Technical Appendix - Methods used to estimate the global burden of disease caused by TB

This online technical appendix explains the methods that were used to produce estimates of the global burden of disease caused by TB (measured in terms of incidence, prevalence and mortality). It has eight major sections:

- **General approach**. This section provides some background information about the methods used to produce estimates of disease burden.
- **Definitions**. This section defines TB incidence, prevalence and mortality, the case fatality rate (CFR) and the case notification rate. It also explains the regions for which estimates of disease burden are produced and sources of information on population estimates.
- **Estimates of TB mortality, 1990–2013**. This section explains the three methods used to estimate TB mortality, and the countries for which they were applied. Methods for estimating the number of HIV-associated TB deaths and for disaggregation of TB mortality by age and sex are also described.
- **Estimates of TB incidence, 1990–2013**. This section explains the main methods used to estimate TB incidence, and the countries for which they were applied. Methods to estimate the prevalence of HIV among incident TB cases are described.
- **Estimates of TB prevalence, 1990–2013**. This section explains the two methods used to estimate TB prevalence, and the countries for which they were applied.
- **Estimates of multidrug-resistant TB (MDR-TB) incidence and mortality**. This section explains the main methods used to estimate MDR-TB mortality and incidence based on drug resistance surveillance data and parameters obtained from a recent literature review.
- **Projections of TB incidence, prevalence and mortality**. This section explains how projections for 2014 and 2015 were produced.
- **Uncertainty framework**. This section explains the general approach to including uncertainty in all estimates.

1.   General approach

Estimates of the burden of disease caused by TB (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 and in-depth analyses of surveillance data), expert opinion and consultations with countries. Two recent publications provide up-to-date guidance about how TB incidence, prevalence and mortality should be measured,[1] based on the work of the WHO Global Task Force on TB Impact Measurement.[2] The methods used to estimate the burden of disease

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[1] *TB impact measurement: policy and recommendations for how to assess the epidemiological burden of TB and the impact of TB control*. Geneva, World Health Organization, 2009 (Stop TB policy paper, no. 2; WHO/HTM/TB/2009.416). The policy paper is available on the Task Force web site: www.who.int/tb/advisory_bodies/impact_measurement_taskforce

[2] For further details, see the Task Force web site at: www.who.int/tb/advisory_bodies/impact_measurement_taskforce

were updated in 2009 following 18 months of work by an expert group convened by the Task Force. These updates were endorsed at a meeting of the full Task Force in March 2010. Improvements to methods included systematic documentation of expert opinion and how this has been used to produce estimates of disease burden, simplification of models, [1] updates to parameter values based on the results of systematic reviews, much greater use of mortality data from vital registration (VR) systems and systematic documentation of uncertainty (hence the uncertainty intervals shown on all of the estimates of disease burden in this report).

Estimates are based on a snapshot of the online database taken on 29 July 2014.

2.   Definitions

2.1   Incidence, prevalence, mortality, case fatality rate, case notification rate

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 (Box 4.1, Chapter 4). In the remainder of this online technical appendix, 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, 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.[2]

The **case notification rate** refers to new and recurrent episodes of TB notified to WHO for a given year, expressed per 100 000 population. 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. When data on treatment history are not available, recurrent cases cannot be distinguished from cases whose treatment was changed, since both are registered and reported in the category 'retreatment'. Patients reported in the 'unknown history' category are considered incident TB episodes (new or relapse). This is a change from previous years in view of past difficulties to estimate with NTPs the proportion of true

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[1] For example, some parameter values are now estimated only at global level or for regions, rather than for each country individually.

[2] Straetemans M et al. Assessing tuberculosis case fatality ratio: a meta-analysis. *PLoS One*. 2011, 6(6):e20755.

new or relapse TB episodes in this category of patients (previously, patients with unknown treatment history were not considered new or relapse cases). This change affects relatively few countries, mostly in Western Europe.

2.2   Regions

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. These were African countries with high HIV prevalence, African countries with low HIV prevalence, Central Europe, Eastern Europe, high-income countries,[1] 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 countries in these nine regions are listed in Appendix 1.

2.3   Population estimates

The source of population estimates needed to calculate various TB indicators was the 2013 revision of the *World Population Prospects,* which is produced by the United Nations Population Division (UNPD).[2] The UNPD estimates sometimes differ from those made by countries.

