Chapter 11

Tuberculosis

Barry R. Bloom, Rifat Atun, Ted Cohen, Christopher Dye, Hamish Fraser, Gabriela B. Gomez, Gwen Knight, Megan Murray, Edward Nardell, Eric Rubin, Joshua Salomon, Anna Vassall, Grigory Volchenkov, Richard White, Douglas Wilson, and Prashant Yadav

OVERVIEW

Despite 90 years of vaccination and 60 years of chemotherapy, tuberculosis (TB) remains the world's leading cause of death from an infectious agent, exceeding human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) for the first time (WHO 2015b, 2016a). The World Health Organization (WHO) estimates that there are about 10.4 million new cases and 1.8 million deaths from TB each year. One-third of these new cases (about 3 million) remain unknown to the health system, and many are not receiving proper treatment.

Tuberculosis is an infectious bacterial disease caused by *Mycobacterium tuberculosis* (Mtb), which is transmitted between humans through the respiratory route and most commonly affects the lungs, but can damage any tissue. Only about 10 percent of individuals infected with Mtb progress to active TB disease within their lifetime; the remainder of persons infected successfully contain their infection. One of the challenges of TB is that the pathogen persists in many infected individuals in a latent state for many years and can be reactivated to cause disease. The risk of progression to TB disease after infection is highest soon after the initial infection and increases dramatically for persons co-infected with HIV/AIDS or other immune-compromising conditions.

Treatment of TB disease requires multiple drugs for many months. These long drug regimens are challenging for both patients and health care systems, especially in low- and middle-income countries (LMICs), where the disease burden often far outstrips local resources. In some areas, the incidence of drug-resistant TB, requiring even longer treatment regimens with drugs that are more expensive and difficult to tolerate, is increasing.

Diagnosis in LMICs is made primarily by microscopic examination of stained smears of sputum of suspected patients; however, smear microscopy is capable of detecting only 50–60 percent of all cases (smear-positive). More sensitive methods of diagnosing TB and detecting resistance to drugs have recently become available, although they are more expensive. The time between the onset of disease and when diagnosis is made and treatment is initiated is often protracted, and such delays allow the transmission of disease. Although bacille Calmette–Guérin (BCG) remains the world's most widely used vaccine, its effectiveness is geographically highly variable and incomplete. Modeling suggests that more effective vaccines will likely be needed to drive tuberculosis toward elimination in high-incidence settings.

The basic strategy to combat TB has been, for 40 years, to provide diagnosis and treatment to individuals

Corresponding author: Barry R. Bloom, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, United States; bbloom@hsph.harvard.edu.

who are ill and who seek care at a health facility. The premise is that, if patients with active disease are cured, mortality will disappear, prevalence of disease will decline, transmission will decline, and therefore incidence should decline. The reality in many countries is more complex, and overall the decline in incidence (only about 1.5 percent per year) has been unacceptably slow.

Chemotherapy for TB is one of the most cost-effective of all health interventions (McKee and Atun 2006). This evidence has been central to the global promotion of the WHO and Stop TB Partnership policy of directly observed therapy, short course (DOTS) strategy, the package of measures combining best practices in the diagnosis and care of patients with TB (UN General Assembly 2000). The DOTS strategy to control tuberculosis promotes standardized treatment, with supervision and patient support that may include, but is far broader than, direct observation of therapy (DOT), where a health care worker personally observes the patient taking the medication (WHO 2013a).

Thanks in part to these efforts and national and international investments, much progress has been made in TB control over the past several decades. Between 1990 and 2010, absolute global mortality from TB declined 18.7 percent, from 1.47 million to 1.20 million (Lozano and others 2012) and by 22 percent between 2000 and 2015 (WHO 2016a). By 2015, an estimated 49 million lives had been saved (WHO 2016a). The internationally agreed targets for TB, embraced in the United Nations (UN) Millennium Development Goals (MDGs), sought "to halt and reverse the expanding incidence of tuberculosis by 2015," and this target has been met to some extent in all six WHO regions and in most, but not all, of the world's 22 high-burden countries (WHO 2014c).

Despite progress, major gaps persist. Although the Sustainable Development Goals (SDGs) seek to end the tuberculosis epidemic altogether (WHO 2015a, 2015c), the decline in incidence has been disappointing. One of every three TB patients remains "unknown to the health system," many are undiagnosed and untreated, and case detection and treatment success rates remain too low in the high-burden countries. Ominously, rates of multidrug-resistant (MDR) TB—defined as resistance to the two major TB drugs, isoniazid and rifampicin—are rising globally (WHO 2011a) with the emergence of extensively drug-resistant (XDR) TB, resistant to many second-line drugs, as well as strains resistant to all current drugs (Dheda and others 2014; Udwadia and others 2012; Uplekar and others 2015). These are now primarily the result of transmission rather than inadequate treatment (Shah and others 2017).

Moreover, the TB problem has become more pressing because of co-infection with HIV/AIDS. While globally HIV/AIDS and TB co-infection represents only 11 percent of the total TB burden, in some areas of Sub-Saharan Africa with a high burden of TB, as many as three-quarters of TB patients are co-infected with HIV/AIDS. In those countries, efforts to control TB are overwhelmed by the rising number of TB cases occurring in parallel with the HIV/AIDS epidemic. And after decades of steady decline, the incidence of TB is also increasing in some high-income countries (HICs), mainly as the result of outbreaks in vulnerable groups (WHO 2015b).

If the ultimate goal of controlling an infectious disease is to interrupt transmission, turning the tide on TB will require early and accurate case detection, rapid commencement of and adherence to effective treatment that prevents transmission, and, where possible, preventive treatment of latent TB. It is universally understood that new strategies and more effective tools and interventions will be required to reach post-2015 targets (Bloom and Atun 2016; WHO 2015a). These interventions must be not only cost-effective, but also affordable and capable of having an impact on a very large scale.

TB control will need three new advances—development of new point-of-care diagnostics, more effective drug regimens to combat drug-susceptible and drug-resistant TB, and more effective vaccines. As argued in this chapter, these require new strategies and tools that include moving away from the traditional DOTS passive case finding and toward more active case finding in high-burden regions; service delivery that is targeted to the most vulnerable populations and integrated with other services, especially HIV/AIDS services; and care that is based at the primary health care and community levels. Specifically, in high-burden countries, many individuals with TB are asymptomatic, such that waiting for patients to become sick enough to seek care has not been sufficient to reduce transmission and incidence markedly (Bates and others 2012; Mao and others 2014; Willingham and others 2001; Wood and others 2007). A more active and aggressive approach is needed that tackles health system barriers to effective TB control.

The strategies for controlling TB recommended by the WHO have evolved significantly over time. In the early formulations, the central tenets of the global TB control strategy were clinical and programmatic in nature, focusing principally on the delivery of standardized drug regimens; the underlying assumption was that the problem could be solved largely by existing biomedical tools (Atun, McKee, and others 2005; Schouten and others 2011).

Yet, in many LMICs, health system weaknesses in governance, financing, health workforce, procurement and supply chain management, and information systems have impeded TB control (Elzinga, Raviglione, and Maher 2004; Marais and others 2010; Travis and others 2004) and not been adequately addressed by TB control efforts. The current global TB strategy, formulated as the End TB Strategy, is the most comprehensive ever, with three major pillars:

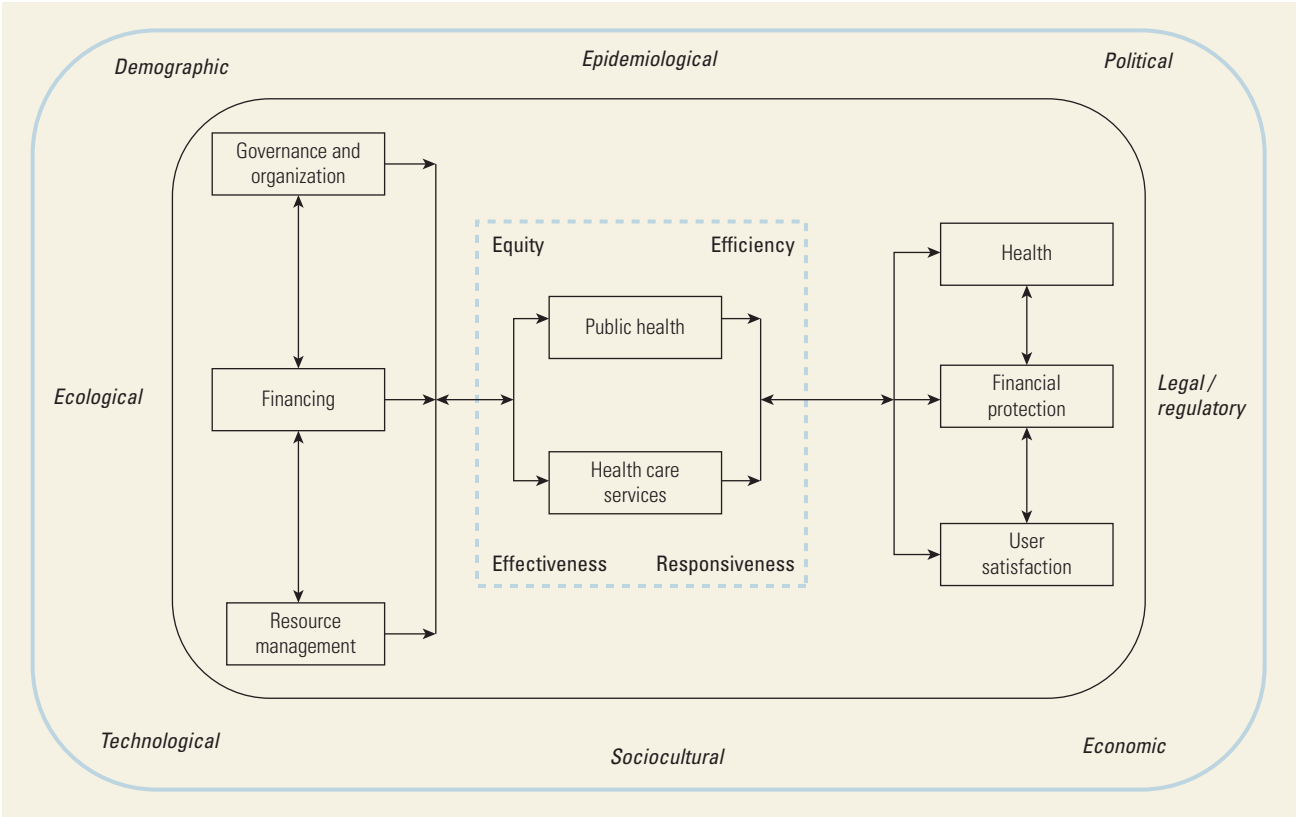
- Integrated, patient-centered care and prevention
- Social and political action to address determinants of disease
- Recognition of the urgent need for research to provide new tools (WHO 2015a).

Health systems are important and need to be strengthened. As with other health interventions, the success of tuberculosis treatment and control in a country is often determined by the strength of its health system (McKee and Atun 2006; WHO 2003). A health system can be defined in many ways, perhaps best as "all the activities whose primary purpose is to promote, restore, or maintain health" (WHO 2000, 5).

In a sense, the major risk factor for acquiring TB is breathing. Thus, people of all social and economic statuses are at risk. While TB disproportionately affects the poor, the narrative that TB is a disease only of the poor is misleading and counterproductive, if it leads either to further stigmatization of the disease or to the view that middle- and high-income countries need not worry about the disease. In the case of co-infection with HIV/AIDS, evidence suggests that HIV/AIDS is often more prevalent in better-off populations in Africa that suffer high rates of TB.

The analytical framework underlying this chapter defines key functions of the health system, ultimate goals, and contextual factors that affect the health system (figure 11.1). It builds on the WHO framework (WHO 2000) as well as health system frameworks developed by Frenk (1994), Hsiao and Heller (2007), and Roberts and others (2004), and national accounts (OECD, Eurostat, and WHO 2011). It also draws on earlier studies by Atun (2012); Atun and Coker (2008); Atun, Samyshkin, and others (2006); Samb and others (2009); and Swanson and others (2012).

Figure 11.1 Schematic Health Systems Framework



The four key health system functions represented in the framework are as follows:

- *Governance and organization.* The policy and regulatory environment; stewardship and regulatory functions of the ministry of health and its relation to other levels of the health system; and structural arrangements for insurers and purchasers, health care providers, and market regulators
- *Financing.* The way funds are collected, funds and risks are pooled, finances are allocated, and health care providers are remunerated
- *Resource management.* The way resources—physical, human, and intellectual—are generated and allocated, including their geographic and needs-based allocation
- *Service delivery.* Both population- and individual-level public health interventions and health care services provided in community, primary health care, hospitals, and other health institutions.

Each of these functions is influenced by the economic, demographic, legal, cultural, and political context.

As the framework suggests, health system goals include better health, financial protection, and user satisfaction. Personal health services and public health interventions should be organized to achieve an appropriate balance of equity (including reducing out-of-pocket [OOP] expenditures and impoverishment of individuals and families), efficiency, effectiveness (that is, the extent to which interventions are evidence based and safe), responsiveness, equity, and client satisfaction (as perceived by the users of services).

This chapter is organized as follows. First, we provide a detailed discussion of the global burden of disease and clinical context, followed by a review of approaches to diagnosis, treatment, and prevention. The aim throughout is to approach TB through a health system lens and, in the latter part of the chapter, to provide recommendations for improving delivery strategies and strengthening health systems, including care, supply chain, and information systems. Because the current tools for combating TB are seriously inadequate, we conclude with sections on critical research and development and economic analyses of new interventions for diagnosis, treatment, and vaccines. Throughout, emphasis is placed on data or modeling of the economic costs and benefits, where available, of current or possible future interventions to combat this disease.

The chapter recommends moving toward active case finding in high-burden countries; greater investments in health systems; community-based rather than hospital-based service delivery; and greater support for research on new tools—that is, developing better diagnostics, treatment regimens, and vaccines. Most of these approaches were included in earlier WHO policies, but were not emphasized. They are now part of the WHO's End TB Strategy, with which this report is fully consistent (WHO 2015a, 2015c).

HISTORICAL TRENDS, CURRENT BURDEN, AND GLOBAL RESPONSE

TB has been a major killer worldwide for centuries and has now exceeded HIV/AIDS and malaria as the world's largest cause of death from an infectious disease (Dye 2015; WHO 2016a).

Historical Trends

TB rates have been declining in North America and Western Europe since the early nineteenth century, prior to the introduction of chemotherapy in the 1950s. The decline may be partly due to the natural waning of the epidemic (Blower and others 1995), but the trend has been too prolonged for this to provide the whole explanation. Researchers have recently suggested that dramatic differences between cities experiencing marked declines prior to chemotherapy (for example, New York City in the United States; London in the United Kingdom) and cities where TB remained high (Cape Town in South Africa) may be explained by the quality and organization of the local health system (Hermans, Horsburgh, and Wood 2015). Other potential explanations for the 150-year decline have been the subject of debate and include the following:

1. Reduced opportunities for transmission per case, which may have occurred due to lower living density, better ventilation within homes, patient isolation within sanatoriums, and declining contacts among elderly cases (McFarlane 1989)
2. Reduced susceptibility of contacts, which may have been the result of improved nutrition and genetic pressures (Lipsitch and Sousa 2002; McKeown and Record 1962; Shetty and others 2006)
3. Reduced virulence of the pathogen, although there is little evidence to that effect.

While untreated TB has traditionally had a case fatality rate of 50 percent, there are differing opinions on the role of natural selection in resistance to pulmonary TB in humans prior to the availability of TB drugs

(Lipsitch and Sousa 2002). It is not possible to disentangle all of the factors that contributed to the decline of TB before the widespread introduction of chemotherapy or the reasons why progress has since stalled. What is clear is that the TB death rate in Western Europe fell 5 percent a year in the era before chemotherapy, with declines in the United States and Western Europe associated with active case finding, for example, X-ray screening.

By the 1990s, however, TB had emerged as a major global health issue, driven largely by an increase in the number of cases in the former Soviet Union and Sub-Saharan Africa. As the number of cases fell in other parts of the world, TB incidence per capita rose in these two regions.

In the Russian Federation and other former Soviet countries, TB incidence and deaths rose sharply between 1990 and 2000. Understanding precisely why is nearly as difficult as understanding the decline in Europe and North America. It is clear that there was a marked deterioration in case finding and cure rates in Russia, but this likely does not explain all of the increase (Shilova and Dye 2001). Other factors include enhanced transmission due to the mixing of prison and civilian populations; an increase in susceptibility to disease following infection, likely linked to alcoholism and stress; poor nutrition; emphasis on hospital-based treatment and extended hospitalization; poor service delivery; the spread of drug resistance; and, more recently, the rise of HIV/AIDS infection (Atun, Samyshkin, and others 2005; Toungoussova, Bjune, and Caugant 2006).

Current Burden

Global Progress

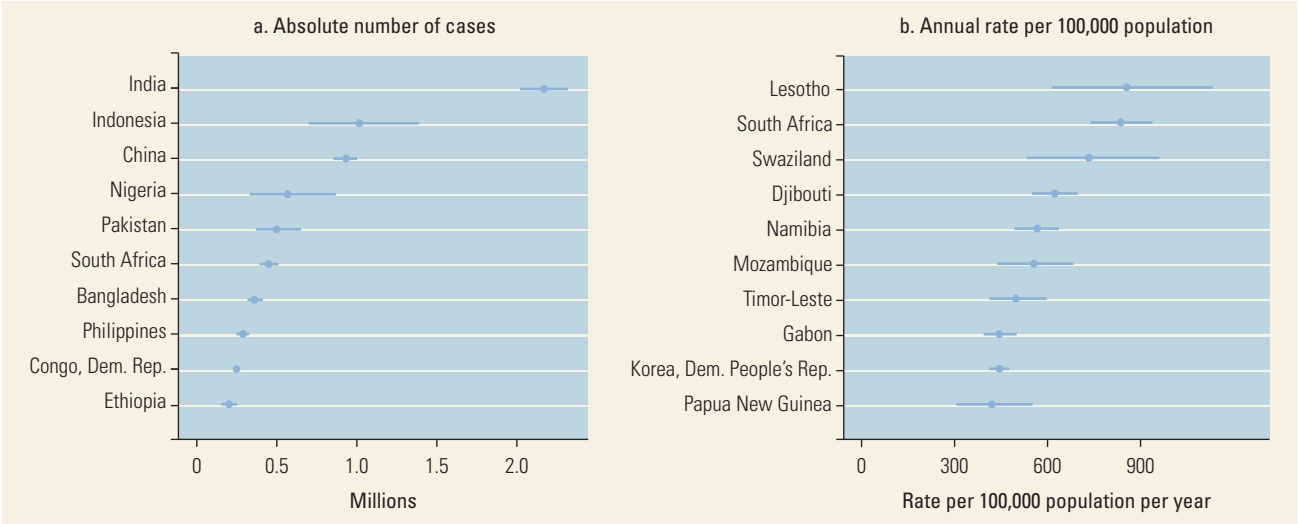
Although the overall burden of disease remains large, substantial progress has been made in TB control worldwide. Between 1995 and 2013, the TB case detection rate increased from 46 percent to 64 percent. In the same period, between 41 million and 56 million people were successfully treated, and by 2015 as many as 49 million lives were saved (Glaziou and others 2011; WHO 2015b, 2016a). TB prevalence worldwide fell 47 percent by 2015, and the TB-attributable mortality rate had declined 45 percent compared with a 1990 baseline.

Since the mid-2000s, the global incidence of TB has been declining, albeit slowly, along with the absolute number of new TB cases reported each year. However, incidence rates remain discouragingly high in high-burden countries in South-East Asia and Sub-Saharan Africa (figure 11.2).

Despite global progress, uncertainties remain in the burden and trends in TB. For example, while estimates of the WHO and of the Institute for Health Metrics and Evaluation (IHME) were similar on prevalence of TB in 2012, the trends differed: the WHO estimated a decline in cases, while the IHME estimated an increase in cases over the same interval.

The progress of individual countries, organized by major international TB targets and goals in 22 high-burden countries—that is, those defined by the WHO as the 22 countries accounting for approximately 80 percent of the world's TB cases in 2015—is shown in table 11.1 (WHO 2015b).

Figure 11.2 Estimated TB Incidence: Top-10 Countries, 2014



Source: WHO 2015b.
Note: TB = tuberculosis. The range shows the lower and upper bounds of the 95% uncertainty interval. The bullet indicates the best estimate.

Table 11.1 2015 Target Assessment: Global, WHO Regions, and 22 High-Burden Countries

Indicator		TB/HIV: 2015 Global Plan Targets			MDR-TB: 2015 Global Plan Targets	
		TB patients with known HIV status (%)	Notified HIV-positive TB patients started on ART (%)	People living with HIV newly enrolled in HIV care who were started on IPT	Estimated MDR-TB cases that were detected and notified (%)	Treatment success rate: confirmed MDR-TB cases, 2011 cohort (%)
Target		**100%**	**100%**	**50%**	**100%**	**≥75%**
Global						
Global		48	70		45	48
WHO region						
African (AFR)		76	69		74	47
Americas (AMR)		69	65		47	56
Eastern Mediterranean (EMR)		11	38		22	64
European (EUR)		59	54		61	46
South-East Asia (SEAR)		43	81		45	54
Western Pacific (WPR)		35	60		16	52
22 High-burden countries						
AFR	Congo, Dem. Rep	44	48		9	59
	Ethiopia	71	68		40	72
	Kenya	94	84		6	70
	Mozambique	91	72	17	19	31
	Nigeria	88	67	3.5	18	63
	South Africa	90	66	>100	>100	45
	Uganda	91	65		12	77
	Tanzania	83	73	0.4	10	75
	Zimbabwe	92	77	3.5	53	81
AMR	Brazil	65			39	56
EMR	Afghanistan	26		23	6	29
	Pakistan	2.8			20	70
EUR	Russian Federation				33	37
SEAR	Bangladesh	1.1	100	0	22	68
	India	63	88		57	50
	Indonesia	2.3	21		13	60
	Myanmar	12	74	19	22	71
	Thailand	83	59		12	
WPR	Cambodia	82	89	55	24	86
	China	39	67		8	50
	Philippines	2.1			47	41
	Vietnam	70	61		24	72

table continues next page

Table 11.1 2015 Target Assessment: Global, WHO Regions, and 22 High-Burden Countries (continued)

	TB/HIV: 2015 Global Plan Targets			MDR-TB: 2015 Global Plan Targets	
Indicator	TB patients with known HIV status (%)	Notified HIV-positive TB patients started on ART (%)	People living with HIV newly enrolled in HIV care who were started on IPT	Estimated MDR-TB cases that were detected and notified (%)	Treatment success rate: confirmed MDR-TB cases, 2011 cohort (%)
Target	**100%**	**100%**	**50%**	**100%**	**≥75%**
Classification					
	≥80% tested	≥80%	≥50%	≥80% detected and notified	≥75%
	50–79% tested	50–79%	25–49%	50–79% detected and notified	50–74%
	<50% tested	<50%	<25%	<50% detected and notified	<50%

Source: WHO 2015b.
Note: A blank cell indicates that no data are available. TB = tuberculosis; MDR TB = multidrug-resistant TB; HIV = human immunodeficiency virus; ART = antiretroviral treatment; IPT = isoniazid preventive therapy; WHO = World Health Organization.

Remaining Challenges

Despite significant progress, TB remains a formidable global health threat. The overall rate of decline in incidence, by any calculation, has been frustratingly slow (1.5 percent a year), and some countries and regions are still reporting rises in TB incidence, particularly in drug-resistant TB. Based on notification reports and surveys, there were an estimated 10.4 million new TB cases in 2015 (WHO 2016a). Assuming lifelong latent infection, about one-third of humanity could still be infected with Mtb (Dye and others 1999; Sudre, ten Dam, and Kochi 1992).

The estimation of TB incidence and prevalence remains imprecise, especially in high-burden countries where precision is most needed. Over the past decade, national surveys of the prevalence of tuberculosis disease have been undertaken in more than 20 countries, including 15 of the 22 highest-burden countries (WHO 2015b). These prevalence surveys provide vital data in high-burden settings. Great investment is needed in high-quality routine surveillance that builds on existing systems and produces robust data for assessment and future planning (Dye and others 2008; WHO 2012b). Since a quarter of TB patients are in India, the National Survey planned for 2017–18 will be very important.

Many factors drive the persistence and fatality of the disease. First, case detection has been insufficient: in 2014, only about 64 percent of people who developed TB were notified as newly diagnosed cases, leaving approximately 3 million to 4 million cases that either were not diagnosed or were diagnosed but not reported to national TB programs.

The emergence of highly drug-resistant tuberculosis, including MDR TB (resistance to at least isoniazid and rifampicin) and XDR TB (MDR plus resistance to at least one fluoroquinolone and one injectable antituberculosis antibiotic), has proved a serious hurdle for effective control of tuberculosis in many settings. The most recent estimates of the burden of MDR TB suggest that approximately 480,000 new cases of MDR TB occur each year, of which only 20 percent are enrolled in treatment (WHO 2016a). Sufficiently strong surveillance and drug resistance laboratory testing are not yet adequate to establish whether MDR TB is rising or falling in most countries where MDR is of concern.

HIV/AIDS is another factor that challenges effective control of TB, especially in Southern African countries. Of the 10.4 million new cases of TB in 2014, 1.2 million occurred in HIV-positive individuals. Among the approximately 1.5 million deaths from TB in 2014, 400,000 were among individuals co-infected with HIV/AIDS (WHO 2015b). Globally, around half of patients diagnosed with TB were tested for HIV/AIDS, although that number has increased to 79 percent in the African region. Treating TB patients co-infected with HIV/AIDS with antiretroviral therapy (ART) rose to 77 percent globally, which is crucial, given that treating HIV-positive patients with ART reduces the risk of clinical TB by 64 percent.

Although dramatic improvements in TB control have been achieved over the last 25 years, the benefits have not been equally distributed among geographic regions. Falling mortality rates were often fueled by rapid

economic development in Asian countries. Three WHO regions—the Americas, South-East Asia, and Western Pacific—reduced prevalence 50 percent by 2013, but the other three regions have not yet achieved that goal.

In 2014, the WHO Africa region had the highest incidence rates (about 280 cases per 100,000 population) and 28 percent of the estimated number of cases globally. Asia had 58 percent of total cases. China and India alone accounted for more than one in three (35 percent) of the world's new TB cases in 2013. Approximately 78 percent of total TB deaths and 73 percent of TB deaths among HIV-negative people occurred in the Africa and South-East Asia regions.

The spatial and temporal variation in TB incidence in Africa is strongly correlated with the prevalence of HIV/AIDS infection (Corbett and others 2003). Globally, an estimated 11 percent of all new adult TB cases were infected with HIV/AIDS in 2015. In the WHO Africa region, the percentage of incident TB cases with HIV/AIDS varied from 8 percent in Eritrea to 77 percent in Swaziland.

Many of the gains in TB control globally are stalling, with TB incidence no longer falling in some East Asian settings, notably Hong Kong SAR, China; Japan; the Republic of Korea; and Singapore. Part of the explanation could be that more cases are arising by reactivation from a previously infected aging human population (Vynnycky and others 2008; Wu and others 2010). Additionally, immigration from high-incidence countries is part of the reason why the decline of TB in North America and Western Europe has plateaued. Immigrants infected in their country of origin contribute, in varying degrees, to further transmission and outbreaks in the country where they have come to live or work (Verver and others 2005).

Global Response

Following its declaration in 1993 that tuberculosis was a global health emergency, the WHO launched the DOTS strategy in 1994 (WHO 1994). Prior to DOTS, there were at least five recommended regimens for treatment of TB, with varying effectiveness, serious adverse effects, and varying costs (Murray, Styblo, and Rouillon 1990). DOTS aimed to create a single common best-practice strategy that would be applicable to all countries and would include not just observing treatment but also securing political commitments as well as adequate and sustained financing:

- Ensure early case detection and diagnosis through quality-assured bacteriology
- Provide standardized treatment with supervision and patient support
- Ensure effective drug supply and management
- Monitor and evaluate performance and impact.

Emerging drug resistance compelled the WHO to introduce DOTS-plus in 1998, with two additional requirements: (1) the capacity to perform drug-sensitivity testing (DST) and (2) the ability to ensure access to second-line drugs (Stop TB Working Group on DOTS-Plus for MDR-TB 2003).

DOTS expanded further in 2014 to reflect six programmatic actions critical to an effective global TB control strategy (box 11.1). Thus, the history of TB response reflects attempts to tackle ever more fundamental causes of TB by addressing health system drivers of the epidemic.

Major organizational initiatives have sought to intensify the fight against TB: the TB Alliance in 2000; the Green Light Committee at the WHO in 2000; the Stop TB Initiative in 2001; the Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund), which was created as a major funder of country programs in 2002; UNITAID in 2006; and the Stop TB Partnership in 2008, which was created to coordinate, together with the WHO, the many provider, advocacy, and donor groups engaged in fighting TB. The Stop TB Partnership has 1,200 partners in 100 countries. Further, the Global Laboratory Initiative was established in 2007 to strengthen laboratory capacity in LMICs.

Increased attention and initiatives have been coupled with significant increases in international and domestic funding for TB. Funding for TB prevention, diagnosis, and treatment reached US$6.6 billion in 2016, almost double the level in 2006 (WHO 2015b). Overall about 84 percent (US$5.5 billion) of reported TB funding was derived from domestic sources; nevertheless, low-income countries (LICs) have benefited from Global Fund financing, which accounts for about 67 percent of total TB funding for these countries. In 2016, most TB

Box 11.1

WHO DOTS Strategy, 2014

- Pursue high-quality DOTS expansion and enhancement
- Address TB and HIV/AIDS co-infection, MDR TB, and the needs of poor and vulnerable populations
- Contribute to health system strengthening based on primary health care
- Engage all care providers
- Empower people with TB and communities through partnership.

Source: WHO 2014b.

funding (US$ 4.9 billion) was spent on drug-susceptible TB, with MDR TB receiving about US$1.7 billion. The WHO estimates that the gap in funding to achieve the SDG for TB is on the order of US$2 billion per year (WHO 2015a, 2016a).

Evolving Targets

The initial DOTS targets aimed to achieve a global tuberculosis detection rate of 70 percent and a treatment success rate of 85 percent. In 2000, the UN Millennium Declaration (UN General Assembly 2000), which established the MDGs, set in motion worldwide concerted efforts to alleviate poverty and improve global health. Astonishingly, the MDG goals did not specifically mention tuberculosis, which was then causing more than 9 million new cases and 1.5 million deaths annually. However, MDG 6, which aimed to halt and begin to reverse HIV/AIDS, malaria, and "other infectious diseases," provided sufficient language for international targets to be established for TB control.

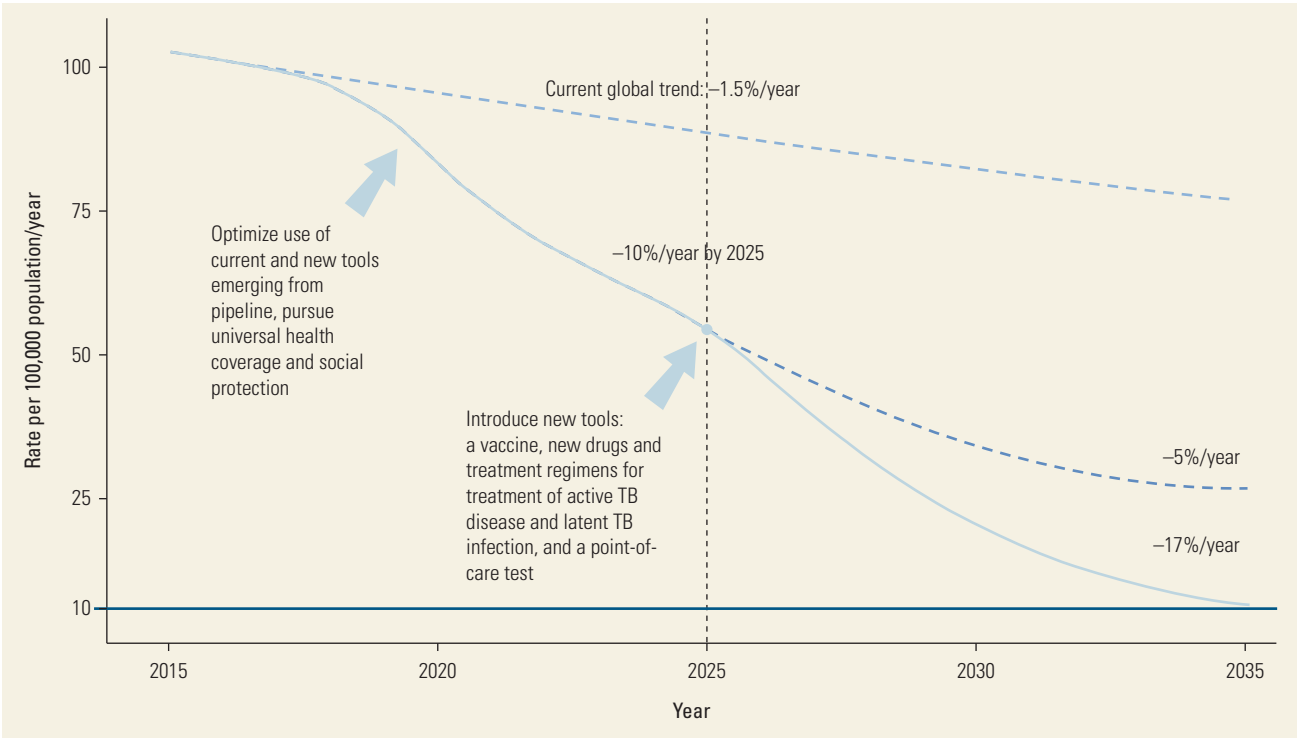
The Global Plan to Stop TB 2001–15 of the Stop TB Partnership established two targets in addition to the general goal in MDG 6, for a total of three targets often referred to in the TB literature:

- Halt and reverse the global growth in TB incidence
- Decrease TB prevalence 50 percent from 1990 baseline levels by 2015
- Decrease TB mortality 50 percent from 1990 baseline levels by 2015.

The current UN Sustainable Development Goals seek to reduce tuberculosis deaths 95 percent and reduce the TB incidence rate 90 percent by 2035, effectively eliminating the disease. These are ambitious goals, and experts have outlined milestones in five-year increments to track progress and hold governing bodies accountable. With evidence that transmission and treatment failures in many countries continue at high levels, other metrics, including case detection and treatment success rates, are important indicators of progress.

Dye and others (2013) modeled what would be required to eliminate TB as a public health problem (less than 1 case per 100,000 population) by 2015. A projection of the decline in incidence at current rates (around 1 percent annually) indicates that MDG goals would not be met for more than 50 years. An updated model requires that incidence decrease 10 percent in 2020 and 17 percent a year thereafter (figure 11.3).

Figure 11.3 Projected Acceleration in the Decline of Global Tuberculosis Incidence Rates to Target Levels, 2015–35



Source: WHO 2015c.
Note: TB = tuberculosis.

Box 11.2

WHO End TB Strategy

Integrated, patient-centered care and prevention

- Early diagnosis of tuberculosis, including universal drug-susceptibility testing and systematic screening of contacts and high-risk groups
- Treatment of all people with tuberculosis, including drug-resistant tuberculosis, and patient support
- Collaborative tuberculosis and HIV/AIDS activities and management of comorbidities
- Preventive treatment of persons at high risk and vaccination against tuberculosis.

Bold policies and supportive systems

- Political commitment with adequate resources for tuberculosis care and prevention
- Engagement of communities, civil society organizations, and public and private care providers
- Universal health coverage policy and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
- Social protection, poverty alleviation, and actions on other determinants of tuberculosis.

Intensified research and innovation

- Discovery, development, and rapid uptake of new tools, interventions, and strategies
- Research to optimize implementation and impact and to promote innovations.

Source: WHO 2015a, 2015c.

However, such a "rate of decline has never been achieved on any geographical scale for any period of time and is not possible globally with the present suite of tools and systems for their delivery" (Dye 2013, 272–73).

It is difficult to conceive that significant progress will be realized by 2035 without the development and application of new tools and investment in health systems for TB, including reinstituting active case finding, devising more effective delivery strategies, investing in the supply chain and information management systems, conducting research and development into new diagnostics, and implementing new and more effective treatment regimens and vaccines.

The WHO's current strategic plan for TB control, the End TB Strategy (Uplekar and others 2015; WHO 2015c, 2016a) is a multifaceted program far more extensive than previous iterations. Recognizing both the successes of previous programs in reducing both mortality and prevalence and the failure of present programs to reduce incidence at a rate that will enable countries to meet the SDG targets by 2035, it proposes a broader and more ambitious program based on three pillars (box 11.2).

These are very ambitious and important goals that, to a large extent, will depend on investments in research and development of new tools and more effective use of the available tools.

INFECTION AND DISEASE IN INDIVIDUALS AND POPULATIONS

Tuberculosis is an infectious bacterial disease caused by *Mycobacterium tuberculosis*, which is transmitted by aerosols and most commonly affects the lungs. Mtb is essentially found only in humans, although the related pathogenic mycobacteria, *M. bovis,* causes disease in cattle and, before Pasteurization of milk, was the cause of scrofula, TB of the lymph nodes. A related pathogen, *M. leprae*, is the cause of leprosy in humans. Because there is no animal reservoir for Mtb, the pathogen has evolved to persist in people for long periods of time, with only a portion of people developing clinical disease with lung damage.

TB is transmitted from person to person via aerosol droplets from the throat and lungs of people with active respiratory disease. Individuals with pulmonary or laryngeal tuberculosis produce airborne droplets while coughing, sneezing, or simply speaking (Lin and others 2008; Loudon and Spohn 1969; Rodrigo and others 1997). Inhaled infectious droplets lodge in the lung alveoli and bacilli and are taken up there by macrophages.

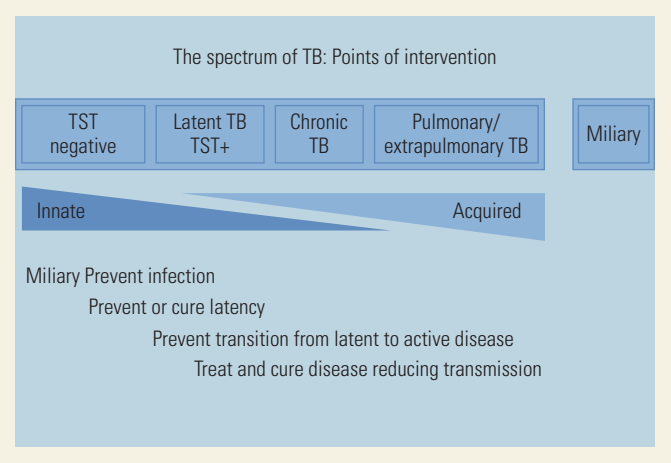
Stages of TB Disease and Intervention Points

TB is best understood not as a single clinical entity but as a spectrum, which generally correlates with the

immune responses. A high, but unknown, percentage of people infected with Mtb develop latent or persistent infection, but only about 10 percent develop disease in a lifetime (Chee and others 2005; Hanifa and others 2009). For immune-compromised individuals, the risk is about 8 percent a year (Selwyn and others 1989). A portion of highly exposed individuals likely to be infected with Mtb fail to develop tuberculin skin tests (TSTs) but remain healthy, suggesting that they are protected by yet-unknown immune mechanisms. Another unknown proportion of individuals with tubercle bacilli in sputum remain asymptomatic but it must be presumed capable of transmitting infection (Bates and others 2012; Mao and others 2014; Willingham and others 2001; Wood and others 2007).

Multiple possible points for interventions exist along the care continuum, including preventing infections, preventing establishment of latency, preventing transition from latent TB to active disease (chemoprophylaxis), and treating persons with active disease to achieve cure, thereby reducing morbidity, mortality, and transmission intensity (figure 11.4).

Figure 11.4 The TB Spectrum and Possible Points of Intervention



Note: TB = tuberculosis; TST = tuberculin skin test. Infection with *Mycobacterium tuberculosis* can lead to subclinical infection, which is cured by innate or acquired immune responses; latent infection that persists; chronic or asymptomatic TB in which tubercle bacilli are found in sputum of otherwise apparently healthy individuals; and active TB disease. In a small proportion of individuals, infection can lead directly to rapidly progressing disease, known as primary progressive TB. Miliary TB is widely disseminated, occurring primarily in children and severely immunodeficient individuals.

In most healthy people, infection with *M. tuberculosis* often causes no symptoms, since the person's immune system, through innate and acquired immunity, acts to kill or wall off the bacteria. Acquired cell-mediated immunity develops two to eight weeks after infection, and granulomas—that is, infiltrating macrophages and lymphocytes—wall off the infection and limit further replication and spread of the organism (Aziz, Ishaq, and Akhwand 1985), although this is only partially protective (Andrews and others 2012; Bates and others 2007; da Silva and others 2014; Lin, Ezzati, and Murray 2007; Slama and others 2007).

There is a widespread belief that infection does not confer significant subsequent immunity (Achkar and Jenny-Avital 2011; Barry and others 2009), which is used to explain why reinfection is not uncommon (Luzze and others 2013; Verver and others 2005). However, recent reanalysis of many studies reveals that latent TB infection does protect against active disease, almost certainly by engendering protective innate or acquired immune responses, but that this protection is only partial (Andrews and others 2012). Molecular fingerprinting techniques can be used to distinguish bacteria obtained during relapses of prior infection from reinfection with new strains. The original infecting strain can reemerge after apparent cure or ineffective treatment and reestablish active disease (relapse) (Khan, Minion, and others 2012; Luzze and others 2013). Reactivation rates vary from 1 percent to 30 percent a year in different populations. Whether latent bacilli remain viable for the full life span of all infected people is unknown, but the risk of reactivation persists into old age (Stead and Dutt 1989).

The phenomenon of reactivation, often long after infection or after treatment, reflects the limitations of immune responses in assuring protection and indicates the challenge facing the development of effective vaccines that can provide long-term protection (Lin and others 2014; Lönnroth and others 2010; Selwyn and others 1989). Bacille Calmette-Guérin (BCG) is the only licensed vaccine available today and has been used for more than 90 years with a good safety record, except in immunodeficient children. However, its efficacy in preventing TB in adults has varied in different parts of the world, while consistently protecting children against the most severe forms of disease: disseminated miliary TB and TB meningitis (Mangtani and others 2014; Roy and others 2014). BCG vaccination is discussed further in the section on prevention.

Primary infection in some individuals leads to active TB (primary progressive tuberculosis) when the host immune response cannot effectively suppress the replication of bacilli. The symptoms of active TB of the lung are coughing, sometimes with blood in sputum; chest pains; weakness; weight loss; fever; and night sweats. Clinical tuberculosis is the sum of complex interactions between the pathogen and an individual's immune response that facilitate mycobacterial replication and cause illness, including wasting and granulomatous inflammation with tissue damage,

for example, caseation, vasculitis, and fibrosis (Jagirdar and Zagzag 1996; O'Garra and others 2013; Shaler and others 2013). The most common clinical manifestation of TB is pulmonary disease, and, in the most infectious patients, bacilli are visible microscopically on stained sputum smears (50–70 percent of pulmonary cases) (Huang, Tchetgen, Becerra, Cohen, Galea, and others 2014; Huang, Tchetgen, Becerra, Cohen, Hughes, and others 2014). Extrapulmonary tuberculosis accounts for 10–30 percent of disease, but is more common among women and children (particularly lymphatic tuberculosis) and in people infected with HIV/AIDS (Chadha and others 2005; Lowell, Edwards, and Palmer 1969; MacIntyre and others 1997).

In the absence of other predisposing conditions, only 5–10 percent of infected people develop progressive primary disease within five years of infection (Chee and others 2005; Hanifa and others 2009; van Rie and others 2013). After five years, there is a much lower annual risk of developing TB by the reactivation of latent infection. However, the risk in HIV-positive individuals is on the order of 10 percent a year after infection (Selwyn and others 1989). The risk of progressing to active disease is relatively high in infancy, is lower in older children, increases quickly during adolescence (earlier in girls), and then increases more slowly throughout adulthood (da Silva and others 2014; Hanifa and others 2009; Isler and others 2013; Lienhardt and others 2003). The lifetime risk of developing TB following infection clearly depends on the prevailing transmission rate, but is generally estimated to be about 10 percent.

Latent TB, which exists in an unknown percentage of people infected with *M. tuberculosis,* has significant impact on the epidemiology and population dynamics of tuberculosis. It represents a huge reservoir of potential disease and further transmission. Concomitantly, long-term latent infection appears to provide partial protection against developing disease (Andrews and others 2012).

Following Mtb infection, whether the infection remains latent or develops into active disease is thought to depend largely on the host's ability to generate protective innate and cell-mediated immunity. There is at present little evidence that serum antibodies provide protection, although recent studies of serum from TST-negative highly exposed individuals indicate they may have antibodies capable of enabling macrophages to kill some bacilli in vitro (Lu and others 2016). Human T-cells are highly heterogeneous. From animal studies, both CD4 cells and cytotoxic CD8 T-cells are important for protection against Mtb infection. CD4+ cells are functionally heterogeneous. In the simplest case, two antagonistic subclasses of CD4+—Th1 and Th2—have been described, each with its own set of cytokine mediators. Th1 responses, characterized by production of interferon gamma (IFN-γ), are associated with protection, while Th2 responses, characterized predominantly by Th2 cytokines (for example, IL-4, IL-10), are associated with antibody, inflammatory responses and tissue damage. A unique subset of human Th1 cells has recently been described that appears strongly to correlate with protection against mycobacterial disease. These Th1* cells constitute a unique subset of human CD4+ T-cells expressing the chemokine receptors—CCR6, CCR4, and the RORγ nuclear transcription factor, which exclusively appears to produce IFN-γ to mycobacteria (Sallusto 2016).

The importance of TB among infectious diseases is attributable to the high case fatality rate among untreated or improperly treated cases. About two-thirds of untreated smear-positive TB cases will die within five to eight years; most will die within the first two years (Huang, Tchetgen, Becerra, Cohen, Hughes, and others 2014; Libshitz and others 1997). As illustrated in figure 11.4, the rest will remain latent, chronically ill, or asymptomatic, or will self-cure. The case fatality rate for untreated microscopy smear-negative cases is lower, but still on the order of 10–15 percent (Chadha and others 2005; Khan, Minion, and others 2012; Libshitz and others 1997). Even among smear-positive patients receiving TB drugs, the case fatality rate can exceed 10 percent if adherence is low or if rates of HIV/AIDS infection and drug resistance are high.

M. tuberculosis Strains

There is striking evidence that the major strains of *M. tuberculosis* co-evolved with the major migrations of humans from Africa to Asia, Europe, and the Americas (Gagneux 2012). Many strains of Mtb can be revealed by molecular analyses, and the diversity is thought to exacerbate drug resistance and to affect the effectiveness of interventions to control the disease. While early targeted genetic analyses suggested only minimal within-species diversity of *M. tuberculosis* (Keane and others 2001; Yokoyama and others 2004), genomic studies have revealed much more variation (Alhajri and others 2011). Subsequent examination has provided increasing understanding of Mtb strains and how they spread globally (Talat and others 2010). Other investigations aim to discover whether differences between or within (according to Cegielski, Arab, and Cornoni-Huntley 2012) strains modify the ability of the pathogen to infect hosts or are associated with differences in the natural history of disease (Alhajri and

others 2011; Wilkinson and others 2000). The number and scope of such studies is still limited, but a recent study has associated differences in Mtb strains with the probability of transmission of disease among household exposures in Brazil (Lopez and others 2003).

