Prospects for Tuberculosis Elimination

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Annu. Rev. Public Health 2013. 34:271–86

First published online as a Review in Advance on December 14, 2012

The *Annual Review of Public Health* is online at publhealth.annualreviews.org

This article's doi: 10.1146/annurev-publhealth-031912-114431

Keywords

diagnosis, drugs, vaccines, transmission, latent infection, human immunodeficiency virus, HIV

Abstract

The target for TB elimination is to reduce annual incidence to less than one case per million population by 2050. Meeting that target requires a 1,000-fold reduction in incidence in little more than 35 years. This can be achieved only by combining the effective treatment of active TB—early case detection and high cure rates to interrupt transmission—with methods to prevent new infections and to neutralize existing latent infections. Vigorous implementation of the WHO Stop TB Strategy is needed to achieve the former, facilitated by the effective supply of, and demand for, health services. The latter calls for new technology, including biomarkers of TB risk, diagnostics, drugs, and vaccines. An important milestone en route to elimination will be reached when there is less than 1 TB death per 100,000 population, marking entry into the elimination phase. This landmark can be reached by many countries within 1–2 decades.

FROM HERE TO ELIMINATION

WHO: World Health Organization

TB elimination: Reduction to less than one case of TB per million population per year

The vision of the Stop TB Partnership and the World Health Organization (WHO) is a tuberculosis (TB)-free world (49), but the internationally agreed target for TB elimination presents a formidable challenge. We must reduce annual incidence to less than one case per million worldwide by 2050 (14, 49, 51). Compared with the present estimate of 1,280 cases/million in 2010, the incidence rate must be cut by a factor of more than one thousand. Approximately 9 million new TB cases in 2010 must be limited to fewer than 9,000 among the 9 billion people expected to be alive in 2050. To meet this target, the incidence rate must fall at an average of 20% annually between 2015 and 2050 (**Figure 1*a***). That rate of decline

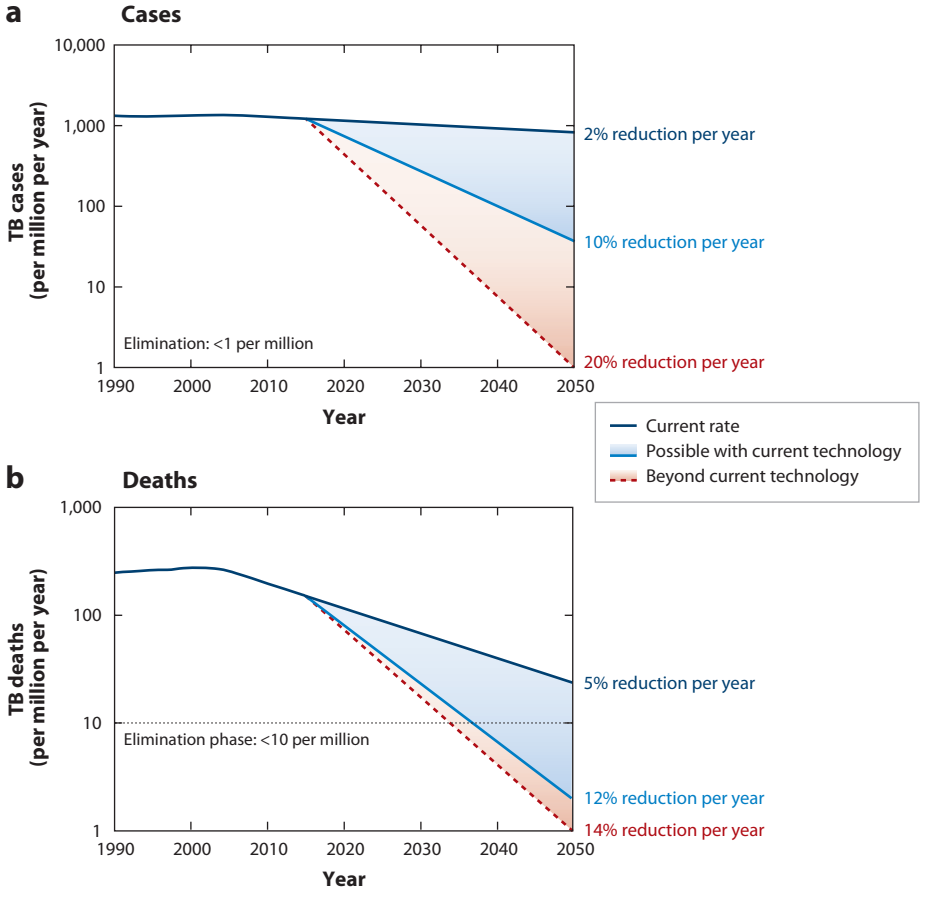


Figure 1

Recent and projected trends in (*a*) global TB incidence (cases) and (*b*) global TB mortality (deaths). (*a*) Assuming that present trends continue until the Millennium Development Goal (MDG) target year 2015, the incidence rate must fall at 20% per year on average from 2015 to achieve elimination by 2050, much faster than the maximum of 10% per year that was achieved in Europe after 1950. If the present decline of 2% per year continues beyond 2015, the incidence rate will still be 1000 times greater than the elimination threshold by 2050. (*b*) Globally, case fatality was 15% in 2010, and the death rate was falling at 5% per year. To reduce case fatality to a minimum of 5% by 2050, mortality must fall at 12% per year from 2015 onward. To reach one death per million in 2050, mortality must be reduced more quickly: by 14% per year from 2015 onward. Scales on the vertical axes are $\log_{10}$.

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.

Eliminating TB by 2050 requires two things: immediate optimization of TB control with the technology we already have, and the concurrent development of a more potent armory of diagnostics, drugs, and vaccines. Furthermore, the effective use of technology—contemporary and forthcoming—depends critically on the supply of, and demand for, health services. As control programs are implemented more vigorously, TB mortality will fall more quickly than incidence because drug treatment rapidly reduces case fatality in addition to the number of future cases. With or without new technology and the means of delivering it, we expect most countries to enter the elimination phase, reporting fewer than 10 deaths per million population (<1/100,000) well before 2050 (**Figure 1*b***). How soon that milestone can be reached is in the hands of the global TB control community.

