The global burden of tuberculosis: results from the Global Burden of Disease Study 2015

GBD Tuberculosis Collaborators

Summary

Background
An understanding of the trends in tuberculosis incidence, prevalence, and mortality is crucial to tracking of the success of tuberculosis control programmes and identification of remaining challenges. We assessed trends in the fatal and non-fatal burden of tuberculosis over the past 25 years for 195 countries and territories.

Methods
We analysed 10 691 site-years of vital registration data, 768 site-years of verbal autopsy data, and 361 site-years of mortality surveillance data using the Cause of Death Ensemble model to estimate tuberculosis mortality rates. We analysed all available age-specific and sex-specific data sources, including annual case notifications, prevalence surveys, and estimated cause-specific mortality, to generate internally consistent estimates of incidence, prevalence, and mortality using DisMod-MR 2.1, a Bayesian meta-regression tool. We assessed how observed tuberculosis incidence, prevalence, and mortality differed from expected trends as predicted by the Socio-demographic Index (SDI), a composite indicator based on income per capita, average years of schooling, and total fertility rate. We also estimated tuberculosis mortality and disability-adjusted life-years attributable to the independent effects of risk factors including smoking, alcohol use, and diabetes.

Findings
Globally, in 2015, the number of tuberculosis incident cases (including new and relapse cases) was 10·2 million (95% uncertainty interval 9·2 million to 11·5 million), the number of prevalent cases was 10·1 million (9·2 million to 11·1 million), and the number of deaths was 1·3 million (1·1 million to 1·6 million). Among individuals who were HIV negative, the number of incident cases was 8·8 million (8·0 million to 9·9 million), the number of prevalent cases was 8·9 million (8·1 million to 9·7 million), and the number of deaths was 1·1 million (0·9 million to 1·4 million). Annualised rates of change from 2005 to 2015 showed a faster decline in mortality (–4·1% [–5·0 to –3·4%]) than in incidence (–1·6% [–1·9 to –1·2%]) and prevalence (–0·7% [–1·0 to –0·5%]) among HIV-negative individuals. The SDI was inversely associated with HIV-negative mortality rates but did not show a clear gradient for incidence and prevalence. Most of Asia, eastern Europe, and sub-Saharan Africa had higher rates of HIV-negative tuberculosis burden than expected given their SDI. Alcohol use accounted for 11·4% (9·3–13·0) of global tuberculosis deaths among HIV-negative individuals in 2015, diabetes accounted for 10·6% (6·8–14·8), and smoking accounted for 7·8% (3·8–12·0).

Interpretation
Despite a concerted global effort to reduce the burden of tuberculosis, it still causes a large disease burden globally. Strengthening of health systems for early detection of tuberculosis and improvement of the quality of tuberculosis care, including prompt and accurate diagnosis, early initiation of treatment, and regular follow-up, are priorities. Countries with higher than expected tuberculosis rates for their level of sociodemographic development should investigate the reasons for lagging behind and take remedial action. Efforts to prevent smoking, alcohol use, and diabetes could also substantially reduce the burden of tuberculosis.

Funding
Bill & Melinda Gates Foundation.

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Introduction
Tuberculosis kills more than 1 million people every year, most of them in low-income and middle-income countries. An understanding of the trends in tuberculosis incidence, prevalence, and mortality is crucial to track the success of tuberculosis control programmes and to identify remaining intervention challenges for tuberculosis care and prevention. Rigorous evaluation of these trends is, however, challenging. The primary data sources used to estimate the epidemiological burden of tuberculosis, including annual case notifications, prevalence surveys, and cause of death data, have various shortcomings. Also, their availability differs across regions and time periods.

In countries where tuberculosis is endemic, health and surveillance systems are usually weak, with underdiagnosis and under-reporting common. Prevalence surveys are designed to provide unbiased measures of tuberculosis prevalence, but low response rates and contamination of tuberculosis specimens affect the quality of these surveys. The validity of imputation methods to correct for low response rates in
Research in context

Evidence before this study

Tuberculosis is a leading cause of morbidity and mortality, especially in low-income and middle-income countries. The global burden of tuberculosis has been estimated by several groups, including the WHO Global TB Programme and the Global Burden of Diseases, Injuries, and Risk Factors Study 2013. However, the contribution of potentially modifiable risk factors to tuberculosis burden and how the burden changes as countries progress through the epidemiological transition have not been well characterised. We searched PubMed with the search terms “tuberculosis” AND (“burden” OR “estimates”) AND “trend”, with no language restrictions, for articles published up to Nov 21, 2017, which produced 17 studies that provided population-wide tuberculosis burden time trends (incidence, prevalence, or deaths), of which ten were at the country level, six were at the subnational level, and one was at the regional and country level. Of all studies, the most recent period assessed was 1999–2013 in Lebanon. None of these studies assessed the tuberculosis burden attributable to risk factors over time or the epidemiological transition.

Added value of this study

This study provides a comprehensive assessment of the trends in tuberculosis burden and the burden attributable to risk factors (smoking, alcohol use, and diabetes). Moreover, it includes analysis of the relationship between tuberculosis burden and Socio-demographic Index (a composite indicator based on income, education, and fertility developed for the Global Burden of Diseases, Injuries, and Risk Factors Study 2015) to enhance the understanding of a country’s tuberculosis status in the context of its sociodemographic position. It identifies key areas for prioritisation of resources and areas for further research and interventions.

Implications of all the available evidence

Whereas progress is being made in reduction of tuberculosis mortality, tuberculosis is still responsible for an enormous disease burden worldwide. Moreover, incidence is declining more slowly than mortality in many countries. Strengthening of health systems for early detection of tuberculosis and improvements in diagnostics, treatment, and follow-up should therefore be priorities. Countries where the burden of tuberculosis is higher than predicted by their sociodemographic development should work to investigate the reasons for the discrepancy and address them as appropriate. Efforts to prevent smoking, alcohol use, diabetes, and HIV are also likely to substantially reduce the global burden of tuberculosis.

Methods

Overview

The Global Burden of Disease (GBD) is a systematic, scientific effort to quantify the comparative magnitude of health loss due to diseases, injuries, and risk factors by age, sex, and geography over time. GBD 2015 includes 195 countries and territories, 11 of which (Brazil, China, India, Japan, Kenya, Mexico, Saudi Arabia, South Africa, Sweden, the UK, and the USA) were analysed at the subnational level. The conceptual and analytical framework for GBD, with details of the hierarchy of causes and risk factors, data inputs and processing, and analytical methods, has been published elsewhere. 

