

A microscopic view of numerous rod-shaped bacteria, likely Mycobacterium tuberculosis, against a dark background. The bacteria are illuminated from the bottom, creating a bright yellow and orange glow. Some bacteria are in sharp focus, while others are blurred in the background, creating a sense of depth. The overall color palette is dark with a gradient from purple at the top to yellow at the bottom.

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# Tuberculosis in the Age of Drug Resistance and HIV

*Lessons from South Africa's Experience*

*A Report of the CSIS Global Health Policy Center*

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# Contents

Acknowledgments	IV	
Executive Summary	V	
TB Poses an Unprecedented Long-term Threat to South African Interests		1
Drug-resistant Tuberculosis Is a Major Challenge		3
The Reciprocal Impacts of HIV/AIDS and Tuberculosis		5
Diabetes and Tuberculosis	7	
Other Groups in South Africa with Particular TB Risk		7
Other TB-related Challenges for South Africa		9
The Role of the United States	12	
Discussion	12	
Recommendations	15	
Conclusion	16	

## Acknowledgments

We have prepared this report based on meetings and interviews held in South Africa in May 2015 with past and present officials of the South African government and National AIDS Council, representatives of South African and international nongovernmental organizations, civil society leaders, public health and medical researchers, and representatives of the private sector. In addition, we held meetings and interviews in the United States before and after that visit and reviewed available scientific data on TB, TB/HIV, and HIV in South Africa. This paper is part of ongoing CSIS work that focuses on the bilateral health relationship between the United States and South Africa.

The authors are grateful to the U.S. embassy country team and South African government officials for their support and to the staff of the universities and nongovernmental organizations they met with while in South Africa for sharing their insights and experiences. The authors appreciate the thoughtful reviews of this document by several colleagues. This work was made possible by the support of the Bill & Melinda Gates Foundation.

## Executive Summary

Tuberculosis (TB) is a potentially lethal but preventable and usually treatable airborne infection that, in many countries, gets far less attention from policymakers and public health leaders than it deserves. South Africa is one country that cannot afford that outcome given that the disease is that country's number one killer, including among the country's youth and among people living with HIV infection (PLHIV). TB is also the country's third most common cause of maternal mortality.

Recent data confirm the gravity of South Africa's national TB situation (Box 1).

Thanks to the leadership of a dynamic minister of health, there is increasing recognition within South Africa of the gravity of the country's TB challenge, including its link to the ongoing national HIV epidemic. Within its economic and health system constraints, the Department of Health (DOH) leadership in South Africa has taken on TB as a major issue, initiating several important steps, and is planning a large number of other programs and activities in public and community awareness, prevention, and treatment to address the factors that have driven the country's TB problem to this point. In addition to these DOH activities, published output from the country's extremely productive TB and HIV research communities provides important potential advantage to the national TB response, particularly in terms of the kinds of operational research needed to improve program effectiveness.

At the moment, the overall approach to TB control in South Africa is improving steadily in many respects; the annual number of drug-sensitive TB cases has been falling in recent years. However, current efforts are not yet sufficient to address a national TB problem that is fueled by expanding epidemics of multidrug resistant TB (MDR-TB) and HIV. This gap is related in part to a lack of adequate health system resources and to other persistent weaknesses in the country's health and political systems. About a third of people identified with active TB are not started on treatment or notified of their disease.<sup>1</sup> Treatment success rates for those started on treatment, while slowly rising, remain below global norms. Infection control programs to keep TB from spreading within communities and within health facilities are not yet sufficient.<sup>2</sup> Public awareness of TB and its links to HIV is still suboptimal; stock-outs of TB drugs are still reported, and TB and HIV data systems are not yet fully integrated. The national primary care system is still struggling with shortages of funding and

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<sup>1</sup> Laura Jean Podewils, Nonkqubela Bantubani, Claire Bristow et al., "Completeness and Reliability of the Republic of South Africa National Tuberculosis (TB) Surveillance System," *BMC Public Health* 15 (2015): 765, <http://www.biomedcentral.com/1471-2458/15/765>.

<sup>2</sup> Infection control procedures for TB include steps such as increasing airflow and ventilation, use of face masks, separating people with known or suspected contagious TB from uninfected people by limiting their time in congregate settings, etc.

## Box 1. Highlights of Recent South African TB and TB/HIV Data<sup>a</sup>

**Overall:** South Africa has the world's highest population rate of new TB cases.

**TB Mortality in South Africa:** TB is the leading cause of death, including among young adults (from Statistics South Africa, 2014).

89,000 TB deaths total, 64,000 of those among HIV-infected people;

TB is the third most common cause of maternal mortality (National TB Management Guidelines, 2014);

TB is the most common cause of death in prisons.<sup>b</sup>

**Latent TB Infection:** That is, an initial quiescent TB infection that does not cause illness or symptoms.

Latent TB Infection rate estimated at 80 percent of entire population (TB FACTS.ORG, TB in South Africa).

**New Active TB Cases:** 450,000 cases/year are estimated to occur; 312,000 (69 percent) were actually diagnosed and reported to the Department of Health in 2013.

**Multidrug-resistant TB (MDR-TB):**

Defined as resistance to the two best first-line TB drugs;

26,000 MDR-TB patients identified; only about 10,600 (41 percent) were started on treatment.

**TB/HIV Coinfection and Codisease:**

62 percent of the 295,000 new TB patients actually tested for HIV were found to be HIV-infected;

just over 50 percent of new HIV-infected TB patients were taking antiretroviral drugs;

only about 10 percent of PLHIV received isoniazid preventive [drug] therapy (IPT) to prevent TB.

**TB Follow-up:** Over one-third of a national sample new smear positive TB patients had no notification or treatment records (Podewils et al., *BMC Public Health*, 2015).

**TB Treatment Completion Rates:**

Among all TB cases registered in prior year: 77 percent;

Among HIV-infected TB cases: 74 percent;

Among MDR-TB cases treated with second-line drugs: 45 percent;

Among XDR-TB<sup>c</sup> cases treated with second-line drugs: 15 percent.

**Proportion of National TB Budget Funded with Domestic Resources:** 84 percent.

<sup>a</sup> Unless noted otherwise, data are from the 2014 WHO TB Country Profile for South Africa, [https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO\\_HQ\\_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=ZA&LAN=EN&outtype=pdf](https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=ZA&LAN=EN&outtype=pdf). Numbers are estimates rounded to the nearest thousand. Also see Statistics South Africa, "Mortality and causes of death in South Africa, 2013: Findings from death notification," Statistical release P0309.3, December 2, 2014, <http://www.statssa.gov.za/publications/P03093/P030932013.pdf>; Republic of South Africa, Department of Health, "National Tuberculosis Management Guidelines," <http://www.statssa.gov.za/publications/P03093/P030932013.pdf>; and TB Facts.org, "TB in South Africa, National and Provincial Statistics," 2, <http://www.tbfacts.org/tb-statistics-south-africa/>.

<sup>b</sup> Robin Wood, "What Will It Take to Control TB in South African Prisons?," Editorial, *NSP Review* 7 (July–August 2013): 1, [http://www.nspreview.org/download/NSP\\_Review\\_7\\_Web.pdf](http://www.nspreview.org/download/NSP_Review_7_Web.pdf).

<sup>c</sup> XDR-TB is a more severe form of MDR-TB that is more difficult and more expensive to treat.

trained staff.<sup>3</sup> Finally, because TB is the most common cause of death among PLHIV, the magnitude and severity of the national TB pandemic poses a major threat to the long-term success of South Africa's life-saving HIV treatment program.

The United States has large equities in South Africa's struggle with TB and HIV, having spent over US\$5 billion in South Africa since 2004 through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR).<sup>4</sup> About 9 percent of recent PEPFAR/South Africa funds have been allocated to direct TB/HIV coinfection and codisease issues. In addition, the health system strengthening efforts of PEPFAR, the U.S. Agency for International Development (USAID), and the Centers for Disease Control and Prevention (CDC) have supported the South African government's overall approach to TB control. However, the U.S. government's major health priority in South Africa has been the country's serious HIV epidemic—and the host government's energetic treatment-oriented response to it—which has overshadowed TB control efforts and other national health challenges.