Within that outline, the challenges and opportunities facing a TB elimination campaign are laid out in the following sections. The next section describes the magnitude of the problem we now face: the burden of cases and deaths around the world. This section also summarizes progress made under the WHO Stop TB Strategy (32), guided by the Global Plan to Stop TB (51), toward the 2015 target defined by the United Nations Millennium Development Goals (MDGs) (44). Having set the scene, the third section gives an overview of how elimination could be achieved in principle, making use of the interventions and procedures available now and anticipating new technologies in the future. The fourth section then applies these principles to four countries with contrasting TB epidemics: South Africa, India, China, and the United States. Finally, melding principles and practice, the concluding section considers the prospects for elimination during the course of this century.

GEOGRAPHICAL VARIATION IN DISEASE BURDEN AND TRENDS

Elimination phase: a milestone en route to elimination, passed when there are fewer than 10 deaths per million population per year

MDG: Millennium Development Goal

Supplemental Material

In 2010, the WHO African region (mainly sub-Saharan Africa) had by far the highest incidence rate (256 per 100,000 population) among the six WHO regions of the world, but the more populous countries of Asia carried the largest numbers of cases (**Figure 2**; see **Supplemental Material**. Follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**). The Southeast Asian and Western Pacific Regions together accounted for more than half (58%) of the global total (5.2 million out of 8.8 million cases), mostly among the inhabitants of India, China, Indonesia, and Bangladesh (49). Among the 1.4 million TB deaths in 2010 (including those among people infected with HIV), the largest numbers were in Southeast Asia (558,000) and Africa (507,000).

The global TB epidemic is on the threshold of decline, albeit a slow decline. The incidence rate per capita was growing during the 1990s but stabilized during the decade 2000–2010 and may now be falling (1–2% per year). This technically satisfies the target for reducing incidence under MDG 6, although the potential rates of decline are much faster (49) (**Figure 1*a***). The total number of new TB cases arising each year stabilized later than did the rate per capita because those countries most heavily affected by TB still have growing populations.

This rather static picture of the global epidemic close to its peak conceals much variation in the dynamics of TB among regions (**Figure 2**). Although the burden of disease is carried predominantly by Asian countries, global trends have been determined by events in Africa and, to a lesser extent, Eastern Europe. The countries of sub-Saharan Africa and the former Soviet Union showed the most striking increases in caseload during the 1990s, owing to the spread of HIV in Africa (10) and to the collapse of health and health care in the Soviet Union, respectively (9, 43). These rises offset the slow decline in case numbers in other parts of the world between 1996 and

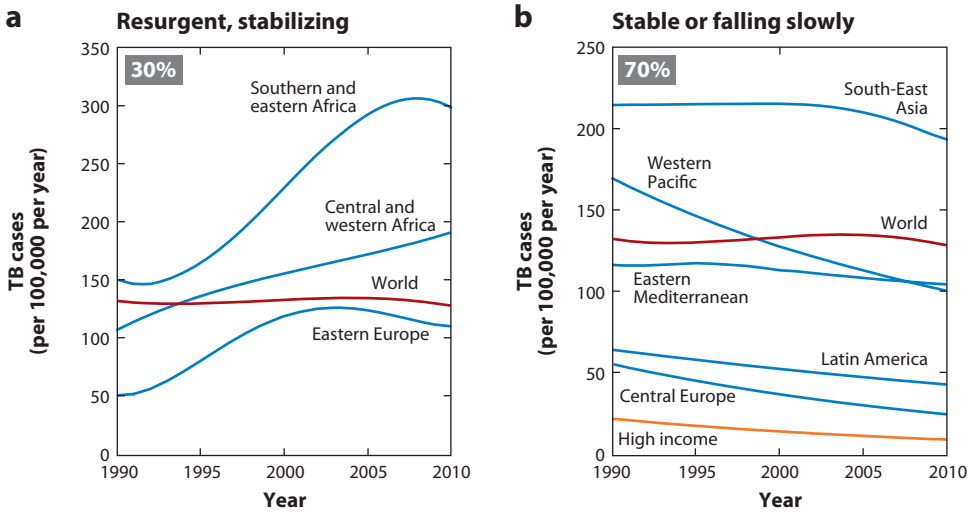


Figure 2

Estimated TB case rates and trends for nine regions of the world, 1990–2010. (*a*) Three regions with epidemics that were resurgent during the 1990s but that are now stabilizing, bearing 30% of incident cases in 2010. (*b*) Six regions that have stable or slowly declining epidemics, accounting for 70% of cases in 2010. To portray these epidemiological differences, the WHO African and European regions have been subdivided, and the high-income OECD countries separated from the rest. The **Supplemental Material** contains a list of countries in each region (follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**). Based on WHO data and estimates (49).

Supplemental Material

2010: West and Central Europe (decline 4% per year), the Americas (2% per year), and the Eastern Mediterranean (<1% per year), Southeast Asia (<2% per year), and Western Pacific (>2% per year) regions.

The majority of countries reported slow declines in the number of cases per capita between 1996 and 2010, but there were marked international differences (**Supplemental Figure 1**). Over the past decade, few countries have achieved the 5–10% annual rates of decline comparable with those seen in postwar Western Europe (**Figure 3*a***) and in some rapidly developing Asian countries (e.g., the Republic of Korea; **Figure 3*b***). National and regional trends in TB deaths partly reflect the trends in cases, although mortality can change more quickly than incidence depending on the success of drug treatment in reducing case fatality (**Figure 3*c*,*d***; global decline 5–6% per year).

In short, regionally and globally in 2010, incidence and mortality were falling more slowly than were the maximum rates of decline feasible with current technology and much more slowly than the rates of decline needed for elimination (**Figure 1**).

ELIMINATION IN PRINCIPLE

Because elimination, and the impact of the tools needed to achieve it, is beyond the experience of any TB control program, we use mathematical modeling to make new inferences from a synthesis of established facts. Illustrated with numerical examples, this section aims to outline the general principles of elimination; the next section applies these principles to four epidemiologically different countries. Our main conclusions concern order-of-magnitude changes in numbers of cases and deaths, which are robust to the choice of examples and the uncertainties in the calculations.