We summarise the methods used for analysis of the burden of tuberculosis.

prevalence surveys has been questioned; even in countries with a more than 90% response rate, imputation can increase the prevalence of smear-positive tuberculosis by 6–13%. The need for large sample sizes makes prevalence surveys expensive and hence they are carried out only intermittently or not at all by countries with a substantial burden. In many tuberculosis-endemic countries where reliable vital registration systems are unavailable, verbal autopsy is commonly used to measure cause-specific mortality. Verbal autopsy studies are prone to misclassification errors as they have to rely on information recalled by family members of the deceased. Given the imperfections in data sources, we propose that statistical triangulation of multiple data sources could provide a more robust assessment of tuberculosis epidemiology than has been done so far.

An assessment of the contribution of potentially modifiable risk factors is also a crucial input into tuberculosis control policy. Moreover, an assessment of how incidence, prevalence, and mortality change as countries progress through the epidemiological transition (ie, an epidemiological shift from communicable to non-communicable causes of disease burden related to sociodemographic development) can enhance understanding of a country’s tuberculosis status in the context of its sociodemographic position. Knowledge of which countries lag behind the sociodemographic development trajectory for these measures can inform both investments in research and subsequent intervention efforts that aim to meet the Sustainable Development Goal to end tuberculosis by 2030.

For the Global Burden of Diseases, Injuries, and Risk Factors Study 2015 (GBD 2015), we assessed the levels and trends in the fatal and non-fatal burden of tuberculosis over the past 25 years for 195 countries and territories. We also analysed the relationship between tuberculosis burden and Socio-demographic Index (SDI), a composite indicator based on income, education, and fertility and developed for GBD 2015. We also estimated tuberculosis deaths and disability-adjusted life-years (DALYs) attributable to the independent effects of risk factors including smoking, alcohol use, diabetes, and HIV.
Case definition
Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* complex. The case definition includes all forms of tuberculosis, including pulmonary and extrapulmonary tuberculosis, which are bacteriologically confirmed or clinically diagnosed. The International Classification of Diseases (ICD)-10 codes are A10–19.9, B90–90.9, K623, K93.0, M49.0, and P370, and the ICD-9 codes are 010–19.9, 137–379, 138.0–38.9, and 730.4–30.6. For HIV–tuberculosis, the ICD 10 code is B20.0.

Tuberculosis mortality among HIV-negative individuals
The appendix shows the input data, analytical process, and output from the analysis of tuberculosis mortality among HIV-negative individuals. Input data for this analysis included 106 911 site-years of vital registration data, 768 site-years of verbal autopsy data, and 361 site-years of mortality surveillance data. Country-specific data sources and citations are available online. The assessment and adjustment of vital registration data for completeness had been reported in detail previously.1 Vital registration data were adjusted for garbage coding (including ill-defined codes and use of intermediate causes) following GBD algorithms and classified HIV deaths (ie, HIV deaths being assigned to other underlying causes of death, such as tuberculosis or diarrhoea because of stigma or misdiagnosis). Country-specific data before and after garbage code redistribution are available in the online data visualisation tool. Verbal autopsy data in countries with high HIV prevalence (using an arbitrary cutoff of 5% age-standardised HIV prevalence) were removed because of a high probability of misclassification, as verbal autopsy studies have a poor ability to distinguish HIV deaths from HIV–tuberculosis deaths (ie, tuberculosis deaths among HIV-positive people).

We used our Cause of Death Ensemble modelling (CODEm) strategy,2,12–14 which has been widely used to generate global estimates of cause-specific mortality. The CODEm strategy evaluates potential models that apply different functional forms (mixed-effects models and spatiotemporal Gaussian process regression models) to mortality rates or cause fractions with varying combinations of predictive covariates. These covariates consist of alcohol consumption (litres of pure alcohol per person per year), diabetes (fasting plasma glucose concentration in mmol/L), education (years per person), health system access, lag-distributed income (LDI; gross domestic product per capita that has been smoothed over the preceding 10 years), the proportion of malnutrition (children younger than 5 years of age who are underweight), indoor air pollution prevalence, population density (people per km²), smoking prevalence, sociodemographic status, and a summary exposure variable (SEV scalar). The SEV scalar reflects the exposure to risk factors related to tuberculosis weighted by their relative risk value. The methods used to develop the SEV scalar covariate for GBD 2015 have been described in detail elsewhere.15 The ensemble of CODEm models that performed best on out-of-sample predictive validity tests was then selected.

HIV–tuberculosis mortality
To establish tuberculosis deaths in HIV-positive individuals, we first computed the fraction of HIV–tuberculosis deaths among all tuberculosis deaths using 144 country-years of high-quality vital registration data (appendix). Second, we calculated the proportion of HIV–tuberculosis cases among all tuberculosis cases with an HIV test result as reported in the WHO tuberculosis register. We used a mixed-effects regression on the logit of the proportion of HIV–tuberculosis cases among all tuberculosis cases to predict the proportions of HIV-positive tuberculosis cases for all locations and years, using an adult HIV death rate covariate and country random effects. Third, we assumed that the fraction of HIV–tuberculosis deaths among all tuberculosis deaths in each location and year ($D_{c,y}$) is a function of the prevalence of HIV–tuberculosis among tuberculosis cases ($P_{c,y}$) and that the relative risk (RR) of tuberculosis death among patients with HIV infection and tuberculosis can be generalised over time and between locations:

$$D_{c,y} = \frac{P_{c,y} \cdot RR}{P_{c,y} \cdot RR + 1 - P_{c,y}}$$

Solving the equation for RR gives:

$$RR = \frac{D_{c,y} \cdot P_{c,y} - D_{c,y}}{D_{c,y} \cdot P_{c,y} - P_{c,y}}$$

We took the RR from each location and year for which we had data for the fraction of HIV–tuberculosis deaths among all tuberculosis deaths to estimate a median RR. We then applied that median RR to the predicted proportions of HIV–tuberculosis cases among all tuberculosis cases to estimate the fraction of HIV–tuberculosis deaths among all tuberculosis deaths for all locations and years. Next, we calculated location-year-specific HIV–tuberculosis deaths ($Deaths_{HIV-\text{TB}c,y}$) using the following equation:

