Global TB Report 2015: Technical appendix on methods used to estimate the global burden of disease caused by TB

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Contents

Abstract ........................................... 2

1 Introduction .................................... 2

2 Definitions ..................................... 3

3 Short historical background .................. 4

4 Incidence ........................................ 5

\hspace{1em} 4.1 Four main methods ...................... 6
\hspace{2em} 4.1.1 Case notification data combined with expert opinion about case detection gaps. ............... 6
\hspace{2em} 4.1.2 Results from national TB prevalence surveys. ....... 8
\hspace{2em} 4.1.3 Notifications in high-income countries adjusted by a standard factor to account for under-reporting and under-diagnosis. ........................................ 12
\hspace{2em} 4.1.4 Capture-recapture modelling. ............... 12

\hspace{1em} 4.2 Disaggregation of incidence ................ 12

\hspace{2em} 4.2.1 HIV-positive TB incidence ................. 12

\hspace{2em} 4.2.2 Disaggregation by age and sex ............. 16

5 Prevalence ....................................... 19

\hspace{1em} 5.1 Population-based surveys .................. 19

\hspace{1em} 5.2 Indirect estimates .......................... 19
Abstract

This document is a technical appendix to Global TB Report 2015. It presents case definitions and methodological details used by WHO 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 (120 countries representing 51% of global incidence); (ii) results from national TB prevalence surveys (19 countries, 46% of global incidence); (iii) notifications in high-income countries adjusted by a standard factor to account for under-reporting and under-diagnosis (73 countries, 3% of global incidence) and (iv) capture-recapture modelling (5 countries, 0.5% of global incidence). Prevalence was obtained from results of national prevalence surveys in 21 countries, representing 69% of global prevalence). In other countries, prevalence was estimated from incidence and disease duration. Mortality was obtained from national vital registration systems of mortality surveys in 129 countries (43% of global HIV-negative TB mortality). In other countries, mortality was derived indirectly from incidence and case fatality ratio.

1 Introduction

Estimates of the burden of disease caused by TB and measured in terms of incidence, prevalence and mortality are produced annually by WHO using information gathered through surveillance systems (case notifications and death registrations), special studies (including surveys of the prevalence of disease),
mortality surveys, surveys of under-reporting of detected TB and in-depth analysis of surveillance data, expert opinion and consultations with countries. This document provides case definitions and describes the methods used in Global TB Report 2015 to derive TB incidence, prevalence and mortality.

2 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. In the remainder of this technical document, relapse cases are referred to as recurrent cases because the term is more useful when explaining the estimation of TB incidence. Recurrent cases may be true relapses or a new episode of TB caused by reinfection. In current case definitions, both relapse cases and patients who require a change in treatment are called *retreatment cases*. However, people with a continuing episode of TB that requires a treatment change are prevalent cases, not incident cases.

**Prevalence** is defined as the number of TB cases (all forms) at a given point in time.

**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 to WHO for a given year. The case notification rate for new and recurrent TB is important in the estimation of TB incidence. In some countries, however, information on treatment history may be missing for some cases. Patients reported in the *unknown history* category are considered incident TB episodes (new or recurrent).

**Regional analyses** are generally undertaken for the six WHO regions (that is, the African Region, the Region of the Americas, the Eastern Mediterranean Region, the European Region, the South-East Asia Region and the Western Pacific Region). For analyses related to MDR-TB, nine epidemiological regions were defined (Figure 1). These were African countries with high HIV prevalence, African countries with low HIV prevalence, Central Europe, Eastern Europe, high-income countries, Latin America, the Eastern Mediterranean Region (excluding high-income countries), the South-East Asia Region (excluding high-income countries) and the Western Pacific Region (excluding high-income countries).

The source of population estimates needed to calculate various TB indicators
was 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.

### 3 Short historical background

Historically, a major source of data to derive incidence estimates were results from tuberculin surveys conducted in children [28]. Early studies showed the following relationship between the annual risk of infection denoted $\lambda$ and the incidence of smear positive TB denoted $I^+$: one smear positive case infects on average 10 individuals per year for a period of 2 years and an annual risk of infection of 1% corresponds approximately to an incidence of 50 smear positive cases per 100,000 per year.

$$I^+ = \lambda \times \frac{10^5}{2 \times 10}$$  

However, the above relationship no longer holds in the context of modern TB control and in HIV settings [32]. In addition to uncertainty about the relationship between $\lambda$ and $I^+$, estimates of incidence obtained from tuberculin surveys suffer from other sources of uncertainty, including unpredictable diagnostic performance of the tuberculin test, digit preference when reading and recording the size of tuberculin reactions, sensitivity to assumptions about reaction sizes attributed to infection, 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 ($46 - 55 \times 10^{-5} y^{-1}$) [29]. A second major reassessment was published in 1999 [11], 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 using equation (1) and 14 prevalence surveys of TB disease were used.

Starting in 1997, global TB reports were published annually by WHO, providing updated data on case notifications and estimated TB burden. In June 2006, the WHO Task Force on TB Impact Measurement was established [10] (see Chapter 2, Box 2.1). The Task Force subgroup on TB estimates reviewed methods and provided recommendations in 2008, 2009 and most recently in March 2015. Methods described in this document reflect short-term recommendations from the 2015 review.

