Global Epidemiology of Tuberculosis

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Abstract

Tuberculosis (TB) was the underlying cause of 1.3 million deaths among human immunodeficiency virus (HIV)-negative people in 2016, exceeding the global number of HIV/acquired immune deficiency syndrome (AIDS) deaths. In addition, TB was a contributing cause of 374,000 HIV deaths. Despite the success of chemotherapy over the past seven decades, TB is the top infectious killer globally. In 2016, 10.4 million new cases arose, a number that has remained stable since the beginning of the 21th century, frustrating public health experts tasked to design and implement interventions to reduce the burden of TB disease worldwide. Ambitious targets for reductions in the epidemiological burden of TB have been set within the context of the Sustainable Development Goals (SDGs) and the End TB Strategy. Achieving these targets is the focus of national and international efforts, and demonstrating whether or not they are achieved is of major importance to guide future and sustainable investments. This article reviews epidemiological facts about TB, trends in the magnitude of the burden of TB and factors contributing to it, and the effectiveness of the public health response.

Keywords
- tuberculosis
- epidemiology
- disease burden
- incidence
- mortality
- risk factors
- latent infection

The discovery and wide use of antimicrobials effective against tuberculosis (TB) starting in the middle of the 20th century allowed dramatic reductions in TB mortality. However, despite the success of chemotherapy, the disease became the first infectious killer seven decades later, claiming 1.3 million lives among human immunodeficiency virus (HIV)-negative people in 2016, a number exceeding the total number of deaths caused by HIV. In addition, TB was a contributing cause of 374,000 HIV deaths,[1] also making TB the first killer of people infected with HIV. TB takes a huge morbidity toll globally, especially among the poorest, and those who are cured from TB can be left with sequelae that substantially reduce their quality of life.[2] The global number of new TB cases has remained stable since the beginning of the 21st century, frustrating public health experts tasked to design and implement interventions to reduce the burden of TB disease worldwide. The following sections review epidemiological facts about TB, trends in the magnitude of TB burden and factors contributing to it, and the principles and effectiveness of the public health response.

Basic Facts about TB

TB is an infectious disease caused by mycobacteria belonging to the *Mycobacterium tuberculosis* complex. A small percentage of human cases are caused by *M. africanum*, *M. canetti*, *M. caprae*, *M. microti*, and *M. pinnipedii*.[3] *M. bovis* was once an important cause of human disease, but its relative importance has considerably declined. It was responsible for an estimated 1.4% of incident TB cases in 2016.[1]

Following exposure to an infectious patient, disease is an uncommon outcome of the host–bacilli interaction in the newly infected contact. The most common outcome is a subclinical (latent), asymptomatic infection. Whether one can achieve a spontaneous or drug-induced complete eradication of latent infection from the host is unclear,[4] but latent infection is typically kept under control through a cell-mediated immune response, preventing the activation of infection into disease. Histopathological damages of an uncontrolled infection are responsible for clinical signs and symptoms of TB disease.[5] TB typically affects the lungs but, in up to a third of patients, can also affects other sites.[6] It is not

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practically possible to identify *M. tuberculosis* strains present in the body in patients latently infected.[4]

The disease is airborne and spread when people with pulmonary TB expel aerosolized bacteria especially when coughing. Transmission through ingestion of contaminated milk is uncommon today.[7] The average risk of acquisition of *M. tuberculosis* infection depends on the prevalence of infectious pulmonary TB in the population. Disease prevalence is proportional to the duration of infectiousness of incident cases. Duration is reduced if diagnosis is timely and immediately followed by proper administration of an effective combination of anti-TB drugs. Drug resistance delays cure, thereby contributing to increased duration and, therefore, prevalence. HIV significantly reduces survival in the absence of adequate treatment for HIV and TB, offsetting the impact on TB prevalence of an increased TB incidence attributable to HIV. The intensity of exposure to TB infection is associated with the quantity of droplet nuclei produced by the infectious patient; aerosolized particles should be 1 to 5 µm to be retained in the lung alveoli and trigger the infection. Particles greater than 5 µm are blocked in the upper airways by the nasal vibrissae and the mucociliary system, whereas those sized less than 1 µm in diameter are too small to be retained in the alveolar space. The load of the contaminated droplet nuclei decreases in case of appropriate room ventilation.[8] Contagious patients should wear surgical masks to decrease the spread of mycobacteria. Health care workers or persons in close contact with contagious patients should wear high-efficiency particulate air-filter respirators to protect themselves.

Overall, a relatively small proportion (5–15%) of the currently estimated 1.7 billion people (a quarter of humanity) infected with *M. tuberculosis*[9] will develop TB disease during their lifetime.[10] The risk of developing TB is higher in the first 12 to 18 months following the acquisition of infection but activation of disease can occur decades after infection. Several medical conditions impair innate and acquired immunity and favor the occurrence of TB disease in individuals who are latently infected.[11–13] The risk is increased among people infected with HIV, and TB is one of the most frequent opportunistic infections in HIV-infected persons, the cause of death in a quarter of them, and an acquired immune deficiency syndrome (AIDS)-defining illness.[6,14] Malnutrition and protein imbalance can also impair the immune system and increase the risk of TB.[13] Other less common conditions, including chronic renal failure[15] and hemodialysis, can cause alterations of acquired immunity similar to those detected in people with diabetes mellitus.[16] Another important disease increasing the risk of pulmonary and extrapulmonary TB is silicosis.[17,18] Exposure to silica dust without silicosis also increases the risk of TB.[16] Among other risk factors, treatment with immunosuppressive drugs such as tumor necrosis factor-alpha inhibitors prescribed for the treatment of chronic inflammatory diseases increases the risk of TB to an estimated 1.6 to 25.1,[19] due to the inhibition of a proinflammatory factor favoring the recruitment of inflammatory cells, activating macrophages, and stabilizing the lung granuloma. The role of corticosteroids on the risk of TB disease is controversial.[6] Evidence about the role of solid and hematological neoplasias, psychiatric disorders (including alcohol and drug abuse), gastrectomy, and jejunoileal bypass is weak or inconclusive.[6,20] Smoking increases the risk of TB infection (relative risk: 1.7) and disease (relative risk: 2.3–2.7) and so does indoor (and likely outdoor) air pollution[6,21] due to a negative effect of exposure on innate and acquired immunity.

The case fatality ratio (CFR) of TB was dramatically reduced by effective combination therapy, from about 50% of incident disease cases during the prechemotherapy era prior to World War II to less than 10% in industrialized countries with universal access to health care (the CFR can be approximated from the ratio of mortality over incidence; secular trends of incidence and mortality are shown for two countries in ►**Fig. 1**). The introduction of the first anti-TB drugs was soon followed with reports of emerging drug resistance. Combination therapy was recommended to avoid the selection of resistant strains.[22] However, therapeutic errors[23] (in particular monotherapy) led to the emergence of resistance to most anti-TB drugs in many parts of the world. Multidrug-resistant TB (MDR-TB), which is caused by bacilli strains resistant to both isoniazid and rifampicin, the two most potent first-line anti-TB drugs, has become common since the 1990s. Extensively drug-resistant tuberculosis (XDR-TB), defined as MDR-TB with further resistance to any fluoroquinolones and to at least one of the second-line injectable drugs (amikacin, capreomycin, and kanamycin), caused major outbreaks in different parts of the world, and is now reported in most countries able to test for susceptibility to the relevant drugs entering in the definition of XDR-TB.[1]

Data Sources

The burden of disease caused by TB can be measured in terms of: incidence, defined as the number of new and recurrent cases of TB arising in 1 year; prevalence, defined as the number of cases of TB at a given point in time; and mortality, defined as the number of deaths caused by TB in 1 year. Historically, a major source of data to derive incidence estimates was results from tuberculin surveys conducted in children that measured presumed latent infection prevalence.[24] Early studies showed the following relationship between the annual risk of infection, denoted λ, and the incidence of smear-positive TB (I_{s+}): one smear-positive case infects on average 10 individuals per year for a period of 2 years and a risk of infection of 10^{-2} per year corresponds approximately to an incidence rate of 50×10^{-5} per year. However, this relationship no longer holds in the context of modern TB control and in HIV settings.[25] In addition to uncertainty about the relationship between λ and I_{s+}, estimates of incidence obtained from tuberculin surveys suffer from other sources of uncertainty and bias, including unpredictable diagnostic performance of the tuberculin test,[26] digit preference when reading and recording the size of tuberculin reactions,[27] sensitivity to assumptions about reaction sizes attributed to infection,[28] sensitivity to the common assumption that the annual risk of infection is age