$$Deaths_{HIV-\text{TB}c,y} = \frac{D_{c,y} - Death_{5\text{TB}c,y}}{1 - D_{c,y}}$$

where $Deaths_{5\text{TB}c,y}$ is location-year-specific deaths from the CODEm tuberculosis HIV-negative model. Finally, we applied the age-sex pattern of the HIV mortality estimates to these HIV–tuberculosis deaths to generate HIV–tuberculosis deaths for all locations and years by age and sex. Since the HIV–tuberculosis deaths were estimated on the basis of the fraction of HIV–tuberculosis deaths among all tuberculosis deaths, the total number of HIV–
tuberculosis deaths could exceed the total number of HIV deaths in some locations. To avoid this occurrence, we applied a cap of 45% to the fraction of HIV–tuberculosis deaths among HIV deaths on the basis of the largest fraction reported in a review by Cox and colleagues and a systematic review and meta-analysis by Ford and colleagues. We estimate point prevalence for tuberculosis. Point prevalent cases represent people in the population who at any point during a given calendar year have active tuberculosis. We included data from prevalence surveys reporting on pulmonary smear-positive tuberculosis and bacteriologically positive tuberculosis. Because all forms of tuberculosis are included in notification data, we adjusted prevalence surveys to account for extrapulmonary cases. We predicted proportions of extrapulmonary tuberculosis among all tuberculosis cases for all locations and years by age and sex using data for the three forms of tuberculosis from the notification data and LDI as a covariate and applied them to data from prevalence surveys. We included a covariate to adjust smear-positive tuberculosis estimates to the value of bacteriologically positive tuberculosis. We found no systematic bias comparing data from studies that used both symptoms and chest x-rays as screening methods and studies that used only one of these methods. We therefore did not adjust these data but allowed DisMod-MR 2.1 to estimate the additional uncertainty associated with datapoints from studies that had used only one of the screening methods. Similarly, we added uncertainty to datapoints from subnational surveys. The method used to increase the uncertainty around datapoints in the dataset has been described in detail elsewhere. We also included the SEV scalar as a covariate for prevalence.

Non-fatal tuberculosis and HIV–tuberculosis

We used all available cause of death data, case notifications, and data from prevalence surveys to produce consistent estimates of tuberculosis epidemiology (appendix). From these inputs, we calculated priors (expected values) on excess mortality and remission to guide the model. We used DisMod-MR 2.1 to fit the GBD Bayesian meta-regression tool that adjusts for differences in methods between data sources and imposes consistency between data for different parameters. We explain in detail below the preparation of each of these data sources and the modelling in DisMod-MR 2.1.

We used the age-specific and sex-specific notifications (from WHO and our network of collaborators) in our modelling of tuberculosis incidence. Our definition of incident cases include new and relapse cases diagnosed within a given calendar year. If the notification data represented new and relapse cases combined, we used the data as they were. If cases were broken down by case type (new pulmonary smear-positive, new pulmonary smear-negative, new extrapulmonary, and relapse), we summed them to represent all forms of tuberculosis. Smear-positive notification data were missing for at least one age group for at least 1 year in 41 countries. These countries were from sub-Saharan Africa, Asia, Latin America and the Caribbean, north Africa and the Middle East, eastern, central, and western Europe, and high-income north America. Smear-negative and extrapulmonary tuberculosis data were missing for at least one age group for at least 1 year in almost all countries. We imputed missing age groups for three forms of tuberculosis notifications (pulmonary smear-positive, pulmonary smear-negative, and extrapulmonary). We increased smear-positive age-specific notifications by the proportions of smear-unknown and relapsed cases that were only reported at the country-level. Some countries reported pulmonary smear-negative positive cases only for selected years (eg, 67 countries in 2006 and 33 in 2012). Most of these countries were from sub-Saharan Africa and southeast Asia. We predicted missing smear-negative and extrapulmonary cases from adjusted smear-positive cases using a seemingly unrelated regression approach. We then added all three types of notifications. We categorised countries on the basis of WHO’s estimates of country-year-specific case detection rates (CDRs) into ten bins using a 5 year moving average. We assumed all high-income countries to be in the highest decile of CDR. For all other countries, we used covariates for their CDR decile as an initial guide for how much notifications need to be increased in DisMod-MR 2.1 to reflect the incidence of all tuberculosis. We then generated a final incidence estimate that is consistent with prevalence data and cause-specific mortality estimates using Bayesian meta-regression. We included SEV as a location-level covariate to help inform variation over year and geography, with priors that at higher SEV values, incidence increases.

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We therefore did not adjust these data but allowed DisMod-MR 2.1 to estimate the additional uncertainty associated with datapoints from studies that had used only one of the screening methods. Similarly, we added uncertainty to datapoints from subnational surveys. The method used to increase the uncertainty around datapoints in the dataset has been described in detail elsewhere. We also included the SEV scalar as a covariate for prevalence.

We matched each prevalence survey datapoint and tuberculosis cause-specific mortality rate (CSMR) among HIV-positive and HIV-negative individuals by location, year, age, and sex to calculate the excess mortality rate (EMR) as the ratio of CSMR to prevalence. We also matched each notification datapoint and tuberculosis CSMR by location, year, age, and sex to calculate EMR for data-rich countries (defined as countries with vital registration more than 95% complete for more than 25 years’ [appendix]), assuming a remission of 2—ie, an average duration of 6 months (1/0.5 years). We estimated priors on remission for countries where both incidence and prevalence data were available. We matched incidence and prevalence data by location, year, age, and sex and calculated remission as the ratio of incidence to prevalence minus the EMR. We ran two DisMod-MR 2.1 models, one for data-rich countries using the assumed remission, and another for remaining countries for which we used the estimated priors on remission. To reflect a gradient in EMR and remission, we added the log-transformed LDI as a covariate, with priors that as LDI values increase, EMR decreases and remission increases. For final results, we combined results from the two DisMod-MR 2.1 models. β coefficients and exponentiated values for covariates from the two models are shown in the appendix.
For each location, we included the following inputs in the DisMod model: case notifications representing all forms of tuberculosis, prevalence survey data (adjusted for extrapulmonary tuberculosis) if available, excess mortality priors, remission priors, and cause-specific mortality estimates (tuberculosis and HIV–tuberculosis combined) by age and sex. DisMod-MR 2.1 generated internally consistent estimates for each 5-year interval between 1990 and 2015 for 195 countries and territories.