3.   Estimates of TB mortality, 1990–2013

The best sources of data about deaths from TB (excluding TB deaths among HIV-positive people) are 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;
- indirect estimates derived from multiplying estimates of TB incidence by estimates of the CFR.

Each method is described in more detail below. Details on the method used for each country are available online at
www.who.int/tb/publications/global_report/gtbr14_mortality_source.csv.

3.1   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*

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[1] High-income countries are defined by the World Bank as countries with a per capita gross national income (GNI) of ⩾US$ 12 746 in 2013.
[2] http://esa.un.org/unpd/wpp/ (accessed June 2013).

(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 understanding trends in TB disease burden where case notifications have incomplete coverage or their coverage is not documented through an inventory study. An updated description of the global coverage and quality of VR data is available in *World Health Statistics 2013*.[1]

As of July 2014, 130 countries had reported mortality data to WHO (including data from sample VR systems and mortality surveys), among 219 countries and territories from which TB data had been requested at least once since 1990. These 130 countries included 9 of the 22 high TB burden countries (HBCs): Brazil, China, India, the Philippines, the Russian Federation, South Africa, Thailand, Viet Nam and Zimbabwe. However, the VR data on TB deaths from South Africa and 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,[2] and options for specific post-hoc adjustments for misclassification errors in the measurement of TB mortality will be reviewed extensively by the WHO Global Task Force on TB Impact Measurement in early 2015.

Among the countries for which VR data could be used (see Figure 2.11 in Chapter 2), there were 2186 country-year data points 1990–2013, after 27 outlier data points from systems with very low coverage (<20%) or very high proportion of ill-defined causes (>50%) were excluded for analytical purposes. On average, 17 data points were retained for analysis per country (standard deviation (SD) of 7).

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).[3]

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 d_a was obtained from the VR report d as follows:

$$d_a = \frac{d}{c(1-g)}$$

[1] www.who.int/gho/publications/world_health_statistics/2013/en/ (accessed July 2013) (see particularly pages 15–16).
[2] Birnbaum JK, Murray CJL, Lozano R. Exposing misclassified HIV/AIDS deaths in South Africa. *Bulletin of the World Health Organization*, 2011, 89:278–285.
[3] Mathers CD et al. Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bulletin of the World Health Organization*, 2005, 83:171–177.

where c 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 with standard deviation $SD = d/4 \left[1/c(1-g) - 1 \right]$. The uncertainty calculation does not account for miscoding, such as HIV deaths miscoded as deaths due to TB.

Missing data between existing adjusted data points were interpolated. Trailing missing values were predicted using exponential smoothing models for time series. [1] 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 1990. A total of 865 country-year data points were thus imputed.

Results from mortality surveys were used to estimate TB mortality in India and Viet Nam.

In 2013, 36% 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 64% was estimated using the indirect methods described in section 3.2.

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

In 94 countries lacking VR data of the necessary coverage and quality, TB mortality was estimated as the product of TB incidence (see section 4) and the CFR after disaggregation by case type as shown in Table A1.1, following a literature review of CFRs by the TB Modelling and Analysis Consortium (TB-MAC[2]):

$M = (I\text{-}N)F_u + NF_n$, where M denotes mortality, I incidence. F_u and F_n denote CFRs untreated and treated, respectively. N denotes the number of notified TB cases. In countries where the number of treated patients that are not notified (under-reporting) is known from an inventory study, N is adjusted upwards to account for under-reporting.

Table 1. Case Fatality Ratio, HIV-negative

Population stratum	CFR (range)	Sources
HIV negative		
Not on TB treatment F_u	0.43 (0.28- 0.53)	3,4
On TB treatment F_n	0.03 (0.00-0.07)	5

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[1] Hyndman R et al. *Forecasting with exponential smoothing: the state space approach.* Springer Series in Statistics, 2008.

[2] tb-mac.org

[3] Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, et al. (2003) The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 163: 1009-1021.

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

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

The above indirect estimation of TB mortality for HIV-negative TB is implemented in Spectrum (see also section 3.4). It 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.

3.3 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[1].

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

$$M = (I-N)F_u + NF_n$$

where I represents incident TB cases among people living with HIV, N represents HIV-positive cases that are notified, ($I-N$) represents HIV-positive TB cases that are not notified and M represents TB mortality among HIV-positive people. F_n and F_u are the case fatality ratios for notified and non-notified 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 2.