We begin with a general model of a typical, poorly controlled epidemic in a high-burden country. The structural and quantitative characteristics of the model have a heritage in

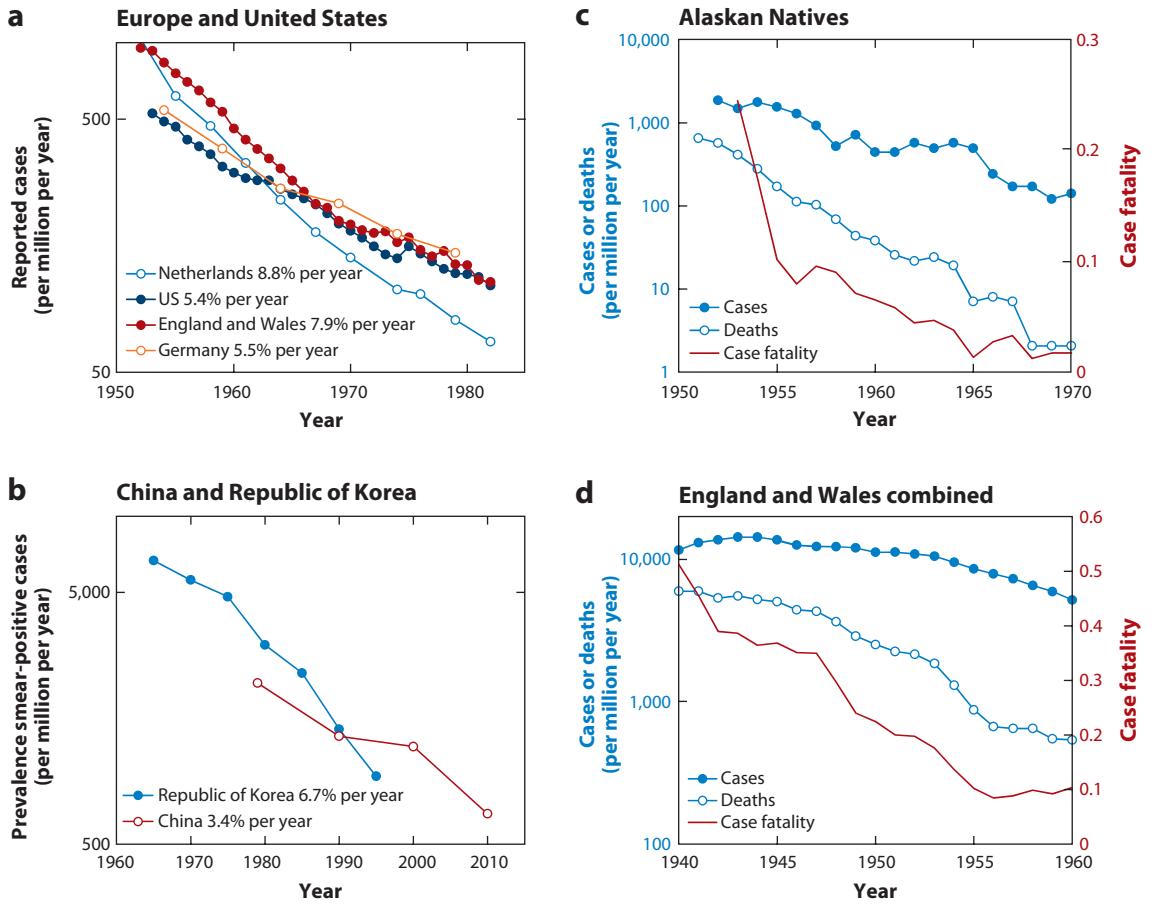


Figure 3

Examples of the decline in TB incidence, prevalence, and mortality nationally and subnationally. (*a*) Case notifications from three European countries plus the United States (5, 18, 39, 40). (*b*) National population-based prevalence surveys in the Republic of Korea (1965–1995) and China (1979–2010) (6, 20, 52). (*c*) TB cases and deaths recorded from an intensively studied population of Alaskan natives (1952–1970). Case fatality is estimated as the ratio of deaths to cases (17). (*d*) National case and death notifications from England and Wales, 1940–1960, with case fatality estimated as in panel *c* (18). Scales on the vertical axes are $\log_{10}$.

previous analytical studies of TB (13, 41, 45; see **Supplemental Material**) and are briefly summarized as follows. In the example in **Figure 4**, incidence is stable at 1,100 cases per million per year with 200 deaths and a case fatality rate of 16% (close to global averages of these indicators). Of the 1,100 cases, the majority (73%) arise from recent infection: 800 from first or primary infections and 90 from reinfection, with a mean time from infection to disease of 1.5 years. Some 140 cases come from the reactivation of latent infection (incidence 500 per million infected per year), and 70 come from relapse after treatment (**Supplemental Figure 2*a***). The lifetime risk of TB following infection is 16%, within the bounds of previous analyses (13, 46). Each infectious case (550/1,100) infects 12 others in an episode lasting about a year on average (0.94 years), generating an annual risk of infection of 0.64%. We assume that incidence is amplified by a risk factor similar to diabetes (21) or tobacco smoking (25, 35), which doubles the proportion of new infections that lead to primary TB,

Latent infection: presumed viable subclinical infection in persons showing an immunological response to *M. tuberculosis* (tuberculin skin test or interferon-γ release assay)

doubles the rate of progression from latent to active TB, and affects 20% of the population. Under this scenario, one-third of cases (34%) arise in the population at risk. The basic case reproduction number (2, 11), R_0, of the system is 2.4 in the absence of any intervention, but the use of drugs—65% of cases arising each year are detected and 70% are cured—brings R_0 down to unity in the steady state prior to 2015.