As an example, the internally consistent modelling of tuberculosis (all forms) for male individuals in rural Gujarat, India, in 2015 is shown in the appendix. Statistical triangulation of death, prevalence, and adjusted notifications shows inconsistencies between data sources, as evident in the incidence model, showing a pattern in under-reporting increasing with age. The internally consistent modelling for each country and territory is available online.

The output from the DisMod-MR 2.1 model described above is for all forms of tuberculosis in HIV-negative and HIV-positive individuals. We applied the predicted location-specific and year-specific proportions of HIV–tuberculosis cases among all tuberculosis cases (as described in the HIV–tuberculosis mortality section above) to tuberculosis incident and prevalent cases from DisMod-MR 2.1 to generate HIV–tuberculosis incident and prevalent cases by location and year. Subsequently, we split the estimates on the basis of the age-sex pattern of estimated HIV prevalence by country-year to generate HIV–tuberculosis incident and prevalent cases for all locations and years by age and sex.

SDI
The methods used to develop the SDI for GBD 2015 have been described in detail elsewhere. Briefly, the SDI was computed on the basis of the geometric mean of three indicators: income per capita, average years of schooling, and total fertility rates. SDI scores were scaled from 0 (lowest income, lowest average years of schooling, and highest fertility) to 1 (highest income, highest average years of schooling, and lowest fertility), and each location was assigned an SDI score for each year. Average relationships between SDI and rates of tuberculosis incidence, prevalence, and mortality were estimated using spline regressions, which were then used to estimate expected values at each level of SDI. Five SDI quintiles were also created for country-year combinations. The results presented for SDI quintiles in this study reflect each country’s position based on its SDI values in 2015.

Comparative risk assessment
The basic approach for the GBD 2015 comparative risk assessment was to calculate the proportion of deaths and DALYs attributable to risk factors (eg, tuberculosis attributable to smoking) as a counterfactual to the hypothetical situation that populations had been exposed to a theoretical minimum level of exposure in the past. As in previous GBD studies, a set of behavioural, environmental and occupational, and metabolic risks were evaluated in GBD 2015. Inclusion of a risk–outcome pair was based on the evidence of convincing or probable causal relationship between the risk and the outcome. We had evidence for such a relationship between diabetes, alcohol use, and smoking and risk of tuberculosis. Some risk factors (eg, indoor air pollution and malnutrition) have been hypothesised to have a strong link with tuberculosis, but we did not quantify the burden attributable to these risk factors because of insufficient evidence of a causal relationship. For example, evidence for indoor air pollution was based on cross-sectional studies (which are limited by their inability to establish a temporal relationship) and case-control studies (which are prone to recall bias as none of the studies measured indoor air pollution objectively).

To date, we have not quantified the contribution of other classes of risk factors (eg, social, cultural, economic, and genetic factors).

DALYs were computed as the sum of years of life lost and years lived with disability for each location, age, sex, and year. Estimates of attributable DALYs (or number of deaths) were computed by multiplying DALYs (or number of deaths) for the outcome by the population-attributable fraction (PAF) for the risk-outcome pair for a given age, sex, location, and year. Full details of methods used in the comparative risk assessment have been reported elsewhere and are also provided in the appendix. To generate estimates of alcohol consumption in g per day, data from population surveys were used in combination with estimates of per-person consumption from the Food and Agriculture Organization and Global Information System on Alcohol and Health. For smoking, we included 2818 sources of primary data from the Global Health Data Exchange database. In addition to these primary data sources, we supplemented these data with secondary database estimates from the WHO InfoBase and International Smoking Statistics databases for sources for which primary data were unavailable. We included 281 sources from WHO InfoBase and 313 sources from International Smoking Statistics. For diabetes, we included 717 sources of population-based survey data identified through our systematic search of PubMed and the Global Health Data Exchange. A full list of data sources and citations for the three risk factors and RRIs for the associations between risk factors and tuberculosis are provided in the appendix.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
Results
Levels and trends of tuberculosis incidence, prevalence, and mortality

Globally, in 2015, 10·2 million (95% uncertainty interval [95% UI] 9·2 million to 11·5 million) tuberculosis incident cases occurred, 10·1 million (9·2 million to 11·1 million) prevalent cases occurred, and 1·3 million (1·1 million to 1·6 million) deaths from tuberculosis (HIV negative and HIV positive combined) occurred. Among individuals who were HIV negative, the number of incident cases was 8·8 million (8·0 million to 9·9 million), the number of prevalent cases was 8·9 million (8·1 million to 9·7 million), and the number of deaths was 1·1 million (0·9 million to 1·4 million). Globally, among HIV-negative individuals, more incident cases and deaths occurred in men than in women in most age groups (figure 1). The age-standardised tuberculosis incidence rate (per 100 000 people) among men (154·4 [140·0–172·2]) was 1·8 times higher than that among women (86·3 [78·0–97·4]), and the age-standardised tuberculosis mortality rate (per 100 000 people) among men (21·9 [16·5–29·5]) was about twice as high as that among women (10·8 [8·5–13·1]). We estimated that 690 262 (551 275–859 100) incident cases of tuberculosis, 612 183 (498 242–744 815) prevalent cases, and 69 681 (57 982–88 962) deaths from tuberculosis occurred among children younger than 15 years in 2015.

Age-standardised tuberculosis mortality rates (HIV negative and HIV positive combined) changed at –1·8% (95% UI –2·4 to –1·4) per year from 1990 to 2005, with accelerated improvements from 2005 to 2015 (–4·6% [–5·4 to –3·9] per year; appendix). The corresponding change among individuals who were HIV negative was –3·1% (–3·6 to –2·6) per year from 1990 to 2005 and –4·1% (–5·0 to –3·4) per year from 2005 to 2015 (table 1). A much slower decrease has occurred in global age-standardised tuberculosis incidence and prevalence annualised rates of change (ARCs) than in mortality rates among HIV-negative individuals. We observed a similar pattern when including HIV-positive individuals (appendix).