Evidence is accumulating that strain lineages vary in strength and mechanism of host-immune stimulation after infection (Baker and others 2012), within-host competitive ability (Boelaert and others 2007), rates of acquiring mutations (Bellamy and others 1998; Ford and others 2013) and drug resistance (Borrell and Gagneux 2011), and the specific mutations acquired (Fenner and others 2012), each of which may affect the within-host course of infection, disease, and response to therapy (Gagneux 2012). In general, the fitness of pathogens diminishes as mutations accumulate. A variety of evidence indicates that MDR TB strains are heterogeneous in their transmissibility in animal models and human populations (Grandjean and others 2015; Lee, Radmonski, and others 2015). It is likely that compromised transmissibility can change if compensatory mutations arise that reestablish fitness. A particular concern is the enhanced transmissibility of the Beijing strain with antibiotic resistance (Ford and others 2013; Hanekom and others 2007). Mathematical modeling similarly indicates that strain diversity may affect the emergence of drug resistance (Basu and Galvani 2008) and interventions (Cohen and others 2008; Colijn and others 2009), but improved projections will require additional data, especially from whole-genome sequencing and long-term monitoring of strain types within human populations.

TB and HIV/AIDS Co-Infection

The extent to which HIV/AIDS is fueling TB transmission (in addition to provoking reactivation) remains poorly understood. One analysis suggested that 1–2 percent of all transmission events were from HIV-positive, smear-positive TB cases in 2000 (Corbett and others 2003). The co-infection of TB and HIV/AIDS is geographically heterogeneously distributed. In countries in Eastern Europe and Southern Africa, as many as 75 percent of all TB patients are HIV-positive; in others, such as China and India, only a small fraction of TB cases are HIV-positive (Dye 2015).

The fraction of TB infections attributable to persons co-infected with HIV/AIDS depends on the prevalence of HIV/AIDS as well as on the infectiousness of HIV/AIDS-associated Mtb compared with that of TB cases not affected by HIV/AIDS. This fraction is influenced by biological factors (for example, the probability of smear-positive pulmonary disease) and how rapidly individuals are diagnosed and receive effective treatment. The duration of HIV/AIDS-associated TB appears to be shorter than the duration of HIV-negative TB (Corbett and others 2004) or about the same (Wood and others 2007), depending on the setting.

Clearly, HIV/AIDS infection exerts a multifaceted suppression of the innate and acquired T-cell responses. In a sense, TB is often a sentinel for HIV/AIDS infection in high HIV/AIDS-endemic areas. Even prior to significant CD4+ T-cell depletion, individuals with latent TB can progress to active disease. Not only does HIV/AIDS infection suppress immune responses to Mtb, but the stimulation of T-cells by antigens of Mtb may contribute to T-cell activation, leading to the increased production of HIV/AIDS and acceleration of the disease process.

Clinically, the prevalence of extrapulmonary TB and disseminated TB are both increased in HIV-positive patients. Low CD4 cell counts are associated with an increased frequency of extrapulmonary TB, positive mycobacterial blood cultures, and atypical chest radiographic findings, reflecting an inability of the impaired immune response to contain infection. The rise in TB incidence attributable to HIV/AIDS appears to have peaked in most countries, as HIV/AIDS incidence has declined (Dye 2015).

Effect of TB on the Distribution of Other Diseases

TB affects the presence and nature of other diseases, possibly conferring protective effects. Microbial infections have the potential to influence the balance between CD4+ T-cell functional subsets by stimulating innate immune responses and by altering cytokine profiles, with positive or negative consequences for health (Sallusto 2016). Mtb infection may also protect against asthma, possibly by shifting the innate and acquired Th2 response to a Th1 subset that reduces the inflammatory response. One study of Japanese children found that strong tuberculin responses following BCG immunization were associated with less asthma, rhinoconjunctivitis, and eczema in later childhood (Shirakawa and others 1997). A study of South African children found an inverse association between *M. tuberculosis* infection and atopic rhinitis (Obihara and others 2005). Comparisons among countries have found that asthma tends to be more common where TB is less common (Shirtcliffe, Weatherall, and Beasley 2002; von Mutius and others 2000).

Interactions between other infections have also been investigated. Vigorous Th2 responses are seen in protective immune reactions to helminth infections, and helminths can shift the balance of immune responses to enhance allergic responses and thus compromise

Th1 immune responses to BCG and *M. tuberculosis* (Hopkin 2000). Conversely, a mycobacterial-based vaccine could potentially be constructed to prevent allergic responses and reduce asthma. Mtb infection may protect against leprosy, as does BCG (Karonga Prevention Trial Group 1996), and natural TB transmission may have contributed to the decline of leprosy in Europe (Lietman, Porco, and Blower 1997).

There is no information at present on whether the human microbiome affects responses to mycobacteria, but this is an area of research worthy of investigation. While the synergistic and antagonistic interactions between bacterial, viral, and parasitic infections are complex and unresolved, these examples raise the general likelihood that mycobacteria influence, and are influenced by, the presence of other infections.

Risk Factors for TB

Risk factors influence the probability of infection, disease, or outcome and operate on many scales (physiological, genetic, environmental, and behavioral). Once an individual has been exposed to a person with infectious pulmonary TB, his or her risk of developing subclinical TB infection depends on factors that influence either the ability of the person infected to transmit the disease or the susceptibility of the person exposed to infection and disease. Infected persons who are acid-fast bacillus smear- or culture-positive (Riley and Moodie 1974; Ross and Willison 1971; Tornee and others 2005), who have cavitary disease (destructive lesions in the lung where the bacilli multiply to high levels; Rodrigo and others 1997) or frequent cough (Loudon and Spohn 1969), or who have delayed treatment (Aziz, Ishaq, and Akhwand 1985; Lin and others 2008) are major transmitters of TB infection.

Risk factors relevant to the exposed host most often reflect the social and environmental determinants of heavy exposure and include living in densely populated spaces (Chadha and others 2005; Lowell, Edwards, and Palmer 1969; MacIntyre and others 1997), being incarcerated (Chadha and others 2005; Chee and others 2005), and working in occupations such as health care that involve frequent social or direct contact with TB patients (Hanifa and others 2009; Isler and others 2013; van Rie and others 2013). Most studies suggest that, among similarly exposed contacts, the risk of TB infection does not vary much by host attributes. However, some recent studies report that genetic loci are associated with differential risk of infection among household contacts exposed to an infectious case (da Silva and others 2014; Lienhardt and others 2003), while evidence indicates that smoking increases the risk of TB (Bates and others 2007; Lin, Ezzati, and Murray 2007; Slama and others 2007).

In contrast to infection, disease progression is known to be highly dependent on host risk factors, the most important of which include HIV/AIDS co-infection (Selwyn and others 1989), low body mass index (Lönnroth and others 2010), exposure to tobacco (WHO 2015d) and biomass fuels (indoor air pollution; Bates and others 2007; Lin, Ezzati, and Murray 2007; Lin and others 2014; Slama and others 2007), diabetes mellitus (Jeon and Murray 2008), and heavy alcohol use (Lönnroth and others 2008; Rehm and others 2009; WHO 2014a). Host-specific risk factors also affect TB outcomes, including the risks of failing therapy, relapsing after treatment, and dying a TB-related death. In addition to HIV/AIDS, smoking and diabetes are recognized biological risk factors for poor treatment outcomes (Kim and others 2014), and some studies have implicated other comorbidities such as iron overload (Yokoyama and others 2004), renal dysfunction (Keane and others 2001), and hematological malignancies (Keane and others 2001).

Abundant evidence indicates that undernutrition is associated with TB in LMICs. In national surveys in India, the population-attributable risk of TB in undernourished adults and adolescents was two-fold or greater and greatest in rural areas (Bhargava and others 2014).

Table 11.2 lists the risk factors for TB progression and summarizes the relative risks for selected determinants for which meta-analyses have been conducted. Although HIV/AIDS is a much stronger risk factor for disease progression than other exposures, the relatively frequent occurrence of other determinants means that they explain a higher proportion of global TB cases than does HIV/AIDS. Table 11.3 estimates the most common

Table 11.2 Key Risk Factors for Tuberculosis from Meta-Analyses of Randomized Controlled Trials

Key risk factor	Odds ratio
Cigarette smoking	2.01–2.66
Indoor air pollution	1.4
Low body mass index	2.45[a]
Alcohol use (daily or alcohol use disorder)	2.94
Diabetes mellitus	3.11

Source: International Institute for Population Sciences and Macro International 2007.
Note: Human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) does not appear in the table because once it was clear that HIV/AIDS was a major risk factor for TB, it became unethical to do a prospective study that did not offer HIV-positive patients isoniazid.
a. Odds of tuberculosis for body mass index of 18.5 compared to 25.

Table 11.3 Attributable Fraction of Key Risk Factors for Tuberculosis Disease Progression in India, by Socioeconomic Strata

Key risk factor	Population-Attributable Fraction (%)		
	Lowest socioeconomic stratum	Middle socioeconomic stratum	Highest socioeconomic stratum
Cigarette smoking	16	10	6
Indoor air pollution	29	25	6
Low body mass index	34	27	20
Alcohol use, daily	4	2	1
HIV/AIDS seroprevalence	9	10	6

Source: Oxlade and Murray 2012.
Note: HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome.

Table 11.4 Global Prevalence, Relative Risk, and Attributable Fraction for Incident Tuberculosis

Key risk factor	Global prevalence	Relative risk	Attributable fraction (%)	References
HIV/AIDS	0.008	8.3	5.5	WHO 2009a
Undernourishment	0.11	2.1	10.7	Lönnroth and others 2010
Diabetes mellitus	0.085	3.0	14.5	Jeon and Murray 2008
Heavy alcohol use	0.075	2.9	12.5	Lönnroth and others 2008
Cigarette smoking	0.21	2.6	25.1	Lin, Ezzati, and Murray 2007; Slama and others 2007
Indoor air pollution	0.41	1.5	17.0	Lin, Ezzati, and Murray 2007

Note: Relative risk estimates the magnitude of an association between exposure and disease on the basis of the incidence of disease in the exposed group relative to the unexposed group. Attributable risk is the absolute difference in incidence between an exposed and unexposed group that quantifies the risk of disease in the exposed group attributable to the exposure by removing the risk that would have occurred due to other causes.

attributable risk factors in different economic strata in India using data from the Indian National Family Health Survey (International Institute for Population Sciences and Macro International 2007). These data show that multiple risk factors often converge in individuals living in poverty, further amplifying their risk of disease.

HIV/AIDS is associated with only about 11 percent of TB patients worldwide. Other risk factors, such as diabetes mellitus and smoking, occur more widely. The population-attributable fraction is the proportional reduction in population disease or mortality that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario, for example, no smoking. A global estimate of population-attributable factors for TB is given in table 11.4. It is not possible to estimate accurately the number of people with each of the risk factors because the data on background risk are uncertain and risks overlap. Nevertheless, the greater numbers of smokers and rapidly expanding number of people with diabetes mellitus allow us to infer that the proportion of all cases due to malnutrition and diabetes is five times higher and the proportion due to smoking is eight times greater than the proportion due to HIV/AIDS.

Risk factors also vary by socioeconomic status, as illustrated for India. While infection with Mtb is a risk for people of any economic stratum, the data from India indicate that some known risk factors for TB are greatest in the lowest socioeconomic group, a finding likely to be true for most populations.

Other less common comorbidities also modify the risk of disease. Persons are more likely to progress to active tuberculosis if they suffer from silicosis (Corbett and others 2000; Snider 1978), kidney disease (Mitwalli 1991), or solid (Libshitz and others 1997) and hematological (Khan and others 2005) malignancies; have undergone gastrectomy or ileojejunal bypass surgery (Choi and others 2015; Kim and others 2014; Yokoyama and others 2004); or have received the tumor necrosis factor alpha (TNF-α) inhibitor infliximab for the treatment of rheumatoid arthritis (Keane and others 2001). While these exposures are rare, some dramatically increase the risk of TB; older forms of weight-loss surgery, for example, can profoundly increase risk. To date, although several case reports document TB among patients undergoing gastric bypass, no systematic epidemiologic studies have been conducted on this risk factor (Alhajri and others 2011).

In addition to low body mass index, several micronutrient deficiencies have been associated with TB progression. In vitro studies suggest a role for vitamin D in host susceptibility to disease and, in one clinical study conducted in Pakistan, 25-hydroxy-vitamin D—25(OH)D—levels less than 9 nanograms per milliliter increased the risk of progression to active disease fivefold (Talat and others 2010). Vitamin A deficiency was found to be associated with a 2.8 increased risk of TB in the United States, although this finding was not statistically significant (Cegielski, Arab, and Cornoni-Huntley 2012), and reciprocal seasonal variation in vitamin D levels in South Africa correlate with TB notifications (Martineau and others 2011).

Nutritional factors may also interact with genetic polymorphisms to increase TB risk. Polymorphisms in the 25(OH)D receptor have been associated with TB risk, and several studies have demonstrated a gene-environment interaction between 25(OH)D levels and 25(OH)D receptor mutations (Wilkinson and others 2000); there is considerable evidence that 25(OH)D3 is essential for human macrophages to kill Mtb in vitro (Fabri and others 2011; Liu and others 2007). Vitamin D is produced in the skin by exposure to ultraviolet light, and seasonal variation in vitamin D has been correlated with the number of TB cases (Wilkinson and others 2000). This finding and the role of the skin pigment melanin to absorb ultraviolet light may explain the increased susceptibility of dark-skinned individuals to TB infection and more severe disease (Martineau and others 2011; Modlin and Bloom 2013). But correlation does not imply causation, and there is a critical need for well-designed clinical trials to ascertain the importance of these factors.

Much recent work has focused on identifying the genetic determinants of TB progression (Abel and others 2014). Twin studies strongly support the hypothesis that genetic factors play a role in TB susceptibility, and multiple loci have been implicated through candidate gene studies (Snider 1978). Some of these are rare variants that lead to alterations in the interferon-γ pathway required to develop acquired immunity to mycobacteria. Multiple defects in this pathway result in Mendelian susceptibility to mycobacterial diseases, which predisposes individuals not only to disseminated infections with nontuberculous mycobacteria, but also to tuberculosis (Bustamante and others 2014; Mitwalli 1991). Other studies have implicated candidate genes that affect innate immune responses (Png and others 2012). Several genome-wide association studies have also been reported, as reviewed in Naranbhai (2016). Some have identified alleles, which occur in "gene-free" regions of the human genome, but these have not been consistently validated in separate populations. A locus on chromosome 11 has been associated with susceptibility in multiple populations (Chimusa and others 2014; Thye and others 2012). Of particular interest is a locus on chromosome 5 that encodes a component of interleukin 12 (IL-12) required for differentiating T-cells, which appears to confer resistance in highly susceptible HIV-positive populations in East Africa and for which there is evidence of positive selection (Sobota and others 2016).

TB DIAGNOSIS AND SCREENING

In simplest terms, the DOTS strategy for TB control has been to test individuals who seek care at a health facility for clinical symptoms of TB and to provide appropriate drug treatment for a period of 6–24 months. With timely diagnosis and correct treatment, almost all people with drug-sensitive TB can be cured, and even a short duration of treatment reduces the bacillary load and likelihood of transmission. Nevertheless, worldwide, the TB case detection rate remains low: in 2012, about 66 percent (5.7 million) of the estimated 10.4 million people who developed TB were newly diagnosed cases, with an estimated 3 million to 4 million cases remaining undiagnosed or unknown to health systems. Case detection in children is of particular concern: an estimated 1 million children developed tuberculosis in 2010, with about 32,000 children contracting multidrug-resistant TB disease (Seddon and others 2015).

In most countries, the most common diagnostic test is microscopic scanning of acid-fast stained bacilli in sputum smears—a technique dating to the 1880s. It is convenient but insensitive, diagnosing only about half of all TB cases in adults (Frieden 2004) and fewer in children (Detjen and others 2015) and HIV-positive individuals (Harries 1997). Diagnostic certainty is obtained when the organism is demonstrated in a laboratory after clinical evaluation of symptoms (usually cough) compatible with tuberculosis. In the absence of diagnostic laboratory tests, clinicians need to review clinical information and decide whether to initiate treatment for tuberculosis, weighing the risks of leaving possible TB untreated against adverse drug reactions and the social and financial costs of committing to months of therapy (WHO 2007). Often treatment, appropriate or not, is instituted before it is clear whether the patient has TB and whether the infection is drug-susceptible or drug-resistant.

Diagnosis of MDR and XDR TB

Diagnosis and treatment of MDR TB, in particular, has largely faltered worldwide. Only 30 of 107 countries are treating 75 percent or more of patients with MDR TB, with countries experiencing high levels of loss to follow-up (WHO 2013a). Of the estimated 450,000 people who developed MDR TB in 2012, only 94,000 (20.9 percent) were detected, and just 77,000 were started on second-line treatment. MDR and XDR TB also represent a threat to health care personnel and health infrastructure. Unknown numbers of nurses and physicians have acquired MDR and XDR TB, and in 2014, there were an estimated 210,000 deaths from MDR TB (WHO 2015b).

The diagnosis of drug-resistant TB and its treatment are complex, requiring laboratory capability for drug-sensitivity testing and between 9 and 20 months of daily administration of drugs that are both more toxic and less efficacious than the drugs used to treat drug-sensitive TB (Nathanson and others 2010). Inadequate human resources, poor access to laboratory services, and low capacity to do drug-susceptibility testing and analysis partly account for low case detection for MDR TB (Shin and others 2008). Health system approaches that favor hospital-based management of MDR TB frequently have limited access to service delivery, and scale-up of new diagnostic tools and treatment regimens is often weak in health systems where MDR TB dominates (Keshavjee and Farmer 2010; Nardell and Dharmadhikari 2010).

Several economies—including Estonia; Hong Kong SAR, China; Latvia; and Singapore—that have strengthened their health systems by improving access to diagnosis and primary care treatment have halted the rise in MDR TB incidence (Cohen and others 2014; Cuevas and others 2011; Dye 2009). Strong laboratory capacity, which has enabled rapid and definitive determination of drug sensitivity, strong supply chain management systems, and successful scale-up of effective treatment regimens have contributed to this success (Gandhi and others 2010). In this context, it is technically difficult for countries to diagnose patterns of drug resistance. For this reason, the WHO created the TB Supranational Reference Laboratory Network of 24 quality-control laboratories, which are located in every continent and able to carry out sophisticated testing for drug resistance (WHO 2015a).

Recent Advances in TB Diagnostics

Tuberculosis diagnostics have advanced steadily over the past decade (see box 11.3). As a result, between 2007 and 2012, the WHO issued 10 new policy statements on TB diagnosis covering an array of approaches (Lawn 2015).

Box 11.3

New Strategies for TB Diagnosis

- Use of light-emitting diode (LED) microscopy as an alternative to conventional Ziehl-Neelsen light microscopy, which has been the mainstay of TB diagnosis for decades (Cuevas and others 2011)
- Use of nucleic acid amplification tests (NAATs) for diagnosis of active TB, including manual technologies such as loop-mediated isothermal amplification as well as automated technologies such as Xpert MTB/RIF (Pai, Kalantri, and Dheda 2006)
- Use of nucleic acid amplification technology approaches for rapid screening for drug resistance, for example, based on line probe assays (Pai, Kalantri, and Dheda 2006)
- Use of liquid culture systems as a more rapid and sensitive alternative to conventional solid culture (Palacios and others 1999).

Other avenues for developing new TB diagnostics hold promise:

- Urine-based diagnostics for detecting *M. tuberculosis* antigen, for example, assays to detect lipoarabinomannan, especially in HIV-positive patients (Green and others 2009; Nakiyingi and others 2014)
- Immunochromatographic tests for rapid confirmation of Mtb in culture (Hasegawa and others 2002)
- Exhaled air mass spectrometry for volatiles and chemical analysis (Phillips and others 2007).

Among the new diagnostic options that have emerged in recent years, the Xpert MTB/RIF test has received the most attention. Xpert MTB/RIF is an automated deoxyribonucleic acid (DNA) amplification test that provides rapid and sensitive detection of TB and rifampicin resistance. It uses a cartridge-based system that integrates sample processing and real-time polymerase chain reactions, accommodates use by relatively unskilled health care workers, and provides results in less than two hours. The system is expensive, costing about US$17,000 per unit, and the tests, currently subsidized, cost about US$10. The ability to diagnose TB and identify MDR TB from sputum in less than two hours is a major step forward in linking diagnosis to rapid initiation of treatment. However, Xpert MTB/RIF is currently not a technology for point-of-care diagnosis. In December 2010, the WHO recommended that the device be used for initial diagnosis in patients suspected of having MDR TB or HIV/AIDS-associated TB disease. Subsequently, some countries, including China, India, and South Africa, have purchased Xpert equipment at reduced prices and taken advantage of volume pricing to purchase test cartridges.

The Xpert system is a significant advance in accelerating the diagnosis of TB, particularly MDR TB, and will likely be a valuable new tool for major hospital and TB diagnostic laboratories, despite being dependent on a sophisticated and expensive device and relatively expensive costs for each sample tested. However, a multicenter trial in four African countries failed to demonstrate lower TB-related morbidity (Theron and others 2014). A new device model being developed, the GeneXpert Omni, which is portable and battery operated, has the potential to become a point-of-care diagnostic test in many more sites and is to be released later in 2017.

Since shortening the time between diagnosis and initiation of appropriate treatment is a major factor in reducing transmission, technologies that allow diagnosis and drug-sensitivity testing at the point of care are ideal. Some innovative research is under way to achieve that goal, but point-of-care testing remains a formidable challenge. Considering the sheer number of patients queued in busy outpatient departments, it is unlikely that cough screening and sputum testing can be effectively implemented in many of the highest-risk ambulatory settings—or in all resource-limited settings. Even the DNA amplification methods lack the sensitivity to detect many patients with early disease. Potentially infectious TB cases will be missed, delays in diagnosis will occur, and patients with XDR TB will likely not respond promptly to current therapy. Traditional methods of control will be necessary for the foreseeable future (WHO 2009a).

A recently developed molecular approach examining gene expression of peripheral blood cells rather than sputum has the potential to identify the subset of healthy individuals with latent TB who are likely to progress to active disease (Zak and others 2016). Rather than detecting components of the pathogen, this novel method measures gene expression signatures in peripheral white blood cells that are elevated in healthy individuals with latent infection prior to their progression to active TB. In a panel of 16 gene probes in three separate cohorts in different countries, it was possible to predict persons who progressed to active disease six months to one year before any symptoms could be detected clinically. At the one-year point prior to diagnosis, the specificity of the test was around 61 percent; in HIV-positive individuals, it was significantly higher, at around 80 percent. The molecular exploration of host responses offers new possibilities for diagnosing infection and defining the gene signatures of persons who do not progress to active disease, potentially enabling understanding of the genes required for resistance to disease. In a similar approach, gene expression in the whole blood of patients with either latent tuberculosis or other diseases versus patients with active tuberculosis was compared using a validated multicohort analytical framework. The diagnostic capacity of a three-gene set was found to be 88–90 percent in active and latent TB in samples from children and adults in 10 countries (Sweeney and others 2016). Such molecular host signatures could potentially serve as biomarkers for defining determinants of protection against infection or disease in future studies and vaccine trials.

TB TREATMENT

Treatment aims to cure the disease process, rapidly stop transmission, and prevent relapse (WHO 2006). Current treatment of tuberculosis requires multiple antibiotics, guided by predicted or demonstrated antibiotic susceptibility and taken for many months. Context-specific treatment guidelines are usually developed by local health authorities with guidelines and oversight from the WHO. Clinical trials in the twentieth century established current first-line drug regimens (Fox, Ellard, and Mitchison 1999; Mitchison 2004). Treatment success rates of 85 percent or more for new drug-sensitive cases are regularly reported to the WHO from a wide variety of clinical settings (WHO 2012a, 2015b).

Treatment effectiveness has been eroded, however, by the evolution and transmission of multidrug-resistant

tuberculosis. Treatment for MDR TB, which is defined as resistance to isoniazid and rifampicin (the two most effective TB drugs) is longer and requires more expensive and more toxic drugs. For most patients with MDR TB, the current regimens recommended by the WHO last 18–24 months, and treatment success rates are much lower, around 60 percent. The WHO now conditionally recommends using seven drugs to reduce the time of treatment to nine months for uncomplicated pulmonary disease (WHO 2016b). New drug combinations, for example, including bedaquiline or delaminid, which are thought to act on new molecular targets, are being introduced, but an ideal combination is likely several years away (Villemagne and others 2012; Zumla, Nahid, and Cole 2013).

Patients who are effectively treated for tuberculosis usually show clinical response within 8–12 weeks, both subjectively (reduced cough, fatigue, fevers, and sweats; increased appetite) and objectively (sputum smear or culture conversion from positive to negative; weight gain) (WHO 2010). Failure to respond to treatment is typically due to poor drug quality, underdosing or malabsorption, nonadherence, drug resistance (which may broaden while on treatment), paradoxical reactions or immune reconstitution inflammatory syndrome (IRIS), adverse drug effects, or another disease process (bronchiectasis, malignancy, pneumoconiosis, autoimmune disease, or organ failure).

One of the embarrassing deficits in the field of TB control is the ambiguous definition of "cure." In the twenty-first century, it should be shocking that accurate biomarkers for treatment response, or in fact cure, are essentially nonexistent, as is the ability to predict relapses after treatment (Walzl and others 2008). Within clinical trials, cure is defined as no relapse after one year after completing therapy. In LMICs the general criterion of cure for individual patients is two negative sputum smears a month apart (WHO 2014b). Yet sputum smears are not sufficiently sensitive or precise to be certain that there is true sterilization of the infection. Bacterial culture, though more sensitive, is also more time-consuming and less frequently used in resource-poor countries (Phillips and others 2016). There are no microbiological or molecular biomarkers to establish whether an individual's infection has been sterilized by treatment. Recurrence can be due either to reactivation of a previously treated strain or to reinfection with a new strain. Reinfection in previously treated patients may be as common as relapse and can be distinguished from relapse by comparing mycobacterial DNA sequences from both the original isolate and the recurrence (Marx and others 2014).

Treatment Regimens

Effective tuberculosis treatment needs to overcome the organism's ability to persist in diverse microenvironments under extreme conditions, including immunological attack, prolonged antibiotic exposure, and nutrient and oxygen depletion (Islam, Richards, and Ojha 2012; Shaler and others 2013). Standardized treatment regimens and fixed-dose combination medications simplify good clinical care in resource-limited settings. Table 11.5 presents current treatment regimens, with an intensive phase followed by a continuation phase (Chakraborty and others 2013; Donald and McIlleron 2009; Shi and others 2011; WHO 2010, 2013b, 2016a, 2016b).

First-Line Treatment of Drug-Susceptible TB

Rifampicin and isoniazid are the most potent drugs for susceptible TB and are taken throughout the course of first-line treatment (Donald and McIlleron 2009; WHO 2010). Pyrazinamide synergistically reinforces the sterilizing activity of rifampicin and, when added to the first two months of treatment, reduces the duration of treatment to six months (Fox, Ellard, and Mitchison 1999; Hong Kong Chest Service and British Medical Research Council 1979). Ethambutol is added to the regimen for two months to reduce on-treatment development of drug resistance (WHO 2010) and is continued for the full duration of therapy in settings with high background prevalence of isoniazid resistance. As effective as standard treatment has been, resistance to isoniazid, rifampicin, and pyrazinamine is increasing in many countries, indicating that new regimens will need to be increasingly incorporated into TB treatment.

Second-Line Treatment of MDR TB

The treatment of drug-resistant TB is evolving, and recommendations are changing rapidly. Four factors make it difficult to arrive at clear, generalizable recommendations. First, individual strains vary in their susceptibility, and customized regimens might be more appropriate, when possible. Second, testing susceptibility to pyrazinamide and second- and third-line agents is neither widely available nor consistently reliable. Third, many agents have limited availability due to their cost or limited production. Finally, few comparative studies are available to provide data on which to make optimal treatment decisions.

While drug-resistant disease is curable, the cure rate in several studies is lower than for drug-sensitive disease. In some studies of MDR TB, only 54 to 70 percent of patients achieve treatment completion or cure (Ahuja and others 2012; Bassili and others 2013;

Table 11.5 Tuberculosis Treatment Regimens Currently Recommended by the WHO

Type of case and phase	Length of regimen (months)	Drug used
New tuberculosis case		
Intensive phase	2	Rifampicin, isoniazid, pyrazinamide, ethambutol
Continuation phase	4	Rifampicin, isoniazid (low risk of isoniazid resistance) or rifampicin, isoniazid, ethambutol (high risk[a] of isoniazid resistance)
Previously treated tuberculosis case (relapse or default)[b]		
Intensive phase	2	Rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin
Continuation phase	1	Rifampicin, isoniazid, pyrazinamide, ethambutol
	5	Rifampicin, isoniazid, ethambutol
Previously treated tuberculosis case (treatment failure)[c]		
Intensive phase	8	MDR TB regimen (see below)
Continuation phase	12	MDR TB regimen (see below)
MDR TB cases		
2010 guideline	20	Kanamycin (or amikacin), moxifloxacin[d] (ethionamide, cycloserine (or terizidone), pyrazinamide
Intensive phase	8	Bedaquiline or delamanid, where sensitivity following the initial regimen cannot be assured (up to six months)
Continuation phase	12	Moxifloxacin,[d] ethionamide, cycloserine, pyrazinamide
2016 short regimen (conditional recommendation)		
Intensive phase	4–6	Kanamycin, moxifloxacin,[d] prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, ethambutol
Continuation phase	5	Moxifloxacin,[d] clofazimine, ethambutol, and pyrazinamide

Note: MDR TB = multidrug-resistant tuberculosis defined as resistance to isoniazid and rifampicin; WHO = World Health Organization.
a. Using local epidemiological data.
b. Low risk of MDR TB using local epidemiological data. The WHO recommends treatment guided by drug-susceptibility testing, especially rapid molecular tests, and suggests that standard first-line treatment be used if there is no evidence of drug resistance to isoniazid and rifampicin.
c. Defined as smear positive after five months of first-line treatment, relapse or default after second or subsequent course of treatment, or active tuberculosis after contact with an MDR TB case.
d. Or high-dose levofloxacin or gatifloxacin.

James and others 2011; Loveday and others 2012; Nathanson and others 2010). Treatment requires new drugs, with regimens containing anywhere from three to seven drugs that have not been previously employed (Mitnick and others 2008). In general, these second- and third-line agents are less potent and must be administered for a more extended period of time, ranging from 9 to 24 months. They are also more difficult to administer, as most regimens contain agents such as kanamycin and amikacin that must be administered by injection. These drugs are far more toxic than first-line agents, causing a range of drug-specific side effects. Nevertheless, it has been possible to achieve MDR TB cure rates of 60–80 percent irrespective of HIV/AIDS status in settings with severe resource constraints and patients with advanced disease (Meressa and others 2015; WHO 2016a).

Key strategies that have contributed to successful treatment include intensive management of adverse effects, nutritional supplementation, adherence interventions, and collaboration between the public health service and nongovernmental organizations (NGOs). These approaches should be routinely incorporated into programs wherever possible.

Generally, MDR TB has substantial human, economic, and social consequences (Rouzier and others 2010). The cost of treating MDR TB using conventional regimens ranges from US$2,500 to US$10,000, compared with US$100–US$1,000 for drug-susceptible TB cases (Floyd and others 2013), placing substantial costs

on high-burden countries. For example, in South Africa, although MDR TB and XDR TB represent less than 3 percent of all TB cases detected, they consume an estimated 35 percent of the national health budget allocated to tuberculosis control (Pooran and others 2013). In some countries, the costs to treat MDR TB are estimated to exceed the total budget for TB control.

In May 2016, the WHO issued a conditional recommendation on use of the shorter MDR TB regimen, which would shorten the duration of treatment (to 9–12 months), increase adherence and retention in care, and lower costs (about US$1,000 in drug costs per patient) (WHO 2016a). Routine analysis of mutations conferring resistance to isoniazid may further inform the choice of MDR TB treatment: isolates with mutations in the promoter region of the *inhA* gene are susceptible to high-dose isoniazid but resistant to ethionamide, while those with *katG* mutations are resistant to high-dose isoniazid but sensitive to ethionamide (WHO 2016a).

Ongoing clinical studies are beginning to form the evidential basis for the WHO guidelines given in table 11.5, and are discussed in more detail in the section titled "Research and Development." In this rapidly changing area, encouraging data suggest that higher cure rates are possible, perhaps with shorter courses using newer agents (see the review by Zumla, Nahid, and Cole 2013). Bedaquiline and delamanid, two newly approved drugs, both lead to more rapid clearance of organisms and higher cure rates for MDR TB when administered with an optimized regimen. Similarly, the oxazolidinone antibiotic linezolid, which is used largely to treat Gram-positive infections, accelerates clearance and increases cure. Clofazimine, a riminophenazine dye used to treat leprosy, is now recommended for the shortened MDR TB regimen. These new treatments may cause significant side effects. Clofazamine may cause skin discoloration. For unclear reasons, bedaquiline therapy has been associated with a higher death rate, while linezolid produces a range of dose-limiting toxicities, including neuropathy and myelosuppression.

Treatment in Specific Situations

Regimens for treating tuberculosis in children are identical to those for adults. Correct dosing by weight is essential, and the most appropriate formulation of combination medications receives ongoing advocacy (WHO 2013c).

Tuberculosis in pregnancy can be treated with isoniazid, rifampicin, pyrazinamide, and ethambutol. Streptomycin, amikacin, and kanamycin may cause fetal ototoxicity and should not be used if possible (Donald 2016). The safety of other drugs used to treat MDR TB has not been well studied in pregnancy. Treatment should be individualized, with expert review. Contraceptive advice during MDR TB treatment is essential.

Glucocorticoids may limit the inflammatory damage associated with tuberculosis (Critchley and others 2013). Evidence supports the use of glucocorticoids for tuberculous meningitis (Prasad and Singh 2008). Additionally, surgery may be necessary to improve the chance of cure by removing localized disease (Marrone and others 2013) and to decompress vital structures that are compromised by the tuberculous cavities.

A particularly devastating form of TB, tuberculous meningitis, has a rapid onset and is frequently fatal. Current treatments are less effective for TB meningitis, and higher doses of drugs may be needed to reach therapeutic levels in the central nervous system (Donald 2016).

Drug Toxicities and Interactions

Prompt detection and effective management of adverse drug effects is essential to the integrity of a treatment program. TB antibiotics, like other medications, may interfere with drug metabolism and excretion. Rifampicin potently induces expression of hepatic cytochrome P450 enzymes (McIlleron and others 2007), substantially reducing levels of several clinically important drugs including HIV/AIDS protease inhibitors, warfarin, phenytoin, carbamazepine, and estrogen-containing contraceptives. Antiretroviral drugs nevirapine and efavirenz interact with rifampicin; however, only the nevirapine interaction is clinically significant, and current recommendations are to use efavirenz with rifampicin. The newer drugs, bedaquiline and delamanid, which in small studies seem to be effective against MDR- or XDR-TB, increase the QT interval with a risk of arythmia, and linezolid has serious effects on bone marrow and neurologic function. Clinically significant interactions should be checked regularly online.[1]

Antiretroviral Therapy

In 2014, there were 10.4 million new cases of TB, of which 1.2 million (11 percent) were among people living with HIV/AIDS. Over the past 30 years, antiretroviral therapy for HIV/AIDS infection has improved to the point where effective therapy is widely available in LMICs, with strikingly improved mortality in patients co-infected with HIV/AIDS and tuberculosis (Khan, Minion, and others 2012).

Early initiation of ART reduces mortality risk in HIV-positive patients co-infected with tuberculosis and is therefore recommended, irrespective of CD4 count

(WHO 2013a). To reduce mortality risk, it should be commenced within two weeks of TB treatment.[2] The goal of ART is to achieve long-term viral load suppression assessed with regular viral load measurements. Cotrimoxazole prophylaxis for *Pneumocystis* pneumonia, toxoplasmosis, bacterial sepsis, and malaria reduces mortality in patients co-infected with TB and HIV/AIDS and should be given until the CD4 count recovers to above 200 cells per microliter after at least six months of ART.

One significant adverse effect of combined treatment is the development of IRIS, which is characterized by persisting or recurring fevers and a worsening of the focal tuberculous process (in profoundly immune-suppressed patients with CD4 count below 50 cells per microliter) starting combination ART shortly after commencing tuberculosis treatment (Meintjes and others 2008; Meintjes and others 2010). IRIS can usually be controlled with steroids and non-steroid anti-inflammatory agents.

Antidiabetic Treatment

Diabetes is a significant risk factor for tuberculosis but has received less attention than HIV/AIDS in LMICs. This will likely change given the increasing life expectancy and prevalence of obesity and type 2 diabetes globally. All patients with tuberculosis should be screened for diabetes (Faurholt-Jepsen and others 2012; WHO 2011a). Diabetic patients should have their glucose control assessed regularly while on TB treatment as part of integrated clinical care, and treatment should be optimized with oral antidiabetic agents and insulins.

Surgery

With treatment outcomes for multidrug-resistant tuberculosis patients achieving only about 50 percent success, surgery, once a major tool in the pre-antibiotic era, has reemerged as an adjuvant therapeutic strategy. A systematic review and meta-analysis to assess the evidence for the effect of surgery as an adjunct to chemotherapy found that there was little substantial data on which to base recommendations, but there appeared to be some enhancement of successful outcomes from surgery on adults treated for MDR TB (Harris and others 2016).

Palliative Care

Tuberculosis remains a leading cause of death in LMICs. Suffering and the process of dying are important clinical consequences of advanced tuberculosis that should be detected and communicated by an experienced clinician who can initiate effective palliative treatment (Connor and others 2012; Smart 2010). Terminally ill patients may decide to improve their quality of life by discontinuing tuberculosis treatment. Physical discomfort, psychological distress, and unresolved end-of-life social issues can all potentially be addressed by trained community health workers (CHWs) once the need has been identified. These structures need ongoing local support and advocacy (Harding and others 2012).

The Cascade of Care and Completion of Treatment

The DOTS strategy to control tuberculosis promotes standardized treatment, with supervision and patient support, which may include direct observation of therapy, where a health care worker personally observes the patient taking the medication (WHO 2013b). The scientific evidence on the effectiveness of DOT compared to self-administered therapy is mixed. Despite the galvanizing impact of the DOTS strategy in mobilizing support and treatment activities, a systematic comparison of the effectiveness of DOT relative to self-medication in 11 random control trials failed to establish its unique effectiveness in ensuring either compliance or cure (Karumbi and Garner 2015).

DOTS has been associated with reduced prevalence of drug resistance in the United States (Moonan and others 2011; Pasipanodya and Gumbo 2013); other HICs; and many LMICs, such as Cambodia, China, and Ethiopia (WHO 2014b, 2015b). However, in highly endemic countries, especially those burdened with HIV/AIDS, even where adequate diagnosis and effective treatment are provided, the strategy has not dropped incidence or transmission as much as needed. As discussed in the section on research and development, additional strategies will be needed where the forces of infection, environment, and HIV/AIDS are driving the infection rate, despite effective treatment of incident cases (Middelkoop and others 2015).

Some countries have experimented with involving community members to make treatment supervision more acceptable to individual patients (Datiko and Lindtjørn 2009), but the operational issues are substantial, and a meta-analysis after DOTS implementation that included community members in China found that 52 percent of patients still took self-administered therapy (Hou and others 2012). Nonadherent patients need to be identified early and offered practical interventions to assist their return into care (Toczek and others 2013; Yin and others 2012), including hospitalization for supervised treatment and physical rehabilitation. Clinic staff who know the patient and community are in the best position to decide which patients need the intense adherence support implicit in DOTS.

It is important to emphasize that early case detection, whether by passive or active case finding, is a necessary but not sufficient condition for effective control of TB. A recent analysis of the cascade of care of TB in India reveals the challenges of ensuring treatment completion (Subbaraman and others 2016). In this important study of about 2 million cases of conventional TB evaluated through the Revised National Tuberculosis Control Program, the authors created a framework and followed the cascade of care from the number of prevalent cases to those reaching TB diagnostic centers, those diagnosed with TB, those registered for treatment, those who completed treatment, and finally those with recurrence-free survival at one year. The results indicated for conventional TB that 45 percent completed treatment and 39 percent were disease free after one year. Of patients diagnosed with MDR TB, only 14 percent completed treatment and 11 percent remained disease free at one year. These striking results clearly indicate the critical need for support of treatment to enable greater treatment completion in India and most LMICs.

TB PREVENTION

There are three obvious strategies for preventing TB: vaccination, infection control, and chemoprophylaxis or isoniazid preventive therapy (IPT). Arguably, the most useful but perhaps least appreciated preventive intervention is simply the early diagnosis and rapid initiation of effective treatment of TB cases, thus reducing the infectious burden and reducing transmission. TB is unusual among infectious diseases, in that appropriate (and effective) treatment of the individual patient may be the most effective public health intervention to protect the population.

Vaccination: Natural and Acquired Immunity

BCG Vaccine

The most widely used vaccine in the world is BCG, which is given to about 100 million children annually. Isolated in 1908, following attenuation through 431 passages of a virulent *M. bovis* isolated from a human TB case, BCG was found to be protective to some extent in multiple animal models of TB. In its first human trial in 1921, it was found to protect a child heavily exposed in a household at high risk.

BCG has several advantages: it can be given at birth or at any time after birth; a single inoculation produces long-lasting skin test positivity to tuberculin; it is relatively stable; it produces a scar useful for epidemiological surveillance of access to immunization; and it is inexpensive.

Considerable evidence indicates that giving BCG to young children is effective at preventing tuberculous meningitis and disseminated (miliary) TB (Mangtani and others 2014; Rodrigues, Diwan, and Wheeler 1993). Random control trials and case control studies have shown consistently high protective efficacy of BCG against serious childhood forms of disease (73 percent), meningitis, and miliary TB (77 percent). The most complete analysis of the effect of BCG vaccine suggests that giving BCG to children born in 2002 prevented about 29,000 cases of childhood meningitis and 11,500 cases of miliary TB during the first five years of life or one case of meningitis for every 3,400 vaccinated children and one case of miliary TB for every 9,300 vaccinated children (Trunz, Fine, and Dye 2006). A recent report indicates that deferring BCG immunization to six weeks after birth generates stronger and longer-lasting specific Th1 cellular immune responses (Kagina and others 2009; Lutwama and others 2014). In some countries, children were repeatedly vaccinated over time, and there is some evidence from Taiwan, China, that multiple vaccinations may increase protection (Chan and others 2013). A worrisome drawback, however, is the incidence of disseminated BCG infection in HIV-positive children (Hesseling and others 2007).

Successful vaccines ideally prevent both infection and disease among persons exposed to the pathogen. While it is generally believed that BCG protects against disease rather than infection, recent findings, using Interferon-Gamma Release Assays (IGRAs) that can distinguish Mtb infection from BCG vaccination, suggest that BCG may protect to varying degrees against infection as well (Eisenhut and others 2009; Mangtani and others 2014; Soysal and others 2005).

The cost-effectiveness of BCG was estimated in 2006 to be between US$40 and US$170 per disability-adjusted life year (DALY), US$8,000 and US$11,000 per life saved, or US$5,000 and US$8,000 per case averted (Dye 2006), making it a very cost-effective intervention.

Despite positive evidence regarding the impact of BCG on children, BCG remains the most controversial of all currently used vaccines, because its protective efficacy has varied widely in different parts of the world, from 77 percent protection in adolescents in the United Kingdom (Sutherland and Springett 1987) to 0 percent protection in all age groups in South India (Bloom 1994; Mangtani and others 2014). Because young children represent only a minor contributor to TB transmission, BCG immunization of infants has only a relatively small impact on transmission within populations (Knight and others 2014). This finding is

borne out by outcomes in parts of Europe and North America that did not use BCG, where TB declined at rates that were not measurably different from those in regions that used the vaccine (Styblo 1991). In a recent analysis using South African data, Dye (2013) found that BCG vaccination would reduce TB in HIV-negative individuals by about 17 percent, to which would be added the value of preventing transmission to HIV-positive individuals. He estimated that revaccination with BCG would be highly cost-effective at all combinations of cost (US$1–US$10 per child) and efficacy (10–80 percent).

BCG immunization has also been shown to have extremely variable protective efficacy against adult TB in randomized trials and observational studies (Bloom and Fine 1994; Fine 1995; Mangtani and others 2014). Explanations for the variation remain unclear. Suggestions include the fact that BCG lacks more than 100 genes of Mtb, including some putative protective antigens; the genetic make-up of different human populations; the variable persistence of different BCG strains or preparations; and the interference by atypical mycobacteria in the environment. It was shown many years ago that guinea pigs immunized with different species of environmental atypical mycobacteria showed different degrees of protection against Mtb. Some, such as *M. kansasii,* were as effective as BCG in animals (Palmer and Long 1966). It is often forgotten that *M. microti,* a murine mycobacterium, was as effective as BCG in the British Medical Research Council human vaccine trials (Bloom and Fine 1994; Hart and Sutherland 1977). This suggests that, if exposure to environmental mycobacteria in a population provides some degree of protection, the effects of BCG observed in that population will be comparably less than in a naïve population. This could explain the large differences in BCG efficacy in populations living in different geographic locations (Weir and others 2006), where children in tropical latitudes show less protection (Mangtani and others 2014). For example, in the South India trial area, two-thirds of the individuals were positive to an *M. avium* purified protein derivative skin test by age 9 years and 97 percent were positive by ages 15–19 years (Tuberculosis Prevention Trial 1979). Understanding the degree of environmental exposure to nontuberculous mycobacteria will be important in planning and evaluating any new vaccines against TB.

A Rationale for Vaccines: Latent Infection Can Prevent Reinfection

It is widely believed that a protective vaccine is unlikely to be developed against TB because natural infection with Mtb is ineffective at preventing reinfection. However, there is a remarkable amount of epidemiologic evidence that, in fact, Mtb latent infection does indeed provide significant protection against reinfection by engendering protective immune responses that likely persist (reviewed by Andrews and others 2012). Early experiments of Heimbeck (1938) in Norwegian nurses and Sutherland, Svandova, and Radhakrishna (1982) found that, among healthy young individuals, being TST-positive provided up to 80 percent protection against reinfection (ranging from 45 to 81 percent in multiple studies) compared to being TST-negative. In a more recent study from South Africa where it was possible to measure infections in the apparently uninfected group and to observe cases of tuberculosis directly, the estimated immunological protection conferred by latent TB infection was 79 percent (Andrews and others 2012). These results encourage the view that new vaccines with better efficacy than BCG could provide relatively high levels of protection, if the protective immune responses generated are sustained over time, as is the case of latent TB.

Innate Immune Responses

The body's immune response is critical in protecting against infection and disease, through both innate and acquired immunity. This is perhaps best exemplified by the fact that, although only 10 percent of persons infected with TB develop disease in their lifetime, immune-compromised individuals have a risk of almost 10 percent *per year* (Selwyn and others 1989). Immunodeficient individuals, such as persons infected with HIV/AIDS (Gandhi and others 2006) or receiving anti-TNF immunotherapy for autoimmune diseases (Wolfe and others 2004), have a markedly increased incidence of TB. In immune-compromised HIV-positive patients in KwaZulu-Natal, the mean time from diagnosis to death from XDR or drug-resistant TB was an astonishing 16 days (Gandhi and others 2006). And the increased prevalence of drug-resistant TB in immune-compromised individuals is consistent with the view that the effectiveness of antibiotics depends to some extent on the antimicrobial immune response. It is intriguing that a population of healthy contacts exists in high-burden countries, who almost certainly have been exposed repeatedly to infection yet remain TST-negative, IGRA-negative, and apparently healthy. This suggests that mechanisms of innate immunity may have the ability to kill the relatively small numbers of infecting tubercle bacilli early after respiratory infection even before they can grow to numbers able to sensitize and expand T-cells able to respond to TB antigens. These mechanisms are currently not understood, and greater research is needed.

Preventive Therapy

There are two approaches to preventive therapy. For HIV-positive individuals at high risk for many opportunistic infections, cotrimoxazole is recommended routinely, and in high-burden countries between 50 and 87 percent of HIV-positive patients are receiving this preventive therapy (WHO 2015b).