An improved control program that focuses on the diagnosis and treatment of active disease—the dominant intervention in the Stop TB Strategy—can cut the number of transmitted infections further by early case detection, by increased diagnostic accuracy and treatment outcomes, and by a reduction in case fatality. Any improvements in case management will bring clinical and epidemiological benefits, but our purpose here is to investigate what must be done to reduce incidence by more than three orders of magnitude (>1000-fold). For example, if, by early case finding coupled with high diagnostic accuracy and high cure rates, the number of infections transmitted by each case could be reduced from 12 to 3, cutting the duration of infectious TB from one year to 3 months, incidence would fall from 1,100 per million to 130 per million by 2050 (6% per year on average; **Figure 4*a***). Given that 73% of cases were due to recent infection before the intervention, and allowing for the extra benefits of reducing transmission over several decades, this

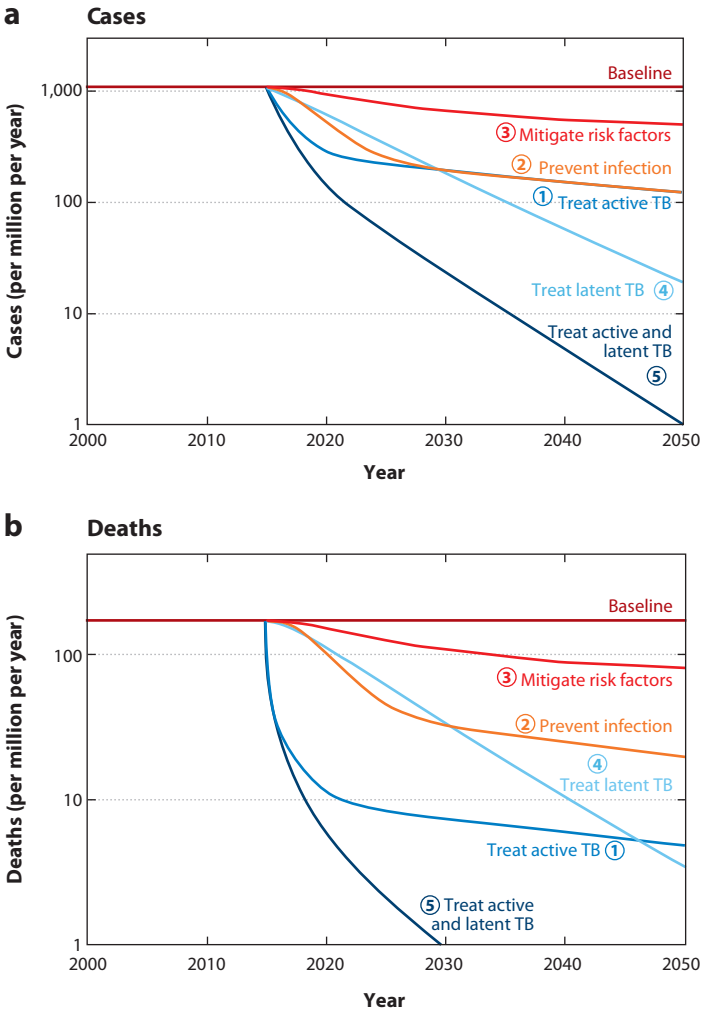


Figure 4

Strategies for (*a*) eliminating TB (<1 case per million per year) and (*b*) approaching the elimination phase (<10 deaths per million per year or <1 death per 100,000 per year) in a hypothetical high-incidence country with a poorly controlled epidemic (65% case detection, 70% cure) and an initial, stable incidence of 1,100 cases and 200 deaths per million per year, close to the global average in 2010. [1] Improvements in the treatment of active TB (earlier case detection, higher diagnostic sensitivity, and higher treatment success) can reduce incidence by a factor of roughly 10, but not by a factor of 100 or 1,000. More effective treatment of active TB could move an epidemic into the elimination phase, with fewer than 10 deaths per million per year. [2] Vaccination to prevent infection could also reduce incidence by a factor of about 10. However, unlike drug treatment, vaccination has no direct effect on case fatality. [3] Mitigation of risk factors will contribute to TB control but will play a small part in an elimination campaign. [4] Making further reductions in incidence and mortality requires a drug or vaccine to neutralize latent infection. [5] Very low incidence rates approaching 1 per million can be achieved only by treating both latent infection and active TB; these interventions work synergistically in combination. Scales on the vertical axes are $\log_{10}$. Further details are given in the **Supplemental Material**. (Follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**.)

88% or 8.5-fold reduction in incidence accords with expectation. This reduction in incidence is close to the best that could be achieved by 2050 through early case detection and effective treatment, whether the intervention is introduced quickly or slowly. Even if transmission were interrupted completely and instantly in 2015, reactivation and relapse of old infections would still generate more than 100 cases per million population in 2050 (**Figure 4*a***).

The same result could be obtained by a control method that interrupts transmission, not at the source by using TB drug treatment but by preventing infection in the rest of the population (**Figure 4*a***). The instrument might be infection control on a small scale [e.g., in clinics and hospitals (48)] or a hypothetical preinfection vaccine on a larger scale (54). By whatever means it is achieved, the protection of 25% of uninfected people against TB each year would, like drug treatment above, cut incidence to 130 per million by 2050. A combination of preinfection vaccination, even at high levels of effectiveness, with the treatment of active TB would not do much better and could not force incidence down to 100 per million by 2050. The similar impact of better case management and preinfection immunization shown in **Figure 4*a*** (overlapping lines) is not coincidental. It happens because both interventions interrupt transmission. If one can be done well, there is little to be gained from doing the other.

With these dramatic drug- or vaccine-induced reductions in the number of infections transmitted by each case, the basic reproduction number falls well below the threshold for persistence ($R_0 = 0.23 < 1$ in the example of drug treatment), and TB is ultimately doomed to extinction. The problem is that incidence falls very slowly because long-living people with long-standing viable infections generate new cases by reactivation and relapse over decades (**Supplemental Figure 2*a***).

To force case incidence down more quickly, we must not only cut transmission but also neutralize the reservoir of latent infection, both among people who have not yet suffered an episode of TB and among those who have recovered from illness but who still carry live bacilli. One way to do this is by mitigating risk factors, such as diabetes or tobacco smoking. Tobacco control and diabetes management will certainly help reduce the risk of TB, but they will not play a large part in an elimination campaign. In the example shown in **Figure 4*a***, an extremely ambitious mitigation program, by which, each year, 25% of at-risk people have their risk removed completely, would only halve incidence by 2050 (to 510 per million).

Achieving TB elimination requires a direct attack on the reservoir of latent infection, with a drug or a vaccine (or both) that is effective against established infection. For instance, if just 8% of people infected with *M. tuberculosis* are fully and permanently protected each year, incidence would fall to 90 per million by 2050 with no other intervention. Protecting 14% per year would cut incidence to 20 per million by 2050 (**Figure 4*a***). Combining these interventions with the drug treatment program proposed above would achieve elimination by cutting the number of cases that arise via all four etiological pathways (**Supplemental Figure 2*b***), reducing overall incidence to 1 per million by 2050 (**Figure 4*a***).

