

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 2016 to estimate TB incidence, prevalence 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 (74 countries representing 22% of global incidence in 2015); (ii) results from TB prevalence surveys (20 countries, 62% of global incidence); (iii) notifications in high-income countries adjusted by a standard factor to account for under-reporting and underdiagnosis (118 countries, 15.5% 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 128 countries (52% of global HIV-negative TB mortality). 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 established¹, 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 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 HIV 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.

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 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 (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 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:

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 74 countries that accounted for 22% of the estimated global number of incident cases in 2015.

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 20 countries (19 with national survey data and one – India – with a survey in one state) that accounted for 62% of the estimated global number of incident cases in 2015.

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 118 countries accounted for 15.5% of the estimated global number of incident cases in 2015.

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 2015.

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 moments¹², as follows

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

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

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

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

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 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

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

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

Where I denotes Incidence, μ and θ denote mortality and self-cure 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). Figure 2 shows recent changes in estimates as new data became available.

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 predicted from a random-effects model fitting data from 6 countries with data collected over the period 2012-2015 (Malawi, Rwanda, Tanzania, Uganda, Zambia and Zimbabwe), using a restricted maximum likelihood estimator and setting HIV among notified cases as an effect modifier¹³, using the R package metafor¹⁴ (Figure 3). The model 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 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

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

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

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: Egypt¹⁵, Iraq¹⁶, the Netherlands¹⁷, the United Kingdom¹⁸ and Yemen¹⁹. Capture-recapture modelling was considered in studies with at least 3 lists and estimation of list dependencies⁹. 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 surveys²⁰. 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)²¹. 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 4.

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, convenient-sampled 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.

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 approach²⁶ updated to incorporate recent data²⁷. 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 prevalence²⁸.

Using the sex disaggregated reporting of TB case notification data we calculated the ratio of the number of TB cases notified in men compared with women as a measure of

the ratio r_1 for incident cases, assuming no sex differential in the detection of incident cases. Evidence from prevalence surveys consistently show bigger recording and detection gaps in men²⁹. The assumption of no sex differential in the detection of incident cases may thus lead to underestimating the proportion of men among incident cases. With currently available data, it is not possible to estimate male and female case detection ratios for all countries.

Overall incidence in adults 15 years or over (I_a) can be disaggregated into estimates among men (I_m) and women (I_w) as shown

$$I_m = I_a \frac{r_1}{1 + r_1} \tag{6}$$

$$I_w = \frac{I_a}{1 + r_1}$$

where $r_1 = I_m/I_w$ and $I_a = I_m + I_w$.

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.

Drug resistance

Following a revision of policy recommendations for the treatment of drug-resistant TB issued by WHO in May 2016³⁰ 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 2015 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 60% of notified new pulmonary TB cases must have a documented DST result for at least rifampicin. For retreatment cases, some surveys are also considered if at least 75% retreatment 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 (including multiple imputation) 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. 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)³¹. 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:

$$m = M.p.r$$

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.

Prevalence from population-based surveys

The best way to measure the prevalence of TB is through national population-based surveys of TB disease^{32,33}. 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 (128 countries, in green in Figure 5);
- 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 2015, mortality data from 128 countries were used, representing 52% of the estimated number of TB deaths (among HIV-negative TB) globally in 2015. The VR data on TB deaths from Zimbabwe were not used because large numbers of HIV deaths were miscoded as TB deaths. Improved empirical adjustment procedures for such miscoding have recently been published³⁴. Estimates for India and for South Africa (adjusted for HIV/TB miscoding) were obtained from the Institute of Health Metrics and Evaluation at <http://vizhub.healthdata.org/cod/>, 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. Results from mortality surveys were used to estimate TB mortality in India and Viet Nam as an interim measure.

Among the countries for which VR data could be used (Figure 5), there were 1518 country-year data points 2000–2015, after 10 outlier data points from systems with very low coverage (<20%) as estimated by WHO³⁵ or very high proportion of ill-defined causes (>50%) were excluded for analytical purposes.