Table 2. Estimates of the case fatality ratio among HIV-positive TB cases

Population stratum	CFR (range)	Sources
HIV positive not on ART		
Not on TB treatment	0.78 (0.65-0.94)	2
On TB treatment	0.09 (0.03-0.15)	1,3,4
HIV positive, on ART for less than one year before TB episode		
Not on TB treatment	0.62 (0.39-0.86)	Data from review + assumptions
On TB treatment	0.06 (0.01-0.13)	Data from review + assumptions
HIV positive, on ART for one year or more before TB episode		
Not on TB treatment	0.49 (0.31-0.70)	Assumptions
On TB treatment	0.04 (0.00-0.10)	Assumptions

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[1] http://www.futuresinstitute.org/spectrum.aspx

[2] Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, et al. (2003) The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 163: 1009-1021.

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

[4] Mukadi YD, Maher D, Harries A (2001) Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *AIDS* 15: 143-152.

The disaggregation of incident TB into notified and not notified cases is based on the ratio of the point estimates for incident and notified cases. 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.

3.4 TB mortality disaggregated by age and sex

For countries with VR data, it was possible to estimate TB deaths (excluding TB deaths among HIV-positive people) among children (aged <15 years) and adults (aged ≥ 15 years) separately. It was also possible to disaggregate TB deaths by sex. For these countries, male:female and child:adult ratios of TB deaths (expressed as rates per 100 000 population) were calculated (after correction for ill-defined causes of deaths and VR coverage). Multiple imputation modelling was used to fill in the missing data for countries with no VR data and estimate a global ratio (with uncertainty accounting for the missing data). Directly measured (i.e. based on VR data for the latest available year) or predicted from the multiple imputation step country-level ratios were then used to estimate global and WHO regional ratios. These were then used to age and sex disaggregate global number of estimated TB deaths among HIV-negative TB cases.

TB deaths among HIV-positive people were disaggregated by sex using the assumption that the male:female sex ratio is the same as the sex ratio of AIDS deaths estimated by UNAIDS. Further details are provided in Box 2.3, Chapter 2. Disaggregation of TB deaths by age and sex will be one of the future developments of the TB component of the Spectrum software (also see section 3.3).

4. Estimates of TB incidence, 1990–2013

No country has ever undertaken a nationwide survey of TB incidence because of the large sample sizes required and associated major logistic and financial challenges. As a result, there are no direct measurements of the incidence of TB. Theoretically, data from TB surveillance systems that are linked to health systems of high coverage and performance may capture all (or almost all) incident cases of TB. The WHO Global Task Force on TB Impact Measurement has developed a set of TB surveillance standards and benchmarks that, if met, would allow direct measurement of TB cases and deaths from surveillance data (Chapter 2).

In the absence of direct measurements, estimates of TB incidence for almost all countries rely on methods described in sections 4.1–4.3.

It should be emphasized that incidence estimates are no longer derived from surveys of the prevalence of TB infection as measured in tuberculin surveys. The WHO Global Task Force on TB Impact Measurement has agreed that methods for deriving incidence from the prevalence of infection are unreliable. The Task Force has also

stated that, with a few exceptions, repeat tuberculin surveys do not provide a reliable estimate of the trend in TB incidence.[1]

4.1 Estimating TB incidence from estimates of the proportion of cases detected

Notification data for new and recurrent cases have been analysed in combination with evidence about the coverage of the TB surveillance system and expert opinion in six regional workshops and country missions held during the period 2009–2014, according to methods developed by the WHO Global Task Force on TB Impact Measurement. By June 2014, these workshops and country missions had covered 96 countries (Figure 2.1, Chapter 2), with several countries re-assessed multiple times.

For the 96 countries covered by these regional workshops and country missions, incidence was estimated according to the following equation:

$$\text{incidence} = \frac{\text{case notifications}}{1 - \text{underreporting}}$$

Expert opinion about the proportion of TB cases[2] that were not reported was elicited for three reference years (1997, 2003 and, depending on when the workshop was held, 2008–2013). This was done following in-depth analysis of notification data (including data from sub-national administrative levels), programmatic data reflecting efforts in TB care and control (for example, data on infrastructure, staffing, the performance of services and funding) and (where available) data from inventory studies.[3] In addition, data on access to health care from Demographic and Health Surveys and the overall performance of health systems (using indicators such as the infant mortality rate) were used to substantiate opinion on the proportion of cases with no or very limited access to health care (Table 3). Results from inventory studies combined with capture–recapture modelling were used to estimate the gap between notified cases and TB incidence in three countries that participated in regional workshops: Egypt, Iraq and Yemen.

