

Methods used by WHO to estimate the global burden of TB disease

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Abstract

This paper describes methodological details used by WHO in 2020 to estimate TB incidence and mortality. Incidence and mortality are disaggregated by HIV status, age and sex. Methods to derive MDR-TB burden indicators are detailed. Four main methods are used to derive incidence: *(i)* results from TB prevalence surveys (29 countries, 66% of global incidence); *(ii)* notifications in high-income countries adjusted by a standard factor to account for under-reporting and underdiagnosis (139 countries, 6% of global incidence) and *(iii)* national inventory studies (8 countries, 17% of global incidence); *(iv)* case notification data combined with expert opinion about case detection gaps (39 countries representing 11% of global incidence in 2019). Mortality was obtained from national vital registration systems of mortality surveys in 123 countries (60% of global HIV-negative TB mortality), and among 21 of them, based on estimates published by the Institute of Health Metrics and Evaluation. In other countries, mortality was derived indirectly from incidence and case fatality ratio.

1. Introduction

Estimates of the burden of disease caused by TB and measured in terms of incidence, prevalence and mortality are produced annually by WHO using information gathered through surveillance systems (case notifications and death registrations), special studies (including surveys of the prevalence of disease), mortality surveys, “inventory studies” of under-reporting of detected TB, in-depth analysis of surveillance and other data, expert opinion and consultations with countries. In June 2006, the WHO Task Force on TB Impact Measurement was established¹, with the aim of ensuring that WHO’s assessment of whether global targets were achieved should be as rigorous, robust and consensus-based as possible. The Task Force reviewed methods and provided recommendations in 2008, 2009, 2015, 2016 and most recently in April 2019.

2. Historical background

Historically, a major source of data to derive incidence estimates were results from tuberculin surveys conducted in children². Early studies showed the following relationship between the annual risk of infection denoted λ and the incidence of smear positive TB denoted I_{s+} : one smear positive case infects on average 10 individuals per year for a period of 2 years and a risk of infection of $10^{-2}y^{-1}$ corresponds approximately to an incidence rate of $50 \times 10^{-5}y^{-1}$. However, this relationship no longer holds in the context of modern TB control and in high HIV prevalence settings³. In addition to uncertainty about the relationship between λ and I_{s+} , estimates of incidence obtained from tuberculin surveys suffer from other sources of uncertainty and bias, including unpredictable diagnostic performance of the tuberculin test⁴, digit preference when reading and recording the size of tuberculin reactions⁵, sensitivity to assumptions about reaction sizes attributed to infection⁶, sensitivity to the common assumption that the annual risk of infection is age invariant, and lastly, sensitivity of overall TB incidence estimates to the assumed proportion of TB incidence that is smear positive.

A first global and systematic estimation exercise led by WHO in the early 1990s estimated that there were approximately 8 million incident TB cases in 1990 ($152 \times 10^{-5}y^{-1}$) and 2.6-2.9 million deaths ($46-55 \times 10^{-5}y^{-1}$)⁷. A second major reassessment was published in 1999⁸, with an estimated 8 million

incident cases for the year 1997 ($136 \times 10^{-5}y^{-1}$), and 1.9 million TB deaths ($32 \times 10^{-5}y^{-1}$). The most important sources of information were case notification data for which gaps in detection and reporting were obtained from expert opinion. In addition, data from 24 tuberculin surveys were translated into incidence and 14 prevalence surveys of TB disease were used.

3. Incidence

TB incidence has never been measured through population based surveys at national level because this would require long-term studies among large cohorts of people (hundreds of thousands), involving high costs and challenging logistics. Notifications of TB cases provide a good proxy indication of TB incidence in countries that have both high-performance surveillance systems (for example, there is little under-reporting of diagnosed cases) and where the quality of and access to health care means that few cases remain undiagnosed and overdiagnosis is limited. In the large number of countries where these criteria are not yet met, better estimates of TB incidence can be obtained from an inventory study. An inventory study aims at quantifying the level of under-reporting of detected TB cases; if certain conditions are met, capture-recapture methods can also be used to estimate TB incidence⁹.

The ultimate goal of TB surveillance is to directly measure TB incidence from national case notifications in all countries. This requires a combination of strengthened surveillance, better quantification of under-reporting and over-reporting (i.e. the number of newly diagnosed cases that are missed by surveillance systems and the number of cases over-diagnosed with TB) and universal access to quality health care (to minimize under-diagnosis of cases and overdiagnosis). A TB surveillance checklist developed by the WHO Global Task Force on TB Impact Measurement defines the standards that need to be met for notification data to provide a direct measure of TB incidence¹⁰.

Methods currently used by WHO to estimate TB incidence can be grouped into four major categories. Figure 1 shows the distribution of countries according to the four categories - in reality, methods are often combined to estimate entire time series and the shown distribution of countries reflects the dominant method used to estimate incidence over the most recent years:

1. **Results from TB prevalence surveys.** Incidence is estimated using prevalence survey results and estimates of the distribution characteristics of duration of disease, accounting for the impact of HIV coinfection and ART. This method is used for 29 countries, of which 28 have national survey data and one – India – has a survey in one state. The 29 countries accounted for 66% of the estimated global number of incident cases in 2019.

2. **Notifications in high-income countries adjusted by a standard factor to account for under-reporting, under-diagnosis and overdiagnosis/overreporting.** This method is used for 139 countries that comprise all high-income countries except Germany, the Netherlands and the United Kingdom, plus selected upper-middle income countries with low levels of underreporting, including Brazil, China and the Russian Federation. For three countries (France, Republic of Korea and Turkey) the adjustment was country specific, based on results from reports of underreporting. These 139 countries accounted for 6% of the estimated global number of incident cases in 2019.

3. **Results from inventory/capture-recapture studies.** This method is used for 8 countries: China, Egypt, Germany, Indonesia, Iraq, the Netherlands, the United Kingdom and Yemen. They accounted for 17% of the estimated global number of incident cases in 2019.

4. **Case notification data combined with expert opinion about case detection gaps.** Expert opinion, elicited in regional workshops or country missions, is used to estimate levels of under-reporting and under-diagnosis. Trends are estimated using either mortality data, surveys of the annual risk of infection or exponential interpolation using estimates of case detection gaps for three years. This method is considered generally unreliable and used when other methods are not applicable due to missing or poor quality data. In this report, this method is used for 39 countries that accounted for 11% of the estimated global number of incident cases in 2019.

The code implementing the different estimation methods is available at the following public repository: <https://github.com/glaziou/gtb2020>

Four main methods

Method 1 - Case notification data combined with expert opinion about case detection gaps.

Expert opinion, elicited in regional workshops, national consensus workshops or country missions, is used to estimate levels of under-reporting, over-reporting (false positive diagnoses that may occur

particularly in the context of systematic screening in populations with relatively low probability of TB disease) and under-diagnosis. Trends are estimated using either mortality data, national repeat surveys of the annual risk of infection or exponential interpolation using estimates of case detection gaps for specific years. The estimation of case detection gaps is essentially based on an in-depth analysis of surveillance data; experts provide their educated best guess about the range of the plausible detection gap g , and incidence I is obtained from

$$I = \frac{f(N)}{1 - g}, g \in [0, 1[$$

where N denotes case notifications, f denotes a cubic spline function in countries with large year-to-year fluctuations in N , or else, the identity function. The incidence series are completed using assumptions about changes in CFR over time in countries with evidence of improvements in TB prevention and care, such as increased detection coverage over time or improved treatment outcomes, ensuring that the following inequality holds

$$0 \leq \left| \frac{\Delta I}{\Delta t} \right| \leq \left| \frac{\Delta M}{\Delta t} \right|$$

where M denotes mortality.