When examining ARCs by SDI quintile, we observed a gradient in ARCs for tuberculosis age-standardised mortality rates among HIV-negative individuals during the period 2005–15: ARCs ranged from –2·8% (95% UI –4·8 to –0·9) in the lowest SDI quintile to –7·2% (–7·9 to –6·5) in the highest quintile. We did not see a clear gradient, however, in ARCs for tuberculosis incidence and prevalence among HIV-negative individuals across the SDI quintiles (table 1). Across regions, in the period 2005–15, incidence ARCs among people who were HIV negative ranged from 0·3% (–0·4 to 1·1) in Australasia to –3·5% (–4·1 to –2·7) in eastern Europe (table 2). South Asia accounted for 35·8% of incident cases and 49·2% of deaths in 2015. Southeast Asia accounted for 14·6% of incident cases and 15·5% of deaths in 2015. In eastern Europe, during the period 1990–2005, mortality, incidence, and prevalence all increased. In the period 2005–15, however, the trends for all three indicators reversed to show decreasing trends.

Figure 2 shows maps of age-standardised incidence and death rates for tuberculosis in HIV-negative individuals in 2015. The age-standardised incidence rate of tuberculosis in HIV-negative people was more than 210 per 100 000 population in 17 countries in sub-Saharan Africa as well as India, Indonesia, and the Philippines. Death rates in HIV-negative individuals were more than 50 per 100 000 population in 25 countries in sub-Saharan Africa as well as Indonesia, Kiribati, Myanmar, and Nepal. Death rates varied greatly in north Africa and the Middle East, ranging from 0·1 (95% UI 0·1–0·2) per 100 000 in Palestine in 2015 to 30·1 (18·2–44·5) per 100 000 in Afghanistan. Detailed results, broken down by age and sex, are available online.

Observed versus expected tuberculosis incidence, prevalence, and mortality

Globally and in most regions, age-standardised tuberculosis incidence, prevalence, and mortality rates showed a steady decline with rising SDI (figure 3). Many regions (eg, southeast Asia, south Asia, central Asia, eastern Europe, Andean Latin America, and sub-Saharan Africa) had higher than expected incidence, prevalence,
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<td>Global</td>
<td>119·6</td>
<td>108·1-134·0</td>
<td>120·3</td>
<td>100·0-131·6</td>
<td>160</td>
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<td>-1·5%</td>
<td>-1·2%</td>
<td>-3·1%</td>
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<td>High SDI</td>
<td>28·2</td>
<td>25·7-32·0</td>
<td>16·3</td>
<td>15·2-17·5</td>
<td>13</td>
<td>1·3-1·4</td>
<td>-1·1%</td>
<td>-0·6%</td>
<td>-1·1%</td>
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<td>Middle SDI</td>
<td>89·1</td>
<td>80·1-101·3</td>
<td>84·7</td>
<td>76·5-93·6</td>
<td>57</td>
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<td>-0·7%</td>
<td>-3·9%</td>
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<tr>
<td>Low-middle SDI</td>
<td>57·8</td>
<td>43·2-76·3</td>
<td>17·6</td>
<td>13·9-19·4</td>
<td>17·3</td>
<td>10·6-22·7</td>
<td>-2·0%</td>
<td>-1·8%</td>
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<td>189·2</td>
<td>170·3-210·8</td>
<td>187·8</td>
<td>168·8-207·3</td>
<td>44·6</td>
<td>35·4-55·5</td>
<td>-2·4%</td>
<td>-1·9%</td>
<td>-3·6%</td>
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<tr>
<td>East Asia</td>
<td>294·4</td>
<td>241·0-346·9</td>
<td>210·9</td>
<td>183·4-235·5</td>
<td>44·2</td>
<td>34·0-54·0</td>
<td>-2·7%</td>
<td>-1·9%</td>
<td>-3·6%</td>
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<td>South Asia</td>
<td>207·8</td>
<td>192·8-229·7</td>
<td>228·7</td>
<td>213·4-245·6</td>
<td>35·1</td>
<td>29·4-66·5</td>
<td>-2·9%</td>
<td>-2·8%</td>
<td>-4·0%</td>
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<tr>
<td>Oceania</td>
<td>72·7</td>
<td>65·1-82·3</td>
<td>48·0</td>
<td>42·7-54·2</td>
<td>8·0</td>
<td>6·4-13·8</td>
<td>-7·0%</td>
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<td>Central Asia</td>
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<td>-2·8%</td>
<td>-5·6%</td>
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<tr>
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<td>21·0-28·6</td>
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<td>23·4-29·4</td>
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<td>11·1</td>
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<td>-0·9-0·4</td>
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<td>124·4-169·0</td>
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<td>8·8-16·0</td>
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<td>123·4-162·7</td>
<td>134·3</td>
<td>122·4-147·8</td>
<td>40·3</td>
<td>32·2-60·6</td>
<td>-1·1%</td>
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Table 1: Age-standardised rates of tuberculosis incidence, prevalence, and mortality per 100 000 population and annualised rates of change in HIV-negative individuals.
## Incidence, prevalence, and deaths in 2015

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<th>Deaths</th>
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<td>(9 090 679 to 13 927 892)</td>
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<td>35 162</td>
<td>7 270</td>
</tr>
<tr>
<td>(71 440 to 79 143)</td>
<td>(32 791 to 37 782)</td>
<td>(58 006 to 77 825)</td>
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<td>13</td>
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<tr>
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<td>(13 424 to 16 361)</td>
<td>(3 672 to 4 929)</td>
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<td>1 983</td>
<td>948</td>
<td>63</td>
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<td>(838 to 1 058)</td>
<td>(54 to 74)</td>
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<td>322</td>
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<td>(63 414 to 7 5385)</td>
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<td>(4 010 554 to 7 634 44)</td>
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<td>746</td>
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### Annualised rate of change (%)

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<td>(3.7% to 4.3%)</td>
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(Tables 2 continues on next page)
### Incidence, prevalence, and deaths in 2015

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### Annualised rate of change (%)

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<th>Prevalence</th>
<th>Deaths</th>
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<td>(21 615 to 25 456)</td>
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Incidence, prevalence, and deaths in 2015

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| Articles     | Published online December 6, 2017 | http://dx.doi.org/10.1016/S1473-3099(17)30703-X |

www.thelancet.com/infection
### Incidence, prevalence, and deaths in 2015

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<th>Deaths</th>
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### Annualised rate of change (%)

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### Incidence, prevalence, and deaths in 2015

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### Annualised rate of change (%)

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### Incidence, prevalence, and deaths in 2015

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### Annualised rate of change (%)

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### Incidence, prevalence, and deaths in 2015

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#### Annualised rate of change (%)

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</tr>
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<td>Zimbabwe</td>
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<td>Western sub-Saharan Africa</td>
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<td>-0·8%</td>
</tr>
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<td>Benin</td>
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<td>Burkina Faso</td>
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Data in parentheses are 95% uncertainty intervals.