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)³⁵. 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 exponential smoothing models for time series³⁶. A penalized likelihood method based on the in-sample fit was used for country-specific model selection. Leading missing values were similarly predicted backwards to 2000.

In 2015, 52% 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 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):

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

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

From the age-specific adjusted (for coverage and ill-defined causes) number of deaths from VR, we first estimate the ratio r_2 of rates in children (M_{0-14}) compared to adults (M_{15+}) (equation 7). The estimation of r_2 is based on a chained equations multiple imputation approach. The imputation model covariates include total notifications, population proportion aged more than 65 years, an indicator variable for the epidemiological region and whether a country was one of the 30 HBCs³⁷. The overall mortality rate for all ages (M) can be expressed as a weighted average of mortality in children and adults, where c is the proportion of children among the general population (equation 8)

$$r_2 = \frac{M_{0-14}}{M_{15+}} \quad (7)$$

$$M = cM_{0-14} + (1 - c)M_{15+} \quad (8)$$

In countries with VR or mortality survey data, M_{0-14} is directly measured. For the sex disaggregation of TB mortality among adults (M_{15+}), sex-specific adjusted (for coverage and ill-defined causes) number of deaths from VR to estimate mortality rates in men M_m and women M_w were used. The ratio of these rates $r_3 = M_m/M_w$ is either directly measured in countries with VR data or imputed in countries without and sex-specific mortality rates are then derived in a manner similar to shown in equation 6.

TB deaths among HIV-positive people were disaggregated by age and sex using the assumption that the child to adult and men to women ratios are the same as the corresponding ratios of AIDS deaths estimated by UNAIDS.

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 draw values from specified distributions in Monte Carlo simulations or else, uncertainty was propagated analytically by approximating the mean and the second central moment of functions of random variables using higher-order Taylor series expansion³⁸ in a matrix based approach³⁹.

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 Evaluation⁴⁰, 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 system³⁵.

WHO's post-2015 global TB strategy, known as the End TB Strategy⁴¹, 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 the 2015 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 (<i>n</i>)	T (<i>n</i>)	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)	42,43
On TB treatment f_t	0.03 (0-0.07)	44

Table 5: Distribution of CFR in HIV-positive individuals

ART	TB treatment	CFR	Sources
off	off	0.78 (0.65-0.94)	42
off	on	0.09 (0.03-0.15)	44,45
< 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

Fig. 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.