A full description of the methods used in regional workshops where expert opinion was systematically elicited following an in-depth analysis of surveillance data is publicly available in a report of the workshop held for countries in the African Region (in Harare, Zimbabwe, December 2010)¹¹. In some countries, case reporting coverage changed significantly during the period 2000-2019 as a result of disease surveillance reforms (e.g. disease surveillance was thoroughly reformed after the SARS epidemic in China, the Ministry of Justice sector notified cases among prisoners in Russia starting in the early 2000s). Trends in incidence are derived from repeat tuberculin survey results in Bhutan, India and Yemen and from trends in mortality or case notifications.

Case proportions are assumed to follow a beta distribution, with parameters a and β obtained from the expected value E and variance V using the method of moments¹², as follows

$$\alpha = E \left(\frac{E(1 - E)}{V} - 1 \right) \tag{1}$$

$$\beta = (1 - E) \left(\frac{E(1 - E)}{V} - 1 \right)$$

Time series are built according to the characteristics of the levels of under-reporting and under-diagnosis that were estimated for specific reference years (three reference years in regional workshops conducted around 2010). A cubic spline extrapolation of V and E , with knots set at the reference years, is used for countries with low-level or concentrated HIV epidemics. In countries with a generalized HIV epidemic, the trajectory of incidence is based on the annual rate of change in HIV prevalence and time changes in the fraction F of incidence attributed to HIV, determined as follows

$$F = \frac{h(\rho - 1)}{h(\rho - 1) + 1} = \frac{\vartheta - h}{1 - h}$$

where h is the prevalence of HIV in the general population, ρ is the TB incidence rate ratio among HIV-positive individuals over HIV-negative individuals and ϑ is the prevalence of HIV among new TB cases.

If there are insufficient data to determine the factors leading to time-changes in case notifications, incidence are assumed to follow a horizontal trend going through the most recent estimate of incidence.

Limitations of the method based on eliciting expert opinion about gaps in case detection and reporting include a generally small number of interviewed experts; lack of clarity about vested interests when eliciting expert opinion; lack of recognition of over-reporting (due to over-diagnosis, e.g. in some countries implementing a large-scale systematic population screening policy that may result in many people with abnormal chest X-ray but no bacteriological confirmation of TB disease being notified and treated as new TB cases) or in countries where cases with confirmed non-TB mycobacteria were not systematically reviewed and those judged non-TB were not de-notified;

incomplete data on laboratory quality and high proportion of patients with no bacteriological confirmation of diagnosis are a potential source of error in estimates.

Method 2 - Results from TB prevalence surveys.

Two approaches were used to derive incidence from prevalence.

In a first approach, incidence is estimated using measurements from national surveys of the prevalence of TB disease combined with estimates of the duration of disease. Incidence is estimated as the prevalence of TB divided by the average duration of disease assuming epidemic equilibrium: let N denote the size of a closed population with the number of birth and deaths the same for a period $\Delta t > 0$, let C be the number of prevalent TB cases, P the prevalence rate so that $P = C/N$. Let m denote the rate of exit from the pool of prevalent cases through mortality, spontaneous self-cure or cure from treatment, and I the rate at which new cases are added to the pool. At equilibrium during the time period Δt and further assuming exponentially distributed durations d such that $d = m^{-1}$

$$I(N - C) = mC$$

$$I = \frac{mC}{N - C} = \frac{P}{d(1 - P)} \approx \frac{P}{d} \quad (3)$$

In practice, the average duration of presence in the pool of prevalent cases cannot be directly measured. For example, measurements of the duration of symptoms in prevalent TB cases that are detected during a prevalence survey are systematically biased towards lower values, since survey investigations truncate the natural history of undiagnosed disease. Measurements of the duration of disease in notified cases ignore the duration of disease among non-notified cases and are affected by recall biases.

Literature reviews have provided estimates of duration of disease in untreated TB cases from the pre-chemotherapy era (before the 1950s). The best estimate of the mean duration of untreated disease (for smear-positive cases and smear-negative cases combined) in HIV-negative individuals is about three years. There are few data on the duration of disease in HIV-positive individuals. The assumed distributions of disease durations are shown in Table 1.

A second approach consists of estimating disease duration using three compartments: susceptibles (S), untreated for TB (U) and treated for TB (T). The size of U and T is obtained from the results of the prevalence survey. Transition rates from U to T are determined as follows

$$\frac{dU}{dt} = IS - (\mu_u + \theta_u + \delta)U$$

$$\frac{dT}{dt} = \delta U - (\mu_t + \theta_t)T$$

Where I denotes Incidence, μ and θ denote mortality and self-cure (remission) or cure (with subscripts u and t indicating untreated and treated cases), respectively, δ denotes the rate of removal from U through detection and treatment. At equilibrium, the above two equations simplify to

$$I = \frac{U}{d_U}$$

$$\delta U = \frac{T}{d_T}$$

Disease duration (untreated) is obtained from

$$d_U = (1 - \pi) \frac{U}{T} d_T$$

where

$$\pi = 1 - \frac{\delta U}{IS}$$

is the proportion of incidence that dies or self-cures before treatment. π is assumed to be a distributed uniform with bounds 0 and 0.05¹³. Table 2 shows estimates of incidence from four recent prevalence surveys using this method.

Limitations of this method include the insufficient power of disease prevalence surveys to estimate the number of prevalent TB cases on treatment with sufficient precision. Further, in most surveys, cases found on treatment during the survey do not have a bacteriological status at onset of treatment

documented based on the same criteria as survey cases (particularly when culture or Xpert were not performed routinely). The method, however, provides more robust estimates of incidence compared with those obtained from expert opinion (method 1).

In countries with high-level HIV epidemics that completed a prevalence survey, the prevalence of HIV among prevalent TB cases was found systematically lower than the prevalence of HIV among newly notified TB cases, with an HIV prevalence rate ratio among prevalent TB over notified cases ranging from 0.07 in Rwanda (2012) to 0.5 in Malawi (2013). The HIV rate ratio was pooled using random-effects model fitting data from countries with data collected over the period 2012-2019, including Kenya, Malawi, Rwanda, Tanzania, Uganda, Zambia and Zimbabwe, using the R package metafor¹⁴ (Figure 2). The pooled ratio value is used to predict HIV prevalence in prevalent cases from HIV prevalence in notified cases in African countries that were not able to measure the prevalence of HIV among survey cases.

The above two methods to derive incidence from prevalence are compared in Table 3. It is not clear a priori which method will perform better. The second method requires a sufficient number of cases on treatment at the time of the survey (as a rule of thumb, at least 30 cases) to generate relatively stable estimates. When both methods can be applied (so far only in selected low-HIV settings), results from two methods may be combined in a statistical ensemble approach as follows:

The incidence rate obtained using method i is assumed distributed Beta with shape and scale parameters α_i+1 and β_i+1 , respectively, and determined using the method of moments based on equation 3: $I_i \sim B(\alpha_i+1, \beta_i+1)$ so that

$$\text{Prob}(x = \text{TB}) = \int_0^1 xB(\alpha_i, \beta_i) dx = \frac{\alpha_i + 1}{\alpha_i + \beta_i + 2}$$

The combined probability is then expressed as

$$\begin{aligned} \text{Prob}(x = \text{TB}) &= \frac{\sum \alpha_i + 1}{\sum \alpha_i + \sum \beta_i + 2} \\ \text{Var} &= \frac{(\sum \alpha + 1)(\sum \beta + 1)}{(\sum \alpha + \sum \beta + 2)^2 (\sum \alpha + \sum \beta + 3)} \end{aligned} \tag{4}$$

Indirect estimation of incidence from prevalence relies on a number of assumptions difficult to verify, including (i) epidemic in a stable state of equilibrium; (ii) correctly assumed distribution of disease duration for each case category; (iii) size of the unmeasured prevalence of clinically diagnosed TB and childhood TB correctly estimated.

