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 2017 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 were used to derive incidence: (*i*) case notification data combined with expert opinion about case detection gaps (54 countries representing 17% of global incidence in 2016); (*ii*) results from TB prevalence surveys (24 countries, 68% of global incidence); (*iii*) notifications in high-income countries adjusted by a standard factor to account for under-reporting and underdiagnosis (134 countries, 15% of global incidence) and (*iv*) capture-recapture modelling (5 countries, 0.5% of global incidence). Mortality was obtained from national vital registration systems of mortality surveys in 129 countries (57% of global HIV-negative TB mortality), and among 18 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.

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, surveys of under-reporting of detected TB, in-depth analysis of surveillance and other data, expert opinion and consultation with countries. In June 2006, the WHO Task Force on TB Impact Measurement was established[1], with the aim of ensuring that WHO's assessment of whether 2015 targets were achieved should be as rigorous, robust and consensus-based as possible. The Task Force reviewed methods and provided recommendations in 2008, 2009 and most recently in March 2015 and April 2016.

Historical background

Historically, a major source of data to derive incidence estimates were results from tuberculin surveys conducted in children[2]. 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 HIV settings[3]. In addition to uncertainty about the relationship between λ and I_{s+}, estimates of incidence obtained from tuberculin surveys suffer from other sources of uncertainty and bias, including unpredictable diagnostic performance of the tuberculin test[4], digit preference when reading and recording the size of tuberculin reactions[5], sensitivity to assumptions about reaction sizes attributed to infection[6], 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 × $10^{-5}y^{-1}$) and 2.6-2.9 million deaths (46-55 × $10^{-5}y^{-1}$)[7]. A second major reassessment was published in 1999[8], with an estimated 8 million incident cases for the year 1997 (136 × $10^{-5}y^{-1}$), and 1.9 million TB deaths (32 × $10^{-5}y^{-1}$). 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.

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. 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 is a survey to quantify the level of under-reporting of detected TB cases; if certain conditions are met, capture-recapture methods can also be used to estimate TB incidence [9].

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 (i.e. the number of newly diagnosed cases that are missed by surveillance systems) and universal access to health care (to minimize under-diagnosis of cases). 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 incidence[10].

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:

1. **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. In this report, this method is used for 54 countries that accounted for 17% of the estimated global number of incident cases in 2016.

2. **Results from TB prevalence surveys**. Incidence is estimated using prevalence survey results and derived from a model that accounts for the impact of HIV on the distribution of disease duration. This method is used for 24 countries (23 with national survey data and one – India – with a survey in one state) that accounted for 68% of the estimated global number of incident cases in 2016.

3. **Notifications in high-income countries adjusted by a standard factor to account for under-reporting and under-diagnosis**. This method is used for 118 countries: all high-income countries except the Netherlands and the United Kingdom, plus selected upper-middle income countries with low levels of under-reporting, including Brazil and China. For three countries (France, Republic of Korea, Turkey) the adjustment was country-specific, based on results from studies of under-reporting. These 134 countries accounted for 15% of the estimated global number of incident cases in 2016.

4. **Results from inventory/capture-recapture studies**. This method is used for 5 countries: Egypt, Iraq, the Netherlands, the United Kingdom and Yemen. They accounted for 0.5% of the estimated global number of incident cases in 2016.

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 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 three 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*

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

where *I* denotes incidence, *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 2000-2015 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 were derived from repeat tuberculin survey results in

Bhutan, India and Yemen and from trends in mortality in 40 countries (including most countries in Eastern Europe).

The proportion of cases that were not reported were assumed to follow a Beta distribution, with parameters α and β obtained from the expected value E and variance V using the method of moments[12], as follows

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

Time series for the period 2000–2014 were built according to the characteristics of the levels of under-reporting and under-diagnosis that were estimated for the three reference years. A cubic spline extrapolation of V and E, with knots set at the reference years, was used for countries with low-level or concentrated HIV epidemics. In countries with a generalized HIV epidemic, the trajectory of incidence was 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 were insufficient data to determine the factors leading to time-changes in case notifications, incidence was 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 included 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 of the former Soviet Union 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); 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 new cases are added to the pool. At equilibrium during the time period Δt and further assuming exponentially distributed durations d such that $d=m^{-1}$

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

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

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 model compartments: susceptibles (*S*), untreated TB (*U*) and treated TB (*T*). The size of *U* and *T* is obtained from the prevalence survey. Transitions from *U* to *T* are determined as follows

$$\frac{\mathrm{d}U}{\mathrm{d}t} = IS - (\mu_u + \theta_u + \delta)U$$

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \delta U - (\mu_t + \theta_t)T$$

Where I denotes Incidence, μ and θ denote mortality and self-cure 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 distributed uniform with bounds 0 and 0.1. Table 2 shows estimates of incidence from four recent prevalence surveys using this method.

