immune systems will develop TB disease in their lifetime.¹⁸ (The only TB vaccine, Bacille Calmette-Guerin vaccine, offers some protection against severe forms of TB most often contracted by children, but is not effective against adult pulmonary TB.)

TB disease can be triggered by anything that reduces a person's immunity, such as HIV infection, diabetes, kidney failure, or cancer treatment. HIV-infected people are anywhere from 50 to 400 times more likely than their HIV-uninfected counterparts to develop active TB disease. Children are also more at risk of developing active TB than adults, because their immune systems are not fully developed.¹⁹

Standard TB disease can usually be treated with a course of four first-line anti-TB drugs over a period of six months, a regimen that costs about \$20.²⁰ But if these drugs are substandard or if good quality drugs are misused or mismanaged, multidrug-resistant TB can develop and transmission and deaths rise. In addition, if drug-resistant TB is misdiagnosed or mistreated as drug-susceptible TB, the development of further resistance is likely.

In 2008, there were an estimated 9.4 million new cases of active TB disease, including half a million in women and more than 250,000 in children. TB claimed more than 1.8 million lives. It is the 3rd leading global cause of death among women aged 15 to 44, and the fourth leading killer of young girls in low-income countries.²¹ And because of the deadly synergy between HIV and TB, tuberculosis case rates have more than tripled and deaths have quadrupled over the past 15 years in African countries with the highest rates of HIV infection.^{22, 23}

MDR-TB

Multidrug-resistant TB is a form of tuberculosis that's resistant to the two most powerful first-line TB drugs, isoniazid and rifampin. There are two avenues by which drug-resistant TB occurs. The first is acquired resistance, in which the drug-susceptible strain of TB develops resistance during a course of treatment, often because the patient takes the medicine inconsistently (non-adherence), or because of stock-outs, which happen when TB programs run out of TB drugs. It can also happen if clinicians fail to prescribe an adequate multi-drug treatment regimen to counter development of drug resistance. The second avenue is more alarming, and of great concern across the globe, in which an infectious patient passes their drug-resistant strain of TB bacteria directly to others through a cough or a conversation.^{24, 25}

The treatment for MDR-TB patients involves drugs that are more toxic, cost 50 to 200 times more than standard TB medicines, and must be taken for 18 to 24 months.²⁶ Such drugs are often not available in resource-poor countries. In fact, only about 1 percent of new MDR and XDR-TB patients in 2008 received treatment under WHO-approved guidelines.

In 2008, the WHO estimates there were about 440,000 new multidrug-resistant cases, approximately 3.6 percent of total new TB cases; about one-third of those—150,000—were fatal. These figures are based on modeling, not actual reported data of patients sick or dying of MDR-TB. Globally, there are too many gaps in the available data for experts to provide exact figures. In the U.S., of the 12,898 new TB cases reported in 2008, 125 were MDR-TB.

XDR-TB

XDR-TB stands for extensively drug-resistant TB. It is resistant to almost all drugs used to treat TB, including the two best first-line drugs (isoniazid and rifampin) and the best second-line medications (known as the fluoroquinolones), as well as at least one of three injectable drugs (amikacin, kanamycin, or capreomycin).²⁷ XDR-TB develops when MDR-TB is not adequately treated with high-quality, second-line TB drugs.²⁸ As with MDR, this highly resistant strain of TB can be transmitted from person-to-person, and this is frequently the case in people with HIV infection.²⁹

Because XDR-TB is resistant to first- and second-line drugs, treatment options are seriously limited, involving toxic and expensive drugs that must be taken for a period of 18 to 24 months. One case of XDR-TB can cost \$600,000 or more to

Dr. Sarita Shah, of the Albert Einstein College of Medicine, Discusses How XDR-TB is Becoming More Resistant

In 2005, a tuberculosis “superbug” took root in the rural South African town of Tugela Ferry. Doctors soon diagnosed 53 patients with XDR-TB; 52 of those patients died within an average of 16 days after they sought medical care. Now, XDR-TB is becoming even more widespread—and remains just as deadly. Since those first cases emerged, over 500 patients in Tugela Ferry have been diagnosed with XDR-TB, and cases of this deadly infection have been reported in 58 countries, from the U.S. to India, China, Russia, Lithuania, Peru, Sweden, Germany, and Thailand. And because of inadequate treatment, XDR-TB strains have developed resistance to an even greater number of drugs than before. Dr. Sarita Shah, an assistant professor of medicine and of epidemiology and population health at Albert Einstein College of Medicine, recently presented new research showing that the majority of XDR-TB strains in Tugela Ferry, initially resistant to 4 to 5 key TB medicines, are now resistant to at least 6 drugs. In this Q&A, Dr. Shah describes a global health system that essentially guarantees the continued spread of MDR and XDR and talks about innovative efforts to transform the treatment of drug-resistant TB.

Q: *You presented new research at the Union World Conference on Lung Health in 2009 showing that XDR has become more resistant. Why and how is this happening?*

A: In July 2005, most of the XDR we analyzed in Tugela Ferry was resistant to four to five drugs. By 2009, 100% of patients in our study had XDR that was resistant to at least 6 drugs—and most to 8 drugs. This is a very worrying trend.

But it’s not a surprise that drug resistance is going to increase if we have weak TB programs, not enough support, and not enough attention to this critical issue. This is happening because in many places, MDR is being treated in a completely unsupported, chaotic way. That treatment fails, and then we get XDR. And it’s not surprising that if we don’t treat XDR properly, it’s going to get ever more resistant. We will run out of letters soon, and we’ll be at the end of the road, with no more medicines available.

Q: *Can you talk about the lineage of XDR and how it was initially passed along?*

A: XDR has been around for a very long time. It was present in South Africa as early as 2001. Now that people are looking for it, we’re finding it everywhere. It isn’t a person spreading it around. It’s the conditions that create XDR, and those are everywhere—weak public health infrastructure and inadequate patient support for completing treatment, plus HIV/AIDS.

Q: *Can you describe what’s happening on the ground now in KwaZulu-Natal Province, where you and your colleagues do much of your work on drug-resistant TB?*

A: What happens in South Africa—and in many other countries around the world—is there’s a centralized, specialty hospital that treats all patients with MDR-TB, because the drugs used for treatment are complicated, expensive and specialized. So, it is felt that treatment should be by specialists who can use the drugs correctly and monitor for side effects appropriately. In KwaZulu-Natal, this hospital used to be able to admit all MDR patients for six months, during which patients are assured to take their medicines every single day. And then for the remaining year and a half of MDR treatment, the patients are supposed to come back every month for a check-up and more medicines. You can probably imagine that not everyone comes back. They live far away. They’re probably feeling better. They can’t afford to miss a day of work. So what happens? In South Africa, we had an MDR default rate of 15–20% percent, so you’re at XDR.

Starting about four years ago, that referral hospital became completely overwhelmed. They have 160 beds, and we diagnose over 2,500 MDR cases in our province alone per year, so you can see how that math doesn’t work

out. Since the central hospital couldn't admit everyone anymore, there were long waiting lists to get into the hospital, which is the only way to get the MDR medicines. Half of the diagnosed cases might die before being admitted. The same thing happens in other places as well—or worse, no MDR treatment is available in the country at all—so it's important to realize South Africa isn't unique in this sense. The issue of getting MDR patients access to good drugs in a timely way is a major global effort led by the Green Light Committee.