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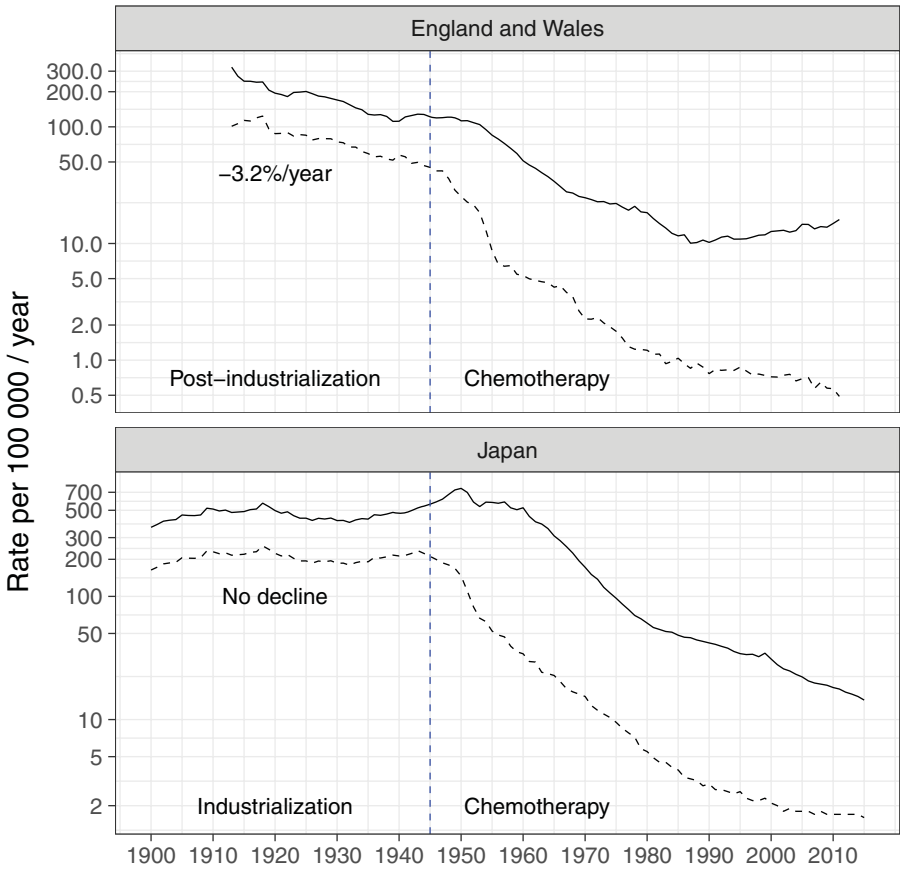

Fig. 1 Historical trends since the early 20th century in TB incidence (solid line) and mortality (dashed line) rates in England and Wales and in Japan.

invariant, and, lastly, sensitivity of overall TB incidence estimates to the assumed proportion of TB incidence that is smear-positive. A first global and systematic estimation exercise led by the World Health Organization (WHO) in the early 1990s estimated that there were about 8 million incident TB cases in 1990 and 2.6 to 2.9 million deaths.[29] A second major reassessment was published in 1999,[30] with an estimated 8 million incident cases for the year 1997 and 1.9 million TB deaths. The most important sources of information were case notification data for which gaps in detection and reporting were obtained from expert opinion. Data from 24 tuberculin surveys and from 14 prevalence surveys of TB disease were also used.

Global trends of TB were not fully recorded and assessed until the launch of the WHO global surveillance and monitoring system in 1996,[31] showing TB as a still major, often forgotten epidemic affecting especially low- and middle-income countries without exception.[29,32] Measuring the incidence of TB at a nationally representative level has never been achieved because it would require a cohort study with active follow-up over 1 or 2 years of tens of thousands of people at high cost, with extremely challenging logistics and limited accuracy of the estimate. Surveys of infection based on tuberculin skin testing have been used during the 1990s to derive estimates of incidence of TB disease, but the interpretation of such surveys is usually very difficult, in particular where a high prevalence of HIV infection has altered the natural course of the disease.[33] The best alternative is to estimate incidence from routine surveillance systems in which case reports are more or less accurate and complete, such that notifications can be considered a close proxy of incidence. This is possible in countries where there is a long tradition of legally mandatory reporting of TB cases, in settings with universal health care coverage,[34] where all sick people can access quality health services with no financial or other barriers. Surveillance systems in many countries do not provide a direct measure of TB incidence: many cases are either treated but not notified (particularly in the private sector or in general hospitals) or go undiagnosed (e.g., when people with no health insurance and no social protection lack access to health care or when the laboratory network is underperforming). In countries with weak TB surveillance, estimating incidence requires an evaluation of the quality and coverage of available TB notification data, including analyses of the completeness of reporting, the extent of duplicate or misclassified records,[35] and national and subnational data consistency.[36] An example from Kenya illustrates how the effect of the HIV epidemic and case-finding efforts on trends in TB notifications can be separated, and used to improve estimates of trends in TB incidence rates.[37] The reported data are not necessarily sufficient to estimate TB incidence in absolute terms. To do this, an analysis of the fraction of TB cases that are being captured in official notification systems is required,[38] accounting for

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cases missed from official notification data due to laboratory errors,[39] lack of notification of cases by public[30] and private providers,[40] failure of people accessing health services to be identified as potential TB cases,[41] and lack of access to health services.[42] Operational research (such as capture-recapture studies) as well as supporting evidence (such as whether prescriptions for TB drugs are available in the private sector, and practices of staff managing people suspected of having TB in primary health care facilities) can be used to assess the fraction of cases that are missing from official notification data.[38,43–49] Duplicated or misclassified records, inconsistent case notifications at the subnational level, and inconsistent time trends or knowledge about TB epidemiology contribute to uncertainty about TB incidence estimates.[1]

In countries with a high burden of TB, prevalence of pulmonary disease can be directly measured in representative nationwide surveys using typical sample sizes of around 50,000 people[50]; costs range from US$ 1 to US$ 4 million per survey.[51] In recent years, several countries have successfully measured the prevalence of pulmonary TB through such surveys,[1,51,52] despite logistic challenges and high operational costs. Since prevalence typically falls more quickly than TB incidence in response to public health interventions, a series of surveys conducted at intervals of several years may meaningfully capture changes in the epidemiological burden of TB. The WHO Global Task Force on TB Impact Measurement has provided guidance and support on these topics to countries since 2006.[1] In 2016, WHO estimates of TB incidence were based on direct measurements from recent national surveys of the prevalence of TB disease for 24 countries that accounted for 68% of the global burden of cases (►**Fig. 2**) and on a standard adjustment (to account for underreporting and underdiagnosis) to routine notification data for 134 countries with 15% of the global burden. In the period 2007–2016, 25 national prevalence surveys (13 in Asia, 12 in Africa) were completed using methods recommended by the WHO.[50]

The best sources of data about deaths from TB (excluding TB deaths among HIV-positive people) are vital registration (VR) systems that meet quality and coverage standards[53] and in which causes of death are coded according to ICD-10 (although the older ICD-9 and ICD-8 classification are still in use in several countries), using ICD-10: A15-A19 and B90 codes, equivalent to ICD-9: 010–018, and 137. When people with AIDS die from TB, HIV is registered as the underlying cause of death and TB is recorded as a contributory cause. Since one-third of countries with VR systems report to the WHO only the underlying causes of death and not contributory causes, VR data usually cannot be used to estimate the number of TB deaths in HIV-positive people. In the absence of direct measurement, mortality may be estimated as the product of the incidence of the disease and the case fatality rate or using ecological modeling.[1] In 2016, WHO estimates of TB deaths were based on national VR with coding of cause of death for 129 countries that collectively accounted for 57% of estimated TB deaths.