Table 3. Sources of information and data on TB incidence used in regional workshops and country missions

Possible categories of incident cases	Sources of data	
Do not have physical or financial access to health care	Demographic and health surveys, KABP[a] surveys	Capture–recapture modelling
Seek care, but TB not diagnosed	Survey	
TB diagnosed, but not reported	'Inventory' survey	
Reported cases	TB surveillance	

[a] KABP = knowledge, attitudes, behaviour and practices.

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[1] *TB impact measurement: policy and recommendations for how to assess the epidemiological burden of TB and the impact of TB control*. Geneva, World Health Organization, 2009 (Stop TB policy paper, no. 2; WHO/HTM/TB/2009.416).

[2] Defined as cases of all forms of TB, including sputum smear-positive pulmonary cases, sputum smear-negative pulmonary cases and extrapulmonary cases.

[3] Measurements from 'inventory' studies can be used to quantify the number of cases that are diagnosed but not reported to national surveillance systems.

A full description of the methods used in these workshops is available in a report of the workshop held for countries in the African Region (in Harare, Zimbabwe, December 2010).[1]

Table 4. Parameter estimates used to produce estimates of TB incidence, prevalence and mortality

Model parameter	Distribution	Distribution parameters[b]
Incidence, high-income countries	Beta[a]	$\alpha = \bar{I} \cdot \left(\dfrac{\bar{I}(1-\bar{I})}{V} - 1 \right)$ $\beta = (1-\bar{I}) \cdot \left(\dfrac{\bar{I}(1-\bar{I})}{V} - 1 \right)$ *where $\bar{I}$ was set at 1.3 times the notification rate, noted N, and V is defined by:* $V = \left[\dfrac{0.3}{4} N \right]^2$
HIV prevalence among incident TB	Beta[a]	$\alpha = \bar{x} \cdot \left(\dfrac{\bar{x}(1-\bar{x})}{V} - 1 \right)$ $\beta = (1-\bar{x}) \cdot \left(\dfrac{\bar{x}(1-\bar{x})}{V} - 1 \right)$ *Where $\bar{x}$ is the expected value and V is given by:* $V = \left[\dfrac{(u-l)}{4} \right]^2$
Duration of disease, non-notified HIV-negative cases of TB	Uniform	l = 1, u = 4 (years)
Duration of disease, non-notified HIV-positive cases of TB	Uniform	l = 0.01, u = 0.2 (years)
Duration of disease, notified HIV-negative cases of TB	Uniform	l = 0.2, u = 2 (years)
Duration of disease, notified HIV-positive cases of TB	Uniform	l = 0.01, u = 1 (years)

[a] The probability density function of the Beta distribution is: $f(x; \alpha, \beta) = \dfrac{x^{\alpha-1}(1-x)^{\beta-1}}{\int_0^1 u^{\alpha-1}(1-u)^{\beta-1} du}$

[b] u and l denote upper and lower bounds.

Distributions of the proportion of cases that were not reported in the three reference years were assumed to follow a Beta distribution (Table 4). Reasons for using Beta distributions include the following:

- They are continuous and defined on the interval (0, 1). Since the variance of the proportions of cases that were not reported tend to be large as a result of high uncertainty, random draws of numbers from a normal distribution would

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[1] See www.who.int/tb/advisory_bodies/impact_measurement_taskforce.

yield numbers outside the interval (0, 1). The use of truncated normal distributions may result in excess density towards one of the bounds.

- They are not necessarily symmetrical.
- They are defined with two parameters that can be estimated from available data using the method of moments.[1]

The shape and scale parameters necessary to define the Beta distribution were computed using the method of moments, as follows:

First, the variance for the distribution was taken as:

$$V = ((u - l)/4)^2$$

where l and u are the lower and upper bounds of the plausible range for the proportion of incident cases that were reported (also referred to as the case detection rate in Chapter 4).