Among limitations of this method is the insufficient power of surveys to estimate the number of prevalent TB cases on treatment with great 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 is 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 7 countries with data collected over the period 2012-2016 (Kenya, Malawi, Rwanda, Tanzania, Uganda, Zambia and Zimbabwe), using the R package metafor[13] (Figure 2). The pooled ratio ratio was then 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 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 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

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

The combined probability is then expressed as

$$\text{Prob}(x = \text{TB}) = \frac{\sum \alpha_i + 1}{\sum \alpha_i + \sum \beta_i + 2} \tag{4}$$

$$\text{Var} = \frac{\left(\sum \alpha + 1\right)\left(\sum \beta + 1\right)}{\left(\sum \alpha + \sum \beta + 2\right)^2 \left(\sum \alpha + \sum \beta + 3\right)}$$

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 selected countries in the upper-middle income group were assumed to perform similarly well on average. The exceptions were 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 the ratio of TB deaths / TB notifications (M/N ratio), which may be indicative of reporting problems.

Method 4 - Capture-recapture modelling.

This method was used for 5 countries: Egypt[14], Iraq[15], the Netherlands[16], the United Kingdom[17] and Yemen[18]. Capture-recapture modelling was considered in studies with at least 3 lists and estimation of list dependencies[9]. The estimate of the surveillance gap in the UK and the Netherlands was assumed time invariant. In Yemen, trends in incidence were derived from results of two consecutive tuberculin surveys[19]. In Egypt and Iraq, trends were derived using methods described in section describing method 1.

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 5 for data from a nationally representative survey, 0.8 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. The TB incidence rate ratio (HIV-positive/HIV-negative) was 19 (17 – 22) in 2015.

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)[20]. This current revision requests the reporting of all new and relapse case notifications by age and sex. Global progress in reporting of TB cases among children is shown in Figure 3.

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[14,16,21], none have produced precise results by age. Small-scale, convenient-sampled studies indicate that under-reporting of childhood tuberculosis can be very high[22,23] 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 children[24].

Results from two methods are combined to estimate TB incidence in children, using a statistical ensemble approach based on equation 4. The first method estimates the proportion of all TB cases that are in children as a function of expected age-specific proportions of smear positive TB, according to a previously published approach[25] updated to incorporate recent data[26]. The second method is based on a dynamic model 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 prevalence[27]. 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).

Producing estimates of TB incidence among children is 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.

Adult TB incidence was disaggregated by age and sex proportionally to notifications for countries where incidence estimates were based on notifications. For other countries, a hierarchical prior for prevalence risk ratios was developed based on prevalence survey data and Horton et al's systematic review of prevalence sex ratios[28]. 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. To disaggregate adult TB incidence by age and sex in these countries, 1 million samples were drawn from the prior and the mean over samples that were consistent with notification data was used (i.e. samples where the incidence exceeded notifications for every age/sex category). Where none of the samples had incidence > notifications in every category, the prior mean was used to disaggregate incidence.

Drug resistance

Following a revision of policy recommendations for the treatment of drug-resistant TB issued by WHO in May 2016[29] all people with TB resistant to rifampicin with or without resistance to other drugs should be treated with an MDR-TB regimen. This includes patients with MDR-TB as well as any other patient with TB resistant to rifampicin. For this reason all global, regional, and country level estimates of incidence and mortality of drug-resistant TB published in this report refer to cases of TB resistant to rifampicin, with or without additional resistance to other drugs (MDR/RR-TB).

Global and regional estimates of the proportion of new and retreatment cases of TB that had MDR/RR-TB in 2016 were calculated using country-level information. If countries had reported data on the proportion of new and retreatment cases of TB that have rifampicin resistance from routine surveillance or a survey of drug resistance, the latest available information was used. For data from routine surveillance to be considered representative, at least 80% of notified new pulmonary laboratory-confirmed TB cases must have a documented DST result for at least rifampicin. For retreatment cases, some surveys are also considered if at least 80% of notified previously treated pulmonary laboratory-confirmed cases have a documented DST result for at least rifampicin. For countries that have not reported such data, estimates of the proportion of new and retreatment cases of TB that have MDR/RR-TB were produced using modelling (multiple imputation by chained equations) that was based on data from countries for which data do exist. Estimates for countries without data were based on 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 have 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.

MDR/RR-TB incidence

First we calculate proportions of new (p_n) and retreated (p_r) patients with MDR/RR-TB resistance from routine surveillance or survey of drug resistance data, as described above. For each of the new and retreated TB patient groups, these proportions are calculated as the sum of patients who are:

(i) MDR-TB among those with DST results for Rifampicin (R) and Isoniazid (H)

(ii) R but not H resistant TB among those with DST for R and H, and

(iii) RR-TB among those with a gene Xpert result for R

divided by the sum of patients

(iv) with DST results for R and H, and

(v) gene Xpert result for R.