Method 3 - Notifications in high-income countries adjusted by a standard factor to account for under-reporting and under-diagnosis.

TB surveillance systems from countries in the high-income group and other selected countries in the upper-middle income group are assumed to perform similarly well on average in terms of under-diagnosis and under-reporting. Exceptions include the Republic of Korea, where the under-reporting of TB cases has recently been measured using annual inventory studies and France, where the estimated level of under-reporting was communicated by public health authorities, based on unpublished survey results. In the United Kingdom and the Netherlands, incidence was obtained using capture-recapture modeling (see next section). Surveillance data in this group of countries are usually internally consistent. Consistency checks include detection of rapid fluctuations in notification rates and in the ratio of TB deaths / TB notifications (M/N ratio), which may be indicative of reporting problems.

Method 4 - Inventory studies, capture-recapture modelling.

This method was used for 7 countries: China, Egypt¹⁵, Indonesia, Iraq¹⁶, the Netherlands¹⁷, the United Kingdom¹⁸ and Yemen¹⁹. Capture-recapture modelling is considered in studies with at least 3 sources (lists) and estimation of between source dependences⁹. The surveillance gap (proportion of unreported incident cases) in the UK and the Netherlands was assumed time invariant. In Yemen, trends in incidence were derived from results of two consecutive tuberculin surveys²⁰. In Egypt, Indonesia and Iraq, trends were derived using methods described in section describing method 1.

Capture recapture modelling for estimating TB incidence requires the following six assumptions: (i) all cases should be observable (preclinical stages are rarely detected before they become symptomatic); (ii) low proportion of mismatches and matching failures, which typically requires a large sampling fraction; (iii) closed population during the study period (typically 3-6 months); (iv)

dependences between S data sources ($S \geq 3$) accounted for in the model design but S -way interaction assumed null - referrals between sources (e.g. clinic to lab) may imply an S -way interaction, invalidating the approach (of note, in many high-burden countries, there will not be 3 sources meeting requirements); (v) homogeneity of within-source observation probabilities across subpopulation groups such as defined by socio demographic characteristics; (vi) consistent case definitions across sources. It is anticipated that capture recapture may only be successfully implemented in very few high-burden countries planning an inventory study.

HIV-positive TB incidence

Provider-initiated testing and counselling with at least 50% HIV testing coverage is the most widely available source of information on the prevalence of HIV in TB patients. However, this source of data is affected by selection biases, particularly when coverage is closer to 50% than to 100%. As coverage of HIV testing continues to increase globally, biases will decrease. Other sources of information on the prevalence of HIV among new TB cases include sero-surveys of a random sample of newly diagnosed TB cases and HIV sentinel surveillance systems when they include TB as a sentinel group. The different data sources were combined using local polynomial regression fitting by weighted least squares, using weight values of 1 for data from a nationally representative survey, 0.2 for data based on HIV sentinel surveillance, and a value equal to testing coverage in the case of data from provider-initiated HIV testing with coverage greater than 50%, and zero weights when testing coverage was less than 50%. In countries with no surveillance data on HIV among TB cases, the prevalence of HIV was derived indirectly from the prevalence of HIV in the general population, based on the relationship between the prevalence of HIV in TB and the prevalence of HIV in the general population shown in Annex 2.

Disaggregation by age and sex

Estimates for men (males aged ≥ 15 years), women (females aged ≥ 15 years) and children (aged < 15 years) are derived as follows. Age and sex disaggregation of smear-positive tuberculosis case notifications has been requested from countries since the establishment of the data collection system

in 1995, but with few countries actually reporting these data to WHO. In 2006, the data collection system was revised to additionally monitor age disaggregated notifications for smear-negative and extrapulmonary tuberculosis. The revision also included a further disaggregation of the 0–14 age group category to differentiate the very young (0–4) from the older children (5–14). While reporting of age disaggregated data was limited in the early years of the data collection system, reporting coverage kept improving. For 2012 case notifications, age-specific data reached 99%, 83% and 83% of total smear-positive, smear-negative and extrapulmonary tuberculosis global case notifications. Finally in 2013, another revision of the recording and reporting system was necessary to allow for the capture of cases diagnosed using WHO-approved rapid diagnostic tests (such as Xpert MTB/RIF)²¹. This current revision requests the reporting of all new and relapse case notifications by age and sex.

While there are some nationwide surveys that have quantified the amount of under-reporting of cases diagnosed in the health sector outside the network of the NTPs^{15,17,22}, none have produced precise results by age. Small-scale, convenience-sample studies indicate that under-reporting of childhood tuberculosis can be very high^{23,24} but extrapolation to national and global levels is not yet possible. Plans for implementation of nationwide surveys are under way in selected countries to measure under-reporting of tuberculosis in children²⁵. However, producing estimates of TB incidence among children remains challenging primarily due to the lack of well-performing diagnostics to confirm childhood TB and the lack of age-specific, nationwide, robust survey and surveillance data.

In order to maintain consistency with the total TB incidence and its uncertainty, the approach to estimating TB incidence by age and sex sought to disaggregate the total incidence into the incidence in each age group and sex. For countries where incidence was based on either a capture-recapture study or a standard factor adjustment of notification, and the implied case detection ratio was over 85%, we disaggregated total tuberculosis incidence by age and sex in proportion to the notifications. For these countries, surveillance systems were assumed to function well enough to inform patterns by age and sex directly. We also disaggregated incidence proportionally to notifications in countries

where fewer than 1,000 TB cases were reported in total. In these countries, the stochasticity is strong and modelled estimates less appropriate.

For other countries, one million samples were from a country 'prior' for the proportion of incidence in each age and sex group, and the mean over samples where the implied incidence in every category exceeded the corresponding notifications was used. Where no samples had this property, the 100 samples with the smallest undershoot were used.

The prior for each country was based for adults on a hierarchical analysis for prevalence risk ratios was developed based on prevalence survey data and Horton et al's systematic review of prevalence sex ratios²⁶. This prior closely followed age and sex patterns for prevalence in countries with surveys, and made predictions (with greater uncertainty) for countries without prevalence surveys informing the age patterns with prevalence surveys in the same WHO region, and sex ratios from Horton's WHO region specific meta-analysis. The prior for children was based on based on a mathematical modelling approach that simulates the course of natural history of TB in children, starting from estimates of tuberculous infection in children as a function of demographic and adult TB prevalence and subsequently modelling progression to pulmonary and extra-pulmonary tuberculosis disease taking into account country-level BCG vaccination coverage and HIV prevalence²⁷. The disaggregation by sex in children was based on a random-effects meta-analysis of the sex ratio in notification data for children (0-14 years).

Finally, for a small number of countries the approach above generated results lacked face validity and a standard factor adjustment of notifications was used instead.

Incidence of TB due to *Mycobacterium bovis*

Mycobacterium bovis is the most common cause of bovine TB in cattle and zoonotic TB in people, globally. Incidence of zoonotic TB is calculated by applying TB incidence estimates from 2019 to the regional proportions of all TB cases that are estimated to be caused by *M. bovis*²⁸. A standard

deviation of 50% relative to the best estimate of each regional proportion was assumed when propagating uncertainty. Due to an absence of routine reporting in most countries where bovine TB is endemic, these proportions were drawn from scientific studies^{28,29} that lack regional representativeness. As a result, estimates have a large uncertainty range. Mortality (excluding TB deaths in HIV-infected individuals) was similarly calculated based on the same proportions but this time applied to aggregated estimates of TB mortality by WHO region, reduced by a 20% factor to account for a higher proportion of extra-pulmonary TB with lower case fatality. Given that other mycobacterial species can also cause zoonotic TB, the true incidence and mortality may be higher than these estimations. There is a need to strengthen surveillance of zoonotic TB in order to understand the true burden of disease. One of the major barriers for diagnosis is that the most commonly used laboratory tests for TB do not differentiate the *M. tuberculosis* complex into its separate species.