4 Incidence

TB incidence has never been measured 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[39].

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[41]. By August 2015, a total of 38 countries including 16 HBCs had completed the checklist.

Methods currently used by WHO to estimate TB incidence can be grouped into four major categories. Figure 2 shows the distribution of countries according to the four categories:

1. Case notification data combined with expert opinion about case detection gaps (120 countries in red in Figure 2);
2. Results from national TB prevalence surveys (19 countries in blue);

3. Notifications in high-income countries adjusted by a standard factor to account for under-reporting and under-diagnosis (73 countries in green);

4. Capture recapture modelling (5 countries in purple).

Figure 2: 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.

4.1 Four main methods

4.1.1 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, 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 120 countries (Figure 2) that accounted for 51% of the estimated global number of
incident cases in 2014. 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 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 improvements in CFR over time in countries with evidence of improvements in TB control performance such as an 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 $I$ denotes incidence and $M$ 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[37]). In some countries, case reporting coverage changed significantly during the period 1990-2013 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 in the three reference years were assumed to follow a Beta distribution, with parameters $\alpha$ and $\beta$ obtained from the expected value $E$ and variance $V$ using the method of moments[22], as follows

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

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

Time series for the period 1990–2014 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 from 1990 to the first reference year (usually 1997) 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, using equation (4) in section 4.2.1

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

$$= \frac{\vartheta - h}{1 - h}$$

where $h$ is the prevalence of HIV in the general population, $\rho$ is the TB incidence rate ratio among HIV-positive individuals over HIV-negative individuals and $\vartheta$ 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.

### 4.1.2 Results from national TB prevalence surveys.

Incidence was estimated using prevalence survey results in 19 countries that accounted for 46% of the estimated global number of incident cases in 2014. 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 that the rate of change of prevalence with respect to time is negligible: 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 $P = C/N$. $C$ is small relative to $N$ and $(1 - P) \approx 1$. 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 $\Delta t$ and further assuming exponentially distributed durations $d$ such that $d = m^{-1}$

$$I(N - C)\Delta t = mC\Delta t$$
<table>
<thead>
<tr>
<th>Case category</th>
<th>Distribution of disease duration (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notified, HIV-negative</td>
<td>Uniform (0.2 – 2)</td>
</tr>
<tr>
<td>Not notified, HIV-negative</td>
<td>Uniform (1 – 4)</td>
</tr>
<tr>
<td>Notified, HIV-positive</td>
<td>Uniform (0.01 – 1)</td>
</tr>
<tr>
<td>Not notified, HIV-positive</td>
<td>Uniform (0.01 – 0.2)</td>
</tr>
</tbody>
</table>

Table 1: Distribution of disease duration by case category

\[ I = \frac{mC}{N - C} = \frac{P}{d(1 - P)} \approx \frac{P}{d} \]  

In practice, the average duration of disease \( d \) 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 commissioned by the WHO Global Task Force on TB Impact Measurement have provided estimates of the 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 through a simple dynamical model with three compartments: susceptibles \((S)\), untreated TB \((U)\) and treated TB \((T)\). The size of \(U\) and \(T\) is estimated from the prevalence survey findings. 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, \( \mu \) and \( \theta \) denote mortality and self-cure or cure (with subscripts \( u \) and \( t \) indicating untreated and treated cases), respectively, \( \delta \) 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 $d_U = (1 - \pi)U_Td_T$, where $\pi$ is the proportion of incidence that dies or self-cures before treatment. $\pi$ is assumed distributed uniform with bounds 0 and 0.1. Table 2 shows estimates of incidence from four recent prevalence surveys using this method.

Estimates suffer from considerable uncertainty, mostly because surveys are not powered 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). This method provides biased estimates of incidence.

In countries with high-level HIV epidemics that completed a prevalence survey, the prevalence of HIV among prevalent TB cases was found to be 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 5 countries (Malawi, Rwanda, Tanzania, Uganda, Zambia) using a restricted maximum likelihood estimator and setting HIV among notified cases as an effect modifier[35], using the R package metafor[36] (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, validation would require a measurement of incidence. The second method requires a sufficient number of