We then estimate MDR/RR-TB incidence ($I_{mdr/rr}$) by adding the expected number of RR-TB cases among three distinct types of TB case notifications: (i) new all forms (*new*) multiplied by the proportion MDR/RR-TB among new (p_n) from DRS, inflated upwards to adjust for the estimated detection gap of incident cases not identified by the surveillance system (*cdr*), (ii) relapse all forms (*rel*) multiplied by the proportion MDR/RR-TB among relapses (p_r) approximated by $p_n \times RR$ (risk ratio of being a DR-TB patient when a relapse compared to a new TB patient) inflated by a lower detection gap (cdr_u), and (iii) all retreatments that are not relapse forms (ret_{notrel}) multiplied by the proportion MDR/RR-TB among retreatment cases from DRS (p_r) inflated by the lower detection gap (cdr_u), using a uniform distribution bounded by *cdr* and 1. Patients with a previous TB episode are more likely to self-present or be screened for TB, hence the assumption of a lower detection gap (an approach recommended by the WHO Global Task Force on TB Impact Measurement).

$$I_{mdr/rr} = \frac{new \times p_n}{cdr} + \frac{rel \times p_n \times RR + ret_{notrel} \times p_r}{cdr_u}$$

MDR/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.

Second-line drug resistance including XDR-TB

The average proportion of MDR-TB cases with XDR-TB was calculated taking the ratio of identified XDR-TB cases among tested MDR-TB cases in 96 countries accounting for 80% of estimated MDR-TB incidence. Errors were assumed binomial. The proportions of XDR-TB were then pooled using country-specific estimates of MDR-TB incidence as weights. The same approach was followed to estimate the proportion of MDR-TB cases with resistance to fluoroquinolones or any second-line anti TB drug.

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.

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 (129 countries, see Figure 4);

- 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 2017, mortality data from 129 countries were used, representing 57% of the estimated number of TB deaths (among HIV-negative TB) globally in 2016.

Estimates for 18 countries (Figure 4), including India and for South Africa (adjusted for HIV/TB miscoding) were obtained from the Institute of Health Metrics and Evaluation (GBD 2015[33]) at http://embargo.vizhub.healthdata.org/collaborators/gbd-search/, 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, 0.92-1.05).

Among the countries for which VR or mortality survey data could be used, there were 1526 country-year data points 2000–2015, after removing 63 country-year data points with insufficient data quality as estimated by WHO[34] (Figure 5).

Reports of TB mortality were 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)[34]. It was 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 was assumed that the proportion of deaths attributable to TB was the same as the observed proportion in recorded deaths. The adjusted number of TB deaths κ_a was 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 were interpolated. Trailing missing values were 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 2016, 57% 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 was 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 6 shows a comparison of 126 direct mortality estimates for 2015 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 was 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 in children was estimated from TB incidence in children using a case-fatality based approach[35]. This approach distinguished case fatality children by age, anti-TB treatment status, and HIV/ART status.

Adult TB mortality was 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 vital registration systems in place. For countries without VR data, adult mortality was 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). HIV-positive TB deaths in adults were 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 was 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.

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 was 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. The latter two 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 were defined as the 2.5th and 97.5th centiles of outcome distributions. The general approach to uncertainty analyses was 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[36,37]. Using matrix notation, the expected value *E*[*h*(*X*)] and variance of *h*(*X*) were approximated as follows:

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

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

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*.

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 Evaluation[38], 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 periodically[10] and the level of under-reporting should be measured[9] and minimized. Tuberculosis mortality will ideally be measured by counting deaths in a comprehensive vital registration system[34].

WHO's post-2015 global TB strategy, known as the End TB Strategy[39], 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 a 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 the 2017 revision of 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 and bacteriologically unconfirmed TB;
2. estimating overall TB incidence after review and cleaning of case notification data;
3. 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;
4. cleaning of measurements of HIV prevalence among TB patients followed by estimating HIV-positive TB incidence and HIV-positive TB mortality;
5. estimating HIV-negative TB mortality in countries with no VR data;
6. estimating incidence and mortality disaggregated by age and sex and disaggregated by drug resistance status.

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)	[40,41]
On TB treatment f_t	0.03 (0-0.07)	[42]

Table 5: Distribution of CFR in HIV-positive individuals

ART	**TB treatment**	**CFR**	**Sources**
off	off	0.78 (0.65-0.94)	[40]
off	on	0.09 (0.03-0.15)	[42,43]
< 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, notifications are adjusted by a standard amount or measures of under-reporting from inventory studies, to account for case detection gaps.