But what future TB scenario does South Africa potentially face? What might a continued failure to achieve better control of TB and MDR-TB look like in that country?

First, South Africa is at risk of becoming a country in which a TB pandemic evolves to become dominated by MDR-TB. If treatment of drug-sensitive TB remains relatively successful while treatment of MDR-TB remains relatively unsuccessful (and expensive), and if MDR-TB continues to spread, there will be relatively fewer drug-sensitive (and easy-to-treat) TB infections and more MDR-TB infections.<sup>5</sup> Consequently, South Africa's national TB epidemic will increasingly become one of airborne MDR-TB, which has uncertain treatment outcomes and is so expensive to treat that even a small number of MDR-TB infections will have a large economic impact. A 2011 analysis indicated that although MDR-TB represented only 2.2 percent of South Africa's TB cases, treatment of those few cases accounted for 32 percent of the national TB budget.<sup>6</sup>

Second, as the number one killer of PLHIV, TB remains a threat to the success of the country's efforts to control HIV/AIDS—and to PEPFAR's multibillion-dollar efforts thus far to support South Africa. This threat of continued TB-related mortality among

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<sup>3</sup> Richard Downie and Sahil Angelo, *Counting the Cost of South Africa's Health Burden* (Washington, DC: CSIS, July 2015), [http://csis.org/files/publication/150727\\_Downie\\_SouthAfricaHealth\\_Web.pdf](http://csis.org/files/publication/150727_Downie_SouthAfricaHealth_Web.pdf).

<sup>4</sup> See U.S. Diplomatic Mission to South Africa, "About PEPFAR SA," 2014, [http://southafrica.usembassy.gov/pepfar\\_about.html](http://southafrica.usembassy.gov/pepfar_about.html).

<sup>5</sup> An even more drug-resistant subset of MDR-TB, called Extensively Drug-Resistant TB (XDR-TB), may require even longer treatment. XDR-TB care is correspondingly more expensive and its treatment success rates even lower.

<sup>6</sup> If MDR-TB patients were treated entirely as outpatients (as opposed to the traditional practice of treating them as hospital inpatients), total costs would still represent 32 percent of the national TB budget. See Anil Pooran, Elize Pieterse, Malika Davids et al., "What Is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa?" *PLOS ONE* 8, no.1 (January 2013): e54587.

PLHIV who are otherwise being successfully treated for HIV looms regardless of further changes in TB's drug-resistance patterns.

Either of these outcomes would seriously impact South Africa's ability to meet its own health goals, and would undermine U.S. and international investments in national and global HIV and TB control.

South Africa and its senior health leadership need support for mounting a more muscular response to the country's unprecedented TB challenges, particularly those linked to MDR-TB and XDR-TB. A recent investment case for better control of HIV and TB that was prepared for the National Department of Health and for the South African National AIDS Commission (SANAC) pointed out that achieving the new '90-90-90' TB plan would require a 46 percent TB budget increase over a five-year period.<sup>7</sup> Of course, the strategic challenge is the uncertainty of where the financial and human resources will come from to carry out those steps—in addition to the steps required to put millions more PLHIV on ARVs. The potential consequences of continued failure of TB control in South Africa require serious consideration of further expanding the national TB budget, including exploration of all available South African, U.S. and other resource options.

South Africa is one of USAID's "high-priority" TB countries. Beyond its PEPFAR-supported efforts, USAID has had a moderately sized TB program of its own in South Africa. One component of that program ended in fiscal year 2014 but others are continuing. A recent request from USAID/South Africa for TB cooperative agreement proposals focuses on providing "technical assistance to the Government of South Africa (GoSA) in order to reduce the burden of tuberculosis (TB) in the country."<sup>8</sup> The budget for that project is estimated at \$25–50 million over five years.<sup>9</sup> In addition, South Africa is eligible as a country to be included in USAID's new flagship Challenge TB program that runs from 2015–2019.

CDC receives a relatively small amount of TB research funding from USAID and a larger tranche of funds that support CDC's work within PEPFAR. Beyond these dedicated funds, the current CDC budget does not include any global TB funding. However, CDC has additional TB expertise that could be helpful for providing technical assistance to South Africa.

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<sup>7</sup> Gesine Meyer-Rath, Calvin Chiu, Leigh Johnson et al., "South Africa's Investment Case: What Are the Country's 'Best Buys' for HIV and TB?," presented at the Seventh South African AIDS Conference, June 2015, Durban, <http://www.heroza.org/wp-content/uploads/2015/07/IC-presentation-for-SA-AIDS-for-sharing.pdf>.

<sup>8</sup> USAID, "Technical Assistance Contract 4 Africa (TASC4 Africa) IDIQ," <https://www.usaid.gov/sites/default/files/documents/1860/TBSAP%20RFTOP%2020150630.pdf>.

<sup>9</sup> Devex, "USAID Renews Support for Tuberculosis Prevention in South Africa," <https://www.devex.com/projects/pipelines/usaid-renews-support-for-tuberculosis-prevention-in-south-africa/28259>.

The National Institutes of Health is providing small amounts of funding for training South African researchers involved in TB research and for carrying out collaborative TB research.

There is general agreement among South Africans involved in HIV/AIDS and TB control activities that the PEPFAR program has played an important role in South Africa's HIV/AIDS response over the last decade. There is also recognition that a transition to a leaner and more focused PEPFAR program role is unavoidable (and, in fact, reflects reduced U.S. budget realities). However, the need to effectively address South Africa's current TB challenge would seem to warrant additional PEPFAR resources for some period, if only to protect PLHIV in that country from a greater TB disease burden.<sup>10</sup>

Although reallocation of current and future PEPFAR funds toward additional TB-specific projects could be helpful, PEPFAR should at a minimum take care that its process of refocusing resources away from some locations and programs does not inadvertently undercut the country's still-fragile TB control activities. For example, experts expressed concern during our visit that the sites of some of South Africa's MDR-TB and TB/HIV problems most needing additional attention will not correspond in all cases to the HIV hot spots that PEPFAR will be targeting.

Another potential source of U.S. resources will be the forthcoming *National Action Plan for Combating MDR-TB*,<sup>11</sup> a new White House initiative under the National Action Plan for Combating Antibiotic-Resistant Bacteria, which is itself an aspect of the U.S. Global Health Security Agenda.<sup>12</sup> Beyond a pledge to treat 360,000 MDR-TB patients over the next five years in the countries with the highest MDR-TB burdens,<sup>13</sup> the publicly available details of the Action Plan are still ambiguous, including its overall funding level, its start date, the amount of its emphasis on *preventing* MDR-TB, and its specific priority countries. Because South Africa is clearly one of the hottest of the global MDR-TB hot spots, it will presumably be high on the country-specific priority list of that National Action Plan.

In a promising step, South Africa recently submitted a concept note for a new \$380 million HIV/TB grant to the Global Fund to Fight AIDS, Tuberculosis and Malaria.<sup>14</sup> The

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<sup>10</sup> Within any country program, the proportion of PEPFAR's resources devoted to TB (or TB/HIV) control can vary.

<sup>11</sup> USAID, "Stakeholder Forum on the U.S. Government National Action Plan to Combat Multidrug-resistant TB," <https://www.usaid.gov/what-we-do/global-health/tuberculosis/resources/news-and-updates/stakeholder-forum-us-government>.

<sup>12</sup> GlobalHealth.gov, "Global Health Topics," Undated, <http://www.globalhealth.gov/global-health-topics/global-health-security/ghsagenda.html>.

<sup>13</sup> Rabita Aziz, "Ambitious New U.S. Plan May Put Hundreds of Thousands on MDR-TB Treatment," *Science Speaks: HIV & TB News*, Center for Global Health Policy, July 23, 2015, <http://sciencespeaksblog.org/2015/07/23/ambitious-new-u-s-plan-may-put-hundreds-of-thousands-on-mdr-tb-treatment/>.

