Chapter 2

Epidemiology: the current burden of tuberculosis and its determinants

Rita Verstraeten[1,2], Marta Cossa[2], Leonardo Martinez[3], Kristin Nelson[4], Dinis Nguenha[2] and Alberto L. García-Basteiro[1,2,5]

[1]ISGlobal, Hospital Clínic - Universitat de Barcelona, Barcelona, Spain. [2]Centro de Investigação em Saude de Manhiça (CISM), Maputo, Mozambique. [3]Department of Epidemiology, Rollins School of Public Health, Atlanta, GA, USA. [4]Department of Epidemiology, School of Public Health, Boston University, Boston, MA, USA. [5]Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), Barcelona, Spain.

Corresponding author: Alberto L. García-Basteiro (alberto.garcia-basteiro@isglobal.org)

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Global advances in reducing TB burden have been halted or reversed by the impact of the COVID-19 pandemic, with major effects on TB diagnosis and treatment. There is a need for renewed efforts to invert and accelerate the decline of TB figures. https://bit.ly/ERSM101

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Ending TB has been a global struggle for decades. Despite numerous efforts to accelerate the reduction in incidence and mortality, TB continues to be one of the top infectious killers worldwide. Global advances in reducing TB burden have been halted or reversed by the impact of the COVID-19 pandemic, with major effects on TB diagnosis and treatment. This chapter summarises evidence on the current burden of disease and on the different risk factors for TB, as well as their implications for past and current TB burden. There is an urgent need to strengthen our efforts and get back on track to achieve global TB targets, while taking into account risk factors and social determinants to help optimise intervention targets.

Introduction

With 10.6 million cases and 1.6 million deaths in 2021, TB is the 13th leading cause of death worldwide. Until the onset of the COVID-19 pandemic in 2019, TB was the leading cause of death due to a single infectious agent, *Mycobacterium tuberculosis*, and is again at the end 2022 [1, 2]. After more than a decade of decline, TB mortality increased in 2020 and 2021. Goals set by global organisations are increasingly seen as difficult to achieve in the wake of the COVID-19 pandemic.

Burden of disease

In 2014, the World Health Assembly approved the WHO's End TB Strategy as part of the newly adopted sustainable development goals [3]. These goals included a reduction of 90% and 95% in TB incidence and TB deaths, respectively, by 2035, along with universal protection of households from facing catastrophic costs due to TB as of 2020 (table 1). By the end of 2021,

TABLE 1 The End TB Strategy milestones and Sustainable Development Goal (SDG) targets shown as a percentage reduction on 2015 values

	Milestones		SDG targets		Status in 2021
	2020	2025	2030	2035	
Reduction in TB incidence rate	20%	50%	80%	90%	10%
Reduction in TB deaths	35%	75%	90%	95%	5.9%
Protection of people with TB from facing catastrophic costs due to TB	100%	100%	100%	100%	52%

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the estimated global TB incidence rate was 134 per 100 000 population, a mere 10% reduction on that of 2015 and only halfway to the first End TB Strategy milestone. The estimated number of TB deaths was 1.6 million in 2021, a 5.9% reduction from 2015 and approximately 1/5th of the End TB Strategy 2020 milestone. Lastly, in 2021, 48% of people with TB still faced catastrophic costs, which was set out to be prevented for everyone with TB by 2020.

Incidence

One of the purposes of TB surveillance is to measure the occurrence of new TB cases. TB case notification in high-burden countries is often incomplete due to underdiagnosis or underreporting. WHO's TB incidence figures are estimated through different methods, such as prevalence surveys, adjusted notifications (for under-/overreporting or detection error) and inventory/capture–recapture studies. From 2020 onward, dynamic models were used to account for disruptions to health services due to the COVID-19 pandemic [5]. The majority of burden-of-disease measures in this section are based on WHO estimates in the *Global Tuberculosis Report 2022* [1]. Other organisations such as the Institution for Health Metrics and Evaluation (IHME) also report global TB burden estimates, which are currently reasonably similar to those of the WHO [6].