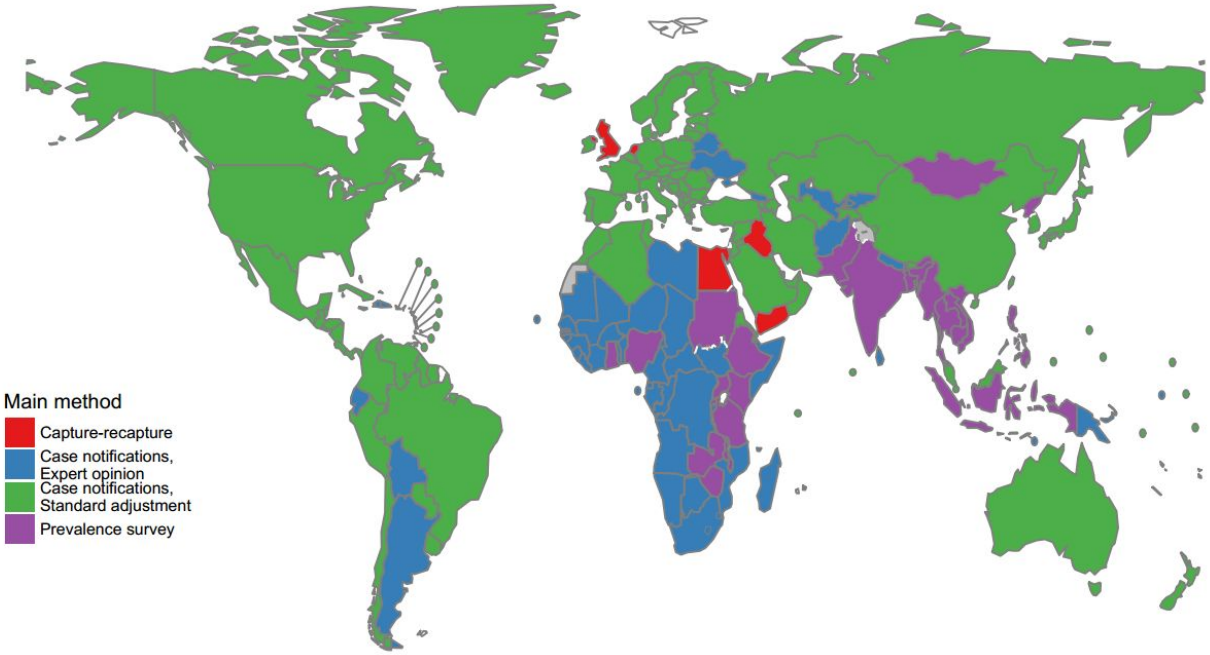


Figure 2. HIV prevalence ratio (prevalence survey / notified TB cases)