Table 2: Tuberculosis incidence, prevalence, and deaths and annualised rates of change of age-standardised rates in HIV-negative individuals.
**Incidence per 100 000 population**

- <10·6
- 10·6 to <19·1
- 19·1 to <26·1
- 26·1 to <35·0
- 35·0 to <53·7
- 53·7 to <75·1
- 75·1 to <105·8
- 105·8 to <157·3
- 157·3 to <210·7
- 210·7 to 951·8

**Mortality per 100 000 population**

- <0·34
- 0·34 to <0·75
- 0·75 to <1·45
- 1·45 to <2·90
- 2·90 to <4·80
- 4·80 to <7·46
- 7·46 to <19·0
- 19·0 to <41·6
- 41·6 to <64·4
- 64·4 to 182·7

*Figures A and B show the distribution of incidence and mortality rates across different regions.*
and mortality rates, whereas a few others (eg, Oceania and north Africa and the Middle East) showed lower than expected levels over time (appendix). Of all regions in 2015, southern sub-Saharan Africa had the largest difference between observed and expected levels, although the observed mortality has begun to fall closer to expected levels since around 2007. The gaps between observed and expected incidence and mortality also gradually decreased over time in several other regions (eg, southeast Asia, south Asia, and Andean Latin America), but we observed little change in the gaps for central, eastern, and western sub-Saharan Africa. In east Asia, we observed little change in the gap between observed and expected levels of incidence and prevalence over time, although the observed mortality converged with expected levels during 2015. In eastern Europe, the observed incidence, prevalence, and mortality increased between 1990 and 2005 but has begun to fall closer to expected levels in the last decade.

Tuberculosis mortality and DALYs attributable to individual risk factors

Table 3 shows the global and regional tuberculosis deaths attributable to smoking, alcohol use, and diabetes in 2015 and the corresponding ARCs for age-standardised rates of death in individuals who are HIV negative (the appendix contains DALYs attributable to the three risk factors and ARCs). Globally, in 2015, among HIV-negative individuals, alcohol use accounted for 126 459 (95% UI 94 124–168 699) tuberculosis deaths, followed by diabetes (118 298 [73 111–169 308] deaths) and smoking (86 849 [41 265–140 152] deaths). The corresponding PAF due to alcohol was 11·4% (9·3–13·0), due to diabetes was 10·6% (6·8–14·8), and due to smoking was 7·8% (3·8–12·0), and we observed no significant difference between the PAFs due to these three risk factors (appendix). Age-standardised tuberculosis deaths attributable to smoking changed at a faster rate per year than did those attributable to alcohol use and diabetes from 2005 to 2015 (table 3).

Across regions, ARCs for age-standardised tuberculosis deaths attributable to smoking varied from –2·4% (–7·3 to 2·3) in central sub-Saharan Africa to –8·7% (–9·7 to –7·6) in eastern Europe and to alcohol use from –1·9% (–6·3 to 2·4) to –8·3% (–9·3 to –7·1). ARCs for age-standardised tuberculosis deaths attributable to diabetes varied from –1·3% (–5·3 to 2·3) in central sub-Saharan Africa to –8·6% (–10·0 to –6·8) in east Asia.

Figure 4 shows the age-standardised PAFs for global tuberculosis deaths due to the three risk factors among HIV-negative male and female individuals in 1990, 2005, and 2015 (the appendix contains PAFs for DALYs). The age-standardised PAFs for tuberculosis deaths due to smoking and alcohol use were between four times and six times higher among men than among women across all three timepoints, whereas they were similar between sexes for diabetes. In both men and women, PAFs for smoking, alcohol use, and diabetes did not change substantially from 1990 to 2005 and 2005 to 2015.

Discussion

Globally, substantial progress has been made in reducing mortality from tuberculosis. However, age-standardised tuberculosis incidence and prevalence are declining much more slowly than mortality in many countries. Despite a powerful interaction between tuberculosis and HIV, most tuberculosis cases and deaths occur among HIV-negative people in south and southeast Asia, where HIV prevalence is relatively low. Most of Asia, eastern Europe, and all of sub-Saharan Africa had higher tuberculosis burden than expected given their level of sociodemographic development.

Despite a decline in mortality from tuberculosis, an estimated 1·1 million deaths still occurred among HIV-negative individuals worldwide in 2015, along with 0·2 million deaths among HIV-positive individuals. Age-standardised mortality rates due to tuberculosis are declining at a slower pace than are those due to HIV and malaria. Where improved access to treatment probably reduced tuberculosis deaths, large funding gaps remain, with the largest gap being for multidrug-resistant (MDR) tuberculosis. WHO and the Global Fund to Fight AIDS, Tuberculosis and Malaria estimated that at least US$1·6 billion of international support was required annually to fill the funding gap for tuberculosis control between 2014 and 2016 in 118 low-income and middle-income countries. However, the growth rate of development assistance for tuberculosis has decelerated substantially since 2010, making it more challenging for health systems to reduce the burden of tuberculosis in low-income countries than in middle-income and high-income countries.