### Table 2: Incidence estimation based on $U/T$ ratio

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Prevalence $(10^{-3})$</th>
<th>Duration (year)</th>
<th>Incidence $(10^{-3}y^{-1})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia</td>
<td>2002</td>
<td>12 (10-15)</td>
<td>2.9 (1.9-4)</td>
<td>4 (2.5-5.8)</td>
</tr>
<tr>
<td>Cambodia</td>
<td>2011</td>
<td>8.3 (7.1-9.8)</td>
<td>1.2 (0.8-1.6)</td>
<td>6.7 (4.5-9.3)</td>
</tr>
<tr>
<td>Myanmar</td>
<td>2009</td>
<td>6.1 (5-7.5)</td>
<td>1.8 (1.1-1.6)</td>
<td>3.3 (2-4.8)</td>
</tr>
<tr>
<td>Thailand</td>
<td>2012</td>
<td>2.5 (1.9-3.5)</td>
<td>1.1 (0.5-1.6)</td>
<td>2.3 (1-3.5)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence $(10^{-3})$</th>
<th>Incidence - method 1 $(10^{-3}y^{-1})$</th>
<th>Incidence - method 2 $(10^{-3}y^{-1})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia</td>
<td>12 (10-15)</td>
<td>4 (2.5-5.8)</td>
<td>2.2 (1.5 – 2.9)</td>
</tr>
<tr>
<td>Cambodia</td>
<td>8.3 (7.1-9.8)</td>
<td>6.7 (4.5-9.3)</td>
<td>3.8 (2.2 – 5.8)</td>
</tr>
<tr>
<td>Myanmar</td>
<td>6.1 (5-7.5)</td>
<td>3.3 (2-4.8)</td>
<td>3.4 (2 – 5.1)</td>
</tr>
<tr>
<td>Thailand</td>
<td>2.5 (1.9-3.5)</td>
<td>2.3 (1-3.5)</td>
<td>1.1 (0.7 – 1.6)</td>
</tr>
</tbody>
</table>
Figure 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.

If both methods can be applied, 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 $\alpha_i + 1$ and $\beta_i + 1$, respectively, and determined using the method of moments based on equation 2: $I_i \sim B(\alpha_i + 1, \beta_i + 1)$ 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

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

$$\text{Var} = \frac{(\sum \alpha + 1)(\sum \beta + 1)}{(\sum \alpha + \sum \beta + 2)^2 (\sum \alpha + \sum \beta + 3)}$$
4.1.3 Notifications in high-income countries adjusted by a standard factor to account for under-reporting and under-diagnosis.

This method is used for 73 high-income countries (Figure 2), which accounted for 3% of the estimated global number of incident cases in 2014.

In the absence of country-specific data on the quality and coverage of TB surveillance systems, it was assumed that TB surveillance systems from countries in the high-income group performed similarly well, although the model does allow for stochastic fluctuations. The exceptions were the Republic of Korea (see Chapter 2, box 2.3), 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, accounting for stochastic fluctuations.

4.1.4 Capture-recapture modelling.

This method is used for 5 countries: Egypt[5], Iraq[13], the Netherlands[33], the United Kingdom[2] and Yemen[4]. They accounted for 0.5% of the estimated global number of incident cases in 2014. Capture-recapture modelling was considered in studies with at least 3 lists and estimation of list dependencies[39]. 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[1]. In Egypt and Iraq, trends were derived using methods described in section 4.1.1.

4.2 Disaggregation of incidence

4.2.1 HIV-positive TB incidence

In this report, TB incidence is disaggregated by HIV-infection status at country level. TB incidence was disaggregated by HIV and CD4 status using the Spectrum software[25]. WHO estimates of TB incidence were used as inputs to the Spectrum HIV model. The model was fitted to WHO estimates of TB incidence, and then used to produce estimates of TB incidence among people living with HIV disaggregated by CD4 category[21]. A regression method was used to estimate the relative risk (RR) for TB incidence according to the CD4 categories used by Spectrum for national HIV projections[26]. Spectrum data were based on the national projections prepared for the UNAIDS Report on the global AIDS epidemic 2013. The model can also be used to estimate TB mortality among HIV-positive people, the resource requirements associated with recently updated guidance on ART and the impact of ART expansion.
A flexible and relatively simple way of modelling TB incidence (or any time-dependent function) is to represent it as k time-dependent m’th order spline functions

\[ I(x) = \sum_{i=1}^{k} \beta_i B^m_i(x) \]

where \( \beta_i \) is the i’th spline coefficient and \( B^m_i(x) \) represents the evaluation of the i-th basis function at time (year) \( x \). The order of each basis function is \( m \) and cubic splines are used, i.e. \( m = 3 \). The equation simply states that any time-dependent function, such as incidence, can be represented as a linear combination of cubic-spline basis functions.

The values of the cubic-spline coefficients \( \beta \) were determined by an optimization routine that minimizes the least squares error between incidence data \( (I_{obs}) \) and the estimated incidence curve \( I(x) \)

\[ I(x) = \sum_{x=1990}^{2012} |I(x) - I_{obs}(x)|^2 + \lambda \beta^T S \beta \]

Here \( |I - I_{obs}|^2 \) is the sum of squared errors in estimated incidence and \( S \) is a difference penalty matrix applied directly to the parameters \( \beta \) to control the level of variation between adjacent coefficients of the cubic-spline, and thus control (through a choice of \( \lambda \)) the smoothness of the time-dependent case incidence curve. Another important purpose of the use of the smoothness penalty matrix \( S \) is to regularize (by creating smoothness dependencies between adjacent parameters) the ill-conditioned inverse problem (more unknown parameters than the data can resolve) that would tend to over fit the data when left ill-conditioned.

The cubic-spline method was then used to fit an indicator (incidence or notification) to a set of bootstrapped data, obtained by sampling from the normal error distribution with zero mean and a standard deviation of the residuals of the spline regression. This bootstrap method produced a sample of projected cubic-spline curves that inherits the temporal biases and systematic errors of the data. Confidence intervals based on the bootstrapped data, namely 2.5\textsuperscript{th} and 97.5\textsuperscript{th} percentile of projected cubic splines, were typically narrow in the years where the model had data to utilize, and 'spread out' after that, according to a Gaussian process with a linearly increasing variance.