The largest proportion of estimated new TB cases is found in the South-East Asian (45%), African (23%) and Western Pacific (18%) WHO regions, with lower proportions in the Eastern Mediterranean (8.1%), American (2.9%) and European (2.2%) regions [1]. Four countries accounted for over half of the estimated TB incidence in 2021: India, Indonesia, China and the Philippines, with 5.4 million new cases every year [1]. In 2021, 6.7% of the estimated incident TB patients were PLHIV. The African region is by far the most affected by HIV-associated TB, with a regional estimated incidence rate of 42 per 100 000 PLHIV per year, which is 4.7 times the global rate among PLHIV [7]. Four WHO regions showed a considerable decrease in estimated TB incidence in the past two decades (European 54%, African 36%, South-East Asian 34% and Western Pacific 32%), while a smaller decrease was observed in the American (22%) and Eastern Mediterranean (17%) regions [1]. The estimated incidence rate of TB among PLHIV has shown a decline from 2010 onwards, dropping from 22 to 8.9 cases per 100 000 population per year in 2021 (−60%) [1]. From 2020 to 2021, the estimated TB incidence rate increased in five out of six WHO regions, reflecting the impact of the COVID-19 pandemic (figure 1). In the African region, estimated TB incidence still declined in 2021, thereby reaching the 2020 End TB Strategy milestone of a 20% decline in TB (compared with 2015). The European region is the only other region where this milestone has been achieved. All other regions have not yet achieved the goal of a 20% decline in incidence; several have a long way still to go [1].

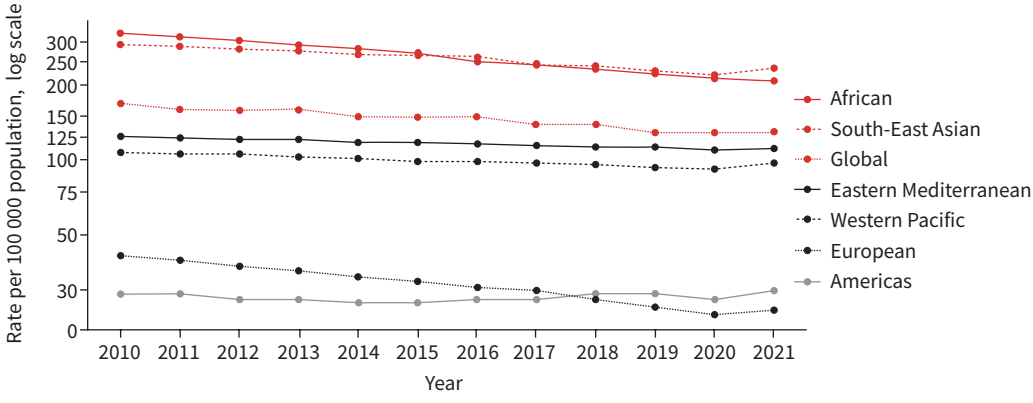

FIGURE 1 Incidence rate per 100 000 population during 2010–2021 in each of the WHO regions. Data from [8].

Men, women and children of all ages are susceptible to TB. However, in 2021, men accounted for the majority (56.5%) of TB cases, and in 2019, the age-standardised mortality rate was twice as large for HIV-negative men as for HIV-negative women in >107 countries [7]. Women and children (aged <15 years) accounted for 32.5% and 11% of TB cases, respectively [1]. The greater proportion of TB amongst men is consistent with the larger male/female ratios reported in national TB surveys. This could be related to differences in human biology, diagnostics, reporting or access to and use of TB services [1, 9–11]. However, more deaths and incident cases occur among HIV-positive women than HIV-positive men [7]. A likely explanation is the larger contribution of unsafe sex and partner violence in high HIV-endemic countries [7]. Among men, global estimated TB incidence is highest within the 25–54 years age group. Among adult women, those of reproductive age (aged 15–34 years) are most affected by TB [1]. A recent systematic review estimated a TB infection prevalence during pregnancy of 30–34% in high-burden settings [12]. Pregnancy has also been shown to increase the risk of TB infection or progression to TB [12, 13]. TB during pregnancy is associated with an increased risk of adverse outcomes for both mother and child [14]. Early diagnosis and treatment are essential to reducing TB-related maternal and neonatal mortality [15].

TB incidence estimates include both new TB episodes and episodes of relapse after treatment; both are referred to as incident TB cases. New and relapse patients accounted for 96% of all TB notifications in 2021. There are large differences between the yearly incidence estimates and the number of new and relapse case notifications (figure 2a); these differences reflect the proportion of people missed by the healthcare system, as well as under-notification of diagnosed patients and those commencing TB treatment. Four countries (India, Indonesia, the Philippines and Pakistan) accounted for over half of the gap between case notifications and estimated TB incidence [1].