But let's say a patient manages to get in to the MDR hospital. The doctors would try to give him or her medicines, but they might discharge the patient after 3 or 4 months because they have to face the daily reality of the long waiting lists of patients who are, literally, dying while waiting to get access to the medicines. So, patients are discharged early—with all the best intentions of trying to get more people into care—but, this is the way you get more resistance and also transmit disease to others.

Q: *What's the fix for this kind of situation that guarantees failed treatment, more transmission, and greater resistance?*

A: We've been able to make significant progress in the last couple of years. In KwaZulu-Natal, MDR treatment has been decentralized to 4 hospitals around the province. So there are more inpatient beds, and the patients don't have to wait nearly as long, on the order of about 1 or 2 weeks. With increased intake for MDR treatment, they have a better chance at surviving and they don't spread disease. The other thing we've done in KwaZulu-Natal is, in the district where Tugela Ferry is located, we're treating MDR patients in their community, at their homes. We're never going to get to the 2,500 beds—we have about 500 right now—nor do I think we should be aiming for that. We need a more patient-centered approach that will help them complete treatment successfully and be cured of MDR. So moving to a community-based model of treatment is key. We provide education on MDR and HIV for the patients and their families, so they know what it is they have, how it is spread, and what the treatment involves. We send nurses to their homes daily to give the injections for the first 6 months. We're in contact with the patients every day, at their homes, so they don't default from treatment.

The other major concern with this approach is placing others in the home at risk, but they have already been exposed, so we're not increasing their risk of transmission. We take infection control very seriously and emphasize masks for our nurses, giving injections outside in the open air, and keeping windows and doors open. But, again, providing treatment—in the hospital or the community—has to be done in an organized, well-supported and monitored way or we will create more resistance.

Q: *Some experts fear we could reach a "tipping point" in which the majority of new TB cases are drug-resistant, rather than standard TB that's easily treated with available drugs. Do you agree with that?*

A: Drug-susceptible TB still accounts for the vast majority of new TB cases. It's curable, diagnosable, and preventable. But, we're losing the war against TB right now for many reasons, most of which have to do with weak public health infrastructure, but also political will. MDR and XDR are certainly going to increase if we don't do something now to prevent creating more of these strains. It starts with susceptible TB; we've got to diagnosis it faster, so infected patients will stop spreading the disease. And we need to treat them faster and make sure they complete treatment, so they will not develop MDR. We also have to diagnose MDR faster—which is more complicated, but is definitely doable—and we've got to treat it properly. With proper treatment for MDR, you generally become uninfected within two to four weeks, so we can do this. It's a long treatment, but it can be done and it is being done in some parts of the world very effectively. It's a matter of infrastructure, support, political commitment, and better diagnostic tools.

treat,³⁰ and even then, a cure is not guaranteed. In 2007, the U.S. Department of Homeland Security labeled XDR-TB “an emerging threat to the homeland.”³¹

Mortality rates for XDR-TB patients are extremely high. The CDC reported in 2008 that in the U.S., 25 percent of XDR-TB patients die within 1 year and 32 percent die during treatment. For MDR-TB, 19 percent of patients die within a year and 23 percent die during treatment. Mortality rates in developing countries are much higher, and among HIV-infected patients, drug-resistant TB is more severe, the risk of death is greater, and it comes faster.³²

Ground zero for XDR-TB is Tugela Ferry, South Africa. In 2005, in South Africa’s KwaZulu-Natal Province near the eastern coast, doctors described the emergence of this deadly new strain of TB. Soon, 53 patients were diagnosed with XDR-TB; 52 of those patients died within an average of 16 days after they sought medical care. Research showed that many of the Tugela Ferry patients were infected with XDR-TB in health care settings. In a follow-up study of cases diagnosed in Tugela Ferry from 2005 to 2007, 71 percent of MDR-TB patients and 83 percent of XDR-TB patients died within one year. Indeed, 40 percent of the MDR-TB patients and 51 percent of the XDR-TB patients died within 30 days of sputum collection.³³ In other words, they likely died before getting test results showing their diagnosis. Almost all were co-infected with HIV.

While Tugela Ferry has demonstrated the explosive potential for XDR-TB, this highly resistant form of TB has been known to exist for some time. Today, XDR-TB is almost everywhere. It has been found in 58 countries across the globe, from the U.S. to Europe to Africa. And new, more resistant strains have emerged. Much of the XDR-TB in Tugela Ferry, for example, was initially found to be resistant to four or five key TB medicines; more recent research shows it is now resistant to at least six drugs.³⁴

“This is happening because in many places, MDR is being treated in a completely unsupported, chaotic way,” says Dr. Sarita Shah, of the Albert Einstein College of Medicine, who conducted this latest research. (See interview with Dr. Shah on page 5.)

The bottom line: Focusing simply on better treatment of drug-susceptible TB, with stronger adherence and follow-up, while essential, will not be sufficient to stamp out the epidemic of drug-resistant TB. Drug-resistant TB requires its own response as an essential component of a comprehensive strategy to finally address to this infectious disease killer at a level commensurate with its impact on human health.

HIV/TB Co-infection: An Engine for Drug-Resistant TB

HIV/AIDS has reignited the TB epidemic across the developing world, and it is fueling increases in MDR and XDR-TB as well. Because HIV-infected patients have compromised immune systems, they are more vulnerable to TB infection and disease. In HIV-infected patients, the risk of recurrent TB disease is higher than among HIV-uninfected patients. If MDR-TB is present in a community, drug-resistant TB disease will appear first in those with HIV, because HIV accelerates the progression of latent TB to active TB disease.

The diagnosis of TB in patients co-infected with HIV is significantly more difficult than in HIV-uninfected patients. The most widely available TB test in the developing world, sputum smear, fails to detect as many as 80 percent of all HIV-associated TB cases.³⁵ It is usually unable to detect so-called “extrapulmonary TB,” or TB outside the lungs, which is more common among HIV-infected patients. In addition, even when HIV patients have pulmonary TB, their sputum smears are often falsely negative.³⁶ This test also cannot distinguish between drug-susceptible TB and drug-resistant TB. Although there is a more accurate test, TB culture, it is simply not widely available in resource-poor settings. Culture capacity, or the availability of newer molecular TB testing, is needed to reliably diagnose TB in smear-negative specimens and to make the distinction between drug-susceptible and drug-resistant strains, including for HIV patients.

In the absence of that diagnostic capacity, the confluence of these two deadly diseases threatens to jeopardize the gains made in both global TB control and in HIV treatment scale up.³⁷

“Because patients with tuberculosis and with HIV infection congregate in the same clinic waiting rooms, offices, laboratories, and hospital wards in much of the world, ongoing transmission is a significant cause of new disease, especially drug-resistant disease,” Drs. Richard Chaisson and Gavin Churchyard write in a March 1, 2010 *Journal of Infectious Diseases* commentary. “HIV and antiretroviral clinics in resource-poor settings have unwittingly become cauldrons of tuberculosis transmission, seriously undermining the impact of HIV therapies.”