The major approach to prevent development of TB in persons at high risk, particularly household contacts and HIV-positive individuals, is to screen them with a TST and, ideally, to offer persons found to be HIV-positive chemoprophylaxis, most commonly IPT, for a latent infection (Rangaka and others 2015). In perhaps the most dramatic studies, a community-based trial of IPT among BCG-unvaccinated Alaska Eskimos, a community with a high risk of infection, produced a 60 percent decline in TB incidence that lasted more than two decades in treated households (Comstock, Baum, and Snider 1979). Overall in an analysis of randomized controlled trials, preventive therapy has clear benefits. In 2011, the WHO began recommending that HIV-positive individuals free of symptoms suggestive of tuberculosis receive treatment with IPT for at least six months (WHO 2011a). The risk of clinically active TB disease is reduced 60 percent in immunocompetent, HIV-negative individuals (Smieja and others 2000) and 32–62 percent in HIV-positive adults who are treated with preventive therapy lasting 3 to 12 months (Akolo and others 2010). Since these guidelines came into force, the number of HIV-positive people receiving IPT has increased sharply, rising to approximately 933,000 in 2014 (WHO 2015b). The high risk of TB among persons co-infected with *M. tuberculosis* and HIV/AIDS motivates those encouraging wider use of preventive therapy, especially in Africa (Stop TB Partnership 2011), but questions have been raised about the methods of screening to ensure that the persons most likely to benefit receive this treatment (Lawn and others 2012) and that the persons with subclinical TB are not inadvertently treated with isoniazid monotherapy that could lead to resistance. Studies among child contacts of active cases have demonstrated that giving isoniazid daily for 12 months provides 30–60 percent protection against active TB (Ayieko and others 2014). Recent work suggests that isoniazid can be continued for longer than six months in HIV-positive adults with minimal adverse effects and longer protection (den Boon and others 2016).

At a population level, a randomized trial in high-incidence urban communities in Brazil found that TB incidence was 15 percent lower in intervention than in nonintervention communities after five years (Cavalcante and others 2010). Yet IPT is not widely used. Of the highest-burden countries, only Brazil and South Africa have policies to scale up the use of IPT. Even with the resources available in the United States, the implementation of contact tracing and IPT has fallen short of recommendations (Lee and others 2006). In trials of IPT in high-burden countries, protection of TST-positive adults infected with HIV/AIDS averaged about 60 percent, but the effects were lost soon after the IPT treatment ended, and there was little or no impact on mortality (Churchyard and others 2012; Samandari and others 2011). By contrast, IPT was shown to reduce both TB incidence and mortality among HIV-positive children (Zar and others 2007). A randomized controlled trial, the Temprano study, compared early versus later treatment with ART and early versus later treatment with IPT and various combinations in 2,050 HIV-positive individuals with high CD4+ counts in Côte d'Ivoire. The results showed that six months of IPT resulted in a 44 percent lower risk of severe HIV/AIDS-related illness and a 35 percent lower risk of death from any cause than the risks with deferred initiation of ART and no IPT and that the combination reduced TB by 73 percent (Temprano ARNS Study Group 2015). Use of IPT for six months reduced the incidence of TB in Brazil not only for the duration of treatment but over a seven-year follow-up (Golub and others 2015). The strong inference from this work is that the combination of early initiation of both ART and IPT in HIV-positive individuals, now adopted by the WHO, should become the norm in HIV/AIDS and TB control.

Real challenges are associated with the use of IPT: active disease must be excluded, where practical by radiography, before isoniazid is taken alone, and adherence to six or more months of daily treatment tends to be poor among healthy people. Even in the United States, fewer than 50 percent of individuals who initiated IPT completed six months of treatment (Hirsch-Moverman and others 2015). Adverse effects include a risk of hepatitis, especially in persons co-infected with HIV/AIDS (Ayles and Muyoyeta 2006), if IPT is administered for long periods of time. In the United States, adverse effects are on the order of 1 percent but rise to 4 percent if IPT is given with rifapentine (Getahun and others 2015). A recent cluster randomized trial of mass screening and IPT was carried out for tuberculosis control among gold miners in multiple mines in Thibela in South Africa, a community known to be at high risk for TB. Miners were given IPT for 9 months, and the effect on prevention of disease was followed for 12 months. Despite the positive effect of isoniazid in preventing

tuberculosis during the period of treatment, IPT had no significant sustained impact on TB control in South African gold mines (Churchyard and others 2014). Most discouraging, the results of a systematic review and meta-analysis of the cascade of care in latent TB indicated that completion of preventive treatment was only 19 percent (Alsdurf and others 2016).

It remains unclear, other than in the case of HIV-positive individuals and child household contacts, how feasible and cost-effective IPT scale-up would be in high-burden countries. It has been a challenge for health systems in LMICs, which are finding it difficult to provide treatment for diagnosed TB patients and to maintain IPT for healthy contacts. A recent approach to shortening preventive therapy derives from studies of a combination of long-acting rifapentine plus isoniazid, which reduced the time of treatment from nine to three months and was better tolerated, if more expensive (Sterling and others 2011).

The critical question of the best preventive therapy with which to combat MDR TB remains unsettled. The significant adverse effects of MDR TB regimens are a serious trade-off against prevention of the 10 percent of cases likely to result from preventive treatment, and no optimal regimen using newer drugs has been established (Moore 2016). The alternative is registering all such contacts, monitoring them carefully, and instituting treatment at the earliest sign of disease.

It may not be altogether fanciful to imagine, with advances in research, that more effective drug regimens for latent infection could have a profound effect on reducing the global burden of TB. It is unknown what proportion of the one-third of people on the planet exhibiting positive TST retain viable tubercle bacilli capable of reactivating and transmitting disease. But, if a practical drug regimen could sterilize the infection in all of these individuals, this enormous reservoir of the pathogen could be eliminated in a short period of time. Rather than passively detecting patients with disease, screening populations for persons who were infected as determined by tuberculin positivity and applying the hoped-for effective mycobactericidal regimen, the great burden of latent TB could conceivably be reduced or eliminated. This approach should be considered in future research.

Impact of Effective Treatment on Transmission

Of the interventions available to control transmission, it has long been taught that effective treatment ranks highest. Treatment can be applied only to known or suspected cases, and, to be effective, requires knowledge of drug resistance. It has traditionally been thought that, for drug-susceptible TB, at least two weeks of effective treatment are required to reduce the risk of transmission substantially, regardless of sputum smear status (Rouillon, Perdrizet, and Parrot 1976). For drug-resistant TB, however, the two-week rule appeared to have failed as a policy during the outbreaks in New York City and Miami in the 1980s and 1990s, when patients with unsuspected drug resistance on conventional four-drug therapy transmitted their infection after isolation ended (Coronado and others 1993). Therefore, current guidelines generally recommend isolating MDR TB patients until smear or culture conversion.

The rate at which treatment renders tuberculosis cases noninfectious was recently reexamined, employing the classic model of transmission from humans to guinea pigs, wherein TB transmission was established by passing exhaust air from the ward past a panel of guinea pigs highly susceptible to TB (Dharmadhikari and others 2014). The study suggested that, like drug-susceptible TB, MDR TB transmission also responds rapidly to effective treatment, well before sputum smear or culture conversion (Dharmadhikari and others 2014). In a series of five exposure studies where mostly smear-positive, coughing patients with confirmed MDR TB were admitted and promptly started on therapy, transmission to guinea pigs appears to have occurred predominantly from patients with unsuspected XDR TB who were not responsive to effective treatment.

Infection Control of TB Transmission in Congregate Settings

Transmission and reinfection, especially of drug-resistant strains, is a key driver of the global TB epidemic (Wood, Lawn, Caldwell, and others 2011; Wood, Lawn, Johnstone-Robertson, and others 2011). The benefit of isoniazid prophylaxis in high-risk HIV-positive populations, for example, has been rapidly reversed by ongoing transmission and reinfection soon after isoniazid is stopped (Samandari and others 2011). Likewise, the challenge in high-transmission settings is to provide greater protection against reinfection than is currently provided by BCG immunization at birth as well as subsequent natural exposure to Mtb and environmental mycobacteria (Tameris and others 2013).

Transmission control was not specifically mentioned in the original Global Plan to Stop TB 2006–15, but the mostly hospital-based outbreak of XDR TB in 2006 dramatically called attention to the problem (Gandhi and others 2006). Since then, control efforts have centered on health care facilities, although it is widely understood that transmission also occurs in homes, schools, churches, shelters, refugee camps, and correctional facilities, among other congregate settings (WHO 2009b).

Still, because they specifically bring together infectious and vulnerable persons, health care facilities dominate the list of environments that amplify transmission at the population level.

Hospitals as Epicenters of Transmission

One key epicenter of transmission is hospitals where TB patients reside. Because hospital exposure is better documented than many other congregate interactions, there is a likely bias toward indicting hospitals, but it is also likely that hospital transmission is underestimated, for example, by not counting infecting strains for which DNA fingerprints are not available.

The significant reduction of the TB epidemic in New York City from 3,800 cases in the 1980s to 577 in 2015 indicates that multifaceted efforts are needed in large urban multicultural environments with large numbers of visitors, migrants, and homeless people and increasing rates of HIV/AIDS.[3] Clearly DOT was helpful in ensuring compliance in a portion of TB patients, but perhaps more significant was the major effort to institute infection control in hospitals, prisons, shelters, and congregate housing facilities (Frieden and others 1995).

Using network analysis, Gandhi and others (2013) concluded that most strain-specific XDR TB transmission in KwaZulu-Natal occurred in hospitals due to prolonged stay, congregate settings, and delayed recognition of drug resistance. Transmission patterns are similar as far away as Tomsk Oblast, Siberia. A retrospective study of the causes of drug resistance in the Tomsk Oblast showed a greater than sixfold higher risk among treatment-adherent patients hospitalized for drug-susceptible TB than among patients not hospitalized (Gelmanova and others 2007). Anyone familiar with treatment practices common to Eastern Europe will understand why this might occur. Although Tomsk predominantly uses ambulatory treatment for new TB cases, hospitalized patients are admitted to poorly ventilated, multibed rooms, tightly sealed against the cold. Drug susceptibility is normally only tested when patients fail to respond to first-line treatment, usually following months of ineffective treatment. Drug susceptibility testing by conventional methods requires additional months. During this prolonged period of ineffective treatment, there is ample opportunity for transmission and reinfection. This scenario is not unique to Tomsk, as delays in drug-susceptibility testing occur in most TB programs where laboratory services are inadequate. Treatment failure is the usual indication for drug-susceptibility testing, and molecular methods are only slowly reducing the time required for results on first-line and, much less often, second-line drugs. However, despite hospital transmission, ambulatory treatment is highly effective, and Tomsk is among the few high-burden places in the world where MDR TB rates may be declining (WHO 2010).

Principles of TB Transmission Control

Since the 1985–92 resurgence of TB in the United States and several European settings, where institutional transmission played an important role, a three-tiered hierarchical approach has been adopted, based on a paradigm used in industry: administrative controls, engineering (or environmental) controls, and personal protection (respirators). Administrative controls entail the rapid diagnosis of symptomatic, potentially infectious cases and drug resistance and the prompt initiation of effective therapy. This has recently been promoted under the acronym, FAST (Find cases Actively by cough surveillance, Separate temporarily, and Treat effectively), as a way to communicate the key components and facilitate adoption. Environmental controls have focused on natural and mechanical ventilation and on the evolving technology of sustainable ultraviolet germicidal (UVGI) air disinfection. Personal respiratory protection is the last tier of protection, assuming incomplete protection from administrative and engineering controls. Ironically, although the last tier of protection, respirators are often the only protection available to health care workers, cannot be worn continuously, and are unlikely to be worn when treating a patient with unsuspected TB.

Measures of the Efficacy of TB Transmission Control

Measuring the efficacy of transmission control interventions has been elusive. Among process indicators are questions regarding whether windows are open or respirators are available, although these factors may be tied too loosely to exposure to be useful. However, to the extent that undiagnosed TB patients and undiagnosed drug resistance are key exposure factors, process indicators tied to unprotected exposure time can be measured and reported. Institutions can document, for example, the percentage of admissions that are screened for cough and had sputum sent to a lab; the turnaround time from submission until results are obtained; and the time from admission until the onset of effective treatment based on drug-sensitivity testing. Such measures should become routine in hospitals with access to rapid diagnostic tests.

Few studies have been conducted not only of the efficacy of TB infection control methods, but also of their cost. Apart from the great difficulty of measuring the efficacy of interventions to prevent transmission, isolating the costs of infection control activities can be challenging, as many infection control interventions are integral to hospital functions more generally. Assuming the presence of unsuspected, untreated patients in the

hospital, ventilation is a key intervention, and natural ventilation ranks high among recommendations in suitable climates. The added cost of designing and constructing a naturally ventilated patient waiting area is difficult to separate from the routine capital costs of hospitals. Some insights can be gleaned from unpublished data from a high-risk setting in Vladimir, Russia, a training center of excellence in TB control (box 11.4).

Cost-Effective Air Disinfection

Natural ventilation alone does not provide adequate ventilation for airborne infection control in many settings. However, mechanical ventilation systems are often prohibitively expensive and often fail due to lack of maintenance. Room air cleaners (with filters, UVGI, or both) are often sold to hospital administrators as a simple, inexpensive fix, but they rarely move enough air to achieve the 12 or more equivalent air changes per hour recommended to control airborne infections. Reentrapment and recirculation of the same air through the device (short-circuiting) also lead to low rates of effective clean air delivery.

As noted in the Vladimir study, upper-room germicidal UVGI (with room air-mixing fans) is among the most effective and least expensive ways to achieve high-volume air disinfection. Hospital studies have shown 70–80 percent efficacy. But like mechanical ventilation and room air cleaners, caution is required. Although they are under development, international standards and guidelines for safe and effective application and maintenance are not widely available. No agency currently regulates this small industry, and few experts are qualified to plan installations. Still, as back-up technology for natural ventilation, they are a logical choice. Low-velocity ceiling fans are recommended to assure essential room air mixing. With the development of LED (light-emitting diode) UVGI, the prospect of solar-powered systems with battery back-up may make upper-room germicidal UVGI more sustainable in the near future.

Masks and Respirators

Assuming incomplete efficacy of both source control and engineering or environmental control strategies, the last-tier intervention is respiratory protection—that is, use of a device designed to exclude infectious droplet nuclei from inhaled air.

Masks and respirators are easily confused. Surgical masks are designed to protect the environment by blocking the aerosolization of some portion of exhaled respiratory droplets and droplet nuclei, but they do not adequately protect the wearer and have a limited role in TB transmission control when worn short-term by patients. MDR TB patients wearing masks were 53 percent less likely to infect guinea pigs breathing exhaust air from the ward (Dharmadhikari and others 2012). Recently, using the same transmission model in South Africa, Mphaphlele and others (2015) tested the efficacy of several control interventions in preventing transmission from patients in hospital rooms to guinea pigs. The study confirmed the previous report and showed 70–80 percent efficacy of upper-room UVGI air disinfection.

Box 11.4

Real Costs of Infection Control in Vladimir Oblast TB Dispensary, Russia

Costs for high-level infection control are difficult to obtain. The TB Dispensary, with assistance from the Centers for Disease Control and Prevention, has over the past decade painstakingly introduced and studied the impact of a variety of conventional and novel TB infection control interventions in Vladimir Oblast, an area with high rates of TB and drug resistance. For the entire Vladimir region (population 1.5 million), accurate estimates of annual cost are US$350 for health care worker training; US$12,000 for ventilation system maintenance; US$10,000 for respirators; US$300 for respirator fit testing; and US$3,000 for health care worker screening. For the multistory hospital, with floor area of 17,000 cubic meters, the capital cost of a new, high-capacity ventilation system with negative-pressure isolation rooms was US$345,000, and the cost of maintenance was US$4,425 per year. Of three ventilation systems studied, the upper-room UVGI system was the least expensive intervention, at US$14 per equivalent-room air change, more than nine times more cost-effective than expensive mechanical systems per equivalent-room air change.

In contrast, respirators are designed to protect the wearer. Properly fitted, certified N-95 (or equivalent) respirators can be 85–90 percent protective. However, as an intervention, respiratory protection often fails either because the face seal leaks due to improper fit or adjustment or, more important, because the masks are not worn consistently. The cost of respirator programs is easily assessed, but their effectiveness is not.

Lessons for Household Transmission

Since TB is transmitted largely by aerosol droplets, transmission is affected by the built household environment. One study from South Africa found evidence that transmission of infection was greater, as determined by DNA fingerprinting of the strains, in modern-built brick housing with windows than in older shacks (Wood and others 2010). The reason may be that residents in modern housing kept windows closed in an effort to maintain cleanliness, whereas shacks simply had more ventilation. Another study measured the effects of increasing natural ventilation in traditional housing and demonstrated that natural ventilation was facilitated by opening doors and windows and extrapolated that such a change could potentially reduce the risk of household transmission by 80 percent (Lygizos and others 2013).

TURNING THE TIDE AGAINST TB

Despite the progress made in TB control over the past two decades, serious gaps persist. Although TB can be treated and cured, it is still one of the deadliest infectious diseases in the world today.

Three key elements are needed to achieve effective TB control and to meet the Sustainable Development Goals: (1) early and accurate diagnosis and drug-sensitivity testing, (2) patient access to and completion of effective treatment, and (3) prevention of progression from latent infection to disease. Obviously, these categories are not distinct; each affects and is related to the others, and all face both technical and system challenges. Without greater effectiveness of these key elements, it will not be possible to bend the curve and dramatically reduce transmission and incidence rates in all countries. Turning the tide against TB therefore requires investing in new technologies—diagnostics, treatment regimens, and vaccines—and tackling the system and strategic challenges that influence the degree to which technological advances reach the people who need them and translate into better heath.

Earlier Diagnosis: Toward Active Case Finding

Limitations of Passive Case Finding

Even with modern technology, effective case detection in resource-poor communities with weak health systems has been difficult to introduce (Kranzer and others 2010; Kranzer and others 2013). The principal paradigm for diagnosing cases of TB is passive case finding, which depends on the TB-infected individual seeking medical care. But passive case finding faces many challenges. TB is most prevalent in marginalized communities that are less visible to conventional health systems. Patients are typically poor, from disadvantaged groups, prone to other diseases such as HIV/AIDS and diabetes that increase their vulnerability to TB, and often migrants. Even when symptoms are present, in many countries, up to a third of TB patients either fail to seek treatment or do so from traditional healers before seeking medical treatment, leading to more severe illness, delayed treatment, and increased transmission (Brouwer and others 1998; Sreeramareddy and others 2014).

TB control is premised fundamentally on the assumption that, if active TB cases are identified and treated, transmission will be diminished and ultimately interrupted. The issue of unsuspected cases is, however, a serious problem that has received very little attention. Traditional guidelines tend to focus on known or suspected cases with classic symptoms and active disease. However, some forms of TB, such as asymptomatic and chronic tuberculosis, do not present with clinical symptoms for months or years and can transmit infection over extended periods of time.

Evidence strongly indicates that the problem of unsuspected or asymptomatic cases of TB and unsuspected cases of drug resistance is significant, contributing to the one-third of TB patients being "unknown to the health system." These patients are capable of transmitting disease but not ill enough to seek care or to be detected by passive case finding. In a teaching hospital in Lusaka, Zambia, for example, 900 newly admitted patients (70.6 percent HIV-positive) who were able to produce sputum without induction were screened. Testing by fluorescent microscopy and automated liquid culture detected TB in 22 percent of patients, of which 13.4 percent were unsuspected (Bates and others 2012). This number included 18 MDR TB cases, 5 of which were unsuspected. In the same hospital, 94 patients with cough, who were admitted primarily for obstetric or gynecological indications (73.4 percent HIV-positive), had sputum processed in the same way; in addition, Xpert MTB/RIF was used for rapid diagnosis (Friedich and others 2013). TB was diagnosed in 28 percent of the

94 sputum specimens, of which the Xpert device detected 80.8 percent compared to 50 percent by standard smear microscopy. Results of this kind are not new: similar results were reported more than a decade ago in a low-HIV/AIDS setting in Lima, Peru, where 250 of 349 consecutive new admissions to a female general medical ward were screened for TB by sputum smear, culture, and radiographs. Of these, 16 percent had culture-proven TB, one-third of which were unsuspected, including 6 unsuspected MDR cases (Willingham and others 2001).

The DOTS strategy in high-burden countries, even when implemented more effectively, will simply not be sufficient to overcome the challenge of unsuspected cases or drug resistance. In a groundbreaking population-based active case finding survey of HIV/AIDS and TB in Sub-Saharan Africa, where the population has a 23 percent prevalence of HIV/AIDS infection, Wood and others (2007) found that, despite a highly effective DOTS TB control program with high rates of compliance, 63 percent of adult cases with pulmonary TB were not known to the health system. Among HIV-negative individuals, passive case finding identified 67 percent of prevalent smear-positive cases, the target recognized for adequate DOTS implementation. But among individuals with HIV/AIDS infection, passive case finding identified only 33 percent of those with smear-positive TB.

Similar findings were obtained in a large survey of 47,000 individuals in Cambodia, in which 12 percent of individuals were examined clinically and sputa were tested by smear and by culture. Only one-third of TB cases were detected by sputum smears. Importantly, 44 percent of the sputum-positive cases and 23 percent of the smear-negative culture-positive cases exhibited none of the signs of clinical tuberculosis (Mao and others 2014). A surprising demographic finding was that people over age 50 years accounted for more than half of all detected infections, a trend evident in other Asian countries.

Clearly, in many parts of the world where the burden of TB is low and control programs have been effective, the need for active case finding is not great, and cost-effectiveness would argue against recommending it. However, in high-burden communities, passive case finding fails to detect early and asymptomatic cases, leaving a third of TB patients not known to the health system.

Active Case Finding: What Does the Evidence Show?

Active case finding—mass screening and surveillance—almost certainly contributed to the rapid decline of TB in European countries and the Americas (5–8 percent a year) following World War II—that is, prior to the introduction of antibiotics (Dye 2015; Golub and others 2005). In 1974, the WHO recommended discontinuing active case finding with radiography, since it was no longer necessary or cost-effective in populations with low prevalence of TB and good access to high-quality health care, particularly in HICs. The WHO reiterated this policy in 2014, again finding that it would not be cost-effective, and recommended that indiscriminate mass screening be avoided (WHO 2013c). However, it did recommend systematic screening for active TB in geographically defined subpopulations with extremely high levels of undetected TB (1 percent prevalence or higher). Regrettably, this WHO recommendation has not been sufficiently emphasized to stimulate countries and donors to initiate and support active case finding in high-burden countries or to have an impact on transmission in those countries.

One strategy for active case finding has been to use X-radiography, particularly mobile X-ray units, to detect lung lesions with computer-assisted detection in people who are relatively asymptomatic (Melendez and others 2016; Philipsen and others 2015). This strategy is able to detect many more patients with infection than is possible through passive case finding, screening for coughs, or self-reporting. In South Africa, for example, the only period in which incidence of TB cases declined occurred between 1950 and 1975, when X-ray surveillance captured about 10 percent of the population annually (R. Wood, personal communication). While in Europe and North America TB control programs dramatically reduced the annual risk of infection in successive cohorts (Cauthen, Pio, and ten Dam 2002), such a decline has not occurred in countries with high prevalence of TB and HIV/AIDS (Kritzinger and others 2009).

In recent studies in Kenya, abnormal chest radiography had high sensitivity (94 percent) and reasonable specificity (73 percent) for detecting tuberculosis (van't Hoog and others 2012). Radiography represents a potentially valuable population-based screen to determine which individuals should have their sputum tested by culture or by an Xpert device for definitive diagnosis. With rapid technical developments, computerized reading of X-radiograms could allow high-throughput screening of larger numbers of individuals in a cost-effective way (see box 11.5). This is particularly true when combined with clinical symptoms, where it was found that a sensitivity of 95 percent and negative predictive value of 98 percent could be achieved. (Melendez and others 2016).

Active Case Finding in Targeted Regions

In many LMICs, patients with TB often seek care from one or more traditional providers before seeking

Box 11.5

Undetected Cases in Hospitals: The Case of FAST

TB infection control needs to focus on prompt screening of admitted patients with chronic cough. This concept has been formulated into a transmission control strategy called FAST (Find cases Actively by cough surveillance, Separate temporarily, and Treat effectively).

Several pilot FAST projects have begun around the world, including in Bangladesh and Russia. In a TB hospital in Veronesh, Russia, of almost 1,000 patients hospitalized with suspected pulmonary TB, 93.5 percent were tested by Xpert MTB/RIF within two days of admission. Of these, 407 were positive, and 161 were rifampin-resistant, of whom 159 received MDR TB treatment within three working days of receiving the result. Under normal operating conditions, treatment failure would have been identified months after admission, and drug-susceptibility testing would have taken several more months, during which time, other patients and staff would have been exposed. FAST, in other words, was a dramatic improvement from the status quo.

Similar results are being obtained in a pilot study at the National Institute of Diseases of the Chest Hospital (NIDCH), a 680-bed facility in Dhaka, Bangladesh. Because respiratory symptoms are common in patients admitted to NIDCH, a decision was made to conduct universal sputum sampling. Of the TB cases identified, 13 percent were unsuspected and an additional 1.3 percent were infected with MDR TB. Diagnoses were available within one to two days of collection, and treatment was initiated within one day of a confirmed diagnosis.

medically appropriate care (Satyanarayana and others 2011). Even symptomatic surveillance for classic signs of TB—cough, fever, and weight loss—fails to detect a substantial number of cases, especially in persons who are HIV-positive (Corbett and others 2010).

In cluster randomized trials in Brazil, intensified case finding had a significant impact on reducing TB (Cavalcante and others 2010). The WHO commissioned several studies on the effectiveness and acceptability of active case finding or systematic screening of active TB (WHO 2013d). The studies reported that active case finding was highly acceptable to populations in Sub-Saharan Africa.

In a recent review of undiagnosed TB that would not be found by passive case finding, Yuen and others (2015) found that it is precisely in high-risk populations, as well as in persons infected with HIV/AIDS, where intensive case finding and early initiation of treatment or preventive therapy would likely have the greatest impact for the fewest resources.

In another study in South Africa (Shapiro and others 2012), a group of 2,800 individuals in households with a detected TB index case were enrolled to determine community prevalence of undetected TB and HIV/AIDS. Field teams screened participants for TB symptoms, collected sputum specimens for smear microscopy and culture, and provided HIV/AIDS counseling and testing. They found that 6,075 per 100,000 of the household contacts were sputum-positive compared with 477 residents of random households without an index case. This finding demonstrated the value of screening contacts of index cases in a high-burden area and cautioned against random screening of total populations. Of the 169 previously unidentified cases with TB detected by culture, only 6 percent were found to be sputum-positive, and only 11 percent were symptomatic; the remaining 89 percent would not have been diagnosed with passive case finding.

However, the evidence is mixed. In a large, complex community randomized trial, the Zamstar study (Ayles and others 2013), 64,000 individuals in Zambia and the Western Cape, South Africa, were surveyed for TB symptoms, sputa were taken for identifying individuals with disease, and one arm employed enhanced household active case finding with counseling. Clearly, screening households with index cases revealed a greater number of TB cases. The adjusted ratio for prevalence and the adjusted ratio for incidence did not differ significantly for the enhanced case finding versus usual practice or for the household versus nonhousehold groups. The study identified no evidence that enhanced case finding had an effect on the burden of tuberculosis at the community level. However, despite not reaching

statistical significance, the findings suggested that the household intervention did reduce the burden of tuberculosis in these communities.

A meta-analysis of controlled studies found that screening increased the number of cases found in the short term and tended to find cases earlier and with less severe disease (Kranzer and others 2013). Treatment outcomes among people identified through screening were similar to outcomes among people identified through passive case finding. Once again, this analysis confirmed that, in many settings, more than half of the prevalent TB cases remain undiagnosed.

A recent transmission modeling study of TB in South Africa suggested that the current DOTS approach of passive case finding is unlikely to permit the country to reach the WHO targets for 2050. The model predicts that interventions such as active case finding, with early initiation of treatment and reduction of pretreatment loss to follow-up, could have a large impact (Knight and others 2015). Thus, defining the high-burden target populations where active case finding is likely to be most effective is an important analysis to be undertaken.

Although most official data on TB incidence and prevalence are estimated for entire countries, a recent innovative epidemiological approach asked whether high-burden regions within countries—TB hot spots—might lend themselves to targeted control efforts. Such hot spots have been identified in a few countries, such as Moldova, and it will be of interest to learn whether targeted control efforts can improve their effectiveness at lower cost than the usual countrywide programs (Dowdy and others 2012; Jenkins and others 2013; Manjourides and others 2012; Zelner and others 2016). These population experiments for TB control need to be supported and evaluated.

We therefore recommend identifying countries and high-risk populations that are not responding effectively to the standard DOTS strategy and designing targeted active case finding interventions that could have a greater impact on earlier case detection and successful treatment.

Initiating active case finding interventions in high-burden countries will clearly require external financial assistance. Nevertheless, given the limitations of current tools and increasing threat of MDR TB, active case finding may be the best strategy for reducing incidence and prevalence in the long run in high-burden areas. And although active case finding is more expensive than passive case finding, added costs will be more than offset by the diagnostic and treatment costs averted—that is, TB transmitted in the hospital and in the community by unsuspected cases, especially MDR TB cases. The questions of how much screening, in what places, and at what cost need to be answered if we are to avert each additional case of drug-susceptible or MDR TB. If interrupting transmission and reducing incidence more rapidly is the goal, the evidence suggests that active case finding targeted to high-burden areas can make a difference.

Community-Based, Integrated Delivery of TB Care

Service delivery—from screening and diagnosing patients to administering treatment and monitoring progress—is a key challenge in TB control, as with other health care services (Farmer 2013; Kim, Farmer, and Porter 2013).

Dominance (and Costs) of Hospital-Based Care

The costs of health service delivery are the largest cost of tuberculosis control. While the mean costs of diagnostics and tests do not vary significantly across income groups, the costs of drugs and hospitalization do (Laurence, Griffiths, and Vassall 2015), particularly the costs of treatment (WHO 2013b, 2014b, 2016a). For example, the costs per patient of drug-sensitive TB treatment were US$14,659 in HICs, US$840 in upper-middle-income countries, US$273 in lower-middle-income countries, and US$258 in LICs, with strong positive correlation with income (Laurence, Griffiths, and Vassall 2015). However, the mean costs of treating drug-susceptible TB were highly variable in countries at the same income level (Floyd and others 2013; Laurence, Griffiths, and Vassall 2015).

Hospitalization accounts for an average of 74 percent of all drug-susceptible TB costs (although this varies widely between individual studies) and 64 percent of all MDR TB costs. Conversely, mean costs of outpatient treatment were 12 times less than hospitalization costs, accounting for 6 percent of total costs. In one study, in the LMIC group, India consistently had the lowest costs for hospitalization and Ukraine had the highest costs for hospitalization and outpatient care (Laurence, Griffiths, and Vassall 2015). In Ukraine, high hospitalization costs, where patients also incurred costs, led to treatment default (Vassall and others 2009). In 2013, in countries with a high burden of TB and MDR TB (excluding China and Russia), almost 38 percent of funding (US$919 million) was allocated to hospital inpatient and hospital outpatient care of drug-susceptible TB (WHO 2013b). In addition, in 2013 Russia spent US$1.6 billion on TB control, most of which went toward hospital-based TB care (Atun, Samyshkin, and others 2006). However, funding allocated to neglected high-transmission areas, such as prisons, remains woefully low (Lee and others 2012).

Efficient and effective delivery of health services for TB is critical for improving TB outcomes globally. Yet, the delivery of TB services is inefficient and ineffective due to the high reliance on hospital services and the vertical delivery of DOTS (Atun, Samyshkin, and others 2006; Atun, Weil, and others 2010; Samb and others 2009). For example, from 2008 to 2010 in most of the world's 22 high-burden countries, the average cost of treating a patient with drug-susceptible TB was US$100–US$500. However, the average costs varied from US$100 to US$10,000 when Russia (a hospital-based service delivery model) was included (Floyd and others 2013).

In 2014, in most of the 22 high-burden countries for drug-susceptible TB, the WHO estimated that the share of hospital inpatient and outpatient costs ranged from 30 to 60 percent, with durations of stay ranging from 5 to 56 days (WHO 2014b). In the 22 high-burden TB countries, the costs of hospital inpatient and outpatient care for managing drug-susceptible TB as a proportion of the national TB program budget were 1–10 percent in the Democratic Republic of Congo, Ethiopia, Tanzania, Thailand, and Uganda; 11–20 percent in Bangladesh, Kenya, Myanmar, and Pakistan; and in excess of 40 percent in India (46 percent), Mozambique (51.8 percent), and Vietnam (74.2 percent) (WHO 2013b). While the WHO report did not have data for China and Russia, earlier studies suggested that, in Russia, where drug-susceptible TB is treated predominantly in hospitals, patients are kept under observation long after treatment completion; as a result, hospital inpatient costs account for around 60 percent of the total costs of treatment (Atun, Samyshkin, and others 2006). It is difficult to understand why China has shifted most TB care from outpatient to hospital-based care.

In South Africa, which has the second-highest number of confirmed cases of MDR TB (WHO 2011b) and the highest number of confirmed cases of XDR TB, MDR TB accounts for only 3.5 percent of the TB disease burden, but absorbs almost half of the US$218 million national TB program budget (WHO 2011c). Patients with MDR TB are hospitalized from the initiation of treatment until culture conversion, and the cost per patient of treating MDR TB was US$17,164, more than 40 times the cost of treating drug-susceptible TB (Schnippel and others 2013), which was estimated to be US$314–US$392 for community-based treatment (Sinanovic and others 2003). Around 95 percent of these costs were hospitalization costs (Schnippel and others 2013). More recent studies in South Africa have put the cost of inpatient treatment of MDR TB at US$6,772 (compared with treatment of drug-susceptible TB at US$256), with estimates suggesting that 45 percent of total costs are hospitalization costs (Pooran and others 2013).

The cost situation in South Africa is similar to that observed in countries where drug-susceptible and MDR TB are treated as inpatient care, such as Estonia (US$10,880) and Russia (Tomsk region, US$14,657). These high costs contrast with the lower costs recorded in countries where MDR TB is managed in outpatient clinics and at home—for example, Peru (US$2,423) and the Philippines (US$3,613). In Estonia and Russia, hospital costs accounted for 43 and 52 percent, respectively, of the total cost of treating an MDR TB patient (Fitzpatrick and Floyd 2012). Estimates suggest that the global average cost per patient of treating MDR TB is US$13,259 (5th–95th percentiles US$2,797–US$42,040) using an outpatient model and US$34,599 (5th–95th percentiles US$6,959–US$109,154) using an inpatient model (Fitzpatrick and Floyd 2012).

High hospital costs crowd out funding for cost-effective interventions, such as those aimed at addressing the social determinants of health, as well as new diagnostics and medicines that could be delivered in the community or in primary care settings.

Worldwide, there is substantial variation in the cost of treating patients using DOTS. Among the 22 high-burden countries, the cost per successfully treated patient varies from less than US$100 to more than US$10,000 for a standardized treatment. Even in countries with similar per capita income levels, the cost per successfully treated patient varies 50-fold (Floyd and others 2013). According to recent cost-effectiveness studies, the cost of treating one MDR TB case ranges from nearly US$15,000 in a hospital-based program in Tomsk, Siberia, to US$2,400 in a community-based program in Lima, Peru (Fitzpatrick and Floyd 2012).

The failure to prioritize MDR TB adequately or to achieve adequate cure rates is a major problem exemplified by the situation in two large countries. In India, the MDR TB cure rate is about 11 percent (Subbaraman and others 2016). In China, only about 5 percent of MDR patients are being treated, and the policy is formulated entirely around hospital-based treatment, with high relapse rates after discharge (Zhao and others 2012).

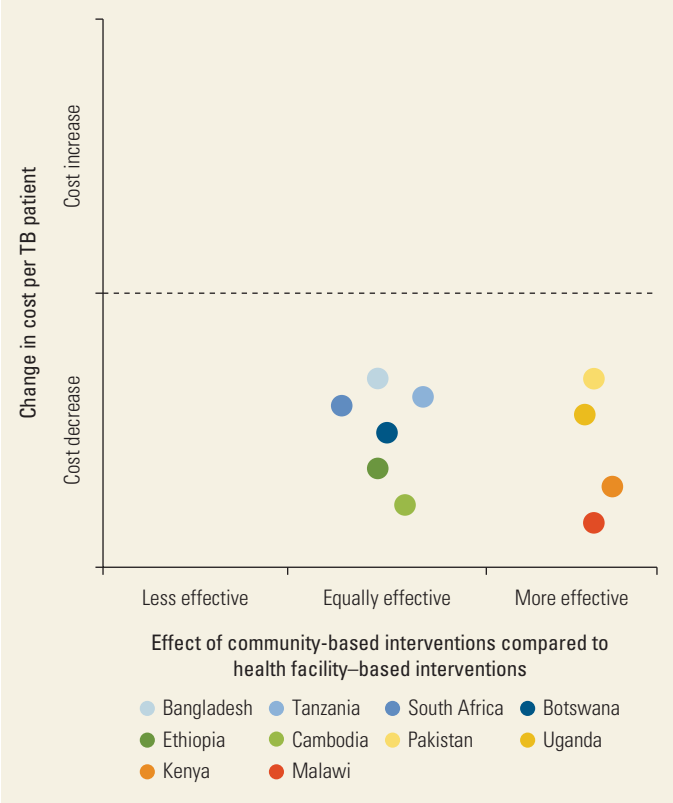
Efficiency and Effectiveness of Community-Based TB Treatment

A great deal of evidence points to the effectiveness of transitioning hospital-based TB care to primary health care settings (Edginton 1999) and to community-based models (Ayles and others 2013; Binagwaho 2013; Cavalcante and others 2007; Cavalcante and others 2010; Corbett and others 2010; Islam and others 2002; Shapiro and others 2012), even for management of MDR TB (Fitzpatrick and Floyd 2012; Furin and others 2011; Heller and others 2010; Luyirika and others 2012;

Mitnick and others 2003; Mukherjee and others 2002; Nathanson and others 2006; Seung and others 2009; Smart 2010). In addition to clinical effectiveness and improved outcomes, community-based models appear to be more acceptable to patients (Horter and others 2014).

A recent community-based model for providing TB treatment was developed in Bangladesh by BRAC, the world's largest NGO (Islam and others 2002; Islam and others 2011). Individuals diagnosed with tuberculosis are given free treatment but asked to provide a small bond, equivalent to about US$3.25, to assure that they will complete treatment. Upon successful completion of treatment, the funds are returned. The treatment cost per patient was US$312 in 2010. For patients unable to afford the bond, the community acts as underwriter, which establishes a social incentive to complete treatment. Program cure rates are up to 92 percent, which is comparable to a government-run program, yet the costs of the community-based program are half those of a public program (Islam and others 2002).

Figure 11.5 Cost-Effectiveness of Community-Based Interventions Compared to Health Facility–Based Interventions for Tuberculosis Treatment in Select Countries



Note: TB = tuberculosis.

Several countries transitioning from hospital-based services to primary health care or community settings have improved quality and outcomes of TB care—for example, Haiti (Farmer and others 1991), Latvia (Leimane and Leimans 2006), Moldova (Soltan and others 2008), Romania (Marica and others 2009), and Zambia (Miti and others 2003). Ethiopia has introduced the use of health extension workers to scale up access to primary health care services, including TB services, with improved compliance and treatment outcomes (Bilal and others 2011; Datiko and Lindtjørn 2009, 2010), and employed village outreach programs in rural settings (Shargie, Mørkve, and Lindtjørn 2006). Similarly, India has engaged urban community volunteers to supervise DOTS (Singh and others 2004). South Africa and Tanzania have used CHWs to expand access to TB services (Sinanovic and others 2015; Wandwalo and others 2004), and Rwanda has achieved effective community-based treatment (Binagwaho and others 2014). In addition to community-based care, a public-private mix with NGOs has been used in India, South Africa, and beyond to expand access to TB services and improve outcomes (Lal and others 2011; Pantoja, Floyd, and others 2009; Sinanovic and Kumaranayake 2006; Wells, Uplekar, and Pai 2015).

In the case of drug-susceptible TB, early indications are that outpatient treatment in the community is not poorer than hospitalized care (Bassili and others 2013; Loveday and others 2012). Although current guidelines recommend isolating MDR TB patients until smear or culture conversion, community-based treatment of drug-resistant TB is growing in acceptance due to its cost-effectiveness and a shortage of long-term hospital beds—for example, in South Africa (Brust and others 2012).

The benefits of transitioning facility-based services to community-based care are substantial. In six studies, where outcomes between community-based and health facility–based TB care were similar, the costs of community-based care were 33 to 70 percent lower (figure 11.5). In the four countries where the treatment outcomes in community-based TB care and health facility-based TB care were better, costs were 32 to 77 percent lower.

Community-based DOTS in Tanzania reduced costs 35 percent: from US$203 per patient treated at a health center to US$128 per patient treated in the community, with almost identical treatment outcomes. This program reduced costs by lowering the number of visits to the clinic (Wandwalo, Robberstad, and Morkve 2005). In Malawi and Kenya, moving to a community-based model reduced costs even more: 67 and 77 percent, respectively (Floyd and others 2003; Nganda and others 2003) (table 11.6).

Table 11.6 Costs and Effectiveness Comparing Community-Based Tuberculosis Care to Health Facility–Based Tuberculosis Care

Study	Study country	Community cost (2012 US$)	Health facility cost (2012 US$)	% difference in cost per patient	Effectiveness of community-based care vs. health facility–based care
Islam and others 2002	Bangladesh	172.80	259.20	33	Similar
Wandwalo, Robberstad, and Morkve 2005	Tanzania	216.10	331.90	35	Similar
Dick and Henchie 1998	South Africa	1,296.10	2,073.10	37	Similar
Moalosi and others 2003	Botswana	5,135.90	8,543.40	40	Similar
Datiko and Lindtjørn 2010	Ethiopia	138.00	332.70	59	Similar
Pichenda and others 2012	Cambodia	639.30	2,131.10	70	Similar
Khan, Khowaja, and others 2012	Pakistan	320.83	471.16	32	Higher
Okello and others 2003	Uganda	796.52	1,405.63	43	Higher
Nganda and others 2003	Kenya	752.65	2,250.51	67	Higher
Floyd and others 2003	Malawi	1,040.94	4,477.99	77	Higher

Human Resource Challenges to Community-Based Care

Despite the evidence, many countries have not transitioned to community-based models of service delivery for TB. Barriers to adoption of innovative models of care delivery are often related to health system governance, organization, and financing, in particular (external and domestic) financing flows that reinforce vertical programing; provider payment systems that allocate large proportions of the budget to structures and inputs (hospitals and hospital activities), rather than health outcomes; and a health workforce that lacks suitable skills (in particular, trained CHWs who underpin community-based service delivery). A general reluctance to adopt innovations may also impinge the move to community-based models, including public-private partnerships, which in several countries have helped to improve outcomes while lowering costs (Atun, de Jongh, and others 2010; Atun, Lazarus, and others 2010; Atun, McKee, and others 2005; Atun and others 2012; Howitt and others 2012; Khan, Khowaja, and others 2012).

Both active case finding and community-based TB delivery models require a competent, motivated health workforce, both at health facilities and in communities. Following patient diagnosis, treatment must be adhered to, and factors that drive patient adherence to medication are complex and relate both to patients' willingness and ability to seek health care and their experiences within the health system (Munro and others 2007; Podewils and others 2013). Clinic staff with limited resources need to provide accurate information to their patients and make it easy for patients to access and take good-quality treatment consistently until cured.

Inadequate human resource capacity remains an important health system barrier for TB control (Figueroa-Munoz and others 2005; Harries and others 2005), especially for MDR TB, which requires longer and more complex interventions than drug-susceptible TB (Keshavjee and Farmer 2010). Several factors, such as weak planning, absolute shortage of health staff, limited training, inadequate skills, lack of incentives to motivate and retain staff, and inappropriate distribution of the available health workforce, have contributed to the human resource crisis confronting global efforts to contain TB (Awofeso, Schelokova, and Dalhatu 2008; Buchan and Dal Poz 2002; Caminero 2003).

While community-based TB treatment certainly requires initial investments, including training, supervision, and management of CHWs, the initial investment is generally offset in the long run by savings accrued from community-based treatment rather than hospital care (Wandwalo, Robberstad, and Morkve 2005).

Private Sector Challenges

Some high-burden countries, such as India, have health care systems in which private sector rather than public sector care predominates. In India, about 75 percent of health care is provided by the private sector, most often based on OOP payments (Pai, Daftary, and Satyanarayana 2016). A high proportion of providers in many countries

are not medically trained, and appropriate care is often not provided (Udwadia, Pinto, and Uplekar 2010). Patients with TB often seek care initially from private providers and may consult three to five providers before receiving a correct diagnosis of TB, which delays the average time to initiate treatment to 60–66 days (Satyanarayana and others 2011; Sreeramareddy and others 2014).

In studies using surrogate patients presenting to physicians with cardinal TB symptoms, correct diagnosis by physicians may be as low as a third (Das and others 2015), and surveying physicians for how they would treat a new patient diagnosed with TB revealed that no more than a third recommended the WHO standard treatment protocol. In this context, private practitioners often do not register TB patients in the health system; without notifications, it is difficult for state and national TB programs to conduct planning and to improve control of TB. Such countries need to improve the communication between private providers and the health system. Innovative approaches in India and Pakistan have included the creation of public-private mixes using interface organizations and information technology to improve treatment of TB (Khan, Minion, and others 2012; Wells, Uplekar, and Pai 2015).

From Vertical to Targeted, Integrated Delivery

Another challenge for TB service delivery is the dominance of vertically organized and financed TB programs, supported by external institutions (Katz and others 2010), which circumvent and fail to strengthen weak health systems in LMICs in an effort to deliver accessible and quality TB services (Atun, Weil, and others 2010; Car and others 2012; Coker, Atun, and McKee 2004; Coker and others 2005; Samb and others 2009; Shigayeva and others 2010; Wood and others 2010).

Integrated service delivery has been shown to be beneficial. By 2008, TB services were being delivered at the primary health care level in 20 of the 22 high-burden countries and 83 percent of 173 countries reported making progress in TB control (WHO 2013b). However, these services were not effectively integrated with other disease control programs as part of comprehensive primary health care. In Cambodia, hospital-based DOTS care was the norm until stronger primary health care enabled the introduction of integrated community-based TB services. Similarly, the National Rural Health Mission in India has expanded integrated service delivery, including rapid scale-up of child health, TB, and combined TB and HIV/AIDS services. Thailand extended access to primary health care–based TB services as part of universal health coverage. In Vietnam, tuberculosis control services, which were historically operated through a vertical network, are now embedded in general health services (Atun, Weil, and others 2010). Integration between care delivery domains—for example, civilian and prison health care (Shin and others 2006)—has also been shown to improve patient outcomes.

Vertical delivery of TB services is especially inefficient in the context of concurrent tuberculosis and HIV/AIDS epidemics (Drobniewski and others 2004). As noted, the burden of TB and HIV/AIDS co-infection is substantial, most acutely in Sub-Saharan Africa, and there is a demonstrable need to integrate TB and HIV/AIDS services (Corbett and others 2006; Creswell and others 2011; DeLuca, Chaisson, and Martinson 2009; Perumal, Padayatchi, and Stiefvater 2009; Sylla and others 2007). Emerging evidence indicates the benefits of integrating TB control with HIV/AIDS control (Gandhi and others 2009; Gasana and others 2008; Harris and others 2008; Huerga and others 2010; Jack and others 2004; Legido-Quigley and others 2013; Miti and others 2003; Pevzner and others 2011; Phiri and others 2011; Uwinkindi and others 2014; Uyei and others 2011; Walton and others 2004; Zachariah and others 2003) and other targeted programs (Howard and El-Sadr 2010; Zwarenstein and others 2011) in the primary health care setting. Integration improves outcomes—for example, through concurrent screening or through provision of cotrimoxazole during routine TB care or isoniazid during routine HIV/AIDS care and at voluntary counseling and testing centers (Uyei and others 2011).