The WHO Global Project on Anti-tuberculosis Drug Resistance Surveillance[54] (DRS) was launched in 1994 based on three major principles that, to this date, still apply. First, drug susceptibility is assessed on a nationally representative

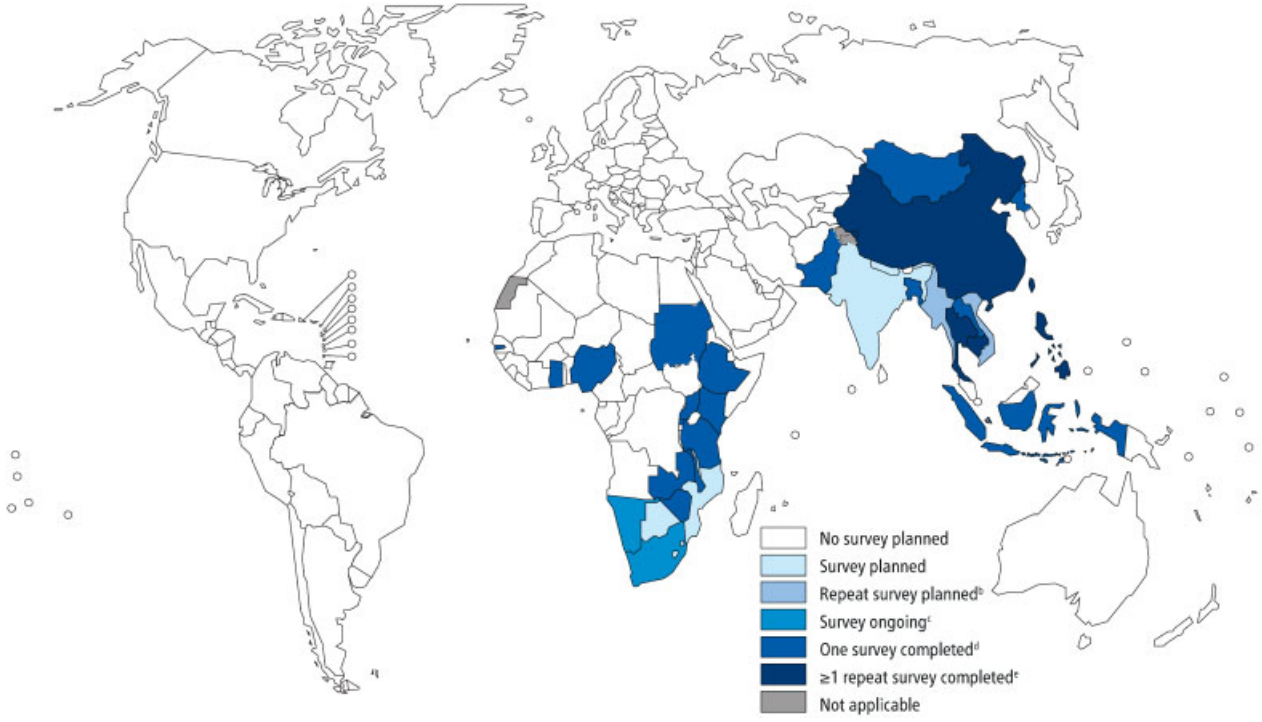

Fig. 2 Countries in which national population-based surveys of the prevalence of pulmonary TB have been implemented using currently recommended screening and diagnostic methods[50] since 2000 or are planned in the near future.

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sample of patients with bacteriologically confirmed pulmonary disease (either sampling is done prior to testing or routine testing data are used without sampling if more than 80% of notified patients in a given year have drug susceptibility test results already available); second, susceptibility testing is quality assured following strict criteria based on a network on supporting supranational reference laboratories; third, drug resistance is assessed separately in previously untreated patients and in previously treated patients. Past exposure to a course of TB treatment is a strong predictor of drug resistance. Since 1994, data on drug resistance have been systematically collected and analyzed for 160 countries that accounted for >99% of the world's TB cases (►**Fig. 3**).

Historical Trends and Determinants of TB

TB is likely to have affected modern humans for most of their history.[55,56] Starting from the postindustrialization period in the late 19th century, the combination of social and

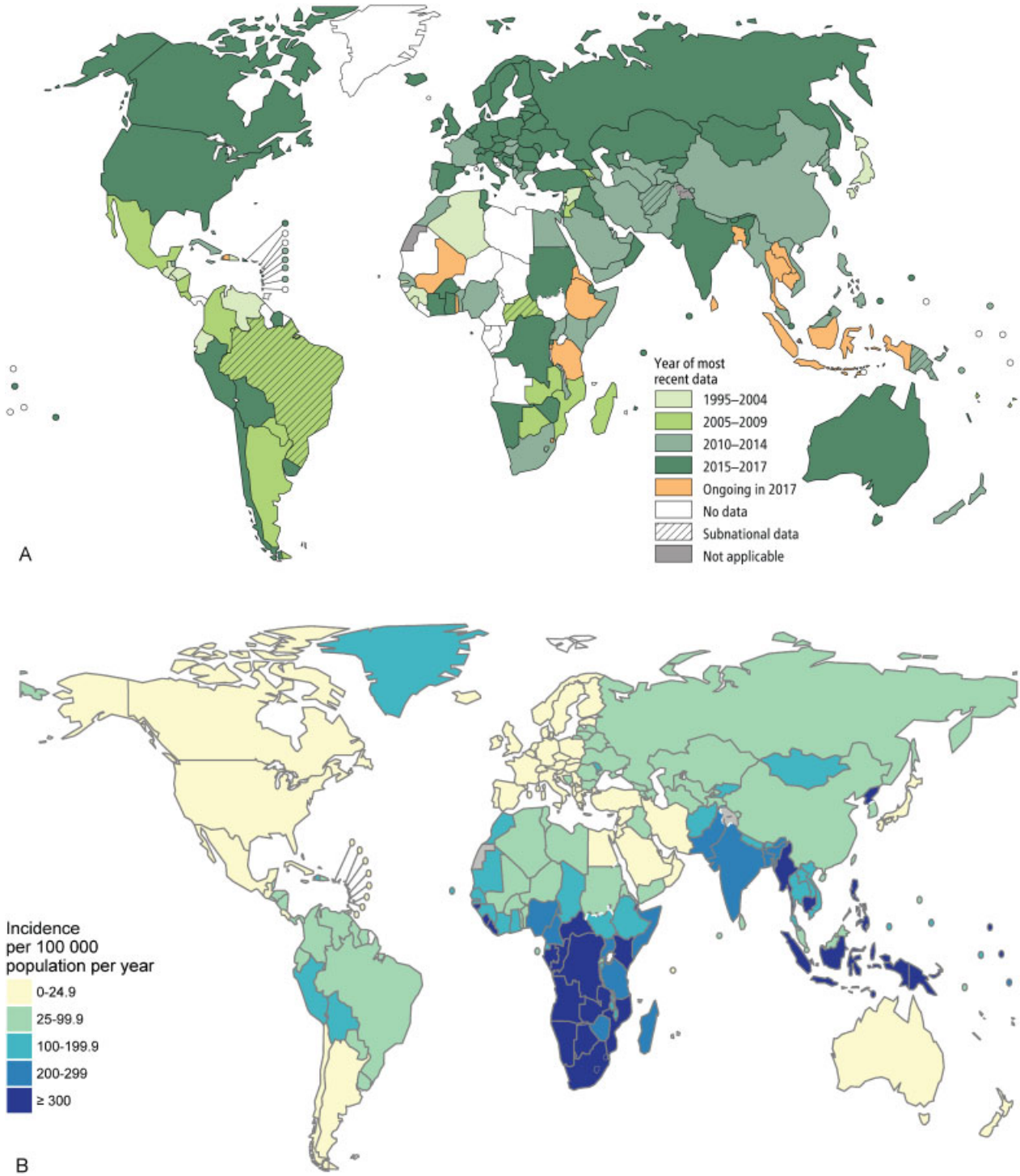

Fig. 3 Global coverage of surveillance data on drug resistance, 1995–2017.

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economic development[6] and the discovery and use of effective drug treatments resulted in rapid declines in case and mortality rates in western Europe, North America, and some other parts of the world,[57,58] accelerating in the 1950s when effective chemotherapy became available.