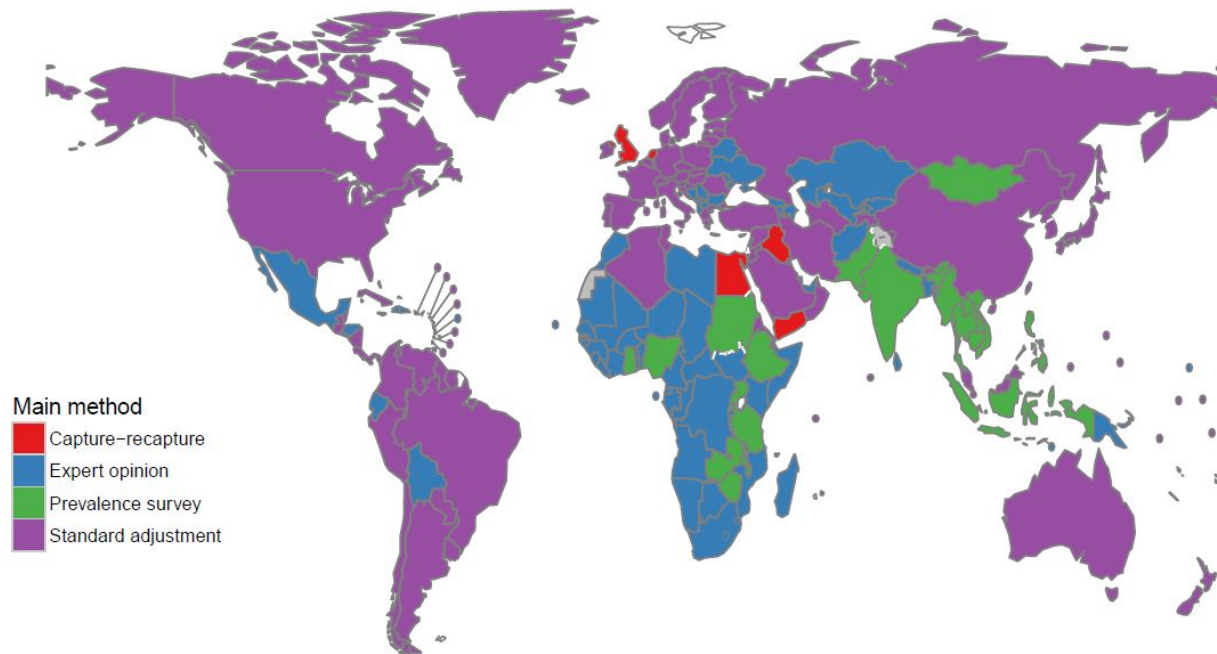


Fig 2. Estimates of TB incidence obtained indirectly (in blue) based on case notifications and expert opinion about detection and reporting gaps prior to a recent national prevalence survey, and derived from prevalence using survey results (in red), corresponding to the survey year (2012-2015). The length of segments indicate uncertainty ranges. Countries are presented in the order of the difference between estimates, grouped by continent. Estimates derived from prevalence are more robust. Post-survey estimates resulted in significant increases in estimated incidence in Nigeria and Indonesia, two countries with large population sizes resulting in a notable impact on global estimates. The often narrow uncertainty ranges of pre-survey estimates reflect a certain level of overconfidence of experts asked to estimate plausibility ranges for incidence. The post-survey estimate in Tanzania is highly uncertain, reflecting data management problems at the time of the survey as well as incomplete laboratory data.