Treatment for both tuberculosis and HIV/AIDS should be integrated at the clinic as a standardized package of care, with adherence support and HIV/AIDS drug-resistance testing. It is essential that all HIV-positive individuals be tested for TB. In 2004, the WHO introduced integrated activities to improve prevention, diagnosis, and treatment of TB in people living with HIV/AIDS (box 11.6), but the achievements have been mixed. Creating positive synergies through effective integration of TB control with HIV/AIDS and other targeted programs has been arduous (Ansa and others 2012; Atun and Cooker 2008; Atun, Lazarus, and others 2010; Marais and others 2010; Okot-Chono and others 2009; Uwimana, Hausler, and Zarowsky 2012; Uwimana and Jackson 2013). Integration must be site- and service-specific.

While integrating diagnostic and laboratory services makes great sense, integrating patients with undiagnosed TB in health care clinics and hospitals without the benefit of proper infection control measures poses serious risks to persons with HIV/AIDS. Moreover,

Box 11.6

WHO-Recommended Collaborative TB and HIV/AIDS Activities

In 2004, the WHO recommended a set of collaborative activities to improve prevention, diagnosis, and treatment of TB in people living with HIV/AIDS (WHO 2004). These recommendations were updated in 2010 and 2011 (WHO 2012b). Collaborative activities include the following:

1. Establish and strengthen coordination mechanisms for delivering integrated TB and HIV/AIDS services.
2. Test TB patients for HIV/AIDS.
3. Provide ART and cotrimoxazole preventive therapy to TB patients living with HIV/AIDS.
4. Provide HIV/AIDS prevention services for TB patients.
5. Intensify TB case finding among people living with HIV/AIDS.
6. Offer isoniazid preventive treatment to people living with HIV/AIDS who do not have active TB.
7. Control the spread of TB infection in health care and congregate settings.
8. Use Xpert MTB/RIF as the primary test for diagnosing TB in people living with HIV/AIDS who have signs and symptoms of TB.

an anticipated consequence of integrating HIV/AIDS and TB care is the exposure of immune-compromised HIV-positive patients to undiagnosed TB, making it essential to control infection and separate patients.

Effective TB control will require health systems to interact with sectors that address the social determinants of health. However, it has been argued that the programmatic and biomedical focus fostered by DOTS may have, in some instances, hindered multisectoral collaboration and effective coverage of vulnerable communities (Ayles and others 2009; den Boon and others 2007; Gler, Podewils, and others 2012; van't Hoog and others 2011; Wood and others 2007); geographically concentrated groups (de Vries and others 2014); groups at risk, such as women, children, and adolescents (Ettehad and others 2012; Isaakidis and others 2013; Marais and others 2010; Moyo and others 2014; Sheriff and others 2010); and disenfranchised populations (Corbett and others 2009), for example, persons imprisoned in penitentiary facilities (O'Grady, Hoelscher, and others 2011; O'Grady, Maeurer, and others 2011).

Stronger Supply Chains

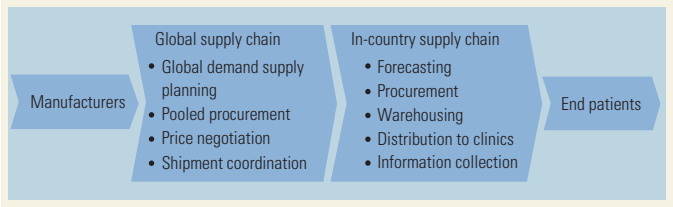
A robust and well-functioning supply chain is a complex but essential component of any country's health system. An uninterrupted supply of high-quality drugs is imperative to treat TB effectively and to prevent transmission of the disease or its escalation to drug-resistant strains. Weak systems of supply chain management, with inadequate demand forecasting, ineffective drug procurement, long procurement cycles, poor-quality drugs, and delays in the delivery of diagnostics and medicines, have led to treatment interruptions, exacerbating drug-susceptible and MDR TB epidemics (Mathew and others 2006; van der Werf and others 2012; Victor and others 2007). The lack of availability or poor quality of TB drugs in public clinics run by national TB programs or in private facilities leads to patients missing doses, creating increased risks for relapse and the emergence of drug-resistant forms of the disease.

Stock-outs of TB medicines have many causes. While some stock-outs are related to poor planning, distribution bottlenecks, and poor demand visibility, there are global shortages for some drugs. The problem of global shortages affects many antimicrobials, especially generic injectable agents. Very often, given the small number of manufacturers, when one manufacturer experiences problems related to quality or manufacturing, global shortages can arise.

Global Supply Chain

The global supply chain of TB medicines, from the manufacturer to the patient, can be divided into two distinct segments: the upstream supply chain (global supply chain) and the in-country supply chain (figure 11.6). The global, or upstream, segment consists of the processes related to global demand forecasting, procurement, and financing. The in-country segment includes the quantification of needs by national TB programs,

Figure 11.6 A Simplified Supply Chain from Manufacturer to Patient



Source: Yadav 2010.

procurement by ministries of health, warehousing, distribution, and information collection about patients regarding treatment and future needs.

The upstream supply chain for TB medicines is fraught with market shortcomings. All commonly used TB drugs are off-patent, holding little interest for large pharmaceutical companies. As a consequence, there are few producers for most drugs. In particular, timely provision of life-saving second-line medicines for MDR TB has been woefully inadequate, with estimates suggesting that less than 0.5 percent of the MDR TB cases in 2002–09 were treated with drugs of known quality (Keshavjee and Farmer 2012). Stock-outs of TB medicines are frequent in LICs, and shortages exist even in HICs, where standard isoniazid has not been available for more than a year.

Apart from the lack of manufacturer interest in these low-demand, limited-profit-potential medicines, the lack of procurement coordination across low- and high-demand countries further fragments the small market. Lack of proper quantification at the country level translates into a lack of robust global forecasts for TB medicines. The upstream supply chain for the donor-funded portion of the TB market currently operates through a pooled procurement mechanism operated by the Global Drug Facility. The Global Drug Facility attempts to coordinate the orders from multiple countries, especially lower-demand countries. For MDR TB medicines, it also runs a strategic rotating stockpile to reduce stock-outs and volatility in orders to the manufacturer. However, the global supply chain is far from optimal and requires significant strengthening of its technical capacity to manage a small market with highly uncertain demand and a fragile supply base (Institute of Medicine 2013).

It is important to examine how the global supply chain for TB medicines has evolved over time. The Green Light Committee was developed in the 2000s to approve programs that deliver MDR TB treatment and provide access to low-cost second-line drugs. However, the Green Light Committee approved a small number of MDR TB treatments, creating long delays in receiving approvals and drugs, limited demand for second-line drugs, and constrained supply, with few producers providing medicines that met stringent regulatory approval.

In a typical healthy pharmaceutical supply chain, some upstream steps such as active pharmaceutical ingredient (API) manufacturing, formulation, and packaging are carried out before the buyer places an order. These forecast-driven steps lead to the finished product or the API manufacturer holding some inventory, which reduces the time required to fulfill a confirmed order.

In the TB medicines supply chain, however, many of these processes are order driven as opposed to forecast driven. Manufacturers hold little, if any, finished product inventory and little, if any, API inventory. All steps in the upstream supply chain start only after a confirmed order is placed. And the order stream from the pooled purchaser is lumpy, meaning that it occurs in large quantities at certain times of the year. These problems lead to suboptimal holding of inventory, poor planning of batch size, subscale manufacturing of the finished product, higher costs, and excessively long lead times. These issues constrain national TB programs, which are unable to plan much in advance due to uncertain financing and delayed disbursement and thus face further delays in receiving supplies after they place an order. Together, these factors contribute to stock-outs of TB medicines at the national level.

Possible mechanisms to address these problems include the creation of an accurate global demand forecast system, the development of supply-contracting structures that provide limited-volume guarantees to manufacturers, and a buffer inventory or stockpile to smooth demand. Their applicability and cost-effectiveness depend on careful analysis of the nature of demand uncertainty, supply lead times, and ability of global program staff to operate these mechanisms.

Some of these mechanisms are now starting to be used by the Global Drug Facility (Arinaminpathy and others 2015), but they require adequate technical resourcing. Also, while Global Drug Facility purchasing may lead to greater coordination and pooling of orders from many LICs, a significant portion of the TB burden is in middle-income countries, which do not procure through the Global Drug Facility. Overcoming the excessive fragmentation in the global TB drug market, especially for low-demand drugs for MDR TB, requires not only robust technical solutions but also strong political will.

In-Country Supply Chains

In HICs, while the nature of health care provision and financing varies considerably, medicines are distributed primarily by private sector agencies. In LICs, and in many

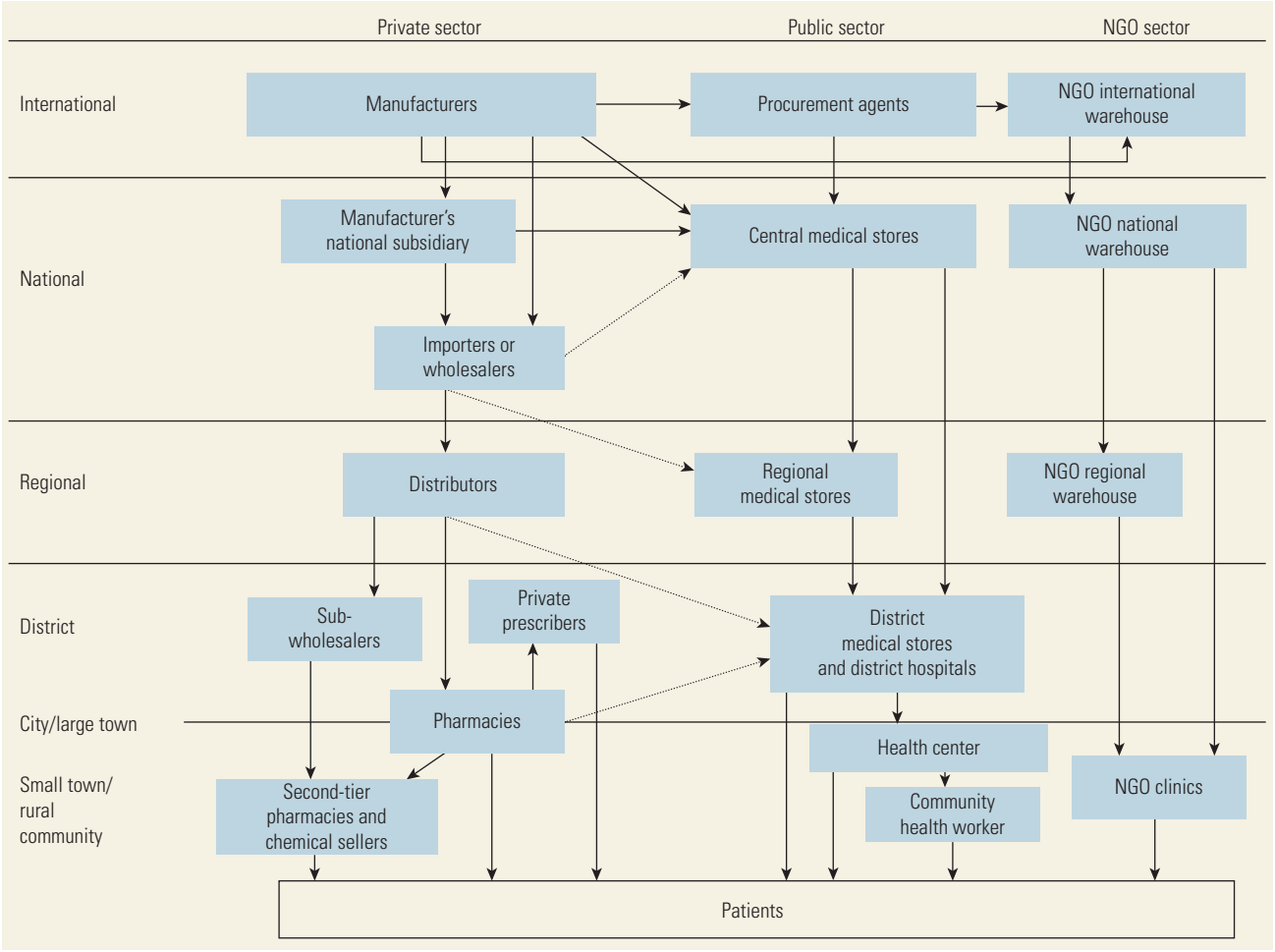
of the TB-endemic countries, in particular, medicines are distributed to health facilities primarily through a central medical store, regional or district stores, or a transport fleet owned by the government or a central medical store. Global donor–funded or national government–funded TB drugs also flow primarily through this government-run distribution system (figure 11.7).

A multitiered distribution structure wherein TB medicines are stored at multiple levels (national, regional, district) before reaching TB clinics is common in most countries. The distribution system maps directly to the administrative structure of the health system, for ease of administration and governance, as opposed to technical or operational imperatives (Yadav 2010).

Successfully managing a multitiered distribution system for TB medicines is an information-intensive operation. Data on stock levels at each stage, past consumption, and future requisitioning need to flow through different levels of the system. Such data are recorded on store ledgers, stock control cards, and requisition forms at the district and health facility levels but rarely get reported to higher levels of the distribution system. The lack of consumption data prohibits better overall supply planning. There is a critical need for a simple and robust logistics management information system to record and report these data systematically.

Staff need to be well trained to forecast need and place orders, yet staff at health facilities often have inadequate capacity to estimate the quantity of medicines needed, resulting in under- or over-ordering. One solution is to deploy trained staff from district or regional delivery teams to visit health facilities, check the stock they have used, help them to estimate how much is needed for the next period, and replenish that quantity

Figure 11.7 Flow of Medicines through the Public, Private, and NGO Sector in Low- and Middle-Income Countries



Source: Yadav, Tata, and Babaley 2011.
Note: NGO = nongovernmental organization.

from the supply they carry with them. Zimbabwe has implemented such a system, called Delivery Team Top Up (Yadav, Tata, and Babaley 2011). In a large-scale randomized pilot study in Zambia, relatively simple changes to the information and product flow system significantly improved the availability of essential drugs (Vledder and others 2015). HIV/AIDS medicine programs in multiple countries have also experimented with different variants of the distribution, requisitioning, and information flow model. Such innovation has been lacking for the distribution of TB medicines.

With the recent explosion of inexpensive information technology such as mobile phones, new options have become available for collecting and using information about clinic-level consumption. However, technology will not fix all of the problems in the distribution system.

Apart from lack of information, another crucial cause of poor supply chain performance relates to the lack of incentives (Yadav, Stapleton, and Van Wassenhove 2013): public sector supply chains often lack the ability to reward good performance or to remove incompetent workers. Better mechanisms are needed to align incentives and motivate the supply chain workforce (Spisak and others 2016), but greater accountability in the distribution system for TB drugs requires richer information about stock and consumption data. These models have not yet been leveraged to their fullest, but they have the potential to be the backbone of planning in the supply system.

Having a healthy and robust supply chain for TB medicines in the private sector is as important as improving the publicly run supply chain. Significant proportions of TB patients in high-burden countries such as China and India seek TB treatment in private clinics or obtain medicines in private pharmacies (Wells, Uplekar, and Pai 2015); in some countries, public-private models rely on the availability and quality of drugs in the private sector. While countries such as Brazil and China have created social insurance programs to help patients to cover the cost of private sector services, in most countries patients themselves pay out of pocket for private sector treatment for TB.

TB medicines in the private sector are distributed through a network of importers, wholesalers, subwholesalers, pharmacies, and drug stores. Compared to private sector pharmaceutical supply chains in HICs, private sector supply chains in most TB-endemic countries are excessively fragmented, with myriad small wholesalers and distributors; intermediaries between the manufacturer and the patient; and poor information technology and communication systems, which result in poor coordination across the distribution channel. Fragmentation of the supply chain makes it difficult to achieve scale economies and to improve or verify quality, especially given the severe resource constraints of regulatory authorities.

In some countries where medicine wholesaling is highly fragmented, consolidation of wholesaling and distribution in the supply chain is being driven by policy measures such as better enforcement of distribution practices and stricter reporting requirements. For instance, when a nationwide Good Supply Practice enforcement campaign was launched in China in 2004, the number of pharmaceutical wholesalers dropped from 16,000 to 7,445 (Yadav 2015).

Better Information Management and New Technologies

The lack of reliable and timely information impedes the organization of TB control and effective discharge by ministries of health of their stewardship function. In 2009, only 4 of the 22 high-burden countries had well-functioning vital registration systems that appropriately coded causes of death (Glaziou and others 2011).

Challenges

As both an infectious and chronic disease, TB presents a range of challenges for collecting and managing information. First, there is the challenge of case finding and surveillance. Once patients are identified, diagnosis requires sputum smear and, ideally, culture and drug-sensitivity testing, a challenge in low-income settings where good laboratory facilities are rare. Sputum smears can be collected in small clinics, but culture and DST is a specialized process. New diagnostic techniques, particularly GeneXpert, have improved the situation significantly, avoiding the need for sputum smear or culture in initial diagnostic work-up in sites that have the machines. However, many clinics have to send samples to other sites with machines, and any patient found positive for Mtb requires follow-up testing to assess their response to treatment. Patients found resistant to rifampicin require follow-up drug-sensitivity testing to permit individualized therapy (Lessem and others 2015). It is therefore critical to capture lab data from all locations and sources, including GeneXpert. Newer, portable models in development (GeneXpert Omni) with potential for point-of-care diagnosis have the ability to transfer results in real time by short message service or through the Internet. Even in countries with sophisticated health care systems, like South Africa, there are enormous problems getting the data on a sputum sample to the appropriate clinic, physician, and patient.

Once patients have been diagnosed successfully, they need to be tracked in a longitudinal record that captures data on demographics, clinical condition, current and previous medication, lab results, complications, and treatment response and outcomes. For first-line TB treatment with DOTS, the record is typically a paper register in the clinic. This usually supplements other registers, including primary care visits and maternal health. While well-designed paper registers can be effective, they are typically challenging for busy staff to keep up to date and accurate and lead to much duplication of data. This problem becomes much more severe with large numbers of patients and mobile populations. Drug-resistant TB is a particular challenge due to the complexity of recording treatment and clinical data and the long treatment times.

E-health systems are playing an increasingly important role in the management of TB and are especially important for drug-resistant TB in LMICs. Labrique and others (2013) describe 12 key functions of m-health (and e-health tools more generally). All of these are relevant to TB care:

1. Client education and behavior change communication (short message service reminders to take medication or attend appointments)
2. Sensors and point-of-care diagnostics (attachments for microscopy)
3. Registries and vital events tracking (community case finding and registration)
4. Data collection and reporting (research data collection; Fraser and others 2012)
5. Electronic health (medical) records
6. Electronic decision support (information, protocols, algorithms, checklists)
7. Provider-to-provider communication (telemedicine consultations)
8. Provider work planning and scheduling (to help community health workers to manage their patients)
9. Provider training and education (Web-based resources and video on mobile phone memory cards)
10. Human resource management (tracking activities, patient contacts, and location of community health workers)
11. Supply chain management
12. Financial transactions and incentives.

New Technologies to Improve TB Information Management

Several recent e-health applications have addressed case finding. An m-health application was developed to assist nonclinical CHWs to screen patients in general medical clinics in Karachi, Pakistan (Theron and others 2015). Staff used the built-in interactive questionnaire to identify symptoms and signs of TB in patients who were coughing for two weeks or more. In the intervention area overall, notification of TB cases to the national TB program increased from 1,569 to 3,140 cases between 2010 and 2011. Increasingly, CHWs in rural communities in LMICs are using m-health applications to find unknown patients with TB and other diseases (Were and others 2009).

Some groups have developed Web-based electronic medical record (EMR) systems for managing drug-resistant TB (Fraser and others 2013). EMRs were one of the first e-health applications for managing TB. Partners In Health developed and deployed a Web-based medical record for managing MDR TB in Peru in 2001, with tools to allow clinicians to view trends in lab data and changes in medications as well as to create reports for the national TB program and funders (Fraser and others 2002). The system was also used to collect core data for subsequent research studies after additional data collection and cleaning. Image data of chest X-rays captured with a digital camera were included for most patients, and psychiatric records were added later. The system was extensively evaluated to determine its performance and potential impact on quality of data and delivery of care (Fraser and others 2006).

From 2000 onward, Peru scaled up the individualized treatment of drug-resistant TB, including upgrading laboratory facilities at local, district, and national levels. Two e-health systems were implemented as part of Peru's system. The first was an early m-health application to assist staff in collecting smear and culture data from 98 small clinics in northern Lima. The system reduced the median processing time for cultures from 23 days to 8 days and for smears from 25 days to 12 days and significantly reduced the number of errors. The intervention reduced the number of work-hours necessary to process results by 70 percent and was preferred by all users.

Blaya and others (2007) evaluated a Web-based laboratory management and reporting system, eChasqui, also in Lima, in a large random control trial of 1,671 patients in 44 clinics, 12 of which were randomized to receive initial access to the system. Error rates (mainly missing results) fell 87 percent for cultures and 82 percent for DSTs. Delays for cultures were reduced from a median of 8 days to 5 days and for DSTs from a median of 17 days to 11 days. In addition, the time to culture conversion fell 20 percent (Blaya and others 2014). Results similar to those seen here in TB patients have been replicated for other diseases, particularly HIV/AIDS (Amoroso and others 2010; Siedner and others 2015).

Several EMR systems have been developed to assist in the management of MDR TB, including eTB manager,

initially developed in Brazil and now deployed in many countries (Fraser and others 2013).

In 2008, a new EMR system was developed for MDR TB care based on the open-source EMR system OpenMRS platform (Mamlin and others 2006). The OpenMRS-TB system provided similar functionality to Peru's EMR, but was embedded in a general-purpose EMR platform that was also used to support a range of clinical care, including HIV/AIDS, primary care, maternal health, and oncology. It has been deployed in Haiti, Indonesia, Pakistan, and several African countries. A version of OpenMRS-TB was created and deployed in Peru for a large epidemiological study of MDR TB (Fraser and others 2012). A new version of OpenMRS-TB is currently under development for clinical and research purposes in a collaboration between Partners In Health, Médecins Sans Frontières, and ThoughtWorks. OpenMRS has been developed as open-source software and also supports open standards for the coding of medical data. OpenMRS is now used to support the care of patients in more than 40 LMICs (Mohammed-Rajput and others 2011; Seebregts and others 2009), with versions to support the management of HIV/AIDS, maternal-child health, and, more recently, heart disease and primary care.

The design of OpenMRS offers some advantages for the development of research data management tools. Due to the focus on safe collection, storage, and management of clinical data, it includes auditing of data changes in the main database tables. This feature allows tracking of the history of changes in data items linked to the login of the user. OpenMRS is designed around a flexible data dictionary, called the concept dictionary, which allows new data items to be added without changing the underlying structure of the database. The dictionary simplifies the translation and maintenance of items in additional languages like Spanish and has led to the development of a core dictionary mapped to coding standards such as ICD-10 and SNOMED-CT and shared by most users of the system. A major advantage of OpenMRS from a developer's perspective is its modular software architecture, which allows software modules, either from the OpenMRS module library or newly developed modules, to be plugged into the main system, adding functions without changing the core system.

Telemedicine to Support Health Workers

While clinics can generally manage the DOTS protocols for treating drug-sensitive TB, management of drug-resistant TB can be complex, especially for patients with second-line resistance, including XDR TB. Expertise in managing such patients is limited, which is one of the reasons why only a minority of patients receive fully effective treatment. Telemedicine is a potential strategy to support clinicians with limited knowledge of these complex treatment protocols. This can be as simple as an e-mail question to a specialist for advice on a specific patient's drug regimen and resistance or a video conference with both clinicians and the patient. Many projects use "store and forward telemedicine" typically involving e-mailing text and attached images (Della Mea 1999). Studies have shown that even modest-specification digital cameras can capture images of chest X-rays good enough for diagnosis and management of TB (Szot and others 2004).

Telemedicine approaches often work well in small-scale projects but are difficult to scale up. Individual e-mails are not suitable for large numbers of referrals due to the difficulty of ensuring that all of the correct information is recorded accurately in the referral and the resulting assessment is recorded in the patients' notes. A more effective approach is to share data in a secure, Web-based EMR system like Peru's EMR, OpenMRS-TB, or eTB manager (Fraser and others 2013), giving the remote specialist access to the individual patient's record. The remote specialist can see the full range of clinical data, lab results, and often imaging and record an assessment directly in the clinical record. Another challenge with scale-up is that clinical expertise is limited and cannot be "spread too thin." A more effective and scalable strategy can be to use telemedicine as part of training initiatives (Geissbuhler and others 2003), along with better clinical guidelines and decision support for local staff.

SMS Reminders to Improve Adherence

With the importance of achieving good adherence for managing TB and preventing the emergence of drug resistance, there is great interest in tools and strategies to improve adherence. DOT is the best-established approach, but questions have been raised about its scalability and cost. With mobile phones widely available in LMICs, m-health may provide tools to support treatment adherence. Most work has focused on improving adherence to ART with text messages or interactive voice prompts, with evidence of improvements in adherence in some random control trials (Lester and others 2010; Pop-Eleches and others 2011), but also some negative results (Cameroon, India).

Analysis of these studies suggests that messages customized to each patient and the ability of patients to communicate with actual staff (not just automated prompts) improve adherence. To date, these tools have not matched the adherence rates of effective DOT, and there is evidence of messaging fatigue among patients.

Further work is under way to design interventions based on established psychological models of behavior change accompanied by rigorous evaluation.

Information Technology to Manage Supply Chains

An additional challenge for managing drug-resistant TB has been establishing effective medication supply chains, and information systems are increasingly important for forecasting requirements, tracking medication shipments, and managing inventory at clinics.

Lack of supply of second-line TB medications is a key factor in poor scale-up of treatment. While first-line drugs are low cost and generally widely available, second-line drugs are mostly used for drug-resistant TB and often manufactured to order. Orders have to be placed months in advance to ensure continuity of care, and accurate forecasting is essential. Information systems can assist in multiple steps in this process, including forecasting, ordering, tracking shipments, and managing inventory.

In Peru, the EMR was used to forecast medication requirements for treating drug-resistant TB. Combining data on the number of patients enrolled, their length of time in treatment, recruitment rate, and current regimens resulted in error rates of 3 percent or less for more than 1,000 patients in both 2003 and 2004 (Fraser and others 2013). A related study looked at forecasting medication for 68 patients in the same cohort and compared that to the usual manual methods. In one study, Peru's EMR predicted 99 percent of one year's needed supply of medicines, while more manual methods predicted 149 percent (Fraser and others 2013).

New tools are becoming available for managing shipments and inventory in LMICs.[4] One information system for drug-resistant TB, eTB Manager, includes inventory management for each clinic linked to requirements forecasting (Fraser and others 2013). These tools are now available for general use in drug forecasting. M-health tools are also being used to track inventory in local clinics in East Africa using text messages (SMS for Life) and have been shown to reduce stock-outs dramatically for antimalarial drugs (Barrington and others 2010). They are also being used for TB medication. Other systems have been developed to detect counterfeit medication in countries like Nigeria by allowing patients to text a unique code printed on the medication container to a free number.[5]

As noted, the OpenMRS-TB EMR platform supports the management of a wide range of diseases and primary care. Its use of open standards for storing and exchanging data supports interoperability with other e-health systems, allowing systems with a range of functionality to be linked together—for example, EMR systems, laboratory information systems, pharmacy systems, m-health applications, and national reporting systems, such as the District Health Information System (DHIS 2).

Such e-health architecture approaches are being deployed in several LMICs, including Bangladesh, India, Kenya, the Philippines, and Rwanda. Many countries have now adopted the DHIS 2 to collect, manage, and report on health data at the district and national levels. The system can take direct feeds of data from systems such as OpenMRS and some m-health applications, improving the accuracy and timeliness of data. Embedding the specialized data collection and analysis tools for TB care in broader e-health systems has large benefits, such as facilitating case finding through primary care visits and lab data, identifying potential risk factors like diabetes, maintaining a complete and accurate list of medications, and providing effective decision support based on the sharing of all key data.

Further evaluation is needed on the performance of e-health systems in LMICs as well as the clinical impact on TB management. In addition, there are only limited data at present on the costs of deploying such systems and maintaining good performance and usage levels in the long term (Blaya, Fraser, and Holt 2010). There is, however, some evidence that effective EMR and laboratory information systems can save money in LMICs by reducing errors and waste and speeding patient management (Driessen and others 2013). It is also very likely to be more cost-effective to embed TB management tools in existing e-health systems than to run parallel systems.

RESEARCH AND DEVELOPMENT

In addition to requiring new care delivery and health system strategies, turning the tide against TB will likely require technological advances that could accelerate cure, reduce transmission and incidence, and prevent disease. Despite the effectiveness of standard drug regimens for drug-sensitive TB, resistance is increasing, compliance with long treatment times is problematic, and new drugs and regimens are needed.

Current TB therapy has many advantages: the standard drugs are remarkably safe, with little toxicity even in vulnerable populations such as pregnant women and children; a complete course is highly effective against drug-sensitive disease; and the drugs themselves are affordable in the poorest parts of the world. Despite these advantages, first-line drugs are ineffective against multidrug-resistant strains. And rifampin, perhaps the most effective agent in the current first-line therapy, has pharmacologic interactions with many other drugs, most notably HIV/AIDS protease inhibitors taken by many co-infected individuals.

The most important limitation of the current regimen is the extended time required for effective therapy. "Short course" chemotherapy is anything but short; failing to complete six months of treatment leads to significant rates of relapse. Because patients feel better in a matter of weeks, they often have little motivation to continue taking their medications. In addition, the extended course means that a substantial investment is needed to ensure a continuous drug supply. These requirements add substantially to the cost of what otherwise would be an inexpensive undertaking. This, together with the training and logistics necessary to ensure adequate DOTS implementation, has led to remarkably poor results and continued treatment failure, leading to millions of deaths each year. Thus, the challenge is to develop not just new drugs, but ideally new drug regimens effective in treating drug-sensitive and drug-resistant TB and shortening the time of treatment.

Better drugs and regimens could have a substantial impact. To be most useful, they would have the following attributes:

- Rapid activity, shortening the course of therapy required for cure
- Safety, allowing use in a wide range of patients without requiring substantial prescreening
- Easy administration, preferably oral, so that health professionals are not required
- Limited interactions with other drugs, particularly antiretroviral drugs
- Limited cost, making them affordable in the poorest parts of the world.

There are two general paths to achieving these goals: optimizing the use of currently available medications and developing completely new drugs. Phase III clinical trials are expensive and will always be rare. It will likely be impossible to test each new drug serially.

Given the enormous cost of developing new drugs (the average cost of developing a new drug to licensure is on the order of US$1 billion or more), the former is the most attractive path to making rapid changes to recommended therapy.

Optimizing the Use of Current Medications

Is it possible to reconfigure the current drug regimen to produce better efficacy against a broader range of organisms? The evidence so far is mixed. Animal studies and human pharmacokinetic observations have suggested some modifications of TB drug therapy that might produce better results. For example, many patients who receive rifampin at recommended doses have low serum levels. Increasing the dosage of rifampin or using a different rifamycin might enhance the clearance of infection. Several studies are looking at altered dosing regimens for rifampin or substitution of the long-acting drug rifapentine. As measured by a surrogate endpoint—culture conversion at two months—rifapentine is no better than rifampin. In multiple short-term controlled trials that included fluoroquinolones to shorten therapy, the failure rate of cures at two to four months was unacceptably high. None of those shortened regimens was effective enough to offer substantial advantages in treatment (Gillespie and others 2014; Jindani and others 2014; Merle and others 2014).

The fluoroquinolone trials were phase III studies designed to permit U.S. Federal Drug Administration (FDA) approval for these regimens, if successful. Performing such a trial is an enormous undertaking. The current treatment regimen is highly successful in some patients, with a less than 5 percent relapse rate in most settings. Showing improved efficacy requires an enormous number of patients, which is why the fluoroquinolone study was designed to show noninferiority, a criterion that does not require the same level of evidence. Nevertheless, these studies require thousands of patients to provide confidence in the results and investments in infrastructure in the low-income settings where the trials are conducted, making them extremely expensive and logistically challenging.

To mitigate the costs associated with such trials, some studies are experimenting with alternative trial designs. For example, one study investigated the efficacy of the oxazolidinone linezolid. Instead of recruiting patients with drug-sensitive disease, these investigators studied patients with MDR TB, a group where success rates are historically lower (Gler, Skripconoka, and others 2012; Lee, Song, and others 2015). They compared regimens that had been individually designed for each patient with the same regimen plus linezolid. This study showed a faster rate of clearance of bacteria and a lower relapse rate in the linezolid-treated patients, suggesting that this drug has properties that might allow a shorter regimen, at least in this setting. However, linezolid treatment was associated with very high levels of toxicity, far higher than could be tolerated by patients with drug-sensitive disease. Still, this class of compounds shows promise. In another study, delamanid (OPC-67683), a nitro-dihydro-imidazooxazole derivative, was found to accelerate sputum clearance of Mtb by 45 percent in two months, somewhat better than standard treatment (30 percent). These studies suggest that the priority given to shortening treatment time to

sputum conversion may be compromising the need to assure cure and prevent treatment failure and relapse.

Finding New Treatments

Producing novel agents is in some ways superior to optimizing the use of current drugs. The length of therapy cannot be shortened with current drugs. And because antibiotic resistance arises from mutations rather than acquisition of broad determinants of resistance, virtually all bacteria, including MDR TB strains, should be sensitive to completely new classes of antibiotics. These advantages must be balanced, however, against the substantial costs involved in developing new drugs. Preclinical development costs tens of millions of dollars, while completing all of the clinical studies necessary for drug approval can run into the hundreds of millions. And there are substantial risks along the way: only a small minority of compounds that enter clinical trials are approved; many more fail to make it into clinics.

Nonetheless, new drug development for TB already has achieved some notable successes (Hoagland and others 2016). Two new drugs have recently received approval for human use for MDR TB under certain conditions. Both bedaquiline and delamanid have been approved in Europe; bedaquiline also has received FDA approval. These agents have interesting and novel mechanisms of action. Bedaquiline, a diarylquinoline, inhibits bacterial adenosine triphosphate synthesis by directly blocking the adenosine triphosphate synthase complex. Delamanid, a nitroimidazole, is converted by bacterial enzymes to its active form, which may liberate toxic nitric oxide in the process. As predicted for drugs with new molecular mechanisms, there is little cross-resistance to existing antibiotics (although altered activity of an efflux pump might decrease the efficacy of both clofazimine and bedaquiline). It is not clear how these agents will be used. In rather small clinical trials, bedaquiline was effective, but patients who received the drug had higher death rates, largely after treatment was completed, for unknown reasons (Cox and Laessig 2014; Diacon and others 2014; Gupta and others 2015). Until more is known, bedaquiline use will likely be restricted to persons with drug-resistant TB (WHO 2013e). Less is known about delamanid and its optimal use at this point.

The path to obtaining approval for bedaquiline and delamanid is both interesting and illustrative. Both were tested in patients with MDR disease in much the way that linezolid was used, adding them to optimized therapies. Patients treated with the new drugs cleared infection significantly more rapidly and had lower rates of relapse when treatment was stopped. The small numbers in these trials provided the basis for "conditional" approval of both drugs for use in MDR infections. However, final approval and an expanded indication for drug-sensitive disease will require larger phase III trials.

Several new regimens are currently undergoing testing in clinical trials. Like the fluoroquinolone trials, many of these target drug-sensitive TB with the aim of shortening the duration of therapy without compromising the rate of cure. As of this writing, trials are planned, enrolling participants, or under way that will test whether treatment can be shortened to as little as two months using a variety of regimens. Of these, a phase III trial testing pretomanid/moxifloxacin/pyrazinamide (PaMZ) was the farthest along. However, the trial was put on hold due to unexpected toxicity, and its future is uncertain.

In addition to drugs that either have already been approved or are in late clinical trials, several preclinical compounds are undergoing development. These include both new members of existing classes, such as oxazolidinones that might have less toxicity than linezolid, and completely new classes of compounds. Compounds with novel mechanisms of action are particularly attractive. Not only are they generally active against drug-resistant disease, but they may exploit pathways that could clear disease more rapidly.

However, two issues have arisen with these new compounds. First, many compounds with antibacterial activity seem to target a very limited number of bacterial processes. These often induce cross-resistant mutations. Therefore, there is far less diversity than desired. Second, and perhaps more concerning, much remains unknown about the fundamental biology of infection. A principal goal of new drug development is to shorten the course of therapy. However, there are no in vitro correlates that confidently predict that an early-stage compound will result in more effective therapy. This presents a considerable obstacle to the drug development process. And differences in the effectiveness of drugs between laboratory studies and patients question whether in vitro and animal models adequately predict the most effective compounds.

Do standard markers of rapid clearance in clinical trials correlate with ultimate treatment success? It is likely that some drugs used in TB act more slowly and might not be seen to be effective in early bacterial clearance studies and, conversely, that some drugs act rapidly but do not sustain their effects and control infection over the longer term. Without biomarkers for the state of viability and magnitude of the TB bacillus in the host, answering these questions will likely require large trials (Wallis and Nacy 2013).

Even in the best of circumstances, serial testing of individual drugs in large trials is unlikely ever to be affordable. Moreover, these drugs will never be used alone; instead,

they will always be used in combination with other drugs. And these combinations might be more (or, conceivably, less) efficacious than would be predicted for individual drugs. Indeed, experiments in animal models suggest that some drugs can act synergistically to effect much more rapid cure. This has led to the model of testing regimens rather than individual drugs. In this model, which has been advanced by the TB Alliance, new drugs would be tested and approved in combinations. While the characteristics of individual drugs might never be determined (and, in this model, would not necessarily be approved as individual agents), this strategy would provide a much more rapid and practical path to drug approval, albeit at the risk of missing information about individual agents.

Because of the cost of developing new drugs and regimens and the fact that the populations in greatest need are in LMICs, an enormous challenge remains: how can countries afford new more effective regimens, and how can the international community contribute to making them available to the populations that need them? Pharmaceutical companies have few private sector incentives to invest in TB drug development or, more generally, in antibiotic development at present, and some sort of public-private mechanisms will need to be developed.

Developing New Vaccines

In the past two decades, there has been a renewed effort to develop vaccines against TB that would provide greater protection than BCG. There are at least three strategies for contributing to TB control where vaccines are being tested in clinical trials. One strategy is to determine whether vaccines can prevent infection with TB (prevention-of-infection trial), in which IGRAs are used to detect infection by Mtb. A second is to test whether vaccines can prevent recurrence of TB or MDR TB after treatment (prevention-of-recurrence trial) or possibly be used therapeutically with chemotherapy to accelerate cure. Finally, the ultimate goal is large-scale immunization for prevention of disease (POD). About 40 vaccine candidates are at various stages of preclinical testing, and 15 vaccine candidates are currently in clinical trials (Jiménez-Levi 2012).

Among the candidates in the pipeline (Evans and others 2013) are (1) recombinant vaccine candidates expressing Mtb antigens in BCG, adenovirus, cytomegalovirus (CMV), or other vectors; (2) genetically attenuated whole-cell Mtb strains, lacking either virulence determinants or ability to replicate; (3) and a variety of subunit protein antigen candidates with adjuvants that would be used as boosters in children or adolescents primed with BCG. All of these vaccines are being tested in preclinical studies in experimental animals, and some are being tested in nonhuman primates.

The scientific basis for development of any effective vaccine includes (1) significant understanding of immunological mechanisms of protection against infection or disease; (2) molecular correlates of mechanisms that would diminish the need for large, multiyear efficacy trials; (3) definition of Mtb antigens that engender those protective mechanisms; (4) means of delivering those antigens that generate or prime for protective rather than pathogenic responses; and (5) animal models that are more predictive of protection in humans than current models appear to be. None of these criteria has been met for any TB vaccine candidate at present.

Several special considerations are necessary in vaccine testing. Since vaccines, in contrast to most drugs, are given to healthy children or adults, their safety must be the foremost concern. In addition, they need to be tested in places with a high TB burden that have laboratories capable of analyzing the immune correlates of protection; they cannot compromise the ability to test for infection with Mtb in IGRAs; and the preexposure to environmental mycobacteria in places where they are tested cannot compromise detection of protection.

From animal studies and human Mendelian genetic studies, it appears that both CD4+ and CD8+ T-cells and IFN-γ, TNF-α, and other cytokines are *necessary* to protect against disease (Modlin and Bloom 2013; O'Garra and others 2013). The challenge is to learn what responses are *sufficient* for protection. It is unclear how faithful small animal models of TB will be to the human response to vaccine candidates. There is hope that nonhuman primates may be the most predictive model of human protection. Human vaccine trials showing at least partial protection may be the only way to establish those conditions. The first new candidate, MVA85A, expressing a major Mtb antigen, 85A, in modified vaccinia Ankara vector, was tested in more than 3,000 South Africa infants in a well-executed phase IIb trial (Tameris and others 2013). The candidate, which was reported to induce IFN-γ and engender some protection in four animal species, failed to protect children against either infection or disease.

BCG is known to induce Th1 T-cells and a number of cytokines—for example, IFN-γ, TNF-α, IL-12—that, in animal models and in human Mendelian genetic deficiency studies, appear to be *necessary* for protection against TB. However, the immunological factors that are *sufficient* to engender protection are not yet understood (Modlin and Bloom 2013). It is very unlikely that large-scale trials of new vaccines, such as the South India trial, which followed 360,000 people for 15 years and failed to show protection in any age group, will soon be

undertaken for new candidate vaccines. Thus, there is an urgent scientific need to develop molecular "correlates of protection" that can be measured in small numbers of recipients, that will predict which new vaccine candidates are likely to protect against infection and disease, and that will identify which individuals are likely to remain susceptible or relapse after treatment. In the absence of molecular markers of protection—for example, either involved in protecting against infection or preventing latent TB from progressing to active disease—serious consideration will have to be given to the development of a safe, attenuated, but live genetically engineered Mtb challenge. This development could be as valuable to TB vaccine development as live challenges have been in malaria and enteric vaccines.

Modeling the impact of possible new TB vaccines has been enormously valuable. It has shown that, because children contribute little to transmission, giving a more effective vaccine than BCG only to infants and children would have little effect on the epidemic (Knight and others 2014). Modeling suggests that, in high-endemic countries, vaccinating adolescents, who were the recipient population found to be highly protected (about 80 percent) in the original trials of BCG and *M. microti* in the United Kingdom (Hart and Sutherland 1977; Sutherland and Springett 1987), would be more effective than vaccinating infants. Immunizing or boosting adolescents just before they enter the age of highest risk would likely have the greatest impact on the disease burden.

Because of the need to immunize large numbers of people in a general population to obtain enough statistical power to establish vaccine efficacy, the approach of the field is to test smaller numbers of individuals in high-burden countries to learn about immunological parameters that may correlate with protection. For example, an experimental trial with a small targeted population could ascertain whether immunization could prevent reinfection and relapse (at the end of treatment). Targeting vaccines to a group of treated patients would shorten the time to learn whether there was an effect on relapse and reduce the costs and time required for disease prevention trials in large populations. It is remarkable how little research has been devoted to combining chemotherapy and immunotherapy in TB.

Understanding the Immune Mechanisms Necessary and Sufficient for Protection

Current thinking is that a single vaccine given at birth is unlikely to provide sufficient protection to prevent disease in adults, who have the highest risk of developing disease. Because the duration and costs of vaccine efficacy trials are great, several strategies are being developed to gain insights into the critical immune mechanisms necessary for protection in humans. Testing vaccine candidates in TST-negative individuals and evaluating their ability to prevent infection as measured by IGRAs could be accomplished in a shorter time than disease prevention trials. As discussed, vaccinating patients at the completion of drug treatment to prevent relapses or reinfection in high-burden areas could provide information in as little as one to two years. In all such trials, it will be essential to study multiple molecular and immunological markers to develop correlates of protection. Finally, the most promising candidates need to be tested in small groups of volunteers to understand which of the different mechanisms each candidate engenders, which are likely to correlate with protection, and which can be used as biomarkers for protection. Here innovative trial designs, such as matched-pair randomized trials, could provide power and information with much fewer volunteers (King and others 2009).

Relevant are the older studies indicating that latent TB seems to engender persisting immune responses that afford significant protection from disease (Andrews and others 2012), when compared with the risks of reinfection of TB patients who have been cured (Middelkoop and others 2015). This raises the concern that, if chemotherapy kills most of the Mtb organisms, the susceptibility of people successfully cured of TB will revert back to that of naïve individuals. This suggests that the immunologic value of latency may lie in the persistence of the pathogen and microbial antigens. Thus, the duration of protective immune responses engendered by new vaccines may be critical to protecting against reinfection and relapse. These findings reinforce the approach of vaccinating or revaccinating individuals who have been "cured" by treatment to test whether vaccination will reduce the incidence of relapse or reinfection.

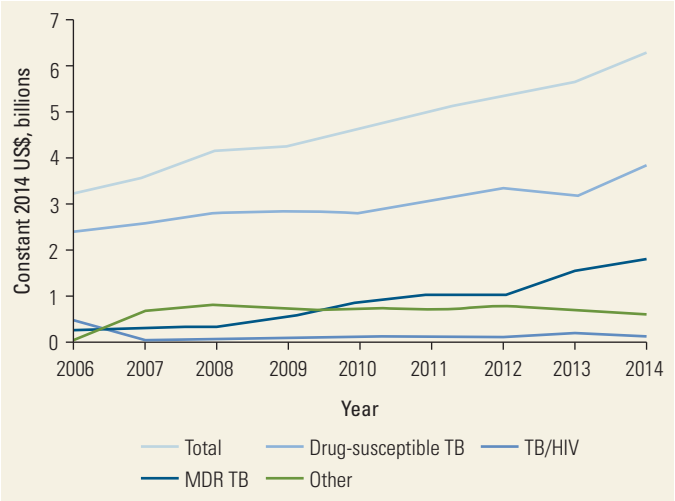
Since BCG is the most widely used vaccine in the world, particularly in high-burden TB countries, the most likely vaccine strategy will be priming with BCG or another whole-cell candidate in early childhood and boosting with a live attenuated TB vaccine, a vaccine with Mtb antigens expressed in a viral vector (such as an adenovirus or CMV), or a subunit vaccine containing multiple epitopes plus an adjuvant. Particularly exciting are new vaccine platforms that offer the possibility of generating long-enduring immune responses to Mtb antigens, including recombinant BCG vaccines designed to engender both CD4 and CD8 T-cells (Kaufmann and others 2014), attenuated TB vaccine (Spertini and others 2015), attenuated recombinant CMV vectors (Hansen and others 2013), and mRNA (messenger ribonucleic acid) vaccines (Chahal and others 2016; Petsch and others 2012). Clearly, vaccine trials

comparing multiple candidate vaccines in phases II and III are enormously expensive and time-consuming (on the order of US$50 million per trial over a period of three to five years). This is why there is an urgent need to define molecular or immunological correlates of protection that would enable the up-selection of the most promising candidates from small-scale human studies.

An alternative being pursued is developing a safe, genetically engineered Mtb live challenge strain that could persist long enough to enable rapid assessment of the effectiveness of a vaccine to induce killing of the challenge strain, but totally lacking the potential to cause disease. With phase I human studies in a small number of individuals, the ability of a vaccine candidate to kill the challenge strain would support conducting a small number of phase II and phase III clinical trials to test the efficacy of a particularly effective vaccine candidate against TB infection and disease. Historically, all vaccines have been iterative processes with continuous learning and improvements. The development of biomarkers of protection that would enable identification of the most promising candidates for large clinical trials would profoundly accelerate TB vaccine development.

Effective new vaccines are essential for TB control, yet their development, testing, and regulatory approval require many years and considerable investment. The slow decline in TB incidence globally, especially in high-burden countries, even as mortality and prevalence are declining, compels us to recognize the serious possibility that tuberculosis may not be controlled without a protective vaccine.

Figure 11.8 Funding for Tuberculosis Prevention, Diagnosis, and Treatment, by Intervention Area, 2006–14



Source: WHO 2015b.
Note: TB = tuberculosis; HIV = human immunodeficiency virus; MDR = multidrug-resistant.