The global proportion of new and relapse TB patients who were diagnosed with PTB and EPTB was 83% and 17%, respectively, in 2021. Approximately 5.3 million people worldwide were diagnosed with PTB in 2021, of which 3.34 million (63%) were bacteriologically confirmed. This was a significant rise on the almost-steady 57% of diagnosed PTB cases with bacteriological confirmation in 2010–2020 [1, 16, 17]. These proportions were largest in the American region (79%) and lowest in the Western Pacific region (56%). There is considerable

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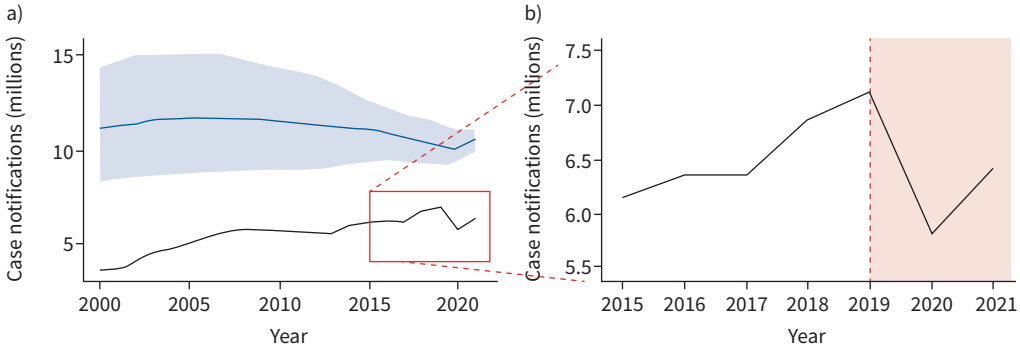

FIGURE 2 Trends in estimated case incidence (blue) and case notifications (black) of people newly diagnosed with TB in a) 2000–2021 and b) 2015–2021. The blue area represents the 95% uncertainty interval. The red area represents the period after the onset of the COVID-19 pandemic. Reproduced and modified from [8] with permission.

variation among countries, following a general trend of lower rates of bacterial confirmation in low-income countries and higher rates in high-income countries, where there is increased access to and quality of diagnostic tests.

In recent years, evidence has emerged of a new stage in the natural history of TB, called subclinical TB (defined in Box 1) [19–21]. Recent estimates show that ∼50% of individuals with bacteriological confirmation do not report TB-compatible symptoms [22, 23]. It remains uncertain how much subclinical TB cases contribute to global transmission and what implications this will have for TB prevention and treatment strategies [22, 24].

Mortality

The WHO TB mortality estimates are produced using different sources, including vital registration data and mortality surveys when available, or by multiplying incidence estimates by case fatality rates (CFRs) (mostly in low- and middle-income countries). For PLHIV, the WHO mortality estimates are calculated using treatment-adjusted CFRs. Higher CFRs are applied to undiagnosed (and thus untreated) TB patients.

BOX 1 Terminology definitions of TB and *Mycobacterium tuberculosis* infection, as defined by the latest WHO guidelines [18], and subclinical TB, as defined by the Stop TB Partnership [19]

TB
Clinical disease state resulting from *M. tuberculosis* infection; it is associated with symptoms and can be clinically diagnosed or bacteriologically confirmed.

TBI
State of persistent immune response to stimulation of *M. tuberculosis* antigens with no evidence of clinical manifestation of TB disease.

Subclinical TB
State of persistent immune response to stimulation of *M. tuberculosis* antigens with no evidence of clinical manifestation of TB disease. A positive result to TST or IGRA is frequently used as a proxy of TBI.

In 2021, there were ~1.4 million and 187 000 TB deaths in the HIV-negative population and PLHIV, respectively [1]. The estimated number of global TB deaths had fallen by 30% and 69% during the two decades preceding 2019 in the HIV-negative population and PLHIV, respectively [1, 6]. For PLHIV, this progress primarily related to massive distribution of ART and implementation of HIV preventive measures, along with intensified screening for TB among PLHIV [25, 26].

Between 2019 and 2021, the estimated number of TB deaths rose from 1.4 to 1.6 million (the same number of deaths recorded in 2017) [1]. The End TB Strategy set the target of a 35% reduction in TB mortality between 2015 and 2020; in 2021, only a 5.9% decline has been achieved.

Among the HIV-negative population, men, women and children (<15 years old) accounted for 54%, 32% and 14%, respectively, of the estimated global TB deaths in 2021 [1].

In the HIV-negative population, estimated TB mortality in men was highest in those aged ⩾35 years. In contrast, estimated TB mortality among HIV-negative women is highest between the age groups ranging from birth to 24 years [1]. This proportion of childhood deaths is higher than the 11% of estimated cases accounted for by children, indicating difficulties in TB diagnosis and treatment in children that result in disproportionate mortality rates [1].

The South-East Asian and African regions account for 82% of the total estimated TB mortality among the HIV-negative population and 86% of estimated TB deaths among PLHIV [1]. However, it is important to note that nearly all TB mortality estimates in the African region rely heavily upon TB incidence estimates, which may be subject to underdiagnosis, case underreporting and other biases.