<sup>14</sup> South Africa does not have a current TB-specific Global Fund grant although some of the resources in the six current HIV grants are being used to address TB/HIV coinfection, including the integration of HIV and TB programs.

country's particularly challenging TB situation should be taken into account as that proposal is reviewed. Another potential source of additional TB control resources is the World Bank, which currently has a small multi-country grant that addresses TB in underground miners in several southern African countries, including South Africa.<sup>15</sup> All other possible nongovernment funding sources should be considered, including the potential benefits of additional public-private partnerships within South Africa. Beyond seeking additional external funds, the government has the options of internally reallocating some of its current budget resources and providing new resources of its own.

Beyond securing resources, an additional priority for South African TB control programs is emphasizing programmatic and staff activities for *prevention* of new TB cases, including earlier diagnosis and treatment of active (and thus contagious) TB cases, expanded treatment of latent TB infection among PLHIV, and better infection control in health facilities and in communities.<sup>16</sup>

PEPFAR and USAID staff should be charged with carefully and jointly monitoring the epidemiologic and programmatic impacts on TB control in South Africa of changes in U.S. funding and technical assistance. To allow that monitoring to occur efficiently, it will be important for South African officials to share openly with U.S. staff the information about TB epidemiology and program responses as it emerges.

Pursuit of all these steps will require leadership from the United States, including maintaining a continued high U.S. priority on TB control, an ongoing open dialogue with South Africa's Department of Health and National AIDS Commission, and close attention to the country's TB challenges and responses by staff of the U.S. mission, the Office of the [U.S.] Global AIDS Coordinator (OGAC), USAID, and CDC.

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<sup>15</sup> In a previous blog, World Bank President Jim Kim commented on South Africa's TB challenge. Stop TB Partnership, "World Bank president Blogs on Tuberculosis, Mining and Africa," [http://stoptb.org/news/stories/2012/ns12\\_055.asp](http://stoptb.org/news/stories/2012/ns12_055.asp).

<sup>16</sup> These three interventions comprise the World Health Organization's "Three I's" of TB/HIV prevention, which are also supported by USAID, CDC, and PEPFAR.

# Tuberculosis in the Age of Drug Resistance and HIV

## Lessons from South Africa's Experience

Phillip Nieburg and Sahil Angelo<sup>1</sup>

### TB Poses an Unprecedented Long-term Threat to South African Interests

In recent years, much of the external and internal attention to health issues in South Africa has focused on the huge challenges posed by the country's still expanding HIV epidemic and the increasing cost of providing antiretroviral (ARV) treatment and other HIV/AIDS services to the growing numbers of people living with HIV (PLHIV). However, although the laudable treatment-related successes of the country's ARV drug programs are well documented and help reduce the numbers of active TB cases, some observers are concerned that the amount of attention paid to HIV/AIDS efforts has obscured other long-term national health challenges, including TB.<sup>2</sup>

As we learned during our visit, the enduring threat of TB in South Africa can be explained by a number of factors, some relating to the long-term history of TB disease and TB control efforts in southern Africa, others to recent social and economic factors, and still others to biologic factors such as the relatively recent advent of HIV/AIDS and of MDR-TB. In order to explain the scope and complexity of the TB problem now facing South Africa and its partners, we briefly describe examples of the TB-related social, economic, biologic, and administrative challenges facing that country.

In common with many other middle- and low-income countries, South Africa faces significant challenges in achieving its health goals: widespread poverty; stigma and discrimination against people with disease; a stagnating economic situation; and a two-class health system that cannot yet adequately address the basic health needs of the larger national population. However, for a number of reasons, the situation in South Africa regarding TB, TB/HIV coinfection, and multidrug-resistant TB (MDR-TB) is even more complex than that of most other low- and middle-income countries.

In the past, poor access to health care and the crowded living and working conditions associated with rural poverty, informal peri-urban settlements, and apartheid aided the

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<sup>2</sup> See, for example, Todd Summers, "Success on HIV Overshadows Failures on TB," CSIS, 2015, <http://www.smartglobalhealth.org/blog/entry/successes-in-hiv-overshadows-failures-in-tb/>.

spread of TB in South Africa.<sup>3</sup> Even greater crowding and greater TB risk was—and is—still found in prisons and underground mines. In fact, 80 percent of South Africans are estimated to have latent TB infections that, although not symptomatic or contagious themselves, can progress to active TB disease when combined with other adverse health circumstances such as HIV infection, malnutrition, diabetes, or exposure to the silica dust found in many underground mines.<sup>4</sup>

Second, some areas of South Africa have rising rates of infection with multidrug-resistant TB (MDR-TB), which can sometimes be transmitted from person-to-person and which is difficult and expensive to treat successfully. The highly lethal combination of HIV and airborne MDR-TB has been called a “perfect storm”<sup>5</sup> and poor infection control practices in and around hospitals and other health facilities have likely amplified TB transmission, including to many health workers.

Third, the quality of service delivery by the national primary health care system is often quite problematic.<sup>6</sup> New TB cases are not always identified as completely or as quickly as they might be nor are all persons identified as having active TB told about their diagnosis or started on treatment.<sup>7</sup> Once started on treatment, many patients are not adequately followed to ensure that they complete treatment. Many “default” (drop out) from treatment.

In terms of administrative challenges, the South African government is a federal system in which the country’s nine provinces are able to—and often do—act independently of the central government with regard to health issues.<sup>8</sup> Not surprisingly, available resources, TB epidemiology, and the quality of TB programs vary by province.<sup>9</sup> In addition, the country’s relatively centralized national health system is also hobbled by a sluggish national economy and by shortages of well-trained middle managers and primary care staff.

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<sup>3</sup> Hoosen Coovadia, Rachel Jewkes, Peter Barron et al., “The Health and Health Systems of South Africa: Historical Roots of Public Health Challenges,” *Lancet* 374, no. 9692 (September 5, 2009): 817–34.

<sup>4</sup> Latent tuberculosis infection (LTBI) is the initial phase of TB infection, when the immune system of the infected person is able to at least temporarily prevent TB bacteria from multiplying and progressing to active TB disease. Progression of LTBI to active TB disease is responsible for the majority of new TB cases.

<sup>5</sup> Charles D. Wells, J. Peter Cegielski, Lisa J. Nelson et al., “HIV Infection and Multidrug-resistant Tuberculosis—The Perfect Storm,” *Journal of Infectious Diseases* 196 (Supplement 1), 2007: S86–S107.

<sup>6</sup> Chris Bateman, “SA’s Ailing Public Health Sector ‘Responding to Treatment?’,” *South African Medical Journal* 105 (January 2015): 11–13.

<sup>7</sup> Laura Jean Podewils, Nonkqubela Bantubani, Claire Bristow et al., “Completeness and Reliability of the Republic of South Africa National Tuberculosis (TB) Surveillance System,” *BMC Public Health* 15 (2015): 765.

<sup>8</sup> Wide variations have been noted among South Africa’s nine provinces in their rates of infection with HIV, drug-sensitive TB, and MDR-TB and in their use of various programmatic interventions.

<sup>9</sup> “TB in South Africa | National & Provincial Statistics,” TBfacts.Org, <http://www.tbfacts.org/tb-statistics-south-africa/#sthash.3szjcGu3.dpuf>.

## Drug-resistant Tuberculosis Is a Major Challenge

TB disease that is resistant to treatment by the usual TB drugs can occur by one of two mechanisms. First, TB bacteria can become resistant to the usual “first-line” TB drugs when they are exposed to small but inadequate amounts of those drugs. This can happen in situations where patients have reduced access to treatment because they cannot afford transport costs to reach the clinic, because of drug stock-outs, because of poor adherence to recommended doses, or if they stop taking their drugs too soon. TB’s tendency toward drug resistance, first noted in the 1940s, led to the development of the current first-line four-drug treatment regimen used to successfully control drug-sensitive TB.<sup>10</sup>

Patients can also become infected with drug-resistant TB through direct person-to-person airborne transmission of TB bacteria that are already drug-resistant. Many drug-resistant TB infections in South Africa are thought to occur through this mechanism.

