Estimates of the burden of disease caused by multidrug-resistant TB and monitoring the programmatic response: what indicators should be used and for what purpose?

April 2014

Summary

The first global and country-specific estimates of the disease burden associated with drug-resistant TB were published by WHO in 2001. Among incident cases of TB, it was estimated that there were 272 906 (95% confidence interval, 184 948–414 295) cases of multidrug-resistant TB (MDR-TB) globally in 2000. In a 2006 publication by WHO authors, this analysis was updated and expanded to include incident cases of MDR-TB among previously treated TB cases as well as those newly diagnosed with TB. The resulting global estimate was 424 203 (95% CI, 376 019–620 061) incident cases in 2004. In a WHO report on MDR-TB issued in 2010, this estimate was updated to 440 000 (95% CI 390 000 – 510 000) incident cases globally in 2008; country-specific estimates were also published.

Since 2010, WHO has not published country-specific estimates of the incidence of MDR-TB. This followed concerns expressed by some national TB programmes and technical agencies that assessment of country progress by comparing numbers of MDR-TB patients enrolled on treatment with estimated incidence was unfair and misleading. First, many of the estimated cases are not even diagnosed or reported with TB (let alone MDR-TB); and second, not all cases of MDR-TB could be detected with the limited availability of diagnostic tests in many countries. In recent WHO global TB reports, country-specific estimates related to the burden of MDR-TB have thus focused on the estimated number of MDR-TB cases among notified TB patients with pulmonary TB (newly diagnosed and previously treated) as well as a global estimate for this indicator (a best estimate of about 300 000 cases). Reports have also continued to include country-specific data about the estimated proportion of new and previously treated TB patients that have MDR-TB, as measured in drug resistance surveys or via continuous surveillance systems in which TB patients are routinely tested for drug resistance. A global estimate of MDR-TB prevalence was included in the 2011 and 2012 global TB reports, with a best estimate of 630 000 cases in 2011. Updated global estimates of MDR-TB incidence and mortality (best estimates of 450 000 incident cases and 150 000 deaths in 2012) were presented in the 2013 global TB report.

As attention to the challenge of MDR-TB and the programmatic response has intensified at global and country levels, so too there has been increased attention to and scrutiny of the indicators used to estimate disease burden and to measure the programmatic response. At the June 2013 meeting of WHO's Strategic and Technical Advisory Group for TB (STAG-TB), it was agreed that a broad consultation on these topics would be useful, with the aim of reaching consensus on what indicators to use and for what purposes. A half-day session at the global MDR-TB stakeholders meeting held in Paris in October 2013 was organized for this purpose.

This document summarizes the main content of the presentations at the global MDR-TB stakeholders meeting and the key recommendations regarding the use of each of the indicators that were considered. The main recommendations were:

- **MDR-TB cases among notified cases of pulmonary TB**. This should continue to be used for assessing programmatic performance in diagnostic and treatment coverage, at country and global levels. It is also appropriate for planning and budgeting purposes. In some instances it may be useful for advocacy purposes, especially at country level.
- **MDR-TB incidence**. A global estimate is useful for global advocacy. Country-specific numbers become increasingly relevant as a) overall detection of TB cases approaches 100% and b) treatment coverage among notified TB cases approaches 100%.
- **MDR-TB prevalence**. A global estimate is useful for global advocacy. Since incidence and prevalence can be confused, global publications should focus on only one of these two indicators (for example, in abstracts, executive summaries of global reports and advocacy brochures). Prevalence numbers are not appropriate at the country level unless prevalence has been directly measured in a national TB prevalence survey (e.g. China).
- **MDR-TB mortality**. A global estimate is useful for global advocacy. Country-specific estimates are only appropriate for countries in which there is a vital registration system of high quality and coverage *and* there is a specific code for MDR-TB as a cause of death.
- **Proportion of new and previously treated TB cases with MDR-TB**. This indicator is useful for monitoring trends in levels of drug resistance at global and country levels.

1. Background including a brief history of MDR-TB burden estimates

Drug-resistant TB (DR-TB) threatens global TB control and is a major public health concern in several countries. Drug resistance arises due to improper use of antibiotics in the treatment of drug-susceptible TB patients. This improper use includes the administration of inappropriate treatment regimens and failure to ensure that patients complete the full course of treatment according to national or WHO recommendations. Essentially, drug resistance emerges in areas with weak TB control programmes. A patient who develops active disease with a drug-resistant TB strain can transmit this form of TB to other individuals in exactly the same way as drug-susceptible TB.