Data from the period of the industrial revolution in Japan, which occurred nearly a century later than in Western Europe, show no reduction in incidence rates (►**Fig. 1**, bottom panel). There are no reliable data on the magnitude of TB during the industrialization revolution in Western Europe from the second half of the 18th century to the early 19th century, but as observed during the first half of the 20th century in Japan,[59–61] a rapidly growing population of factory workers experiencing difficult working and living conditions in a crowded environment with increased exposure to air pollution may initially have had detrimental effects on TB transmission. Societal and environmental implications of recent industrialization may similarly play a negative role in countries such as the Philippines were no reductions were observed over the past decade in the prevalence rate of pulmonary disease, one the highest in the world,[1] despite a sustained economic growth and commitment to TB control, possibly in relation to insufficient progress in addressing poverty, undernourishment,[62] and other social determinants.[11,12,63]

Since the 1990s, the HIV/AIDS epidemic has been one of the main causes of the slow decline, if not of increases, of TB incidence worldwide. The estimated fraction of HIV-attributable global TB incidence was about 10% in 2015 (►**Table 1**). The median TB incidence rate ratio in people with HIV compared with uninfected people living in the same country was 22 in 2016 (interquartile range: 19–41).[1] The epidemiological impact of TB risk factors depends on their prevalence in the general population and on the intensity of the association. ►**Table 1** shows global population attributable fractions and the number of cases attributable to a selection of risk factors. Although the relative risk of acquiring TB disease is much higher for HIV/AIDS, the prevalence of malnutrition and diabetes mellitus is considerably higher than that of HIV/AIDS, leading to comparable numbers of attributable TB cases globally. The growth in the prevalence of risk factors among chronic diseases can be expected to have a negative impact on the decline in TB incidence, including tobacco use and diabetes mellitus, the prevalence of which is expected to increase globally in the forthcoming years.[7,64,65]

Table 1 Selected TB risk factors and their attributable contribution to the estimated number of incident cases in 2015

Risk factor	Relative risk[1,63]	Exposed (million in 2015)	PAF,[1] (%)	Attributable TB cases (million in 2015)
Under-nutrition	3.1–3.3	734	18	1.9
HIV infection	22	36	9.4	1.0
Cigarette smoking	1.6–2.5	1,047	7.9	0.83
Diabetes	2.3–4.3	460	7.5	0.79
Alcohol abuse	1.9–4.6	407	4.7	0.49

Abbreviation: PAF, population attributable fraction (global).

TB Burden in 2016 and Recent Trends

Incidence and Mortality

Globally, 23% (uncertainty interval [UI]: 20–26) of the world's population were estimated to be infected with *M. tuberculosis* complex in 2014, equivalent to a best estimate of 1.7 billion people.[9] Global estimates of TB incidence and deaths in the period 2000–2016 are shown in ►**Fig. 4**. In 2016, there were an estimated 10.4 million (95% UI: 8.8–12.2 million) incident cases (►**Table 2**); 1 (95% UI: 0.91–1.6) million of the estimated incident cases (10%; 95% UI: 8–12%; ►**Fig. 5**) were among people living with HIV. TB affects all countries; the number of incident cases relative to total population size (including nonlatently infected people) varied from under 10 per 100,000 population in most high-income countries to above 500 in a few countries including the Democratic People's Republic of Korea, Lesotho, Mozambique, the Philippines, and South Africa (►**Fig. 6**). Most TB cases are in adults (90%) and in males (65%; ►**Fig. 7**). The number of incident cases per 100,000 population has been falling slowly, at an average rate of 1.4% per year during the period 2000 – 2016 and 1.9% between 2015 and 2016. Regionally, the TB incidence rate is falling fastest in the WHO European Region (4.6% from 2015 to 2016; ►**Fig. 8**).

The number of TB deaths has been falling, from a best estimate of 1.7 million in 2000 to 1.3 million in 2016 among HIV-negative people (a reduction of 24%) and from 0.5 million to 0.4 million among HIV-positive people (these deaths are officially classified as having HIV/AIDS as the underlying cause and TB as a contributory cause).[66] The TB mortality rate among HIV-negative people is falling at 3.4% per year (4% when deaths among HIV-positive people are included), and decreased by 37% between 2000 and 2016. Since 2012, TB has been the leading cause of death from a single infectious agent, ranking above HIV/AIDS (►**Fig. 9**). In 2016, about 82% of TB deaths among HIV-negative people occurred in the WHO regions of Africa (32%) and South-East Asia (50%); these regions also accounted for 85% of the combined total of TB deaths in HIV-negative and HIV-positive people. India accounted for 33% of global TB deaths among HIV-negative people.

The global CFR estimate for 2016 was 16%. However, the CFR varied widely among countries, from under 5% in some countries to above 20% in most African countries (►**Fig. 10**), illustrating large inequities in access to diagnosis and treatment.

Drug-Resistant Tuberculosis

Globally, an estimated 4.1% (95% confidence interval [CI]: 2.8–5.3%) of new cases and 19% (95% CI: 9.8–27%) of previously treated cases had rifampicin-resistant TB (RR-TB) or

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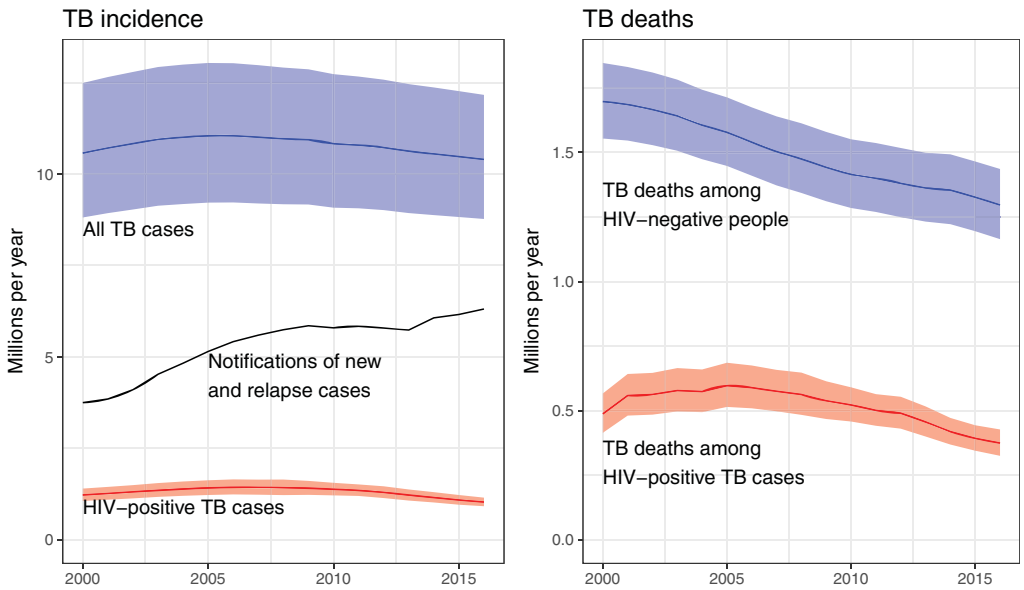

Fig. 4 Global trends in the estimated number of incident TB cases and the number of TB deaths (in millions), 2000–2016. Shaded areas represent uncertainty intervals.

MDR-TB in 2016 and thus required treatment with second-line drugs. The estimated number of incident cases worldwide in 2016 was 600,000 (540,000–660,000), of which 490,000 (82%) had MDR-TB. Three countries accounted for almost half the global total: India (25%), China (12%), and the Russian Federation (10%). Proportions of cases harboring bacilli strains resistant to rifampicin are reported separately for new and previously treated TB cases and vary widely between countries, as shown in ►**Fig. 11**. There is no evidence that the burden of RR-TB/MDR-TB is increasing globally.

Global Public Health Response

Strategy

Prior to the availability of effective anti-TB treatment, the first public health interventions against TB included isolation in sanatoria and bacillus Calmette–Guérin (BCG) vaccination. The impact on TB incidence of both measures was somewhat evident, but difficult to quantify given multiple other factors, mainly linked with poverty reduction, that played a role.