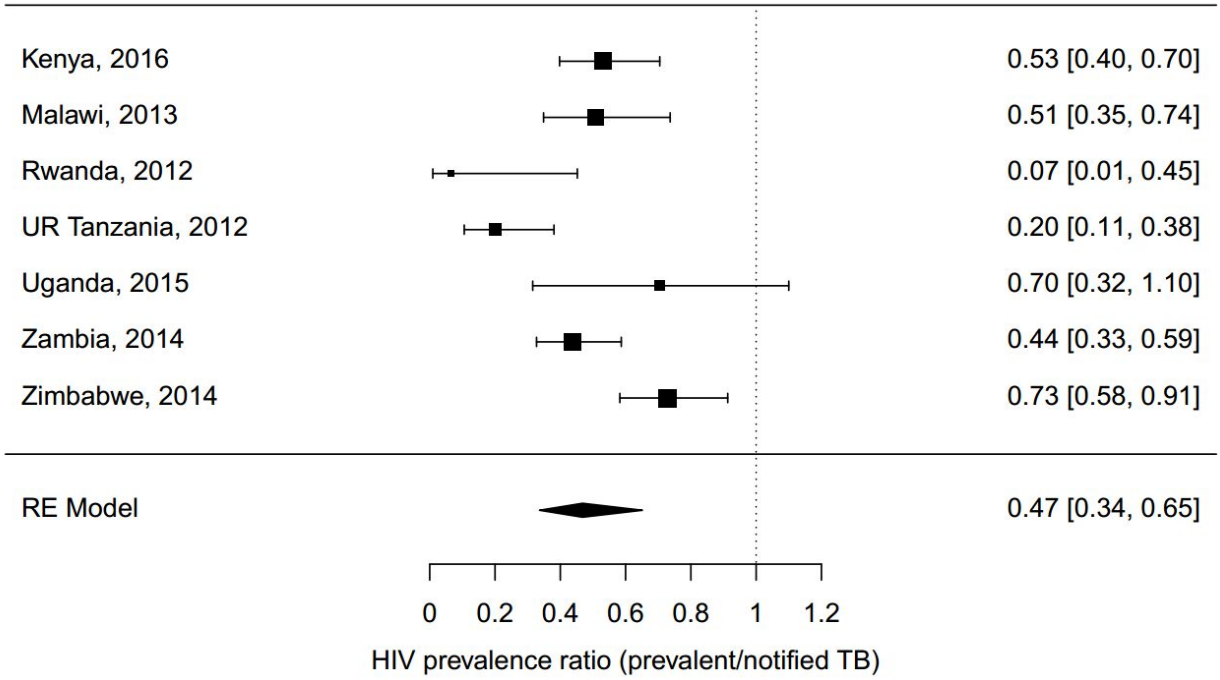
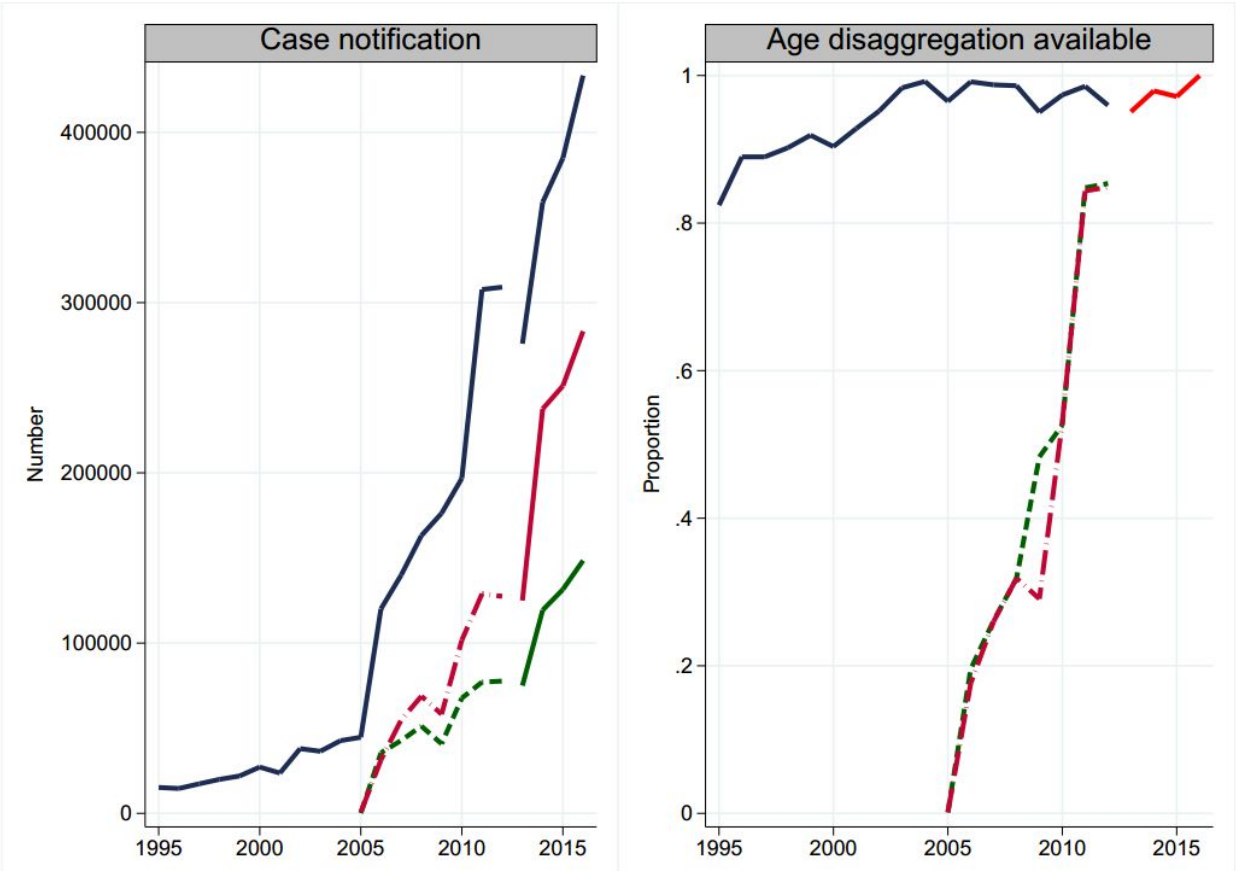


Figure 3. Global progress in reporting of TB cases among children, 1995–2015(a). Left panel: Number of notifications of cases among children reported to WHO (blue: 0-14, red: 5-14, green: 0-4). Right panel: Percentage of case notifications reported to WHO that are age-disaggregated (blue: new smear positive, green-dashed: new smear-negative and smear not done, red dash: new extra-pulmonary, red: new and relapse all forms)



(a) Before 2013 childhood case notifications included smear-positive, smear-negative, smear not done and extrapulmonary TB for all new patients. After 2013 (shown as a gap in the graph) childhood case notification include all new and relapse cases irrespective of case type.