The first global and country-specific estimates of the disease burden associated with DR-TB were published by WHO in 2001.[1] A focus on the monitoring of drug resistance to both rifampicin and isoniazid was traditionally given on the grounds of the importance of these drugs in the overall first line anti-TB regimen. This pattern of drug-resistance was defined as multidrug-resistant TB (MDR-TB).[2] Among incident cases of TB, it was estimated that there were 272 906 (95% CI, 184 948–414 295) cases of multidrug-resistant TB (MDR-TB) globally in 2000. In a 2006 publication by WHO authors, this analysis was updated and expanded to include incident cases of MDR-TB among previously treated TB cases as well as those newly diagnosed with TB. The resulting global estimate was 424 203 (95% CI, 376 019–620 061) incident cases in 2004[3]. In a WHO report on MDR-TB issued in 2010, this estimate was updated to 440 000 (95% confidence interval 390 000 – 510 000) incident cases globally in 2008; country-specific estimates were also published.[4]

Since 2010, WHO has not published country-specific estimates of the incidence of MDR-TB. This followed concerns expressed by some national TB programmes and technical agencies that assessment of country progress by comparing numbers of MDR-TB patients enrolled on treatment with estimated incidence was unfair and misleading. First, many of the estimated cases are not even diagnosed or reported with TB (let alone MDR-TB); and second, not all cases of MDR-TB could be detected with the availability of diagnostic tests. In recent WHO global TB reports, country-specific estimates related to the burden of MDR-TB have thus focused on the estimated number of MDR-TB cases among notified TB patients with pulmonary TB (newly diagnosed and previously treated) as well as a global estimate for this indicator (a best estimate of about 300 000 cases). Reports have also continued to include country-specific data about the estimated proportion of new and previously treated TB patients that have MDR-TB, as measured in drug resistance surveys or via continuous surveillance systems in which TB patients are routinely tested for drug resistance. A global estimate of MDR-TB prevalence was included in the 2011 and 2012 global TB reports, with a best estimate of 630 000 cases in 2011. Updated global estimates of MDR-TB incidence and mortality (best estimates of 450 000 incident cases and 150 000 deaths in 2012) were presented in the 2013 global TB report.

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[1] Espinal MA et al. Global Trends in Resistance to Antituberculosis Drugs. *N Engl J Med* 2001;**344**:1294-1303.
[2] The focus of this document is MDR-TB. However, the material presented here can be used to deduce respective discussions on indicators and estimates of disease burden for other patterns of drug resistance such as extensive drug-resistance (XDR) or mono-(such as rifampicin)-resistance.
[3] Zignol M et al. Global Incidence of Multidrug-Resistant Tuberculosis. *J Infect Dis* 2006;**194(4)**:479-485.
[4] WHO. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response.

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This document summarizes the main content of the presentations at the global MDR-TB stakeholders meeting and the key recommendations regarding the use of each of the indicators that were considered. The five major topics covered are:

- **Concepts and definitions (section 2)**. Four possible burden indicators are defined: MDR-TB incidence; MDR-TB prevalence; MDR-TB mortality; and the number of cases of MDR-TB among notified TB patients. The two key mechanisms through which MDR-TB cases emerge and the associated concepts of primary and acquired resistance are described and discussed. The terms used to define TB cases according to their treatment history (new, relapse and retreatment excluding relapse) are explained. The epidemiological dynamics and relationship between the key indicators of incidence, prevalence and mortality for TB in general, as well as disaggregated by drug susceptibility status, are then illustrated and explained.
- **Surveillance of MDR-TB (section 3)**. An overview of the WHO Global Project on Anti-tuberculosis Drug Resistance is provided, including the geographical coverage of data from surveys and continuous surveillance by the end of 2013.
- **Key epidemiological indicators (section 4)**. The four key epidemiological indicators that can be used disease burden estimation are defined and the methods that can be used to estimate them are explained. The strengths and weaknesses (including data gaps) of each indicator are discussed.
- **Country examples (section 5)**. The strengths and weaknesses of each of the four indicators discussed in section 4 are illustrated using the examples of India, Kazakhstan and South Africa.
- **Recommendations (section 6)**. The main recommendations arising from the global MDR-TB stakeholders meeting, in terms of the most appropriate application for each indicator, are summarized.

Appendix 1 (pages 21-24) contains the document that was used for group discussions at the global MDR-TB stakeholders meeting in October 2013, updated according to the recommendations arising from the meeting.