Three decades of success of effective chemotherapy and the conviction that integration of services would have

Table 2 Epidemiological burden of TB by WHO Region and globally

	Population (billions)	HIV-negative TB mortality	HIV-positive TB incidence	Total TB incidence	HIV-positive TB incidence
WHO Region[a]					
AMR	0.996	17,000 (16,100–17,900)	6,240 (5,570–6,940)	274,000 (255,000–294,000)	30,100 (27,700–32,700)
EMR	0.669	81,700 (69,100–95,400)	3,020 (1,810–4,530)	766,000 (573,000–985,000)	9,850 (5,930–14,800)
AFR	1.02	417,000 (351,000–488,000)	320,000 (272,000–372,000)	2,590,000 (2,310,000–2,900,000)	764,000 (660,000–876,000)
EUR	0.916	26,100 (25,500–26,800)	5,060 (3,910–6,360)	290,000 (251,000–333,000)	33,600 (26,200–41,800)
WPR	1.89	103,000 (84,600–123,000)	4,960 (3,040–7,340)	1,800,000 (1,500,000–2,130,000)	29,100 (23,100–35,800)
SEA	1.95	652,000 (542,000–772,000)	34,700 (24,800–46,200)	4,670,000 (3,190,000–6,440,000)	163,000 (120,000–211,000)
Global	7.44	1,300,000 (1,160,000–1,440,000)	374,000 (325,000–427,000)	10,400,000 (8,770,000–12,200,000)	1,030,000 (915,000–1,150,000)

[a]The six WHO Regions are as follows: AFR, Africa; AMR, the Americas; EMR, Eastern Mediterranean; EUR, Europe; WPR, Western Pacific. Countries in each region are listed in Global TB Report 2017.[1]

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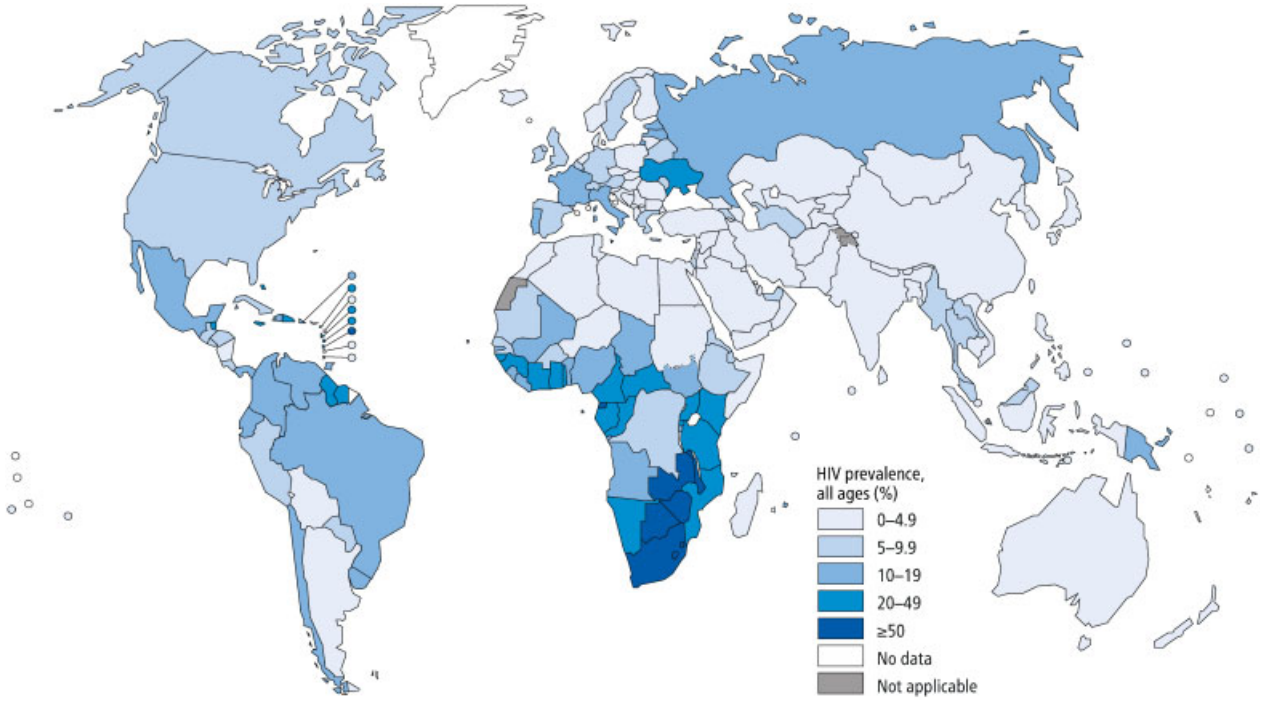

Fig. 5 Estimated HIV prevalence in new and relapse TB cases, 2016.

addressed care challenges resulted in a relaxation of public health measures in many countries in the 1980s.[67–69] Simultaneously, other important factors contributed to rises in TB incidence in several countries: the HIV/AIDS epidemic particularly in Africa, the spread of MDR-TB particularly in countries of the former Soviet Union following social and economic collapse, and sustained migration flows from high TB incidence settings toward lower-incidence countries.[19,70] Evidence that short-course chemotherapy was one of the most cost-effective of all health care interventions[71] and a global concern about the emergence of MDR-TB and XDR-TB have emphasized the need to address TB more effectively on

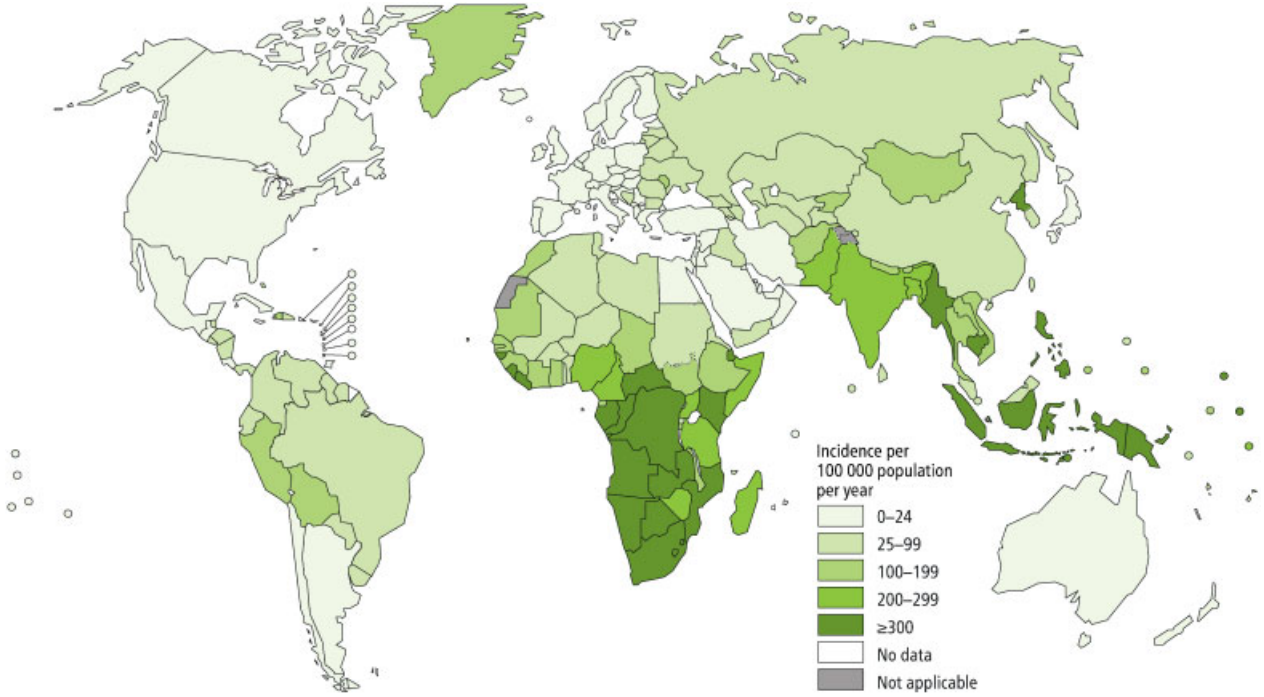

Fig. 6 Estimated TB incidence rates, 2016.