The disaggregation of TB incidence by CD4 category among people living with HIV was based on the idea that an increase in the relative risk for TB incidence is a function of CD4 decline. Williams et al captured this idea in a model for the relationship between the RR for TB and CD4 decline.[43] They suggested a 42\% (+/- 17\%) increase in RR for TB for each unit of 100\( \mu l \) CD4 decline.

The Spectrum-TB model’s disaggregation method is based on the Williams et al. model. The model first estimates incidence among people living with
HIV, and then calculates the 'risk of TB' \( F = I^- / P^- \), where \( I^- \) is TB incidence among people living with HIV and \( P^- \) is the number of people living with HIV who are susceptible to TB.

An assumption is made that the risk of TB infection among people living with HIV with CD4 count > 500 µL is proportional to \( F \) (it was assumed that it was higher by a factor of 2.5).\[24\] For each 100µl CD4 decline in the remaining categories (350-499, 250-349, 200-249, 100-199, 50-99 CD4 cells/µL, and CD4 count less than 50 cells µL), the risk of infection is represented as

\[
F(c < 500) = F(c > 500) \cdot p(1) \cdot p(2) \cdot dc
\]

where \( p(1) \) is a parameter that is used to recognize that people living with HIV and who have high CD4 counts could be at higher risk of TB infection relative to those who are HIV-negative, and \( p(2) \) controls the exponential increase in RR that occurs with CD4 decline. \( dc \) is the number of 100µl CD4 decline associated with the midpoint of each CD4 category relative to 500: \( dc = (3.0, 4.4, 8.6, 12.9, 19.2, 28.6, 37.3) \) for the six CD4 categories.

A reduction in RR is applied for those who have been on ART for more than one year.

To match total TB incidence and estimates of the number of HIV-positive TB cases from HIV testing data where available, it was assumed that \( p(1) = 2.5 \) and \( p(2) \) was fitted accordingly.

In the RR-approach, the 'biological meaning' that should be attached to the parameters and the interpretation of these parameters as regression coefficients need careful consideration. Both parameters can be fitted or both can be fixed. Varying at least \( p(2) \) captures the variation among countries that is expected due to variation in the baseline (HIV-negative) CD4 count, and it strikes a balance between the biological and regression mechanisms.

The RR model approach to estimation of TB incidence was used for people on ART. Although an estimate of TB incidence among people on ART could be obtained from surveillance data reported to WHO (such that it is arguably not necessary to use the RR model), limitations of the ART data (in particular that some countries appear to report cumulative totals of people on ART) meant that the RR approach needed to be used.

Hazard ratios (HR) of 0.35 were assumed for all CD4 at ART initiation categories. Suthar et al have reported HRs of 0.16, 0.35 and 0.43 for those on ART with CD4 count < 200, 200-350 and > 350,\[30\] and these values could in principle be used. However, Spectrum tracks only CD4 at initiation, thus limiting the use of CD4-specific HRs for people on ART.

It was further assumed that the HR of 0.35 applies only to patients on ART for more than six months. Spectrum’s ART-mortality estimates, derived mostly from ART cohorts in Sub-Saharan Africa, suggest that mortality remains very high in the first six months of ART. Since TB is a leading contributor to mortality among HIV-positive people, it was judged that the HR for patients on ART for less than 6 months is likely to remain high; therefore, a reduction factor due to ART was not applied for this subset of patients.
A simple least squares approach was used to fit the model to total TB incidence, and to all available estimates of TB incidence among people living with HIV. These estimates of TB incidence among people living with HIV were obtained by three sampling methods: population surveys of the prevalence of HIV among TB cases (least biased, but scarce due to logistical constraints), sentinel HIV data (biases include more testing of people with advanced HIV-related disease) and routine HIV testing of reported TB patients (variable coverage). To increase the influence of survey data, replicas of the survey data were included in the likelihood function. In other words, for years for which data from HIV testing were available, identical copies of the HIV-test data were added to the likelihood function. The estimate of total TB incidence was based on much more data, evenly spread out in the estimation period 1990–2015.

Model testing showed that using two replicates of the HIV survey data (i.e. duplicating the survey data) and two replicates of the routine testing data with coverage greater than 90%, was the best approach to disaggregating TB incidence: the fit passed close to the survey or high-coverage routine testing data points that were available. For each of a) HIV sentinel and b) routine testing with coverage between 50–90%, data were not used.

As with the main indicators, confidence intervals are based on a bootstrap method. For this method all data sources are sampled from assumed underlying distributions: total incidence data is sampled from normally bootstrap result set for total incidence, survey and sentinel HIV data are sampled from beta distributions and routine HIV testing among reported cases are sampled from a normal distribution, using the variance of the sample number of the number who tested HIV positive.