Shape 1 (noted α) and 2 (noted β) follow from:

$$s = \frac{E(1 - E)}{V} - 1$$
$$\alpha = sE$$
$$\beta = s(1 - E)$$

where E is the expected value of the distribution.

Time series for the period 1990–2013 were built according to the characteristics of the levels of underreporting 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. Incidence trajectories were derived from the series of notified TB cases using Monte Carlo simulations from which expected values, 2.5th and 97.5th centiles were extracted. All computations were conducted in the R statistical environment.[2]

In two countries, incidence rates were estimated to be similar to those in a neighbouring country because information from surveillance systems was insufficient: estimates for West Bank and Gaza Strip were extrapolated from estimates for Jordan and estimates for South Sudan were extrapolated from estimates for Sudan. The estimates for West Bank and Gaza Strip and South Sudan should therefore be considered as preliminary.

Trends in incidence were derived from repeat tuberculin survey results in Bhutan, India and Yemen and for 40 countries (including countries in Eastern Europe) from trends in mortality.

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[1] Rényi A. *Probability theory*. New York, Dover Publications Inc., 2007.

[2] R Development Core Team. *R: a language and environment for statistical computing*. Vienna, R Foundation for Statistical Computing, 2009 (www.R-project.org).

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.

4.2   Estimating TB incidence from data on case notifications and expert opinion for high-income countries

For high-income countries, the level of TB incidence was assumed to be distributed between the notification rate for new and recurrent cases combined, including reported cases with undocumented treatment history as explained in section 2.1 (lower uncertainty bound, noted *l*) and 1.3 times the notification rate (upper uncertainty bound, noted *u*), as informed by expert opinion. The distribution of incidence was assumed to follow a Beta distribution with shape and scale parameters computed using the method of moments, as described above.

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 United Kingdom and the Netherlands, where the underreporting of TB cases has been measured using inventory studies and capture–recapture modelling.[1][2] For these two countries, the results from these studies were used to measure TB incidence directly.

4.3   Estimating TB incidence from empirical measurements of disease prevalence

Incidence can be 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.

In practice, the duration of disease 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 active case-finding truncates the natural history of undiagnosed disease. Measurements of the duration of disease in notified cases ignore the duration of disease among non-notified and untreated cases.

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 disease (for smear-positive cases and smear-negative cases combined) in HIV-negative individuals is about three years. However, the proportion of incident cases that remain untreated is unknown. There are few data on the duration of disease in HIV-positive individuals.

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[1] *Tuberculosis in the UK: annual report on tuberculosis surveillance in the UK 2010.* London, Health Protection Agency Centre for Infections, 2010 (also available at: www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1287143581697; accessed July 2011).
[2] van Hest NA et al. Completeness of notification of tuberculosis in The Netherlands: how reliable is record-linkage and capture–recapture analysis? *Epidemiology and Infection*, 2007, 135(6):1021–1029.

The assumed distributions of disease durations are shown in Table 5.

Table 5. Distribution of disease duration by case category

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

A second approach consists in 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:

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

$$\frac{dT}{dt} = \delta U - (\mu_T + \theta_T)T$$

Where I denotes Incidence, $\mu_u + \theta_u$ denote mortality (untreated) and self-cure (untreated), respectively, δ denotes the rate of removal from U through detection and treatment, $\mu_T + \theta_T$ denote mortality (treated) and cure, respectively. At equilibrium, the above two equations simplify to:

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

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

And disease duration (untreated) is obtained from $d_U = (1 - \pi)\frac{U}{T}d_T$, where π is the proportion of incidence that dies or self-cures before treatment. π is assumed distributed uniform with bounds 0 and 0.1. Table 6 shows estimates of incidence from four recent prevalence surveys using this method.

Table 6. Incidence estimation based on U/T ratio

	U	T	Prevalence (per 1000)	Duration (year)	Incidence (per 1000/yr)
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)

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 does not provide unbiased estimates of incidence.

The above two methods to derive incidence from prevalence are compared below.

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Table 7. Estimates of incidence derived from prevalence survey results, based on two estimation methods

	Prevalence (per 1000)	Incidence – method 1 (per 1000/yr)	Incidence – method 2 (per 1000/yr)
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)	3.4 (2 – 5.1)
Thailand 2012	2.5 (1.9-3.5)	2.3 (1-3.5)	1.1 (0.7 – 1.6)

It is not clear which method will perform better as validation would require a measurement of incidence. The second method requires a sufficient number of cases on treatment at the time of the survey (at least 30 cases) to be applied. When the number of cases on treatment is too small, the amount of propagated uncertainty renders estimates of incidence unusable.

