Latest developments in WHO estimates of TB disease burden

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Introduction

This background document reviews updates to estimates of TB disease burden in relation to recommendations made at the 2016 Task Force meeting. The recommendations from the meeting, which were all related to drug-resistant TB, are summarized in section 1. This is followed in section 2 by an explanation of current methods used to estimate the burden of drug-resistant TB.

The third section of the document compares selected global estimates from IHME and WHO. The fourth section discusses options for estimating the burden of TB at subnational levels. There is growing interest in this topic and requests for guidance are increasing.

1. Recommendations from April 2016 Task Force meeting

The meeting of the Task Force in April 2016 was used to review and discuss methods for estimating the incidence of drug-resistant TB.

Two specific recommendations on estimates of MDR-TB incidence were agreed:

1. Continue to use Method I (based on case notifications disaggregated by treatment history and an estimate of the detection gap), with three suggested refinements listed in the presentation. These were (i) updating a previous literature review to inform values used for key parameters (e.g. the risk of MDR in relapse cases relative to previously untreated cases); (ii) refinements to the inflation factor used for retreatment cases that are not relapses, for example based on findings from inventory studies; and (iii) an approach to correct for the double-counting of relapse cases with primary resistance. In addition, the use of drug resistance surveillance (DRS) data to cross-check the relative share of relapse/retreatments from notification data, as the basis for updating the estimated proportion of resistance among relapse cases and to test the hypothesis that levels of MDR-TB are higher in the private sector using data from public-private (PPM) sites, was suggested.
2. Produce country-level estimates using Method II (incidence derived from an estimate of MDR-TB mortality and a literature-review based estimate of the mortality risk ratio compared with non-MDR) and compare the two sets of estimates.

Three next steps were also agreed:

1. Advance communication from WHO to countries about the planned publication of country-specific estimates of MDR-TB incidence in the 2016 WHO global TB report. This was done in July 2016, three months in advance of report publication.
2. The establishment of a small working group on the topic of MDR-TB disease burden estimates, composed of the seven people who volunteered during the meeting. This was done and Pete Dodd is actively involved in relevant modelling work.
3. Investigation of the possibility of grading of estimates based on data quality, which could accompany published country estimates. This has not been done to date, but the published relative uncertainty of estimates can be used as a measure of the quality of estimates. The underlying data are systematically assessed in national TB epidemiological reviews (see also Background document 1) that include analysis of a standardized set of indicators related to the quality of TB surveillance (including mortality indicators). Findings will be included in upcoming WHO Global TB Reports.

Two alternative approaches that merited investigation in the next 1–2 years were also defined. These were:

1. Estimating MDR-TB incidence in two groups only (primary and acquired). This would require additional data, in particular cohort studies to measure the rate of acquisition of resistance during first-line treatment; and
2. Development of a deterministic mathematical model to fit estimates of TB incidence and DRS data by country. This work was commissioned to Pete Dodd and will be presented on Day 3 of the meeting (3 May).
2. Estimates of the incidence of MDR/RR-TB

2.1 Current approach used by WHO

Following a revision of policy recommendations for the treatment of drug-resistant TB issued by WHO in May 2016,¹ all people with TB resistant to rifampicin, with or without resistance to other drugs, should be treated with an MDR-TB treatment regimen. For this reason, all global, regional, and country level estimates of incidence and mortality of drug-resistant TB published in WHO’s last two global TB reports (2016, 2017) refer to cases of TB resistant to rifampicin, with or without additional resistance to other drugs (MDR/RR-TB).

Global and regional estimates of the proportion of new and retreatment cases of TB that had MDR/RR-TB in 2016 were calculated using country-level information.

If countries had reported data on the proportion of new and retreatment cases of TB that have rifampicin resistance from routine surveillance or a survey of drug resistance, the latest available information was used. For data from routine surveillance to be considered representative, at least 80% of notified new pulmonary laboratory-confirmed TB cases must have a documented DST result for at least rifampicin. For retreatment cases, some surveys were also considered if at least 80% of notified previously treated pulmonary laboratory-confirmed cases had a documented DST result for at least rifampicin.

For countries that had not reported such data, estimates of the proportion of new and retreatment cases of TB that had MDR/RR-TB were produced using modelling (multiple imputation by chained equations), based on data from countries for which data do exist. For each country, estimates were based on data from countries that were considered to be similar in terms of TB epidemiology. The observed and imputed estimates of the proportion of new and retreatment cases of TB that had MDR/RR-TB were then pooled to give a global estimate, with countries weighted according to their share of global notifications of new and retreatment cases.

To calculate the proportions of new ($p_n$) and retreated ($p_r$) patients with MDR/RR-TB resistance from routine surveillance or survey of drug resistance data for each of the new and retreated TB patient groups, the proportions are calculated as the sum of:

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

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

(iii) patients with RR-TB among those with a geneXpert result for R

divided by the sum of patients with DST results for R and H, and with geneXpert results for R.