MDR-TB

Drug resistance is a major threat to TB care and control. TB that does not respond to both rifampicin and isoniazid is referred to as MDR-TB; TB that does not respond to rifampicin is referred to as RR-TB. Globally, there were an estimated 450 000 incident cases of MDR/RR-TB in 2021 [1]. That is 13% less than 2015, but 3.1% more than 2020 [1]. This represents 3.6% of estimated new TB cases, whereas the proportion among previously treated TB cases was 18%. In addition to person-to-person transmission, TB drug resistance is the result of poor TB management [27–29]. Inappropriate treatment regimens, reduced drug quality (due to low-storage conditions) and poor treatment adherence can result in selection and spread of resistant *M. tuberculosis* mutants, leading to an increase in drug resistance [28]. The WHO European region has the highest estimated proportion of MDR/RR-TB among new and previously treated TB cases (26% and 57%, respectively) [1].

TB treatment coverage and outcomes

With treatment, most people who develop TB can be cured. The End TB Strategy target is minimal treatment coverage of 90% by 2025 [4]. WHO treatment coverage is approximated as the number of people reported with TB divided by estimated incidence; this will therefore exclude all unreported cases on treatment and include all reported cases off treatment. Over the last few years, the global treatment coverage (for both DR-TB and drug-susceptible TB) has shifted considerably, from 72% in 2019, to 59% in 2020, and 61% in 2021. For MDR/RR-TB the coverage levels are much lower, with an estimated one in three people developing MDR/RR-TB on treatment [1]. Approximately 70% of the gap in estimated incidence and treatment

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initiation for MDR/RR-TB is attributed to 10 countries, with India, Indonesia, the Philippines, Nigeria and Pakistan making up with more than half of this gap [1].

In 2020, the treatment success rate for first-line regimens was 86% overall; the rate is lower (77%) for PLHIV and higher (88%) in children (aged <15 years). WHO treatment success rates are calculated as the proportion of individuals whose outcome is either classed as cured (conversion to smear- or culture-negative) or treatment completed (completed treatment without of smear or culture results), among all bacteriologically confirmed and clinically diagnosed TB cases in the same period [30]. These rates have been almost constant over the last 20 years. The success rate for MDR/RR-TB treatment is lower overall but has improved in recent years, with success rates for second-line regimens in 2019 estimated at 60%, compared with 50% in 2012 [28]. Despite the COVID-19 pandemic, treatment success estimates in 2020 remained at the same level as 2019 (68%). Treatment outcomes measured for PLHIV diagnosed with TB in 2020 were: 77% success, 1.4% failure and 11% death. The remaining cases were either lost to follow-up or not evaluated [1]. In the global population (including both PLHIV and the HIV-negative population), treatment failure and death represented 0.7% and 4.2% of treatment outcomes, respectively. In children, the global treatment success rate in 2020 was 88% [31]. In MDR/RR-TB globally, treatment failure has remained more or less constant at 10% from 2012 to 2019 [31].

Costs

One of the End TB Strategy targets is the complete elimination of catastrophic costs related to TB for affected households [4]. The term "catastrophic cost" is used when over 20% of a household pre-TB annual income is used for TB-related expenditures (including income loss) [1]. This target was set to prevent financial and economic burden from impeding TB diagnosis and treatment. Currently, even though TB treatment is free of charge, over half of TB patients and their households face catastrophic costs as a result of the disease. The WHO has survey data for 27 countries on the percentage of TB households facing catastrophic costs, which show a broad range, from 13% in El Salvador to 92% in the Solomon Islands. For people with DR-TB the average was much higher, at 82% [1].

The impact of COVID-19

The COVID-19 pandemic set back the fight against TB by at least several years. At present, this impact is most acutely felt in a sharp decline in the number of people with newly diagnosed TB. Assuming this decrease indicates a reduction in diagnosis (and not a true decline in TB incidence), the number of undiagnosed and untreated TB cases in the community will accumulate, as transmission from undiagnosed cases in communities continues, and with some lag-time, the number of people dying from TB will rise. Model projections estimate an increase in TB mortality of up to 20% in high-burden settings over the next 5 years [1, 32]. The question remains whether a partial decline in TB notifications might represent a true reduction in TB incidence. The vast majority of this decrease is believed to be due to underreporting as TB care (equipment and health professionals) and funding were diverted to the COVID-19 response [33]; however, this does not preclude the possibility of a simultaneous decline in *M. tuberculosis* transmission due to COVID-19 mitigation measures.