Furthermore, treatment of co-infected patients is highly complex and not adequately understood. For example, scientists do not know enough about drug interactions and overlapping toxicities between second-line anti-TB medications and antiretroviral therapy. Research is still

underway to determine precisely how best to sequence HIV and TB treatment, but it now appears that antiretroviral therapy (ART) is best given while TB treatment is in progress rather than afterwards.³⁸ More research in this area is needed, and it is vital that new tools to diagnose and treat drug-resistant TB be evaluated for their effectiveness in patients with HIV infection.

MDR and XDR-TB: The Failures, the Bottlenecks, and the Unknowns

Perhaps more disconcerting than what we know about MDR and XDR-TB is what we don't know—and as a result, what we're not doing to control the epidemic. For example, while WHO experts believe drug-resistant TB is on the rise globally, poor surveillance data and inadequate lab and diagnostic capacity prevent us from fully capturing the scope of the threat.³⁹

For example, in 2008, only 29,423 cases of MDR-TB were actually reported—about 7 percent of the 440,000 cases that WHO experts estimate occurred that year.

This means that the vast majority of people with MDR-TB are never diagnosed or treated.⁴⁰ And because this is an airborne disease, it is critical that the existing cases are treated. Otherwise, the spread continues unabated until the patient dies.

“We're in the dark” about the scope of the epidemic in large swaths of the world, says Diana Weil, coordinator of policy and strategy for the World Health Organization's Stop TB Department.⁴¹ She said a “tipping point,” in which the majority of new TB cases are caused by drug-resistant strains of this deadly germ, as opposed to standard TB, could come to some places in Eastern Europe within a decade.⁴² Already, in 2008, three oblasts, or districts, in the northwestern section of the Russian Federation reported that about one in four of their new TB cases were MDR-TB. Those were: the Arkhangelsk Oblast, at 23.8 percent; Pskov Oblast, at 27.3 percent; and Murmansk Oblast, at 28.3 percent.

Other areas of Eastern Europe have seen a steady uptick in drug-resistant TB:

- Azerbaijan, Baku City, where 5 percent of new TB cases were MDR-TB in 2002⁴³ was at 22.3 percent by 2008.⁴⁴
- Moldova, where 6.3 percent of new cases were MDR-TB in 2001⁴⁵ hit 19.4% 2008.⁴⁶
- Donetsk, Ukraine, where 8.9 percent of new cases were MDR-TB in 2002,⁴⁷ climbed to 16 percent by 2008.⁴⁸

There are significant blanks in our scientific picture of how much drug-resistant TB there is. Among the gaps:

- 41 percent of all countries worldwide cannot provide reliable data on drug-resistant TB,⁴⁹ and of the 22 high TB burden countries, only 12 of them provide any data on drug-resistant TB.⁵⁰
- Of the 46 countries in the African region, fewer than half—22—have provided data on drug-resistant TB. And much of the data that is reported is outdated or incomplete. For example, 10 countries have conducted surveys only at a subnational level or have not repeated the survey in the last decade, or both.
- In the 27 high-burden MDR-TB countries, only 1 percent of new TB cases and 3 percent of previously treated TB cases underwent testing to determine if the patients had a drug-resistant form of TB.
- There is very limited data on the scope of drug-resistant TB disease among patients with HIV, particularly in sub-Saharan Africa. This is, in large part, because current surveillance tools only measure drug resistance in smear-positive cases, i.e. cases in which a patient is found to have the TB bacteria in their sputum on microscopic examination. But many patients, particularly those co-infected with HIV, may test smear-negative even if they have TB.⁵¹

Only 1 to 2 percent of MDR-TB cases are treated according to internationally recognized medical standards—a scenario that invites more drug resistance. The reason so few cases are treated according to WHO-approved guidelines is that many developing countries simply do not have the capacity to launch MDR-TB treatment programs, which are complex, difficult, and expensive. MDR-TB patients must be treated under direct observation for at least two years, with drugs that produce severe adverse effects.⁵²

TB Laboratory Capacity

Any effort to get a handle on the TB epidemic must start with accurate, rapid diagnosis. But that is simply impossible today because of a severe lack of laboratory capacity. “Arguably the weakest component of health systems, laboratory services have historically been grossly neglected and underfunded,” the WHO reported in a briefing paper in advance of an April 2009 ministerial meeting in Beijing on MDR and XDR-TB.

Across the developing world, TB labs are woefully understaffed and inadequately equipped; the majority of these labs do not even meet basic biosafety and technical

The Green Light Committee Initiative

Dr. Salmaan Keshavjee likes to compare implementing a drug-resistant TB program to flying a jumbo jet. “It’s very possible to do,” he says, “but you can’t just mail somebody the users’ manual. It requires appropriate support, training, and equipment.”

Dr. Keshavjee is an assistant professor of medicine at Harvard University who worked with Partners in Health to launch MDR-TB treatment programs in Tomsk, Russia, and in Lesotho. He also currently chairs the Green Light Committee (GLC) Initiative, a WHO-supported program established in 2000. The GLC plays a central role in the fight against MDR and XDR-TB by working with national TB control programs to increase patient access to high-quality treatment for drug-resistant TB in a way that also prevents further emergence of drug resistance. In particular, the GLC works with the WHO and the Stop TB Partnership to help countries gain access to affordable, quality-assured second-line anti-TB drugs for MDR-TB and provides technical assistance to help countries build programs that meet international standards.

If a country’s health ministry decides it wants to implement a GLC-approved MDR-TB treatment program, for example, officials submit an application to the GLC, outlining how many patients the program would serve and detailing its capacity to diagnose and treat drug-resistant TB. If all the pieces are in place, GLC experts give the country a green light. If not, GLC consultants work with the country to address gaps in its plan.⁵³ Thanks to U.S. support, the GLC also provides critical technical assistance to Global Fund grant recipients to enable them to purchase MDR-TB medications at discounted prices.

As of February 2010, the GLC has approved treatment for 72,620 patients in 72 countries; however, only 19,637 MDR-TB patients had been enrolled in treatment projects in 44 countries by the end of 2009.⁵⁴

Dr. Keshavjee notes that despite the GLC’s significant progress, this is less than 2% of the WHO-estimated burden of approximately 440,000 new MDR-TB cases each year. “The GLC has approved about 70,000 patients for treatment. PEPFAR has put 2.4 million on HIV treatment during that same period,” Dr. Keshavjee notes, referring to the President’s Emergency Plan for AIDS Relief. “The question we should be asking ourselves is how PEPFAR has achieved this, and what lessons can be brought to bear on the drug-resistant TB crisis?”

His answer: MDR-TB has not been treated as an emergency, as HIV/AIDS was when PEPFAR was created. And TB has never been adequately funded.

“If you make the resources available, people will bring the drugs and diagnostics to the table. Before there was large U.S. federal government funding, there were not a lot of people making novel and interesting diagnostics for HIV or making HIV drugs available to poor countries,” Dr. Keshavjee says. “When PEPFAR came to the table, people saw there was a market.” The same kind of dynamic must be created for drug-resistant TB.

Currently, developing countries simply do not have the ability to launch MDR-TB programs without significant assistance. How hard can it be? Here’s where Dr. Keshavjee’s jumbo jet analogy comes in. To diagnose and treat drug-resistant TB, you need laboratory infrastructure, you need quality-assured drugs and a reliable drug supply network, and you need the capacity to implement and manage a complex medical intervention. You also need trained human resources capable of carrying out all these steps.