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

$$I_{rr} = \frac{Np_n}{C} + \frac{Lp_n\rho + Rp_r}{C_u}$$

2.2 Alternative approach to avoid double counting of retreatment cases with primary resistance

To avoid the problem of double counting cases with primary resistance among non-relapse retreatment groups, the following approach is considered:

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

3. Approximate RR incidence as:

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

where $I$ is total TB incidence.

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

The incidence of primary RR can be estimated as

$$
I_{rr}^P = Ip_n
$$

The incidence of acquired RR is then

$$
I_{rr}^A = I_{rr} - Ip_n
$$

Outputs from the two approaches will be compared in 2018.

A third approach based on modelling (developed by Pete Dodd) will be presented and discussed during the Task Force meeting.

3. Comparison of WHO and IHME estimates (GBD 2016)

3.1 TB mortality

TB mortality estimates from WHO are slightly higher globally, with 1.3 million deaths in 2016 (excluding TB deaths in HIV-positive individuals) versus 1.21 million recently reported by IHME in their GBD 2016 exercise. There is general consistency in estimates in countries with vital registration systems and standard coding of causes of deaths of good quality, and differences in other countries particularly where estimates are indirect model-based estimates predicted using other data, due to WHO-IHME differences in methods and modelling approaches. There will be convergence in
mortality estimates from WHO and IHME when all countries are able to document the distribution of causes of deaths through vital registration systems meeting international quality standards.

3.2 TB incidence

The global WHO estimate for 2016 is 10.4 million new cases, while IHME estimated 10.38 million cases globally. The global numbers are therefore very similar, but there are differences in some countries, most particularly countries with underperforming TB surveillance or weak performance of overall health systems (low life expectancy, high infant mortality, low coverage of health insurance or equivalent provide evidence of poor health system performance).

3.3 Variability of estimates in consecutive reports

TB estimates vary from one report to the next in view of new information, including results from recent nationally representative population-based surveys. Entire times series are recalculated every year by both WHO (starting 2000) and IHME (starting 1990).

WHO, TB deaths HIV-negative (3.8% year-to-year difference), HIV-positive (2% difference), total (2.9% difference):

2017 report, mortality in 2015: 1.33m; 392k; 1.72m
2016 report, mortality in 2015: 1.38m; 389k; 1.77m

GBD (IHME), TB deaths (7.8% difference adjusting for the decline between 2015 and 2016)

GBD2016, 2016: 1.21m; (2015 not available)
GBD2015, 2015: 1.11m

Major revisions to global TB estimates in recent WHO global TB reports (e.g. in 2014, 2015 and 2016) have been due to major revisions in just one country on each occasion (Nigeria, Indonesia, India) that have a large share of the global TB burden — as opposed to lots of major updates to lots of countries.
The variation of estimates between consecutive reports is not specific to TB estimates, as shown below:

**Variability in HIV mortality estimates, UNAIDS (4.5% difference)**

This year, 2015: 1.06m  
Last year, 2015: 1.11m

**Variability in HIV estimates, IHME (7% difference after removing the expected decline between 2015 and 2016)**

GBD2016, 2016: 1.03m; (2015 not available)  
GBD2015, 2015: 1.2m

**Variability in malaria mortality estimates, WHO (2% difference)**

2016 global malaria report, 2015: 429k  
2015 global malaria report, 2015: 438k

**Variability in malaria mortality estimates, IHME (1.5% difference, 1.6 times greater than WHO’s estimate)**

GBD2016, 2016, 720k (2015 not available)  
GBD2015, 2015, 731k

4. Subnational estimates of TB burden

There is increasing global demand for estimates of TB incidence at the subnational or subpopulation level in low and middle income countries, to improve TB programme planning, forecasting and budgeting. This section briefly examines options to derive such estimates.

4.1 Geographical heterogeneity in case notifications

While case notifications are the best source of information in countries with universal health coverage and high-performance TB surveillance, in other countries, case notifications cannot be expected to accurately mirror patterns in incidence. There are several reasons for this:

- Cases from one district may be diagnosed in neighbouring districts or even provinces as a result of better service availability or quality (countries with case-based electronic reporting may have
the ability to map cases by area of residence instead of the usual reports of cases by administrative level or by reporting facility);

- In many countries, case notifications do not account for every diagnosed case: under-reporting may be more frequent in the private sector when case notification is not legally mandatory, as well as in the public sector in settings where notifications are limited to cases started on treatment (excluding diagnosed cases who did not return for their test results).

- The lack of universal access to health care means that some cases may not be diagnosed.

Forecasting case notifications at national and subnational levels can be done based on historical trends as notification rates tend to change relatively slowly from one year to the next, unless a large problem of under-reporting is being effectively addressed by the national TB programme. WHO has posted an online tool\(^2\) to help forecast time-series of case notifications at any geographical level.