Appendix 2 provides a list of the participants at the global MDR-TB stakeholders meeting in October 2013.

2. Concepts and definitions

2.1 Incidence, prevalence and mortality of TB, and number of MDR-TB among notified pulmonary TB patients

TB incidence is defined as the number of new and recurrent episodes of TB (all forms) occurring in a given year (also see **section 2.3**). **MDR-TB incidence** comprises a sub-group of incident TB and a sub-group of prevalent TB on first-line treatment improperly used (also see **section 2.4**).

TB prevalence is defined as the number of TB cases (all forms) at a given point in time. **MDR-TB prevalence** is always a sub-group of TB prevalence.

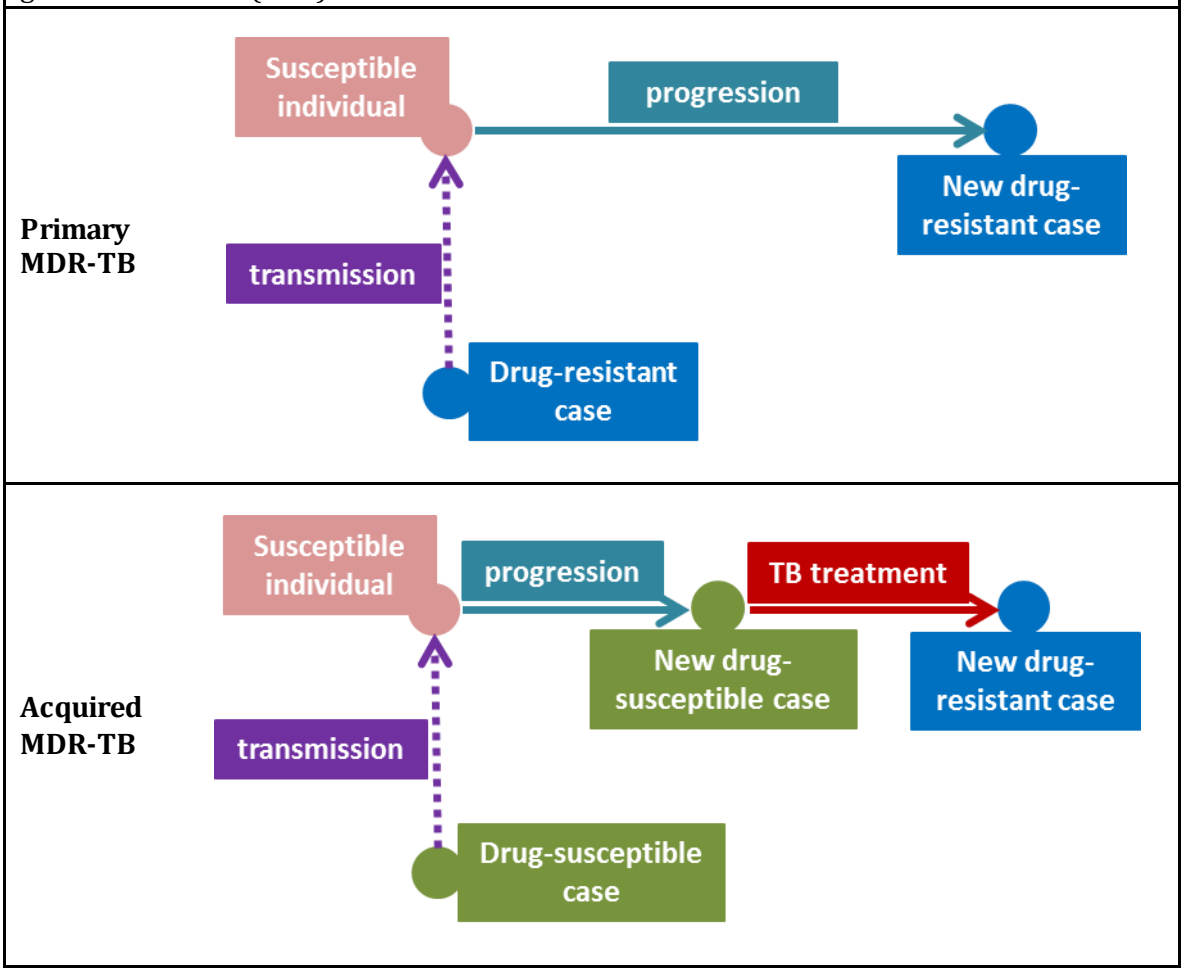
TB mortality is defined as the number of deaths caused by TB in HIV-negative people, according to the latest revision of the *International classification of diseases* (ICD-10). TB deaths among HIV-positive people are classified as HIV deaths in ICD-10. For this reason, WHO estimates of deaths from TB in HIV-positive people are always presented separately from those in HIV-negative people. **MDR-TB mortality** is always a sub-group of TB mortality.