Bacteriologically confirmable TB incidence

Country-specific estimates of the number of incident cases of pulmonary TB that could be bacteriologically confirmed are produced as the product of a) estimated TB incidence b) observed country-specific proportion of notified cases diagnosed with pulmonary TB and c) expected proportion of pulmonary cases that could be bacteriologically confirmed if the best tests were used. The latter parameter is derived from the weighted average (83%) and standard deviation (5.9%) of the proportion of bacteriologically confirmed cases among pulmonary cases notified in the group of high-income countries in 2019.

4. Drug resistance

Global and regional estimates of the proportion of new and retreatment cases of TB that had MDR/RR-TB in 2019 were calculated using country-level information. If countries had reported data on the proportion of new and retreatment cases of TB that have MDR/RR-TB from routine continuous surveillance or an anti-TB drug resistance survey, the latest available data from the previous 15 years were used. For data from routine surveillance to be considered representative for new patients, two criteria must be met: (i) at least 80% of notified new pulmonary

bacteriologically-confirmed TB cases must have a documented DST result for at least rifampicin, and (ii) the ratio of pulmonary bacteriologically-confirmed TB cases classified as new versus unknown treatment history must be at least 4:1. For data from routine surveillance to be considered representative for retreatment patients, at least 80% of notified retreatment pulmonary bacteriologically-confirmed TB cases must have a documented DST result for at least rifampicin.

For countries that had no such data available, estimates of the proportion of new and retreatment cases of TB that had MDR/RR-TB were produced using modelling (multiple imputation by chained equations), based on available data from countries that were considered to be similar in terms of TB epidemiology. The observed and imputed estimates of the proportion of new and retreatment cases of TB that had MDR/RR-TB were then pooled to give a global estimate, with countries weighted according to their share of global notifications of new and retreatment cases.

RR-TB incidence

The following approach is considered, based the proportions of new (p_n) and retreated (p_r) patients with MDR/RR-TB:

1. Estimate the proportion r of relapses out of the sum of new and relapse cases;
2. Estimate f the cumulative risk for incident cases to receive a non-relapse retreatment (retreatment following previous treatment failure or return after default);
3. Approximate RR incidence as:

$$I_{rr} = I[(1 - f)p_n((1 - r) + r\rho) + fp_r]$$

where I is total TB incidence and ρ is the risk of MDR/RR-TB in relapses relative to previously untreated cases.

f may be estimated based on reported counts of cases disaggregated by treatment history over the most recent years.

HR-TB incidence

A similar approach as for RR-TB incidence is used to generate global estimates of Isoniazid-resistant (HR-TB) incidence. Country-specific estimates are not published due insufficient DRS data.

RR TB mortality

The VR mortality data reported to WHO by Member States does not differentiate between MDR-TB and non-MDR-TB as a cause of death (there is no specific ICD-9 or ICD-10 codes for MDR-TB, although countries such as South Africa have allocated two specific codes U51 and U52 to classify deaths from MDR-TB and XDR-TB respectively)³⁰. Therefore, a systematic review and meta-analysis of the published literature was undertaken to estimate the relative risk of dying from MDR-TB compared with non MDR-TB. We are assuming this relative risk of death is the same as that for MDR/RR-TB. The global estimate of MDR/RR-TB deaths is based on the following formula:

$$m = Mpr$$

Where:

m = global MDR/RR-TB mortality,

M = global TB mortality,

p = overall proportion of MDR/RR-TB among prevalent TB cases, approximated by the weighted average of the proportion of new and retreated cases that have MDR/RR-TB,

r = the relative risk of dying from MDR/RR-TB versus non-MDR/RR-TB.

Resistance to isoniazid

For data from routine continuous surveillance to be considered representative for isoniazid resistance among RR-TB patients, the two criteria described above for rifampicin must be met. Additionally, at least 80% of RR-TB cases must have a documented DST result for isoniazid.

Resistance to fluoroquinolones

For data from routine surveillance to be considered representative for second-line drug resistance among RR-TB patients, two criteria described above for rifampicin must be met. Additionally, at least 80% of RR-TB cases must have a documented DST result for fluoroquinolones. The average proportion of RR-TB cases with fluoroquinolone resistance is calculated by taking the ratio of identified fluoroquinolone-resistant cases among tested RR-TB cases. Errors are assumed to be binomial. The proportions of fluoroquinolone resistance are then pooled using country-specific estimates of RR-TB incidence as weights to generate a global estimate.

Prevalence from population-based surveys

The best way to measure the prevalence of TB is through national population-based surveys of TB disease^{31,32}. Measurements of prevalence are typically confined to the adult population, exclude extrapulmonary cases and do not allow the diagnosis of cases of culture-negative pulmonary TB.

TB prevalence all forms and all ages (P) is measured as: bacteriologically-confirmed pulmonary TB prevalence (P_p) among those aged ≥ 15 measured from national survey (P_a), adjusted for pulmonary TB in children (P_c) and the proportion e of extra-pulmonary TB all ages

$$P_p = cP_c + (1 - c)P_a$$

where c is the proportion of children among the total country population.

$$P = \frac{P_p}{1 - e}$$

The estimate of overall prevalence P is affected by sampling uncertainty (relative precision is typically about 20%), and uncertainty about e (of note, values for e vary widely among countries with high-performance TB surveillance) and P_c . The quality of routine surveillance data to inform levels of pulmonary TB in children and extra-pulmonary TB for all ages is often questionable.

5. Mortality

The best sources of data about deaths from TB (excluding TB deaths among HIV-positive people) are vital registration (VR) systems in which causes of death are coded according to ICD-10 (although the older ICD-9 and ICD-8 classification are still in use in several countries), using ICD-10: A15-A19 and B90 codes, equivalent to ICD-9: 010-018, and 137. When people with AIDS die from TB, HIV is registered as the underlying cause of death and TB is recorded as a contributory cause. Since one third of countries with VR systems report to WHO only the underlying causes of death and not contributory causes, VR data usually cannot be used to estimate the number of TB deaths in HIV-positive people. Two methods were used to estimate TB mortality among HIV-negative people:

- direct measurements of mortality from VR systems or mortality surveys (see Figure 3);
- indirect estimates derived from multiplying estimates of TB incidence by estimates of the CFR.

Estimating TB mortality among HIV-negative people from vital registration data and mortality surveys

As of July 2019, mortality data from 123 countries were used, representing 60% of the estimated number of TB deaths (among HIV-negative TB) globally in 2019.

Estimates for 21 countries (Figure 3), including India and for South Africa (adjusted for HIV/TB miscoding) were obtained from the Institute of Health Metrics and Evaluation at <http://ghdx.healthdata.org/gbd-results-tool>, readjusted to fit WHO mortality envelopes (the estimated number of deaths in total) by using a multiplication factor equal to the ratio of WHO to IHME envelopes. The median country-year envelope ratio (WHO/IHME) was 1.03 (interquartile range, 0.94-1.11) among 391 country-year data points.

Among the countries for which VR or mortality survey data could be used, there were 1586 country-year data points 2000–2019, after removing 120 country-year data points with insufficient data quality as estimated by WHO³³ (Figure 4).