Resistance of TB bacteria to a single TB drug occurs occasionally but can usually be easily overcome by the other three first-line drugs. The more complex *multidrug-resistant TB* (MDR-TB) is characterized by resistance of TB bacteria to at least the best two of the widely available and relatively inexpensive drugs that are part of the current four-drug treatment regimen.

An even more extreme—and particularly dangerous—subset of MDR-TB is *extensively drug-resistant TB* (XDR-TB), characterized by resistance to those same two drugs *plus* resistance to at least two of the best of the “second-line” drugs that are usually used to treat MDR-TB. These increasing degrees of drug resistance can occur progressively, with resistance developing to one drug after another as patients fail a sequence of TB treatment regimens.

South Africa has one of the world’s highest rates of XDR-TB infections and that rate appears to be slowly but steadily rising.<sup>11</sup> In contrast to MDR-TB, person-to-person transmission of already XDR-TB is now thought to be the most common way that XDR-TB occurs in parts of South Africa.<sup>12</sup> This observation means that without better infection control to prevent person-to-person transmission and without better access to newer and

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<sup>10</sup> The rationale for using multiple drugs to forestall development of drug resistance is that, for example, if a specific TB organism has a one-in-a-million chance of becoming resistant to one TB drug during treatment, the chance of its becoming resistant to two drugs simultaneously is one-in-a-million times one-in-a-million. Using four TB drugs at the same time practically guarantees that, if the drugs are taken as prescribed, development of resistant TB bacteria will be exceedingly rare.

<sup>11</sup> Jennifer R. Lim, Neel R. Gandhi, Thuli Mthiyane et al., “Incidence and Geographic Distribution of Extensively Drug-Resistant Tuberculosis in KwaZulu-Natal Province, South Africa,” *PLOS ONE* 10, No. 7 (July 2015). In fact, South Africa had mounted a national TB drug resistance survey in 2012–2014 but, at this writing, the survey results are not yet publicly available.

<sup>12</sup> N. Sarita Shah et al., *Majority of XDR-TB cases are due to transmission in a high-HIV-prevalence setting*, 2015 Conference on Retroviruses and Opportunistic Infections (CROI), abstract 92, Seattle, 2015.

more effective TB drugs, MDR-TB and XDR-TB will continue to spread on their own in South Africa.

Greater drug resistance among TB patients is associated with worse treatment outcomes, including higher death rates. A particularly striking example of a highly lethal XDR-TB outbreak occurred in 2005 in Tugela Ferry, a small South African community (Box 2).

The inability of the health system to provide adequate initial and follow-up care to many patients is directly linked to the spread of MDR- and XDR-TB. A recent survey of South African XDR-TB patients who had not been cured of their TB disease but were nevertheless living without treatment in the community<sup>13</sup> found that those patients' needs and the needs of their family members were often not being met. Some patients reported nonsupportive experiences with clinic staff, leading to lack of clinic attendance. In addition, concern about being stigmatized by others resulted in some patients not wearing masks. Some other infection control measures were ignored due to patients and families having "a belief in God who will protect them." There is little doubt that continued failure of household and community infection control measures will result in more TB transmission in those places.

MDR- and XDR-TB are a threat to South Africa in yet another way. The cost of treating drug-sensitive TB, MDR-TB, and XDR-TB were recently estimated at US\$257, \$6,772, and \$26,392 respectively<sup>14</sup> while the annual ARV drug cost per PLHIV is \$113.<sup>15</sup> The cost of treating one XDR-TB case is therefore equal to the treatment cost of more than 100 patients with drug-sensitive TB. In terms of HIV/AIDS, the cost of treating a single case of XDR-TB is equivalent to about 230 person-years of ARV drug treatment. A 2011 analysis indicated that although MDR-TB represented only 2.2 percent of South Africa's TB cases, treatment of those few cases accounted for 32 percent of the national TB budget.<sup>16</sup>

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<sup>13</sup> Meera Senthilingham, Elize Pietersen, Ruth McNerny et al., "Lifestyle, Attitudes and Needs of Uncured XDR-TB Patients in the Communities of South Africa: a Qualitative Study," *Tropical Medicine and International Health* 20 (September 2015): 1155–61.

<sup>14</sup> Pooran, Pieterse, Davids et al., "What Is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa?"

<sup>15</sup> UNAIDS, "Around 10 million people living with HIV now have access to antiretroviral treatment," press release, June 30, 2013, <http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2013/june/20130630prtreatment>.

<sup>16</sup> If MDR-TB patients were treated entirely as outpatients, total costs would represent 32 percent of the national TB budget. Pooran, Pieterse, Davids et al., "What Is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa?"

## **Box 2. Fatal Outbreak of Extensively Drug-Resistant TB among HIV Patients in Tugela Ferry**

Although the existence of extensively drug-resistant TB (XDR-TB) had been documented for some time, it catapulted into the public eye in 2006 when a medical journal reported on an outbreak of XDR-TB in a population of PLHIV in Tugela Ferry, a small South African community located in KwaZulu-Natal province. In that outbreak, 52 (98 percent) of the 53 patients infected with XDR-TB died within 30 days of their diagnosis, despite receiving the best TB drugs then available ([http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(06\)69573-1.pdf](http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(06)69573-1.pdf)).

Among that group of 53 patients, all 44 who were tested for HIV were found to be HIV-infected. Because none of the 53 patients had any family members with active TB disease, one alarming conclusion was that these patients had become infected with XDR-TB transmitted directly from other patients being cared for at the same clinic, a place where antiretroviral drugs were being distributed to HIV/AIDS patients.

The circumstances of this outbreak highlight the need for better TB infection control programs to prevent patient-to-patient TB transmission in health facilities.

The number of MDR-TB and XDR-TB treatment sites in South Africa has been increasing at a rapid rate, from 11 in 2009 to 45 in early 2013. This increase has been supported in part by resources from USAID. However, several TB experts both within and outside of South Africa expressed their mounting concern that drug-resistant TB disease is still viewed by many in South Africa as much more of a disease-treatment problem (i.e., difficulties in diagnosis, difficulties in clinic access, and a need for better drugs) than as a disease-prevention problem.<sup>17</sup> Although there is a clear need for adequately *treating* patients already infected with active TB disease, more effectively *preventing* the development and spread of new drug-resistant TB cases may be a major missed opportunity.<sup>18</sup>

## **The Reciprocal Impacts of HIV/AIDS and Tuberculosis**

A major reason that South Africa's TB problem is so challenging is the country's overwhelming HIV epidemic. South Africa has almost 7 million people infected by HIV and a high rate of new HIV infections. The weakened immune system that is the hallmark of HIV infection allows latent TB infections and TB disease to progress more rapidly and with greater severity than in people not infected by HIV. The relationship between these two infections is reciprocal in that TB coinfection accelerates the production of HIV virus, speeding up the disease process of AIDS.

About 60 percent of new TB patients in South Africa are HIV-infected and the country's fourfold increase in TB case numbers over the last two decades has clearly been driven

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<sup>17</sup> In addition, the occurrence of the difficult-to-treat and highly fatal MDR-TB/HIV was suggested to be an endemic disease problem rather than just the series of outbreaks that have been noted. Jason R. Andrews, Neel R. Gandhi, Prashini Moodley et al, Exogenous Reinfection as a Cause of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis in Rural South Africa," *Journal of Infectious Disease* 198 (December 1, 2008): 1582–89.