Inventory studies provide detailed information on the level of under-reporting of detected cases, which can be used for programme planning at subnational levels. Results at the national level have been successfully used in some countries such as Indonesia to generate TB incidence estimates using capture-recapture modelling. Exploration of options for more complex models derived from the family of capture-recapture models, that would allow the estimation of incidence at a more granular geographical level, have not yet been explored.

4.2 Disease prevalence surveys and small area estimation

In most countries that have implemented a national TB disease prevalence survey, results only allow the generation of reasonably precise estimates of TB prevalence at the national level, or in a small number of strata (e.g. 3 geographical regions in the most recent survey conducted in Indonesia).

Small area estimation\(^3\) (SAE) has become a widely used technique in official statistics. When the sample size is not large enough to provide reliable estimates at a very particular level, the power of models and auxiliary information is applied to exploit similarity and borrow strength from available

\(^2\) http://tbprojections.herokuapp.com/
\(^3\) https://journal.r-project.org/archive/2015/RJ-2015-007/RJ-2015-007.pdf
information. National surveys large enough to identify several hundred prevalent cases may be analysed in relation to external data available at the survey cluster or district level in SAE models. External data will typically include economic indicators or health indicators that are predictive of TB, such as HIV prevalence in the adult population. Selected models based on the best out-of-sample predictions can then be used to predict TB prevalence in clusters or districts not covered by the survey.

An attempt at such modelling has been made by LSHTM in Indonesia, and will be presented on Day 3 of the meeting.

Theoretical difficulties with the approach can be anticipated, including (i) the validity of predictions outside of the data space (predicted prevalence in clusters or districts having covariate data values falling well outside of the range observed in surveyed clusters or districts); (ii) the limited predictive power of models based on a small number of detected prevalent cases with observed overdispersion in the distribution of clusters by case count; (iii) the favoured disease burden indicator used for programme planning is incidence, which can be derived from prevalence with bias and increased relative uncertainty.

4.3 Surveys of infection

Surveys of infection based on the tuberculin skin test have long been used to indirectly estimate the incidence of smear-positive TB, assuming a linear relationship between incidence and the annual risk of infection. Over the past decade, evidence of the poor validity of the assumed relationship combined with the unpredictable diagnostic performance of the tuberculin test have contributed to a decline in interest in tuberculin surveys. IGRA\(^4\) tests have a more predictable and less variable specificity than tuberculin and could be the test of choice for future infection surveys until a better test becomes available. Nineteen studies simultaneously estimating sensitivity and specificity among 2,067 TB suspects demonstrated a pooled sensitivity of 83% (95% CI 70% - 91%) and pooled specificity of 58% (42% - 73%) for TSPOT.TB, and a pooled sensitivity of 73% (61% -82%) and pooled specificity


of 49% (40% - 58%) for Quantiferon TB Gold In-Tube. Survey results could be adjusted to account for the above measures of diagnostic performance (see Appendix).

The proposed objective of IGRA surveys would be to describe the age-standardized distribution of the prevalence of infection at the subpopulation or subnational level, and identify areas or subpopulations with a higher risk of TB. Given the high level of infection prevalence in the general population in high TB burden countries, sample size requirements will be a small fraction of sample size requirements for a disease prevalence survey aiming at a similar level of relative precision. Such surveys could be combined with household surveys of HIV or other household survey requiring blood samples. The Republic of Korea conducted a national IGRA survey\(^6\) in 2017, allowing identification of provinces and subpopulations with a higher risk of infection, including health care workers.

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Appendix. Survey results adjusted for distributions of the selected test sensitivity and specificity

Let $\Theta$ denotes the apparent prevalence of infection as measured using IGRA testing.

Let $\phi$ denote the bias-corrected (true) prevalence as determined using phenotypic testing. $\phi$ is expressed in terms of $\Theta$, sensitivity denoted $se$ and specificity denoted $sp$, as follows

$$\phi = \frac{\Theta + sp - 1}{se + sp - 1}$$  \hspace{1cm} (1)

Uncertainty about $se$ and $sp$ is propagated as well as uncertainty around $\Theta$ that is due to survey sampling.

Uncertainty is propagated using a Bayesian model. To set up the model, it can be assumed that $se$ and $sp$ followed a Beta distribution with parameters obtained using the method of moments. An uninformative prior is set on $\phi$. The likelihood function is then obtained by solving equation (1) for $\Theta$

$$L(\Phi, se, sp|\Theta) = se\Phi$$

The conditional probability distribution of $\phi$ is proportional to the product of the likelihood and the prior

$$\text{Prob}(\Phi|\Theta) \propto L(\Phi|\Theta)\text{Prob}(\Phi)$$

from which the usual summary statistics are extracted.