FINANCING FOR TB PROGRAMS

The WHO estimates that funding for prevention, diagnosis, and treatment of TB reached US$6.6 billion, of which US$5.3 billion was for diagnosis and treatment of drug-susceptible TB and US$1.8 billion was for MDR TB (WHO 2014b). Of those funds, 84 percent derives from domestic sources, which vary across countries (WHO 2016a).

In 2014, development assistance allocated US$1.4 billion to TB (IHME 2015), a drop of 9 percent from 2013, two-thirds of which came from the Global Fund. The WHO estimates the shortfall in funds necessary to expand TB programs at about US$2.0 billion (WHO 2016a). The Global Fund is the single largest funder of TB assistance globally committing about 55 percent of its funds to HIV/AIDS, 27 percent to malaria, and 18 percent to TB (IHME 2015). Yet financing from the Global Fund represents about 50 percent of all current development assistance for health devoted to TB. The United States does not have a separate entity for funding TB as it does for HIV/AIDS and malaria, instead channeling half of its US$500 million in TB assistance through the Global Fund; the remainder is channeled bilaterally. In 2014, the Bill & Melinda Gates Foundation provided about 12.6 percent of all development assistance for health dedicated to TB. Other government donors were the United Kingdom (7.7 percent), France (7.0 percent) Germany (5.1 percent), Japan (3.4 percent), Canada (4.7 percent), and Australia (2.2 percent) (IHME 2015). Of these funds, about 78 percent were provided through the Global Fund.

The WHO estimates that the level of funding required to enable a comprehensive approach to controlling TB would be on the order of US$8.8 billion, two-thirds of which would be for diagnosis and treatment of drug-susceptible TB and 20 percent for drug-resistant TB (WHO 2016a). This figure does not include the costs of research needed to develop new drugs, vaccines, and diagnostics, which the WHO estimates would require an additional US$2.0 billion.

Given the magnitude of the TB epidemic, the emergence of MDR and XDR TB, and the need to strengthen health systems for TB, a greater level of funding will be required to extend current efforts and enable the new approaches recommended here to reduce incidence and transmission of the disease dramatically (figures 11.8 and 11.9). A summary of the latest 2015 recommendations of the Copenhagen Consensus Center, a consortium of international economists, suggested that additional investment in TB would represent a good buy (*Economist* 2015). For every US$1 invested, the return was estimated to be US$43. Were US$2 billion invested to cover the shortfall, the potential economic savings could

be on the order of US$300 billion (Lundgrun 2015). But despite increases in domestic and international financing, the WHO estimates the current funding gap to be US$2.0 billion for extending current measures and an additional US$1.3 billion for research and new technologies. That leaves a funding gap of US$2.7 billion per year to assure a full response to the TB epidemic.

ECONOMIC ANALYSES AND COST-EFFECTIVENESS

As the pipeline for new TB diagnostic technologies continues to expand, health and economic evaluations are needed to inform decisions about the most promising options to pursue in different settings and patient populations. Economic evaluation of new diagnostic approaches can seem deceptively simple, but several factors should be considered if these evaluations are to provide credible and useful guidance for policy. These factors pertain both to quantifying potential impact and to estimating costs.

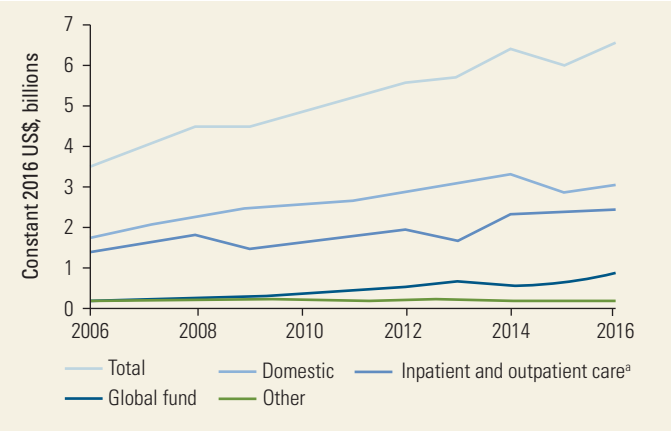
First, it is important to consider the pathway(s) by which new diagnostics are expected to lead to improved health outcomes. For instance, aspirations for new point-of-care diagnostics point to the benefits of returning rapid test results, which can reduce loss to follow-up by eliminating the need for a return visit. Quicker diagnosis may increase the rate of initiating treatment, improve patient outcomes, and reduce transmission by decreasing the period of infectiousness. However, imperfections in implementation may cause real-world application to fall short of the maximum theoretical potential.

Moreover, evaluating the impact and cost-effectiveness of a new approach requires comparing the new approach to the status quo that it will displace. For example, a comparative evaluation of a new diagnostic approach should specify (1) where the diagnostic will be used (for example, only in central facilities such as district hospitals or also in peripheral health centers); (2) the sequence of tests and associated responses that will guide decision making in different types of individuals or be based on particular population-level factors (for example, in individuals with HIV/AIDS or a history of treatment or in a setting with a particular population-level HIV/AIDS prevalence); and (3) the current diagnostic approach in these settings that constitutes the status quo comparator (that is, the extent to which bacterial culture or drug-sensitivity testing is currently being used).

It is also crucial to estimate the costs associated with scale-up and implementation, which are often significantly greater than the costs of the commodities per se or even the costs including other health care services that are consumed at the patient level (for example, the opportunity costs of provider time). At the simplest level, scaling up new technologies often involves economies (or costs) of scale that relate to the shape of the average cost function in relation to the quantity, which reflects different mixtures of fixed and variable costs at different scales. At a more complex level, achieving population coverage requires paying attention to health system capacity, reflecting constraints not only on the budget but also on infrastructure and human and other resources. The validity of cost-effectiveness estimates depends on quantifying the costs of delivering an intervention or strategy in a way that is consistent with the benefits ascribed to that intervention or strategy. Many published studies fail to meet this requirement.

With regard to diagnostic approaches, important questions should be addressed regarding patient pathways to care, how a new diagnostic technology or strategy will alter the pathways, and where delays or loss to follow-up may occur, particularly as these might attenuate the expected benefits of a diagnostic. In HIV/AIDS, considerable attention has recently been given to the so-called "cascade of care," and similar considerations are highly salient to tuberculosis control interventions, including those relating to diagnosis (Subbaraman and others 2016).

Figure 11.9 Funding for Tuberculosis Prevention, Diagnosis, and Treatment by Funding Source, 2006–16



Source: WHO 2016a.

a. 91 percent of funding for inpatient and outpatient care is accounted for by middle- and high-income countries; such countries do not typically receive international donor funding for inpatient and outpatient care services. Data are estimates based on country-reported utilization.

Cost-Effectiveness of Using Xpert MTB/RIF

Xpert MTB/RIF represents a significant technological advance in accelerating diagnosis of TB and MDR disease in many settings. However, it has significant limitations. Several studies have examined the cost-effectiveness of Xpert MTB/RIF in different LMICs. A cost-effectiveness study published in 2011 by Vassall and colleagues (2011)

and focusing on India, South Africa, and Uganda estimated that Xpert devices used in combination with smear would have an incremental cost-effectiveness ratio of between US$41 and US$110 compared to conventional use of smear plus clinical diagnosis. A 2012 modeling study (Abimbola and others 2012) estimated cost-effectiveness of Xpert at the regional level in Sub-Saharan Africa and found that Xpert would reduce mortality and lower overall costs. Another 2012 study focusing on screening with Xpert prior to initiating ART in HIV/AIDS patients (Andrews and others 2012) found much less favorable results, indicating that using Xpert would cost US$5,100 per year of life saved compared to the next most attractive strategy, which involved smear and culture. A third study from 2012 (Menzies and others 2012) examined the cost-effectiveness of Xpert in five Southern African countries and found a cost-effectiveness ratio of around US$1,000 per DALY averted. Other studies have shown smaller-than-projected benefits of Xpert.

Widely divergent results reflect the many challenges of evaluating new diagnostic technologies and point to several areas for further investigation, including the extent to which frequent empirical treatment would reduce the potential benefit of Xpert technology measured against a counterfactual of diagnosis based strictly on the results from smear microscopy. As dramatic scale-up of Xpert has been pursued in South Africa and other settings, other implementation challenges have come to light, including the high overall budgetary impact of seeking high coverage of Xpert, the feasibility of deploying Xpert at the point of care, inability to link Xpert findings to health information systems, and limits on the potential benefit of faster diagnosis arising from the failure to translate diagnostic improvements into faster initiation of treatment (Lawn 2015).

New technologies that can be used at the point of care are needed, and portable devices (for example, GeneXpert Omni) are under development that can be used as a point-of-care diagnostic test. Nevertheless, expanding their capacity for drug-sensitivity testing against the multiple drugs used in secondary and tertiary drug regimens remains a daunting challenge.

Cost-Effectiveness of Developing New Drugs and Regimens

The public health case for investing in new TB drugs is clear (Zumla, Nahid, and Cole 2013), but the substantial cost of drug development remains a significant obstacle to progress. Even if the efficiency of new drug development can be improved, new TB drug development is likely to remain a challenging investment decision for many years to come.

The cost-effectiveness and affordability of first-line regimens for TB treatment have been long established (World Bank 1993), and attention has focused on exploring the most cost-effective way to deliver treatment. For countries providing TB treatment through hospitals, studies have demonstrated the relative cost-effectiveness of ambulatory treatment (Floyd, Wilkinson, and Gilks 1997; Vassall and others 2002; Vassall and others 2009). Economic analysis in other settings has focused on delivering care through community structures (Floyd and others 2003; Moalosi and others 2003; Nganda and others 2003) and ensuring effective cooperation with the private sector (Floyd, Arora, and others 2006; Pantoja, Floyd, and others 2009; Pantoja, Lönnroth, and others 2009). Although these studies demonstrate feasible and cost-effective approaches to delivering TB treatment, the high costs of delivering relatively long antibiotic therapies in poorly resourced health systems is a concern, as are the high default rates in some settings (Kruk, Schwalbe, and Aguiar 2008). These concerns are heightened by evidence of the substantial economic and poverty impact of TB treatment on patients (and households), with numerous studies finding that the multiple health service visits required can have a severe impact on the economic welfare of TB patients (Barter and others 2012).

The current approach to the treatment of MDR TB presents a particular challenge from an economic perspective. Several studies (Floyd and others 2012; Resch and others 2006; Suarez and others 2002; Tupasi and others 2006) have suggested that the treatment of MDR TB is cost-effective. A recent systematic review found that the cost per DALY averted was lower than gross domestic product per capita in all 14 of the WHO subregions considered (Fitzpatrick and Floyd 2012). However, the absolute price of second-line drug regimens, even for LICs, can run into the thousands of dollars, with a three- or fourfold burden on total costs of the health system. For example, in South Africa, treating MDR TB costs more than half of the total national budget for TB control (Schnippel and others 2013), with hospitalized treatment costing more than US$15,000 per person treated (Pooran and others 2013; Schnippel and others 2013). However, these costs may be substantially reduced given the efforts to decentralize MDR TB treatment and care. Also potentially cost-effective, the cost of drug-susceptibility testing required to confirm a diagnosis of MDR TB treatment can also be substantial (Acuna-Villaorduna and others 2008; Floyd and others 2012), and, as highlighted in previous sections, culture-based DST provides a substantial practical challenge in settings with limited laboratory capacity. Additionally, the economic burden of MDR TB on households may be substantially higher than the costs of first-line treatment

and is likely to be catastrophic (Ramma and others 2015; survey of MDR TB patient costs in South Africa, unpublished data).

In light of these challenges, increasing attention is being placed on developing low-cost models of MDR TB diagnosis and treatment for scale-up—for example, new ambulatory models of care (Sinanovic and others 2015; Weiss and others 2014). In short, although the current approaches to the treatment of both drug-susceptible TB and MDR TB are widely accepted to be cost-effective, the relatively high cost of treatment for both patients and health systems, the cost of DST, the high levels of default, and the limited effectiveness of MDR TB treatment in low- and middle-income health systems make a strong economic and public health case for investing in new TB drugs.

In recent years, substantial investments have been made in clinical trials of new TB drugs and regimens (Hoagland and others 2016; Zumla, Nahid, and Cole 2013). Candidate drugs affect treatment efficacy or effectiveness and cost through different pathways, but the broad aim has been to improve one or more of the following three dimensions:

- Shorten the duration of treatment; trialed examples for first-line regimens include four-month moxifloxacin-based regimens (Gillespie and others 2014; Jindani and others 2014) and the Bangladesh regimen and bedaquiline-based regimens for MDR TB (Diacon, Donald, and others 2012).
- Increase the efficacy of treatment, particularly for MDR TB; trialed examples include delamanid (Gler, Skripconoka, and others 2012) and bedaquiline (Diacon, Donald, and others 2012).
- Develop regimens that are effective in both drug-susceptible and MDR TB. This will require new drugs for which drug resistance does not currently exist in most populations.

In order to justify and support investment, various economic and modeling efforts have explored the potential gains from improving these dimensions of TB treatment in terms of cost-effectiveness, direct effect on treatment success, broader impact on transmission, and patient and provider costs. In recent years, academic interest in both the investment in new drugs and these analyses has increased. At the time of writing, considerable work is ongoing, with much new work expected on the horizon.

Shortening Treatment Regimens to Reduce Incidence

To date, modeling analyses of TB treatment have focused on the population-level health gains from investing in shortening treatment regimens. For example, examining first-line treatment, both Salomon and others (2006) and Abu-Raddad and others (2009) used a transmission model calibrated to the South-East Asia region and found a substantial impact on incidence due to the introduction of shortened regimens. Salomon and others (2006) found that a noninferior two-month first-line regimen would prevent around 13–21 percent of all new TB cases and 19–25 percent of TB deaths, depending on assumptions made regarding the scale-up of current regimens over an 18-year period. The study suggested that, if the cost savings generated by treatment shortening were invested in TB case detection, two- or threefold reductions in incidence might be possible. Abu-Raddad and others (2009) found that a four-month regimen with efficacy similar to that of the standard of care would achieve up to a 10 percent reduction in incidence over 35 years and a two-month regimen with increased efficacy would achieve a 23 percent reduction in incidence over the same period of time. A more recent effort by Fofana and others (2014) suggested a more modest, but still positive, impact, estimating a 3 percent reduction in incidence from a four-month regimen and a 7 percent reduction from a two-month regimen over a 10-year period.

The analysis of the economic gains from treatment shortening has relied primarily on decision analytic models of patient cohorts. A study by Owens, Fofana, and Dowdy (2013) examined a hypothetical noninferior first-line regimen and explored trade-offs between drug price, treatment duration, and health system treatment costs for a cohort of new TB patients. This study found that a novel regimen with a four-month duration costing US$1 per day would at worst be highly cost-effective and at best be cost saving, depending on the current level of treatment costs.

Ongoing work using an individual-based cohort model is exploring these trade-offs in specific country settings, using primary cost data from Bangladesh, Brazil, South Africa, and Tanzania (Zwerling and others 2016). This study found that, at the cost of US$1 per day, a four-month noninferior first-line TB drug regimen would be cost saving in South Africa (reducing costs about 10 percent) and in Brazil (reducing costs 20 percent), highly cost-effective in Tanzania (saving about US$120 per DALY averted), but not cost-effective in Bangladesh. Even if new first-line drugs cost up to US$10 and US$58 in South Africa and Brazil, respectively, using threshold analysis, Trajman and others (2016) found that the new TB regimen would be a cost-effective option compared to the standard regimen. This threshold price is US$0.97 in Bangladesh and US$1.13 in Tanzania (Zwerling and others 2016). In all settings, the impact on health would be modest and dependent on current default rates;

settings with higher health system and TB treatment delivery costs would have the highest gain. Unfortunately, the initial first-line regimens with potential regimen-shortening effects coming out of trials in 2014 (moxifloxacin-based regimens) failed to achieve adequate levels of cure, so these gains, at the time of writing, remain hypothetical.

Zwerling and others (2016) also drew attention to the importance of patient costs, with the largest savings achieved through reductions in the economic burden of TB treatment on households. Patient cost savings ranged from US$175 (South Africa) to US$45 (Bangladesh), depending on the setting.

Improving Therapeutic Efficacy in Patients with MDR TB

Compared to drug-resistant TB treatment regimens, much less research has been conducted on the potential cost-effectiveness and impact of new MDR TB regimens. In the last few years, two new MDR TB drugs (bedaquiline and delamanid) have come up for regulatory authority and programmatic approval by the WHO. As part of the process, an exploratory cost-effectiveness analysis was conducted using a decision analytic model of a cohort of new MDR TB cases (Vassall 2013). These analyses found both drugs to be potentially cost-effective, given their impact on efficacy. However, uncertainty around bedaquiline's impact on mortality and, in the case of delamanid, the lack of randomization used when assessing long-term outcomes, combined with the potential cardiotoxic effects, have raised concerns. The DALYs averted varied by setting, with countries already having good outcomes benefiting less. However, increased efficacy, even without treatment shortening, also reduced costs in some cases, as the need for MDR TB retreatment and management of chronic cases was reduced. The results were less certain for LICs; because the potential benefits of increased efficiency for transmission were not included, no definitive conclusion could be reached for these settings.

In the case of bedaquiline, the impact on cost-effectiveness of a shortened MDR TB regimen was also examined, given that the trial results suggested that time to sustained sputum conversion may be reduced (Vassall 2013). Examining a reduction in treatment of two months, the cost-effectiveness analysis found cost savings at current drug prices. However, the extent of cost savings depended on the duration of hospitalization during treatment. The benefits in terms of DALYS averted were less clear due to the trade-off between the reduction in default and cure rates. Further trials, with an integrated economic analysis, are ongoing that test the use of bedaquiline as part of a nine-month MDR TB regimen, the STREAM (Standardized Treatment Regimen of Anti-Tuberculosis Drugs for Patients with Multi-Drug-Resistant Tuberculosis) Trial (Nunn and others 2014). In 2016, the WHO recommended the new shortened regimen, which offers the promise of both lower drug prices and lower health system costs, while being as effective as longer-course treatments (WHO 2016b). Economic analyses are ongoing.

Developing New Drugs for Treating Drug-Susceptible and MDR TB as First-Line Therapies

For the drugs discussed here, most of the work to date has explored the economic and health benefits of reducing the length of treatment and improving efficacy. However, new drugs or regimens that hold promise for treating both drug-susceptible and rifampicin-resistant TB also may have significant benefits. One example is PaMZ (Diacon and others 2010; Diacon, Dawson, and others 2012), a trial currently on hold. This new treatment regimen was assumed to have a dual benefit: a shortened first-line treatment for drug-susceptible patients (four months) with an efficacy noninferior to the current standard treatment and a shortened second-line treatment for patients with rifampicin-resistant TB (six months) with an efficacy noninferior to first-line treatment for drug-susceptible TB patients. In this case, introduction of the new regimen could result in substantial cost savings (at least 35 percent reduction) from a societal perspective. The mean cost per presumptive TB patient was reduced by US$23 (28 percent) for health service treatment-related costs and US$42 (42 percent) for patient treatment-related costs in South Africa. When the introduction of PaMZ in a cohort of only rifampicin-resistant patients was modeled, both the reduction in costs and the gain in effect were greater. The clinical safety and effectiveness of this new regimen remains to be determined, but the economic modeling can be applied to any new regimen effective for treating both drug-resistant and drug-susceptible TB.

This model can be extended to explore the gains from a drug with the following optimal characteristics in all dimensions:

1. Short duration (two weeks maximum shortening)
2. High efficacy (95 percent cure rate for drug-susceptible TB, 85 percent for rifampicin-resistant TB)
3. Ability to treat all forms of TB (that is, with no circulating resistance and no need for initial DST)
4. Drug price set at US$5 per day.

Using the same model, Zwerling and others (2016) found that such a drug would be cost saving in a setting such as South Africa. Even with a comparatively high daily cost compared to current treatment, these authors

estimated a potential reduction of 51 percent of total TB diagnostic and treatment costs when modeling a cohort of 10,000 presumptive TB patients from a societal perspective. This is primarily a gain on the patient side, including a reduction in the direct costs of treatment and a more rapid return to full productivity. In this high-HIV/AIDS-prevalence setting, there is a slight increase in ART-related costs (from the health service perspective) of 4 percent and an increase in DALYs averted of 6.5 percent, primarily from a reduction in defaults and an increase in cure rates for persons with MDR TB.

In summary, while much of the evidence on the potential economic and health benefits of investment in new TB drugs is based on models, emerging findings suggest that reducing the duration, improving the efficacy, and expanding the range of use of TB regimens may have the potential for substantial economic and public health gains in most settings (table 11.7). In a field with no new drugs for the last half century up until the past five years, the biomedical and drug development challenges cannot be underestimated, but new drugs are now being trialed, and much work refining and validating these nascent predictions is expected to emerge in the coming years.

Costs to Patients of TB Treatment

For diagnosis and many months of treatment for TB, out-of-pocket costs can be catastrophic for patients and their families. Data on patient costs in LMICs are limited and incomplete. In a systematic analysis of 11 publications on patient costs in eight countries in Africa, Ukwaja and others (2012) estimated that mean patient prediagnostic costs varied between US$36 and US$196, corresponding to 10.4 and 35.0 percent of their annual income, respectively. Average patient treatment costs ranged between US$3 and US$662, corresponding to 0.2–30.0 percent of their annual income. Prediagnostic household costs accounted for 13–18.8 percent of patients' annual household income, while total household treatment costs ranged between US$26 and US$662, accounting for 2.9–9.3 percent of annual household income. Consequently, 18 percent to 61 percent of patients received financial assistance from outside their household to cope with the cost of TB care. Patient costs in South Africa for diagnosis and treatment of MDR TB were even more expensive: only 3 percent of patients were still employed, and disability grants were the primary source of income for 44 percent of patients

Table 11.7 Population Impact, Patient Impact, Cost, and Cost-Effectiveness of New Tuberculosis Drugs

Study and goal	Regimen	Setting	Time horizon	Impact (reduction)	Cost	Cost-effectiveness
Shortening treatment duration						
Salomon and others 2006	First-line, 2 month	South-East Asia	2012–30: 18 years	13–21% incidence; 19–25% mortality	—	—
Abu-Raddad and others 2009	First-line, 4 month, noninferior to standard	South-East Asia	2015–50: 35 years	10% incidence	—	—
	First-line, 2 month, 90% efficacy in drug-resistant cases			23% incidence		
	First-line, 10 days, 90% efficacy in drug-resistant cases			27% incidence		
Fofana and others 2014	First-line, 4 month, noninferior to standard	Global, nonspecific	10 years	1.9% incidence; 3.5% mortality	—	—
	First-line, 2 month, noninferior to standard			4.3% incidence; 7.5% mortality		
	First-line, 2 weeks, noninferior to standard			6.7% incidence; 13.1% mortality		

table continues next page

Table 11.7 Population Impact, Patient Impact, Cost, and Cost-Effectiveness of New Tuberculosis Drugs (continued)

Study and goal	Regimen	Setting	Time horizon	Impact (reduction)	Cost	Cost-effectiveness
Owens, Fofana, and Dowdy 2013	First-line, 4 month, noninferior to standard, US$1 per day	Global, nonspecific	Cohort lifetime	7.9 DALYs averted (100 cohort)	Health service cost: cost saving to US$5,900 (2012)	Highly cost-effective to cost saving, depending on current treatment costs
	First-line, 2 month, noninferior to standard, US$5 per day			14.6 DALYs averted (100 cohort)	Health service cost: cost saving to US$20,200 (2012)	Cost saving
Trajman and others 2016	First-line, 4 month, noninferior to standard, US$1 per day	South Africa	Cohort lifetime	Equivalent effect	10% societal cost reduction	Cost saving
		Brazil			20% societal cost reduction	Cost saving
		Bangladesh			3.5% cost increase	Not cost-effective (ICER: 997)
		Tanzania			Cost neutral	Cost-effective (ICER: 120)
Increasing efficacy for MDR TB treatment						
Vassall 2013	Bedaquiline	China, Estonia, Nepal, Russian Federation, Peru, Philippines	Cohort lifetime	Varied by setting from 0.94 to 5.27 incremental DALYs, depending on current treatment success	Varied by setting from US$823 to US$2,930, depending on ability to reduce retreatment costs	Varied from US$202 to US$2,042 per DALY averted; likely to be cost-effective in all settings except low income, but ICER highly uncertain, depending on assumptions regarding trial results
Vassall 2013	Delamanid	China, Estonia, Nepal, Russian Federation, Peru, the Philippines	Cohort lifetime	Varied by setting from 0.94 to 1.65 incremental DALYs depending on current treatment success	Varied by setting from US$757 to US$2,548	Varied from US$501 to US$1,654 per DALY averted; likely to be cost-effective in all settings except low income, but ICER highly uncertain, depending on assumptions regarding trial results
Developing regimens that are effective in both drug-susceptible and MDR TB						
Gomez and others 2016	First- (4 month) and second-line (6 month), PaMZ, noninferior to standard for first-line and equivalent to first-line treatment of drug-sensitive TB for MDR patients, less than US$1 per day	South Africa	Cohort lifetime	Equivalent effect estimated, presumptive TB cohort	35% societal cost reduction	Cost saving
				16% increase in DALYs averted, MDR cohort	60% societal cost reduction	Cost saving
Future developments						
Gomez and others 2016	Optimal: first- and second-line, 2 weeks, high efficacy, US$5 per day, no extra DST	South Africa	Cohort lifetime	6.5% increase in DALYs averted	51% societal cost reduction; 58.1% patient costs reduction; 56.5% treatment costs reduction; no change in diagnosis costs	Cost saving

Note: DALY = disability-adjusted life year; ICER = incremental cost-effectiveness ratio; MDR = multidrug resistant; TB = tuberculosis; PaMZ = pretomanid/moxifloxacin/pyrazinamide; DST = drug-sensitivity testing; — = not available.

(Ramma and others 2015). Many of the patients reported having no source of income before (56 percent) and during (47 percent) treatment. These costs were likely catastrophic for many patients.

Modeling the Impact of New Vaccines

The last decade has seen a significant increase in the level of investment in TB vaccine development: more than 14 TB vaccine candidates have been tested in 50 human trials, with funding of more than US$600 million (Jiménez-Levi 2012). Despite the significant costs of vaccine development (Brennan and Thole 2012), the complex task of selecting vaccine candidates must now occur. Therefore, there is an effort to determine globally acceptable criteria for differentiating and subsequently maintaining the most promising candidates in the vaccine pipeline (Brennan and Thole 2012).

Mathematical modeling can be used to differentiate candidates on the basis of the potential impact that different vaccine characteristics targeted at different population groups may have on the future TB burden. For example, modeling the impact of vaccines targeted at uninfected infants in South-East Asia has suggested that a novel vaccine introduced in 2015 could avert more than 40 percent of the TB burden by 2050 (Abu-Raddad and others 2009) and that, to have the most rapid impact on TB burden, such a vaccine would need to be efficacious in both uninfected and latently infected individuals (Dye and Williams 2008). Linking such work to the economics of TB vaccines has shown that different TB vaccine profiles can also be cost-effective (BIO Ventures for Global Health 2006; Ditkowsky and Schwartzman 2014; Tseng and others 2011). However, uncertainty remains about how various vaccine characteristics (efficacy, duration of protection) and targeting strategies (age, HIV/AIDS status) may combine to maximize impact in countries with the largest TB burden.

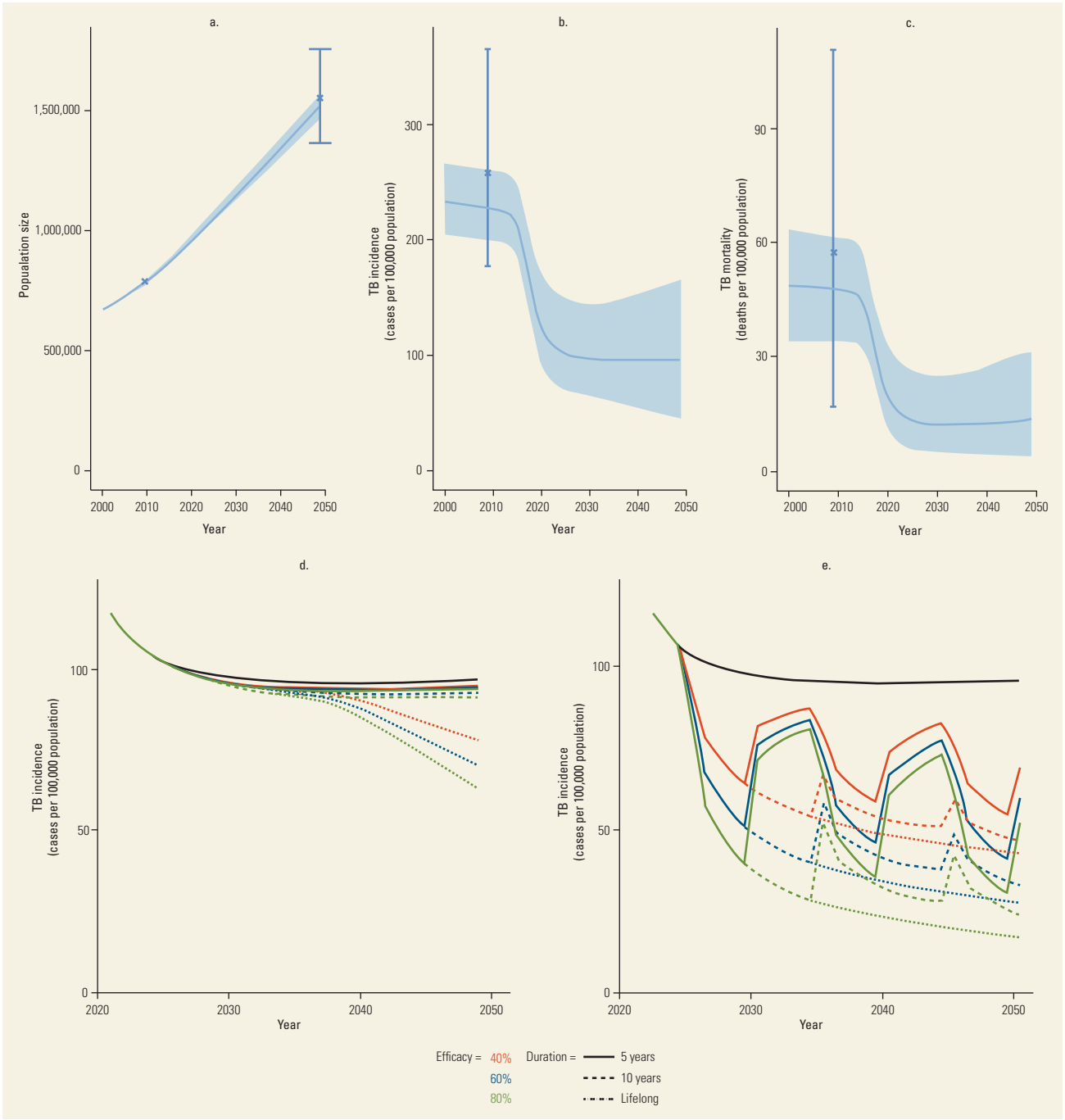
The underlying economics of TB vaccines are also unclear. For example, depending on the vaccine profile, the likely price of both vaccine delivery and dose remains uncertain. TB vaccines for infants could be incorporated into the standard infant vaccination program (DTP3 [diphtheria-tetanus-pertussis]), and cost estimates are straightforward to generate. However, the economics of targeting adolescents and older populations are largely unknown, and only recently are these populations being considered as a new platform for other vaccines, such as human papillomavirus (Sinanovic and others 2009) or measles booster. In the future, with these and other potential vaccines (for example, measles, human papillomavirus, or a future HIV/AIDS vaccine) for adolescents and adults, the targeting of adolescents via schools is likely to become increasingly common, and thus the costs may decrease. Due to the pervasiveness of Mtb infection in high-burden settings, TB vaccines targeted at adults may be used in mass campaigns to prevent disease. There are few precedents for such campaigns, and the levels of coverage that could be achievable are open to debate. Similarly, the lack of acceptability of frequent mass campaigns could limit the potential impact of a TB vaccine for adults. Finally, it is possible that vaccines could be targeted to patients being treated with TB or MDR TB either to accelerate treatment times or to prevent recurrence after drug treatment.

Knight and others (2014) have explored a wide range of vaccine profiles to understand what type of vaccine profile, targeted at what age group, would have the biggest impact on TB incidence in LMICs (Knight and others 2014). Vaccine profiles were defined by both efficacy and duration of protection, with a range from 40 to 80 percent and from five years to lifetime, respectively. The vaccine was assumed to be introduced in 2024. A comparison was then made between targeting infants and targeting adolescents or adults in mass campaigns. A new TB vaccine would likely be used as a booster to BCG, due to the broad use of BCG and its efficacy in infants. The vaccine was assumed to prevent active disease in both uninfected and latently infected individuals, with 40 percent less efficacy in persons with HIV/AIDS. Vaccine "take" was modeled with an exact duration of protection. Each country was modeled separately, with calibration methods used to capture both uncertainty in natural history parameters and the data on TB burden (WHO 2013b). Vaccine coverage was taken from similar mass campaigns in each country, such as for rubella, and were timed to occur with a frequency of every 10 years or the duration of protection (whichever was shorter) from 2024 onward. Cost-effectiveness was defined as cost per DALY averted compared against gross national income per capita from a health sector perspective, with tiered vaccine pricing by income group.

By estimating the burden of TB in all LMICs for which data were available, the model was able to predict that a vaccine targeted at adolescents or adults would have a far greater impact on TB burden before 2050 than one targeted at infants (figure 11.10) (Knight and others 2014). This is due to the differential burden of disease between these two age groups, with infants suffering from greater levels of extrapulmonary TB and therefore contributing less to transmission (Styblo 1991). This conclusion remained valid over the 2024–50 period, even when considering lifetime duration of protection.

Knight and others (2014) reported that vaccines targeted at adolescents or adults with 10-year durations of protection and 60 percent efficacy could be cost-effective in LICs at US$149 (95 percent range cost saving of US$387) per DALY averted at a cost of US$1 per dose.

Figure 11.10 Model Calibration and Vaccine Impact in Low-Income Countries



Note: Model calibration (panels a–c) and vaccine impact (panels d–e) in low-income countries. Panels a–c show median (solid dark blue line) and 95% range (blue cloud) of model fits to data. (Panel a) Human population size (per 1,000) in low-income countries, 2000–50. (Panel b) Tuberculosis (TB) incidence: cases per 100,000 population per year, 2000–50 (Panel c) TB mortality: deaths per 100,000 population per year, 2000–50. (Panels d–e) TB incidence (cases per 100,000 population per year), 2000–50, with median model output (black line) and vaccine profile impact: characteristics of efficacy (color) and duration of protection (line type) for vaccines targeted at infants (panel d) or at adolescent or adults (panel e). A vaccine targeted at infants (panel d) has a smaller impact on TB disease incidence than one targeted at adolescents or adults (panel e). The "waves" within the adolescent or adult incidence figure (panel e) are due to the impact of mass campaigns.

The same profile targeted at infants would avert only 0.89 (0.42–1.58) million TB cases while averting 17 (11–24) million TB cases in adolescents or adults and would not be considered cost-effective at US$1,692 (US$634–US$4,603) per DALY averted. In threshold analysis, the price per dose at which the vaccine profile would be cost-effective was determined. For example, a vaccine with 10-year duration of protection and 60 percent efficacy targeted at adolescents or adults could be priced at up to US$20 in upper-middle-income countries and still be considered cost-effective. This reflects the large number of cases that could be averted by targeting the age group in which most cases of disease occur and in which most sources of transmission are found. Vaccines with short duration (five years) and low efficacy (40 percent) were also found to be cost-effective if targeted at adolescents and adults.

A recent review pointed out that funding for TB vaccine development significantly lacks the same support provided to other vaccine development efforts (Manjelievskaia and others 2016). For example, funding to develop an Ebola vaccine ramped up quickly following the 2013–14 epidemic in Guinea, Liberia, and Sierra Leone, an outbreak that killed approximately 11,310 persons. The global response to the outbreak was enormous; the U.S. government alone appropriated more than US$5.4 billion for the Ebola emergency response in 2015, of which a large portion was directed to research, including developing Ebola vaccines. In comparison, funding to develop a TB vaccine received only US$85 million to US$90 million in 2015 (based on prior years' funding numbers), despite an estimated 29,000 people dying of TB per week (based on 2014 mortality estimates) and little sign of meaningful diminution in the global spread of Mtb and the continuing spread of MDR and XDR TB (Frick, Henry, and Lessem 2016; TAG 2016).

In conclusion, vaccines have an enormous potential to reduce the incidence and prevalence of TB if they are targeted at adolescents or adults, suggesting that increased investments in candidate vaccines targeting this group are warranted. Vaccines are also likely to be highly cost-effective, even if only having relatively modest clinical effectiveness. Given the age-dependent period of risk, special consideration should be given to developing candidate vaccines providing long-term protection.

EXTENDED COST-EFFECTIVENESS ANALYSIS OF UNIVERSAL PUBLIC FINANCING OF TB TREATMENT

Tuberculosis causes approximately 28 million active infections and 480,000 deaths in India annually (WHO 2016a). The disease burden is concentrated largely within the poorer parts of the population: TB has a four times greater incidence among persons in lower socioeconomic groups, and incidence is greater in rural than urban areas (Muniyandi and others 2007). Private health expenditures also constitute a large majority of India's total health expenditures, and most TB patients consult private practitioners for their first visit, resulting in substantial OOP spending on TB (Satyanarayana and others 2011; Uplekar and others 1998; Uplekar, Pathania, and Raviglione 2001). In India, as in many countries, OOP medical costs are a leading cause of impoverishment. Kruk, Goldmann, and Galeo (2009) and Sengupta and Nundy (2005) found, for example, that about 40 percent of Indian households borrowed money or sold assets to pay for health care. In light of such findings, the government is increasingly assuming responsibility for financing TB treatment (Jha and Laxminarayan 2009).

Universal public finance (UPF) is when government finances an intervention irrespective of who is receiving it. For any given health intervention, UPF entails consequences in multiple domains. First, UPF increases intervention uptake. Second, it eliminates the need for private expenditures. Finally, it provides financial risk protection (insurance) by covering catastrophic expenditures that would otherwise throw households into poverty. This section reports on these three consequences of UPF using extended cost-effectiveness analysis (ECEA) findings on DOTs expansion in India (Verguet, Laxminarayan, and Jamison 2015).

Because of the importance of OOP costs, international agencies have supported the use of health sector policies to attenuate health-related financial risks (WHO 1999, 2010; World Bank 1993). Despite the attention paid to its significant potential as part of broader social insurance, UPF in practice covers few interventions in most LMICs, with little consensus on what to cover in highly resource-constrained environments. In India, UPF has typically financed condition-specific programs (for example, against leprosy, HIV/AIDS, and cataract blindness) or, more recently, secondary and tertiary care insurance such as the Rashtriya Swasthya Bima Yojana and the Arogyasri (in Andhra Pradesh) programs. These insurance programs are thought to provide significant financial protection since they defray the high OOP costs associated with hospitalizations.

Currently, about 70 percent of TB cases receive DOTS; only about half of these services are obtained for free in the public sector. People do not always obtain TB treatment at the public hospital level for various reasons, including transportation cost and waiting time. Most lower-income people prefer to see a private physician after working hours than to take a day off work without pay to visit a public hospital (Kumar and Kumar 1997).

Table 11.8 Public Finance of Tuberculosis Treatment to 90 Percent Coverage in India, by Income Quintile

per million population

Outcome	Total	Income Quintile				
		I	II	III	IV	V
TB deaths averted	80	40	25	12	3	0
Private expenditures crowded out[a]	29	6	6	7	6	4
Insurance value[a]	9	5	2	1	1	0

Note: TB = tuberculosis.

a. Figures expressed in 2011 US$, thousands.

Table 11.9 Borrowing to Finance Tuberculosis Treatment in India, by Income Quintile

per million population

Outcome	Total	Income Quintile				
		I	II	III	IV	V
TB deaths averted	29	13	10	5	1	0
Private expenditures crowded out[a]	–25	–12	–8	–4	–1	0
Insurance value[a]	0	0	0	0	0	0

Note: TB = tuberculosis.

a. Figures expressed in 2011 US$, thousands.

Yet, privately purchased TB treatment is often ineffective because private doctors do not necessarily provide the standard regimen with proven efficiency (Satyanarayana and others 2011; Udwadia, Pinto, and Uplekar 2010; Uplekar and Shepard 1991). A potential virtue of UPF is to eliminate low-quality treatment in the private sector, enabling the uptake of higher-quality treatment and increasing technical efficiency. However, this requires a well-managed public sector program, something widely achieved only in parts of India.

We estimated the results of expanding DOTS through UPF to cover 90 percent for an Indian population of 1 million (table 11.8). The total number of lives saved would be about 80 per 1 million per year, and the health benefits would be concentrated among the bottom two income quintiles (80 percent), as TB has a higher incidence among these socioeconomic groups. The total number of private expenditures averted by the program would be about US$30,000 per 1 million population per year, and the bottom two quintiles would benefit from about 40 percent of the private expenditures averted. The total financial protection provided for this population sample (measured as a money-metric value of insurance) would be about US$10,000, 80 percent of which would accrue to the bottom two quintiles. The total (incremental) treatment costs incurred by UPF for the sample would be about US$65,000.

This analysis illustrates how UPF can be used to improve financial protection and technical efficiency by eliminating the purchase of lower-quality treatments. It is only a limited take on greater possibilities. For example, a detailed assessment could provide more comprehensive estimates of TB costs (for example, households' transportation costs, earnings, and productivity impacts). The focus here is on the OOP cost of treatment and excludes the cost of earnings reduced by the disease. For example, the number of working days lost due to TB can range from 30 to 90 in South India (Muniyandi and others 2006; Muniyandi and others 2008). Indirect costs from lost earnings can be substantial (Ananthakrishnan and others 2012), which would—in the absence of other forms of social insurance—increase the insurance benefits provided by UPF.

A limitation of focusing on the financial cost of treatment is that individuals do not get care for other reasons as well, including lack of information about TB and its treatment. Primary health centers in India may be difficult to reach due to poor travel conditions (Muniyandi and others 2006), be overcrowded, and not respect the dignity of patients. Health services may not always be available, even after informational and financial barriers have been removed: increasing coverage may thus not be feasible, and the extent of subsequent health gains from UPF may be significantly reduced in the absence of supply-side intervention. If demand for TB treatment for any of these reasons does not match disease incidence, the level of coverage achievable will be constrained.

Yet, using ECEA, Verguet, Laxminarayan, and Jamison (2015) demonstrated that the potential benefits of UPF for health and financial risk protection would accrue primarily to the poor. Reductions in OOP expenditures would also benefit the poor because UPF crowds out private financing of the inferior treatments frequently purchased by persons with income constraints. Lowering the costs of borrowing for the poor could potentially achieve some of the health gains of UPF, but at the cost of leaving the poor more deeply in debt (table 11.9).

SUMMARY AND RECOMMENDATIONS

While much progress has been made over the past several decades, particularly in reducing mortality, TB remains a major infectious disease, whose severity is exacerbated by the growing problem of multidrug-resistant TB, extensively drug-resistant TB, and co-infection with HIV/AIDS. Progress in TB control requires early and accurate case detection, rapid commencement of and adherence to effective treatment, and prevention of transmission.

The great challenge is to reduce transmission by identifying and treating patients with TB who are asymptomatic, unaware of their status, or unable to gain access to treatment.

This chapter offers four overarching recommendations: (1) strengthen the current WHO End TB Strategy to emphasize active case finding in targeted high-burden countries; (2) strengthen health systems in those countries, particularly emphasizing community-based care; (3) strengthen information systems; and (4) invest far more in research to develop the tools necessary to control TB. Fundamentally, it is necessary to revise the current global TB control strategies in most high-burden countries and to make significant new investments in health systems and research.

Rethinking and Revising the DOTS Strategy

Since the WHO designated tuberculosis as a global emergency in 1993, the DOTS strategy has been the mainstay of TB control worldwide. It is based on the premise that patients with TB will be sufficiently ill to seek care from the health system and, if appropriately treated, be cured and that transmission will be reduced. Since 1994, the DOTS strategy has significantly improved the diagnosis and treatment of individuals identified with tuberculosis in all countries and reduced mortality. The prevalence and treatment of drug-susceptible TB is a "best buy" at US$100–US$500 per case cured. Treatment of MDR TB remains limited and more expensive. Yet the decline of TB incidence globally, particularly in the 22 highest-burden countries, has lagged the declines in HIV/AIDS and malaria and is far below the MDG targets set by the Stop TB Partnership to reduce TB incidence, prevalence, and mortality by 50 percent compared with a baseline of 1990. With TB exceeding HIV/AIDS and malaria as the largest cause of death from any single infectious disease and drug resistance increasing, it is critical to reconsider how to control the epidemic more effectively.

DOTS has the great advantage of being a single, unifying global strategy that, in principle, can be applied to all patients in all countries. Yet, while effective in countries with strong health systems, DOTS is failing to bend the incidence curve rapidly, especially in LICs with high TB burdens and weak health systems. Management of TB has been particularly challenging in LMICs with high incidence and prevalence of co-infection with HIV/AIDS, which makes treatment more difficult and relapse or reinfection more common. Of particular concern is the limited impact of DOTS on the effective control of MDR TB, which requires complex diagnostic testing and is enormously expensive (US$5,000–US$10,000 per case cured) and only partially effective. TB, especially MDR TB, represents a serious threat to health personnel in high-burden countries. Even with high patient treatment compliance, in these contexts, DOTS as commonly implemented is not reducing the transmission and incidence of disease sufficiently rapidly. As this chapter discusses, substantial numbers of individuals with TB have tubercle bacilli in their sputa and yet are asymptomatic and not likely to report to a health facility and thus be detected by passive case finding.

In this context, the WHO has revised and promulgated the End TB Strategy, which emphasizes patient-centered care, treatment for all patients with drug-susceptible and drug-resistant TB, increased community engagement, and, for the first time, an explicit focus on research. Consistent with the End TB Strategy (WHO 2015a), this chapter suggests that a stratified approach with improved targeting in high-burden countries will be necessary in these contexts. Such a diversified and better-targeted strategy, should seek to accomplish the following:

1. Identify high-transmission countries and hot spots within countries where targeted efforts can be more effective and cost-effective.
2. Increase the capacity for surveillance.
3. Strengthen early TB detection and diagnosis by active case finding in certain countries and populations.
4. Provide rapid diagnosis and enable more rapid initiation and better maintenance of treatment for both drug-susceptible and multidrug-resistant TB.
5. Expand preventive therapy of the contacts of TB patients, children, and HIV-positive individuals.
6. Combine these strategies with an approach rooted in community-based delivery of TB services and support, wherever possible.
7. Improve the drug supply chain to improve access to TB treatments that have very small markets, and improve information technology to enable more effective control.
8. Significantly increase resources for research on developing new diagnostic technologies, development and testing of new drug regimens, and new vaccines to prevent TB.

All of these recommendations, while at some variance with previous DOTS protocols, are fully consistent with the new WHO End TB strategic goals (WHO 2015a). The new Stop TB Partnership's Zero TB Initiative seeks to apply these recommendations to demonstrate in a small number of high-burden cities that a comprehensive program of active case finding, effective treatment, and prevention in households can be effective in limiting transmission and reducing the incidence of TB (Stop TB Partnership 2016).

Expanding Active Case Finding

In high-burden, low-income countries, particularly those with a high incidence and prevalence of TB and HIV/AIDS co-infection, earlier and more comprehensive case finding and treatment are required. Passive case finding and screening of populations for classic symptoms clearly fail to detect a major proportion of existing TB cases, which are asymptomatic or unknown to the health system—representing up to one-third or 3 million cases—leading to continued transmission of TB infection. In low-burden countries where DOTS is effective in reducing incidence, prevalence, and mortality, the current approach should be expanded, and investments in active case finding are not likely to be cost-effective. But, in high-burden countries, targeted introduction of active case finding with modern rapid and point-of-care diagnostic tests and mobile X-radiography for screening populations could significantly improve early diagnosis and early institution of treatment and dramatically reduce transmission. As this chapter discusses, TB treatment regimens are lengthy and not without drug-related adverse events, which, in weak health systems, create challenges to maintaining consistent adherence to recommended drugs (Schaaf and others 2009; Verma and others 2004). Health systems that can provide patient support, including mechanisms to incentivize treatment completion, can bolster the effectiveness of active case finding.