For countries with no data, a range for \( p(2) \) was estimated from countries with survey or testing data, which suggest that \( p(2) = 1.96[1.8 - 2.1] \). The RR-model was then fitted to total TB incidence only. There is no satisfactory way to verify results for TB incidence among people living with HIV when no HIV-testing data are available. However, comparison of the global estimate for TB incidence among people living with HIV produced by Spectrum and estimates based on a different method using HIV prevalence instead of CD4 distributions and using HIV-test data in a different way suggests that the RR-model works reasonably well. The comparative method to disaggregate TB incidence by HIV is derived as follows, where the \( I \) and \( N \) denote incident cases and the total population, respectively, superscripts + and - denote HIV status, \( \vartheta \) is the prevalence of HIV among new TB cases, \( h \) is the prevalence of HIV in the general population and \( \rho \) is the incidence rate ratio (HIV-positive over HIV-negative).
\[ \rho = \frac{I^+/N^+}{I/N} > 1 \]

\[ \rho I^+ = N^+ \]

\[ \rho I^+ - I^- = \frac{N^-}{N^+} \]

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

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

The TB incidence rate ratio \( \rho \) is estimated by fitting the following linear model with a slope constrained to 1

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

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 (Table 8). However, this source of data is affected by biases, particularly when coverage is closer to 50% than to 100%. In all countries with repeat data from testing, the relationship between the prevalence of HIV in TB patients and the coverage of HIV testing was examined graphically. In some countries, the prevalence of HIV in TB patients was found to decrease with increasing HIV testing coverage while in others it increased with increasing HIV testing coverage; in most countries, the prevalence of HIV followed highly inconsistent patterns (with repeat changes in direction) as HIV testing coverage increased. Therefore, it was not possible to adjust for the effect of incomplete coverage of HIV testing on estimates of the prevalence of HIV among TB patients. The assumption was thus made that TB patients with an HIV test result were statistically representative of all TB cases. As coverage of HIV testing continues to increase globally, biases will decrease.

4.2.2 Disaggregation by age and sex

This section describes how estimates of TB incidence and TB mortality are disaggregated by age and sex. Specifically, estimates are estimated for men (defined as males aged \( \geq 15 \) years), women (defined as females aged \( \geq 15 \) years) and children (defined as people aged \( < 15 \) years). The cut-off of 15 years is used because it is consistent with the age categories for which notification data are reported and with the cut-off used in current guidelines to define people eligible to participate in a TB prevalence survey.

TB incidence disaggregated by age. Age and sex disaggregation of acid-fast 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, coverage kept improving until for 2012 case notifications it reached 99%, 83% and 83% out of total acid-fast smear-positive, smear-negative and extrapulmonary tuberculosis case notifications notified respectively that were age and sex disaggregated. 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)\[40\]. This current revision requests the reporting of all new and relapse case notifications by age and sex (but not separately by case type). The countries that reported age-disaggregated data in 2014 can be seen in Figure 4.

![Graph showing reporting of new and relapse TB case notifications disaggregated by age, 2014](image)

Figure 4: Reporting of new and relapse TB case notifications disaggregated by age, 2014

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\[5\]\[33\]\[34\], none have produced precise enough age-disaggregated results. Small-scale, convenient-sampled studies in some settings indicate that under-reporting of childhood tuberculosis is very high\[17\]\[7\] but extrapolation to nationally representative, regional and global settings is not yet possible. This shortcoming is currently being addressed through the plans for implementation of national scale surveys in high priority countries in Asia to measure under-
reporting of tuberculosis in children[42].

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. However, progress is being made, based on collaborations established in 2013 between WHO and academic groups working on the estimation of TB disease burden among children, as well as recommendations from a global consultation on methods to estimate TB disease burden held earlier in 2015. As a result, methods to estimate TB incidence were updated for this report compared with those used to produce estimates published in 2013 and 2014. The updated methods involve use of a statistical ensemble approach in which results from two independent methods are combined with the original WHO approach that featured in the 2012 Global TB Report.

The first method is based on the original WHO approach that estimated incidence of TB among children using case notification data among ages 0-14 combined with expert opinion about case detection gaps (as described in section 4.1.1) assuming these were the same in children as in TB cases of all ages. For the first time in this year’s report child specific case detection gaps are being used as estimated according to a previously published method[15] that has been updated to use more recent notification and other available data[23]. This method estimates the proportion of all TB cases that are in children as a function of expected age-specific proportions of smear-positive TB among different age groups.

A second method, independent of case notification data, estimates TB incidence in children using 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[9].

Both methods produce country level estimates which are then aggregated at the regional and global levels.

Since the two methods can be assumed independent in their approach to estimate the same parameter, they have been combined using the same ensemble approach described in section 4.1.3.

**TB incidence disaggregated by sex.** 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 national prevalence surveys of bacteriologically-positive pulmonary TB consistently show bigger recording and detection gaps in men as suggested by consistently higher prevalence to case notifications ratios in men compared with women[20]. This suggests that our assumption of no sex differential in the detection of incident cases may 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

\[
\begin{align*}
\rho_1 &= \frac{I_m}{I_w} \\
I_a &= I_m + I_w
\end{align*}
\]

(6) (7)

Country level estimates are generated and then aggregated at the regional and global levels.