In 2020, the number of TB case notifications fell by 18% (figure 2b), with a partial recovery in 2021 [34]. Among the 30 countries with a high TB burden and the three global TB watchlist countries (Cambodia, the Russian Federation and Zimbabwe, countries that exited the high-burden category but remain a priority for WHO support [1]), the highest relative reduction was seen in the Philippines, Lesotho, Indonesia, Zimbabwe, India, Myanmar and Bangladesh,

with TB-notification drops of ⩾20% [34]. The African region remarkably only showed a modest decline of 2.3% in 2020, with notification levels in 2021 above those of 2019 (figure 1) [34].

Declines in TB notifications were due to reduced access to TB services, along with increased stigma relating to the similarity between COVID-19 and TB symptoms [1, 35, 36]. These factors led to a decrease in the number of people seeking healthcare. At the same time, there were disruptions in the availability of medical care due to the enormous demands of the COVID-19 response on healthcare systems [37]. The result was that almost half of those with incident TB in 2021 were not diagnosed or treated – this was nearly 30% in 2019 (figure 2a) [1, 38]. In addition to disruptions to health services, people with TB were shown to be at additional risk of severe COVID-19 [39].

Along with the rise in TB mortality and the reduction in TB case notifications, the COVID-19 pandemic impacted the number of people accessing TB treatment (table 2), with a decline from 69% in 2019 to 58% in 2020, followed by a slight recovery to 61% in 2021 [31]. The number of people developing MDR/RR-TB was relatively stable throughout 2015–2020 but grew in 2020. This proportion partially recovered in 2021 but is not yet at pre-COVID-19 levels [1].

The COVID-19 pandemic also took a considerable toll on global funding for essential TB services and BCG vaccination [38], particularly in the American, South-East Asian and Western Pacific WHO regions [31]. This is consistent with reported reductions in childhood immunisation coverage, dropping from 86% in 2019 to 81% in 2021 [40]. In low- and middle-income countries, which account for 98% of the reported TB cases of 2021, investment in TB diagnostics, treatment and prevention dropped from US$6 billion in 2019 to US$5.4 billion in 2021, representing a further setback to reaching the global target for 2022 of US$13 billion [1].

While regions with a high TB burden did not necessarily feel the largest impact of the COVID-19 pandemic, they also did not have equal access to many of the tools used to counter the pandemic in other countries. For instance, by the end of January 2023, the African region only accounted for a cumulative 1.4% and 2.6% of all confirmed COVID-19 cases and deaths, respectively [41], which cannot be fully explained by underreporting or under-diagnosis [38, 42]. The COVID-19

TABLE 2 Number of people diagnosed and treated for TB/DR-TB, and TB deaths, in 2019–2021

	2019	2020	2021	Percentage change 2019–2021
TB				
Incidence estimate	10 300 000	10 100 000	10 600 000	2.9%
Case notifications[#]	7 120 000	5 830 000	6 420 000	−9.8%
Receiving preventive treatment	3 600 000	3 200 000	3 500 000	−2.8%
Treatment coverage[¶]	69%	58%	61%	−11.6%
MDR/RR-TB				
Incidence estimate	450 000	437 000	450 000	0.0%
Case notifications[#]	202 000	157 000	167 000	−17.3%
Receiving treatment	181 000	150 000	162 000	−10.5%
Treatment coverage[¶]	40%	34%	36%	−10.0%
TB deaths	1 400 000	1 500 000	1 600 000	14.3%

[#]: newly diagnosed. [¶]: estimated as TB notification divided by the TB incidence. Therefore, those who are diagnosed and reported but not treated are included; those who are diagnosed and treated but not reported are excluded. Data from [31, 34].

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pandemic laid bare the wide and existing inequities in global health. High-income countries raised funds for COVID-19 diagnostics, treatment and vaccination at an unprecedented speed. While this benefited those countries and significantly slowed the global pandemic, many of these tools still remain inaccessible to low-resource countries [41, 43]. Modelled projections provided by the WHO show a further increase in TB incidence and mortality in future years, emphasising the importance of redoubling our commitment in the fight against TB [1].

Inidividual and socioeconomic determinants of TB

Bringing an end to TB relies on effective prevention and treatment. This requires early detection, which in turn depends on the identification and screening of TB-exposed individuals. Together, these underscore the importance of quality diagnostic methods and treatment strategies [44]. However, this will not be enough to end the TB epidemic. Rates of TB infection and development can also be reduced by addressing the determinants of TB. These include individual health-related risk factors (such as HIV, diabetes and smoking) and broader socioeconomic determinants (such as poverty, working and living conditions, and lack of food security) [45]. Evidence of the role of socioeconomic risk factors in TB epidemiology continues to grow [46–50], with an impact on all stages, from risk of exposure to clinical outcome [51].