<sup>18</sup> Giovanni Batista Migliori, Giovanni Sotgiu, Neel R. Gandhi et al., "Drug Resistance beyond Extensively Drug-resistant Tuberculosis: Individual Patient Data Meta-analysis," *European Respiratory Journal* 42 (2013): 169–79.

by the spread of HIV.<sup>19</sup> People who have a latent TB infection but who are not infected with HIV have about a 10 percent risk of developing active TB disease over their *entire lifetime*. On the other hand, PLHIV with a latent TB infection, which includes most PLHIV in South Africa, have a 10 percent risk *every year* of developing active TB disease. The resulting TB/HIV codisease is now considered an epidemic in South Africa.<sup>20</sup>

The scale-up of ARV use to control HIV infections in South Africa has undoubtedly contributed to TB control by reducing—but not eliminating—the risk of developing active TB disease among the millions of PLHIV who have begun taking these drugs.<sup>21</sup> However, the TB risk remains high among the millions of PLHIV in South Africa who have not yet begun taking those drugs. Among PLHIV, TB treatment success rates (79 percent in newly diagnosed patients and 66 percent in retreatment patients) are below the World Health Organization (WHO) standard of 85 percent. Still another TB challenge among PLHIV in South Africa is their low rate of receiving recommended preventive therapy with isoniazid, a drug that can further reduce the risk of progression of latent TB infection to active TB disease.<sup>22</sup>

Another challenge for the national health system is the still limited awareness among South African patients and even among some health workers of the links between TB and HIV (including the existence of coinfection and codisease). Finally, despite some progress in integrating TB and HIV diagnosis and treatment activities at local (primary care) levels, the data systems used to track PLHIV and TB patients are still in the process of being linked electronically. The two diseases are not yet well integrated programmatically in other ways at national and provincial levels.<sup>23</sup>

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<sup>19</sup> In a 2009 video about TB in South Africa, Dr. Salim Karim noted that, compared to earlier times, TB patients are sicker, younger, more female, and more likely to be HIV-infected than patients in earlier years. See Ray Suarez, “TB, HIV Form Deadly Partnership in South Africa,” *PBS Newshour* (March 24, 2009), <http://video.pbs.org/video/1856318343/>.

<sup>20</sup> Charles S. Wysonge, Keren Middelkoop, Kogieleum Naidoo et al., “A Systematic Review of the Epidemiology and Programmatic Response to Tuberculosis in HIV-infected Patients in South Africa,” *EVISAT*, April 2014, <http://www.afro.who.int/en/south-africa/country-programmes/4247-tuberculosis-tb.html>.

<sup>21</sup> Max O. Bachmann, Venessa Timmerman, and Lara R. Fairall, “Effect of Antiretroviral treatment on the risk of tuberculosis during South Africa’s Programme Expansion: a cohort study,” *AIDS* 29 (August 2015).

<sup>22</sup> A July 2015 presentation at the International AIDS Society meeting in Vancouver, Canada, confirmed the effectiveness of isoniazid in further reducing risk of death or development of TB in PLHIV who are already taking antiretroviral drugs.

<sup>23</sup> Republic of South Africa, Department of Health, *Joint review of HIV, TB and PMTCT Programmes in South Africa: Main report* (Pretoria: Department of Health, April 2014), [http://www.hst.org.za/sites/default/files/WHO-final-report-of-joint-hiv-tb-pmtct-main\\_April2014.pdf](http://www.hst.org.za/sites/default/files/WHO-final-report-of-joint-hiv-tb-pmtct-main_April2014.pdf). Regardless of whether TB and HIV programs are actually integrated (v. “coordinated”), arguments have been put forward emphasizing the clear programmatic benefits of harmonizing the components of TB and HIV programs and in fact, some progress has been made in this regard in South Africa, especially at the primary care level. However, because of the serious risks and consequences of cross-infection, putting TB patients in close proximity to PLHIV must obviously be done with great attention and the program harmonization process will need to emphasize the importance of infection control activities.

## Diabetes and Tuberculosis

As in many other countries, South Africa is witnessing an increase in the occurrence of diabetes, a disease associated with a three-fold risk of progression of latent TB infection to active TB disease.<sup>24</sup> To add further to South Africa's diabetes challenge, long-term use of many of the ARV drugs used to treat HIV is associated with a greater risk of developing diabetes.<sup>25</sup>

The South African health system has yet to completely address the diabetes-TB issue. However, it is receiving political attention from South Africa's first lady, who has recently become involved in a public education program, supported in part by USAID, about the link between TB and diabetes.<sup>26</sup>

## Other Groups in South Africa with Particular TB Risk<sup>27</sup>

Other subgroups of South Africans particularly affected by TB include pregnant women, children, health care workers, underground miners, prisoners, and migrants and others living in informal settlements.

### TB in Pregnancy and the Perinatal Period

TB is now the third-most-common cause of maternal death in South Africa.<sup>28</sup> Current national TB control guidelines include explicit guidance on TB diagnosis and management during pregnancy.<sup>29</sup>

### TB in South African Children

As a global response to childhood TB, WHO, USAID, CDC, and other international organizations have created recently a "roadmap" for better control of childhood TB.<sup>30</sup>

Since children rarely spread TB to others, TB identified in childhood nearly always represents relatively recent exposure to an adult with active TB. Thus, South Africa's

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<sup>24</sup> World Diabetes Foundation, "Diabetes and Tuberculosis Service Integration, WDF12-706," <http://www.worlddiabetesfoundation.org/projects/south-africa-wdf12-706>.

<sup>25</sup> Il Joon Paik and Donald M. Kotler, "The Prevalence and Pathogenesis of Diabetes Mellitus in Treated HIV-Infection," *Clinical Endocrinology and Metabolism* 25, no. 3 (June 2011): 469–78.

<sup>26</sup> USAID TB Care II, "USAID TB Program Partners with South Africa's First Lady to Promote TB/Diabetes Awareness," <http://tbsouthafrica.org/node/323>.

<sup>27</sup> Some of these risk groups were recently addressed in evidence-based systematic reviews commissioned by the World Health Organization (WHO) in *Evidence to Inform South African TB Policies*, a project conducted by the Centre for Evidence-based Health Care at Stellenbosch University, <http://www.cebhc.co.za/research-key-outputs/research-evisat/>.

<sup>28</sup> Republic of South Africa Department of Health, "National Tuberculosis Management Guidelines," Pretoria, 2014, 62–64, [http://www.sahivsoc.org/upload/documents/NTCP\\_Adult\\_TB%20Guidelines%2027.5.2014.pdf](http://www.sahivsoc.org/upload/documents/NTCP_Adult_TB%20Guidelines%2027.5.2014.pdf).

<sup>29</sup> Ibid.

<sup>30</sup> Anne Detjen, Marianne Gale, Ines Garcia Baena et al., "Roadmap for Childhood Tuberculosis: Towards Zero Deaths," World Health Organization, 2013, [http://apps.who.int/iris/bitstream/10665/89506/1/9789241506137\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/89506/1/9789241506137_eng.pdf).

high burden of TB in young children is seen as additional evidence of an ongoing gap in TB control.<sup>31</sup> An evidence-based review of the occurrence and management of childhood TB<sup>32</sup> and a set of recently updated TB guidelines from the DOH that address TB in infancy and childhood<sup>33</sup> are signs of increasing attention in South Africa to childhood TB.

The three remaining major TB control challenges for addressing childhood TB in South Africa include the difficulties of diagnosing TB in childhood, the effective delivery of primary care to children with TB, and a worldwide absence of pediatric formulations of many important TB drugs.<sup>34</sup>

## TB among South African Health Workers

The risk of becoming infected with TB in clinics and other health facilities is not restricted to patients and their families. In 2011, a study found the rate of new TB cases among health care workers was twice that of the general population, making TB the third most commonly reported occupational illness in South African health workers.<sup>35</sup>

Health workers' risk of acquiring TB was not confined to those working in TB wards; the overall risk of contracting the disease was higher among all health workers in facilities with greater numbers of TB patients. In addition, the HIV epidemic has worsened the TB problem for health workers in other ways. For example, many health workers are themselves PLHIV.

## TB in Underground Miners<sup>36</sup>

TB in miners is increasing in frequency, recently reaching over 40,000 cases per year.<sup>37</sup> Recurrent TB disease, poor ventilation, silicosis, HIV, and general lack of access to ARV drugs each contribute to astoundingly high disease rates that result annually in nearly

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<sup>31</sup> Anthony J. Garcia-Prats, Folasade Adeniyi, Karen du Preez et al., "A systematic review of the epidemiology and programmatic response to tuberculosis in South African children," EVISAT, <http://www.afro.who.int/en/south-africa/country-programmes/4247-tuberculosis-tb.html>.