Take just one part of that—the treatment component. One of the standard drugs currently used in treating MDR-TB is para-aminosalicylic acid (PAS). It causes stomach upset in almost all patients and makes many patients vomit daily. It must be taken with something acidic, like juice. And it has a serious side effect—hindering the function of a patient’s thyroid gland. A second drug in the regimen, ethionamide, causes nausea so reliably, that some patients experience anticipatory vomiting. In other words, they throw up just from the smell and thought of taking it. Ethionamide also affects the ability of the thyroid gland to work properly. These are just two of the five

drugs a patient with MDR-TB must take. All this can be managed with appropriate monitoring and medicines, but it's hard and requires a capable health system. Patients on PAS and ethionamide require monitoring of their thyroid hormone, administration of drugs to augment their thyroid function and deal with other side effects, and providing electrolytes if the patient is vomiting frequently, among other steps.

"This isn't happening for one week," notes Dr. Keshavjee. "This is happening for two years."

So it's no wonder the GLC and country TB programs have not been able to move faster. Dr. Keshavjee says there is no shortage of models for how to scale up MDR and XDR-TB treatment programs, from Russia to Peru to Lesotho. In each place, there are successful treatment programs that already serve as regional technical assistance centers, helping neighboring countries develop needed expertise to duplicate these programs elsewhere. What is missing in many parts of the world is both linkage to these technical assistance centers, and a mechanism for long-term technical assistance—technical *accompaniment*—that can help countries actually build and expand programs rapidly.

These efforts need to be dramatically expanded to all countries heavily impacted by this threat. "Someone needs to show leadership in that," Dr. Keshavjee said.

proficiency standards and do not have trained technicians able to do the necessary tests.⁵⁵ In the WHO African region, for example, there are 53 labs that have the capacity to conduct drug-susceptible testing for first-line drugs and 9 labs that can test for susceptibility to second-line drugs.

What would it take to ease the global TB laboratory bottleneck? At least 2,000 new labs worldwide, capable of doing culture and drug-susceptible testing, and at least 20,000 newly trained lab technicians, according to the WHO. Equally important, countries heavily affected by the TB epidemic must develop systematic laboratory strengthening programs and implement clear policies for screening and diagnosing MDR and XDR-TB.

An international collaboration that includes the WHO, the Global Laboratory Initiative, and the Foundation for Innovative New Diagnostics (FIND) is working to upgrade and modernize national TB reference laboratories in 27 developing countries in an effort known as the EXPAND-TB Project. This project receives technical support from many agencies and partners involved in laboratory strengthening at the country level and it is funded by UNITAID, an agency founded by France and other countries and hosted by the WHO, which uses innovative financing mechanisms to help increase access to drugs to combat TB and other diseases. U.S. agencies such as the CDC, PEPFAR, the American Society for Microbiology, the American Public Health Laboratory network and others are closely involved. The goal is to upgrade laboratory infrastructure, install required testing equipment, provide

training in diagnostic and biosafety practices, and provide ongoing technical and mentoring assistance.⁵⁶

Already, the project has seen significant successes. Last spring, for example, Ethiopia opened two new state-of-the-art TB labs in Addis Ababa. These are biosafety level 3 facilities (a requirement for doing culture and drug-susceptible testing of TB specimens) that have the capacity to use liquid culture and line probe assay technologies—two new diagnostic tools that have been approved by WHO for TB diagnosis and detection of MDR-TB and are now being used in high-burden countries.⁵⁷

But much greater investment is needed. Over the next five years, from 2010 to 2015, it would take \$5.9 billion to provide adequate laboratory diagnosis and monitoring of MDR and XDR-TB cases, according to estimates included in the Global Plan to Stop TB. The effort to revamp and strengthen labs requires a much more comprehensive, intensive effort. The U.S., with its leading role in global scientific and medical innovation, must provide robust support, in terms of funding and leadership, to advance this effort.

Currently the CDC and USAID, through bilateral TB programs, provide support for building laboratory capacity at the country level, including renovating and upgrading facilities to meet proper biosafety standards, capacity building, and technical assistance. USAID also supports the development and dissemination of global guidelines and standards for laboratories. But both agencies are hampered by limited funding.



One Lab's Leap in TB Diagnosis

MASERU, Lesotho – Just three years ago, a person with advanced tuberculosis in this mountainous country in southern Africa would have to wait six to eight weeks for lab results showing whether common drugs would work to cure their disease. A second test – determining whether second-line drugs would work—took another four weeks, adding up to a three-month-plus wait in some cases on how to treat the disease.

“By then, either the patient had died, or the doctor made a diagnosis based on clinical

evidence,” said Kekeletso Kao, who was director at the National TB Reference Laboratory at Queen Elizabeth II Hospital in Maseru from the end of 2006 until mid-2008.

Then something extraordinary happened—the government of Lesotho told its partners outside government that it needed emergency help to fight the spread of multidrug-resistant TB, or MDR-TB. Lesotho’s health officials had been spooked by the news out of neighboring South Africa about the deadly spread of extensively drug-resistant TB, named XDR-TB, in Tugela Ferry

Brought together by the government, a coalition consisting of the Foundation for Innovative New Diagnostics (FIND), Partners In Health, and the World Health Organization began renovations at the TB lab in 2007; Partners In Health paid for the renovations. Within just a few months, they had introduced a new test for rapid detection of MDR-TB. Using this new technology, a person in Lesotho with MDR-TB was properly diagnosed in just 14 days. Lesotho now was performing TB tests as quickly as wealthy Western countries.

And it did it with a lab that was just 450 square feet—three rooms, plus a bathroom, and a couple of closet-sized spaces.

“The biggest lesson here is you don’t need to have a fancy lab to produce good work that meets the needs of the country and its patients,” Kao said. “With just a tiny space, we were able to start providing an effective service for patients.”

The other big lesson: Countries with high burdens of TB, with the right assistance, could provide the highest quality diagnostics for their people.

Lesotho Health and Social Welfare Minister Mphu K. Ramatlapeng, who took her post in 2007, marveled in a 2009 interview about the transformation of her national TB laboratory. She said that FIND’s assistance was particularly critical in moving the project ahead.

“I had never seen technology regarding TB that was so advanced,” she said. “We now have this platform that can help us not only in MDR or XDR-TB cases, but also for other things, such as identifying whether children born to HIV-positive mothers are positive themselves.”

In addition, her ministry requested help from the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR) to build up overall laboratory capacity in the country. Through a PEPFAR grant beginning in 2006, U.S. volunteers from the American Society for Clinical Pathology, based in Chicago, started a wide range of training—teaching 19 laboratory workers on phlebotomy training; 37 on chemistry, hematology, and CD4 training; and 23 on basic

laboratory operations training. In addition, the group has recently started work on reviewing and revising curriculum on laboratory practices at the National Health Training College in Maseru.

“They have helped quite a lot in strengthening labs in Lesotho,” said Kao, who is now a senior technical officer at FIND. “They played a big role when we wrote our national laboratory policy in 2008. They have also sent volunteers to conduct trainings with a main focus on quality assurance and HIV monitoring.”

FIND, meanwhile, focused its attention on the national TB lab. It is a non-profit Swiss-based organization formed in 2003 at the World Health Assembly to accelerate the development process of diagnostic tests for poverty-related diseases. Part of its mission also was to test these new diagnostics in developing countries.