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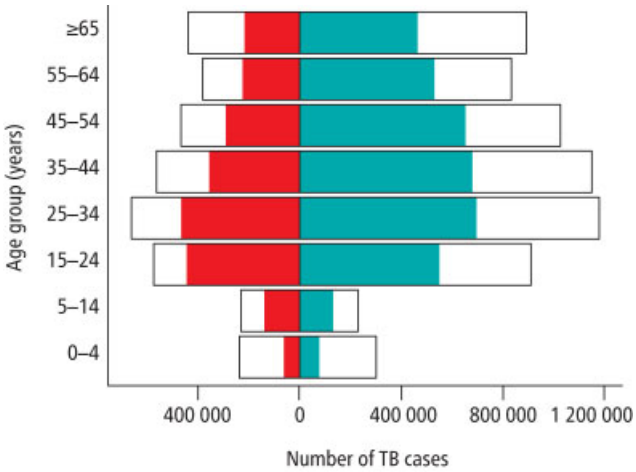

Fig. 7 Global distribution of incident cases (black line) by age and sex (female in red, male in blue), 2016. The outer boundary shows estimated incidence. The blue and red shaded portions of the bars show the number of incident cases that were officially reported to WHO in 2016, for men and women, respectively.

a global scale. This prompted the WHO in the mid-1990s to develop and disseminate a new standard approach to TB control: the DOTS strategy.[42] This strategy emphasized the five essential elements of TB control: government commitment; bacteriological diagnosis mainly on patients spontaneously seeking care at health centers; standardized short-course chemotherapy under proper case management conditions; an effective drug supply system; and a monitoring and evaluation system allowing assessment of notifications and treatment outcomes. At the same time, TB was declared a global health emergency by the WHO in 1993.[72] In 2006, the DOTS strategy that had been implemented in most of the world was enhanced by the WHO to further emphasize new challenges to be addressed such as HIV-associated TB, MDR-TB, the need for TB-sensitive health systems, community and private sector engagement, and research. Further progress followed the implementation of the Stop TB Strategy in 2006.[69,73] However, the lack of acceleration of the incidence and mortality decline, and the need to align with the new thinking and toward the Sustainable Development Goals (SDG) 2015–2030 required a new global strategy. Thus, the End TB Strategy, proposed after long consultations with all partners and civil society, was unanimously endorsed by all WHO Member States at the 2014 World Health Assembly for the period 2016–2035.[74] A year later, the SDGs were adopted by the UN in September 2015.[75] The SDGs and End TB Strategy share the common aim of ending the global TB epidemic to less than 10% of the global incidence rate of 2015 and less than 5% of the global mortality rate of 2015. The End TB Strategy has four underlying principles and three pillars. The principles are government stewardship and accountability, with monitoring and evaluation; coalition with civil society organizations; protection and promotion of human rights, ethics and equity; and adaptation of the strategy and targets to each country's situation. The three pillars are integrated, patient-centered TB care and prevention; bold policies and supportive systems (including universal health coverage, social protection and action on TB determinants); and intensified research and innovation. The WHO/World

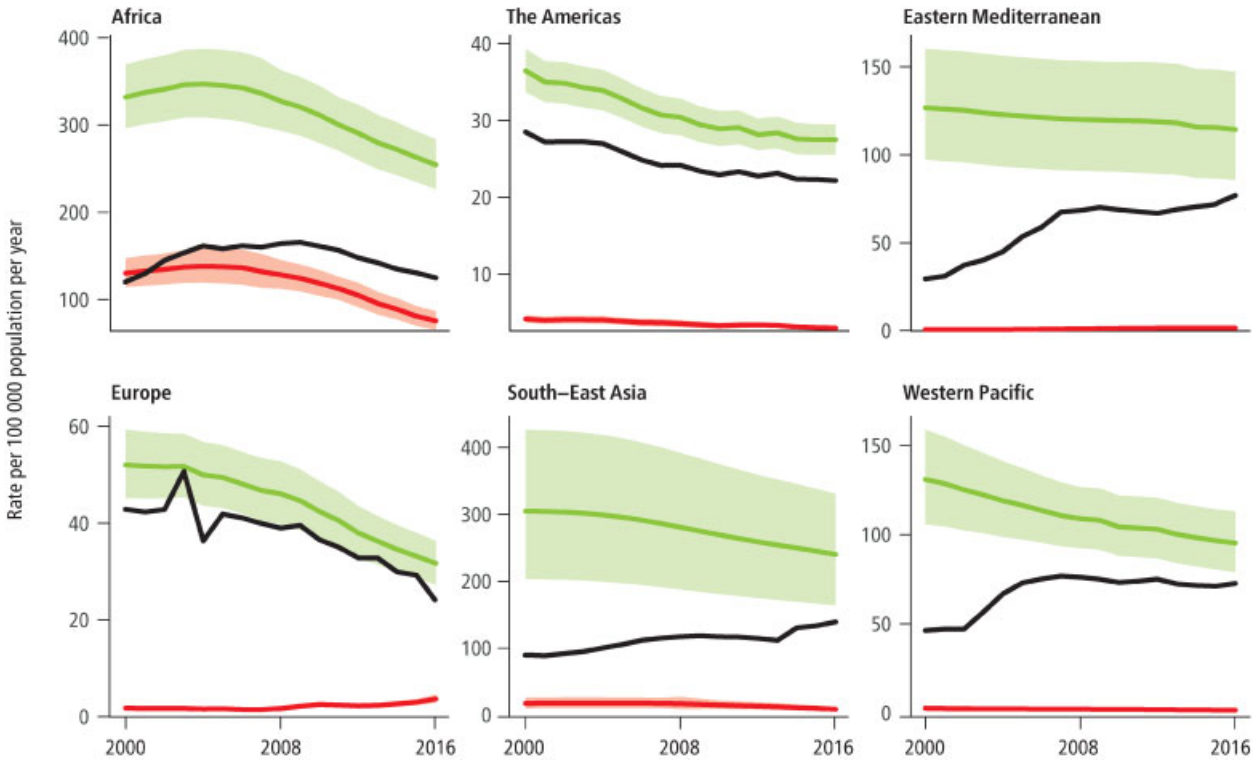

Fig. 8 Regional trends in estimated TB incidence rates by WHO region, 2000–2016. Total TB incidence rates are shown in green and incidence rates of HIV-positive TB are shown in red. Shaded areas represent uncertainty intervals. The black lines show notifications of new and relapse cases for comparison with estimates of the total incidence rate.

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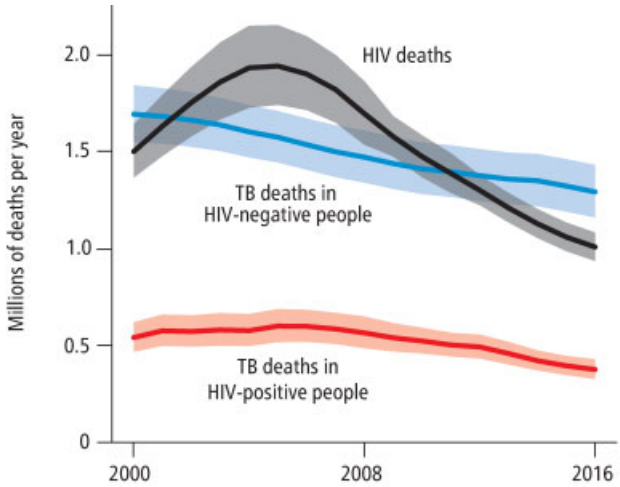

Fig. 9 Estimated deaths caused by TB and HIV, 2000–2016. For HIV/AIDS, the latest estimates of the number of deaths in 2016 that have been published by UNAIDS are available at www.unaids.org/en/resources/documents/2017/HIV_estimates_with_uncertainty_-bounds_1990-2016. For TB, the estimates for 2016 are those published in this report. Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the international classification of diseases. Deaths from TB among HIV-positive people accounted for 37% of deaths classified as caused by HIV/AIDS in 2016.

Bank definition of universal health coverage is that all people receive the health services they need, while at the same time ensuring that the use of these services does not expose the user to financial hardship.[76] The level and nature of social protection spending has a bearing on TB burden even in countries with fundamental welfare mechanisms. WHO's new global TB strategy for the 2015–2035 era puts a renewed focus on social determinants and emphasizes the essential role of actions both within and outside the health care sector to ensure universal social protection.[76] One of the targets for the new strategy is that no TB-affected household should experience catastrophic costs, a target that should be achieved globally by 2020.[77] Reaching TB targets requires provision of diagnostic and treatment services within the broader context of universal health coverage and multi-sectoral action to address the social and economic determinants of TB infection and progression to disease. Success will also depend on technological breakthroughs from the research and development pipelines possibly by 2025, so that incidence can fall at much faster rates than observed in countries with best historical declines.