Strengthening Health Systems

With drug-resistant TB now a global crisis, early diagnosis and effective treatment, either through improved access to bacterial culture and drug-sensitivity testing (Dowdy and others 2008; Uys and others 2009) or through rapid molecular diagnostics (Lin and others 2012), are essential to reduce the burden of drug-resistant TB in high-prevalence settings. Modeling studies suggest that these interventions could be highly cost-effective, because they provide not only potentially life-saving care but also prevent further spread of drug-resistant disease (Menzies and others 2012). Modeling studies also suggest that infection-control interventions can be very cost-effective (Basu and others 2007), especially when aimed at health care workers and the patients responsible for most transmission (Andersson 2006; Woolhouse and others 1997).

Although some new diagnostics and care delivery models have emerged, the uptake of new tools and innovations for TB control has been suboptimal in weak health systems (Cobelens and others 2012). New tools such as the Xpert MTB/RIF assay enable rapid and effective diagnosis of TB and MDR TB (Boehme and others 2010; Boehme and others 2011; Chang and others 2012), do not require highly skilled health workers (Rachow and others 2011), and have been demonstrated to be cost-effective (Vassall and others 2011). However, their rapid introduction has been hindered by weak health systems, specifically weak supply chain management systems, weak information systems linking diagnostic data to the site of treatment, and the need to address false-positive indications of rifampicin resistance (Dowdy and others 2011; Kirwan, Cárdenas, and Gilman 2012; Lawn and others 2011; Scott and others 2011; Trébucq and others 2011).

Increased numbers of better trained and motivated health workers at multiple levels, better information systems, and functioning logistics and supply chains are critical if TB is to be effectively controlled. TB transmission can be prevented through investments in infection control in clinics and hospitals; preventive therapy for household and HIV-positive contacts; better-designed housing for low-income populations; and better nutrition for at-risk populations. Efforts like these require technical and financial support, not only in TB programs per se, but also in complementary activities that support the delivery of TB services. Without improving health systems, extending the scope and targeting of TB programs, and providing additional technical and financial support, it is questionable how significantly and rapidly high-burden countries can improve TB control.

Expanding Community-Based Care

While in many countries, TB treatment has traditionally been hospital-based, in an increasing number of settings community-based treatment has been shown to be as clinically effective and significantly more cost-effective, even when compared with clinic-based management of TB. Efforts should be undertaken to transition health systems from hospital-based to community-based care in countries where doing so is feasible. Community-based care and treatment are effective and may offset some of the increases in financing required for active case finding. It will be important, in countries with large private health care providers, to develop public-private partnerships to engage the private sector in offering the best possible diagnostic and treatment protocols. Strengthening health systems to support more effective community-based TB care—including investing in community-based health workers, information systems, and supply chains—can have significant impact, not only on TB, but also on other infectious and chronic diseases, including HIV/AIDS and noncommunicable diseases such as diabetes and cardiovascular disease, which similarly require long-term or continuous treatment.

Strengthening Research and Development

The current tools for combatting TB are woefully inadequate, yet funding for TB research lags that for HIV/AIDS and malaria. Reducing the burden of TB and MDR TB will require greater funding for more intensive research into new approaches to point-of-care diagnosis, shorter and more effective treatment regimens for both TB and MDR TB, and better service delivery. But the current drug pipeline is thin. There is an urgent need for new drugs and regimens that will be cost-effective and affordable. Of particular urgency is the need to develop new multidrug regimens that shorten the duration of treatment, increase the number of cures of drug-susceptible TB, and, ideally, increase the number of cures of both drug-susceptible *and* drug-resistant TB. A small number of new drugs appear promising in this regard, but require further clinical evaluation. New regimens capable of effectively treating both drug-susceptible and drug-resistant TB would reduce the need for expensive drug-sensitivity testing and could be highly cost-effective. Several molecular tools are being developed that could allow prediction of risk for patients with latent infection to progress to active disease and, possibly, of when treated cases are truly cured. This approach could enable preventive treatment of individuals at high risk of progression to disease. The same molecular tools may be able to identify host gene signatures that would identify protective immune responses that could become biomarkers for predicting the efficacy of new vaccines.

Developing more effective vaccines to prevent TB infection, disease, relapse, or reinfection will be essential, since even a modestly successful vaccine would be highly cost-effective. BCG remains the most widely used vaccine in the world; while its ability to prevent severe childhood consequences of TB is cost-effective, its impact on preventing disease in adults is questionable at best. Preventing infection and disease is the major goal of vaccine research, and, given the challenges to case detection, drug resistance, and cure, it remains uncertain whether TB can be eliminated as a global public health problem without an effective preventive vaccine.

Drug, device, and vaccine companies are essential to developing the new tools required for TB, but they have few incentives to invest in a disease that occurs primarily in resource-poor countries where the returns on investments in long-term development and trials will be few, if any. Public-private collaborations could make a major difference to developing new technologies for TB.

The Bottom Line

TB remains the largest cause of death from an infectious disease, and, in contrast to HIV/AIDS and malaria, the incidence is not declining at a rate required to bring this epidemic under control. This chapter urges that the traditional strategy to control TB most commonly implemented in many countries, which has been successful in low-burden countries of the Americas and Europe, needs to evolve into a more stratified and targeted approach in order to meet the needs of high-burden populations where it has not been effective in controlling transmission and reducing incidence of TB. The WHO's End TB Strategy now emphasizes differences in the epidemic in different countries and the need for research to develop new tools (WHO 2015a, 2015c). The recommendations of this chapter are fully consistent with the WHO's End TB Strategy.

This chapter argues that new investments are needed to make health systems more responsive and effective by providing greater access to improved technologies for rapid diagnosis and to drug-sensitivity testing. It advocates for introducing new modalities, such as active case finding and community-based care in high-burden settings. Finally, it emphasizes the urgent need for greater investments in research to develop new tools for diagnosis, drug regimens for treatment, and vaccines for prevention. Such investments will be costly—and more funding will be required to extend current efforts and enable the new approaches recommended here—but ultimately highly cost-effective for both individuals and countries. Only with new thinking and new approaches will it be possible to transform TB control to a level that can achieve the ultimate goal of eliminating TB as a global public health problem. To reduce significantly the largest cause of death from infectious disease in the world and to improve the lives of people who suffer from it, greater financial investments will be necessary and indeed justified.

NOTES

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  (a) lower-middle-income = US$1,046 to US$4,125
  (b) upper-middle-income (UMICs) = US$4,126 to US$12,745
- High-income countries (HICs) = US$12,746 or more.

1. For example, http://reference.medscape.com/drug-interactionchecker or http://www.hiv-druginteractions.org.
2. For the WHO recommendations, see http://www.who.int/hiv/topics/tb/art_hivpatients/en.
3. Described at http://www1.nyc.gov/assets/doh/downloads/pdf/tb/tb2015.pdf.

4. For example, OpenBoxes (https://openboxes.com) and OpenLMIS (https://www.villagereach.org).
5. Sproxil (https://www.sproxil.com).

REFERENCES

Abel L, J. El-Baghdadi, A. A. Bousfiha, J. L. Casanova, and E. Schurr. 2014. "Human Genetics of Tuberculosis: A Long and Winding Road." *Archive of Philosophical Transitions of the Royal Society of London* 12: 369 (1645): 20130428.

Abimbola, T. O., B. J. Marston, A. A. Date, J. M. Blandford, N. Sangrujee, and others. 2012. "Cost-Effectiveness of Tuberculosis Diagnostic Strategies to Reduce Early Mortality among Persons with Advanced HIV Infection Initiating Antiretroviral Therapy." *Journal of Acquired Immune Deficiency Syndromes* 60 (1): e1–7.

Abu-Raddad, L. J., L. Sabatelli, J. T. Achterberg, J. D. Sugimoto, I. M. Longini Jr., and others. 2009. "Epidemiological Benefits of More-Effective Tuberculosis Vaccines, Drugs, and Diagnostics." *Proceedings of the National Academy of Sciences* 106 (33): 13980–85.

Achkar, J. M., and E. R. Jenny-Avital. 2011. "Incipient and Subclinical Tuberculosis: Defining Early Disease States in the Context of Host Immune Response." *Journal of Infectious Diseases* 204 (Suppl 4): S1179–86.

Acuna-Villaorduna, C., A. Vassall, G. Henostroza, C. Seas, H. Guerra, and others. 2008. "Cost-Effectiveness Analysis of Introduction of Rapid, Alternative Methods to Identify Multidrug-Resistant Tuberculosis in Middle-Income Countries." *Clinical Infectious Diseases* 47 (4): 487–95.

Ahuja, S. D., D. Ashkin, M. Avendano, R. Banerjee, M. Bauer, and others. 2012. "Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-Analysis of 9,153 Patients." *PLoS Medicine* 9 (8): e1001300.

Akolo, C., I. Adetifa, S. Shepperd, and J. Volmink. 2010. "Treatment of Latent Tuberculosis Infection in HIV Infected Persons." *Cochrane Database of Systematic Reviews* 20: CD000171.

Alhajri, K., N. Alzerwi, K. Alsaleh, H. Bin Yousef, and M. Alzaben. 2011. "Disseminated (Miliary) Abdominal Tuberculosis after Laparoscopic Gastric Bypass Surgery." *BMJ Case Reports* 2011 (May 12): bcr1220103591.

Alsdurf, H., P. C. Hill, A. Matteelli, H. Getahun, and D. Menzies. 2016. "The Cascade of Care in Diagnosis and Treatment of Latent Tuberculosis Infection: A Systematic Review and Meta-Analysis." *The Lancet Infectious Diseases* 16: 1269–78.

Amoroso, C., B Akimana, B. Wise, and H. S. F. Fraser. 2010. "Using Electronic Medical Records for HIV Care in Rural Rwanda." *Studies Health Technology and Informatics* 160 (Pt. 1): 337–41.

Ananthakrishnan, R., M. Muniyandi, A. Jeyaraj, G. Palani, and B. W. C. Sathiyasekaran. 2012. "Expenditure Pattern for TB Treatment among Patients Registered in an Urban Government DOTS Program in Chennai City, South India." *Tuberculosis Research and Treatment* 2012: 747924.

Andersson, D. I. 2006. "The Biological Cost of Mutational Antibiotic Resistance: Any Practical Conclusions?" *Current Opinion in Microbiology* 9 (5): 461–65.

Andrews, J. R., F. Noubary, R. P. Walensky, R. Cerda, E. Losina, and others. 2012. "Risk of Progression to Active Tuberculosis Following Reinfection with *Mycobacterium tuberculosis*." *Clinical Infectious Diseases* 54 (6): 784–91.

Ansa, G. A., J. D. Walley, K. Siddiqi, and X. Wei. 2012. "Assessing the Impact of TB/HIV Services Integration on TB Treatment Outcomes and Their Relevance in TB/HIV Monitoring in Ghana." *Infectious Diseases of Poverty* 1 (December 24): 13.

Arinaminpathy, N., T. Cordier-Lassalle, K. Lunte, and C. Dye. 2015. "The Global Drug Facility as an Intervention in the Market for Tuberculosis Drugs." *Bulletin of the World Health Organization* 93 (4): 237–48A.

Atun, R. 2012. "Health Systems, Systems Thinking and Innovation." *Health Policy and Planning* 27 (Suppl 4): iv4–8.

Atun, R., and R. Coker. 2008. "Health Systems and Communicable Disease Control: Emerging Evidence and Lessons from Central and Eastern Europe." In *Health Systems and the Challenge of Communicable Diseases: Experiences from Europe and Latin America*, edited by R. Coker, R. Atun, and M. McKee, 193–208. Maidenhead, U.K.: Open University Press.

Atun, R., T. de Jongh, F. Secci, K. Ohiri, and O. Adeyi. 2010. "Integration of Targeted Health Interventions into Health Systems: A Conceptual Framework for Analysis." *Health Policy and Planning* 25 (2): 104–11.

Atun, R., F. M. Knaul, Y. Akachi, and J. Frenk. 2012. "Innovative Financing for Health: What Is Truly Innovative?" *The Lancet* 380 (9858): 2044–49.

Atun, R., J. V. Lazarus, W. Van Damme, and R. Coker. 2010. "Interactions between Critical Health System Functions and HIV/AIDS, Tuberculosis, and Malaria Programmes." *Health Policy and Planning* 25 (Suppl 1): 11–13.

Atun, R., M. McKee, F. Drobniewski, and R. Coker. 2005. "Analysis of How the Health Systems Context Shapes Responses to the Control of Human Immunodeficiency Virus: Case-Studies from the Russian Federation." *Bulletin of the World Health Organization* 83 (10): 730–38.

Atun, R., N. Menabde, K. Saluvere, M. Jesse, and J. Habicht. 2006. "Introducing a Complex Health Innovation—Primary Health Care Reforms in Estonia (Multimethods Evaluation)." *Health Policy* 79 (1): 79–91.

Atun, R., Y. Samyshkin, F. Drobniewski, Y. Balabanova, I. Fedorin, and others. 2006. "Costs and Outcomes of Tuberculosis Control in the Russian Federation: Retrospective Cohort Analysis." *Health Policy and Planning* 21 (5): 353–64.

Atun, R., Y. Samyshkin, F. Drobniewski, N. M. Skuratova, G. Gusarova, and others. 2005. "Barriers to Sustainable Tuberculosis Control in the Russian Federation Health System." *Bulletin of the World Health Organization* 83 (3): 217–23.

Atun, R., D. E. Weil, M. Tan Eang, and D. Mwakyusa. 2010. "Health-System Strengthening and Tuberculosis Control." *The Lancet* 375 (9732): 2169–78.

Awofeso, N., I. Schelokova, and A. Dalhatu. 2008. "Training of Front-line Health Workers for Tuberculosis Control:

Lessons from Nigeria and Kyrgyzstan." *Human Resources for Health* 6 (20): 1–9.

Ayieko, J., L. Abuogi, B. Simchowitz, E. A. Bukusi, A. H. Smith, and others. 2014. "Efficacy of Isoniazid Prophylactic Therapy in Prevention of Tuberculosis in Children: A Meta-Analysis." *BMC Infectious Diseases* 14: 91.

Ayles, H., and M. Muyoyeta. 2006. "Isoniazid to Prevent First and Recurrent Episodes of TB." *Tropical Doctor* 36 (2): 83–86.

Ayles, H., M. Muyoyeta, E. Du Toit, A. Schaap, S. Floyd, and others. 2013. "Effect of Household and Community Interventions on the Burden of Tuberculosis in Southern Africa: The ZAMSTAR Community-Randomised Trial." *The Lancet* 382 (9899): 1183–94.

Ayles, H., A. Schaap, A. Nota, C. Sismanidis, R. Tembwe, and others. 2009. "Prevalence of Tuberculosis, HIV, and Respiratory Symptoms in Two Zambian Communities: Implications for Tuberculosis Control in the Era of HIV." *PLoS One* 4 (5): e5602.

Aziz, A., M. Ishaq, and R. Akhwand. 1985. "Infection Risk of Sputum Positive Tuberculosis Patients to Their Family Contacts with and without Chemotherapy." *Journal of Pakistan Medical Association* 35 (8): 249–52.

Baker, M. A., D. Wilson, K. Wallengren, A. Sandgren, O. Iartchouk, and others. 2012. "Polymorphisms in the Gene That Encodes the Iron Transport Protein Ferroportin 1 Influence Susceptibility to Tuberculosis." *Journal of Infectious Diseases* 205 (7): 1043–47.

Barrington, J., O. Wereko-Brobby, P. Ward, W. Mwafongo, and S. Kungulwe. 2010. "SMS for Life: A Pilot Project to Improve Anti-Malarial Drug Supply Management in Rural Tanzania Using Standard Technology." *Malaria Journal* 9 (298): 1–9.

Barry, C. E., H. I. Boshoff, V. Dartois, T. Dick, S. Ehrt, and others. 2009. "The Spectrum of Latent Tuberculosis: Rethinking the Biology and Intervention Strategies." *Nature Reviews Microbiology* 7 (12): 845–55.

Barter, D. M., S. O. Agboola, M. B. Murray, and T. Bärnighausen. 2012. "Tuberculosis and Poverty: The Contribution of Patient Costs in Sub-Saharan Africa—A Systematic Review." *BMC Public Health* 12 (November 14): 980.

Bassili, A., C. Fitzpatrick, E. Qadeer, R. Fatima, K. Floyd, and others. 2013. "A Systematic Review of the Effectiveness of Hospital- and Ambulatory-Based Management of Multidrug-Resistant Tuberculosis." *American Journal of Tropical Medicine and Hygiene* 89 (2): 271–80.

Basu, S., J. R. Andrews, E. M. Poolman, N. R. Gandhi, N. S. Shah, and others. 2007. "Prevention of Nosocomial Transmission of Extensively Drug-Resistant Tuberculosis in Rural South African District Hospitals: An Epidemiological Modelling Study." *The Lancet* 370 (9597): 1500–07.

Basu, S., and A. P. Galvani. 2008. "The Transmission and Control of XDR TB in South Africa: An Operations Research and Mathematical Modelling Approach." *Epidemiology and Infection* 136 (12): 1585–98.

Bates, M., J. O'Grady, P. Mwaba, L. Chilukutu, J. Mzyece, and others. 2012. "Evaluation of the Burden of Unsuspected Pulmonary Tuberculosis and Co-Morbidity with Non-Communicable Diseases in Sputum Producing Adult Inpatients." *PLoS One* 7 (7): e40774.

Bates, M. N., A. Khalakdina, M. Pai, L. Chang, F. Lessa, and K. R. Smith. 2007. "Risk of Tuberculosis from Exposure to Tobacco Smoke: A Systematic Review and Meta-Analysis." *Archives of Internal Medicine* 167 (4): 335–42.

Bellamy, R., C. Ruwende, T. Corrah, K. P. McAdam, H. C. Whittle, and others. 1998. "Variations in the NRAMP1 Gene and Susceptibility to Tuberculosis in West Africans." *New England Journal of Medicine* 338 (10): 640–44.

Bhargava, A., A. Benedetti, O. Oxlade, M. Pai, and D. Menzies. 2014. "Undernutrition and the Incidence of Tuberculosis in India: National and Subnational Estimates of the Population-Attributable Fraction Related to Undernutrition." *National Medical Journal of India* 27 (3): 128–33.

Bilal, N. K., C. H. Herbst, F. Zhao, A. Soucat, and C. Lemiere. 2011. "Health Extension Workers in Ethiopia: Improved Access and Coverage for the Rural Poor." In *Yes Africa Can: Success Stories from a Dynamic Continent*, edited by P. Chuhan-Pole and M. Angwafo, 433–43. Washington, DC: World Bank.

Binagwaho, A. 2013. "Resistant TB: Use the Tools Available." *Nature* 494 (7436): 176.

Binagwaho, A., P. E. Farmer, S. Nsanzimana, C. Karema, M. Gasana, and others. 2014. "Rwanda 20 Years on: Investing in Life." *The Lancet* 384 (9940): 371–75.

BIO Ventures for Global Health. 2006. "Tuberculosis Vaccines: The Case for Investment." Washington, DC: BIO Ventures for Global Health. http://www.bvgh.org/Portals/0/Reports/2006_10_tb_vaccines,_the_case_for_investment.pdf.

Blaya, J. A., H. S. F. Fraser, and B. Holt. 2010. "E-Health Technologies Show Promise in Developing Countries." *Health Affairs* 29 (2): 244–51.

Blaya, J. A., S. S. Shin, M. Yagui, C. Contreras, P. Cegielski, and others. 2014. "Reducing Communication Delays and Improving Quality of Care with a Tuberculosis Laboratory Information System in Resource Poor Environments: A Cluster Randomized Controlled Trial." *PLoS One* 9 (4): e90110.

Blaya, J. A., S. S. Shin, M. Yagui, G. Yale, C. Z. Suarez, and others. 2007. "A Web-Based Laboratory Information System to Improve Quality of Care of Tuberculosis Patients in Peru: Functional Requirements, Implementation and Usage Statistics." *BMC Medical Informatics and Decision Making* 7: 33.

Bloom, B. R. 1994. *Tuberculosis: Pathogenesis, Protection, and Control*. Washington, DC: ASM Press.

Bloom, B. R., and R. Atun. 2016. "Rethinking Global Control of Tuberculosis." *Science Translational Medicine* 8 (329): 329.

Bloom, B. R., and P. E. M. Fine. 1994. "The BCG Experience: Implications for Future Vaccines against Tuberculosis." In *Tuberculosis: Pathogenesis, Protection, and Control*, edited by B. R. Bloom, 531–57. Washington, DC: ASM Press.

Blower, S. M., A. R. Mclean, T. C. Porco, P. M. Small, P. C. Hopewell, and others. 1995. "The Intrinsic Transmission Dynamics of Tuberculosis Epidemics." *Nature Medicine* 1 (8): 815–21.

Boehme, C. C., P. Nabeta, D. Hillemann, M. P. Nicol, S. Shenai, others. 2010. "Rapid Molecular Detection of Tuberculosis and Rifampin Resistance." *New England Journal of Medicine* 363 (11): 1005–15.

Boehme, C. C., M. P. Nicol, P. Nabeta, J. S. Michael, E. Gotuzzo, and others. 2011. "Feasibility, Diagnostic Accuracy, and

Effectiveness of Decentralised Use of the Xpert MTB/RIF Test for Diagnosis of Tuberculosis and Multidrug Resistance: A Multicentre Implementation Study." *The Lancet* 377 (9776): 1495–505.

Boelaert, J. R., S. J. Vandecasteele, R. Appelberg, and V. R. Gordeuk. 2007. "The Effect of the Host's Iron Status on Tuberculosis." *Journal of Infectious Diseases* 195 (12): 1745–53.

Borrell, S., and S. Gagneux. 2011. "Strain Diversity, Epistasis, and the Evolution of Drug Resistance in *Mycobacterium tuberculosis*." *Clinical Microbiology and Infection* 17 (6): 815–20.

Brennan, M. J., and J. Thole. 2012. "Tuberculosis Vaccines: A Strategic Blueprint for the Next Decade." *Tuberculosis* 92 (Suppl 1): S6–13.

Brouwer, J. A., M. J. Boeree, P. Kager, C. M. Varkevisser, and A. D. Harries. 1998. "Traditional Healers and Pulmonary Tuberculosis in Malawi." *International Journal of Tuberculosis and Lung Disease* 2 (3): 231–34.

Brust, J. C., N. S. Shah, M. Scott, K. Chaiyachati, M. Lygizos, and others. 2012. "Integrated, Home-Based Treatment for MDR-TB and HIV in Rural South Africa: An Alternate Model of Care." *International Journal of Tuberculosis and Lung Disease* 16 (8): 998–1004.

Buchan, J., and M. R. Dal Poz. 2002. "Skill Mix in the Health Care Workforce: Reviewing the Evidence." *Bulletin of the World Health Organization* 80 (7): 575–80.

Bustamante, J., S. Boisson-Dupuis, L. Abel, and J. L. Casanova. 2014. "Mendelian Susceptibility to Mycobacterial Disease: Genetic, Immunological, and Clinical Features of Inborn Errors of IFN-y Immunity." *Seminars in Immunology* 26 (6): 454–70.

Caminero, J. 2003. "Is the DOTS Strategy Sufficient to Achieve Tuberculosis Control in Low- and Middle-Income Countries? 1. Need for Interventions in Universities and Medical Schools [Unresolved Issues]." *International Journal of Tuberculosis and Lung Disease* 7 (6): 509–15.

Car, J., T. Paljärvi, M. Car, A. Kazeem, A. Majeed, and others. 2012. "Negative Health System Effects of Global Fund's Investments in AIDS, Tuberculosis. and Malaria from 2002 to 2009: Systematic Review." *Journal of the Royal Society of Medicine Short Reports* 3 (10): 70.

Cauthen, G. M., A. Pio, and H. G. ten Dam. 2002. "Annual Risk of Tuberculosis Infection." *Bulletin of the World Health Organization* 80 (6): 503–11.

Cavalcante, S., B. Durovni, G. L. Barnes, F. B. A. Souza, R. F. Silva, and others. 2010. "Community-Randomized Trial of Enhanced DOTS for Tuberculosis Control in Rio de Janeiro, Brazil." *International Journal of Tuberculosis and Lung Disease* 14 (2): 203.

Cavalcante, S., E. Soares, A. G. F. Pacheco, R. E. Chaisson, B. Durovni, and others. 2007. "Community DOT for Tuberculosis in a Brazilian Favela: Comparison with a Clinic Model." *International Journal of Tuberculosis and Lung Disease* 11 (5): 544–49.

Cegielski, J. P., L. Arab, and J. Cornoni-Huntley. 2012. "Nutritional Risk Factors for Tuberculosis among Adults in the United States, 1971–1992." *American Journal of Epidemiology* 176 (5): 409–22.

Chadha, V., P. Kumar, P. S. Jagannatha, P. S. Vaidyanathan, and K. P. Unnikrishnan. 2005. "Average Annual Risk of Tuberculous Infection in India." *International Journal of Tuberculosis and Lung Disease* 9 (1): 116–18.

Chahal, J. S., O. F. Khan, C. L. Cooper, J. S. McPartlan, J. K. Tsosie, and others. 2016. "Dendrimer-RNA Nanoparticles Generate Protective Immunity against Lethal Ebola, H1N1 Influenza, and *Toxoplasma gondii* Challenges with a Single Dose." *Proceedings of the National Academy of Sciences* 113 (29): E4133–42.

Chakraborty, S., T. Gruber, C. E. Barry, H. I. Boshoff, and K. Y. Rhee. 2013. "Para-Aminosalicylic Acid Acts as an Alternative Substrate of Folate Metabolism in *Mycobacterium tuberculosis*." *Science* 339 (6115): 88–91.

Chan, P. C., C. H. Yang, L. Y. Chang, K. F. Wang, Y. C. Kuo, and others. 2013. "Lower Prevalence of Tuberculosis Infection in BCG Vaccinees: A Cross-Sectional Study in Adult Prison Inmates." *Thorax* 68 (3): 263–68.

Chang, K., W. Lu, J. Wang, K. Zhang, S. Jia, and others. 2012. "Rapid and Effective Diagnosis of Tuberculosis and Rifampicin Resistance with Xpert MTB/RIF Assay: A Meta-Analysis." *Journal of Infection* 64 (6): 580–88.

Chee, C., M. Teleman, I. C. Boudville, and Y. T. Wang. 2005. "Contact Screening and Latent TB Infection Treatment in Singapore Correctional Facilities." *International Journal of Tuberculosis and Lung Disease* 9 (11): 1248–52.

Chimusa, E. R., N. Zaitlen, M. Daya, M. Moller, P. D. van Helden, and others. 2014. "Genome-Wide Association Study of Ancestry-Specific TB Risk in the South African Coloured Population." *Human Molecular Genetics* 23 (3): 796–809.

Choi, I. J., Y. W. Kim, H. S. Lee, K. W. Ryu, H. M. Yoon, and others. 2015. "Risk Factors for TB in Patients with Early Gastric Cancer: Is Gastrectomy a Significant Risk Factor for TB?" *Chest* 148 (3): 774–83.

Churchyard, G., K. Fielding, J. Lewis, L. Coetzee, E. Corbett, and others. 2012. "Community-Wide Isoniazid Preventive Therapy Does Not Improve TB Control among Gold Miners: the Thibela TB Study, South Africa." Paper presented at the 19th Conference on Retroviruses and Opportunistic Infections, Seattle, March 5–8.

———. 2014. "A Trial of Mass Isoniazid Preventive Therapy for Tuberculosis Control." *New England Journal of Medicine* 370 (17): 301–10.

Cobelens, F., S. van Kampen, E. Ochodo, R. Atun, and C. Lienhardt. 2012. "Research on Implementation of Interventions in Tuberculosis Control in Low- and Middle-Income Countries: A Systematic Review." *PLoS Medicine* 9 (12): e1001358.

Cohen, T., C. Colijn, A. Wright, M. Zignol, A. Pym, and others. 2008. "Challenges in Estimating the Total Burden of Drug-Resistant Tuberculosis." *American Journal of Respiratory and Critical Care Medicine* 177 (12): 1302–06.

Cohen, T., H. E. Jenkins, C. Lu, M. McLaughlin, K. Floyd, and others. 2014. "On the Spread and Control of MDR-TB Epidemics: An Examination of Trends in Anti-Tuberculosis Drug Resistance Surveillance Data." *Drug Resistance Updates* 17 (4–6): 105–23.

Coker, R., R. A. Atun, and M. McKee. 2004. "Health-Care System Frailties and Public Health Control of Communicable Disease on the European Union's New Eastern Border." *The Lancet* 363 (9418): 1389–92.

Coker, R., B. Dimitrova, F. Drobniewski, Y. Samyshkin, J. Pomerleau, and others. 2005. "Health System Frailties in Tuberculosis Service Provision in Russia: An Analysis through the Lens of Formal Nutritional Support." *Public Health* 119 (9): 837–43.

Colijn, C., A. Brandes, J. Zucker, D. S. Lun, B. Weiner, and others. 2009. "Interpreting Expression Data with Metabolic Flux Models: Predicting *Mycobacterium tuberculosis* Mycolic Acid Production." *PLoS Computational Biology* 5 (8): e1000489.

Comstock, G. W., C. Baum, and D. E. Snider Jr. 1979. "Isoniazid Prophylaxis among Alaskan Eskimos: A Final Report of the Bethel Isoniazid Studies." *American Review of Respiratory Disease* 119 (5): 827–30.

Connor, S., K. Foley, R. Harding, and E. Jaramillo. 2012. "Declaration on Palliative Care and MDR/XDR-TB." *International Journal of Tuberculosis and Lung Disease* 16 (6): 712–13.

Corbett, E. L., T. Bandason, Y. B. Cheung, B. Makamure, E. Dauya, and others. 2009. "Prevalent Infectious Tuberculosis in Harare, Zimbabwe: Burden, Risk Factors and Implications for Control." *International Journal of Tuberculosis and Lung Disease* 13 (10): 1231.

Corbett, E. L., T. Bandason, T. Duong, E. Dauya, B. Makamure, and others. 2010. "Comparison of Two Active Case-Finding Strategies for Community-Based Diagnosis of Symptomatic Smear-Positive Tuberculosis and Control of Infectious Tuberculosis in Harare, Zimbabwe (DETECTB): A Cluster-Randomised Trial." *The Lancet* 376 (9748): 1244–53.

Corbett, E. L., S. Charalambous, V. M. Moloi, K. Fielding, A. D. Grant, and others. 2004. "Human Immunodeficiency Virus and the Prevalence of Undiagnosed Tuberculosis in African Gold Miners." *American Journal of Respiratory and Critical Care Medicine* 170 (6): 673–79.

Corbett, E. L., G. J. Churchyard, T. C. Clayton, B. G. Williams, D. Mulder, and others. 2000. "HIV Infection and Silicosis: The Impact of Two Potent Risk Factors on the Incidence of Mycobacterial Disease in South African Miners." *AIDS* 14 (17): 2759–68.

Corbett, E. L., B. Marston, G. J. Churchyard, and K. M. De Cock. 2006. "Tuberculosis in Sub-Saharan Africa: Opportunities, Challenges, and Change in the Era of Antiretroviral Treatment." *The Lancet* 367 (9514): 926–37.

Corbett, E. L., C. J. Watt, N. Walker, D. Maher, B. G. Williams, and others. 2003. "The Growing Burden of Tuberculosis: Global Trends and Interactions with the HIV Epidemic." *Archives of Internal Medicine* 163 (9): 1009–21.

Coronado, V. G., C. M. Beck-Sague, M. D. Hutton, B. J. Davis, P. Nicholas, and others. 1993. "Transmission of Multidrug-Resistant *Mycobacterium tuberculosis* among Persons with Human Immunodeficiency Virus Infection in an Urban Hospital: Epidemiologic and Restriction Fragment Length Polymorphism Analysis." *Journal of Infectious Diseases* 168 (4): 1052–55.

Cox, E., and K. Laessig. 2014. "FDA Approval of Bedaquiline—the Benefit-Risk Balance for Drug-Resistant Tuberculosis." *New England Journal of Medicine* 371 (8): 689–91.

Creswell, J., M. Raviglione, S. Ottmani, G. B. Migliori, M. W. Uplekar, and others. 2011. "Tuberculosis and Noncommunicable Diseases: Neglected Links and Missed Opportunities." *European Respiratory Journal* 37 (5): 1269–82.

Critchley, J. A., F. Young, L. Orton, and P. Garner. 2013. "Corticosteroids for Prevention of Mortality in People with Tuberculosis: A Systematic Review and Meta-Analysis." *The Lancet Infectious Diseases* 13 (3): 223–37.

Cuevas, L. E., N. Al-Sonboli, L. Lawson, M. A. Yassin, I. Arbide, and others. 2011. "LED Fluorescence Microscopy for the Diagnosis of Pulmonary Tuberculosis: A Multi-Country Cross-Sectional Evaluation." *PLoS Medicine* 8(7): e1001057.

Das, J., A. Kwan, B. Daniels, S. Satyanarayana, R. Subbaraman, and others. 2015. "Use of Standardised Patients to Assess Quality of Tuberculosis Care: A Pilot, Cross-Sectional Study." *The Lancet Infectious Diseases* 15 (11): 1305–13.

da Silva, R. C., L. Segat, H. L. da Cruz, H. C. Schindler, L. M. Montenegro, and others. 2014. "Association of CD209 and CD209L Polymorphisms with Tuberculosis Infection in a Northeastern Brazilian Population." *Molecular Biology Reports* 41 (8): 5449–57.

Datiko, D. G., and B. Lindtjørn. 2009. "Health Extension Workers Improve Tuberculosis Case Detection and Treatment Success in Southern Ethiopia: A Community Randomized Trial." *PLoS One* 4(5): e5443.

———. 2010. "Cost and Cost-Effectiveness of Smear Positive Tuberculosis Treatment by Health Extension Workers in Southern Ethiopia: A Community Randomized Trial." *PLoS One* 5 (2): e9158.

Della Mea, V. 1999. "Internet Electronic Mail: A Tool for Low-Cost Telemedicine." *Journal of Telemedicine and Telecare* 5 (2): 84–89.

DeLuca, A., R. E. Chaisson, and N. A. Martinson. 2009. "Intensified Case Finding for Tuberculosis in Prevention of Mother to Child Transmission Programs; a Simple and Potentially Vital Addition for Maternal and Child Health." *Journal of Acquired Immune Deficiency Syndromes* 50 (2): 196–99.

den Boon, S., A. Matteelli, N. Ford, and H. Getahun. 2016. "Continuous Isoniazid for the Treatment of Latent Tuberculosis Infection in People Living with HIV." *AIDS* 30 (5): 797–801.

den Boon, S., S. W. P. van Lill, M. W. Borgdorff, D. A. Enarson, S. Verver, and others. 2007. "High Prevalence of Tuberculosis in Previously Treated Patients, Cape Town, South Africa." *Emerging Infectious Diseases* 13 (8): 1189.

Detjen, A. K., A. R. DiNardo, J. Leyden, K. R. Steingart, D. Menzies, and others. 2015. "Xpert MTB/RIF Assay for the Diagnosis of Pulmonary Tuberculosis in Children: A Systematic Review and Meta-Analysis." *The Lancet Respiratory Medicine* 3 (6): 451–61.

de Vries, G., R. Aldridge, J. A. Cayla, W. H. Haas, A. Sandgren, and others. 2014. "Epidemiology of Tuberculosis in Big Cities of the European Union and European Economic Area Countries." *Eurosurveillance* 19 (9): pii=20726.

Dharmadhikari, A. S., M. Mphahlele, A. Stoltz, K. Venter, R. Mathebula, and others. 2012. "Surgical Face Masks Worn by Patients with Multidrug-Resistant Tuberculosis: Impact on Infectivity of Air on a Hospital Ward." *American Journal of Respiratory and Critical Care Medicine* 185 (10): 1104–19.

Dharmadhikari, A. S., M. Mphahlele, K. Venter, A. Stoltz, R. Mathebula, and others. 2014. "Rapid Impact of Effective Treatment on Transmission of Multidrug-Resistant Tuberculosis." *International Journal of Tuberculosis and Lung Disease* 18 (9): 1019–25.

Dheda, K., T. Gumbo, N. R. Gandhi, M. Murray, G. Theron, and others. 2014. "Global Control of Tuberculosis: From Extensively Drug-Resistant to Untreatable Tuberculosis." *The Lancet Respiratory Medicine* 2 (4): 321–38.

Diacon, A. H., R. Dawson, M. Hanekom, K. Narunsky, S. J. Maritz, and others. 2010. "Early Bactericidal Activity and Pharmacokinetics of PA-824 in Smear-Positive Tuberculosis Patients." *Antimicrobial Agents and Chemotheraphy* 54 (8): 3402–07.

Diacon, A. H., R. Dawson, F. von Groote-Bidlingmaier, G. Symons, A. Venter, and others. 2012. "14-Day Bactericidal Activity of PA-824, Bedaquiline, Pyrazinamide, and Moxifloxacin Combinations: A Randomised Trial." *The Lancet* 380 (9846): 986–93.

Diacon, A. H., P. R. Donald, A. Pym, M. Grobusch, R. F. Patientia, and others. 2012. "Randomized Pilot Trial of Eight Weeks of Bedaquiline (TMC207) Treatment for Multidrug-Resistant Tuberculosis: Long-Term Outcome, Tolerability, and Effect on Emergence of Drug Resistance." *Antimicrobial Agents and Chemotheraphy* 56 (6): 3271–76.

Diacon, A. H., A. Pym, M. P. Grobusch, J. M. de los Rios, E. Gotuzzo, and others. 2014. "Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline." *New England Journal of Medicine* 371 (8): 723–32.

Dick, J., and S. Henchie. 1998. "A Cost Analysis of the Tuberculosis Control Programme in Elsies River, Cape Town." *South African Medical Journal* 88 (Suppl 3): 380–83.

Ditkowsky, J. B., and K. Schwartzman. 2014. "Potential Cost-Effectiveness of a New Infant Tuberculosis Vaccine in South Africa—Implications for Clinical Trials: A Decision Analysis." *PLoS One* 9 (1): e83526.

Donald, P. R. 2016. "Chemotherapy for Tuberculous Meningitis." *New England Journal of Medicine* 374 (2): 179–81.

Donald, P. R., and H. McIlleron. 2009. "Antituberculosis Drugs." In *Tuberculosis: A Comprehensive Clinical Reference*, edited by H. S. Schaaf and A. Zumla. Philadelphia: Saunders Elsevier.

Dowdy, D. W., A. Cattamanchi, K. R. Steingart, and M. Pai. 2011. "Is Scale-Up Worth It? Challenges in Economic Analysis of Diagnostic Tests for Tuberculosis." *PLoS Medicine* 8 (7): e1001063.

Dowdy, D. W., R. E. Chaisson, G. Maartens, E. L. Corbett, and S. E. Dorman. 2008. "Impact of Enhanced Tuberculosis Diagnosis in South Africa: A Mathematical Model of Expanded Culture and Drug Susceptibility Testing." *Proceedings of the National Academy of Sciences* 105 (32): 11293–98.

Dowdy, D. W., J. E. Golub, R. E. Chaisson, and V. Saraceni. 2012. "Heterogeneity in Tuberculosis Transmission and the Role of Geographic Hotspots in Propagating Epidemics." *Proceedings of the National Academy of Sciences* 109 (24): 9557–62.

Driessen, J., M. Cioffi, N. Alide, Z. Landis-Lewis, G. Gamadzi, and others 2013. "Modeling Return on Investment for EMR System in Lilongwe, Malawi." *Journal of American Medical Informatics Association* 20 (4): 743–48.

Drobniewski, F. A., R. Atun, I. Fedorin, A. Bikov, R. Coker, and others. 2004. "The 'Bear Trap': The Colliding Epidemics of Tuberculosis and HIV in Russia." *International Journal of STD and AIDS* 15 (10): 641–46.

Dye, C. 2009. "Doomsday Postponed? Preventing and Reversing Epidemics of Drug-Resistant Tuberculosis." *Nature Reviews Microbiology* 7 (1): 81–87.

———. 2013. "Making Wider Use of the World's Most Widely Used Vaccine: Bacille Calmette–Guérin Revaccination Reconsidered." *Journal of the Royal Society Interface* 10 (87): 20130365.

———. 2015. *The Population Biology of Tuberculosis.* Princeton, NJ: Princeton University Press.

Dye, C., A. Bassili, A. L. Bierrenbach, J. F. Broekmans, V. K. Chadha, and others. 2008. "Measuring Tuberculosis Burden, Trends, and the Impact of Control Programmes." *The Lancet Infectious Diseases* 8 (4): 233–43.

Dye, C., and K. Floyd. 2006. "Tuberculosis." In *Disease Control Priorities in Developing Countries* (second edition), edited by D. T. Jamison, J. G. Breman, A. R. Measham, G. Alleyne, M. Claeson, D. B. Evans, P. Jha, A. Mills, and P. Musgrove. Washington, DC: World Bank and Oxford University Press.

Dye, C., P. Glaziou, K. Floyd, and M. Raviglione. 2013. "Prospects for Tuberculosis Elimination." *Annual Review of Public Health* 34 (December 14): 271–86.

Dye, C., S. Scheele, P. Dolin, V. Pathania, and M. C. Raviglione. 1999. "Global Burden of Tuberculosis: Estimated Incidence, Prevalence, and Mortality by Country." *Journal of the American Medical Association.* 282 (7): 677–86.

Dye, C., and B. G. Williams. 2008. "Eliminating Human Tuberculosis in the Twenty-First Century." *Journal of the Royal Society Interface* 5 (23): 653–62.

Economist. 2015. "The Economist Special Online Supplement." *Economist*, Copenhagen Consensus. http://www.copenhagenconsensus.com/post-2015-consensus/economist.

Edginton, M. 1999. "Tuberculosis Patient Care Decentralised to District Clinics with Community-Based Directly Observed Treatment in a Rural District of South Africa." *International Journal of Tuberculosis and Lung Disease* 3 (5): 445–50.

Eisenhut, M., S. Paranjothy, I. Abubakar, S. Bracebridge, M. Lilley, and others. 2009. "BCG Vaccination Reduces Risk of Infection with *Mycobacterium tuberculosis* as Detected by Gamma Interferon Release Assay." *Vaccine* 27 (44): 6116–20.

Elzinga, G., M. C. Raviglione, and D. Maher. 2004. "Scale Up: Meeting Targets in Global Tuberculosis Control." *The Lancet* 363 (9411): 814–19.

Ettehad, D., H. S. Schaaf, J. A. Seddon, G. S. Cooke, and N. Ford. 2012. "Treatment Outcomes for Children with Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis." *The Lancet Infectious Diseases* 12 (6): 449–56.

Evans, T. G., M. J. Brennan, L. Barker, and J. Thole. 2013. "Preventive Vaccines for Tuberculosis." *Vaccine* 31 (Suppl 2): B223–26.

Fabri, M., S. Stenger, D.-M. Shin, J.-M. Yuk, P. T. Liu, and others. 2011. "Vitamin D Is Required for IFN-γ–Mediated Antimicrobial Activity of Human Macrophages." *Science Translational Medicine* 3 (104): 104.

Farmer, P. 2013. "Chronic Infectious Disease and the Future of Health Care Delivery." *New England Journal of Medicine* 369 (25): 2424–36.

Farmer, P., S. Robin, S. L. Ramilus, and J. Y. Kim. 1991. "Tuberculosis, Poverty, and 'Compliance': Lessons from Rural Haiti." *Seminars in Respiratory Infections* 6 (4): 254–60.

Faurholt-Jepsen, D., N. Range, G. PrayGod, K. Jeremiah, M. Faurholt-Jepsen, and others. 2012. "The Role of Anthropometric and Other Predictors for Diabetes among Urban Tanzanians with Tuberculosis." *International Journal of Tuberculosis and Lung Disease* 16 (12): 1680–85.

Fenner, L., M. Egger, T. Bodmer, E. Altpeter, M. Zwahlen, and others. 2012. "Effect of Mutation and Genetic Background on Drug Resistance in *Mycobacterium tuberculosis*." *Antimicrobial Agents and Chemotherapy* 56 (6): 3047–53.

Figueroa-Munoz, J., K. Palmer, M. R. Dal Poz, L. Blanc, K. Bergström, and others. 2005. "The Health Workforce Crisis in TB Control: A Report from High-Burden Countries." *Human Resources for Health* 3 (1): 2.

Fine, P. E. 1995. "Variation in Protection by BCG: Implications of and for Heterologous Immunity." *The Lancet* 346 (8986): 1339–45.

Fitzpatrick, M. C., and K. Floyd. 2012. "A Systematic Review of the Cost and Cost Effectiveness of Treatment for Multidrug-Resistant Tuberculosis." *Pharmacoeconomics* 30 (1): 63–80.

Floyd, K., V. K. Arora, K. J. Murthy, K. Lonnroth, N. Singla, and others. 2006. "DOTS for Tuberculosis Control: Evidence from India." *Bulletin of the World Health Organization* 84: 437–45.

Floyd, K., C. Fitzpatrick, A. Pantoja, and M. Raviglione. 2013. "Domestic and Donor Financing for Tuberculosis Care and Control in Low-Income and Middle-Income Countries: An Analysis of Trends, 2002–11, and Requirements to Meet 2015 Targets." *The Lancet Global Health* 1 (2): e105–15.

Floyd, K., R. Hutubessy, K. Kliiman, R. Centis, N. Khurieva, and others. 2012. "Cost and Cost-Effectiveness of Multidrug-Resistant Tuberculosis Treatment in Estonia and Russia." *European Respiratory Journal* 40 (1): 133–42.

Floyd, K., J. Skeva, T. Nyirenda, F. Gausi, and F. Salaniponi. 2003. "Cost and Cost-Effectiveness of Increased Community and Primary Care Facility Involvement in Tuberculosis Care in Lilongwe District, Malawi." *International Journal of Tuberculosis and Lung Disease* 7 (Suppl 1): S29–37.

Floyd, K., D. Wilkinson, and C. Gilks. 1997. "Comparison of Cost Effectiveness of Directly Observed Treatment (DOT) and Conventionally Delivered Treatment for Tuberculosis: Experience from Rural South Africa." *BMJ* 315 (7120): 1407–11.

Fofana, M. O., G. M. Knight, G. B. Gomez, R. G. White, and D. W. Dowdy. 2014. "Population-Level Impact of Shorter-Course Regimens for Tuberculosis: A Model-Based Analysis." *PLoS One* 9 (5): e96389.

Ford, C. B., R. R. Shah, M. K. Maeda, S. Gagneux, M. B. Murray, and others. 2013. "*Mycobacterium tuberculosis* Mutation Rate Estimates from Different Lineages Predict Substantial Differences in the Emergence of Drug-Resistant Tuberculosis." *Nature Genetics* 45 (7): 784–90.

Fox, W., G. A. Ellard, and D. A. Mitchison. 1999. "Studies on the Treatment of Tuberculosis Undertaken by the British Medical Research Council Tuberculosis Units, 1946–1986, with Relevant Subsequent Publications." *International Journal of Tuberculosis and Lung Disease* 3 (10, Suppl 2): S231–79.

Fraser, H. S., J. Blaya, S. S. Choi, C. Bonilla, and D. Jazayeri. 2006. "Evaluating the Impact and Costs of Deploying an Electronic Medical Record System to Support TB Treatment in Peru." *AMIA Annual Symposium Proceedings* 2006: 265–68.