Lesotho, a country with a gross domestic product per capita of just \$661, became an ideal place to start with new TB diagnostics. It was ideal not only because of government support, but also because of great need: An estimated one in four adults were HIV positive, and testing for TB—a leading cause of death in AIDS patients—was limited to basic smear microscopy.

Smear microscopy means looking for TB bacilli in sputum samples through a microscope. But in HIV-positive patients, most of the sputum samples do not contain any visible bacilli, which means that technicians must grow bacilli in cultures in order to make a lab diagnosis.

FIND first helped introduce liquid culture tests for TB. This test put a person’s sputum sample in culture bottles, which were placed inside an incubator in a machine. The test would show whether the bacterium was growing. If TB was found, laboratory technicians then tested further for whether the TB was susceptible to various drugs. They had their answer in 14 days.

A second innovation came a year later, in 2008, with the introduction of line probe assay tests. In this molecular test, the DNA in a sputum sample is amplified; in six hours, workers learn whether a person has MDR-TB.

Now, the Lesotho lab is a pilot site for testing a third diagnostic innovation—fluorescent microscopy. It enables laboratory workers to read slides faster and detect more TB bacilli in the sputum than with conventional smear microscopy.

Kao, the former TB lab director, said that those working in global health have much to learn from Lesotho’s TB lab overhaul. One lesson, she said, was that donors should give higher priority to improving TB diagnostics.

“Everyone is interested in having well-established HIV labs, but TB labs are really lacking in a lot of things,” she said. “We need to change our focus from just HIV to one that realizes we need to have an integrated system that can produce TB results that are just as good and reliable as HIV results.”

Additional resources for laboratory capacity could have benefits well beyond improved TB diagnosis. With strong planning and careful integration, these investments could be made in a way that bolsters overall lab capacity in resource-poor settings. The CDC’s Global AIDS Program, for example, has used PEPFAR funds to enhance the national lab systems in Ethiopia and Rwanda. Because of the CDC’s integrated approach, those lab systems now have the capacity to respond to everything from cholera to avian flu, as well as HIV and TB testing.⁵⁸ But the agency has not been able to fully

replicate that model when it comes to TB lab strengthening, because of inadequate, piecemeal funding.

TB Diagnosis

Even the best laboratory can only work so well if the diagnostics are outmoded, slow, or unreliable. Indeed, because of antiquated diagnostics, test results confirming MDR or XDR-TB often come too late. So while lab strengthening is vital, it must be undertaken along with an aggressive search for better diagnostics—diagnostic tools

that can provide real-time information to clinicians in the community about the presence of drug-susceptible or drug-resistant TB in their patients. New game-changing TB technologies could significantly reduce the need for new labs and more technicians for TB diagnosis.

Right now, the most commonly used method to diagnose TB in developing countries is sputum microscopy, an archaic, ineffective tool first developed in 1882. It is no match for today's drug-resistant strains.⁵⁹ For example, sputum microscopy:

- Fails to detect as many as 70 to 80 percent of all TB cases globally
- Cannot distinguish between drug-susceptible and drug-resistant TB
- Cannot detect TB outside the lungs, which is a more common condition in HIV patients
- Often gives falsely negative results for patients who do not have a great deal of TB bacteria in their sputum, such as children and HIV-infected patients.

Another diagnostic, TB culture, is a more complex process and provides a more accurate diagnosis, but it's not widely available in the developing world. And it requires sophisticated equipment, well-trained staff, and getting results can take up to 6 weeks. In the time lag, patients are often lost to follow-up, or worse, they are near death. And they have likely continued to transmit the bacterium.

But a revolution in scientific research is in the making, pushing TB diagnostics from the biological to the molecular arena in a shift that promises to bring speedier, more accurate tests for both standard and drug-resistant TB. Experts are cautiously optimistic that transformative tools are within reach—innovations that could eliminate the need for high-tech biosafety equipment, reduce the level of training for lab workers, and perhaps most importantly, bring the TB test for drug-susceptible and drug-resistant TB much closer to the patient and clinic level.⁶⁰ The priority in TB diagnostics is a rapid, point-of-care test that can be used at a local health outpost by a health care worker without highly specialized training.

“We are close—so close—to a breakthrough that can change the world,” the WHO declares in “Pathways to better diagnostics for tuberculosis: A blueprint for the development of TB diagnostics,” a December 2009 report. Transforming promising new technologies into rapid, easy-to-use tests “can be the linchpin in rolling back TB and reducing the misery it causes in so many poor communities.”⁶¹

Take, for example, Cepheid geneXpert, a new TB test jointly developed by Cepheid, FIND, and the University of Medicine and Dentistry of New Jersey (UMDNJ), with funding from the National Institute of Allergy and Infectious Diseases (NIAID). It can be used in a district health setting—eliminating the need to send specimens to a far-away lab with high-tech equipment—and produce results in less than two hours, before a patient leaves the doctor's office.⁶²

If approved and made widely available for TB diagnosis, experts believe it could lead to earlier, more appropriate treatment and an earlier break in the cycle of transmission. The WHO will be reviewing such technologies for possible policy guidance this September.⁶³

Cepheid geneXpert is just one of several new tools in the TB diagnostic pipeline. But to move these scientific innovations out of the testing arena and into developing-world clinics will require operational research, to ensure adequate understanding of its role in national TB programs, and dramatic scale up of funding for field evaluation studies. Despite a promising array of diagnostic innovations, there is very little financing available for the critical final step—phase III field evaluations—that will determine whether tools should be brought to market or not.⁶⁴ Currently, test developers and research funding agencies are not willing or able to fund these studies. And once evaluations are completed, technical assistance and training will be needed to integrate these new diagnostics into country programs.

Filling the TB Funding Gap

The Global Plan to Stop TB, with its goal of saving 14 million lives from TB from 2006 to 2015, has an estimated price tag of \$56 billion, including \$9 billion for research and development and \$6 billion for improving access to MDR-TB treatment.⁶⁵ The Global Plan was developed by the Stop TB Partnership, a network of international organizations which includes the U.S. and other donor government participation, as well as civil society groups. The approximate funding gap for implementing the Plan: \$31 billion.

TB research and control programs have been underfunded for decades, creating a chasm between the scope of the threat and the resources available to confront it. The most vocal recognition of this gap came last summer, when Anthony Fauci, MD, longtime director of the NIAID at the National Institutes of Health, called for a sustained and transformative research effort. Importantly, he also argued that a newly energized and creative research response in



Dr. Giorgio Roscigno, of the Foundation for Innovative New Diagnostics, on Game-Changing Tools for TB Diagnosis

Dr. Giorgio Roscigno is CEO of the Foundation for Innovative New Diagnostics (FIND), a non-profit Swiss foundation at the forefront of diagnostics development whose mission is to develop and roll out better and more affordable diagnostic tools for poverty-related diseases. Since its inception in 2003, FIND has received WHO endorsement for four new TB technologies, which are currently being scaled up in over 27 countries. Next in the pipeline: a potentially revolutionary tool that could significantly increase the number of TB patients who will be diagnosed earlier—including those with hard-to-detect MDR-TB and those co-infected with HIV. This could, in turn, interrupt the chain of transmission of TB and help to halt the spread of the epidemic.