This combined assault on transmitted and latent infections is synergistic (15). In these examples, incidence in 2050 is 3.5 times lower than it would be if the two interventions acted independently. Consequently, elimination should be carried out not as a sequential, two-step process—first interrupt transmission and then remove the latent reservoir—but rather as a simultaneous attack on two components of the *M. tuberculosis* life cycle.

As case incidence falls in response to control efforts, so too does mortality, but the number of deaths averted depends on the type of intervention (**Figure 4*b***). Whereas the treatment of active TB reduced incidence 8.5-fold by 2050 (**Figure 4*a***), it cut mortality by a factor of more than 30 to 5 per million. This is because, in addition to the reduction in incidence, case fatality dropped from 16% to 5%. A case fatality rate of 5% can be achieved on a large scale, as

Preinfection vaccination: Bacille Calmette-Guérin (BCG) is consistently efficacious against meningitis and miliary TB in children but not against pulmonary TB in adults

Supplemental Material

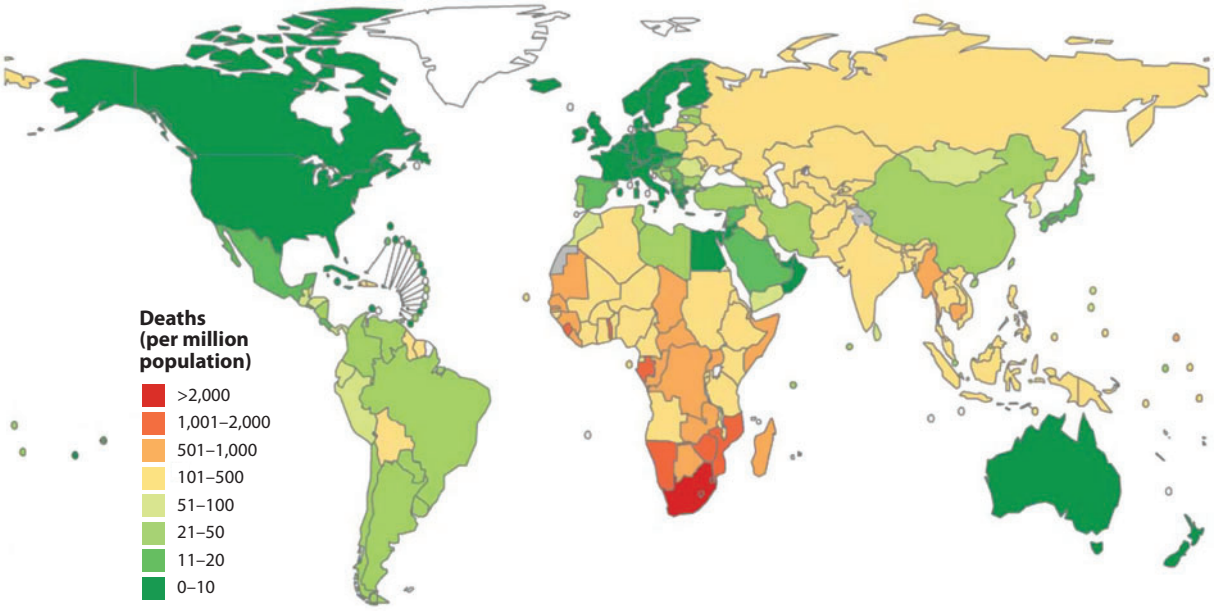


Figure 5

Geographical distribution of TB death rates per million population (including HIV-infected cases) for 165 countries. Some 35 countries with populations exceeding 100,000 were in the elimination phase in 2010, having less than 1 death per 100,000 (or <10 deaths per million). Estimates from the WHO (49). See also **Supplemental Figure 2**. (Follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**.)

reported from the United States in 2010. The general point, however, is that, in the absence of complications such as high rates of HIV coinfection or drug resistance, reducing mortality to less than 10 per million (<1 per 100,000) by 2050 appears feasible, even for high-burden countries. For this reason, we define a TB mortality rate of 10 per million per year (1 per 100,000 per year) as the point of entry to the TB elimination phase, a milestone en route to the true elimination target of 1 case per million per year. Using current estimates of mortality, 47 countries and territories are already in the elimination phase (5 with populations greater than 100,000), another 22 countries are close (mortality 10–19 per million), and 38 have mortality rates of 20–49 per million (**Figure 5**; see **Supplemental Material**).

Notice in **Figure 4*b*** that neither preinfection vaccination nor the treatment of latent infection (with a drug or a vaccine) is as immediately effective as the treatment of active TB in reducing mortality because these approaches have no effect on case fatality. By contrast, the combined treatment of active and latent TB profoundly reduces the number of TB deaths.

PATHWAYS TO ELIMINATION

Because the burden of TB and the characteristics of TB epidemics vary enormously among countries, so too will the pathways to elimination. Using a more detailed mathematical model tailored to the epidemics in four contrasting countries (see **Supplemental Material**), we now illustrate the spectrum of challenges and opportunities faced by national TB control programs. From the largest to the smallest numbers of cases and deaths per capita the countries are South Africa, India, China, and the United States.

South Africa

South Africa has the highest per capita incidence of TB among the WHO's 22

high-burden countries, approaching 1% (9,800 per million) in 2010, with 60% of cases being HIV-positive (**Figure 6*a***). The combined mortality rate among HIV-positive and HIV-negative TB cases was 0.2% (2,180 per million; **Figure 6*b***). The calculations in **Figure 6** assume that HIV incidence is falling at 3% per year from 2010 onward. A more rapid decline, if that can be achieved by HIV/AIDS control programs, would also lower the numbers of TB cases and deaths. Widespread coverage of antiretroviral therapy (ART) for HIV-positive people at risk for TB (40% receiving ART in 2010, rising to 80% in 2050) would reduce incidence, but not greatly because the efficacy of ART in preventing TB per unit time (67%) is offset by a reduction (50%) in the mortality rate, which extends the number of life-years at risk of TB.