<sup>32</sup> Ibid.

<sup>33</sup> Republic of South Africa Department of Health, "Guidelines for the Management of Tuberculosis in Children 2013," <http://www.sahivsoc.org/upload/documents/National-Childhood-TB-Guidelines-2013.pdf>.

<sup>34</sup> Pediatric formulations of TB drugs (e.g., in liquid form) have only recently become available in South Africa.

<sup>35</sup> Carrie Tudor, Martie Van der Walt, Bruce Margot et al., "Tuberculosis among Health Care Workers in KwaZulu-Natal, South Africa: A Retrospective Cohort Analysis," *BMC Public Health* 14 (2014): 891–99.

<sup>36</sup> Shingai Machingaidze, Piotr Hippner, Paul Van Helden, and Liesl Nicol, "A Systematic Review of the Epidemiology and Programmatic Response to TB in Mine Workers and the Mining Community in South Africa," EVISAT, <http://www.afro.who.int/en/south-africa/country-programmes/4247-tuberculosis-tb.html>. Reports of drug resistance range up to 21 percent in recurrent cases, with increasing reports of MDR-TB and XDR-TB.

<sup>37</sup> Aaron Motsoaledi, "South Africa's TB Burden," presented at the 4th South African TB conference, June 13, 2014, Durban, [http://www.tbconference.co.za/Session%20Presentations%20Folder/Friday%2013%20June%202014/Hall%201/Closing%20Plenary%2011h00\\_12h30/7%20minister%20Response%20to%20South%20Africa's%20TB%20epidemic%20-%20Presentation%20by%20Minister%20to%20the%202014%20TB%20conference%20-%20Final%20-%2013%20June%202014%20\[Compatibility%20Mode\].pdf](http://www.tbconference.co.za/Session%20Presentations%20Folder/Friday%2013%20June%202014/Hall%201/Closing%20Plenary%2011h00_12h30/7%20minister%20Response%20to%20South%20Africa's%20TB%20epidemic%20-%20Presentation%20by%20Minister%20to%20the%202014%20TB%20conference%20-%20Final%20-%2013%20June%202014%20[Compatibility%20Mode].pdf).

1,600 deaths and 9.6 million lost work days.<sup>38</sup> A regional approach to TB among miners has recently begun, supported in part by a Global Fund grant<sup>39</sup> and in part by USAID resources.

## TB in South African Prisons<sup>40</sup>

TB is currently the leading cause of death in South African prisons,<sup>41</sup> which held more than 155,000 inmates in 2013. The annual frequency of active TB disease (1.8–2.5 percent per year) was far greater than in the general population, related at least in part to overcrowded cells, poor ventilation, and high rates of HIV coinfection. More than 30 percent of those started on TB treatment were lost to follow-up. Recognizing the magnitude of this problem, the South African government has announced a “massive TB campaign to be rolled out in prisons”<sup>42</sup> and has issued a new set of guidelines explicitly addressing prison TB, although persisting staff shortages in prisons may make the immediate implementation of these guidelines more challenging.<sup>43</sup>

## TB in People Living in Informal Settlements and Others with Limited Access to Care

The differences in epidemiology of drug-resistant TB in urban and rural areas, differences in TB epidemiology and TB control programs in different provinces, and the disease control impacts associated with migration of South African and foreign workers across relatively open borders each add to the complexity of national TB control activities. A multi-country regional approach to TB has recently been advocated as one option for addressing cross-border TB and MDR-TB issues.<sup>44</sup> In addition, TB challenges for the millions of poor people living in crowded informal peri-urban settlements add yet another layer of complexity.<sup>45</sup>

## Other TB-related Challenges for South Africa

A number of other challenges exist to effective and timely TB diagnosis and treatment.

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<sup>38</sup> Ibid.

<sup>39</sup> Ibid.

<sup>40</sup> Fidele K. Mukinda and Hassan Mahomed, “A Systematic Review of the Epidemiology and Programmatic Response to Tuberculosis in Inmates and the Correctional Services in South Africa,” EVISAT, <http://www.afro.who.int/en/south-africa/country-programmes/4247-tuberculosis-tb.html>.

<sup>41</sup> Robin Wood, “What Will It Take to Control TB in South African Prisons?” Editorial, *NSP Review* 7 (July–August 2013): 1, [http://www.nspreview.org/download/NSP\\_Review\\_7\\_Web.pdf](http://www.nspreview.org/download/NSP_Review_7_Web.pdf).

<sup>42</sup> “Massive TB campaign to be rolled out in prisons,” SA News.gov.za, March 30, 2015, <http://www.sanews.gov.za/south-africa/massive-tb-campaign-be-rolled-out-prisons>.

<sup>43</sup> “The Losing Battle against TB in Prisons,” *Daily Maverick*, May 19, 2015.

<sup>44</sup> Kevin P. Cain, Nina Marano, and Maureen Kamene, “The Movement of Multidrug-Resistant Tuberculosis across Borders in East Africa Needs a Regional and Global Solution,” *PLOS Medicine* (February 24, 2015).

<sup>45</sup> Mareli Claassens, Alliance Nikuze, Tawanda Chivese et al., “A systematic review of the epidemiology of and programmatic response to TB in people living in informal settlements in South Africa, April 2014,” EVISAT, <http://www.afro.who.int/en/south-africa/country-programmes/4247-tuberculosis-tb.html>.

## A Need for Expanded TB Screening and Testing

South Africa has announced an expanded national TB testing program that largely relies on relatively expensive GeneXpert MTB/RIF technology.<sup>46</sup> The country is scaling up the number of GeneXpert machines in use and is now the largest global purchaser of GeneXpert test cartridges. That technology and other recently developed TB testing technologies are potentially helpful because they can increase the speed and accuracy of detection of both drug-sensitive and drug-resistant TB. While new diagnostic tools can help identify TB cases (including MDR-TB) more completely and quickly, the critical issues of testing logistics and subsequent patient referral and treatment follow-up still need to be addressed.<sup>47</sup> For example, although GeneXpert MTB/RIF testing can identify patients with one of the many forms of MDR-TB, it cannot identify the specific drugs to which the TB bacteria are still sensitive. Thus, the health system needs to ensure that sputum specimens from newly identified MDR-TB patients are quickly sent to laboratories for the comprehensive drug-sensitivity testing needed to identify precisely which TB drugs can still be used effectively.

## Challenges to the National Health Laboratory Service

We were told that the National Health Laboratory Service (NHLS), a parastatal organization responsible for much of the public facility TB testing and other laboratory testing in the country, has recently been affected by serious budgetary issues, caused in part by two of South Africa's provinces not paying for many of the laboratory tests that NHLS is required to conduct for them.<sup>48</sup> As a result, experienced staff are said to be leaving and there are concerns that institutional capacity may suffer.

## Costs of TB Diagnosis and Care for Patients

WHO, the World Health assembly, and the Stop TB Partnership have recently emphasized the need to address the sometimes-catastrophic costs of TB care to patients and families. Research in South Africa and elsewhere has indicated that reducing the duration of hospital stays can reduce costs to both patients and the health system.<sup>49</sup> However, other data indicate that the greatest economic burdens of TB care to families occur *before* the start of treatment and are largely indirect costs such as transportation to

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<sup>46</sup> Republic of South Africa, "SA to roll out massive TB screening campaign," SAnews.gov.za, March 25, 2015, <http://sanews.gov.za/south-africa/sa-roll-out-massive-tb-screening-campaign>.

<sup>47</sup> The large referral hospital we visited had a large backlog of TB diagnostic specimens waiting to be tested by GeneXpert MTB/RIF. To that point, a recent report noted that, six months after diagnosis, mortality among patients identified by GeneXpert MTB/RIF technology was not lower than the mortality among patients identified by traditional diagnostic methods. See Frauke Rudolph and Christian Wejse, "Tuberculosis Case Detection Revisited: Better Testing Might Not Improve Outcomes," *The Lancet Global Health* 3, no. 8 (August 2015): e424–e425.