Q: Why are the current diagnostic tools so inadequate in the context of today's TB threat?

A: The current technologies we're using are microscopes and culture systems. The microscope has very limited sensitivity. To detect TB using microscopy, a patient needs to have been sick for at least 2 or 3 months. At the beginning of TB disease, the patient might have a little cough and fever, but if you use a microscope at that point, the results usually show up as negative because at this stage there would not be enough TB germs in the sputum sample. And so the patient would go back home and continue to be infectious. He may go to work, ride the bus, and spend time with friends and family.

Culture is a system where a technician puts the TB bacteria into some favorable media, a kind of oven, in which these bacteria can grow, so they multiply much faster. Then you can see them more easily. But even this takes quite some time, 10 days to a month or more. And in order to do the culture, you need a sophisticated set up, including biosafety, which is usually only available in well-equipped laboratories such as the kind found in sophisticated urban settings.

Q: You recently gave a presentation on TB diagnostics and mentioned a new test expected to be endorsed this year, which could diagnose TB and drug-resistant TB in 90 minutes—a vast improvement over today's tools. Tell me more about this test—what would be the impact and what will it take to bring it to market?

A: With a microscope and the naked eye, you need 10,000 mycobacteria to make a positive TB diagnosis. But recently the world has made quite significant advancements in molecular technology. Instead of looking for the bug itself, you can extrapolate that there are mycobacteria by detecting the DNA of the bug. So even if you only had a few, or just one, bacterium, if you were able to detect the DNA and make it visible, you could make a diagnosis.

Until now, this process required very large equipment operated by highly trained technicians. But an American company, Cepheid based in California, has developed, with funding from the Department of Defense, a very simple machine that performs this complex task in a way that doesn't require special training, nor does it require a sophisticated lab environment. You take a sample of sputum, put it in a cartridge, put the cartridge into the machine, and in 90 minutes, it will tell you whether in there are TB mycobacteria and whether those mycobacteria are resistant to rifampicin, a first-line TB drug.

This technology promises to be a major breakthrough. It would allow very early detection of TB in HIV patients as well as very early detection of MDR-TB. On top of this, it would be available in a setting requiring minimal infrastructure. If this technology could be used at the lowest level of the health care system, very near to where the majority of patients go when they first get sick, then the number of patients diagnosed in the very first stages of the disease would be much greater than it is now.

Q: What else is on the horizon that could be a game-changer for TB diagnosis?

A: The next generation of the revolution would be a point-of-care technology—a much simpler test similar to a pregnancy test that could be used in remote villages, performed by community health care workers without any training and that could provide results within minutes. FIND has been working on this rapid, point-of-care test for 6 or 7 years now. It's a little bit more complex than we originally thought and it's taking more time.

Q: *What are the potential synergies between these diagnostic innovations for TB and other laboratory needs in resource-poor settings?*

A: For the last for 4 or 5 years, FIND has not invested in any technologies or any platforms that could only be used for one disease. So integrating various diseases using a common platform is one of the most important criteria for us in terms of new tools development, and it is becoming one of the most important criteria in lab strengthening. The Cepheid test, for example, is already used for several other disease indications in Europe, including MRSA, van A, *C. difficile*, and Flu panel, for example.

In our development of this tool, FIND is hoping to introduce on that same platform a viral load count for HIV. So this platform which can detect TB in HIV patients right at the onset of the disease could also be used to measure the viral load in HIV patients, which is a very important tool to monitor therapy. Unfortunately, at the moment, we don't have sufficient funding to make that HIV viral load platform a reality.

Q: *Looking ahead, what is the biggest challenge in TB diagnostics? Is it a lack of scientific interest, a lack of resources, a lack of political commitment, or something else?*

A: In general, the importance of diagnostics has been greatly underestimated and widely misunderstood—for TB in particular. One of the main reasons for this has been a lack of investment in basic research and development over the last 20 years.

In addition, diagnostic tools require a laboratory. Labs in the developing world have been neglected for at least 10 or 20 years, so when one imagines a new technology that has to be introduced in these labs, one is faced with the complexities involving refurbishing, introducing quality control, ensuring waste management and providing training.

We hope now that the world will begin to invest in this vital area of the health system. There has been important progress and a lot of excitement around diagnostics in the last 7 or 8 years. The need for effective and affordable tests is very great, and the opportunities for R&D are very exciting. Academia and commercial companies are now starting to look at this field with more interest than they did before.

tuberculosis should be accompanied by a concurrent effort—backed by resources and operational research—to ensure that research advances make it rapidly to the TB hot spots around the globe.

“We have had decades of relative neglect given the extent of the problem,” Dr. Fauci said. “There is much catching up to do and this will require a sustained effort,” with major funding commitments. In 2007, Dr. Fauci's NIAID released a comprehensive research agenda for MDR/XDR-TB, but its implementation has been limited by funding constraints.

Dr. Fauci, who took over NIAID nearly a quarter-century ago, made a striking parallel between HIV and TB research over that time. For the past 25 years, no new TB drugs have

come to market. In that same period, 30 HIV/AIDS drugs have.

“To me, the key question ... is why we do not have 30 new drugs for TB, a disease we know is eminently curable?” Dr. Fauci asked. “... A transformative research effort to TB has not begun. That is beginning to change. What we see is the winds of change, but what we really need is a storm.”⁶⁶

That storm has still not hit.

In 2008, worldwide investment in TB research and development, from public and private sources, amounted to only \$510 million, according to an analysis by the Treatment Action Group. That is only about half of the \$900 million annually that the WHO says is needed. Resources for TB

programming are also woefully inadequate given the scale of the problem and the low cost and effectiveness of treatment for drug-susceptible TB, the overwhelming majority of TB cases. Programmatic efforts to actually prevent the development of active TB in those with latent infection—especially in vulnerable persons with HIV infection—have barely gotten off the ground.

The U.S. contribution to the TB funding pot is modest. U.S. investment in basic TB science actually decreased from FY 2009 to FY 2010, and operational research remained flat, the TAG report shows. Funding for diagnostic research was only \$50 million. The TB clinical trial network at the CDC has operated with a budget of under \$10 million for years. It remains to be seen if the U.S. and other donor nations will step up to the plate to provide financing for effectiveness trials when promising new TB tools emerge from the public-private partnerships focused on the development of TB diagnostics, drugs, and vaccines—largely funded by the Bill & Melinda Gates Foundation.

The promise of the Comprehensive TB Elimination Act, which was enacted to provide more adequate financing to state TB control programs in the U.S. and to jump start the effort to develop new tools to fight TB, have yet to be realized. Flat funding for TB control at the federal level, coupled with significant layoffs at state TB control programs as a result of the economic recession, has left us less, not more equipped to deal with another significant outbreak of MDR-TB.

Global TB advocates had greeted the passage of the Lantos-Hyde Act, with its authorization of \$4 billion for tuberculosis activities over five years, as a signal of long overdue leadership from the U.S. in the global battle against TB. This funding level was endorsed by the Institute of Medicine in 2009, which called for \$800 million in TB spending by 2012. Regarding research, the Lantos-Hyde law directs the President to give priority to “enabling and promoting research to develop new diagnostics, drugs, and vaccines, and program-based operational research relating to tuberculosis.” However, that leadership hasn’t been realized as the Obama Administration develops a Global Health Initiative that short-shrifts TB and downsizes the ambitious goals enacted into law less than two years ago. Lantos-Hyde calls for the treatment of 4.5 million new TB patients and the diagnosis and treatment of 90,000 new MDR-TB cases, with both targets to be achieved by 2013. By contrast, a GHI blueprint, released by the Administration in February, sets a goal of treating 2.6 million new TB cases and 57,200 MDR-TB cases by 2014.