Tuberculosis incidence is either stagnant or declining more slowly than mortality in many tuberculosis-endemic countries, suggesting delays in diagnosis and treatment. One untreated patient with tuberculosis can infect many healthy contacts. Although only a small proportion of infected people progress to active tuberculosis, it is difficult to predict who will progress from latent infection to active disease. Early diagnosis of active tuberculosis is challenging; substantial delays in diagnosis and treatment have been linked to multiple factors, including absence of awareness of symptoms, absence of access to health services, shortages of trained clinicians and laboratory personnel to make the diagnosis, and poor diagnostic tools. High proportions of initial default (ie, never starting tuberculosis treatment) have been reported in...
settings relying on passive case finding.39–42 Community-wide active case finding aims to reduce barriers to early detection, but few studies have evaluated the cost-effectiveness of screening for active tuberculosis.43 Evidence suggests that compared with conventional smear microscopy, use of sputum Xpert-MTB/RIF (Cepheid, USA) substantially increases case detection (by almost 50%) during intensified case finding in high-burden community settings.44 Studies evaluating the cost-effectiveness of screening for active tuberculosis using new diagnostic tools, such as Xpert-MTB/RIF, would therefore be very useful. Tuberculosis incidence is also declining more slowly than mortality in various low-tuberculosis-burden countries, with some showing either stagnant or increasing trends in incidence. Several low-tuberculosis-burden countries do not have a national tuberculosis programme or elimination plan to guide control efforts.45

Our results showed a notable difference in the global age distribution of tuberculosis cases and deaths: cases were highest among young adults, but deaths were highest among old adults. This finding might be explained by a greater risk of reactivation of latent tuberculosis in younger adults as reported by longitudinal birth cohort studies46,47 and a higher risk of adverse reactions from anti-tuberculosis drugs48 and mortality in older people.49,50 Our results also showed that age-standardised incidence and mortality from tuberculosis were about twice as high in men than in women. Various explanations have been suggested for the sex difference in tuberculosis risk, including differential access to health care, differential exposure to risk factors (eg, smoking), and genetic variation.51–53 An understanding of the age–sex distribution of tuberculosis cases and deaths has implications for tuberculosis control programmes in terms of targeting of interventions to high-risk groups.

Risk factors also play an important part in the control of tuberculosis. For example, alcohol abuse has been linked to poor tuberculosis treatment compliance and outcomes.54–56 Moreover, tuberculosis risk factors, including diabetes, alcohol use, and smoking, could increase the risk of tuberculosis through suppression of the immune system, especially cell-mediated immunity.57–60 With an increase in diabetes prevalence as countries go through demographic and epidemiological transition,8 many low-income and middle-income countries will increasingly bear the double burden of tuberculosis and diabetes. Globally, in 2015, diabetes, alcohol use, and smoking together accounted for about a quarter of tuberculosis deaths and DALYs. Efforts to prevent these risk factors can therefore have a substantial collateral impact on the burden of tuberculosis.

Our method for computation of tuberculosis burden differs from that used by WHO and results in different estimates in some locations. At the global level, our tuberculosis (all forms) incidence estimate (10·2 million cases) is slightly lower than that of WHO (10·4 million cases) in 2015, but we estimate a higher proportion of HIV–tuberculosis (13%) than does WHO (11%).5 Our estimated number of all tuberculosis deaths (1·3 million) is lower than WHO’s estimate (1·8 million) for 2015. The WHO global prevalence estimates for 2015 were unavailable for comparison. At the country level, our list of countries with a high burden of tuberculosis is

Figure 3: Estimated observed and expected age-standardised rates of tuberculosis incidence (A), prevalence (B), and mortality (C) per 100 000 population among HIV-negative individuals based on SDI, 1990–2015

Each point on a line represents 1 year, starting at 1990 and ending at 2015. In all regions, SDI has increased year on year, so progress in SDI is associated with later years for a given region. The black lines indicate trajectories for each geography expected based on SDI alone. SDI=Socio-demographic Index.
### Tuberculosis deaths attributable to smoking, alcohol use, and diabetes and annualised rates of change of age-standardised rates in HIV-negative individuals (2005–15)

<table>
<thead>
<tr>
<th>Region</th>
<th>Tuberculosis deaths</th>
<th>Annualised rate of change from 2005 to 2015 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smoking</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Global</td>
<td>114 069</td>
<td>86 849</td>
</tr>
<tr>
<td>High SDI</td>
<td>6866</td>
<td>346</td>
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<tr>
<td>High-middle SDI</td>
<td>12 932</td>
<td>848</td>
</tr>
<tr>
<td>Middle SDI</td>
<td>42 667</td>
<td>37 491</td>
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<tr>
<td>Low-middle SDI</td>
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<td>34 828</td>
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<td>Low SDI</td>
<td>7 516</td>
<td>7 538</td>
</tr>
<tr>
<td>High-income Asia Pacific</td>
<td>10 422</td>
<td>6 311</td>
</tr>
<tr>
<td>Central Asia</td>
<td>11 257</td>
<td>7 155</td>
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<tr>
<td>East Asia</td>
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<td>16 697</td>
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<tr>
<td>South Asia</td>
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<td>4</td>
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<tr>
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<td>Andean Latin America</td>
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<td>100</td>
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<td>Tropical Latin America</td>
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<td>North Africa and the Middle East</td>
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<td>1197</td>
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<td>High-income North America</td>
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<tr>
<td>Oceania</td>
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<td>Eastern sub-Saharan Africa</td>
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<td>Southern sub-Saharan Africa</td>
<td>4071</td>
<td>1286</td>
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<tr>
<td>Western sub-Saharan Africa</td>
<td>2624</td>
<td>2726</td>
</tr>
</tbody>
</table>

Data in parentheses are 95% uncertainty intervals. SDI=Socio-demographic Index.

Table 3: Tuberculosis deaths attributable to smoking, alcohol use, and diabetes and annualised rates of change of age-standardised rates in HIV-negative individuals (2005–15)
WHO) would help reduce the discrepancy between GBD estimation (which is being increasingly facilitated by countries and efforts to use a common set of data for surveillance to generate more robust cause-of-death data. Until such systems are fully developed, vital registration systems is needed to improve the quality of time. Strengthening tuberculosis notification and concerns, ignorance of reporting procedure, and scarcity notification include, but are not limited to, confidentiality treated in the private sector are not notified; barriers to high-tuberculosis-burden settings, tuberculosis cases notification data, which increased with age). In many incidence model showed a pattern in under-reporting of and cause of death data in some countries (eg, the revealed discrepancies between notifications, prevalence, statistical triangulation of all sources of data for a country with use of a Bayesian meta-regression method. Our age-specific and sex-specific incidence, prevalence, ultimately based on the logical relationships between the data overall for different parameters and are are statistically consistent with that of WHO, with a few exceptions. The WHO top 20 high-burden countries as assessed by incident case numbers include Angola, Kenya, and North Korea, which in our list are replaced by Uganda, Ukraine, and Zimbabwe.