<sup>48</sup> Jonathan Ancer, "NHLS Crisis Draws Blood," *NSP Review*, Edition 11 (November 2014): 5–6.

<sup>49</sup> E. Sinanovic, L. Ramma, A. Vassall et al., "Impact of Reduced Hospitalisation on the Cost of Treatment for Drug-resistant Tuberculosis in South Africa," *International Journal of TB and Lung Disease* 19, no. 2 (2015): 172–78.

health facilities and loss of income from time away from work.<sup>50</sup> In addition, the longer and far more expensive treatment required for MDR- and XDR-TB adds yet another dimension to the cost challenge: recent costs of appropriate diagnosis and treatment for drug-sensitive TB, MDR-TB, and XDR-TB were US\$257, \$6772, and \$26,392 respectively.<sup>51</sup> A rising prevalence of MDR and XDR-TB will place an increasing strain on the government's ability to fully finance TB control.

## Need for New TB Drugs to Treat MDR-TB

In common with many other countries, South Africa needs expanded access to new drugs and new combinations of drugs that can effectively treat MDR-TB and XDR-TB.<sup>52</sup>

## Community-based Treatment Venues

Research from South Africa<sup>53</sup> and elsewhere has demonstrated the long-term value of TB services that have been decentralized from large urban hospitals to community-level clinics; national plans for the decentralization of TB services are progressing. However, this process, which helps reduce the health care burdens on hospitals, may ultimately require more primary care capacity and more human resources than are currently available at local levels.<sup>54</sup> In addition, province-specific differences in TB epidemiology and TB control programs will need to be addressed.<sup>55</sup>

## Other Health System Resource Constraints

An ongoing shortage of financial and human resources is an enduring challenge to South Africa's health care system, and is constraining the country's ability to tackle TB.<sup>56</sup> In particular, reported stock-outs of TB drugs add yet another barrier to the success of TB prevention and treatment programs at national and local levels.<sup>57</sup> Depending on the specific drug in question, these stock-outs seem to be due to a combination of international drug shortages and domestic supply chain distribution problems.

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<sup>50</sup> Nicola Foster, Anna Vassall, Susan Cleary et al., "The Economic Burden of TB Diagnosis and Treatment in South Africa," *Social Science and Medicine* 130 (2015): 42–50.

<sup>51</sup> Pooran, Pieterse, Davids et al., "What Is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa?"

<sup>52</sup> Resistance to new TB drugs used one at a time develops quickly, requiring combinations of new drugs to be used to delay development of resistance. A study of XDR-TB treatment, using a combination of two current "second line" drugs along with one newer drug, is now underway in South Africa. See Laura Lopez Gonzales, "SA hosts world's first study into better XDR-TB treatment," *Health-E News* (May 14, 2015), <http://www.health-e.org.za/2015/05/14/sa-hosts-worlds-first-study-into-better-xdr-tb-treatment/> www.health-e.org.za/2015/05/14/sa-hosts-worlds-first-study-into-better-xdr-tb-treatment.

<sup>53</sup> H. Cox, J. Hughes, J. Daniels et al., "Community-based Treatment of Drug-resistant Tuberculosis in Khayelitsha, South Africa," *International Journal of Tuberculosis and Lung Disease* 18, no.4, (2014): 441–48.

<sup>54</sup> Bateman, "SA's Ailing Public Health Sector 'Responding to Treatment'?"

<sup>55</sup> TB Facts.org, "TB in South Africa | National & provincial statistics."

<sup>56</sup> Downie and Angelo, "Counting the Cost of South Africa's Health Burden."

<sup>57</sup> Tomlyn Seunanden and Candy Day, "The Extent and Impact of TB Stock-outs," in *South African Health Review 2013/14*, ed. A. Padarath and R. English (Durban: Health Systems Trust, 2014), 173–8, [http://www.hst.org.za/sites/default/files/Extent\\_Impact\\_TB\\_Stockouts.pdf](http://www.hst.org.za/sites/default/files/Extent_Impact_TB_Stockouts.pdf).

## The Role of the United States

The United States has directly and indirectly supported South Africa's disease control efforts. The vast majority of U.S. support routed through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) has focused on the country's massive HIV epidemic. Although the national government pays for most of the ARV drugs distributed in South Africa, the country is still the single-largest national recipient of financial and technical resources from PEPFAR. U.S. support through PEPFAR is highly regarded for its efforts in support of South Africa's HIV/AIDS programs.

PEPFAR has also helped South Africa address its TB challenges, both directly through supporting TB/HIV programs and indirectly through assisting aspects of health system strengthening such as program integration and counseling for adherence to treatment. In addition, USAID, CDC, and NIH each have additional programs in South Africa that directly impact TB control.<sup>58</sup> We were told that U.S. support for TB control through these activities is well regarded among South African health workers at various levels.

However, several observers expressed concerns during our visit that the recently announced PEPFAR 3.0, which focuses programming to a relatively small number of South Africa's HIV "hot spots," may inadvertently complicate or even undermine U.S. efforts to help address the country's TB, TB/HIV, and MDR-TB priorities, particularly in those areas not categorized as HIV hot spots. The TB-related impacts of this transition need to be carefully monitored to preserve the successes of recent U.S. health investments.

## Discussion

Overall, South Africa has made significant headway recently in addressing its TB epidemic (Box 3). A joint HIV and TB program review in 2013 noted many positive developments since 2009<sup>59</sup> and a number of excellent TB-related treatment guidelines have been published recently. Part of this progress is attributable to the leadership of a strong and well-respected minister of health, Aaron Motsoaledi, who is also the current cochair of the global Stop TB Partnership. Dr. Motsoaledi understands the complexity of TB as a public health challenge and appears to emphasize disease *prevention* at every turn. He has put in place and supported high-quality senior staff to drive the country's TB response and has also managed to mobilize additional domestic resources for TB control.

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<sup>58</sup> The non-PEPFAR support from both NIH and CDC includes resources for research on TB drugs.

<sup>59</sup> Republic of South Africa, Department of Health, *Joint review of HIV, TB, and PMTCT Programmes in South Africa*.

### Box 3. Progress in South Africa's TB and TB/HIV Control Efforts<sup>a</sup>

- TB declared national emergency (2005)
- Comprehensive joint DOH, WHO, UNAIDS review of HIV and TB programs (2013)
- Current national vice president with a personal interest in TB control
- Comprehensive adult TB guidelines published in August 2014; other recently published DOH guidelines address TB in pregnancy, correctional facilities, children, and PLHIV (including prevention of mother-to-child HIV transmission)
- Increased attention to TB in health care workers and underground miners
- Numbers of drug-sensitive TB cases falling
- Highly productive TB, MDR-TB, and TB/HIV research infrastructure
- Ambitious new TB diagnosis and treatment targets; numbers of people screened for TB and number of TB testing sites continue to expand
- Mandatory TB screening of underground miners being introduced
- Number of MDR-TB treatment sites continues to expand (e.g., from 11 in 2009 to 45 in early 2013)
- Some progress on harmonization of TB and HIV programs
- Progress on health systems strengthening, including decentralization of TB care away from hospitals and toward community facilities
- More PLHIV taking antiretroviral drugs, thus reducing their risk of developing active TB

<sup>a</sup> Some of these activities have been supported in part by U.S. government resources.

In addition to high-level political support, South Africa benefits from the persistence of a productive TB and TB/HIV research infrastructure. A significant proportion of the research assets have been focused on important operational research questions that have a direct bearing on the effectiveness of the country's TB and MDR-TB prevention, diagnosis, treatment, and care systems.<sup>60</sup>

And yet, all this positive movement may not be enough. Despite the progress and support, significant challenges remain, including a weak primary health care system. Although numbers of drug-sensitive TB cases may be falling in South Africa, numbers of MDR-TB and XDR-TB cases are rising. As noted earlier, successfully addressing South Africa's unprecedented TB and MDR-TB pandemic will require greatly enhanced efforts to prevent new active TB cases while further expanding care and treatment activities. If the treatment success rates of drug-resistant TB continue to be significantly less than the treatment success rates of drug-sensitive TB, South Africa's national TB pandemic will slowly but surely become one comprised increasingly of airborne drug-resistant TB

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<sup>60</sup> As occurs in many other countries, communication of new scientific and programmatic information between South Africa's academic community and its government officials may not have always occurred quickly and, as a consequence, program implementation has not always kept up with research advances. See Chris Bateman, "Eastern Cape Treatment Dysfunction Boosts Virulent New XDR-TB Strain," *South African Medical Journal* 105 (March 2015): 165–7.

bacteria that are expensive to treat and that have uncertain treatment outcomes.<sup>61</sup> This national scenario is unprecedented.