According to the latest estimates from the WHO, a high proportion of new TB cases can be attributed to five risk factors: undernourishment, HIV infection, alcohol-use disorders, smoking and diabetes (figure 3). The two largest contributors to new TB cases, undernourishment and HIV infection, show geographical overlap in the sub-Saharan African region (figure 4), resulting in a large burden of all three conditions [52]. The socioeconomic drivers of this burden include poverty, hunger, unemployment and homelessness [52].

Socioeconomic determinants

Socioeconomic determinants of health as defined by the WHO are non-medical factors that influence health outcomes [53]. For TB, the upstream socioeconomic determinants driving TB burden are elevated levels of migration, fast urbanisation and population increases. These determinants in turn lead to downstream inequalities, such as food security and undernutrition, poor housing conditions, and barriers to medical care (including insufficient funds, length of distance to facilities, and cultural restrictions) [51, 53]. The living environment affects exposure risk to TB. For instance, poor ventilation, overcrowding, and homelessness or housing instability increase the likelihood of exposure to *M. tuberculosis* and therefore increase the risk of TB

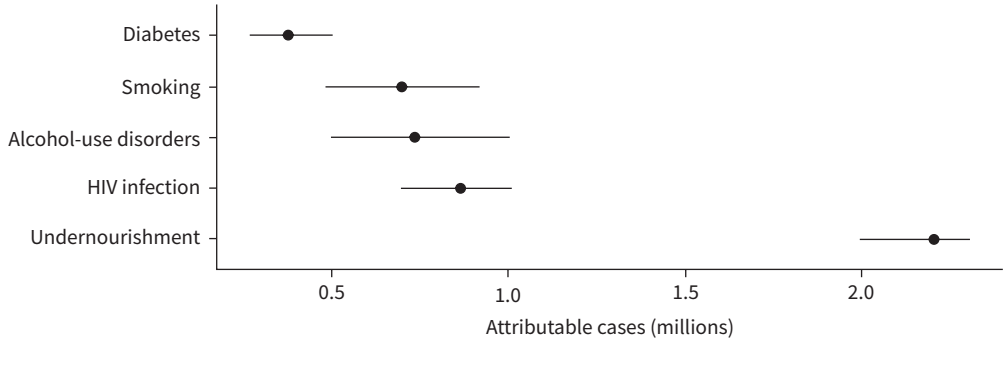

FIGURE 3 Estimated TB incidence attributable to the top five risk factors in 2021. Data points represent estimated attributed cases; bars represent 95% confidence intervals. Reproduced and modified from [44] with permission.

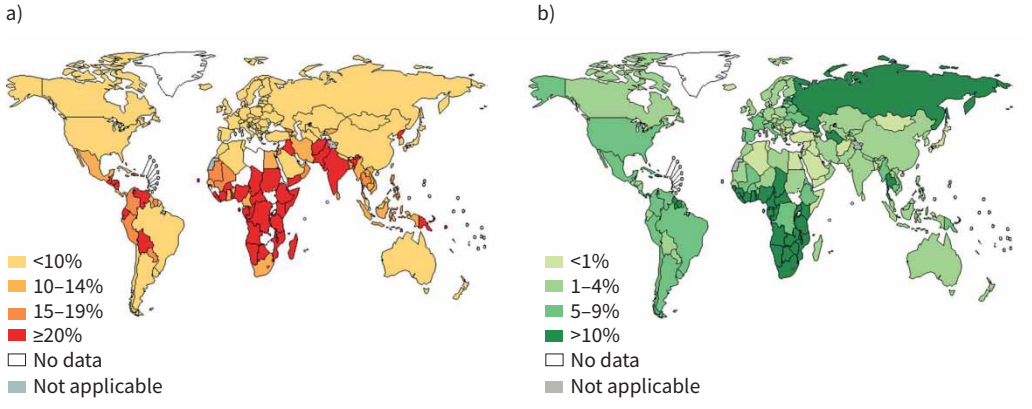

FIGURE 4 Percentage TB cases attributable to two risk factors in 2021: a) undernourishment and b) HIV infection. Reproduced and modified from [44] with permission.

infection [54]. Poverty and hunger increase susceptibility to both infection and progression to disease, along with the severity of TB [46]. There is a strong relationship between TB incidence and per capita gross domestic product [1].