These discrepancies stem from differences in the methods used. WHO generated incidence estimates for 74 countries by adjusting notification data on the basis of expert opinion of the case detection rate. By contrast, our estimates of prevalence and incidence are driven by the statistical triangulation that enforces consistency between the data overall for different parameters and are ultimately based on the logical relationships between age-specific and sex-specific incidence, prevalence, remission, excess mortality, and cause-specific mortality with use of a Bayesian meta-regression method. Our statistical triangulation of all sources of data for a country revealed discrepancies between notifications, prevalence, and cause of death data in some countries (eg, the incidence model showed a pattern in under-reporting of notification data, which increased with age). In many high-tuberculosis-burden settings, tuberculosis cases treated in the private sector are not notified; barriers to notification include, but are not limited to, confidentiality concerns, ignorance of reporting procedure, and scarcity of time. Strengthening tuberculosis notification and vital registration systems is needed to improve the quality of data. Until such systems are fully developed, variation in estimates is unavoidable and should be appreciated by users of these estimates. Various interim improvement options have been suggested, including use of inventory studies to assess under-reporting of notification data and sample-based mortality surveillance to generate more robust cause-of-death data than so far possible. The availability of widely shared, high-quality data for low-income and middle-income countries and efforts to use a common set of data for estimation (which is being increasingly facilitated by WHO) would help reduce the discrepancy between GBD and WHO estimates.

Paediatric tuberculosis incidence has been estimated by different groups. We estimated that 690 262 (95% UI 551 275–859 100) incident cases of tuberculosis occurred among children aged younger than 15 years in 2015. Our estimate is lower than that from WHO (1 000 000 [900 000–1 100 000]) for both 2014 and 2015 and from Dodd and colleagues (847 000 [558 000–1 280 000]) for 2014. These differences are due to differences in the methods used. Dodd and colleagues used WHO tuberculosis prevalence data and demographic information to estimate childhood tuberculosis using a mathematical model. WHO combines the CDR adjustment approach (ie, incidence=notifications/estimated CDR) and the method of Dodd and colleagues to produce their childhood tuberculosis incidence estimates.

This study has several limitations. First, our assessment of tuberculosis mortality in countries without vital registration data is driven by verbal autopsy studies, which have modest sensitivity in identifying tuberculosis deaths. Verbal autopsy studies have poor ability to distinguish HIV deaths from HIV–tuberculosis deaths; for this reason, we excluded verbal autopsy data in countries with high HIV prevalence. We applied various modelling methods by assuming that countries in the same region have a similar age–sex distribution of the tuberculosis burden as do other countries in that region and using many different combinations of covariates to help predict for locations and years with sparse or no data. Estimates for a location with sparse data are reflected by wide uncertainty intervals. Tuberculosis mortality estimates could be improved in the future by inclusion of additional covariates that have proximal relationships with tuberculosis mortality (eg, prevalence of latent tuberculosis infection).

Second, a major challenge in our statistical triangulation exercise has been the difficulty of finding consistent estimates between tuberculosis death rates and prevalence data from surveys, particularly in sub-Saharan Africa, where we have few prevalence surveys and often no usable cause of death data because of high HIV prevalence.

Third, although we used Bayesian meta-regression to generate a final incidence estimate that is consistent with prevalence data and cause-specific mortality estimates, use of CDRs as covariates is controversial since they are based on expert opinion. We plan to avoid using CDRs in the next iteration of GBD.

Fourth, our analysis of the relationship between SDI and tuberculosis incidence, prevalence, and mortality cannot be interpreted as being causal as it only reflects the average historical correlation between SDI and each of the measures. SDI use might also be low in countries with high income inequality. The applicability of SDI could be enhanced in the future by taking into account social heterogeneity within countries.

Fifth, despite the biological plausibility of a strong link between malnutrition and tuberculosis, we have
not quantified the burden of tuberculosis attributable to malnutrition because of insufficient evidence of a causal relationship and a scarcity of information about the relative levels of malnutrition.21,22 We plan to assess the evidence for a causal relationship between low body-mass index in adults and risk of tuberculosis in a future iteration of GBD. We also have not quantified the burden of tuberculosis attributable to indoor air pollution since the evidence is based on cross-sectional (from which a causal relationship cannot be established) and case-control (none of which measured biofuel exposure objectively and were thus prone to recall bias) studies.23

Finally, in our modelling of tuberculosis, we did not separately examine the burden of MDR tuberculosis. Given the epidemiological and clinical importance of MDR tuberculosis, we plan to include MDR and extensively drug-resistant tuberculosis estimates in the next round of GBD estimation. Despite these limitations, we believe the methodological innovation with use of statistical triangulation of data sources has yielded more robust estimates than would be yielded from reliance on a single source of data. This approach could probably be further strengthened by incorporation of population-based surveys of latent tuberculosis infection and then modelling of the progression from latent tuberculosis infection to active tuberculosis disease. Estimation and mapping of tuberculosis incidence, prevalence, and deaths at a finer spatial resolution than current national and subnational estimates could also better inform surveillance and targeting of resources for interventions than at present.27

Strengthening of national surveillance systems to capture all tuberculosis cases is an important public health goal for all countries. Until this goal is achieved, statistical data triangulation methods will be needed to make use of the available data for tracking of the tuberculosis burden. Despite general progress in reduction of tuberculosis mortality, the disease is still an enormous burden globally. Strengthening of health systems for early case detection and improvement of the quality of tuberculosis care, including prompt and accurate diagnostics, early initiation and improvement of the quality of tuberculosis care, and strengthening of health systems for early case detection and improvement of the quality of tuberculosis care, including prompt and accurate diagnostics, early initiation of treatment, and routine follow-up, are priorities.27,23 Countries where the tuberculosis burden is higher than expected based on sociodemographic development should investigate the reasons for lagging behind and address them as appropriate. Efforts to prevent smoking, alcohol use, diabetes, and HIV will also probably have a substantial collateral impact on reduction of the burden of tuberculosis.

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