As the number one killer of PLHIV, TB remains a threat to the long-term success of the country's efforts to control HIV/AIDS—and to PEPFAR's multibillion-dollar efforts thus far to help them. This threat looms regardless of further changes in TB's drug-resistance patterns.

MDR-TB may also be an indirect long-term threat to the country's ART and other health programs in a fiscal sense. Given the treatment costs for drug-sensitive TB, MDR-TB, and XDR-TB of US\$257, \$6,772, and \$26,392 respectively<sup>62</sup> and the annual ARV drug cost per person of US\$113,<sup>63</sup> the treatment cost of each XDR-TB case equals the treatment costs of more than 100 patients with drug-sensitive TB or the cost of treating 230 PLHIV with ARVs for a year. A 2011 analysis indicated that although MDR-TB represented only 2.2 percent of South Africa's TB cases, treatment of those few cases consumed 32 percent of the national TB budget.<sup>64</sup> As numbers of drug-resistant TB cases continue to grow, the resource-stretched South African health system will have an increasingly difficult time carrying the national TB burden. That threat was implicitly acknowledged by the conclusion of the recent HIV and TB investment case calling for a 46 percent increase in the national TB budget.<sup>65</sup>

Finally, the picture of the gravity of South Africa's TB pandemic that emerged during our visit differed from the sense we had before arriving in the country. The complete absence of TB from the important South African diseases listed in a usually authoritative U.S. reference<sup>66</sup> and a significant underestimate of the mortality impact of TB in South Africa provided on a WHO statistics website<sup>67</sup> suggest a limited appreciation outside South Africa of the importance of TB to the country's overall health picture. The risks of TB have also been described as having "a low public profile" even within the country.<sup>68</sup> South Africa's external partners need to better understand and accept the requirement for greater support for TB control.

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<sup>61</sup> Just such a series of events has recently been predicted for China. See M. Mehra, N. Cossow, C Kambili et al., "Assessment of Tuberculosis Burden in China Using a Dynamic Simulation Model," *International Journal of Tuberculosis and Lung Disease* 17, (2013): 1186–94.

<sup>62</sup> Pooran, Pieterse, Davids et al., "What Is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa?"

<sup>63</sup> UNAIDS, "Around 10 million people living with HIV now have access to antiretroviral treatment."

<sup>64</sup> If MDR-TB patients were treated entirely as outpatients, total costs would still represent 32 percent of the national TB budget. Pooran, Pieterse, Davids et al., "What Is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa?"

<sup>65</sup> Meyer-Rath, Chiu, Johnson et al., "South Africa's Investment Case: What Are the Country's 'Best Buys' for HIV and TB?"

<sup>66</sup> Central Intelligence Agency, "The World Factbook: South Africa," <https://www.cia.gov/library/publications/the-world-factbook/geos/sf.html>.

<sup>67</sup> World Health Organization, "South Africa: WHO Statistical Profile," <http://www.who.int/gho/countries/zaf.pdf>.

<sup>68</sup> USAID, "Technical Assistance Contract 4 Africa (TASC4 Africa) IDIQ," 9.

# Recommendations

## To U.S. Government Agencies and Officials

1) Given the magnitude of South Africa's TB and MDR-TB challenges and the risks to South Africans and others posed by that challenge and given increasing U.S. concerns about the slow but steady spread of MDR-TB,<sup>69</sup> the United States should consider South Africa's unique circumstances and should increase financial and epidemiologic support for MDR-TB and TB/HIV control activities in the country. Possible sources and mechanisms for doing this include direct U.S. resources from PEPFAR, bilateral USAID resources, the forthcoming U.S. National Action Plan for Multidrug-resistant TB,<sup>70</sup> and any U.S. global health security or other funds intended to address antimicrobial resistance issues. Innovative financing mechanisms could also be explored. U.S. officials should also encourage the South African government to boost its own domestic allocation to TB control, to consider expanding its public-private partnerships, and, if not included already in the recent Global Fund concept note, to apply for specific TB and TB/HIV funding from the Global Fund.<sup>71</sup>

2) Because ongoing changes in levels of U.S. budgetary and technical support may have inadvertent but still important impacts on the effectiveness of South Africa's TB, TB/HIV, and MDR-TB control programs,<sup>72</sup> and as the United States transitions to a new bilateral health assistance strategy in South Africa, U.S. health officials in-country and in Washington should carefully monitor the impacts of the new PEPFAR strategy and other U.S. programs on South Africa's national, provincial, and local TB epidemiology. In the event that adverse effects are detected, U.S. programs should retain some flexibility for reallocation of resources either within the PEPFAR 3.0 rollout schedule, within the bilateral USAID TB program, or by using resources available from the U.S. *National Action Plan for Combating MDR-TB*.<sup>73</sup>

3) U.S. agencies and their staff should make clear to their South African government counterparts that requests for additional TB program-related technical assistance from the U.S. government would be received favorably.

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<sup>69</sup> Aziz, "Ambitious New U.S. Plan May Put Hundreds of Thousands on MDR-TB Treatment."

<sup>70</sup> The National Action Plan for MDR-TB, still in development, offers an opportunity for intensified U.S. action to support South Africa in addressing what is arguably the world's most complex MDR-TB challenge.

<sup>71</sup> Information about the specifics of the concept note and proposal recently submitted to the Global Fund by South Africa's Country Coordinating Mechanism was not publicly available at the time of this writing.

<sup>72</sup> Much of the PEPFAR-based and other U.S. support for South African TB control has been indirect (e.g., health system strengthening).

<sup>73</sup> USAID, "Stakeholder Forum on the U.S. Government National Action Plan to Combat Multidrug-resistant TB."

## To South African Government Agencies and Officials

Information contained in the large number of recent South African program review and guideline documents addressing TB control make it clear that the Department of Health and its staff are already aware of most of the important steps needed to regain control of TB, MDR-TB, and TB/HIV.

Only a few additional recommendations apply:

1) Because of the magnitude of the TB threat to all South Africans, and particularly to the growing numbers of PLHIV, the various activities being implemented or planned to increase the effectiveness of TB control programs need to be given an added public visibility and an added urgency, with an emphasis on prevention of new active TB cases. In particular, expanding programs focused on the “Three I’s” (intensive TB screening of PLHIV, isoniazid preventive therapy, and infection control practices in health facilities and in communities) need to receive a very high priority in order to minimize numbers of new TB infections, particularly MDR- and XDR-TB infections, the treatment of which is difficult and expensive.

2) Because funding shortages are clearly an important obstacle to improving the effectiveness of national TB control programs, all possible existing sources of additional TB, MDR-TB, and TB/HIV program funding should be explored, including reallocation of current domestic resources, appropriation of additional domestic resources, expanded scope of public-private partnerships, and exploration of the possibility for additional resources from the Global Fund, the World Bank, the U.S. government, various philanthropic organizations, and other current or prospective external funders.

3) Emerging TB-related and HIV-related epidemiological and programmatic data should be shared with U.S. government colleagues in an open and timely manner to allow U.S. staff to monitor—and help respond to—potential effects of changes in U.S. programmatic support.

## Conclusion

Without a more concerted effort from all stakeholders, TB will continue to threaten the people of South Africa, significantly impeding the government’s ability to provide adequate health care to its population. The United States must place a greater emphasis on TB within its bilateral health relationship with South Africa—even as it faces its own need to reorient its health priorities and to reduce funding—in order to help address the looming threat there posed by both drug-sensitive and drug-resistant TB.



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