Reports of TB mortality are adjusted upwards to account for incomplete coverage (estimated deaths with no cause documented) and ill-defined causes of death (ICD-9: B46, ICD-10: R00–R99)³³. It is assumed that the proportion of TB deaths among deaths not recorded by the VR system was the same as the proportion of TB deaths in VR-recorded deaths. For VR-recorded deaths with ill-defined causes, it is assumed that the proportion of deaths attributable to TB is the same as the observed proportion in recorded deaths. The adjusted number of TB deaths κ_a is obtained from the VR report κ as follows:

$$\kappa_a = \frac{\kappa}{v(1 - g)}$$

where v denotes coverage (i.e. the number of deaths with a documented cause divided by the total number of estimated deaths) and g denotes the proportion of ill-defined causes. The uncertainty related to the adjustment was estimated as follows:

$$\hat{\sigma} = \frac{\kappa}{4} \left[\frac{1}{v(1 - g) - 1} \right]$$

The uncertainty calculation does not account for miscoding, such as HIV deaths miscoded as deaths due to TB, except in South Africa.

Missing data between existing adjusted data points are interpolated. Trailing missing values are predicted using a Kalman smoother or using the last observation carried forward or in the case of leading missing values, the next observation carried backwards.

In 2019, 58% of global TB mortality (excluding HIV) was directly measured from VR or survey data (or imputed from survey or VR data from previous years). The remaining mortality was estimated using the indirect methods described in the next section.

Estimating TB mortality among HIV-negative people from estimates of case fatality rates and TB incidence

In countries lacking mortality data of the necessary coverage and quality, TB mortality is estimated as the product of TB incidence and the case fatality rate (CFR) after disaggregation by case type as shown in Table 4, following a literature review of CFRs by the TB Modelling and Analysis Consortium (TB-MAC):

$$M^- = (I^- - T^-)f_u^- + T^- f_t^- \quad (5)$$

where M denotes mortality, I incidence. f_u and f_t denote CFRs untreated and treated, respectively and the superscript denotes HIV status. T denotes the number of treated TB cases. In countries where the number of treated patients that are not notified (under-reporting) is known from an inventory study, the number of notified cases is adjusted upwards to estimate T accounting for under-reporting.

Figure 5 shows a comparison of most recent direct mortality estimates and indirect estimates obtained from the CFR approach for the same countries. Of note, countries with VR data tend to be of a higher socio-economic status compared with countries with no VR data where the indirect approach is used.

Estimating TB mortality among HIV-positive people

TB mortality among HIV-positive is calculated using equation 5, exchanging superscripts - with +. The case fatality ratios were obtained in collaboration with the TB Modeling and Analysis Consortium (TB-MAC), and are shown in Table 5. The disaggregation of incident TB into treated and not treated cases is based on the numbers of notified cases adjusted for under-reporting.

Direct measurements of HIV-associated TB mortality are urgently needed. This is especially the case for countries such as South Africa and Zimbabwe, where national VR systems are already in place. In other countries, more efforts are required to initiate the implementation of sample VR systems as an interim measure.

Disaggregation of TB mortality by age and sex

TB mortality is disaggregated by age and sex using the age- and sex-specific adjusted (for coverage and ill-defined causes) number of deaths from VR data in countries with high-quality vital registration systems in place (ie, where these data have been used to estimate the TB mortality envelope). For other countries, adult mortality is disaggregated by age, sex and HIV-infection status by applying CFRs to disaggregated incidence estimates, distinguishing CFR by anti-TB treatment status and HIV/ART status (see Tables 4 and 5). TB mortality in children for these countries is also estimated from TB incidence in children using a case-fatality based approach³⁴. This approach distinguishes case fatality children by age, anti-TB treatment status, and HIV/ART status. HIV-positive TB deaths in adults are distributed by age and sex proportional to age- and sex-specific HIV prevalence from UNAIDS estimates in such a way as to maintain the estimated total number of HIV-positive TB deaths.

Estimating deaths averted

An estimate of the number of deaths averted is obtained by comparing a counterfactual where all incident cases would be untreated, using CFRs for untreated TB shown in Table 1, to a factual of TB mortality as estimated using methods described above.

6. Estimation of uncertainty

There are many potential sources of uncertainty associated with estimates of TB incidence, prevalence and mortality, as well as estimates of the burden of HIV-associated TB and MDR-TB. These include uncertainties in input data, in parameter values, in extrapolations used to impute missing data, and in the models used. Uncertainty in population estimates is not accounted for.

Notification data are of uneven quality. Cases may be under-reported (for example, missing quarterly reports from remote administrative areas are not uncommon), misclassified (in particular, misclassification of recurrent cases in the category of new cases is common), or over-reported as a result of duplicated entries in TB information systems or due to over-diagnosis. The latter issues can only be addressed efficiently in countries with case-based nationwide TB databases that include patient identifiers. Sudden changes in notifications over time are often the result of errors or inconsistencies in reporting.

Uncertainty bounds and ranges are defined as the 2.5th and 97.5th percentiles of outcome distributions. The general approach to uncertainty analyses is to propagate errors in m real-valued random variables X by approximating a function $h(X)$ using second-order Taylor series expansion about its moments^{35,36}. Using matrix notation, the expected value $E[h(X)]$ and variance of $h(X)$ were approximated as follows:

$$E[h(X)] \approx h(E[X]) + \frac{1}{2!} tr H(h) \Sigma(X)$$

$$Var(h(X)) \approx \nabla(h) \Sigma(X) \nabla(h)^T + \frac{1}{2!} tr((H(h)) \Sigma(X))^2$$

where tr denotes the trace, $H(h)$ the Hessian matrix of partial second-order derivatives of $h(X)$ with respect to each $X_{i=1..m}$, $\nabla(h)$ the gradient matrix of partial first-order derivatives and $\Sigma(X)$ the joint covariance matrix of X .

7. Conclusion

The measurement methods described here can be combined to assess tuberculosis incidence and mortality, to evaluate progress towards targets for tuberculosis control and the SDGs for TB. Alternative TB burden estimation methods have been developed by the Institute of Health Metrics and Evaluation³⁷, with generally consistent results at the global level compared with WHO, but with marked differences in specific countries. Discrepancies in estimates from different agencies reflect

the questionable quality and completeness of the underlying data. Further convergence in estimates will result from improvements in measurements at country level. National control programmes should be able to measure the level and time trends in incidence through well-performing TB surveillance with universal access to health. In countries with incomplete routine surveillance, prevalence surveys of TB disease provide estimates of TB burden that do not heavily rely on expert opinion. The performance of TB surveillance should be assessed periodically¹⁰ and the level of under-reporting should be measured⁹ and minimized. Tuberculosis mortality will ideally be measured by counting deaths in a comprehensive vital registration system³³.

WHO's post-2015 global TB strategy, known as the End TB Strategy³⁸, has the goal of ending the global TB epidemic, with corresponding targets of a 90% reduction in TB deaths and an 80% reduction in the TB incidence rate by 2030, compared with 2015. Improved measurements through substantial investments in health information systems, TB surveillance and the broader SDG agenda will provide a firmer basis for monitoring progress towards the End TB Strategy targets and ultimate TB elimination.

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Annex 1 - Definitions

Incidence is defined as the number of new and recurrent (relapse) episodes of TB (all forms) occurring in a given year. Recurrent episodes are defined as a new episode of TB in people who have had TB in the past and for whom there was bacteriological confirmation of cure and/or documentation that treatment was completed.

Prevalence is defined as the number of TB cases (all forms) at the middle of the year.

Mortality from TB is defined as the number of deaths caused by TB in HIV-negative people occurring in a given year, according to the latest revision of the International classification of diseases (ICD-10). TB deaths among HIV-positive people are classified as HIV deaths in ICD-10. For this reason, estimates of deaths from TB in HIV-positive people are presented separately from those in HIV-negative people.