5 Prevalence

5.1 Population-based surveys

The best way to measure the prevalence of TB is through national population-based surveys of TB disease\cite{12}\cite{38}. Data from such surveys are available for an increasing number of countries and were used for 21 countries (Figure 5), representing 69% of global prevalence in 2014. It should be noted, however, that measurements of prevalence are typically confined to the adult population. Furthermore, prevalence surveys 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 \( \geq 15 \) measured from national survey \( (P_a) \), adjusted for pulmonary TB in children \( (P_c) \) and extra-pulmonary TB all ages \( (P_e) \):

\[
P_p = cP_c + (1-c)P_a
\]

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

\[
P = \frac{P_p}{1 - P_e}
\]

Surveys are logistically demanding, therefore suboptimal quality of prevalence survey data (e.g. low participation rate, missing lab results) may result in biases of estimates. The estimate of overall prevalence \( P \) is affected by sampling uncertainty (relative precision is typically about 20%), and uncertainty about \( P_c \) and \( P_e \). The quality of routine surveillance data to inform levels of pulmonary TB in children and extra-pulmonary TB for all ages is often questionable.

5.2 Indirect estimates

Indirect estimates of prevalence were calculated by solving equation 3 for \( P \):

\[
P = \sum I_{i,j}d_{i,j}, i \in \{1,2\}, j \in \{1,2\}
\]

(8)
where the index variable $i$ denotes HIV+ and HIV−, the index variable $j$ denotes notified and non-notified cases, $d$ denotes the duration of disease in notified cases and $I$ is total incidence. In the absence of measurements, we did not allow duration in notified cases to vary among countries.

When there is no direct measurement from a national survey of the prevalence of TB disease, prevalence is the most uncertain of the three TB indicators used to measure disease burden. This is because prevalence is the sum of products of two uncertain quantities (equation 8): (i) incidence and (ii) disease duration. The duration of disease is very difficult to quantify because it cannot be measured during surveys of the prevalence of TB disease (surveys truncate the natural history of disease). Duration can be assessed in self-presenting patients, but there is no practical way to measure the duration of disease in patients who are not notified to NTPs.

Given their underlying uncertainty, prevalence estimates should be used with great caution in the absence of direct measurements from a prevalence survey. There is scarce empirical data on disease duration (of note, a typically large proportion of bacteriologically confirmed cases detected during TB prevalence surveys did not report symptoms suggestive of TB at the time of survey investigations). Unless measurements were available from national programmes (for example, Turkey), assumptions of the duration of disease were used as shown in Table 1. An important limitation is that duration is considered constant within case categories for all settings and over time.
6 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). Deaths from TB in HIV-positive people are coded under HIV-associated codes. Two methods were used to estimate TB mortality among HIV-negative people:

- direct measurements of mortality from VR systems or mortality surveys (129 countries, in green in Figure 6);
- indirect estimates derived from multiplying estimates of TB incidence by estimates of the CFR (88 countries).

Each method is described in more detail below.

![Figure 6: Countries (in green) for which TB mortality is estimated using measurements from vital registration systems ($n = 127$) and/or mortality surveys ($n = 2$)](image)

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

Data from VR systems are reported to WHO by Member States and territories every year. In countries with functioning VR systems in which causes of death are coded according to the two latest revisions of the International classification
of diseases (underlying cause of death: ICD-10 A15-A19, equivalent to ICD-9: 010-018), VR data are the best source of information about deaths from TB among people not infected with HIV. 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.

TB mortality data obtained from VR systems are essential to understand trends in TB disease burden where case notifications have incomplete coverage or their coverage is not documented through an inventory study.

As of July 2015, 130 countries had reported mortality data to WHO (including data from sample VR systems and mortality surveys). These 130 countries included 10 of the 22 high TB burden countries (HBCs): Brazil, China, India, Indonesia, the Philippines, the Russian Federation, South Africa, Thailand, Viet Nam and Zimbabwe. However, the VR data on TB deaths from Zimbabwe were not used for this report because large numbers of HIV deaths were miscoded as TB deaths. Improved empirical adjustment procedures have recently been published[6]. Estimates for South Africa adjusted for HIV/TB miscoding were obtained from the Institute of Health Metrics and Evaluation at http://vizhub.healthdata.org/cod/. Results from mortality surveys were used to estimate TB mortality in India and Viet Nam.

Among the countries for which VR data could be used (see Figure 6), there were 2361 country-year data points 1990–2014, after 13 outlier data points from systems with very low coverage (<20%) as estimated by WHO[18] or very high proportion of ill-defined causes (>50%) were excluded for analytical purposes. The median number of data points per country was 21 (IQR 15 - 23).

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 code B46, ICD-10 codes R00–R99).[18]

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 \( \kappa_a \) was obtained from the VR report \( \kappa \) 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:
Table 4: Distribution of CFRs by case category

<table>
<thead>
<tr>
<th>Case Category</th>
<th>CFR</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not on TB treatment</td>
<td>0.43 (0.28-0.53)</td>
<td>[8] [31]</td>
</tr>
<tr>
<td>On TB treatment</td>
<td>0.03 (0.00-0.07)</td>
<td>[27]</td>
</tr>
</tbody>
</table>

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. Trail-
ing missing values were predicted using exponential smoothing models for time
series[14]. A penalized likelihood method based on the in-sample fit was used
for country-specific model selection. Leading missing values were similarly pre-
dicted backwards to 1990.