Here’s a more detailed breakdown of U.S. spending on global TB:

- The U.S. Agency for International Development is the primary U.S. government agency for international TB control programming and the leading bilateral donor for TB control efforts. In a September 2009 report to Congress, “Building Partnerships to Control Tuberculosis,” USAID reported that in FY 2008, 80 percent of the agency’s budget was allocated to direct patient services, including resources for Directly Observed Therapy, Short-course (DOTS), anti-TB drugs, MDR-TB, and TB/HIV.⁶⁷ In FY 2009, approximately 19 percent of USAID’s TB budget was programmed for MDR-TB. USAID also supports drug-resistance surveillance through WHO in various countries and funds research where it has direct and near-term implications for country-level TB programs,⁶⁸ including research to develop a shorter MDR-TB treatment regimen. In FY 2010, Congress allocated only \$225 million for global TB programs run by USAID. For FY 2011, the White House requested only a \$5 million increase for global TB efforts, a meager amount for a disease that last year killed more than 1.8 million people.
- The CDC’s Division of TB Elimination spearheads TB control in the United States and also provides support for global TB activities, working with the WHO, USAID, and national TB programs in host countries on everything from epidemiologic support and operational research to clinical studies and laboratory development. In FY 2010, the division received about \$144 million to carry out this vital work, including about \$18 million for research, seriously limiting its ability to conduct meaningful scientific evaluations. In FY 2011, the division would actually see a \$1 million cut under the proposed White House budget, further undermining U.S. capacity to evaluate new diagnostic, treatment, and prevention tools for TB.
- The majority of TB research is funded by the National Institutes of Health, primarily through the NIAID. In 2010, NIH devoted an estimated \$226 million to TB research; because a significant chunk of that came from one-time stimulus funds, the institute expects a decrease in TB research for 2011, to \$215 million.⁶⁹
- PEPFAR has increased support for programs to address HIV/TB co-infection from \$25.5 million in FY 2005 to more than \$140 million in FY 2008. This is a fraction of its overall funding; more attention is required to adequately address the dual HIV and TB epidemics. And despite having robust policies and goals around TB/HIV, including commitments to continue scaling up co-infection services, the Administration has proposed

essentially flat lining PEPFAR funding, which will likely mean a stall in the expansion in its TB/HIV services.

- The Global Fund to Fight AIDS, Tuberculosis and Malaria provides two-thirds of all TB funding to developing countries. In Round 9, the most recent funding cycle, the Global Fund approved 32 TB control proposals, totaling \$500 million, which covers 2 years of each grant. The U.S. has generally contributed about one-third of the resources for the Global Fund. But in FY 2010, Congress approved \$1.05 billion for the Fund, far short of what the Fund had requested and of the \$2 billion called for in Lantos-Hyde. And for FY 2011, the Administration has called for a \$50 million cut in the U.S. contribution to the multilateral organization.

Many of the U.S. commitments on TB spending, such as those in Lantos-Hyde, were made prior to the recent economic downturn and the intensified pressures on the federal budget. However, support in the U.S. Congress for much greater spending on TB remains strong. Forty-one members of the House of Representatives signed a letter urging \$650 million for USAID's TB program for fiscal year 2010, and 12 members of the Senate followed suit. For fiscal year 2011, 98 members of the House signed a letter urging \$1.75 billion for the Global Fund.⁷⁰ And senior leaders in the Congress have expressed their concern to the White House about a failure to meet Lantos-Hyde goals, including those on TB.⁷¹

Conclusion

Drug-resistant TB knows no borders, presenting a clear threat to Americans both at home and abroad. Against that backdrop, the meager funding for tuberculosis is inexplicable.

“In an interconnected world where drug-resistant tuberculosis could be on the next plane landing at Dulles, the answer—emphatically—is that we can't afford *not* to invest in these programs,” Sen. John Kerry, D-Mass., and chairman of the Senate Foreign Relations Committee, said at a March 2010 hearing on U.S. global health funding. “It protects our own citizens.”

Failure to invest in new TB tools—from labs and diagnostics to drugs and vaccines—will have serious consequences for U.S. public health and American taxpayers. The outbreak of MDR-TB in New York City in the mid-1980s, with its \$1 billion price tag, provides stark proof of this.⁷² The U.S., with its biomedical know-how and scientific leadership, must be given the resources to make

sure this kind of outbreak never happens again here at home and to reverse the epidemic now plaguing the developing world. America's leading research institutions, along with our myriad successful global health programs, must be given power to aggressively confront this threat.

This is not just about TB. It's also about our ability to make progress on a gamut of other global health priorities, from HIV/AIDS to child and maternal health. Consider these connections:

- **TB and HIV:** Tuberculosis is the leading killer of people living with HIV in developing countries.⁷³ Failing to address TB jeopardizes existing U.S. investments in AIDS treatment; each year, thousands of people whose lives have been saved by antiretroviral treatment die from undiagnosed or untreated TB.
- **TB and Maternal and Child Health:** TB is one of the leading killers of women each year, particularly among those in their reproductive years,⁷⁴ and it claims the lives of more than 100,000 children every year.⁷⁵ In India alone, it's estimated that 300,000 children are orphaned each year because their mothers have died of TB.⁷⁶
- **TB and Health Systems:** With more than 9 million new TB cases each year, involving long and complex treatment, particularly for drug-resistant TB, this disease is a heavy burden on health systems.⁷⁷ TB also takes a terrible toll on health care workers; one study in Malawi found that AIDS and TB accounted for 75 percent of health worker deaths in mission and district hospitals.⁷⁸

The devastation caused by tuberculosis was front and center in the 2008 debate over the Lantos-Hyde Act, when Congress reauthorized the President's Emergency Plan for AIDS Relief. That law requires the President to devise a comprehensive five-year strategy to combat global TB, including the treatment of 4.5 million new TB patients and the diagnosis and treatment of 90,000 new multidrug-resistant (MDR) TB cases by 2013.⁷⁹

But policymakers seem to be moving in reverse on TB now. The Administration has requested only a \$5 million increase for TB in FY 2011,⁸⁰ a paltry sum given TB's enormous death toll. And in a blueprint detailing plans for its new Global Health Initiative, the Administration scaled back TB targets by roughly half.⁸¹

Aggressive investments now in better TB control, treatment and prevention will save lives immediately—and it will save money in the long term.

Recommendations:

These recommendations are not exhaustive, nor are they new. One high-level report after another—including thorough examinations by experts at the CDC, the Institute of Medicine, the NIAID, and the WHO—has detailed the steps we need to truly confront the TB epidemic. But without the political will, these prescriptions have gathered dust on the shelf, while the threat of tuberculosis has spiraled. What we really need, more than any single step listed below, is for world leaders to recognize the scope of this disease and champion the fight against it.