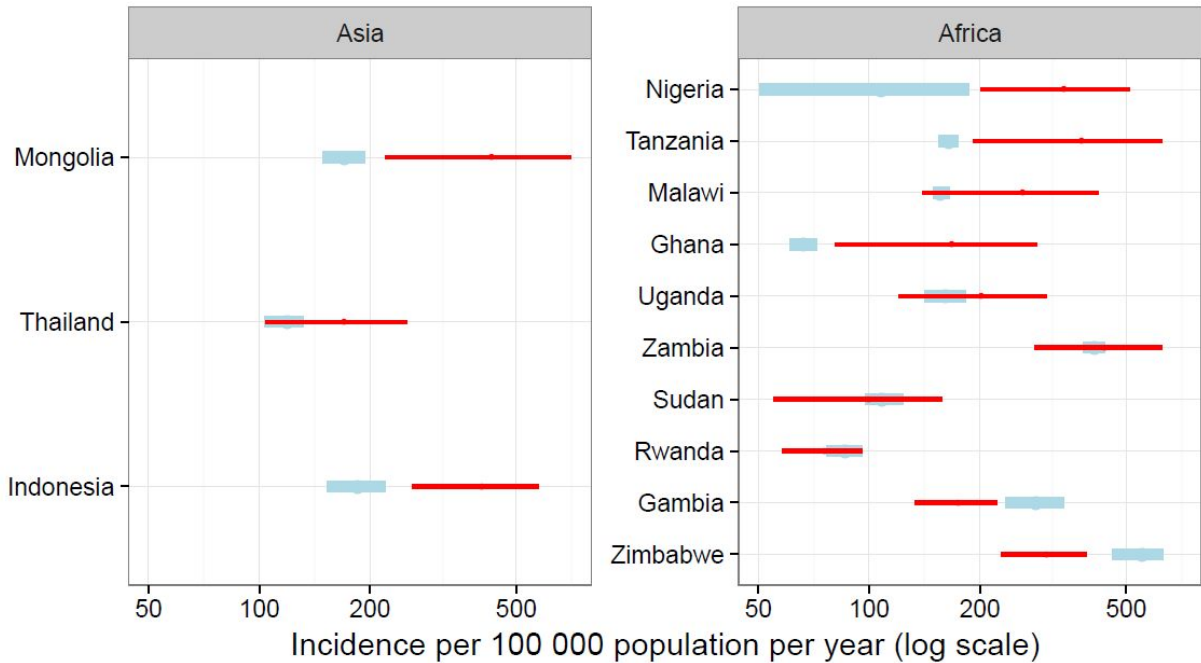


Fig. 3 HIV prevalence rate ratio among prevalent TB cases over notified TB cases in 5 countries (points with area proportional to inverse variance) against HIV prevalence in notified cases. Predicted values of the prevalence rate ratio are shown with a solid line. The dashed lines represent 95% confidence bounds.