Figure 4. Main methods to estimate TB mortality in HIV-negative people

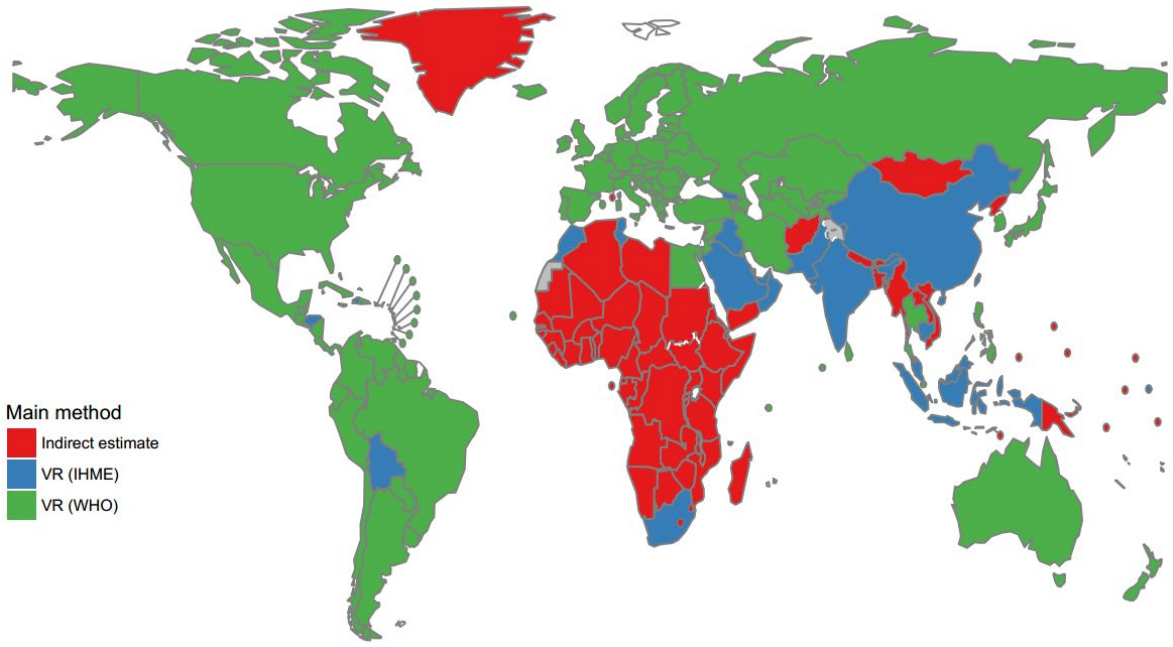


Figure 5. VR data quality

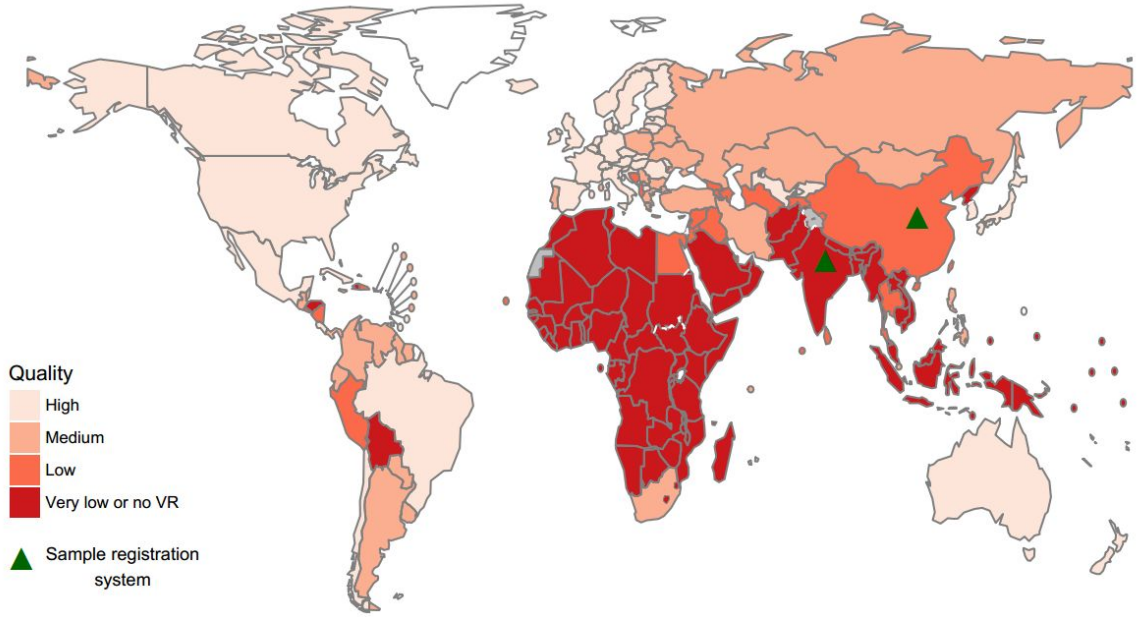
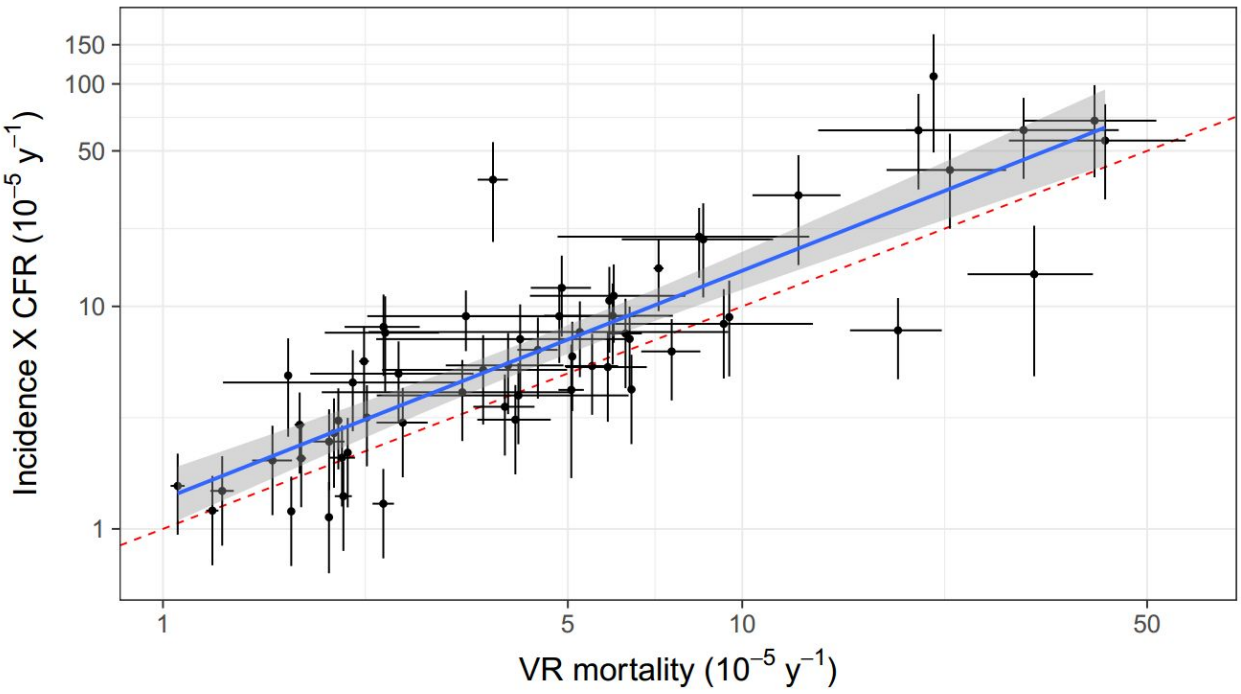