Substantially reducing incidence and mortality requires two major interventions. First, transmission must be interrupted by improved case management: that is, by early case detection, accurate diagnosis, and a high cure rate on treatment. For illustration, **Figures 6*a*** and ***b*** show the effect of linearly reducing the number of infections transmitted per infectious case from 11 in 2010 [annual risk of infection (ARI) 4%] to half that value in 2030. The incidence rate drops fourfold (by 3.7% per year on average) and the mortality rate eightfold (5.1% per year) by 2050. However, that still leaves more than 2,000 cases and more than 300 deaths per million in 2050 (**Figure 6*a*,*b***).

Isoniazid preventive therapy (IPT) for HIV-positive people is already recommended, in addition to ART, by the WHO. If IPT could be scaled up (from zero coverage in 2025 to 75% in 2035), or the equivalent effect achieved with a putative postinfection vaccine, incidence would fall to 1,400 cases per million, and mortality would fall to 200 deaths per million by 2050. Similar reductions in incidence and mortality could be obtained with a hypothetical preinfection vaccine (given to people infected with neither HIV nor TB), introduced in 2025 and protecting 70% of uninfected people by 2050.

In sum, although the technological developments of the coming decades are unpredictable, it is inconceivable that South Africa can reduce incidence 10,000-fold to eliminate TB by 2050. However, a tenfold reduction (i.e., a reduction of 90%) in cases and deaths appears to be within reach.

India

The current, slow declines in incidence (1–2% per year) and mortality (3–4% per year) rates (**Figure 6*c*,*d***) are attributable mainly to the persistent transmission of infection. In 2010, each infectious case transmitted an estimated 11 infections to others, generating an ARI of 1.5%. If enhanced case management in both public and private clinics could halve the number of infections transmitted by each case by 2030, incidence would fall to ~400 cases per million and deaths would fall to 40 per million in 2050. A significant obstacle to elimination in all countries, illustrated here for India, is relapse from the growing population of "cured" cases (assumed to be 1% per year), without which incidence and mortality would fall more quickly (**Figure 6*c*,*d***).

Elimination by 2050 in India is not unimaginable, but it requires far more than improved case management. Most effectively, India would need mass preventive therapy, both for infected people to prevent first episodes of TB and for cured cases to prevent relapse. The treatment could be a drug or a new postinfection vaccine. By using preventive therapy from 2025 onward (scaling up linearly over 10 years to protect one-third of eligible people by 2030 and everyone eligible by 2050), incidence could be reduced to 1 case per million by 2050 and deaths could be reduced to fewer than 10 per million (entry into the elimination phase) by 2035. However, whereas IPT for HIV-infected people in South Africa is already recommended (along with ART), mass preventive therapy in India, largely for HIV-uninfected people, would be a radical departure from current practice.

Achieving high coverage of and adherence to IPT is likely to require biomarkers to target

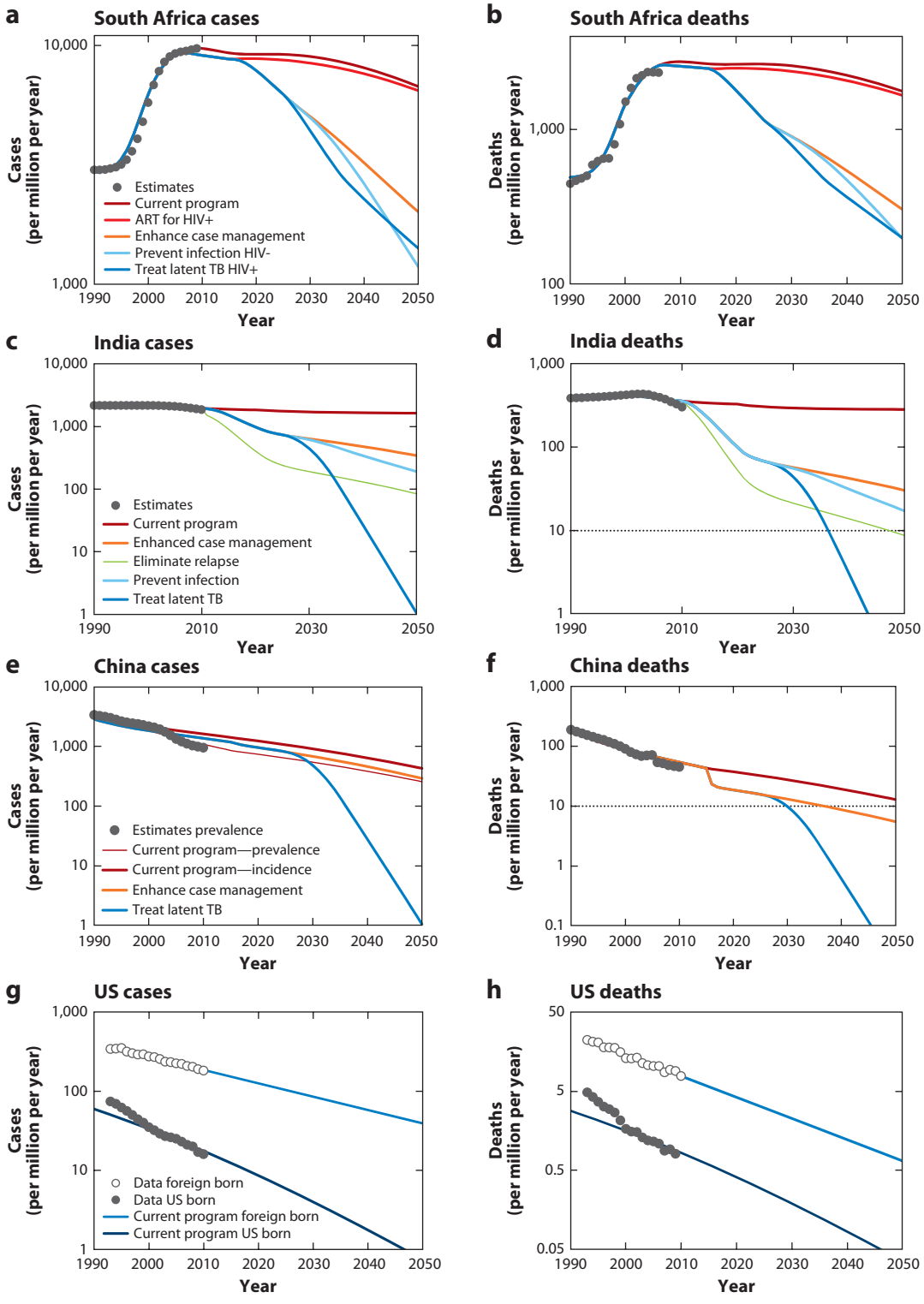
Antiretroviral therapy (ART): improves the survival of HIV-infected people, prevents TB, and is a vital component of treatment for HIV-positive TB patients