The **case fatality rate** is the risk of death from TB among people with active TB disease.

The **case notification** rate refers to new and recurrent episodes of TB notified for a given year. Patients reported in the *unknown history* category are considered incident TB episodes (new or recurrent).

Population estimates were obtained from the World Population Prospects, which is produced by the United Nations Population Division (UNPD, <http://esa.un.org/unpd/wpp/>). The UNPD estimates sometimes differ from those made by countries.

Annex 2 - Relationship between HIV prevalence in new TB cases and HIV prevalence in the general population

Let I and N denote incident cases and the total population, respectively, superscripts $+$ and $-$ denote HIV status, ϑ is the prevalence of HIV among new TB cases, h is the prevalence of HIV in the general population and ρ is the incidence rate ratio (HIV-positive over HIV-negative).

$$\rho = \frac{I^+/N^+}{I^-/N^-} > 1$$

$$\rho \frac{I^-}{I^+} = \frac{N^-}{N^+}$$

$$\rho \frac{I - I^+}{I^+} = \frac{N - N^+}{N^+}$$

$$\frac{I^+}{I} = \frac{\rho \frac{N^+}{N}}{1 + (\rho - 1) \frac{N^+}{N}} = \vartheta$$

$$\vartheta = \frac{h\rho}{1 + h(\rho - 1)}$$

The TB incidence rate ratio ρ can be estimated by fitting the following linear model with a slope constrained to 1

$$\log(\hat{\rho}) = \log\left(\frac{\vartheta}{1 - \vartheta}\right) - \log\left(\frac{h}{1 - h}\right), (\vartheta, h) \in]0, 1[$$

Annex 3 - Implementation steps

The methods described in the paper were implemented in the following steps:

1. Reviewing available prevalence measurements from surveys, adjusting for childhood TB, clinically diagnosed pulmonary and extra-pulmonary TB;
2. Cleaning and adjusting raw mortality data from VR systems and mortality surveys, followed by imputation of missing values in countries with VR or survey data;
3. Cleaning drug resistance survey data;
4. Estimating overall TB incidence after review and cleaning of case notification data;
5. Cleaning of measurements of HIV prevalence among TB patients followed by estimating HIV-positive TB incidence and HIV-positive TB mortality;
6. Estimating RR-TB and MDR-TB incidence;
7. Estimating TB mortality in countries with no VR data and HIV-negative TB mortality;
8. Estimating incidence and mortality disaggregated by age and sex and disaggregated by drug resistance status.

Annex 4 - Estimating the number of household contacts of a bacteriologically confirmed pulmonary cases less than 5 years old

In low TB burden countries (113 high-income or upper middle-income countries with an estimated incidence rate less than 100 per 100 000 population), the number of child household contacts eligible for LTBI treatment is defined as the number of children under 5 years of age who are household contacts of bacteriologically confirmed pulmonary TB cases and have LTBI defined as a positive result to a standard tuberculin test or an IGRA test. In high TB burden countries, the number eligible is defined as the number of child household contacts without active TB, based on the current WHO recommendations that do not require LTBI testing among child household contacts <5 years prior to the provision of preventive treatment in these countries.^{1,2}

The estimated number n of child household contacts eligible for LTBI treatment is

$$n = \frac{b}{c}HpL(1 - t)$$

where b is the number of notified bacteriologically confirmed pulmonary TB, c is the average number of TB cases per household, H is the average household size, p is national proportion of children <5 years, t is proportion of child household contacts with active TB, and L is prevalence of LTBI among child household contacts < 5 years old. In high TB burden countries, L is set to 1 (testing for LTBI is not required). The following sources of uncertainty are accounted for: prevalence of LTBI, variance in the count of TB cases per household, and in the proportion of child household contacts with active TB. Uncertainty about United Nations Population Division (UNPD) population size is not documented. Errors were propagated using methods described in chapter 7.

Parameters	Values	Sources
Number of notified bacteriologically confirmed pulmonary TB in 2015	Differ by country	WHO global TB database
National proportion of children <5 years of age in 2015	Differ by country	2015 Revision of World Population, United Nations Population Division (https://esa.un.org/unpd/wpp/)
National average household size	Differ by country	National censuses, DHS statistical year books, or official websites of the national statistical authorities
Prevalence of LTBI among child household contacts <5years old in LBC	Constant across countries = 27.6% (19.2%-38.0%)	Systematic review of literature from LBC up to Dec 2015 (unpublished)
Average cluster size of active TB per household	Constant across countries =1.06 (95%CI 1.04-1.08)	Systematic review of literature between Jan 2005 and Dec 2015 (unpublished)
Proportion of children < 5 years old with active TB among those who had a household contact with TB cases	Constant across countries =6.1% (95%CI 1.0%-16.3%)	Source: Dodd et al, <i>Lancet Glob Health</i> . 2014 ³

1. World Health Organization Recommendations for Investigating Contacts of Persons with Infectious Tuberculosis in Low- and Middle-Income Countries Geneva, Switzerland: WHO, 2012.
2. World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, Switzerland: WHO, 2011.
3. Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *Lancet Glob Health* 2014; **2**(8): e453-9.

Tables

Table 1: Distribution of disease duration by case category

Case category	Distribution of disease duration (year)
Treated, HIV-negative	Uniform (0.2–2)
Not treated, HIV-negative	Uniform (1–4)
Treated, HIV-positive	Uniform(0.01–1)
Not treated, HIV-positive	Uniform (0.01–0.2)

Table 2: Incidence estimation based on U/T

	U (n)	T (n)	Prevalence (10^{-3})	Duration (year)	Incidence ($10^{-3}y^{-1}$)
Cambodia 2002	260	42	12 (10-15)	2.9 (1.9-4)	4 (2.5-5.8)
Cambodia 2011	205	80	8.3 (7.1-9.8)	1.2 (0.8-1.6)	6.7 (4.5-9.3)
Myanmar 2009	300	79	6.1 (5-7.5)	1.8 (1.1-1.6)	3.3 (2-4.8)
Thailand 2012	136	60	2.5 (1.9-3.5)	1.1 (0.5-1.6)	2.3 (1-3.5)

Table 3: Estimates of incidence derived from prevalence survey results, based on two estimation methods.

	Prevalence (10^{-3})	Incidence - Method 1 ($10^{-3}y^{-1}$)	Incidence - Method 2 ($10^{-3}y^{-1}$)
Cambodia 2002	12 (10-15)	4 (2.5-5.8)	2.2 (1.5-2.9)
Cambodia 2011	8.3 (7.1-9.8)	6.7 (4.5-9.3)	3.8 (2.2-5.8)
Myanmar 2009	6.1 (5-7.5)	3.3 (2-4.8)	3.5 (2-5.1)
Thailand 2012	2.5 (1.9-3.5)	2.3 (1-3.5)	1.1 (0.7-1.6)

Table 4: Distribution of CFRs by case category

	CFR	Sources
Not on TB treatment f_u	0.43 (0.28-0.53)	39,40
On TB treatment f_i	0.03 (0-0.07)	41

Table 5: Distribution of CFR in HIV-positive individuals

ART	TB treatment	CFR	Sources
off	off	0.78 (0.65-0.94)	39
off	on	0.09 (0.03-0.15)	41,42
< 1 year	off	0.62 (0.39-0.86)	Data from review + assumptions
< 1 year	on	0.06 (0.01-0.13)	Data from review + assumptions
≥ 1 year	off	0.49 (0.31-0.70)	Assumptions
≥ 1 year	on	0.04 (0.00-0.10)	Assumptions

Figures

Figure 1. Main method to estimate TB incidence. In the first method, case notification data are combined with expert opinion about case detection gaps (under-reporting and under-diagnosis), and trends are estimated using either mortality data, repeat surveys of the annual risk of infection or exponential interpolation using estimates of case detection gaps for three years. For all high-income countries except the Netherlands and the United Kingdom and selected countries of other income groups, notifications are adjusted by a standard amount or measures of under-reporting from inventory studies, to account for case detection gaps.