Although TB can affect anyone, it is a prime example of a poverty-related disease. Being poor increases the risk and severity of TB, and suffering from TB increases the likelihood of impoverishment [55]. It is only by tackling the foundation causes of poor health, including poverty and the lack of social protection, that we can begin to accelerate the progress made towards ending TB [56, 57].

HIV, diabetes and undernourishment

Undernourishment is the primary population-level risk factor for TB globally (figure 4) [58], with an estimated population-attributable fraction of 2.2 million (20.8%) cases in 2021 [1]. The effect of undernutrition is acutely important in countries with high TB burden. For instance, in India (with 2.9 million new cases in 2021), undernourishment accounts for a quarter of TB cases (738 000 cases) [45]. Undernutrition, which is a physiological condition based on individual nutrition status (most commonly approximated as a body mass index of $<18.5\ kg \cdot m^{-2}$), is increasingly being used as a measure of TB risk instead of undernourishment, which is an indicator of chronic hunger at a national level [59]. Along with an increased risk of progression to TB, undernutrition (deficiency of both macro- and micronutrients) has been associated with higher disease severity, risk of treatment failure, relapse and even TB mortality [58, 60]. Poor treatment outcomes are hypothesised to be caused by changes in pharmacokinetics and pharmacodynamics of anti-TB drugs, along with a delayed and unregulated immune response, caused by impacted T-helper cell type 1 (Th) responses and reduced T-cell signalling [58, 61–63]. Reductions in treatment efficacy are likely to be a result of decreased absorption of some drugs (rifampin and isoniazid) and increased toxicity of others (such as aminoglycosides) [64–66]. Worryingly, food insecurity increased in 2020 due to the effects of the COVID-19 pandemic, with an estimated increase of 3.8%, which is almost equal to the previous 5 years combined (from 22.6% in 2014 to 26.6% in 2019) [67]. The impact of hunger is only expected to grow as climate change, global conflict and economic slowdown continue to affect the food security of vulnerable populations [67, 68].

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Comorbidities such as HIV, diabetes and other chronic illnesses that require the use of immunosuppressants for treatment or control can increase the likelihood of progression to TB after infection [44]. HIV increases the risk of TB and *vice versa* [69]. The cellular targets of HIV and *M. tuberculosis* play a key role in the effect HIV infection has on TB risk. Macrophages are the primary cells infected by *M. tuberculosis*, and are cleared with the help of CD4+ T-cells. HIV-1 infection is associated with CD4+ T-cell depletion, which increases the risk of TB in individuals living with HIV-1 [70]. Pro-inflammatory cytokines, such as INF-γ, TNF and IL-2, which are assumed to be key to CD4+ T-cell protection against *M. tuberculosis*, are also reduced in individuals with HIV-1 [69, 70]. A recent review by SHARAN *et al*. [71] summarised different mechanisms through which TB has been shown to exacerbate HIV. HIV is the second largest contributor to TB after undernourishment, accounting for 0.86 million cases in 2021 (figure 3). In that same year, ∼187 000 deaths among PLHIV accounted for 11.7% of all TB deaths [1]. TB incidence decreases for HIV patients on ART, but even with treatment, the risk of TB remains higher for PLHIV [69, 72].

Diabetes mellitus affects the integrity of the immune system, thereby increasing the risk of TB [73]. Metabolic changes in diabetic patients affect the function of neutrophils, macrophages, dendritic cells and natural killer cells, compromising the ability of the innate immune system to fight off *M. tuberculosis* infection [74]. The adaptive immune system is also affected by impaired antigen-presenting cells, along with an imbalanced cytokine profile that impacts T-cell differentiation in people with diabetes [74]. In 2021, 0.37 million TB cases were attributable to diabetes [45]. Diabetes has an effect on multiple stages of the course of TB, including faster progression to TB, an increase in symptom severity and an escalated likelihood of relapse, treatment failure and death [74–76].

Several studies have shown an association between vitamin D deficiency and increased TB risk [77–83]. Vitamin D deficiency has been linked to an increased risk of diabetes and could therefore have a deteriorating effect on the interaction between diabetes and TB [73]. The mechanism behind this is potentially through both the regulatory influence of vitamin D on insulin secretion and signalling, and the immunomodulatory effect of vitamin D, which involves binding to the macrophage receptor, thereby activating a cascade to kill intracellular *M. tuberculosis*. Vitamin D deficiency is a risk factor for both progression to TB and TB treatment outcomes [73].

Smoking and chronic use of alcohol

Tobacco and alcohol consumption have long been known to be risk factors for TB, with reports published as early as 1961 [84, 85]. Globally, in 2021, 0.74 and 0.69 million cases were attributable to alcohol-use disorders and smoking, respectively (figure 3) [45].