Figure 6. Comparison of VR mortality (HIV-negative), horizontal axis (log scale) and mortality predicted as the product of incidence and CFR, vertical axis (log scale). Horizontal and vertical segments indicate uncertainty intervals. The dashed red line shows equality. The blue line and associated grey banner show the least-squared best fit to the data, with a slope not constrained to one.



References

1 Dye C, Bassili A, Bierrenbach AL, *et al.* Measuring tuberculosis burden, trends, and the impact of control programmes. *Lancet Infect Dis* 2008; **8**: 233–43.

2 Styblo K. Styblo K. The Relationship between the risk of tuberculous infection and the risk of developing infectious tuberculosis. *Bulletin of the International Union against Tuberculosis and Lung Diseases* 1985; : 117–9.

3 Van leth F. Prevalence of tuberculous infection and incidence of tuberculosis; a re-assessment of the Styblo rule. *Bull World Health Organ* 2008; **86**: 20–6.

4 Dinnes J, Deeks J, Kunst H, *et al.* A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. *Health Technol Assess* 2007; **11**: 1–196.

5 Eilers PHC, Borgdorff MW. Modeling and correction of digit preference in tuberculin

surveys. *Int J Tuberc Lung Dis* 2004; **8**: 232–9.

6 Rieder HL. Methodological issues in the estimation of the tuberculosis problem from tuberculin surveys. *Tuber Lung Dis* 1995; **76**: 114–21.

7 Sudre P, ten Dam G, Kochi A. Tuberculosis: a global overview of the situation today. *Bull World Health Organ* 1992; **70**: 149–59.

8 Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC, Others. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. *JAMA* 1999; **282**: 677–86.

9 WHO. Assessing tuberculosis under-reporting through inventory studies. World Health Organization, 2012.

10 WHO. Standards and Benchmarks for tuberculosis surveillance and vital registration systems. WHO, 2014 http://www.who.int/tb/publications/standardsandbenchmarks/.

11 WHO. Improving estimation of TB disease burden via systematic assessment of surveillance data. http://www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/improving_estimates/en/.

12 Renyi A. Probability Theory. New York: Dover Publications Inc, 2007.

13 Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *Journal of Statistical Software* 2010; **36**: 1–48.

14 Bassili A, Grant AD, El-Mohgazy E, *et al.* Estimating tuberculosis case detection rate in resource-limited countries: a capture-recapture study in Egypt. *Int J Tuberc Lung Dis* 2010; **14**: 727–32.

15 Huseynova S, Hashim DS, Tbena MR, *et al.* Estimating tuberculosis burden and reporting in resource-limited countries: a capture-recapture study in Iraq. *Int J Tuberc Lung Dis* 2013; **17**: 462–7.