The Administration should:

Improve Coordination, Funding and Targets

- Launch an initiative on tuberculosis to bring together a focused and coordinated response to TB, domestically and globally, effectively coordinating with all relevant federal agencies.
- Support full appropriations for the authorized spending levels in Lantos-Hyde for bilateral TB—\$4 billion over five years—and support full funding of the U.S.'s fair share of the Global Fund to Fight AIDS, Tuberculosis and Malaria's resource needs.
- Revise the TB targets contained in the Global Health Initiative Consultation Document to be consistent with the United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act of 2003 (P.L. 108-25).
- Support full funding for the Comprehensive TB Elimination Act so that state-based TB control programs remain robust and to finance new tools to combat TB.

Engage with International Partners

- Utilize high-level diplomatic engagement with U.S. allies and international partners to leverage greater contributions to the global fight against TB. Actions the Administration should consider include bringing TB funding issues into the high-level dialogue with China, India, and the Organization of the Islamic Conference; supporting intensified global collaboration on innovative financing for health; and officially hosting the Global Fund replenishment conference in 2013.

Invest in Human Resources

- Investing significant new resources in comprehensive national health workforce plans to help countries improve health care worker density, beyond the target of 140,000 health care workers included in the Global Health Initiative Consultation Document, as well as to improve

infection control, support community-based treatment, and provide training to overcome stigma of tuberculosis.

- The U.S. government should support training for new and existing lab technicians in developing countries.

Expand Surveillance

- Increase capacity to perform drug-susceptibility testing on a routine basis and develop procedures and methods for systematic recording and tracking of data trends.
- The U.S. government, working through USAID and the CDC, should collaborate with the WHO through financial support and technical assistance to conduct TB drug-resistance surveys in high TB prevalence countries. Measures should be developed to assess drug resistance in sputum-negative cases, especially among persons with HIV infection.

Strengthen Laboratories

- The U.S. should mobilize more resources through PEPFAR, USAID and the Global Fund to support international efforts to strengthen and sustain TB laboratory capacity.
- Develop technical assistance approaches and practices for laboratory capacity building in high burden international settings that are coordinated, consistent, and compatible with the efforts of international partners such as the WHO.

Expand MDR-TB Treatment

- In collaboration with the WHO, other relevant agencies, and country governments, USAID should scale up activities to ensure effective treatment of drug-resistant tuberculosis through capacity building, program development technical assistance, health care work training and resources aimed at ensuring an adequate supply of high quality, effective medications.

Expand TB-HIV Activities

- Working through the Office of the Global AIDS Coordinator (OGAC), the Administration should expand access to ART for co-infected individuals, regardless of CD4 count, to reduce TB mortality and morbidity.
- Ensure that HIV patients in U.S.-funded clinics in high TB prevalence countries are screened for TB and treated for TB disease or with preventive therapy as appropriate.
- Monitor and document the incidence of drug-resistant TB in patients with HIV infection.
- Ensure that PEPFAR works with treatment sites they support to ensure compliance with WHO guidelines on

preventing the transmission of TB in clinical settings. In particular, technical and financial support is needed to scale up and implement effective TB infection control measures in health care and community settings in order to prevent transmission of TB including MDR and XDR-TB to HIV-infected patients and health care providers.

Ramp up Research and Development

- Implement the National Institute of Allergy and Infectious Diseases 2007 MDR/XDR-TB research agenda.
- Conduct studies to determine epidemiology and patterns of distribution and transmission of MDR and XDR-TB
- Expand clinical trial capacity at the NIH and the CDC to evaluate new diagnostics, especially point-of-care diagnostics, for drug-susceptible and drug-resistant tuberculosis
- Develop strategies to expedite evaluation and implementation of new rapid methods for laboratory and point-of-care confirmation of TB and identification of drug resistance.
- Enhance research and development to develop diagnostics and drugs to identify and treat drug-resistant TB in infants and children, with and without concurrent HIV infection.
- Expand the availability of clinical trial sites in TB and TB/HIV endemic countries for all phases of clinical testing of vaccines, drugs, and diagnostics.
- Conduct studies to identify determinants of survival among MDR-TB and XDR-TB patients
- Ensure that research and development of new tools including diagnostics and drugs capable of identifying and treating drug-resistant TB is accompanied by a concurrent plan for implementation research aimed at ensuring that new technologies can be quickly introduced into high prevalence, resource-limited settings.
- Perform operational research and implementation science projects to better understand how best to design, implement, and monitor TB infection control strategies and to document their effectiveness.

Congress should:

- **Provide full funding for U.S. global TB programs to support the targets in the United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria.** Congress should provide \$650 million annually for USAID's global tuberculosis program, to begin a five-year scale up to the funding authorized under Lantos-Hyde and to support the development and deployment of better

TB drugs, diagnostics, and vaccines. This law, (P.L. 108-25) requires the Administration to develop a five-year U.S. strategy to treat 4.5 million cases of TB under DOTs, and 90,000 multi-drug resistant (MDR) TB cases.

Congress should also provide an additional \$50 million for CDC's global TB activities through the FY11 Labor-HHS Appropriations legislation to provide the coordinated global TB investment envisioned under the Lantos-Hyde Act, including funds for essential laboratory strengthening. Full funding for PEPFAR is also crucial, since this program is a major contributor to efforts to address TB/HIV co-infection.

- **Exercise strong oversight over Administration plans for its Global Health Initiative to ensure adequate programming and funding for tuberculosis.** Congress should insist that the TB targets identified under the Global Health Initiative reflect the more ambitious targets enacted under Lantos-Hyde.
- **Provide full funding for the U.S. contribution to the Global Fund to Fight AIDS, Tuberculosis and Malaria.** Congress should provide \$1.75 billion for fiscal year 2011 to leverage international support and continue to expand grant making. It is critical that the U.S. provide an increased investment, particularly at this time when the Fund is projecting a significantly increased need for resources, including funding to address MDR-TB. Success on TB also requires robust U.S. support for the WHO and the Global Drug Facility, as well as for UNAIDS, which is taking strong leadership on TB/HIV.
- **Provide full funding for TB programs in the U.S.** Congress should provide a funding level of \$220 million for CDC's Tuberculosis (TB) program in the U.S. for FY2011, as authorized by the Comprehensive TB Elimination act (CTEA). Eroded state program budgets over the last decade place progress made against TB in the U.S. in jeopardy.
- **Expand funding for TB research through the National Institutes of Health.** NIH, through its many institutes and centers, plays the leading role in basic and clinical research into the identification, treatment and prevention of TB. Congress should double spending on tuberculosis research at NIH to \$320 million.

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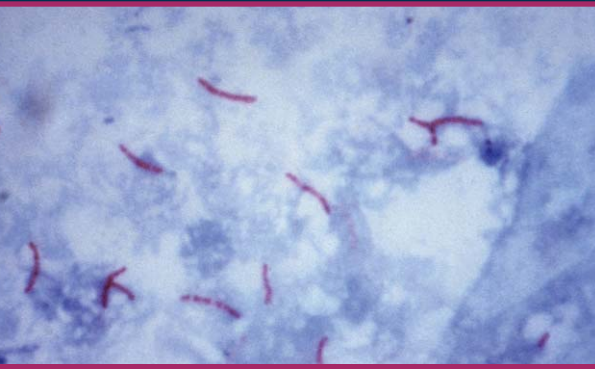
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