Tobacco smoking, passive smoking and exposure to indoor air pollution from burning biomass fuels are all risk factors for TB infection and disease [86, 87]. Both first- and second-hand smoking are risk factors for subclinical TB, unsuccessful treatment and TB-related death. The risk of TB shows a linear relationship with years of smoking [88]. Furthermore, smoking is associated with delayed smear and culture conversion, along with an increased probability of cavitary lesions [87, 89, 90]. Recent studies have shown elevated cure rates, reduced transmissibility, and reduced TB recurrence after smoking cessation compared with persistent smokers [91–93].

Alcohol use increases the rate of TB, treatment default, development of DR-TB and TB-related death [94–96]. Alcohol is also associated with a higher likelihood of adverse treatment outcomes in both drug-susceptible TB and MDR-TB patients [97]. The risk of TB increases as

TABLE 3 Relative risk of TB per risk factor

Risk factor	Relative risk	[Refs]
HIV infection	8.3–18	[46, 103]
Diabetes	1.5–3.1	[103, 104, 105]
Undernourishment	3.2–4.0	[46, 103]
Smoking	1.6–2.6	[92, 103]
Alcohol	2.9–4.9	[96, 103]
Solid organ transplantation	11.3–26.6	[106, 107]
Use of anti-TNF drugs	1.6–25.1	[108–111]

alcohol dosage increases, with evidence of a threshold effect (~40–60 g per day) [95, 98, 99]. Alcohol affects the innate and acquired immune system, thereby increasing susceptibility to progression to TB [100]. Alcohol-use disorders or heavy alcohol consumption can also lead to altered pharmacokinetics, thus affecting TB treatment [96]. There are behavioural pathways linking alcohol to an increased risk of TB and treatment failure through social marginalisation and drift, resulting in social exclusion, financial deterioration and increased likelihood of treatment interruption [96].

Solid organ transplantation and the use of TNF-α inhibitors

Organ transplantation can pose a TB risk in two ways: 1) activation of incipient or subclinical TB in the recipient (and in rare cases, the donor tissue), due to the use of immunosuppressive drugs, and 2) *de novo* infection with *M. tuberculosis* [101]. A systematic review of 60 studies on TB post-transplantation found a pooled prevalence of TB of 3% [102]. The relative risk of TB infection for solid organ transplantation patients ranged 11.3–26.6 compared with the general population, usually measured over the first 2 years following immunosuppression (table 3). Immunosuppression therapy is used to prevent recipients from rejecting their donor organ. However, this also impairs the body's ability to control TB infection [101].

TNF-α inhibitors are often used to treat immune or inflammatory diseases such as rheumatoid arthritis or inflammatory bowel disease. TNF-α antagonists have been shown to increase TB risk by up to 25 times (table 3). This elevated risk is true for both high- and low-endemic regions. TNF-α is an important immune mediator that helps the host control *M. tuberculosis* infection by inducing bactericidal activity of macrophages through production of reactive nitrogen and oxygen intermediates, along with the upregulation of chemokine secretion [112]. The use of TNF-α blockers can therefore have an adverse effect on these immune responses and increase the risk of progression to TB [113]. This is most commonly associated with monoclonal antibody TNF-α inhibitors such as infliximab and adalimumab.

Other risk factors

Additional risk factors for TB infection include occupational exposure to TB among healthcare workers [114]. Other conditions increase the risk of progression from infection to disease. These include silicosis (RR 4–30) [115, 116], kidney failure (RR 10–25) [117, 118], rheumatoid arthritis (RR 2–16) [111] and cancer (RR 2–40) [119–121]. In each of the conditions, the immune system is affected by the required treatment, making the patient less capable of self containing *M. tuberculosis* infection. Finally, previous TB is a risk factor for TB disease [122]. Recurrent TB episodes, which are the result of exogenous TB infection or relapse after cure, are not uncommon. A recent cohort study in South Africa showed TB recurrence rates of 1.64 per 100 person-years and increases in risk with each recurrent episode [123].

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Conclusion

While substantial progress has been made in the field, the COVID-19 pandemic has caused major setbacks in TB control. The cycle of poverty and disease has worsened due to the joint epidemics of COVID-19 and TB. In addition, increasing poverty and hunger, comorbidities such as HIV, diabetes and the use of immunosuppressants, and behavioural risk factors such as smoking and alcohol consumption are expected to continue to contribute to TB epidemics globally. To change the tide and restore progress toward the elimination of TB, a multifaceted approach will be necessary. The global community must commit additional resources towards supporting a holistic approach that addresses the societal, personal and medical needs that would curb the TB epidemic.

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