Where possible, methods based on n independent approaches are combined using an ensemble approach as follows.

The incidence rate obtained using method i is assumed distributed Beta with shape and scale parameters $a_i + 1$ and $b_i + 1$, respectively, and determined using the method of moments (see section 4.1):

$$I_i \sim B(a_i + 1, b_i + 1)$$

so that

$$Prob(x = TB) = \int_0^1 x.B(a_i + 1, b_i + 1)dx = \frac{a_i + 1}{a_i + b_i + 2}$$

Let $c = \sum a_i$ and $d = \sum b_i$

The combined probability of x= TB is then expressed as

$$Prob(x = TB) = \frac{c + 1}{c + d + 2}$$

with an estimated variance as follows:

$$Var = \frac{(c + 1)(d + 1)}{(c + d + 2)^2(c + d + 3)}$$

When measurements from two prevalence surveys were available, trends in TB prevalence were derived by fitting a log-linear model to available measurements. When three or more prevalence measurements were available, the prevalence trajectory was built using cubic spline interpolation. If only one prevalence survey measurement was available, time-trends were assessed using in-depth analysis of surveillance data, as described above.

4.4 Disaggregation of TB incidence

In this report, TB incidence is disaggregated by HIV-infection status (see section 4.5) at country level. The estimation of smear-positive TB incidence was discontinued in 2010, for reasons explained in detail in the global report published in 2010.

Global and WHO regional estimates of sex-disaggregated incidence were also calculated, based on country-level female:male ratios of total new and relapse (all

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case types) TB case notifications, under the assumption that they are a proxy of female:male ratios of incidence. Model-based estimated WHO regional ratios were applied to global incidence for the final sex disaggregation (Chapter 2).

TB incidence was also disaggregated by age, to produce global estimates among children (aged <15 years) and adults (aged ≥ 15 years). Details of methods are provided in Chapter 2, Box 2.3.

4.5   Estimates of HIV prevalence among incident TB cases, 1990–2013

TB incidence was disaggregated by HIV and CD4 status using the Spectrum software.[1] 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.[2] 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. Spectrum data were based on the national projections prepared for the UNAIDS *Report on the global AIDS epidemic 2012*. The model can also be used to estimate TB mortality among HIV-positive people, the resource requirements associated with recently updated guidance on ART [3] 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 cubic-spline functions:

$$I(x) = \Sigma_{i=1 \text{ to } k} \; \beta_i \; B^m i(x)$$

where β_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 β were determined by an optimization routine that minimizes the least squares error between incidence data (I_{obs}) and the estimated incidence curve $I(x)$:

$$\Sigma_{x=1990:2012} |I(x) - I_{obs}(x)|^2 + \; \lambda \; \beta^T S \beta$$

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 β to control the level of variation between adjacent coefficients of the cubic-spline, and thus control (through a choice of λ) the smoothness of the time-dependent case incidence curve. Another important

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[1] http://www.futuresinstitute.org/spectrum.aspx
[2] Stover J, McKinnon R, Winfrey B. Spectrum: a model platform for linking maternal and child survival interventions with AIDS, family planning and demographic projections. *International Journal of Epidemiology* 2010; 39 Suppl 1:i7–10.
[3] http://www.who.int/hiv/pub/arv2013/en/index.html

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.

Cubic-Splines and confidence intervals

The cubic-spline method was then used to fit indicators (incidence, case notifications, etc.) to a set of bootstrapped data, obtained by sampling from the normal error distribution resulting from fitting the 'point estimate'. This bootstrap method produces a sample of projected cubic-spline curves that are practically equivalent to a set that would be obtained from fitting the model to the same number of repeated measurements (or assessments) of the given indicator. Confidence intervals based on the bootstrapped data are typically narrow in the years where the model has data to utilize, and 'spread out' after that, according to a Gaussian process with an increasing variance.

Projecting TB incidence among people living with HIV by CD4 category

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.[1] They suggested a 42% (+/- 17%) increase in RR for TB for each unit of 100uL 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[2]). For each 100uL 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:

$$F(c<500) = F(c>500) \cdot p(1) \cdot p(2)^{dc},$$

where $p(1)$ is a parameter that is used to recognize that people living with HIV 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 100uL 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.