Fraser, H. S., A. Habib, M. Goodrich, D. Thomas, J. A. Blaya, and others. 2013. "E-Health Systems for Management of MDR-TB in Resource-Poor Environments: A Decade of Experience and Recommendations for Future Work." In *MedInfo*, vol. 192, 627–31. Amsterdam: IOS Press E Books.

Fraser, H. S., D. Jazayeri, C. D. Mitnick, J. S. Mukherjee, and J. Bayona. 2002. "Informatics Tools to Monitor Progress and Outcomes of Patients with Drug Resistant Tuberculosis in Perú." *AMIA Annual Symposium Proceedings* 2002: 270–74.

Fraser, H. S., D. Thomas, J. Tomaylla, N. Garcia, L. Lecca, and others. 2012. "Adaptation of a Web-Based, Open Source Electronic Medical Record System Platform to Support a Large Study of Tuberculosis Epidemiology." *BMC Medical Informatics and Decision Making* 12 (1): 125.

Frenk, J. 1994. "Dimensions of Health System Reform." *Health Policy* 27 (1): 19–34.

Frick, M., I. Henry, and E. Lessem. 2016. "Falling Short of the Rights to Health and Scientific Progress: Inadequate TB Drug Research and Access." *Health and Human Rights* 18 (1): 9–24.

Frieden, T. R., ed. 2004. *Toman's Tuberculosis: Case Detection, Treatment, and Monitoring*. Geneva: World Health Organization.

Frieden, T. R., P. I. Fujiwara, R. M. Washko, and M. A. Hamburg. 1995. "Tuberculosis in New York City—Turning the Tide." *New England Journal of Medicine* 333 (4): 229–33.

Friedich, S. O., A. Rachow, E. Saathoff, K. Singth, C. D. Mangu, and others. 2013. "Assessment of the Sensitivity and Specificity of Xpert MTB/RIF Assay as an Early Sputum Biomarker of Response to Tuberculosis Treatment." *The Lancet Respiratory Medicine* 1 (6): 432–70.

Furin, J., J. Bayona, M. Becerra, P. Farmer, A. Golubkov, and others. 2011. "Programmatic Management of Multidrug-Resistant Tuberculosis: Models from Three Countries." *International Journal of Tuberculosis and Lung Disease* 15 (10): 1294–300.

Gagneux, S. 2012. "Host–Pathogen Coevolution in Human Tuberculosis." *Philosophical Transactions of the Royal Society B: Biological Sciences* 367 (1590): 850–59.

Gandhi, N. R., A. P. Moll, U. Lalloo, R. Pawinski, K. Zeller, and others. 2009. "Successful Integration of Tuberculosis and HIV Treatment in Rural South Africa: The Sizonq'oba

Study." *Journal of Acquired Immune Deficiency Syndromes* 50 (1): 37–43.

Gandhi, N. R., A. Moll, A. W. Sturm, R. Pawinski, T. Govender, and others. 2006. "Extensively Drug-Resistant Tuberculosis as a Cause of Death in Patients Co-Infected with Tuberculosis and HIV in a Rural Area of South Africa." *The Lancet* 368 (9547): 1575–80.

Gandhi, N. R., P. Nunn, K. Dheda, H. S. Schaff, M. Zignol, and others. 2010. "Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis: A Threat to Global Control of Tuberculosis." *The Lancet* 375 (9728): 1830–43.

Gandhi, N. R., D. Weissman, P. Moonley, M. Ramathal, I. Elson, and others. 2013. "Nosocomial Transmission of Extensively Drug-Resistant Tuberculosis in a Rural Hospital in South Africa." *Journal of Infectious Diseases* 207 (1): 9–17.

Gasana, M., G. Vandebriel, G. Kabanda, S. J. Tsiouris, J. Justman, and others. 2008. "Integrating Tuberculosis and HIV Care in Rural Rwanda." *International Journal of Tuberculosis and Lung Disease* 12 (Suppl 1): S39–43.

Geissbuhler, A., O. Ly, C. Lovis, and J.-F. L'Haire. 2003. "Telemedicine in Western Africa: Lessons Learned from a Pilot Project in Mali, Perspectives and Recommendations." In *Annual Symposium Proceedings*, vol. 2003, 249. Bethesda, MD: American Medical Informatics Association.

Gelmanova, I. Y., S. Keshavjee, V. T. Goluchikova, V. I. Berzina, A. K. Strelis, and others. 2007. "Barriers to Successful Tuberculosis Treatment in Tomsk, Russian Federation: Non-Adherence, Default, and the Acquisition of Multidrug Resistance." *Bulletin of the World Health Organization* 85 (9): 649–732.

Getahun, H., A. Matteelli, R. E. Chaisson, and M. Raviglione. 2015. "Latent *Mycobacterium tuberculosis* Infection." *New England Journal of Medicine* 372 (May 28): 2127–35.

Gillespie, S. H., A. M. Crook, T. D. McHugh, C. M. Mendel, S. K. Meredith, and others. 2014. "Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis." *New England Journal of Medicine* 371 (17): 1577–87.

Glaziou, P., K. Floyd, E. L. Korenromp, C. Sismanidis, A. Bierrenbach, and others. 2011. "Lives Saved by Tuberculosis Control and Prospects for Achieving the 2015 Global Target for Reducing Tuberculosis Mortality." *Bulletin of the World Health Organization* 89 (8): 573–82.

Gler, M., L. Podewils, N. Munez, M. Galipot, M. I. D. Quelapio, and others. 2012. "Impact of Patient and Program Factors on Default during Treatment of Multidrug-Resistant Tuberculosis." *International Journal of Tuberculosis and Lung Disease* 16 (7): 955–60.

Gler, M. T., V. Skripconoka, E. Sanchez-Garavito, H. Xiao, J. L. Cabrera-Rivero, and others. 2012. "Delamanid for Multidrug-Resistant Pulmonary Tuberculosis." *New England Journal of Medicine* 366 (23): 2151–60.

Golub, J. E., S. Cohn, V. Saraceni, S. C. Cavalcante, A. G. Pacheco, and others. 2015. "Long-Term Protection from Isoniazid Preventive Therapy for Tuberculosis in HIV-Infected Patients in a Medium-Burden Tuberculosis Setting: The TB/HIV in Rio (THRio) Study." *Clinical Infectious Diseases* 60 (4): 639–45.

Golub, J. E., C. I. Mohan, G. W. Comstock, and R. E. Chaisson. 2005. "Active Case Finding of Tuberculosis: Historical Perspective and Future Prospects." *International Journal of Tuberculosis and Lung Disease* 9 (11): 1183–203.

Gomez, G. B., D. W. Dowdy, M. L Bastos, A. Zwerling, S. Sweeney, and others. 2016. "Cost and Cost-Effectiveness of Tuberculosis Treatment Shortening: A Model-based Analysis." *BMC Infectious Diseases*. 16 (1): 726.

Grandjean, L., R. H. Gilman, L. Martin, E. Soto, and others. 2015. "Transmission of Multidrug-Resistant and Drug Susceptible Tuberculosis within Households: A Prospective Cohort Study." *PLoS Medicine* 12 (6): e1001843.

Green, C., J. F. Huggett, E. Talbot, P. Mwaba, K. Reither, and A. Zumla. 2009. "Rapid Diagnosis of Tuberculosis through the Detection of Mycobacterial DNA in Urine by Nucleic Acid Amplification Methods." *The Lancet Infectious Diseases* 9 (8) 505–11.

Gupta, R., M. Gao, A. Cirule, H. Xiao, L. Geiter, and others. 2015. "Delamanid for Extensively Drug-Resistant Tuberculosis." *New England Journal of Medicine* 373 (3): 291–92.

Hanekom, M., G. D. van der Spuy, E. Streicher, S. L. Ndabambi, C. R. McEvoy, and others. 2007. "A Recently Evolved Sublineage of the *Mycobacterium tuberculosis* Beijing Strain Family Is Associated with an Increased Ability to Spread and Cause Disease." *Journal of Clinical Microbiology* 45 (5): 1483–90.

Hanifa, Y., A. Grant, J. Lewis, E. L. Corbett, K. Fielding, and others. 2009. "Prevalence of Latent Tuberculosis Infection among Gold Miners in South Africa." *International Journal of Tuberculosis and Lung Disease* 13 (1): 39–46.

Hansen, S. G., M. Piatak Jr., A. B. Ventura, C. M. Hughes, R. M. Gilbride, and others. 2013. "Immune Clearance of Highly Pathogenic SIV Infection." *Nature* 502 (7469): 100–04.

Harding, R., K. M. Foley, S. R. Connor, and E. Jaramillo. 2012. "Palliative and End-of-Life Care in the Global Response to Multidrug-Resistant Tuberculosis." *The Lancet Infectious Diseases* 12 (8): 643–6.

Harries, A. D. 1997. "Tuberculosis in Africa: Clinical Presentation and Management." *Pharmacology and Therapeutics* 73 (1): 1–50.

Harries, A. D., R. Zachariah, K. Bergström, L. Blanc, F. M. Salaniponi, and others. 2005. "Human Resources for Control of Tuberculosis and HIV-Associated Tuberculosis [Unresolved Issues]." *International Journal of Tuberculosis and Lung Disease* 9 (2): 128–37.

Harris, J. B., S. M. Hatwiinda, K. M. Randels, B. H. Chi, N. G. Kancheya, and others. 2008. "Early Lessons from the Integration of Tuberculosis and HIV Services in Primary Care Centers in Lusaka, Zambia." *International Journal of Tuberculosis and Lung Disease* 12 (7): 773–79.

Harris, R. C., M. S. Khan, L. J. Martin, V. Allen, D. A. Moore, and others. 2016. "The Effect of Surgery on the Outcome of Treatment for Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis." *BMC Infectious Diseases* 16: 262.

Hart, P. A., and I. Sutherland. 1977. "BCG and Vole Bacillus Vaccines in the Prevention of Tuberculosis in Adolescence and Early Adult Life." *BMJ* 2 (6082): 293.

Hasegawa, N, T. Miura, K. Ishii, K. Yamaguchi, T. H. Lindner, and others. 2002. "New Simple and Rapid Test for Culture Confirmation of *Mycobacterium tuberculosis* Complex: A Multicenter Study." *Journal of Clinical Microbiology* 40 (3): 908–12.

Heimbeck, J. 1938. "Incidence of Tuberculosis in Young Adult Women with Special Reference to Employment." *British Journal of Tuberculosis* 32 (3): 154–66.

Heller, T., R. Lessells, C. G. Wallrauch, T. Bärnighausen, C. S. Cooke, and others. 2010. "Community-Based Treatment for Multidrug-Resistant Tuberculosis in Rural KwaZulu-Natal, South Africa." *International Journal of Tuberculosis and Lung Disease* 14 (4): 420–26.

Hermans, S., C. R. Horsburgh Jr., and R. Wood. 2015. "A Century of Tuberculosis Epidemiology in the Northern and Southern Hemisphere: The Differential Impact of Control Interventions." *PLoS One* 10 (8): e0135179.

Hesseling, A. C., B. J. Marais, R. P. Gie, H. S. Schaaf, P. E. Fine, and others. 2007. "The Risk of Disseminated Bacille Calmette-Guerin (BCG) Disease in HIV-Infected Children." *Vaccine* 25 (1): 14–18.

Hirsch-Moverman, Y., R. Shrestha-Kuwahara, J. Bethel, H. M. Blumberg, T. K. Venkatappa, and others. 2015. "Latent Tuberculous Infection in the United States and Canada: Who Completes Treatment and Why?" *International Journal of Tuberculosis and Lung Disease* 19 (1): 31–38.

Hoagland, D. T., J. Liu, R. B. Lee, and R. E. Lee. 2016. "New Agents for the Treatment of Drug-Resistant *Mycobacterium tuberculosis*." *Advanced Drug Delivery Reviews* 102: 55–72.

Hong Kong Chest Service and British Medical Research Council. 1979. "Controlled Trial of 6-Month and 8-Month Regimens in the Treatment of Pulmonary Tuberculosis: The Results up to 24 Months." *Tubercle* 60 (4): 201–10.

Hopkin, J. 2000. "Atopy, Asthma, and the Mycobacteria." *Thorax* 55 (6): 443–45.

Horter, S., B. Stringer, L. Reynolds, M. Shoaib, S. Kasozi, and others. 2014. "'Home Is Where the Patient Is': A Qualitative Analysis of a Patient-Centred Model of Care for Multi-Drug Resistant Tuberculosis." *BMC Health Services Research* 14 (1): 1–8.

Hou, W. L., F. Song, N. X. Zhang, X. X. Dong, S. Y. Cao, and others. 2012. "Implementation and Community Involvement in DOTS Strategy: A Systematic Review of Studies in China." *International Journal of Tuberculosis and Lung Disease* 16 (11): 1433–40.

Howard, A. A., and W. M. El-Sadr. 2010. "Integration of Tuberculosis and HIV Services in Sub-Saharan Africa: Lessons Learned." *Clinical Infectious Diseases* 50 (Suppl 3): S238–44.

Howitt, P., A. Darzi, G. Z. Yang, H. Ashrafian, and R. Atun. 2012. "Technologies for Global Health." *The Lancet* 380 (9840): 507–35.

Hsiao, W. C., and P. S. Heller. 2007. "What Should Macroeconomists Know about Health Care Policy?" Working Paper WP/07/13, International Monetary Fund, Washington, DC.

Huang, C.-C., E. T. Tchetgen, M. C. Becerra, T. Cohen, J. Galea, and others. 2014. "Cigarette Smoking among Tuberculosis Patients Increases Risk of Transmission to Child Contacts." *International Journal of Tuberculosis and Lung Disease* 18 (11): 1285–91.

Huang, C.-C., E. T. Tchetgen, M. C. Becerra, T. Cohen, K. C. Hughes, and others. 2014. "The Effect of HIV-Related Immunosuppression on the Risk of Tuberculosis Transmission to Household Contacts." *Clinical Infectious Diseases* 58 (6): 765–74.

Huerga, H., H. Spillane, W. Guerrero, A. Odongo, and F. Varaine. 2010. "Impact of Introducing Human Immunodeficiency Virus Testing, Treatment and Care in a Tuberculosis Clinic in Rural Kenya." *International Journal of Tuberculosis and Lung Disease* 14 (5): 611–15.

IHME (Institute for Health Metrics and Evaluation). 2015. "Financing Global Health 2014. Shifts in Funding as the MDG Era Closes." IHME, Seattle.

Institute of Medicine. 2013. *Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis: Workshop Summary*. Washington, DC: National Academies Press.

International Institute for Population Sciences and Macro International. 2007. *National Family Health Survey (NFHS-3), 2005–2006.* Mumbai: International Institute for Population Sciences.

Isaakidis, P., R. Paryani, K. Samsuddin, H. Mansoor, M. Manglani, and others. 2013. "Poor Outcomes in a Cohort of HIV-Infected Adolescents Undergoing Treatment for Multidrug-Resistant Tuberculosis in Mumbai, India." *PLoS One* 8 (7): e68869.

Islam, A., M. A. May, F. Ahmed, R. A. Cash, and J. Ahmed. 2011. *Making Tuberculosis History: Community-Based Solutions for Millions*. Dhaka: University Press Limited.

Islam, M. D., S. Wakai, N. Ishikawa, A. M. R. Chowdhury, and J. P. Vaughan. 2002. "Cost-Effectiveness of Community Health Workers in Tuberculosis Control in Bangladesh." *Bulletin of the World Health Organization* 80 (6): 445–50.

Islam, M. S., J. P. Richards, and A. K. Ojha. 2012. "Targeting Drug Tolerance in Mycobacteria: A Perspective from Mycobacterial Biofilms." *Expert Review of Anti-Infective Therapy* 10 (9): 1055–66.

Isler, M., P. Rivest, J. Mason, and P. Brassard. 2013. "Screening Employees of Services for Homeless Individuals in Montréal for Tuberculosis Infection." *Journal of Infection and Public Health* 6 (3): 209–15.

Jack, C., U. Lalloo, Q. A. Karim, S. A. Karim, W. El-Sadr, and others. 2004. "A Pilot Study of Once-Daily Antiretroviral Therapy Integrated with Tuberculosis Directly Observed Therapy in a Resource-Limited Setting." *Journal of Acquired Immune Deficiency Syndromes* 36 (4): 929–34.

Jagirdar, J., and D. Zagzag. 1996. "Pathology and Insights into Pathogenesis of Tuberculosis." In *Tuberculosis*, edited by W. N. Rom and S. Garay, 467–91. Boston: Little, Brown.

James, P., R. Gupta, D. J. Christopher, B. Thankagunam, and B. Veeraraghavan. 2011. "MDR- and XDR-TB among

Suspected Drug-Resistant TB Patients in a Tertiary Care Hospital in India." *Clinical Respiratory Journal* 5 (1): e19–25.

Jenkins, H. E., V. Plesca, A. Ciobanu, V. Crudu, I. Galusca, and others. 2013. "Assessing Spatial Heterogeneity of Multidrug-Resistant Tuberculosis in a High-Burden Country." *European Respiratory Journal* 42 (5): 1291–301.

Jeon, C. Y., and M. B. Murray. 2008. "Diabetes Mellitus Increases the Risk of Active Tuberculosis: A Systematic Review of 13 Observational Studies." *PLoS Medicine* 5 (7): e152.

Jha, P., and R. Laxminarayan. 2009. "Choosing Health in India: An Entitlement for All Indians." University of Toronto and Resources for the Future, New Delhi.

Jiménez-Levi, E. 2012. *Tuberculosis Research and Development: 2012 Report on Tuberculosis Research Funding Trends, 2005–2011.* New York: Treatment Action Group.

Jindani, A., T. S. Harrison, A. J. Nunn, P. P. Phillips, G. J. Churchyard, and others. 2014. "High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis." *New England Journal of Medicine* 371 (October 23): 1599–608.

Kagina, B. M., B. Abel, M. Bowmaker, T. J. Scriba, S. Gelderbloem, and others. 2009. "Delaying BCG Vaccination from Birth to 10 Weeks of Age May Result in an Enhanced Memory CD4 T Cell Response." *Vaccine* 27 (40): 5488–95.

Karonga Prevention Trial Group. 1996. "Randomised Controlled Trial of Single BCG, Repeated BCG, or Combined BCG and Killed *Mycobacterium leprae* Vaccine for Prevention of Leprosy and Tuberculosis in Malawi." *The Lancet* 348 (9019): 17–24.

Karumbi, J., and P. Garner. 2015. "Directly Observed Therapy for Treating Tuberculosis." *Cochrane Database of Systematic Reviews* 5: CD003343.

Katz, I., M. Aziz, M. Olszak-Olszewski, R. Komatsu, D. Low-Beer, and others. 2010. "Factors Influencing Performance of Global Fund-Supported Tuberculosis Grants." *International Journal of Tuberculosis and Lung Disease* 14 (9): 1097–103.

Kaufmann, S. H. E., M. F. Cotton, B. Eisele, M. Gengenbacher, L. Grode, and others. 2014. "The BCG Replacement Vaccine VPM1002: From Drawing Board to Clinical Trial." *Expert Review of Vaccines* 13 (5): 619–30.

Keane, J., S. Gershon, R. P. Wise, E. Mirabile-Levens, J. Kasznica, and others. 2001. "Tuberculosis Associated with Infliximab, A Tumor Necrosis Factor A–Neutralizing Agent." *New England Journal of Medicine* 345 (15): 1098–104.

Keshavjee, S., and P. E. Farmer. 2010. "Picking Up the Pace: Scale-Up of MDR Tuberculosis Treatment Programs." *New England Journal of Medicine* 363 (19): 1781–84.

———. 2012. "Tuberculosis, Drug Resistance, and the History of Modern Medicine." *New England Journal of Medicine* 367 (10): 931–36.

Keshavjee, S., and K. Seung. 2008. "Stemming the Tide of Multidrug-Resistant Tuberculosis: Major Barriers to Addressing the Growing Epidemic." Institute of Medicine report, Institute of Medicine, Washington, DC. https://www.ncbi.nlm.nih.gov/books/NBK45010.

Khan, A. J., S. Khowaja, F. S. Khan, F. Qazi, I. Lotia, and others. 2012. "Engaging the Private Sector to Increase Tuberculosis Case Detection: An Impact Evaluation Study." *The Lancet Infectious Diseases* 12 (8): 608–16.

Khan, B., P. Ahmed, K. Ullah, C. A. Hussain, I. Hussain, and S. Raza. 2005. "Frequency of Tuberculosis in Haematological Malignancies and Stem Cell Transplant Recipients." *Journal of the College of Physicians and Surgeons–Pakistan* 15 (1): 30–3.

Khan, F. A., J. Minion, A. Al-Motiri, A. Benedetti, A. D. Harries, and others. 2012. "An Updated Systematic Review and Meta-Analysis on the Treatment of Active Tuberculosis in Patients with HIV Infection." *Clinical Infectious Diseases* 55 (8): 1154–63.

Kim, C. H., K. H. Im, S. S. Yoo, S. Y. Lee, S. I. Cha, and others. 2014. "Comparison of the Incidence between Tuberculosis and Nontuberculous Mycobacterial Disease after Gastrectomy." *Infection* 42 (4): 697–704.

Kim, J. Y., P. Farmer, and M. E. Porter. 2013. "Redefining Global Health-Care Delivery." *The Lancet* 382 (9897): 1060–69.

King, G., E. Gakidou, K. Imai, J. Lakin, R. T. Moore, and others. 2009. "Public Policy for the Poor? A Randomised Assessment of the Mexican Universal Health Insurance Programme." *The Lancet* 373 (9673): 1447–54.

Kirwan, D. E., M. K. Cárdenas, and R. Gilman. 2012. "Rapid Implementation of New TB Diagnostic Tests: Is it Too Soon for a Global Roll-Out of Xpert MTB/RIF?" *American Journal of Tropical Medicine and Hygiene* 87 (2): 197–201.

Knight, G. M., P. J. Dodd, A. D. Grant, K. L. Fielding, G. J. Churchyard, and others. 2015. "Tuberculosis Prevention in South Africa." *PLoS One* 10 (4): e0122514.

Knight, G. M., U. K. Griffiths, T. Sumner, Y. V. Laurence, A. Gheorghe, and others. 2014. "Impact and Cost-Effectiveness of New Tuberculosis Vaccines in Low- and Middle-Income Countries." *Proceedings of the National Academy of Sciences* 111 (43): 15520–25.

Kranzer, K., H. Afnan-Holmes, K. Tomlin, J. E. Golub, A. E. Shapiro, and others. 2013. "The Benefits to Communities and Individuals of Screening for Active Tuberculosis Disease: A Systematic Review." *International Journal of Tuberculosis and Lung Disease* 17 (4): 432–46.

Kranzer, K., R. M. Houben, J. R. Glynn, L. G. Bekker, R. Wood, and others. 2010. "Yield of HIV-Associated Tuberculosis During Intensified Case Finding in Resource-Limited Settings: A Systematic Review and Meta-Analysis." *The Lancet Infectious Diseases* 10 (2): 93–102.

Kritzinger, F. E., S. den Boon, S. Verver, D. A. Enarson, C. J. Lombard and others. 2009. "No Decrease in Annual Risk of Tuberculosis Infection in Endemic Area in Cape Town, South Africa." *Tropical Medicine and International Health* 14 (2): 136–42.

Kruk, M. E., E. Goldmann, and S. Galeo. 2009. "Borrowing and Selling to Pay for Health Care in Low- and Middle-Income Countries." *Health Affairs* 28 (4): 1056–66.

Kruk, M. E., N. R. Schwalbe, and C. A. Aguiar. 2008. "Timing of Default from Tuberculosis Treatment: A Systematic Review." *Tropical Medicine and International Health* 13 (5): 703–12.

Kumar, M., and S. Kumar. 1997. "Tuberculosis Control in India: Role of Private Doctors." *The Lancet* 350 (9087): 1329–30.

Labrique, A. B., L. Vasudevan, E. Kochi, R. Fabricant, and G. Mehl. 2013. "mHealth Innovations as Health System Strengthening Tools: 12 Common Applications and a Visual Framework." *Global Health: Science and Practice* 1 (2): 160–71.

Lal, S., M. W. Uplekar, I. Katz, K. Lonnroth, R. Komatsu, and others. 2011. "Global Fund Financing of Public-Private Mix Approaches for Delivery of Tuberculosis Care." *Tropical Medicine and International Health* 16 (6): 685–92.

Laurence, Y. V., U. K. Griffiths, and A. Vassall. 2015. "Costs to Health Services and the Patient of Treating Tuberculosis: A Systematic Literature Review." *PharmacoEconomics* 33 (9): 1–17.

Lawn, S. D. 2015. "Advances in Diagnostic Assays for Tuberculosis." *Cold Spring Harbor Perspectives in Medicine* 5 (12): pii=a017806.

Lawn, S. D., S. V. Brooks, K. Kranzer, M. P. Nicol, A. Whitelaw, and others. 2011. "Screening for HIV-Associated Tuberculosis and Rifampicin Resistance before Antiretroviral Therapy Using the Xpert MTB/RIF Assay: A Prospective Study." *PLoS Medicine* 8 (7): e1001067.

Lawn, S. D., A. D. Kerkhoff, M. Vogt, and R. Wood. 2012. "Diagnostic Accuracy of a Low-Cost, Urine Antigen, Point-of-Care Screening Assay for HIV-Associated Pulmonary Tuberculosis before Antiretroviral Therapy: A Descriptive Study." *The Lancet Infectious Diseases* 12 (3): 201–09.

Lee, D., S. S. Lal, R. Komatsu, A. Zumla, and R. Atun. 2012. "Global Fund Financing of Tuberculosis Services Delivery in Prisons." *Journal of Infectious Diseases* 205 (Suppl 2): S274–83.

Lee, D. K., Y.-S. Cho, S. H. Hong, W. H. Chung, and Y. C. Ahn. 2006. "Inflammatory Pseudotumor Involving the Skull Base: Response to Steroid and Radiation Therapy." *Otolaryngology—Head and Neck Surgery* 135 (1): 144–48.

Lee, M., T. Song, Y. Kim, I. Jeong, S. N Cho, and C. E. Barry. 2015. "Linezolid for XDR-TB—Final Study Outcomes." *New England Journal of Medicine* 373 (3): 290–91. http://www.nejm.org/doi/full/10.1056/NEJMc1500286#t=article.

Lee, R. S., N. Radmonski, J. F. Proulx, I. Levade, B. J. Shapiro and others. 2015. "Population Genomics of *Mycobacterium tuberculosis* in the Inuit." *Proceedings of the National Academy of Sciences* 112 (44): 13609–14.

Legido-Quigley, H., C. M. Montgomery, P. Khan, R. Atun, A. Fakoya, and others. 2013. "Integrating Tuberculosis and HIV Services in Low- and Middle-Income Countries: A Systematic Review." *Tropical Medicine and International Health* 18 (2): 199–211.

Leimane, V., and J. Leimans. 2006. "Tuberculosis Control in Latvia: Integrated DOTS." *Eurosurveillance* 11 (3): 29–33.

Lessem, E., H. Cox, C. Daniels, J. Furin, L. McKenna, and others. 2015. "Access to New Medications for the Treatment of Drug-Resistant Tuberculosis: Patient, Provider and Community Perspectives." *International Journal of Infectious Diseases* 32: 56–60.

Lester, R. T., P. Ritvo, E. J. Mills, A. Kariri, S. Karanja, and others. 2010. "Effects of a Mobile Phone Short Message Service on Antiretroviral Treatment Adherence in Kenya (WelTel Kenya1): A Randomised Trial." *The Lancet* 376 (9755): 1838–45.

Libshitz, H. I., H. K. Pannu, L. S. Elting, and C. D. Cooksley. 1997. "Tuberculosis in Cancer Patients: An Update." *Journal of Thoracic Imaging* 12 (1): 41–46.

Lienhardt, C., K. Fielding, J. Sillah, A. Tunkara, S. Donkor, and others. 2003. "Risk Factors for Tuberculosis Infection in Sub-Saharan Africa: A Contact Study in the Gambia." *American Journal of Respiratory and Critical Care Medicine* 168 (4): 448–55.

Lietman, T., T. Porco, and S. Blower. 1997. "Leprosy and Tuberculosis: The Epidemiological Consequences of Cross-Immunity." *American Journal of Public Health* 87 (12): 1923–27.

Lin, H.-H., D. Dowdy, C. Dye, M. Murray, and T. Cohen. 2012. "The Impact of New Tuberculosis Diagnostics on Transmission: Why Context Matters." *Bulletin of the World Health Organization* 90 (10): 739–47.

Lin, H.-H., M. Ezzati, and M. Murray. 2007. "Tobacco Smoke, Indoor Air Pollution, and Tuberculosis: A Systematic Review and Meta-Analysis." *PLoS Medicine* 4 (1): e20.

Lin, H.-H., C. Suk, H. L. Lo, R. Y. Huang, D. A. Enarson, and others. 2014. "Indoor Air Pollution from Solid Fuel and Tuberculosis: A Systematic Review and Meta-Analysis." *International Journal of Tuberculosis and Lung Disease* 18 (5): 613–21.

Lin, X., V. Chongsuvivatwong, L. Lin, A. Geater, and R. Lijuan. 2008. "Dose–Response Relationship between Treatment Delay of Smear-Positive Tuberculosis Patients and Intra-Household Transmission: A Cross-Sectional Study." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 102 (8): 797–804.

Lipsitch, M., and A. O. Sousa. 2002. "Historical Intensity of Natural Selection for Resistance to Tuberculosis." *Genetics* 161 (4): 1599–607.

Liu, P. T., S. Stenger, D. H. Tang, and R. L. Modlin. 2007. "Cutting Edge: Vitamin D-Mediated Human Antimicrobial Activity against *Mycobacterium tuberculosis* Is Dependent on the Induction of Cathelicidin." *Journal of Immunology* 179 (4): 2060–63.

Lönnroth, K., B. G. Williams, P. Cegielski, and C. Dye. 2010. "A Consistent Log-Linear Relationship between Tuberculosis Incidence and Body Mass Index." *International Journal of Epidemiology* 39 (1): 149–55.

Lönnroth, K., B. G. Williams, S. Stadlin, E. Jaramillo, and C. Dye. 2008. "Alcohol Use as a Risk Factor for Tuberculosis–A Systematic Review." *BMC Public Health* 8 (1): 289.

Lopez, B., D. Aguilar, H. Orozco, M. Burger, C. Espitia, and others. 2003. "A Marked Difference in Pathogenesis and Immune Response Induced by Different *Mycobacterium tuberculosis* Genotypes." *Clinical and Experimental Immunology* 133 (1): 30–37.

Loudon, R. G. and S. K. Spohn. 1969. "Cough Frequency and Infectivity in Patients with Pulmonary Tuberculosis." *American Review of Respiratory Disease* 99 (1): 109–11.

Loveday, M., K. Wallengren, A. Voce, B. Margot, T. Reddy, and others 2012. "Comparing Early Treatment Outcomes of MDR-TB in a Decentralised Setting with a Centralised Setting in KwaZulu-Natal, South Africa." *International Journal of Tuberculosis and Lung Disease* 16 (2): 209–15.

Lowell, A. M., L. B. Edwards, and C. E. Palmer. 1969. "Tuberculosis Morbidity and Mortality and Its Control." In *Tuberculosis,* edited by A. M. Lowell, L. B. Edwards, and C. E. Palmer, 129–66. Cambridge, MA: Harvard University Press.

Lozano, R., M. Naghavi, K. Foreman, S. Lim, K. Shibuya, and others. 2012. "Global and Regional Mortality from 235 Causes of Death for 20 Age Groups in 1990 and 2010: A Systematic Analysis for the Global Burden of Disease Study 2010." *The Lancet* 380 (9859): 2095–128.

Lu, L. L., A. W. Chung, T. R. Rosebrock, M. Ghebremichael, W. H. Yu, and others. 2016. "A Functional Role for Antibodies in Tuberculosis." *Cell* 167 (2): 433–43.

Lundgrun, B. 2015. "Ebola Kills Far Fewer Than AIDS, TB, and Malaria. What Should We Prioritise?" *The Guardian*, January 19.

Lutwama, F., B. M. Kagina, A. Waiswa, N. Mansoor, S. Kirimunda, and others. 2014. "Distinct T-Cell Responses When BCG Vaccination Is Delayed from Birth to 6 Weeks of Age in Ugandan Infants." *Journal of Infectious Diseases* 209 (6): 887–97.

Luyirika, E., H. Nsobya, R. Batamwita, P. Busingye, W. Musoke, and others. 2012. "A Home-Based Approach to Managing Multi-Drug Resistant Tuberculosis in Uganda: A Case Report." *AIDS Research and Therapy* 9 (1): 12.

Luzze, H., D. F. Johnson, K. Dickman, H. Mayanja-Kizza, A. Okwera, and others. 2013. "Relapse More Common Than Reinfection in Recurrent Tuberculosis 1–2 Years Post Treatment in Urban Uganda." *International Journal of Tuberculosis and Lung Disease* 17 (3): 361–67.

Lygizos, M., S. V. Shenoi, R. P. Brooks, A. Bhushan, J. C. M. Brust, and others. 2013. "Natural Ventilation Reduces High TB Transmission Risk in Traditional Homes in Rural KwaZulu-Natal, South Africa." *BMC Infectious Diseases* 13 (July 1): 300.

MacIntyre, C. R., N. Kendig, L. Kummer, S. Birago, and N. M. Graham. 1997. "Impact of Tuberculosis Control Measures and Crowding on the Incidence of Tuberculous Infection in Maryland Prisons." *Clinical Infectious Diseases* 24 (6): 1060–67.

Mamlin, B. W., P. G. Biondich, B. A. Wolfe, H. S. F. Fraser, D. Jazayeri, and others. 2006. "Cooking Up an Open Source EMR for Developing Countries: OpenMRS, a Recipe for Successful Collaboration." *AMIA Annual Symposium Proceedings* 2006: 529–53.

Mangtani, P., I. Abubakar, C. A. Ariti, and J. A. C. Sterne. 2014. "Protection by BCG Vaccine Against Tuberculosis: A Systematic Review of Randomized Controlled Trials." *Clinical Infectious Diseases* 58 (4): 470–80.

Manjelievskaia, J., D. Erck, S. Piracha, and L. Schrager. 2016. "Drug-Resistant TB: Deadly, Costly, and in Need of a Vaccine." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 110 (3): 186–91.

Manjourides, J., H. H. Lin, S. Shin, C. Jeffery, C. Contreras, and others. 2012. "Identifying Multidrug Resistant Tuberculosis Transmission Hotspots Using Routinely Collected Data." *Tuberculosis* 92 (3): 273–79.

Mao, T. E., K. Okada, N. Yamada, S. Peou, M. Ota, and others. 2014. "Cross-Sectional Studies of Tuberculosis Prevalence in Cambodia between 2002 and 2011." *Bulletin of the World Health Organization* 92 (8): 573–81.

Marais, B. J., M. C. Raviglione, P. R. Donald, A. D. Harries, A. L. Kritski, and others. 2010. "Scale-Up of Services and Research Priorities for Diagnosis, Management, and Control of Tuberculosis: A Call to Action." *The Lancet* 375 (9732): 2179–91.

Marica, C., C. Didilescu, N. Galie, D. Chiotan, J. P. Zellweger, and others. 2009. "Reversing the Tuberculosis Upwards Trend: A Success Story in Romania." *European Respiratory Journal* 33 (1): 168–70.

Marrone, M. T., V. V Venkataramanan, M. Goodman, A. C. Hill, J. A. Jereb, and others. 2013. "Surgical Interventions for Drug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis." *International Journal of Tuberculosis and Lung Disease* 17 (1): 6–16.

Martineau, A. R., S. Nhamoyebonde, T. Oni, M. X. Rangaka, S. Marais, and others. 2011. "Reciprocal Seasonal Variation in Vitamin D Status and Tuberculosis Notifications in Cape Town, South Africa." *Proceedings of the National Academy of Sciences* 108 (47): 19013–17.

Marx, F. M., R. Dunbar, D. A. Enarson, B. G. Williams, R. M. Warren, and others. 2014. "The Temporal Dynamics of Relapse and Reinfection Tuberculosis after Successful Treatment: A Retrospective Cohort Study." *Clinical Infectious Diseases* 58 (12): 1676–83.

Mathew, T. A., T. N. Ovsyanikova, S. S. Shin, I. Y. Gelmanova, D. A. Balbuena, and others. 2006. "Causes of Death during Tuberculosis Treatment in Tomsk Oblast, Russia." *International Journal of Tuberculosis and Lung Disease* 10 (8): 857–63.

McFarlane, N. 1989. "Hospitals, Housing, and Tuberculosis in Glasgow, 1911–51." *Social History of Medicine* 2 (1): 59–85.

McIlleron, H., G. Meintjes, W. J. Burman, and G. Maartens. 2007. "Complications of Antiretroviral Therapy in Patients with Tuberculosis: Drug Interactions, Toxicity, and Immune Reconstitution Inflammatory Syndrome." *Journal of Infectious Diseases* 196 (Suppl 1): S63–75.

McKee, M., and R. Atun. 2006. "Beyond Borders: Public-Health Surveillance." *The Lancet* 367 (9518): 1224–26.

McKeown, T., and R. Record. 1962. "Reasons for the Decline of Mortality in England and Wales during the Nineteenth Century." *Population Studies* 16 (2): 94–122.

Meintjes, G., S. D. Lawn, F. Scano, G. Maartens, M. A. French, and others. 2008. "Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome: Case Definitions for Use in Resource-Limited Settings." *The Lancet Infectious Diseases* 8 (8): 516–23.

Meintjes, G., R. J. Wilkinson, C. Morroni, D. J. Pepper, K. Rebe, and others. 2010. "Randomized Placebo-Controlled Trial of Prednisone for Paradoxical TB-Associated Immune Reconstitution Inflammatory Syndrome." *AIDS* 24 (15): 2381.

Melendez, J., C. I. Sánchez, R. H. Philipsen, P. Maduskar, R. Dawson, and others. 2016. "An Automated Tuberculosis

Screening Strategy Combining X-Ray-Based Computer-Aided Detection and Clinical Information." *Scientific Reports* 6: 25265. doi:10.1038/srep25265.

Menzies, N. A., T. Cohen, H.-H. Lin, M. Murray, and J. A. Salomon. 2012. "Population Health Impact and Cost-Effectiveness of Tuberculosis Diagnosis with Xpert MTB/RIF: A Dynamic Simulation and Economic Evaluation." *PLoS Medicine* 9 (11): e1001347.

Meressa, D., R. M. Hurtado, J. R. Andrews, E. Diro, K. Abato, and others. 2015. "Achieving High Treatment Success for Multidrug-Resistant TB in Africa: Initiation and Scale-Up of MDR TB Care in Ethiopia: An Observational Cohort Study." *Thorax* 70 (12): 1181–88.

Merle, C. S., K. Fielding, O. B. Sow, M. Gninafon, M. B. Lo, and others. 2014. "A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis." *New England Journal of Medicine* 371 (17): 1588–98.

Middelkoop, K., B. Mathema, L. Myer, E. Shashkina, A. Whitelaw, and others. 2015. "Transmission of Tuberculosis in a South African Community with a High Prevalence of HIV Infection." *Journal of Infectious Diseases* 211 (1): 53–61.

Mitchison, D. A. 2004. "Antimicrobial Therapy of Tuberculosis: Justification for Currently Recommended Treatment Regimens." *Seminars in Respiratory and Critical Care Medicine* 24 (3): 307–15.

Miti, S., V. Mfungwe, P. Reijer, and D. Maher. 2003. "Integration of Tuberculosis Treatment in a Community-Based Home Care Programme for Persons Living with HIV/AIDS in Ndola, Zambia." *International Journal of Tuberculosis and Lung Disease* 7 (9, Suppl 1): S92–98.

Mitnick, C. D., J. Bayona, E. Palacios, S. Shin, J. Furin, and others. 2003. "Community-Based Therapy for Multidrug-Resistant Tuberculosis in Lima, Peru." *New England Journal of Medicine* 348 (2): 119–28.

Mitnick, C. D., S. S. Shin, K. J. Seung, M. L. Rich, S. S. Atwood, and others. 2008. "Extensively Drug-Resistant Tuberculosis: A Comprehensive Treatment Approach." *New England Journal of Medicine* 359 (6): 563–74.

Mitwalli, A. 1991. "Tuberculosis in Patients on Maintenance Dialysis." *American Journal of Kidney Diseases* 18 (5): 579–82.

Moalosi, G., K. Floyd, J. Phatshwane, T. Moeti, N. Binkin, and T. Kenyon. 2003. "Cost-Effectiveness of Home-Based Care versus Hospital Care for Chronically Ill Tuberculosis Patients, Francistown, Botswana." *International Journal of Tuberculosis and Lung Disease* 7 (Suppl 1): S80–85.

Modlin, R. L., and B. R. Bloom. 2013. "TB or Not TB: That Is No Longer the Question." *Science Translational Medicine* 5 (213): 213–16

Mohammed-Rajput, N. A., D. C. Smith, B. Mamlin, P. Biondich, and B. N. Doebbeling. 2011. "OpenMRS, a Global Medical Records System Collaborative: Factors Influencing Successful Implementation." *AMIA Annual Symposium Proceedings* 2011 (October 22): 960–68.

Moonan, P. K., T. N. Quitugua, J. M. Pogoda, G. Woo, G. Drewyer, and others. 2011. "Does Directly Observed Therapy (DOT) Reduce Drug Resistant Tuberculosis?" *BMC Public Health* 11 (1): 19.

Moore, D. A. J. 2016. "What Can We Offer to 3 Million MDRTB Household Contacts in 2016?" *BMC Medicine* 14: 64.

Moyo, S., J. J. Furin, J. Hughes, J. Daniels, L. Snyman, and others. 2014. "Outcomes in Adolescents Undergoing Treatment for Drug-Resistant Tuberculosis in Cape Town, South Africa, 2008–2013." *Archives of Pediatric Infectious Diseases* 3 (3): e17934.

Mphaphlele, M., A. S. Dharmadhikari, P. A. Jensen, S. N. Rudnick, T. H. van Reenen, and others. 2015. "Institutional Tuberculosis Transmission Controlled Trial of Upper Room Ultraviolet Air Disinfection: A Basis for New Dosing Guidelines." *Amerian Journal of Respiratory and Critical Care Medicine* 192 (4): 477–84.

Mukherjee, J. S., S. Shin, J. Furin, M. L. Rich, F. Léandre, and others. 2002. "New Challenges in the Clinical Management of Drug-Resistant Tuberculosis." *Infectious Diseases in Clinical Practice* 11 (6): 329–39.

Muniyandi, M., R. Rajeswari, R. Balasubramanian, and P. R. Narayanan. 2008. "A Comparison of Costs to Patients with Tuberculosis Treated in a DOTS Programme with Those in a Non-DOTS Programme in South India." *Journal of Health Management* 10 (1): 9–24.

Muniyandi, M., R. Ramachandran, R. Balasubramanian, and P. R. Narayanan. 2006. "Socio-Economic Dimensions of Tuberculosis Control: Review of Studies over Two Decades from Tuberculosis Research Center." *Journal of Communicable Diseases* 38 (3): 204.

Muniyandi, M., R. Ramachandran, P. G. Gopi, V. Chandrasekaran, R. Subramani, and others. 2007. "The Prevalence of Tuberculosis in Different Economic Strata: A Community Survey from South India [Short Communication]." *International Journal of Tuberculosis and Lung Disease* 11 (9): 1042–45.

Munro, S. A., S. A. Lewin, H. J. Smith, M. E. Engel, A. Fretheim, and others. 2007. "Patient Adherence to Tuberculosis Treatment: A Systematic Review of Qualitative Research." *PLoS Medicine* 4 (7): e238.

Murray, C. J., K. Styblo, and A. Rouillon. 1990. "Tuberculosis in Developing Countries: Burden, Intervention and Cost. *Bulletin of the International Union Against Tuberculosis and Lung Disease* 65 (December 8): 6–24.

Nakiyingi, L., V. M. Moodley, Y. C. Manabe, M. P. Nicol, M. Holshouse, and others. 2014. "Diagnostic Accuracy of a Rapid Urine Lipoarabinomannan Test for Tuberculosis in HIV-Infected Adults." *Journal of Acquired Immune Deficiency Syndromes* 66 (3): 270–79.

Naranbhai, V. 2016. "The Role of Host Genetics (and Genomics) in Tuberculosis." *Microbiology Spectrum* 4 (5). doi: 10.1128/microbiolspec.TBTB2-0011-2016.

Nardell, E., and A. Dharmadhikari. 2010. "Turning off the Spigot: Reducing Drug-Resistant Tuberculosis Transmission in Resource-Limited Settings." *International Journal of Tuberculosis and Lung Disease* 14 (10): 1233.

Nathanson, E., C. Lambregts-van Weezenbeek, M. Rich, R. Gupta, J. Bayona, and others. 2006. "Multidrug-Resistant Tuberculosis Management in Resource-Limited Settings." *Emerging Infectious Diseases* 12 (9): 1389.

Nathanson, E., P. Nunn, M. W. Uplekar, K. Floyd, E. Jaramillo, and others. 2010. "MDR Tuberculosis: Critical Steps for

Prevention and Control." *New England Journal of Medicine* 363 (11): 1050–58.

Nganda, B., J. Wang'ombe, K. Floyd, and J. Kangangi. 2003. "Cost and Cost-Effectiveness of Increased Community and Primary Care Facility Involvement in Tuberculosis Care in Machakos District, Kenya." *International Journal of Tuberculosis and Lung Disease* 7 (9, Suppl 1): S14–20.

Nunn, A. J., I. D. Rusen, A. Van Deun, G. Torrea, P. P. Phillips, and others. 2014. "Evaluation of a Standardized Treatment Regimen of Anti-Tuberculosis Drugs for Patients with Multi-Drug-Resistant Tuberculosis (STREAM): Study Protocol for a Randomized Controlled Trial." *Trials* 15 (September 9): 353.

Obihara, C. C., N. Beyers, R. P. Gie, P. C. Potter, B. J. Marais, and others. 2005. "Inverse Association between *Mycobacterium tuberculosis* Infection and Atopic Rhinitis in Children." *Allergy* 60 (9): 1121–25.

OECD (Organisation for Economic Co-operation and Development), Eurostat, WHO (World Health Organization). 2011. *A System of Health Accounts.* Paris: OECD Publishing. http://www.who.int/health-accounts/methodology/sha2011.pdf.

O'Garra, A., P. S. Redford, F. W. McNab, C. I. Bloom, R. J. Wilkinson, and others. 2013. "The Immune Response in Tuberculosis." *Annual Review of Immunology* 31 (March): 475–527.

O'Grady, J., M. Hoelscher, R. Atun, M. Bates, P. Mwaba, and others. 2011. "Tuberculosis in Prisons in Sub-Saharan Africa: The Need for Improved Health Services, Surveillance, and Control." *Tuberculosis* 91 (2): 173–78.

O'Grady, J., M. Maeurer, R. Atun, I. Abubakar, P. Mwaba, and others. 2011. "Tuberculosis in Prisons: Anatomy of Global Neglect." *European Respiratory Journal* 38 (4): 752–54.

Okello, D., K. Floyd, F. Adatu, R. Odeke, and G. Gargioni. 2003. "Cost and Cost-Effectiveness of Community-Based Care for Tuberculosis Patients in Rural Uganda." *The International Journal of Tuberculosis and Lung Disease* 7 (9, Suppl 1): S72–79.

Okot-Chono, R., F. Mugisha, F. Adatu, E. Madraa, R. Dlodlo, and others. 2009. "Health System Barriers Affecting the Implementation of Collaborative TB-HIV Services in Uganda." *International Journal of Tuberculosis and Lung Disease* 13 (8): 955–61.

Owens, J. P., M. O. Fofana, and D. W. Dowdy. 2013. "Cost-Effectiveness of Novel First-Line Treatment Regimens for Tuberculosis." *International Journal of Tuberculosis and Lung Disease* 17 (May): 590–96.

Oxlade, O., and M. Murray. 2012. "Tuberculosis and Poverty: Why Are the Poor at Greater Risk in India?" *PLoS One* 7 (11): e47533.