16 van HEST NAH, Smit F, Baars HWM, *et al.* Completeness of notification of tuberculosis in The Netherlands: how reliable is record-linkage and capture-recapture analysis? *Epidemiol Infect* 2007; **135**: 1021–9.

17 Anderson L, Moore J, Pedrazzoli D, *et al.* Tuberculosis in the UK. 2010.

18 Bassili A, Al-Hammadi A, Al-Absi A, *et al.* Estimating the tuberculosis burden in resource-limited countries: a capture-recapture study in Yemen. *Int J Tuberc Lung Dis* 2013; **17**: 456–61.

19 Al-Absi A, Bassili A, Abdul Bary H, *et al.* The decline of tuberculosis in Yemen:

evaluation based on two nationwide tuberculin surveys. *Int J Tuberc Lung Dis* 2009; **13**: 1100–5.

20 WHO. Definitions and reporting framework for tuberculosis 2013 revision WHO. WHO, 2013 http://www.who.int/tb/publications/definitions/.

21 Van Hest NAH, Story A, Grant AD, Antoine D, Crofts JP, Watson JM. Record-linkage and capture–recapture analysis to estimate the incidence and completeness of reporting of tuberculosis in England 1999–2002. *Epidemiol Infect* 2008; **136**: 1606.

22 Lestari T, Probandari A, Hurtig A-K, Utarini A. High caseload of childhood tuberculosis in hospitals on Java Island, Indonesia: a cross sectional study. *BMC Public Health* 2011; **11**: 784.

23 Coghlan R, Gardiner E, Amanullah F, *et al.* Understanding Market Size and Reporting Gaps for Paediatric TB in Indonesia, Nigeria and Pakistan: Supporting Improved Treatment of Childhood TB in the Advent of New Medicines. *PLoS One* 2015; **10**: e0138323.

24 WHO. WHO Global Task Force on TB Impact Measurement - Sub-group on strengthening surveillance. 2014; published online Nov 6. http://www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/sep14indonesia_inventorystudyworkshop/en/ (accessed Oct 15, 2015).

25 Jenkins HE, Tolman AW, Yuen CM, *et al.* Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. *Lancet* 2014; **383**: 1572–9.

26 Sismanidis C, Glaziou P, Law I, Floyd K. The burden of tuberculosis disease in children. *Lancet* 2014; **384**: 1343.

27 Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *The Lancet Global Health* 2014; **2**: e453–9.

28 Horton KC, MacPherson P, Houben RMGJ, White RG, Corbett EL. Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. *PLoS Med* 2016; **13**: e1002119.

29 WHO. WHO treatment guidelines for drug resistant tuberculosis - 2016 Update. WHO, 2016 http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf?ua=1.

30 Mortality and causes of death in South Africa, 2010: Findings from death notification. http://www.statssa.gov.za/publications/p03093/p030932010.pdf (accessed Sept 2016).

31 Glaziou P, van der Werf MJ, Onozaki I, *et al.* Tuberculosis prevalence surveys: rationale and cost. *Int J Tuberc Lung Dis* 2008; **12**: 1003–8.

32 WHO. Tuberculosis Prevalence Surveys: A Handbook. World Health Organization, 2011.

33 GBD 2015 LRI Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infect Dis* 2017; published online Aug 23. DOI:10.1016/S1473-3099(17)30396-1.

34 Mathers CD, Fat DM, Inoue M, Rao C, Lopez AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bull World Health Organ* 2005; **83**: 171–7.

35 Dodd PJ, Yuen CM, Sismanidis C, Seddon JA, Jenkins HE. The global burden of tuberculosis mortality in children: a mathematical modelling study. *Lancet Glob Health* 2017; **5**: e898–906.

36 Ku HH. Notes on the use of propagation of error formulas. *Journal of Research of the National Bureau of Standards, Section C: Engineering and Instrumentation* 1966; **70C**: 263.

37 Lab AS. An Introduction To Error Propagation: Derivation, Meaning and Examples of Equation C_Y=F_X C_X F^X_T. Swiss Federal Institute of Technology, Lausanne, 1998 http://www.nada.kth.se/~kai-a/papers/arrasTR-9801-R3.pdf.

38 Murray CJL, Ortblad KF, Guinovart C, *et al.* Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **6736**: 1–66.

39 Uplekar M, Weil D, Lonnroth K, *et al.* WHO's new end TB strategy. *Lancet* 2015; **385**: 1799–801.

40 Corbett EL, Watt CJ, Walker N, *et al.* The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; **163**: 1009–21.

41 Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJD. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PLoS One* 2011; **6**: e17601.

42 Straetemans M, Glaziou P, Bierrenbach AL, Sismanidis C, van der Werf MJ. Assessing tuberculosis case fatality ratio: a meta-analysis. *PLoS One* 2011; **6**: e20755.

43 Mukadi YD, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *AIDS* 2001; **15**: 143–52.