[1] Williams B. *The impact of ART for HIV on TB*.
http://www.who.int/hiv/topics/artforprevention/williams.pdf (accessed July 2013).
[2] Sonnenberg P, et al. How Soon after Infection with HIV Does the Risk of Tuberculosis Start to Increase? A Retrospective Cohort Study in South African Gold Miners. *Journal of Infectious Diseases.* 2005 Jan 15;191(2):150–8.

Parameter assumptions

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 a more straightforward interpretation of these parameters as regression coefficients need to be balanced. 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,[1] 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 0–6 months is likely to remain high; therefore, a reduction factor due to ART was not applied for this subset of patients.

Likelihood function

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

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[1] Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, et al. (2012) Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis. *PLoS Med* 9(7): e1001270. doi:10.1371/journal.pmed.1001270

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.

A prototype Bayesian importance sampling (IMIS) algorithm was developed to handle complex data weighing possibilities, but it was based on subjective priors and likelihood functions and is more time-consuming to run than simple least squares. For the purposes of producing estimates for all countries automatically, the least squares method was used. In future, least squares and IMIS fitting could be made available to the end user.

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 previously published by WHO (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. 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.

Table 8. Sources of data on HIV prevalence among incident TB cases

Direct measurement of the prevalence of HIV in TB patients	Number of country-years
National surveys*	162
HIV sentinel surveillance	25
Provider-initiated testing and counselling with at least 50% coverage of testing	864
Total, at least one data source available	946

* the reported survey number is over-stated as a number of country reports confused survey and routine testing with near 100% coverage

For the 49 countries for which no surveillance data were available, the prevalence of HIV was estimated indirectly according to the following equation:

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

In this equation, t is HIV prevalence among incident TB cases, h is HIV prevalence among the general population (from the latest time-series provided by UNAIDS) and ρ is the incidence rate ratio (IRR) (defined as the incidence rate of TB in HIV-positive people divided by the incidence rate of TB in HIV-negative people). We then let logit(t) be log(t/(1-t)) and logit(h) be log(h/(1-h)). Using data from countries where HIV prevalence has been estimated by UNAIDS as an independent variable, a linear model of logit-transformed t was fitted using logit-transformed h according to the following equation, written in matrix notation:

$$\hat{T} = X\beta$$

where $\hat{T}$ is a vector of predicted logit(t), X is an n x 2 matrix in which the first column holds 1s, and the second column holds logit(h). The vector β holds estimated model parameters. Models were tested with lags set for logit(h) ranging from no lag to a lag of eight years. The best fit was obtained with a lag of one year.

Models were run using Monte Carlo simulations in which h was drawn randomly from a Beta distribution with shape parameters computed as described in Section 4.1, (low and high uncertainty bounds are provided by UNAIDS). The model was run 50 000 times using country-specific distributions for H and T (noted in capital letters to denote vectors or matrices) based on their uncertainty intervals. The uncertainty bounds for β were chosen as the 2.5th and 97.5th centiles.

5. Estimates of TB prevalence, 1990–2013

The best way to measure the prevalence of TB is through national population-based surveys of TB disease.[1,2] Data from such surveys are available for an increasing number of countries (Chapter 2). 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.

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 product of two uncertain quantities: (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.

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[1] Glaziou P et al. Tuberculosis prevalence surveys: rationale and cost. *International Journal of Tuberculosis and Lung Disease*, 2008, 12(9):1003–1008.
[2] *TB prevalence surveys: a handbook*. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2010.17).

Indirect estimates of prevalence were calculated according to the following equation:

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

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. Given their underlying uncertainty, prevalence estimates should be used with great caution in the absence of direct measurements from a prevalence survey. Unless measurements were available from national programmes (for example, Turkey), assumptions of the duration of disease were used as shown in the last four rows of Table 5.

6.   Estimates of the number of cases of and deaths from MDR-TB

6.1   Proportion of notified cases of TB that have MDR-TB, 2013

Global and regional estimates of the proportion of new and retreatment cases of TB that had MDR-TB in 2013 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 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 Appendix 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.