ARI: annual risk of infection

IPT: isoniazid preventive therapy

Enhanced case management: measures to detect TB early after the onset of disease and to ensure accurate diagnosis and high treatment success rates

Preventive therapy: treatment of latent infection as prophylaxis against active TB with isoniazid alone or in combination with rifamycins



those who are most at risk of progressing from subclinical to active TB, plus short drug regimens (three months or less) that are safe and that can eliminate latent infection. As in South Africa, vaccination preinfection would be an aid to control, but with modest impact by 2050 if efficacious only in uninfected people (an estimated one-third of the Indian population in 2010).

China

TB case and death rates are lower in China than in India and falling a little more quickly (annual rate of change in incidence 3% and mortality 7% in 2010). Even so, China will not eliminate TB by 2050 through enhanced case management alone (**Figure 6*e***). Indeed, because the risk of infection in China is lower than in India (cf. **Supplemental Figures 8** and **9**), a smaller proportion of cases can be prevented by interrupting transmission. Enhanced case management in China is likely to have more visible effects on prevalence and mortality (**Figure 6*f***) than on incidence (**Figure 6*e***), as observed during the 2010 national prevalence survey (52). China should reach the elimination phase well before 2050 (**Figure 6*f***), but elimination per se is a far greater challenge. Immunization with a hypothetical preinfection vaccine—another means of interrupting transmission—would not help much. Thus China, like India, would need to carry out mass preventive therapy, with either drugs or vaccines, to meet the elimination target by mid-century.

United States

The United States is already well into the elimination phase. In 2010, there was ~1 death per million in the American-born population and 10 deaths per million in the foreign-born population, with 2 deaths per million overall (**Figure 6*h***).

The rate of decline in incidence in the foreign-born population (3.9% per year, 2000–2010) has been slower than among people born in the United States (6.2% per year, 2000–2010, slower than during the 1990s; **Figure 6*g***). TB among immigrants made up 60% of all cases in 2010 and, therefore, substantially slowed the rate of decline in the population overall. If the trend in the American-born population is maintained, TB will be eliminated in that group around 2050 (**Figure 6*g***). The best estimate of the elimination year obtained in the thorough analysis of Hill et al. (19) was 2056. Clearly, with additional effort given to interrupting transmission, and/or wider coverage of preventive therapy, elimination could be achieved in the American-born population before 2050 (19).

Supplemental Material

The prognosis for TB control among the foreign-born population depends, in part, on the fraction of cases that arise from transmission within the United States rather than from imported infections. To obtain the result in **Figure 6*g***, we have simply assumed that all cases among the foreign-born population are from imported infections and that the rate of decline observed between 2000 and 2009 will persist. Under these circumstances, there will still be 40 cases per million in 2050. In

Figure 6

Prospects for TB control and elimination in South Africa, India, China (49), and the United States (5). Points are WHO estimates based on the data available for each country, except for the United States, in which cases and deaths are as reported by the Centers for Disease Control and Prevention (CDC). The downward trends in cases (*left panels*) and deaths (*right panels*) can be accelerated by antiretroviral therapy for HIV-infected people; enhanced case management through early case detection, accurate diagnosis, and high cure rate (with or without relapse); treatment of latent infection (preventive therapy for people with subclinical or asymptomatic infection, using a drug or vaccine); and the prevention of infection (infection control or vaccination). Scales on the vertical axes are $\log_{10}$. The horizontal dotted lines in *d* and *f* mark the point of entry to the elimination phase (10 deaths per million per year), which is off the scales in *b* and *h*. In *g* and *h*, data and projections for the United States distinguish American-born from all foreign-born cases. The numbers of reported cases and deaths for both groups are given by the CDC (5). Projections are based on model fits from the year 2000 onward; since then, decline has been slower than during the 1990s. Death rates for each group are estimated by assuming that case fatality (deaths/cases) is the same for American- and foreign-born cases.

contrast, Hill et al. assumed, more realistically, that infection is transmitted between the American-born and foreign-born populations, and they forecast 70–100 cases per million in 2050. Whatever the exact proportions of cases attributable to domestically acquired versus imported infections, and whatever combination of treatments for latent and active TB is used in the United States from now on, TB is unlikely to be eliminated from the foreign-born population by 2050.

CONCLUSIONS

TB cannot be eliminated globally by 2050 with the technology, procedures, and services we have today. In our assessment, this projection is not principally because there are powerful adverse forces, such as widespread tobacco smoking and the rise of diabetes, counteracting the positive effects of drug treatment programs. Rather it is because the efficacy of current tools and the supply and demand of health services are not sufficient to combat a disease in which infectious cases arise insidiously from a large reservoir of infection. Our general model of TB control in a typical highly endemic country, generating 1,100 cases per million in 2010 (**Figure 4**), shows that even if transmission were completely interrupted by 2015, reactivation and relapse would still generate more than 100 cases per million in 2050.

In view of the elimination target of 1 case per million in 2050, this is a dispiriting outlook. But it needs to be kept in perspective in two regards. First, the elimination target set by the TB control community was extremely ambitious, demanding a 1,000-fold reduction in incidence. A tenfold or 90% reduction by 2050 is feasible in most countries, especially if TB control is carried out on a background of social and economic development (26), and would be a remarkable achievement. Coupled with reductions in case fatality, the mortality rate could be reduced to below 10 per million (or <1 per 100,000), here defined as the point of entry to the elimination phase. Thirty-five countries with populations exceeding 100,000 have already achieved that goal, a further 52 such countries have fewer than 50 deaths per million population, and more could reach that target within 1–2 decades.