Case Detection and Cure

In 2016, 6.3 million new cases of TB were reported to national public health authorities, equivalent to 61% (51–72%) of the estimated incidence of 10.4 (8.7–12.2) million. If all notified cases were true TB cases, this figure translates into an estimated 4 (2.9–5) million cases escaping notification or even TB diagnosis, a major challenge to be addressed to achieve the "end of the epidemic." In 2016, there were 476,774 reported cases of TB among people living with HIV, equivalent to 46% (41–52%) of the estimated incidence. Of these, 85% were on antiretroviral therapy. A total of 129,689 people were started on treatment for drug-resistant TB, only 22% (19–25%) of the estimated incidence. The global male: female (M:F) ratio for notifications was 1.7, which is less than ratios observed in national TB prevalence surveys, indicating that notification data understate the share of the burden accounted for by men in some countries. Globally, children (aged < 15 years) accounted for 6.9% of the new TB cases that were notified in 2016 (►**Fig. 7**). In 2016, global coverage of

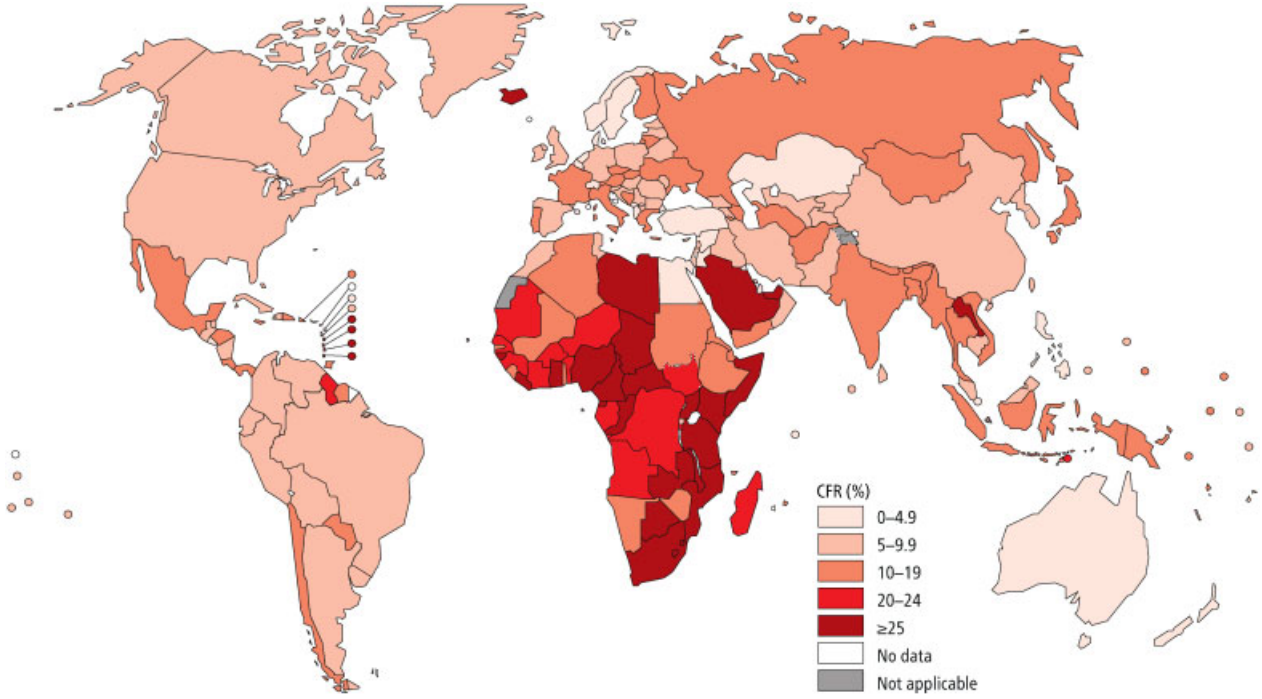

Fig. 10 Estimates of the TB case fatality ratio, including HIV-negative and HIV-positive people, 2016.

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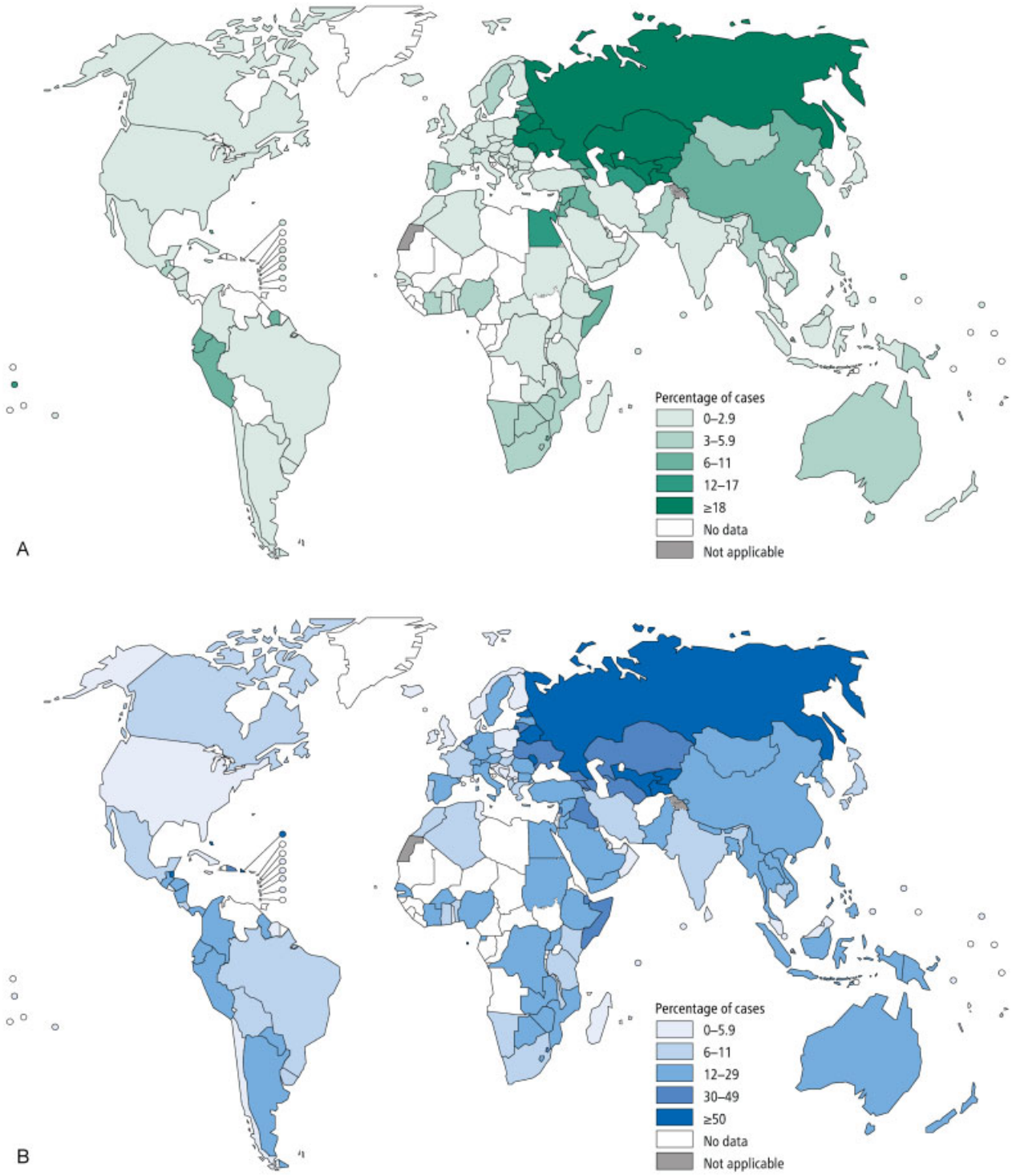

Fig. 11 Burden of rifampicin-resistant (RR-TB) or multidrug-resistant TB (MDR-TB). (**a**) Percentage of new TB cases with RR/MDR-TB. (**b**) Percentage of previously treated TB cases with RR/MDR-TB.

testing for rifampicin resistance was 33% for people with newly diagnosed TB and 60% for those previously treated, and 41% overall.