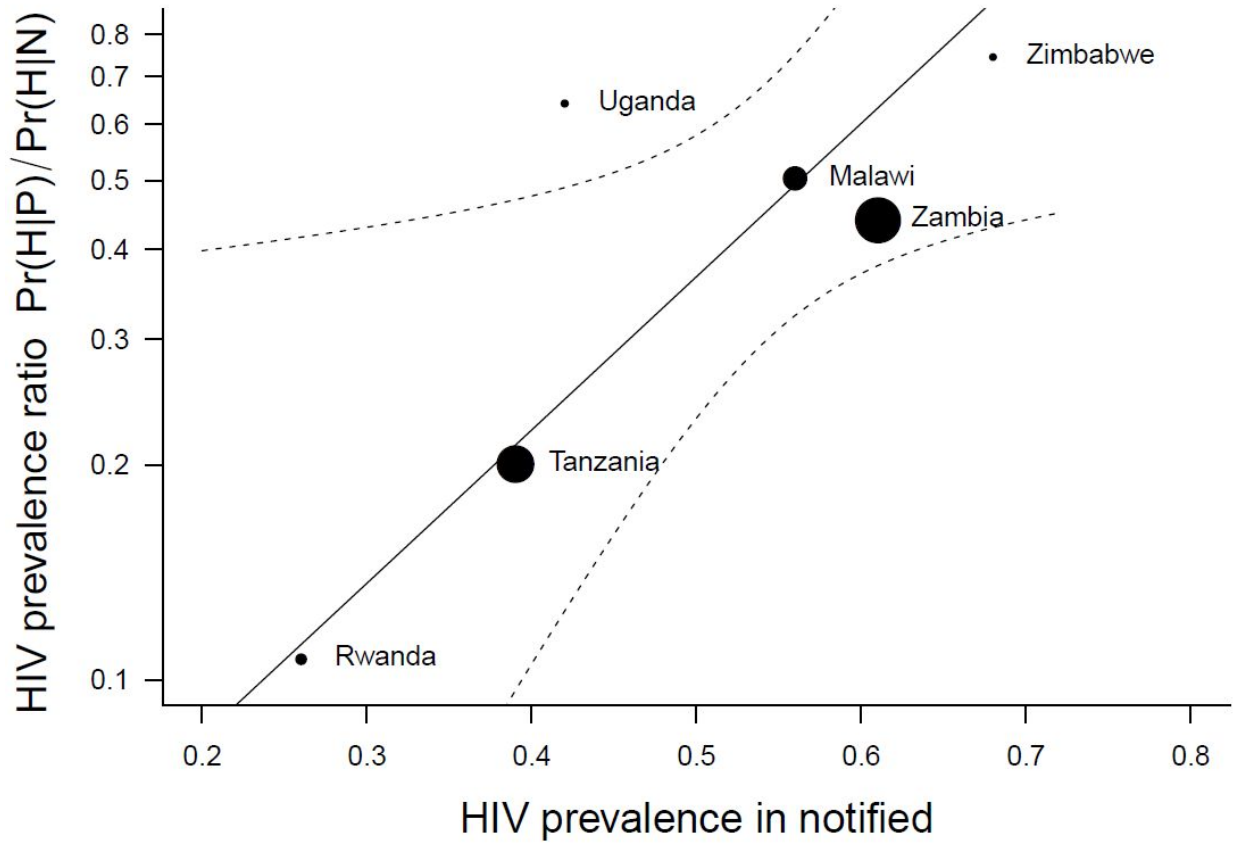
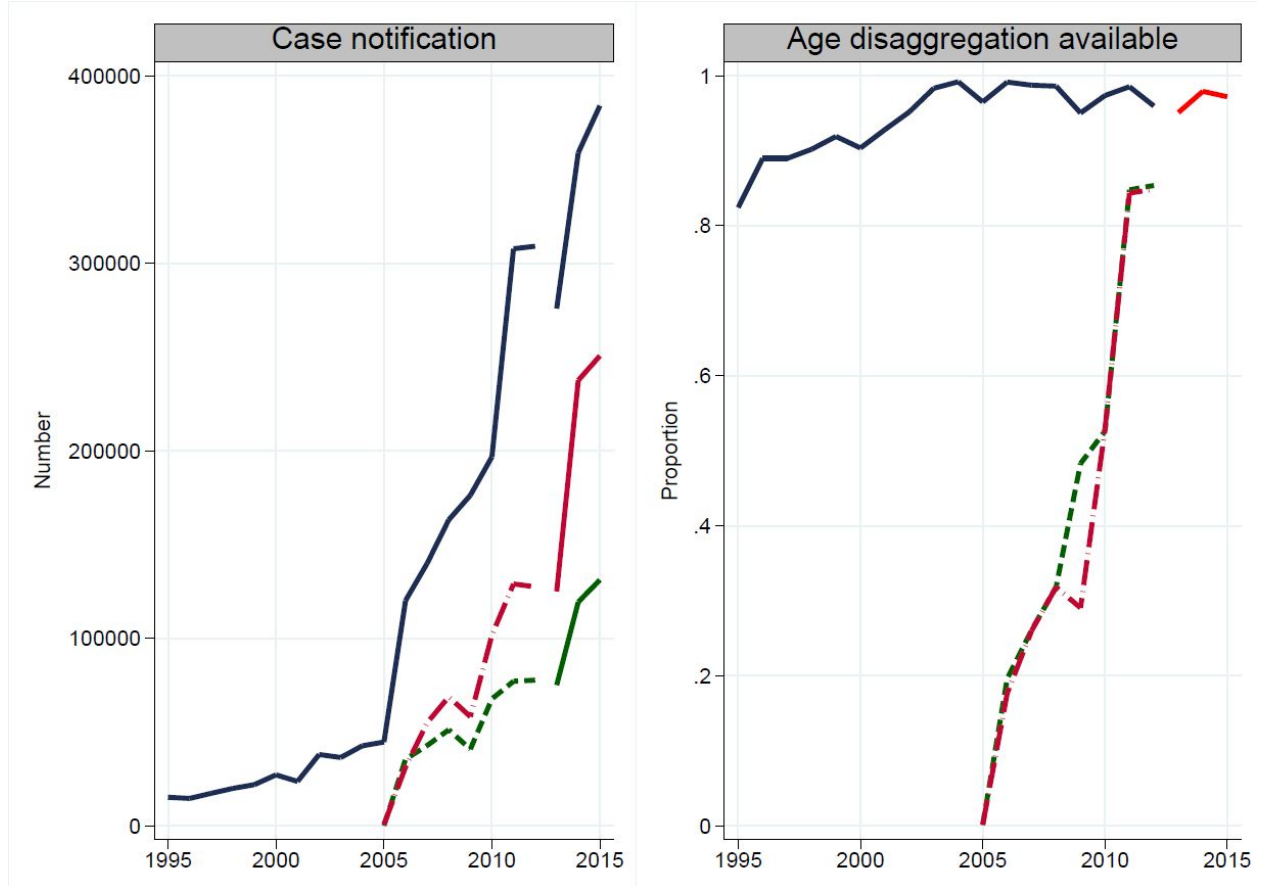