Second, notwithstanding the limitations of present technology, the pathway to elimination is conceptually clear. The principal task in global TB control now is to detect cases earlier, diagnose them accurately, and achieve high cure rates. This is especially true for high-incidence countries (say, >1000 cases per million per year), where the majority of cases still come from recent infections (rapidly progressing primary infections or reinfections). We have said little in this article about the supply of, and demand for, health services, and yet both are fundamental to the success of TB control. On the supply side, a new generation of molecular diagnostics based on nucleic acid amplification has increased the accuracy of diagnosis and shortened the delay between diagnosis and effective treatment, especially in cutting out weeks of mycobacterial culture to identify drug-resistant cases. However, these new diagnostics have not yet brought TB diagnosis to the "point of care," so as to reduce the infectious period significantly before first contact with health services (7, 28, 30, 36, 38, 47). The length of that period depends on the demand for TB diagnosis and treatment, which is a function mainly of health awareness, and on the quality of general health services because patients typically present with undifferentiated symptoms such as prolonged cough.

Where a high fraction of TB cases is also infected with HIV, as in South Africa, preventive treatment for HIV-positive people, with both ART and antituberculosis drugs (isoniazid and others), is vital in addition to improved case management. Indeed, HIV testing is an entry point not only for prophylaxis (ART, isoniazid) but is also a means of actively seeking HIV-positive TB cases. The WHO has already defined feasible mechanisms for delivering integrated TB and HIV services. The three purposes are to initiate early antiretroviral therapy, to reduce the burden of TB in HIV-positive people, and to reduce the

burden of HIV in patients with presumptive and diagnosed TB (50). The challenge is to ensure wide access to all these interventions.

In contrast, for high-burden countries where the prevalence of HIV is low (<1%), China and India among them, early case detection will have to be supplemented with mass preventive therapy for infected people. Preventive therapy for HIV-negative people cannot yet be carried out on a large scale, mainly because those who are not ill and at low risk of TB are generally unwilling to take a drug daily for nine months (8, 12). New three-month drug regimens (24, 37) are likely to be part of the solution to this problem. But their widespread use will still require biomarkers that identify who is carrying a viable infection and who is most at risk of progressing to active TB (22, 27, 42), founded on a better understanding of the mechanism of latency (3, 4, 16, 53, 55). It seems likely that, to be effective, three-month (or shorter) regimens must be able to kill bacteria that have low growth rates and those that undergo occasional growth spurts (sterilizing), in addition to killing those with high growth rates (bactericidal) (24). Otherwise the risk of reactivation will persist after prophylactic treatment has been completed.

Our analysis of the prospects for TB elimination in the United States, which builds on that of Hill et al. (19), highlights the challenges faced by countries that have low incidence and mortality rates and which are already in the elimination phase. To achieve very low incidence rates in the entire population, these countries must maintain low transmission rates and ideally prevent TB arising from old infections in the native-born population. In addition, however, they must prevent TB arising from imported infections in the foreign-born population (33). Because the majority of TB cases occur among immigrants—reflecting the number of immigrants and the incidence rates in their countries of origin—TB is unlikely to be eliminated from the whole population by 2050. This projection underscores the point that, in today's highly interconnected world, elimination in any country depends on effective TB control in every country (34).

In the drive toward elimination, vaccines may become an alternative, or at least an adjunct, to drug treatment (23, 29). The new wave of investment in vaccine research and development is expected to deliver a better vaccine than BCG (Bacille Calmette-Guérin vaccine) (56), although the efficacy and mode of action of a putative new vaccine are not yet known. A safe and efficacious vaccine that can neutralize existing (latent) infection could bypass the problem of inventing a biomarker to identify those eligible for preventive therapy. A vaccine that can be given to uninfected people (preventing infection or at least halting the progression of infection before it causes symptomatic TB) would complement the treatment of active disease in reducing transmission. Ideally, of course, a new vaccine would be efficacious pre- and postinfection (1).

Beyond 2015, TB control will no longer be carried out within the context of the MDGs but within a new UN framework, as yet undefined, that may be oriented toward sustainable development. Health in general, and TB in particular, must appear prominently on the agenda (31). To maintain visibility in the post-MDG world, those concerned with TB control need to set clear and ambitious goals, with defined milestones and measurable indicators, so as to track progress toward the natural end point: elimination.

SUMMARY POINTS

1. The internationally agreed target for TB elimination is to reduce annual incidence to less than one case per million population by 2050.

2. Meeting this target requires a 1,000-fold reduction in incidence in little more than 35 years, corresponding to a 20% annual decline from 2015 onward.
3. The target will not be reached with the technology and procedures we have today. The new technologies needed include biomarkers of TB risk, diagnostics, drugs, and vaccines. New procedures must be devised to accelerate the supply of, and demand for, health services.
4. Entry to the elimination phase, where there are fewer than 10 deaths per million population (or fewer than 1 per 100,000), is an important milestone for TB elimination campaigns, globally and nationally.
5. Thirty-five countries and territories with populations exceeding 100,000 are already in the elimination phase. By reducing case incidence and case fatality simultaneously, many more countries could reach that milestone within 1–2 decades.
6. For countries that still have very high incidence rates, the immediate focus must be on enhanced case management, leading to the elimination phase, and as a precursor to elimination per se.
7. In South Africa, where incidence is ≈1% per year (10,000 times the elimination target), the priorities are enhanced case management and the prevention of TB among people infected with HIV. For high-burden countries where the prevalence of HIV is low (<1%), China and India among them, early case detection must be supplemented by the treatment of latent infection in the HIV-negative population to have any chance of eliminating TB by mid-century.
8. Countries that are already in the elimination phase, such as the United States and countries in Western Europe, must maintain low transmission rates and ideally prevent TB arising from the reactivation of old infections in the native-born population. But they must also prevent TB arising from imported infections in the foreign-born population, which typically account for the majority of cases. In today's highly interconnected world, elimination in any country depends on effective TB control in every country.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The World Health Organization has granted Annual Reviews permission for the reproduction of this article. We thank Andrew Hill and Joel Spicer for helpful comments, Hazim Timimi for preparing the map, and Brian Williams for providing HIV input to the TB models.

The authors alone are responsible for the views expressed in this publication, which do not necessarily represent the decisions, policy, or views of the World Health Organization.

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