Pai, M., A. Daftary, and S. Satyanarayana. 2016. "TB Control: Challenges and Opportunities for India." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 110 (3): 158–60.

Pai, M., S. Kalantri, and K. Dheda. 2006. "New Tools and Emerging Technologies for the Diagnosis of Tuberculosis: Part II. Active Tuberculosis and Drug Resistance." *Expert Review of Molecular Diagnostics* 6 (3): 423–32.

Palacios, J. J., J. Ferro, N. Ruiz Palma, J. M. García, H. Villar, and others. 1999. "Fully Automated Liquid Culture System Compared with Löwenstein-Jensen Solid Medium for Rapid Recovery of Mycobacteria from Clinical Samples." *European Journal of Clinical Microbiology and Infectious Diseases* 18 (4): 265–73.

Palmer, C., and M. W. Long 1966. "Effects of Infection with Atypical Mycobacteria on BCG Vaccination and Tuberculosis." *American Review of Respiratory Disease* 94 (4): 553–68.

Pantoja, A., K. Floyd, K. P. Unnikrishnan, R. Jitendra, M. R. Padma, and others. 2009. "Economic Evaluation of Public-Private Mix for Tuberculosis Care and Control, India. Part I. Socio-Economic Profile and Costs among Tuberculosis Patients." *International Journal of Tuberculosis and Lung Disease* 13 (6): 698–704.

Pantoja, A., K. Lönnroth, S. S. Lal, L. S. Chauhan, M. W. Uplekar, and others. 2009. "Economic Evaluation of Public-Private Mix for Tuberculosis Care and Control, India. Part II. Cost and Cost-Effectiveness." *International Journal of Tuberculosis and Lung Disease* 13 (6): 705–12.

Pasipanodya, J. G., and T. Gumbo. 2013. "A Meta-Analysis of Self-Administered versus Directly Observed Therapy Effect on Microbiologic Failure, Relapse, and Acquired Drug Resistance in Tuberculosis Patients." *Clinical Infectious Diseases* 57 (1): 21–31.

Perumal, R., N. Padayatchi, and E. Stiefvater. 2009. "The Whole Is Greater Than the Sum of the Parts: Recognising Missed Opportunities for an Optimal Response to the Rapidly Maturing TB-HIV Co-Epidemic in South Africa." *BMC Public Health* 9 (1): 243.

Petsch, B., M. Schnee, A. B. Vogel, E. Lange, B. Hoffmann, and others. 2012. "Protective Efficacy of in vitro Synthesized, Specific mRNA Vaccines against Influenza A Virus Infection." *Nature Biotechnology* 30 (12): 1210–16.

Pevzner, E. S., G. Vandebriel, D. W. Lowrance, M. Gasana, and A. Finlay. 2011. "Evaluation of the Rapid Scale-Up of Collaborative TB/HIV Activities in TB Facilities in Rwanda, 2005–2009." *BMC Public Health* 11 (1): 550.

Philipsen, R. H., C. I. Sánchez, P. Maduskar, J. Melendez, L. Peters-Bax, and others. 2015. "Automated Chest-Radiography as a Triage for Xpert Testing in Resource-Constrained Settings: A Prospective Study of Diagnostic Accuracy and Costs." *Scientific Reports* 5:12215. doi: 10.1038/srep12215.

Phillips, M., R. N. Cataneo, R. Condos, G. A. Ring Erickson, J. Greenberg, and others. 2007. "Volatile Biomarkers of Pulmonary Tuberculosis in the Breath." *Tuberculosis* 87 (1): 44–52.

Phillips, P. P., C. M. Mendel, D. A. Burger, A. M. Crook, A. J. Nunn, and others. 2016. "Limited Role of Culture Conversion for Decision-Making in Individual Patient Care and for Advancing Novel Regimens to Confirmatory Clinical Trials." *BMC Medicine* 14 (February 4): 19.

Phiri, S., P. Khan, A. D. Grant, D. Gareta, H. Tweya, and others. 2011. "Integrated Tuberculosis and HIV Care in a Resource-Limited Setting: Experience from the Martin

Preuss Centre, Malawi." *Tropical Medicine and International Health* 16 (11): 1397–403.

Pichenda, K., K. Nakamura, A. Morita, M. Kizuki, K. Seino, and T. Takano. 2012. "Non-Hospital DOT and Early Diagnosis of Tuberculosis Reduce Costs while Achieving Treatment Success." *International Journal of Tuberculosis and Lung Disease* 16 (6): 828–34.

Png, E., B. Alisjahbana, E. Sahiratmadja, S. Marzuki, R. Nelwan, and others. 2012. "A Genome Wide Association Study of Pulmonary Tuberculosis Susceptibility in Indonesians." *BMC Medical Genetics* 13 (January 13): 5.

Podewils, L. J., M. T. S. Gler, M. I. Quelapio, and M. P. Chen. 2013. "Patterns of Treatment Interruption among Patients with Multidrug-Resistant TB (MDR TB) and Association with Interim and Final Treatment Outcomes." *PLoS One* 8 (7): e70064.

Pooran, A., E. Pieterson, M. Davids, G. Theron, and K. Dheda. 2013. "What Is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa?" *PLoS One* 8 (1): e54587.

Pop-Eleches, C., H. Thirumurthy, J. P. Habyarimana, J. G. Zivin, M. P. Goldstein, and others. 2011. "Mobile Phone Technologies Improve Adherence to Antiretroviral Treatment in a Resource-Limited Setting: A Randomized Controlled Trial of Text Message Reminders." *AIDS* 25 (6): 825–34.

Prasad, K., and M. B. Singh. 2008. "Corticosteroids for Managing Tuberculous Meningitis." *Cochrane Database of Systematic Reviews* 23 (1): CD002244.

Rachow, A., A. Zumla, N. Heinrich, G. Rojas-Ponce, B. Mtafya, and others. 2011. "Rapid and Accurate Detection of *Mycobacterium tuberculosis* in Sputum Samples by Cepheid Xpert MTB/RIF Assay: A Clinical Validation Study." *PLoS One* 6 (6): e20458.

Ramma, L., H. Cox, L. Wilkinson, N. Foster, L. Cunnama, and others. 2015. "Patients' Costs Associated with Seeking and Accessing Treatment for Drug-Resistant Tuberculosis in South Africa." *International Journal of Tuberculosis and Lung Disease* 19 (12): 1513–19.

Rangaka, M. X., S. C. Cavalcane, B. J. Marais, S. Thim, N. A. Martinson, and others. 2015. "Controlling the Seedbeds of Tuberculosis: Diagnosis and Treatment of Tuberculosis Infection." *The Lancet* 386 (10010): 2344–53.

Rehm, J., A. V. Samokhvalov, M. G. Neuman, R. Room, C. Parry, and others. 2009. "The Association between Alcohol Use, Alcohol Use Disorders and Tuberculosis (TB). A Systematic Review." *BMC Public Health* 9 (1): 450.

Resch, S. C., J. A. Salomon, M. Murray, and M. C. Weinstein. 2006. "Cost-Effectiveness of Treating Multidrug-Resistant Tuberculosis." *PLoS Medicine* 3 (7): e241.

Riley, R., and A. Moodie. 1974. "Infectivity of Patients with Pulmonary Tuberculosis in Inner City Homes." *American Review of Respiratory Disease* 110 (6): 810–12.

Roberts, M., W. Hsiao, P. Berman, and M. Reich. 2004. *Getting Health Reform Right: A Guide to Improving Performance and Equity*. Oxford: Oxford University Press.

Rodrigo, T., J. A. Caylà, G. de Olalla P., H. Galdós-Tangüis, J. M. Jansà, and others. 1997. "Characteristics of Tuberculosis Patients Who Generate Secondary Cases." *International Journal of Tuberculosis and Lung Disease* 1 (4): 352–57.

Rodrigues, L. C., V. K. Diwan, and J. G. Wheeler. 1993. "Protective Effect of BCG against Tuberculous Meningitis and Miliary Tuberculosis: A Meta-Analysis." *International Journal of Epidemiology* 22 (6): 1154–58.

Ross, J. D., and J. C. Willison. 1971. "The Relationship between Tuberculin Reactions and the Later Development of Tuberculosis: An Investigation among Edinburgh School Children in 1960–1970." *Tubercle* 52 (4): 258–65.

Rouillon, A., S. Perdrizet, and R. Parrot. 1976. "Transmission of Tubercle Bacilli: The Effects of Chemotherapy." *Tubercle* 57 (4): 275–99.

Rouzier, V. A., O. Oxlade, R. Verduga, L. Gresely, and D. Menzies. 2010. "Patient and Family Costs Associated with Tuberculosis, Including Multidrug-Resistant Tuberculosis, in Ecuador." *The International Journal of Tuberculosis and Lung Disease* 14 (10): 1316–22.

Roy, A., M. Eisenhut, R. J. Harris, L. C. Rodrigues, S. Sridhar, and others. 2014. "Effect of BCG Vaccination Against *Mycobacterium tuberculosis* Infection in Children: Systematic Review and Meta-analysis." *BMJ* 349 (August 5): g4643.

Sallusto, F. 2016. "Heterogeneity of Human CD4(+) T Cells against Microbes." *Annual Review of Immunology* 34 (May 24): 317–34.

Salomon, J. A., J. Lloyd-Smith, W. M. Getz, S. Resch, M. S. Sánchez, and others. 2006. "Prospects for Advancing Tuberculosis Control Efforts through Novel Therapies." *PLoS Medicine* 3 (8): e273.

Samandari, T., T. B. Agizew, S. Nyirenda. Z. Tedla, T. Sibanda, and others. 2011. "6-Month Versus 36-Month Isoniazid Preventive Treatment for Tuberculosis in Adults with HIV Infection in Botswana: A Randomised, Double-Blind, Placebo-Controlled Trial." *The Lancet* 377 (9777): 1588–98.

Samb, B., T. Evans, M. Dybul, R. Atun, J.-P. Moatti, and others. 2009. "An Assessment of Interactions between Global Health Initiatives and Country Health Systems." *The Lancet* 373 (9681): 2137–69.

Satyanarayana, S., S. A. Nair, S. S. Chadha, R. Shivashankar, G. Sharma, and others. 2011. "From Where Are Tuberculosis Patients Accessing Treatment in India? Results from a Cross-Sectional Community Based Survey of 30 Districts." *PLoS One* 6 (9): e24160.

Schaaf, H. S., B. J. Marais, A. C. Hesseling, W. Brittle, and P. R. Ronald. 2009. "Surveillance of Antituberculosis Drug Resistance among Children from the Western Cape Province of South Africa—An Upward Trend." *American Journal of Public Health* 99 (8): 1486–90.

Schnippel, K., S. Rosen, K. Shearer, N. Martinson, L. Long, and others. 2013. "Costs of Inpatient Treatment for Multi-Drug-Resistant Tuberculosis in South Africa." *Tropical Medicine and International Health* 18 (1): 109–16.

Schouten, E. J., A. Jahn, D. Midiani, S. D. Makombe, A. Mnthambala, and others. 2011. "Prevention of Mother-to-Child Transmission of HIV and the Health-Related Millennium Development Goals: Time for a Public Health Approach." *The Lancet* 378 (9787): 282–84.

Scott, L. E., K. McCarthy, N. Gous, M. Nduna, A. Van Rie, and others. 2011. "Comparison of Xpert MTB/RIF with Other Nucleic Acid Technologies for Diagnosing Pulmonary Tuberculosis in a High HIV Prevalence Setting: A Prospective Study." *PLoS Medicine* 8 (7): e1001061.

Seddon, J. A., H. E. Jenkins, L. Liu, T. Cohen, R. E. Black, and others. 2015. "Counting Children with Tuberculosis: Why Numbers Matter." *International Journal of Tuberculosis and Lung Disease* 19 (Suppl 1): 9–16.

Seebregts, C. J., B. W. Mamlin, P. G. Biondich, H. S. F. Fraser, B. A. Wolfe, and others. 2009. "The OpenMRS Implementers Network." *International Journal Medical Informatics* 78 (11): 711–20.

Selwyn, P. A., D. Hartel, V. A. Lewis, E. E. Schoenbaum, S. H. Vermund, and others. 1989. "A Prospective Study of the Risk of Tuberculosis among Intravenous Drug Users with Human Immunodeficiency Virus Infection." *New England Journal of Medicine* 320 (9): 545–50.

Sengupta, A., and S. Nundy. 2005. "The Private Health Sector in India." *BMJ* 331 (7526): 1157–58.

Seung, K. J., D. B. Omatayo, S. Keshavjee, J. J. Furin, P. E. Farmer, and others. 2009. "Early Outcomes of MDR-TB Treatment in a High HIV-Prevalence Setting in South Africa." *PLoS One* 4 (9): e7186.

Shah, N. S., S. C. Auld, J. C. M. Brust, B. Mathema, N. Ismail, and others. 2017. "Transmission of Extensively Drug-Resistant Tuberculosis in South Africa." *New England Journal of Medicine* 376: 243–53.

Shaler, C. R., C. N. Horvath, M. Jeyanathan, and Z. Xing. 2013. "Within the Enemy's Camp: Contribution of the Granuloma to the Dissemination, Persistence and Transmission of *Mycobacterium tuberculosis*." *Frontiers in Immunology* 4 (February 14): 30.

Shapiro, A. E., E. Variava, M. H. Rakgokong, N. Moodley, B. Luke, and others. 2012. "Community-Based Targeted Case Finding for Tuberculosis and HIV in Household Contacts of Patients with Tuberculosis in South Africa." *American Journal of Respiratory and Critical Care Medicine* 185 (10): 1110–16.

Shargie, E. B., O. Mørkve, and B. Lindtjørn. 2006. "Tuberculosis Case-Finding through a Village Outreach Programme in a Rural Setting in Southern Ethiopia: Community Randomized Trial." *Bulletin of the World Health Organization* 84 (2): 112–19.

Sheriff, F. G., K. P. Manji, M. M. Chagani, R. M. Mpembeni, A. M. Jusabani, and others. 2010. "Latent Tuberculosis among Pregnant Mothers in a Resource Poor Setting in Northern Tanzania: A Cross-Sectional Study." *BMC Infectious Diseases* 10 (1): 52.

Shetty, N., M. Shemko, M. Vaz, and G. D'Souza. 2006. "An Epidemiological Evaluation of Risk Factors for Tuberculosis in South India: A Matched Case Control Study." *International Journal of Tuberculosis and Lung Disease* 10 (1): 80–86.

Shi, W., X. Zhang, X. Jiang, H. Yuan, J. S. Lee, and others. 2011. "Pyrazinamide Inhibits Trans-Translation in *Mycobacterium tuberculosis*." *Science* 333 (6049): 1630–32.

Shigayeva, A., R. Atun, M. McKee, and R. Coker. 2010. "Health Systems, Communicable Diseases and Integration." *Health Policy and Planning* 25 (Suppl 1): i4–20.

Shilova, M. V., and C. Dye. 2001. "The Resurgence of Tuberculosis in Russia." *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 356 (1411): 1069–75.

Shin, S. S., A. D. Pasechnikov, I. Y. Gelmanova, G. G. Peremitin, A. K. Strelis, and others. 2006. "Treatment Outcomes in an Integrated Civilian and Prison MDR-TB Treatment Program in Russia." *The International Journal of Tuberculosis and Lung Disease* 10 (4): 402–8.

Shin, S. S., M. Yagui, L. Ascencios, G. Yale, C. Suarez, and others. 2008. "Scale-Up of Multidrug-Resistant Tuberculosis Laboratory Services, Peru." *Emerging Infectious Diseases* 14 (5): 701.

Shirakawa, T., T. Enomoto, S. Shimazu, and J. M. Hopkin. 1997. "The Inverse Association between Tuberculin Responses and Atopic Disorder." *Science* 275 (5296): 77–79.

Shirtcliffe, P., M. Weatherall, and R. Beasley. 2002. "An Inverse Correlation between Estimated Tuberculosis Notification Rates and Asthma Symptoms." *Respirology* 7 (2): 153–55.

Siedner, M. J., A. J. Lankowski, M. Kanyesigye, M. B. Bwana, J. E. Haberer, and others. 2015. "A Combination SMS and Transportation Reimbursement Intervention to Improve HIV Care Following Abnormal CD4 Test Results in Rural Uganda: A Prospective Observational Cohort Study." *BMC Medicine* 13 (1): 160.

Sinanovic, E., K. Floyd, L. Dudley, V. Azevedo, R. Grant, and others. 2003. "Cost and Cost-Effectiveness of Community-Based Care for Tuberculosis in Cape Town, South Africa." *International Journal of Tuberculosis and Lung Disease* 7 (9, Suppl 1): S56–62.

Sinanovic, E., and L. Kumaranayake. 2006. "Financing and Cost-Effectiveness Analysis of Public-Private Partnerships: Provision of Tuberculosis Treatment in South Africa." *Cost Effectiveness and Resource Allocation* 4: 11.

Sinanovic, E., J. Moodley, M. A. Barone, S. Mall., S. Cleary, and others. 2009. "The Potential Cost-Effectiveness of Adding a Human Papillomavirus Vaccine to the Cervical Cancer Screening Programme in South Africa." *Vaccine* 27 (44): 6196–202.

Sinanovic, E., L. Ramma, A. Vassall, V. Azevedo, L. Wilkinson, and others. 2015. "Impact of Reduced Hospitalisation on the Cost of Treatment for Drug-Resistant Tuberculosis in South Africa." *International Journal of Tuberculosis and Lung Disease* 19 (2): 172–78.

Singh, A., D. Parasher, D. S. Shekhavat, S. Sahu, D. Wares, and others. 2004. "Effectiveness of Urban Community Volunteers in Directly Observed Treatment of Tuberculosis Patients: A Field Report from Haryana, North India [Notes from the Field]." *International Journal of Tuberculosis and Lung Disease* 8 (6): 800–802.

Slama, K., C. Chiang, D. A. Enarson, K. Hassmiller, A. Fanning, and others. 2007. "Tobacco and Tuberculosis: A Qualitative Systematic Review and Meta-Analysis [Review Article]."

International Journal of Tuberculosis and Lung Disease 11 (10): 1049–61.

Smart, T. 2010. "Decentralised, Patient-Centered Models of Delivering Treatment and Palliative Care for People with M/XDR-TB." *HIV and AIDS Treatment in Practice* 166 (October 8): 2–10.

Smieja, M. J., C. A. Marchetti, D. J. Cook, and F. M. Smaill. 2000. "Isoniazid for Preventing Tuberculosis in Non-HIV Infected Persons." *Cochrane Database of Systematic Reviews* 2: CD001363.

Snider, D. Jr. 1978. "The Relationship between Tuberculosis and Silicosis." *American Review of Respiratory Disease* 118 (3): 455–60.

Sobota, R. S., C. M. Stein., N. Kodaman, L. B. Scheinfeldt, I. Maro, and others. 2016. "A Locus at 5q33.3 Confers Resistance to Tuberculosis in Highly Susceptible Individuals." *American Journal of Human Genetics* 98 (3): 514–24.

Soltan, V., A. K. Henry, V. Crudu, and I. Zatusevski. 2008. "Increasing Tuberculosis Case Detection: Lessons from the Republic of Moldova." *Bulletin of the World Health Organization* 86 (1): 71–76.

Soysal, A., K. A. Millington, M. Bakir, D. Dosanjh, Y. Aslan, and others. 2005. "Effect of BCG Vaccination on Risk of *Mycobacterium tuberculosis* Infection in Children with Household Tuberculosis Contact: A Prospective Community-Based Study." *The Lancet* 366 (9495): 1443–51.

Spertini, F., R. Audran, R. Chakour, O. Karoui, V. Steiner-Monard, and others. 2015. "Safety of Human Immunisation with a Live-Attenuated *Mycobacterium tuberculosis* Vaccine: A Randomised, Double-Blind, Controlled Phase I Trial." *The Lancet Respiratory Medicine* 3 (12): 953–62.

Spisak, C., L. Morgan, R. Eichler, J. Rosen, B. Serumaga, and others. 2016. "Results-Based Financing in Mozambique's Central Medical Store: A Review after 1 Year." *Global Health: Science and Practice* 4 (1): 2–13.

Sreeramareddy, C. T., Z. Z. Qin, S. Satyanarayana, R. Subbaraman, and M. Pai. 2014. "Delays in Diagnosis and Treatment of Pulmonary Tuberculosis in India: A Systematic Review." *International Journal of Tuberculosis and Lung Disease* 18 (3): 255–66.

Stead, W. W., and A. K. Dutt. 1989. "Tuberculosis in the Elderly." *Seminars in Respiratory Infections* 4: 189–97.

Sterling, T. R., M. E. Villarino, A. S. Borisov, N. Shang, F. Gordin, and others. 2011. "Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection." *New England Journal of Medicine* 365: 2155–66.

Stop TB Partnership. 2011. "The Global Plan to Stop TB." World Health Organization, Geneva.

———. 2016. "The 'Zero TB Initiative' Sparks New Action to End TB." World Health Organization, Geneva, July 26. http://us3.campaign-archive2.com/?u=85207b84f0f2d8ddc9bd878de&id=6f3e04fcc9&e=abd33e01a4.

Stop TB Working Group on DOTS-Plus for MDR-TB. 2003. "A Prioritised Research Agenda for DOTS-Plus for Multidrug-Resistant Tuberculosis (MDR-TB)." *International Journal of Tuberculosis and Lung Disease* 7 (5): 410–14.

Styblo, K. 1991. *Epidemiology of Tuberculosis: Selected Papers.* The Hague: KNCV Tuberculosis Foundation.

Suarez, P. G., K. Floyd, J. Portocarrero, E. Alarcon, E. Rapiti, and others. 2002. "Feasibility and Cost-Effectiveness of Standardised Second-Line Drug Treatment for Chronic Tuberculosis Patients: A National Cohort Study in Peru." *The Lancet* 359 (9322): 1980–89.

Subbaraman, R., R. R. Nathavitharana, S. Satyanarayana, M. Pai, B. E. Thomas, and others. 2016. "The Tuberculosis Cascade of Care in India's Public Sector: A Systematic Review and Meta-Analysis." *PLoS Medicine* 13 (10): e1002149. doi:10.1371/journal.pmed.1002149.

Sudre, P., G. ten Dam, and A. Kochi. 1992. "Tuberculosis: A Global Overview of the Situation Today." *Bulletin of the World Health Organization* 70 (2): 149.

Sutherland, I., and V. Springett. 1987. "Effectiveness of BCG Vaccination in England and Wales in 1983." *Tubercle* 68 (2): 81–92.

Sutherland, I., E. Svandova, and S. Radhakrishna. 1982. "The Development of Clinical Tuberculosis Following Infection with Tubercle Bacilli: 1. A Theoretical Model for the Development of Clinical Tuberculosis Following Infection, Linking from Data on the Risk of Tuberculous Infection and the Incidence of Clinical Tuberculosis in the Netherlands." *Tubercle* 63 (4): 255–68.

Swanson, R. C., A. Cattaneo, E. Bradley, S. Chunharas, R. Atun, and others. 2012. "Rethinking Health Systems Strengthening: Key Systems Thinking Tools and Strategies for Transformational Change." *Health Policy and Planning* 27 (Suppl 4): iv54–64.

Sweeney, T. E., L. Braviak, C. M. Tato, and P. Khatri. 2016. "Genome-Wide Expression for Diagnosis of Pulmonary Tuberculosis: A Multicohort Analysis." *The Lancet Respiratory Medicine* 4 (3): 213–24.

Sylla, L., R. D. Bruce, A. Kamarulzaman, and F. L. Altice. 2007. "Integration and Co-Location of HIV/AIDS, Tuberculosis, and Drug Treatment Services." *International Journal of Drug Policy* 18 (4): 306–12.

Szot, A., F. Jacobson, S. Munn, D. Jazayeri, E. Nardell, and others. 2004. "Diagnostic Accuracy of Chest X-rays Acquired Using a Digital Camera for Low-Cost Teleradiology." *International Journal of Medicine* 73 (1): 65–73.

TAG (Treatment Action Group). 2016. *Report on Tuberculosis Research Funding Trends, 2005–2015: No Time to Lose.* New York: TAG. http://www.treatmentactiongroup.org/sites/default/files/TB_FUNDING_2016.

Talat, N., S. Perry, J. Parsonnet, G. Dawood, and R. Hussain. 2010. "Vitamin D Deficiency and Tuberculosis Progression." *Emerging Infectious Diseases* 16 (5): 853–55.

Tameris, M. D., M. Hatherill, B. S. Landry, T. J. Scriba, M. A. Snowden, and others. 2013. "Safety and Efficacy of MVA85A, A New Tuberculosis Vaccine, in Infants Previously Vaccinated with BCG: A Randomised, Placebo-Controlled Phase 2b Trial." *The Lancet* 381 (9871): 1021–28.

Temprano ARNS Study Group. 2015. "A Trial of Early Antiretrovirals and Isoniazid Preventative Therapy in Africa." *New England Journal of Medicine* 373 (9): 808–22.

Theron, G., H. E. Jenkins, F. Cobelens, I. Abubakar, A. J. Khan, and others. 2015. "Data for Action: Collection and Use of Local Data to End Tuberculosis." *The Lancet* 386 (10010): 2324–33.

Theron, G., L. Zijenah, D. Chanda, P. Clowes, A. Rachow, and others. 2014. "Feasibility, Accuracy, and Clinical Effect of Point-of-Care Xpert MTB/RIF Testing for Tuberculosis in Primary-Care Settings in Africa: A Multicentre, Randomised, Controlled Trial." *The Lancet* 383 (9915): 424–35.

Thye, T., E. Owusu-Dabo, F. O. Vannberg, R. van Crevel, J. Curtis, and others. 2012. "Common Variants at 11p13 Are Associated with Susceptibility to Tuberculosis." *Nature Genetetics* 44 (3): 257–59.

Toczek, A., H. Cox, P. du Cros, G. Cooke, and N. Ford. 2013. "Strategies for Reducing Treatment Default in Drug-Resistant Tuberculosis: Systematic Review and Meta-Analysis [Review Article]." *International Journal of Tuberculosis and Lung Disease* 17 (3): 299–307.

Tornee, S., J. Kaewkungwal, W. Fungladda, U. Silachamroon, P. Akarasewi, and others. 2005. "The Association between Environmental Factors and Tuberculosis Infection among Household Contacts." *Southeast Asian Journal of Tropical Medicine and Public Health* 36 (Suppl 4): 221–24.

Toungoussova, O. S., G. Bjune, and D. A. Caugant. 2006. "Epidemic of Tuberculosis in the Former Soviet Union: Social and Biological Reasons." *Tuberculosis* 86 (1): 1–10.

Trajman, A., M. L. Bastos, M. Belo, J. Calaça, J. Gaspar, and others. 2016. "Shortened First-Line TB Treatment in Brazil: Potential Cost Savings for Patients and Health Services." *BMC Health Services Research* 16: 27.

Travis, P., S. Bennett, A. Haines, T. Pang, Z. Bhutta, and others. 2004. "Overcoming Health-Systems Constraints to Achieve the Millennium Development Goals." *The Lancet* 364 (9437): 900–906.

Trébucq, A., D. Enarson, C. Y. Chiang, A. Van Deun, A. D. Harries, and others. 2011. "Xpert® MTB/RIF for National Tuberculosis Programmes in Low-Income Countries: When, Where and How?" *International Journal of Tuberculosis and Lung Disease* 15 (12): 1567–72.

Trunz, B. B., P. Fine, and C. Dye. 2006. "Effect of BCG Vaccination on Childhood Tuberculous Meningitis and Miliary Tuberculosis Worldwide: A Meta-Analysis and Assessment of Cost-Effectiveness." *The Lancet* 367 (9517): 1173–80.

Tseng, C.-L., O. Oxlade, D. Menzies, A. Aspler, and K. Schwartzman. 2011. "Cost-Effectiveness of Novel Vaccines for Tuberculosis Control: A Decision Analysis Study." *BMC Public Health* 11 (1): 55.

Tuberculosis Prevention Trial. 1979. "Trial of BCG Vaccines in South India for Tuberculosis Prevention: First Report." 1979. *Bulletin of the World Health Organization* 57 (5): 819–27.

Tupasi, T. E., R. Gupta, M. I. Quelapio, R. B. Orillaza, N. R. Mira, and others. 2006. "Feasibility and Cost-Effectiveness of Treating Multidrug-Resistant Tuberculosis: A Cohort Study in the Philippines." *PLoS Medicine* 3 (September 12): e352.

Udwadia, Z. F., R. A. Amale, K. K. Ajbani, and C. Rodrigues. 2012. "Totally Drug-Resistant Tuberculosis in India." *Clinical Infectious Diseases* 54 (4): 579–81.

Udwadia, Z. F., L. M. Pinto, and M. W. Uplekar. 2010. "Tuberculosis Management by Private Practitioners in Mumbai, India: Has Anything Changed in Two Decades?" *PLoS One* 5 (8): e12023.

Ukwaja, K. N., O. Modebe, C. Igwenyi, and I. Alobu. 2012. "The Economic Burden of Tuberculosis Care for Patients and Households in Africa: A Systematic Review." *International Journal of Tuberculosis and Lung Disease* 16 (6): 733–39.

UN (United Nations) General Assembly. 2000. "United Nations Millennium Declaration." United Nations General Assembly Resolution A/RES/55/2, UN, New York.

Uplekar, M. W., S. Juvekar, S. Morankar, S. Rangan, and P. Nunn. 1998. "Tuberculosis Patients and Practitioners in Private Clinics in India." *International Journal of Tuberculosis and Lung Disease* 2 (4): 324–29.

Uplekar, M. W., V. Pathania, and M. Raviglione. 2001. "Private Practitioners and Public Health: Weak Links in Tuberculosis Control." *The Lancet* 358 (9285): 912–16.

Uplekar, M. W., and D. S. Shepard. 1991. "Treatment of Tuberculosis by Private General Pracitioners in India." *Tubercle* 72 (4): 284–90. http://www.sciencedirect.com/science/article/pii/004138799190055W.

Uplekar, M. W., D. Weil, K. Lonnroth, E. Jaramillo, C. Lienhardt, and others. 2015. "WHO's New End Tuberculosis Strategy." *The Lancet* 385 (9979): 1799–801.

Uwimana, J., and D. Jackson. 2013. "Integration of Tuberculosis and Prevention of Mother-to-Child Transmission of HIV Programmes in South Africa." *International Journal of Tuberculosis and Lung Disease* 17 (10): 1285–90.

Uwimana, J., D. Jackson, H. Hausler, and C. Zarowsky. 2012. "Health System Barriers to Implementation of Collaborative TB and HIV Activities Including Prevention of Mother to Child Transmission in South Africa." *Tropical Medicine and International Health* 17 (5): 658–65.

Uwinkindi, F., S. Nsanzimana, D. J. Riedel, R. Muhayimpundu, E. Remera, and others. 2014. "Scaling Up Intensified Tuberculosis Case Finding in HIV Clinics in Rwanda." *Journal of Acquired Immune Deficiency Syndromes* 66 (2): e45–49.

Uyei, J., D. Coetzee, J. Macinko, and S. Guttmacher. 2011. "Integrated Delivery of HIV and Tuberculosis Services in Sub-Saharan Africa: A Systematic Review." *The Lancet Infectious Diseases* 11 (11): 855–67.

Uys, P. W., R. Warren, P. D. van Helden, M. Murray, and T. C. Victor. 2009. "Potential of Rapid Diagnosis for Controlling Drug-Susceptible and Drug-Resistant Tuberculosis in Communities Where *Mycobacterium tuberculosis* Infections Are Highly Prevalent." *Journal of Clinical Microbiology* 47 (5): 1484–90.

van der Werf, M. J., M. W. Langendam, E. Huitric, and D. Manissero. 2012. "Multidrug Resistance after Inappropriate Tuberculosis Treatment: A Meta-Analysis." *European Respiratory Journal* 39 (6): 1511–19.

van Rie, A., K. McCarthy, L. Scott, A. Dow, W. D. Venter, and others. 2013. "Prevalence, Risk Factors and Risk Perception of Tuberculosis Infection among Medical Students and Healthcare Workers in Johannesburg, South Africa." *South African Medical Journal* 103 (11): 853–57.

van't Hoog, A. H., K. F. Laserson, W. A. Githui, H. K. Meme, J. A. Agaya, and others. 2011. "High Prevalence of Pulmonary Tuberculosis and Inadequate Case Finding in Rural Western Kenya." *American Journal of Respiratory and Critical Care Medicine* 183 (9): 1245–53.

van't Hoog, A. H., H. K. Meme, K. F. Laserson, J. A. Agaya, B. G. Muchiri, and others. 2012. "Screening Strategies for Tuberculosis Prevalence Surveys: The Value of Chest Radiography and Symptoms." *PLoS One* 7 (7): e38691.

Vassall, A. 2013. "Cost-Effectiveness of Introducing Bedaquiline in MDR-TB Regimens: An Exploratory Analysis." WHO, Geneva.

Vassall, A., S. Bagdadi, H. Bashour, H. Zaher, and P. V. Maaren. 2002. "Cost-Effectiveness of Different Treatment Strategies for Tuberculosis in Egypt and Syria." *International Journal of Tuberculosis and Lung Disease* 6 (12): 1083–90.

Vassall, A., Y. Chechulin, I. Raykhert, N. Osalenko, S. Svetlichnaya, and others. 2009. "Reforming Tuberculosis Control in Ukraine: Results of Pilot Projects and Implications for the National Scale-Up of DOTS." *Health Policy and Planning* 24 (1): 55–62.

Vassall, A., S. van Kampen, H. Sohn, J. S. Michael, K. R. John, and others. 2011. "Rapid Diagnosis of Tuberculosis with the Xpert MTB/RIF Assay in High Burden Countries: A Cost-Effectiveness Analysis." *PLoS Medicine* 8 (11): e1001120.

Verguet, S., R. Laxminarayan, and D. T. Jamison. 2015. "Universal Public Finance of Tuberculosis Treatment in India: An Extended Cost-Effectiveness Analysis." *Health Economics* 24 (3): 318–32.

Verma, G., R. E. Upshur, E. Rea, and S. R. Benatar. 2004. "Critical Reflections on Evidence, Ethics and Effectiveness in the Management of Tuberculosis: Public Health and Global Perspectives." *BMC Medical Ethics* 5 (1): 2.

Verver, S., R. M. Warren, N. Beyers, M. Richardson, G. D. van der Spuy, and others. 2005. "Rate of Reinfection Tuberculosis after Successful Treatment Is Higher than Rate of New Tuberculosis." *American Journal of Respiratory and Critical Care Medicine* 171 (12): 1430–35.

Victor, T., E. Streicher, C. Kewley, A. M. Jordaan, G. D. van der Spuy, and others. 2007. "Spread of an Emerging *Mycobacterium tuberculosis* Drug-Resistant Strain in the Western Cape of South Africa." *International Journal of Tuberculosis and Lung Disease* 11 (2): 195–201.

Villemagne, B., C. Crauste, M. Flipo, A. R. Baulard, B. Déprez, and others. 2012. "Tuberculosis: the Drug Development Pipeline at a Glance." *European Journal of Medicinal Chemistry* 51 (May): 1–16.

Vledder, M., P. Yadav, J. Friedman, M. Sjoblom, amd T. Brown. 2015. "Optimal Supply Chain Structure for Distributing Essential Drugs in Low-Income Countries: Results from a Randomized Experiment." Ross School of Business Paper 1269, University of Michigan, Ann Arbor.

von Mutius, E., N. Pearce, R. Beasley, S. Cheng, O. von Ehrenstein, and others. 2000. "International Patterns of Tuberculosis and the Prevalence of Symptoms of Asthma, Rhinitis, and Eczema." *Thorax* 55 (6): 449–53.

Vynnycky, E., M. Borgdorff, C. C. Leung, C. M. Tam, and P. E. M. Fine. 2008. "Limited Impact of Tuberculosis Control in Hong Kong: Attributable to High Risks of Reactivation Disease." *Epidemiology and Infection* 136 (7): 943–52.

Wallis, R. S., and C. Nacy. 2013. "Early Bactericidal Activity of New Drug Regimens for Tuberculosis." *The Lancet* 381 (9861): 111–12.

Walton, D. A., P. E. Farmer, W. Lambert, F. Léandre, S. P. Koenig, and others. 2004. "Integrated HIV Prevention and Care Strengthens Primary Health Care: Lessons from Rural Haiti." *Journal of Public Health Policy* 25 (2): 137–58.

Walzl, G., K. Ronacher, J. F. D. Siawaya, and H. M. Dockrell. 2008. "Biomarkers for TB Treatment Response: Challenges and Future Strategies." *Journal of Infection* 57 (2): 103–09.

Wandwalo, E., N. Kapalata, S. Egwaga, and S. Morkve. 2004. "Effectiveness of Community-Based Directly Observed Treatment for Tuberculosis in an Urban Setting in Tanzania: A Randomised Controlled Trial." *International Journal of Tuberculosis and Lung Disease* 8 (10): 1248–54.

Wandwalo, E., B. Robberstad, and O. Morkve. 2005. "Cost and Cost-Effectiveness of Community Based and Health Facility Based Directly Observed Treatment of Tuberculosis in Dar es Salaam, Tanzania." *Cost Effectiveness and Resource Allocation* 3 (1): 6.

Weir, R., G. Black, B. Nazareth, S. Floyd, S. Stenson, and others. 2006. "The Influence of Previous Exposure to Environmental Mycobacteria on the Interferon—Gamma Response to Bacille Calmette–Guérin Vaccination in Southern England and Northern Malawi." *Clinical and Experimental Immunology* 146 (3): 390–99.

Weiss, P., W. Chen, V. J. Cook, and J. C. Johnston. 2014. "Treatment Outcomes from Community-Based Drug Resistant Tuberculosis Treatment Programs: A Systematic Review and Meta-Analysis." *BMC Infectious Diseases* 14 (June 17): 333.

Wells, W. A., M. W. Uplekar, and M. Pai. 2015. "Achieving Systemic and Scalable Private Sector Engagement in Tuberculosis Care and Prevention in Asia." *PLoS Medicine* 12 (6): e1001842.

Were, M. C., J. Kariuki, V. Chepng'eno, M. Wandabwa, S. Ndege, and others. 2009. "Leapfrogging Paper-Based Records Using Handheld Technology: Experience from Western Kenya." *Studies in Health Technology and Informatics* 160 (1): 525–29.

WHO (World Health Organization). 1994. "WHO Tuberculosis Programme: Framework for Effective Tuberculosis Control." WHO, Geneva.

———. 1999. *The World Health Report 1999: Making a Difference*. Geneva: WHO.

———. 2000. *The World Health Report 2000: Health Systems, Improving Performance*." Geneva: WHO.

———. 2003. *The World Health Report 2003: Shaping The Future.* Geneva: WHO.

———. 2004. "Interim Policy on Collaborative TB/HIV Activities." WHO, Geneva.

———. 2006. "Improving the Diagnosis and Treatment of Smear-Negative Pulmonary and Extrapulmonary Tuberculosis among Adults and Adolescents." WHO, Stop TB Department, Geneva.

———. 2007. *Global Tuberculosis Control: Surveillance, Planning, Financing*. Geneva: WHO.

———. 2009a. "Global Tuberculosis Control: A Short Update to the 2009 Report." WHO, Geneva.
———. 2009b. "WHO Policy on TB Infection Control in Health-Care Facilities, Congregate Settings, and Households." WHO, Geneva.
———. 2010. "Multidrug and Extensively Drug-Resistant TB: 2010 Global Report on Surveillance and Response." WHO, Geneva.
———. 2011a. "Guidelines for the Programmatic Management of Multidrug Resistant Tuberculosis." WHO, Geneva.
———. 2011b. "Towards Universal Access to Diagnosis and Treatment of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis by 2015." WHO Progress Report 2011, WHO, Geneva.
———. 2011c. "Tuberculosis Country Profiles: South Africa." WHO, Geneva. http://www.who.int/tb/country/data/profiles/en/index.html.
———. 2012a. *Global Tuberculosis Report.* Geneva: WHO.
———. 2012b. "WHO Policy on Collaborative TB/HIV Activities: Guidelines for National Programmes and Other Stakeholders." WHO, Geneva.
———. 2013a. "Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection." WHO, Geneva.
———. 2013b. *Global Tuberculosis Report 2013*. Geneva: WHO.
———. 2013c. *Roadmap for Childhood Tuberculosis.* Geneva: WHO. http://apps.who.int/iris/bitstream/10665/89506/1/9789241506137_eng.pdf.
———. 2013d. "Systematic Screening for Active Tuberculosis: Principles and Recommendations." WHO, Geneva. http://www.who.int/tb/tbscreening.
———. 2013e. "The Use of Bedaquiline in the Treatment of Multidrug-Resistant Tuberculosis: Interim Policy Guidance." WHO, Geneva.
———. 2014a. *Global Status Report on Alcohol and Health 2014*. Geneva: WHO.
———. 2014b. *Global Tuberculosis Report 2014*. Geneva: WHO.
———. 2014c. "Tuberculosis." Fact Sheet 104, WHO, Geneva. http://www.who.int/mediacentre/factsheets/fs104/en/.
———. 2015a. "The End TB Strategy." WHO, Geneva. http://www.who.int/tb/End_TB_brochure.pdf.
———. 2015b. *Global Tuberculosis Report.* Geneva: WHO.
———. 2015c. "The End TB Strategy." Fact Sheet, WHO, Geneva. http://www.who.int/tb/post2015_TBstrategy.pdf?ua=1.
———. 2016a. *Global Tuberculosis Report 2016*. Geneva: WHO.
———. 2016b. *WHO Treatment Guidelines for Drug-Resistant Tuberculosis. 2016 Update*. Geneva: WHO. http://www.who.int/tb/MDRTBguidelines2016.pdf.
———. n.d. "The Five Elements of DOTS." WHO, Geneva. http://www.who.int/tb/dots/whatisdots/en/.
Wilkinson, R. J., M. Llewelyn, Z. Toossi, P. Patel, and G. Pasvol. 2000. "Influence of Vitamin D Deficiency and Vitamin D Receptor Polymorphisms on Tuberculosis among Gujarati Asians in West London: A Case-Control Study." *The Lancet* 355 (9204): 618–21.
Willingham, F. F., T. L. Schmitz, M. Contreras, S. E. Kalangi, A. M. Vivar, and others. 2001. "Hospital Control and Multidrug-Resistant Pulmonary Tuberculosis in Female Patients, Lima, Peru." *Emerging Infectious Diseases* 7 (1): 123.
Wolfe, F., K. Michaud, J. Anderson, and K. Urbansky. 2004. "Tuberculosis Infection in Patients with Rheumatoid Arthritis and the Effect of Infliximab Therapy." *Arthritis and Rheumatism* 50 (2): 372–79.
Wood, R., S. D. Lawn, J. Caldwell, R. Kaplan, K. Middelkoop, and others. 2011. "Burden of New and Recurrent Tuberculosis in a Major South African City Stratified by Age and HIV-Status." *PLoS One* 6 (10): e25098.
Wood, R., S. D. Lawn, S. Johnstone-Robertson, and L.-G. Bekker. 2011. "Tuberculosis Control Has Failed in South Africa: Time to Reappraise Strategy." *South African Medical Journal* 101 (2): 111–14.
Wood, R., S. Johnstone-Robertson, P. Uys, J. Hargrove, K. Middelkeep, and others. 2010. "Tuberculosis Transmission to Young Children in a South African Community: Modeling Household and Community Infection Risks." *Clincal Infectious Diseases* 51 (4): 401–8.
Wood, R., K. Middelkoop, L. Myer, A. D. Grant, A. Whitelaw, and others. 2007. "Undiagnosed Tuberculosis in a Community with High HIV Prevalence: Implications for Tuberculosis Control." *American Journal of Respiratory and Critical Care Medicine* 175 (1): 87–93.
Woolhouse, M. E., C. Dye, J.-F. Etard, T. Smith, J. D. Charlwood, and others. 1997. "Heterogeneities in the Transmission of Infectious Agents: Implications for the Design of Control Programs." *Proceedings of the National Academy of Sciences* 94 (1): 338–42.
World Bank. 1993. *World Development Report 1993: Investing in Health*. Washington, DC: World Bank.
Wu, P., E. H. Y. Lau, B. J. Cowling, C.-C. Leung, C.-M. Tam, and others. 2010. "The Transmission Dynamics of Tuberculosis in a Recently Developed Chinese City." *PLoS One* 5 (May 3): e10468.
Yadav, P. 2010. "In-Country Supply Chains: The Weakest Link in the Health System." *Global Health Magazine* 5 (Winter): 18–20.
———. 2015. "Health Product Supply Chains in Developing Countries: Diagnosis of the Root Causes of Underperformance and an Agenda for Reform." *Health Systems and Reform* 1 (2): 142–54.
Yadav, P., O. Stapleton, and L. Van Wassenhove. 2013. "Learning from Coca-Cola." *Stanford Social Innovation Review* (Winter): n.p.
Yadav, P., H. L. Tata, and M. Babaley. 2011. *The World Medicines Situation 2011: Storage and Supply Chain Management*. Geneva: WHO.
Yin, X., X. Tu, Y. Tong, R. Yang, Y. Wang, and others. 2012. "Development and Validation of a Tuberculosis Medication Adherence Scale." *PLoS One* 7 (12): e50328.
Yokoyama, T., R. Sato, T. Rikimaru, R. Hirai, and H. Aizawa. 2004. "Tuberculosis Associated with Gastrectomy." *Journal of Infection and Chemotherapy* 10 (5): 299–302.

Yuen, C. M., F. Amanullah, A. Dharmadhikari, E. A. Nardell, J. A. Seddon, and others. 2015. "Turning Off the Tap: Stopping Tuberculosis Transmission through Active Case-Finding and Prompt Effective Treatment." *The Lancet* 386 (10010): 2334–43.

Zachariah, R., M.-P. L. Spielmann, C. Chinji, P. Gomani, V. Arendt, and others. 2003. "Voluntary Counselling, HIV Testing, and Adjunctive Cotrimoxazole Reduces Mortality in Tuberculosis Patients in Thyolo, Malawi." *AIDS* 17 (7): 1053–61.

Zak, D., A. Penn-Nicholson, T. Scriba, E. Thompson, S. Suliman, and others. 2016. "A Blood RNA Signature for Tuberculosis Disease Risk: A Prospective Cohort Study." *The Lancet* 387 (10035): 2312–22.

Zar, H. J., M. F. Cotton, S. Strauss, J. Karpakis, G. Hussey, and others. 2007. "Effect of Isoniazid Prophylaxis on Mortality and Incidence of Tuberculosis in Children with HIV: Randomised Controlled Trial." *BMJ* 334 (7585): 136.

Zelner, J., M. B. Murray, M. C. Becerra, J. Galea, L. Lecca, and others. 2016. "Identifying Hotspots of Multidrug Resistant Tuberculosis Transmission Using Spatial and Molecular Genetic Data." *Journal of Infectious Diseases* 213 (2): 287–94.

Zhao, Y., S. Xu, L. Wang, D. P. Chin, S. Wang, and others. 2012. "National Survey of Drug-Resistant Tuberculosis in China." *New England Journal of Medicine* 366 (23): 2161–70.

Zumla, A., P. Nahid, and S. T. Cole. 2013. "Advances in the Development of New Tuberculosis Drugs and Treatment Regimens." *Nature Reviews Drug Discovery* 12 (5): 388–404.

Zwarenstein, M., L. R. Fairall, C. Lombard, P. Mayers, A. Bheekie, and others. 2011. "Outreach Education for Integration of HIV/AIDS Care, Antiretroviral Treatment, and Tuberculosis Care in Primary Care Clinics in South Africa: PALSA PLUS Pragmatic Cluster Randomised Trial." *BMJ* 342 (April 21): d2022.

Zwerling, A., G. B. Gomez, J. Pennington, F. Cobelens, A. Vassall, and D. W. Dowdy. 2016. "A Simplified Cost-Effectiveness Model to Guide Decision-Making for Shortened Anti-Tuberculosis Treatment Regimens." *International Journal of Tuberculosis and Lung Disease* 20 (2): 257–60.