In 2014, 43% 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 57% was estimated using the indirect methods described
in the next section.

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

In 88 countries lacking VR 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):

\[
M^* = (I - T^*)f_u + T^*f_t
\]

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.

This approach tends to overestimate TB mortality in countries with no VR
or mortality survey data and the level of under-reporting of treated TB cases is
unknown and large relative to the number of reported cases.

Figure 7 shows a comparison of 129 VR-based mortality estimates for 2014
and indirect estimates obtained from the CFR approach for the same countries.
It should be noted that 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.

Figure 7: 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.

6.3 Estimating TB mortality among HIV-positive people

No nationally representative measurements of HIV-associated TB mortality were available from VR systems for use in this report. In the absence of direct measurements, TB mortality among HIV-positive people was estimated indirectly according to the following methods (also see section 4.5) implemented in the Spectrum software (available at http://www.futuresinstitute.org/spectrum.aspx).

TB mortality is calculated as the product of HIV-positive TB incidence (see section 4.5) and case fatality ratios:

\[ M^+ = (I^+ - T^+)f_u^+ + T^+ f_t^+ \]
where $I^+$ represents incident TB cases among people living with HIV, $N$ represents HIV-positive cases that are treated, $(I^+ - T^+)$ represents HIV-positive TB cases that are not treated and $M^+$ represents TB mortality among HIV-positive people. $f_t^+$ and $f_n^+$ are the case fatality ratios for treated and non-treated incident cases, respectively. 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 ratio of the point estimates for incident and notified cases, adjusted for under-reporting. A single CFR was used for all bootstrapped mortality estimates.

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 needed to initiate the implementation of sample VR systems as an interim measure.

### 6.4 Disaggregation of TB mortality by age and sex

#### 6.4.1 TB deaths among HIV-negative people

From the age-specific adjusted (for coverage and ill-defined causes) number of deaths from VR, we first estimated the ratio $r_2$ of rates in children ($M_{0-14}$) compared to adults ($M_{15+}$) \((9)\). The estimation of $r_2$ was based on a chained equations multiple imputation approach. The imputation model covariates included total notifications, population proportion aged more than 65 years, an indicator variable for the epidemiological region and whether a country was one of the 22 high-burden countries. 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 \((10)\).

\[
\begin{align*}
  r_2 & = \frac{M_{0-14}}{M_{15+}} \\
  M & = cM_{0-14} + (1-c)M_{15+}
\end{align*}
\]
In countries with VR or mortality survey data, $M_{0-14}$ is directly measured. For countries without VR data, an imputation step is necessary where the ratio $r_2$ is predicted from a regression model with risk factors known to be associated with TB. The following variables were investigated for inclusion in the model: infant mortality rate per 1000 live births; gross domestic product per capita; HIV prevalence among the general population; the percentage of the total population aged $\geq 15$ and $\geq 65$ years; the TB treatment success rate; the total number of newly notified TB cases per year; whether or not a country had a high or low burden of MDR-TB; whether a country was among the 22 HBCs or not. For the sex disaggregation of TB mortality among adults ($M_{15+}$), we use sex-specific adjusted (for coverage and ill-defined causes) number of deaths from VR to estimate mortality rates in men $M_m$ and women $M_w$ (11). The ratio of these rates $r_3$ (12) is either directly measured in countries with VR data or imputed in countries without.

\[
M_{15+} = M_w + M_m \quad (11)
\]
\[
\frac{M_m}{M_w} = r_3 \quad (12)
\]

6.4.2 TB deaths among HIV-positive people

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 sex ratios of AIDS deaths estimated by UNAIDS, which are estimated for all countries in the world. Once ratios are calculated, equations (9)-(12) can be used to complete disaggregation of TB deaths among HIV-positive people in children, men and women.

7 Drug resistance

Global and regional estimates of the proportion of new and retreatment cases of TB that had MDR-TB in 2014 were calculated using country-level information. If countries had reported data on the proportion of new and retreatment cases of TB that have MDR-TB 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-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 (for country groups see Figure 1). The observed and imputed estimates of the proportion of new and retreatment
cases of TB that have MDR-TB were then pooled to give a global estimate, with countries weighted according to their share of global notifications of new and retreatment cases.

7.1 MDR-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. Therefore, a systematic review and meta-analysis of the published literature were undertaken to estimate the relative risk of dying from MDR-TB compared with non MDR-TB. The global estimate of MDR-TB deaths (Chapter 2) was then based on the following formula:

$$m = Mpr$$

where $m$ denotes global MDR-TB mortality, $M$ is global TB mortality, $p$ is the overall proportion of MDR-TB among prevalent TB cases, approximated by the weighted average of the proportion of new and retreated cases that have MDR-TB and $r$ is the relative risk of dying from MDR-TB versus non-MDR-TB.