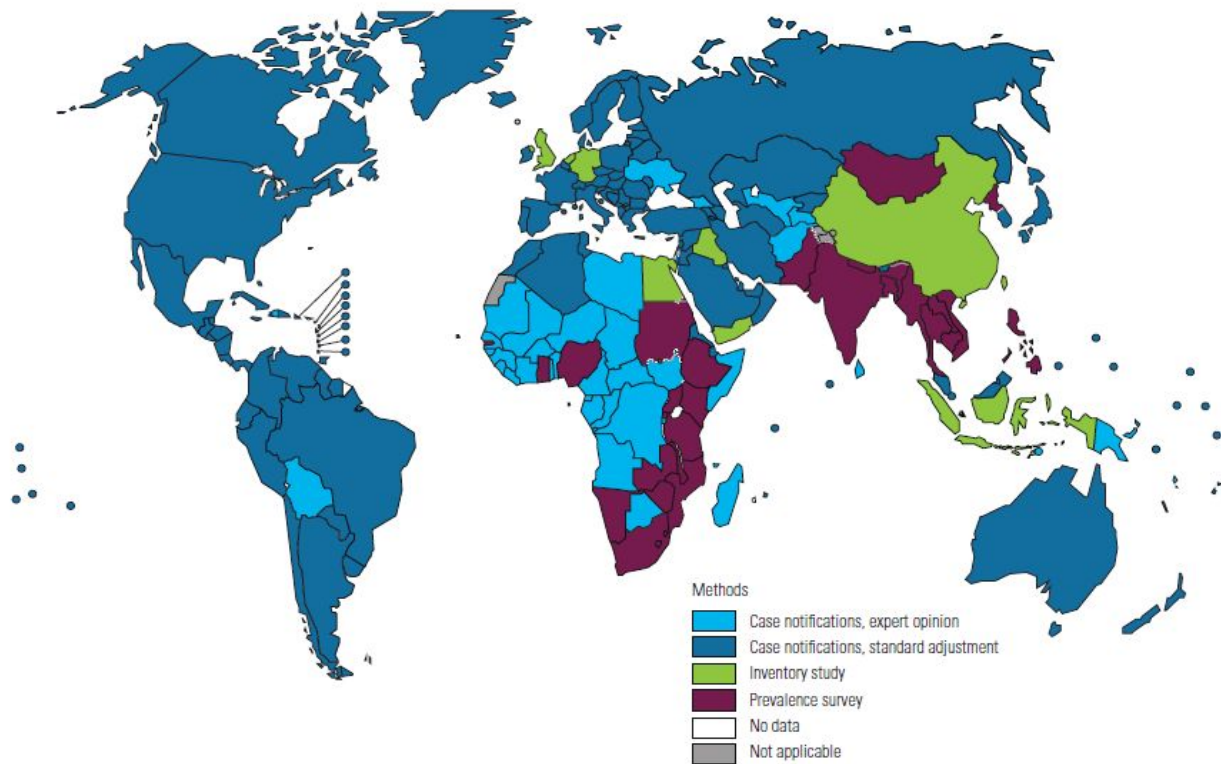


Figure 2. HIV prevalence ratio (prevalence survey / notified TB cases)