6.2   MDR-TB mortality, 2013

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).[1] 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. The global estimate of MDR-TB deaths (Box 2.3) was then based on the following formula:

$m = M.p.r$
Where:
m = global MDR-TB mortality,
M = global TB mortality,

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[1] *Mortality and causes of death in South Africa, 2010: Findings from death notification.*
http://www.statssa.gov.za/publications/p03093/p030932010.pdf

p = 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,
r = the relative risk of dying from MDR-TB versus non-MDR-TB.

6.3   Numbers of incident cases of MDR-TB, 2013

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 min=0, max=upper limit of the global proportion of MDR-TB among retreated cases estimated from DRS.

6.4 Resistance to second-line drugs among patients with MDR-TB

Data from 75 countries 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.

7.   Projections of incidence, prevalence and mortality up to 2015

Projections of TB incidence, prevalence and mortality rates 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 years 2013–2015 were made using exponential smoothing models fitted to data from 2006–2013.

8.   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 underreported (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 overreported 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 the Bayesian model. 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 sequence: (1) Overall TB incidence estimation after review and cleaning of case notification data; (2) cleaning and adjustment of 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) estimation of HIV prevalence among incident cases of TB through modelling in countries with no measurements; (5) estimation of HIV-negative TB mortality in countries with no VR data followed with an update of step 1 in some countries; (6) review of prevalence measurements, adjustments for childhood TB and bacteriologically unconfirmed TB, and estimation of prevalence followed with an update of step 1 in some countries; (7) estimation of 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, uncertainty was propagated analytically by approximating the moments of functions of random variables using Taylor expansions – such as when taking the product or the ratio of two random variables – rather than through Monte Carlo simulations, in order to shorten computing time.

Appendix 1. Epidemiological regions used for analyses

Africa – countries with high HIV prevalence: Botswana, Burundi, Cameroon, the Central African Republic, the Congo, Côte d'Ivoire, the Democratic Republic of the Congo, Ethiopia, Gabon, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, Rwanda, South Africa, South Sudan, Swaziland, Uganda, the United Republic of Tanzania, Zambia, Zimbabwe.

Africa – countries with low HIV prevalence: Algeria, Angola, Benin, Burkina Faso, Cape Verde, Chad, the Comoros, Djibouti, Eritrea, the Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, the Niger, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Somalia, Sudan, Togo.

Central Europe: Albania, Bosnia and Herzegovina, Montenegro, Serbia, the former Yugoslav Republic of Macedonia, Turkey.

Eastern Europe: Armenia, Azerbaijan, Belarus, Bulgaria, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, the Republic of Moldova, Romania, the Russian Federation, Tajikistan, Turkmenistan, Ukraine, Uzbekistan.

High-income countries: Andorra, Aruba, Australia, Austria, the Bahamas, Bahrain, Barbados, Belgium, Bermuda, Brunei Darussalam, Canada, the Cayman Islands, China, Hong Kong SAR, China Macao SAR, Croatia, Cyprus, the Czech Republic, Denmark, Equatorial Guinea, Estonia, Finland, France, French Polynesia, Germany, Greece, Greenland, Guam, Hungary, Iceland, Ireland, Israel, Italy, Japan, Kuwait, Luxembourg, Malta, Monaco, the Netherlands, the Netherlands Antilles, New Caledonia, New Zealand, Northern Mariana Islands, Norway, Oman, Poland, Portugal, Puerto Rico, Qatar, the Republic of Korea, Saint Kitts and Nevis, San Marino, Saudi Arabia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, Trinidad and Tobago, the Turks and Caicos Islands, US Virgin Islands, United Arab Emirates, the United Kingdom, the United States.

Eastern Mediterranean: Afghanistan, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Lebanon, Libya, Morocco, Pakistan, Syrian Arab Republic, Tunisia, West Bank and the Gaza Strip, Yemen.

Latin America: Anguilla, Antigua and Barbuda, Argentina, Belize, Bolivia (Plurinational State of), Bonaire, Saint Eustatius and Saba, Brazil, British Virgin Islands, Chile, Colombia, Costa Rica, Cuba, Curaçao, Dominica, the Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Montserrat, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Sint Maarten (Dutch part), Suriname, Uruguay, Venezuela (Bolivarian Republic of).

South East Asia: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste.

West Pacific: American Samoa, Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated State of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, the Philippines, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, Vanuatu, Viet Nam, Wallis and Futuna Islands.