7.2 Number of incident cases of MDR-TB
The global estimate of MDR-TB incidence was calculated as the addition of three groups of MDR-TB incident cases:

1. incident MDR-TB among new pulmonary and extra-pulmonary incident TB cases, using the proportion of MDR-TB among new cases from drug resistance surveillance (DRS);
2. incident MDR-TB among relapses, using the proportion of MDR-TB among new cases from DRS and the estimated relative risk of MDR among relapse versus new cases; and
3. incident MDR-TB among retreated cases that are not relapses, which was assumed to follow a uniform distribution with bounds 0 and the upper limit of the global proportion of MDR-TB among retreated cases estimated from DRS.

7.3 Resistance to second-line drugs among patients with MDR-TB
Data from 73 countries and 5 territories were used to produce global estimates of the following proportions: (i) patients with MDR-TB who had XDR-TB; (ii) patients with MDR-TB who had fluoroquinolone resistance; (iii) patients
with MDR-TB who had resistance to second-line injectable drugs and fluoroquinolones but not XDR-TB. The latest available national and subnational data from each country were analysed using logistic regression models with robust standard errors to account for the clustering effect at the level of the country or territory. The analysis was limited to countries in which more than 66% of MDR-TB cases received second-line DST.

8 Projections of TB incidence, prevalence and mortality rates up to 2015

Projections of incidence, prevalence and mortality up to 2015 enable assessment of whether global targets set for 2015 are likely to be achieved at global, regional and country levels. Projections for the year 2015 were made using exponential smoothing models fitted to data from 2007–2014. The projection is based on an algorithm that selects the best among models within a family of exponential smoothing models, using a penalized likelihood method as a selection criterion[14]. Tested models include trend components in the following list: no trend, additive, additive damped, multiplicative, or multiplicative damped, with no seasonal components, with additive and multiplicative error terms. Point forecasts are computing using the best model with optimized parameters and uncertainty is propagated using analytical methods described in the next section.

9 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.

We used fixed population values from the UNPD. We did not account for any uncertainty in these values. 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, but may sometimes reflect abrupt changes in TB epidemiology (for example, resulting from a rapid influx of migrants from countries with a high burden of TB, or from rapid improvement in case-finding efforts).

Missing national aggregates of new and recurrent cases were imputed by interpolation. Notification trajectories were smoothed using a penalized cubic...
splines function with parameters based on the data. Attempts to obtain corrections for historical data are made every year, but only rarely do countries provide appropriate data corrections.

Mortality estimates incorporated the following sources of uncertainty: sampling uncertainty in the underlying measurements of TB mortality rates from data sources, uncertainty in estimates of incidence rates and rates of HIV prevalence among both incident and notified TB cases, and parameter uncertainty in models. Time series of TB mortality were generated for each country through Monte Carlo simulations. Unless otherwise specified, uncertainty bounds and ranges were defined as the 2.5th and 97.5th centiles of outcome distributions. Throughout this report, ranges with upper and lower bounds defined by these centiles are provided for all estimates established with the use of simulations. When uncertainty was established with the use of observed or other empirical data, 95% confidence intervals are reported.

The model used the following steps:

1. Estimating overall TB incidence after review and cleaning of case notification data;
2. Cleaning and adjusting raw mortality data from VR systems and mortality surveys, followed by imputation of missing values in countries with VR or survey data – in some countries, step 1 was updated to account for mortality data;
3. Cleaning of measurements of HIV prevalence among TB patients followed by estimating HIV-positive TB incidence using the Spectrum programme and HIV-positive TB mortality;
4. Estimating HIV-negative TB mortality in countries with no VR data followed with an update of step 1 in some countries;
5. Reviewing prevalence measurements, adjusting for childhood TB and bacteriologically unconfirmed TB, and estimating prevalence followed with an update of step 1 in some countries;
6. Estimating incidence and mortality disaggregated by age and sex and disaggregated by drug resistance status;

The general approach to uncertainty analyses was to draw values from specified distributions for every parameter (except for notifications and population values) in Monte Carlo simulations, with the number of simulation runs set so that they were sufficient to ensure stability in the outcome distributions. For each country, the same random generator seed was used for every year, and errors were assumed to be time-dependent within countries (thus generating autocorrelation in time series). Regional parameters were used in some instances (for example, for CFRs). Summaries of quantities of interest were obtained by extracting the mean, 2.5th and 97.5th centiles of posterior distributions.
Wherever possible, to shorten computing time, uncertainty was propagated analytically by approximating the mean and the second central moment of functions of random variables using higher-order Taylor series expansion[16], using a matrix based approach[3] illustrated with the following transformations based on two random variables $x_1$ and $x_2$ with known distributions so that $y = f(x_i)$

$$E[y] = f(\bar{x}_i)$$
$$\sigma^2_y = \nabla_x C_x \nabla^T_x = \left( \sum_{i=1}^{2} \frac{\partial f}{\partial x_i} \sigma_i \right)^2$$

where $E(y)$ denotes the expectation of $y$, $\sigma^2_y$ is the variance of $y$, $\nabla_x$ is the $p \times n$ gradient matrix with all partial first derivatives, $C_x = \text{the } p \times p \text{ covariance matrix}$.

The first order Taylor expansion assumes linearity over $\bar{x}_i$. We used second-order expansions to correct for bias in non-linear expressions.

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