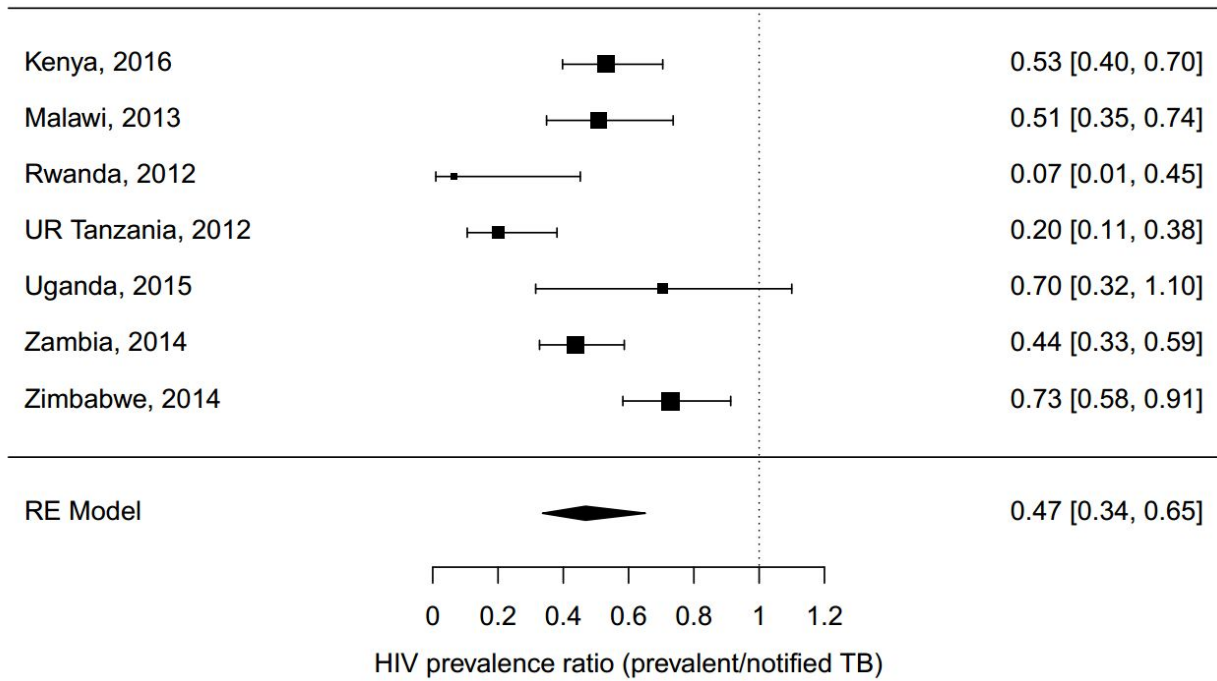


Figure 3. Main methods to estimate TB mortality in HIV-negative people

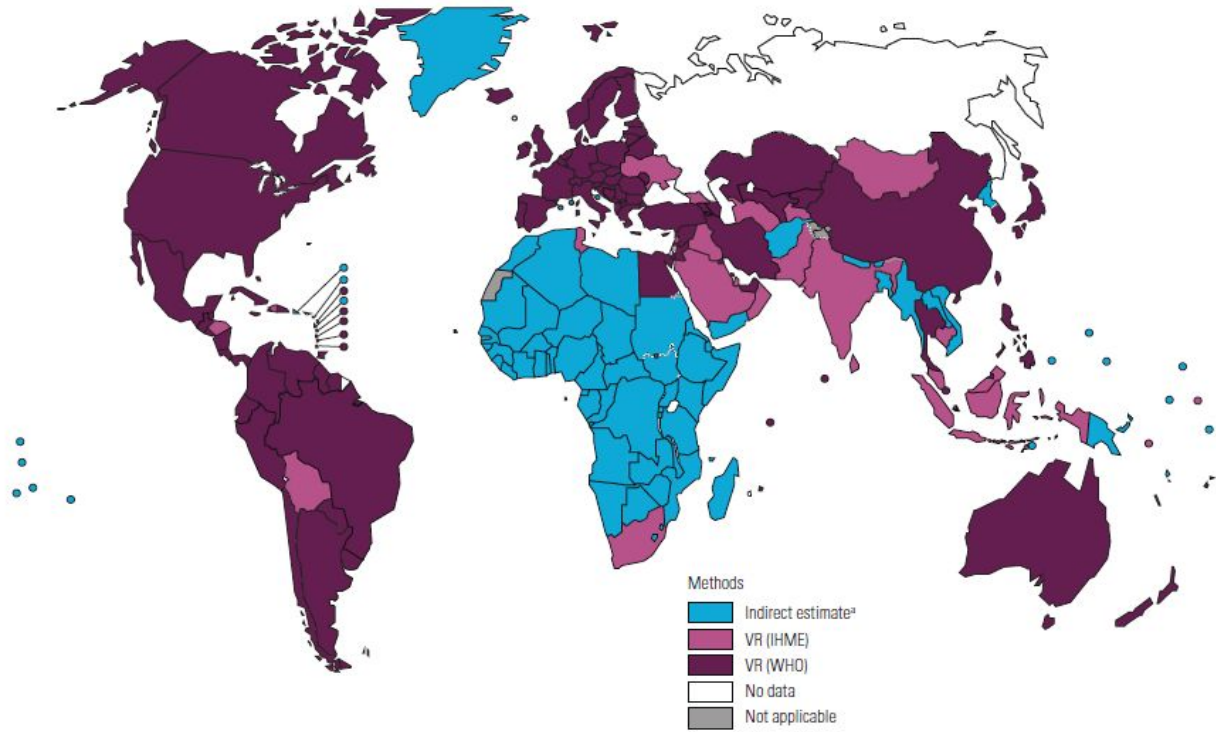


Figure 4. VR data quality

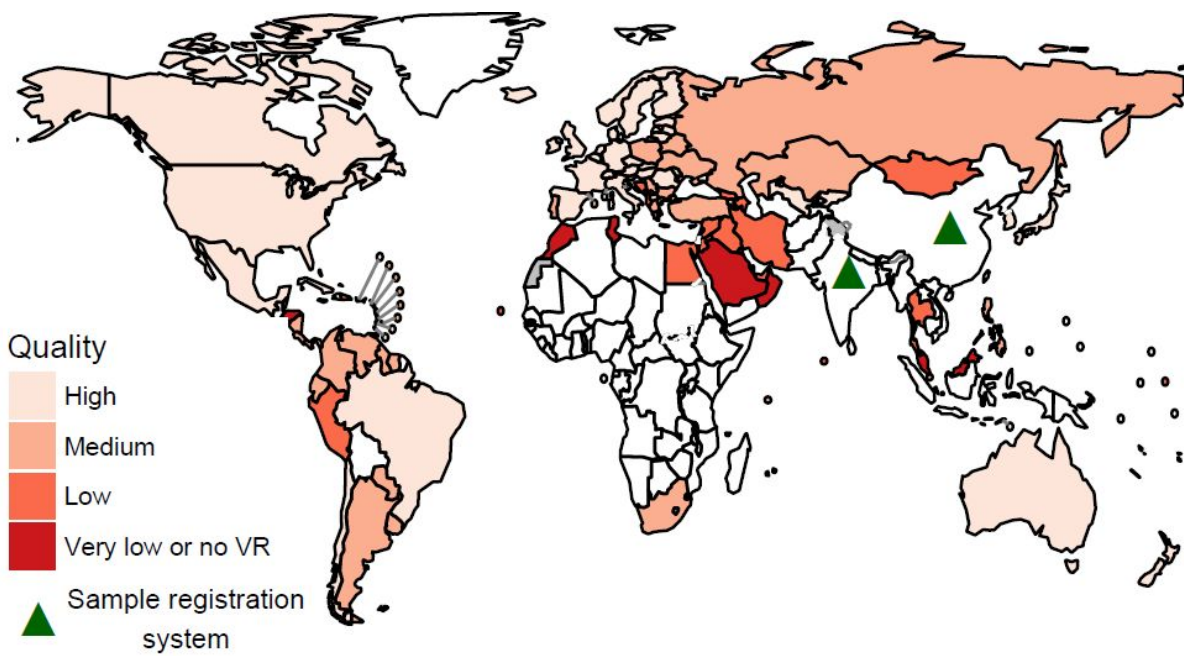
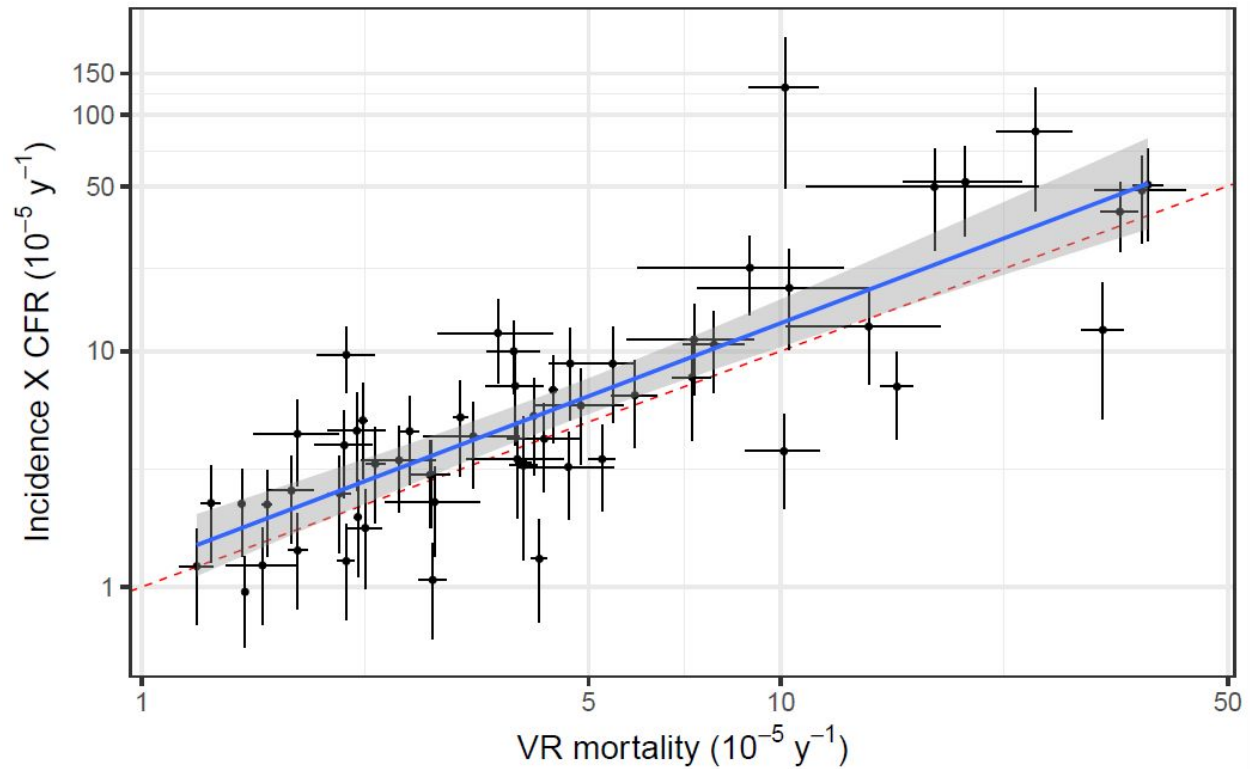


Figure 5. Comparison of VR mortality (HIV-negative), horizontal axis (log scale) and mortality predicted as the product of incidence and CFR, vertical axis (log scale). Horizontal and vertical segments indicate uncertainty intervals. The dashed red line shows equality. The blue line and associated grey banner show the least-squared best fit to the data.



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