In countries with large private sectors, including India, Indonesia, and the Philippines, underreporting may explain a large part of the incidence–notification gaps.[1] Data from recent national TB prevalence surveys show that many of the cases detected during these surveys had previously sought care, and that there were also people who reported symptoms and had relatively advanced disease (based on chest X-ray results) who had not sought care. Despite advances in rapid diagnostics, a considerable proportion of the TB cases reported to the WHO is still clinically diagnosed rather than bacteriologically confirmed. Only 57% of the pulmonary

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cases reported worldwide in 2016 were bacteriologically confirmed. Overdiagnosis of TB may become more likely in settings with systematic detection programs based on chest X-ray screening strategies.[78,79]

The latest treatment outcome data reported to the WHO show treatment success rates of 83% for TB (2015 cohort), 78% for HIV-associated TB (2015 cohort), 54% for drug-resistant TB (RR-TB or MDR-TB) (2014 cohort), and 30% for XDR-TB (2014 cohort). TB treatment (combined with antiretroviral therapy for those living with HIV) is estimated to have averted 53 million deaths during the period 2000–2016.[1]

Prevention

Preventive treatment for latent infection is expanding in people living with HIV and children younger than 5 years who are contacts of infectious cases. However, most people in those two priority groups are not accessing it, with coverage ranging from 2.4% in Indonesia to 73% in Zimbabwe. The number of children contacts younger than 5 years who were reported to have been started on preventive treatment increased by 85% between 2015 and 2016 (from 87,242 to 161,740), but was still only 13% of the estimated 1.3 million eligible children. In 2016, 154 countries reported providing BCG vaccination as a standard part of childhood immunization programs, of which 111 reported coverage above 90%. However, although BCG can avert fatal disseminated cases of TB in the first years of life, the impact of the vaccine on the epidemiology of TB is very limited.

Determinants of Disease Burden

Accelerating declines in TB incidence requires addressing the broader determinants of infection and disease. The WHO developed a TB-SDG monitoring framework that includes 14 indicators under 7 different SDGs for which there is evidence of an association, directly or indirectly, with TB incidence.[12,63,69] The latest status of a selection of these indicators for WHO's list of 30 high TB burden countries is shown in ►**Fig. 12**. Many countries have major challenges ahead to address key determinants having considerable impact on TB incidence such as undernutrition, HIV infection, smoking, and a variety of factors linked to poverty and housing (►**Table 1**).

Growth in total health expenditures is not sufficient to achieve universal health coverage. Financing for health care needs to be generated via pooling of contributions across the population, using mechanisms such as insurance or taxation to prevent those in need from facing excessive financial burdens. Although some countries with a high burden of TB are building or expanding insurance systems that include TB in the benefit package (e.g., Indonesia, the Philippines and Vietnam), in most there is a long way to go. Out-of-pocket

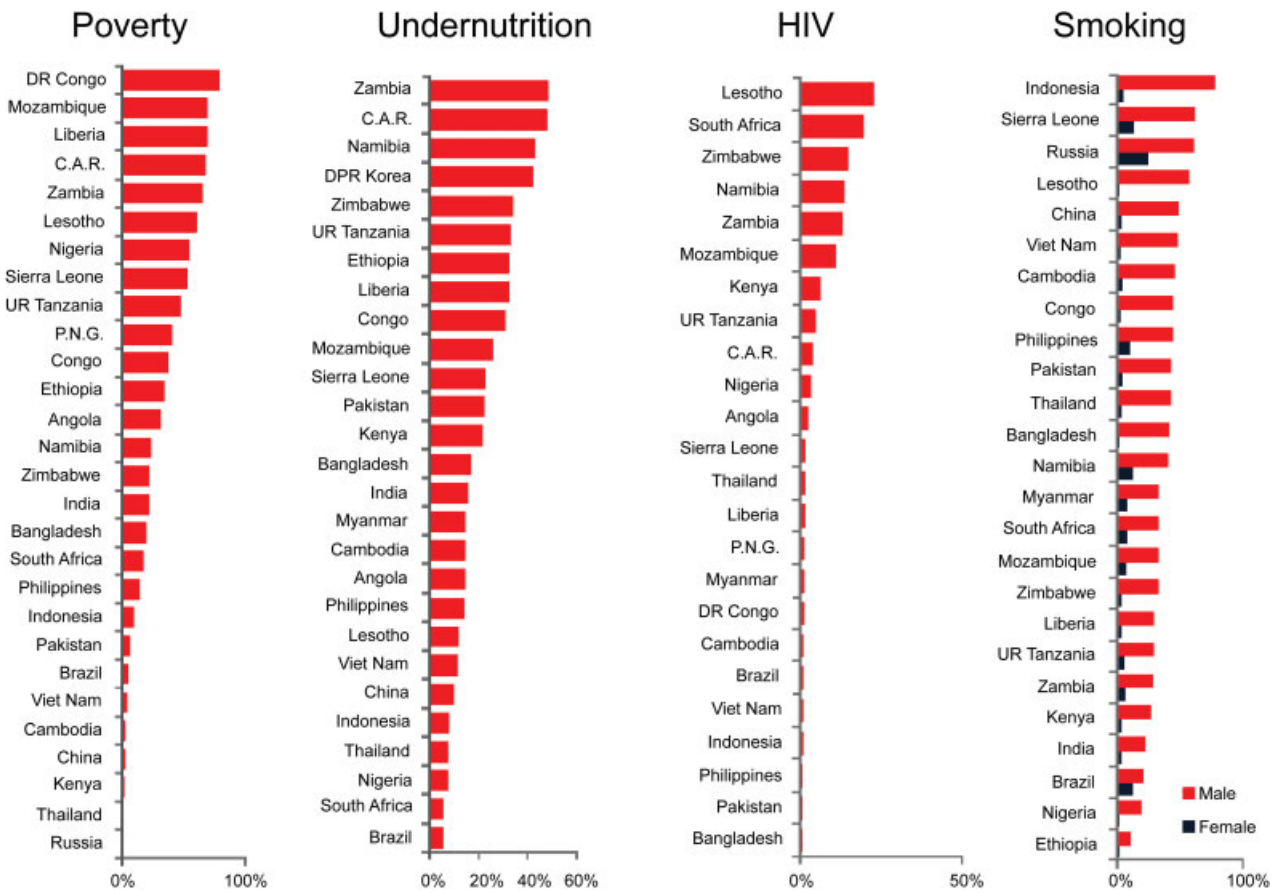

Fig. 12 Status of selected SDG indicators in 30 high TB burden countries, latest available year. The bars show the population prevalence for each indicator (expressed as the percentage of the national population). The data for smoking apply to those aged 15 and above.

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expenditures on health care account for a high proportion (>30%) of total health expenditures in most countries with a high burden of TB[12] and the first surveys of costs faced by TB patients and their households implemented since the launch of the End TB Strategy are revealing a high financial and economic burden.[1]

A new vaccine or equivalent "prophylactic" treatment that will substantially lower the probability of a latent TB infection developing into active disease among the estimated 1.7 billion people already infected is truly needed to achieve the global aim of ending TB. Therefore, increased investments in research and development are essential. Recent data show that about US$ 0.7 billion was invested in 2016,[80] compared with an annual requirement estimated at US$ 2 billion per year,[81] which itself may be too conservative given the burden of disease and the needs for much more effective rapid point-of-care diagnostics for infection and diseases; new, shorter, less toxic regimens for infection and all forms of disease; and ultimately an effective pre- and postexposure vaccine without which elimination will unlikely be reached.

Conclusion

Despite progress in care and prevention, TB remains one of the world's leading causes of ill-health and death, and the current pace of decline in the epidemiological burden of TB is not fast enough to reach targets set in the SDGs and End TB Strategy. Commitments made in the Declaration from the WHO Global Ministerial Conference on Ending TB in the Sustainable Development Era that was held in Moscow, Russian Federation, in November 2017 and the upcoming UN General Assembly High-Level Meeting on TB in September 2018[82,83] provide hope that the multisectoral efforts required to put countries and the world on the path to ending the TB epidemic can be galvanized. The declaration adopted at the WHO Global Ministerial Conference held in 2017 calls for the development of a crucial "multisectoral accountability framework"[84] to stimulate and sustain political commitment and action based on a regular cycle of monitoring, review, and action, including at the highest political levels nationally and globally.

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