Fig. 4 Global progress in reporting of TB cases among children, 1995–2015(a). Left panel: Number of notifications of cases among children reported to WHO (blue: 0-14, red: 5-14, green: 0-4). Right panel: Percentage of case notifications reported to WHO that are age-disaggregated (blue: new smear positive, 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.

Fig. 5 Countries ($n=128$, in green) for which TB mortality is estimated using measurements from vital registration systems and/or mortality surveys

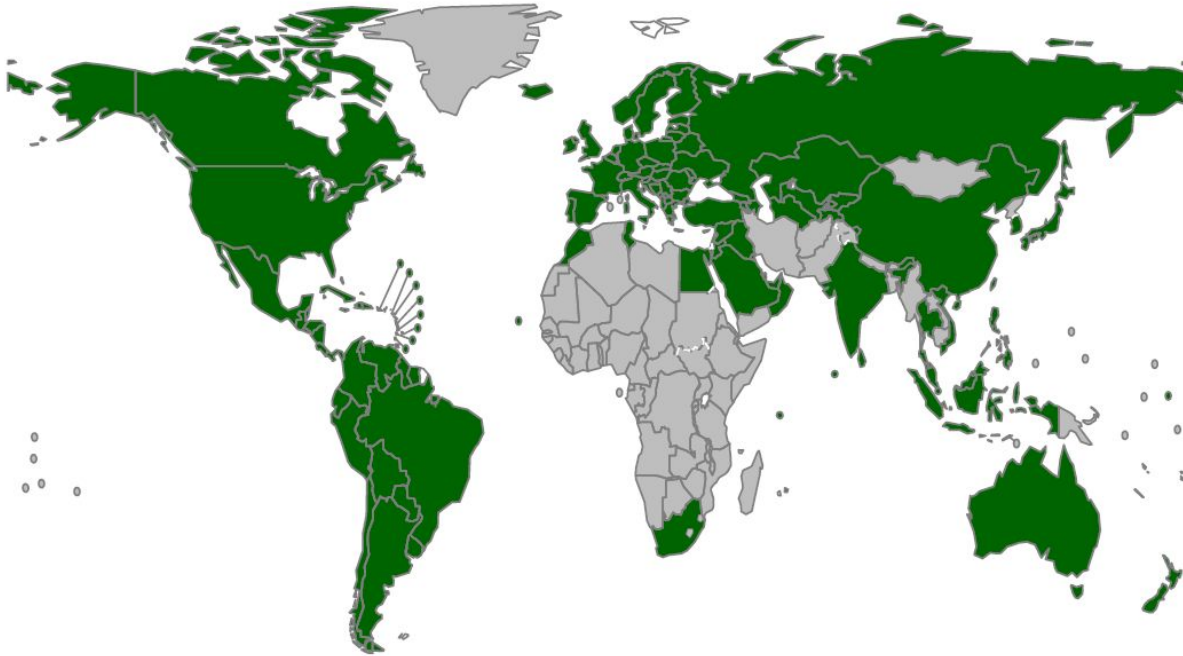
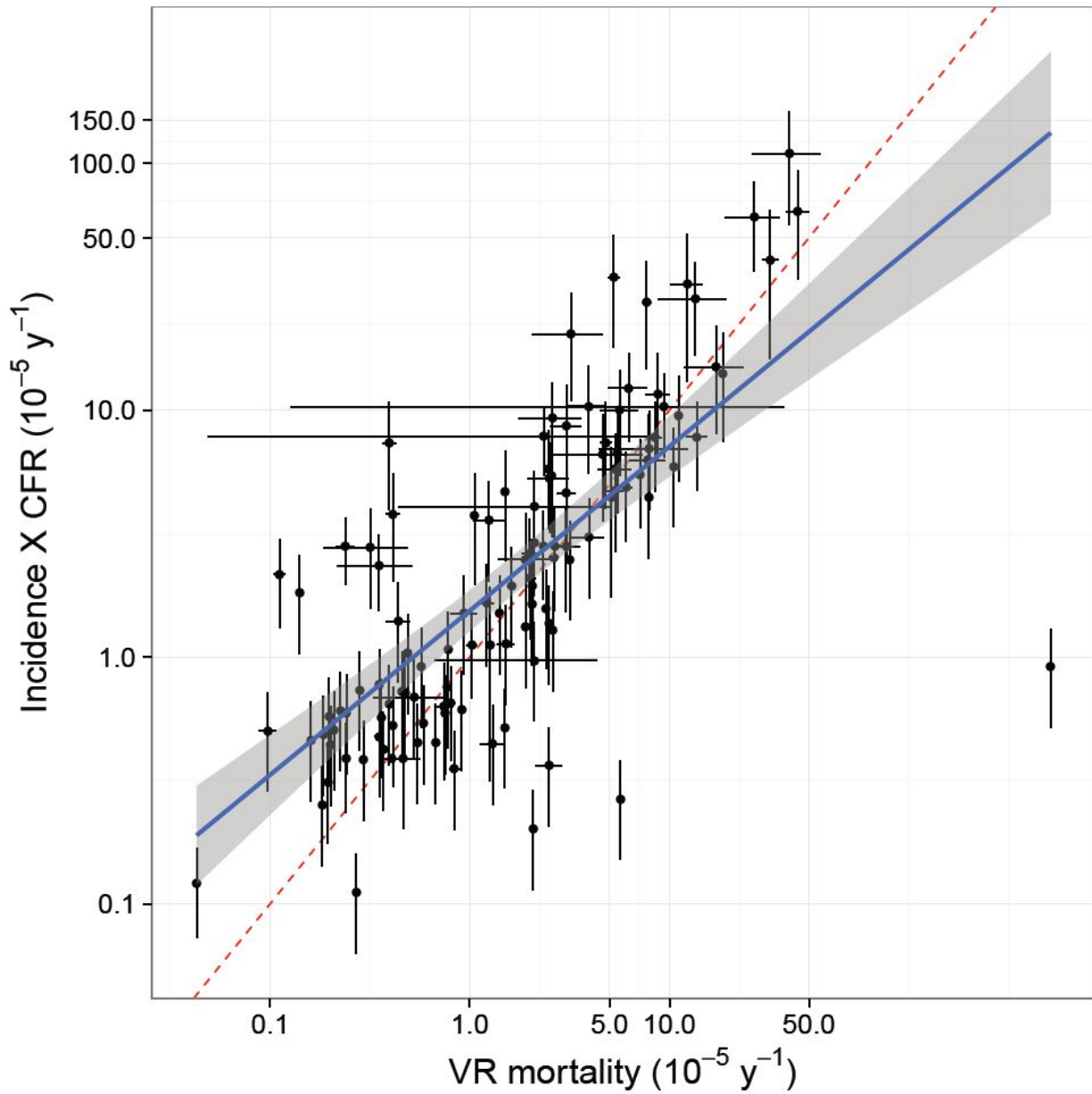


Fig. 6 Comparison of VR mortality (HIV-negative), horizontal axis (log scale) and mortality predicted as the product of incidence and CFR, vertical axis (log scale). Horizontal and vertical segments indicate uncertainty intervals. The dashed red line shows equality. The blue line and associated grey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



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