Number of MDR-TB cases among notified pulmonary TB cases is defined as the estimated number of MDR-TB cases which could be detected if all cases of pulmonary TB notified by a country occurring in a given year were tested for drug susceptibility to isoniazid and rifampicin.

2.2 Primary and acquired MDR-TB

Two mechanisms by which new cases of MDR-TB arise need to be clearly differentiated. Resistance to anti-TB drugs can be due to infection with a strain of *M.tb* that is already resistant to anti-TB drugs – referred to as *primary* MDR-TB; or due to acquisition of drug resistance during the course of treatment with anti-TB drugs – referred to as *acquired* MDR-TB (**Figure 1**).

FIGURE 1. The two mechanisms of transmission of infection and progression to disease that generate incident (new) MDR-TB cases



2.3 Categories of cases according to TB treatment history

New TB cases have no documented or reported history of treatment for active TB with anti-TB drugs for one month or more.

Relapses are TB cases with a recurrent TB episode after documented successful treatment (i.e. cure or treatment completion).

Retreatments that are not relapses include TB cases who have been treated with TB drugs for one month or more and (i) have failed one or more treatment regimens using first and/or second line drugs, or (ii) have returned after being lost to follow up, or (iii) whose outcome after their most recent course of treatment is unknown or undocumented.

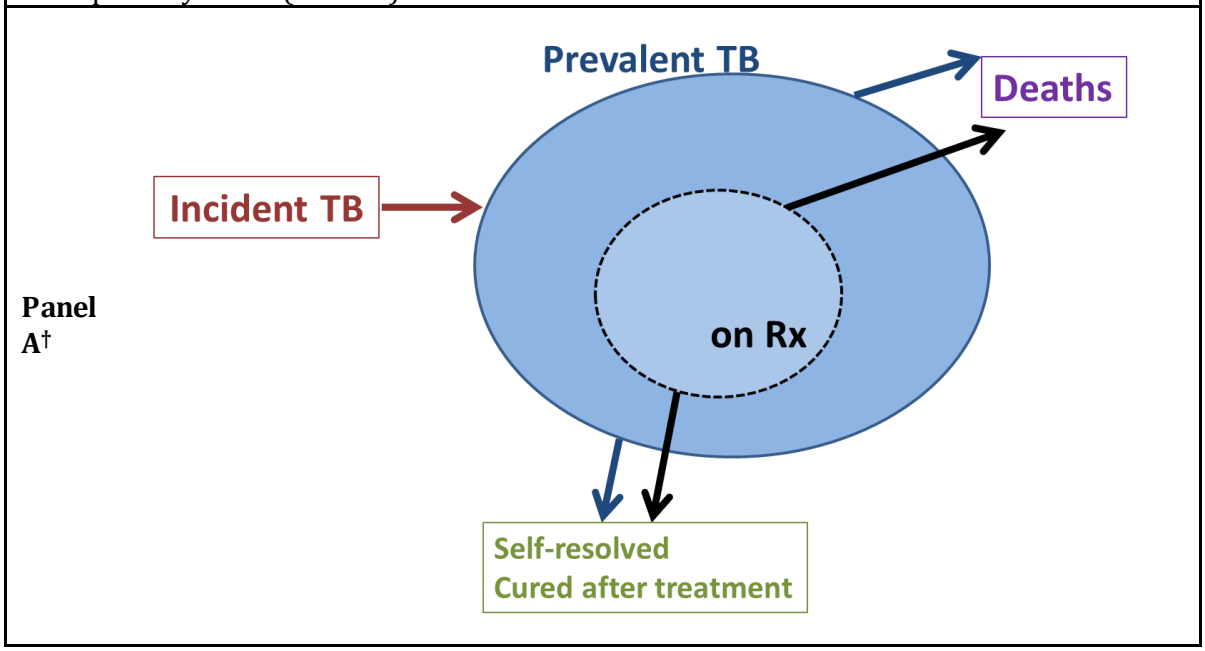
2.4 Epidemiological dynamics of TB disease

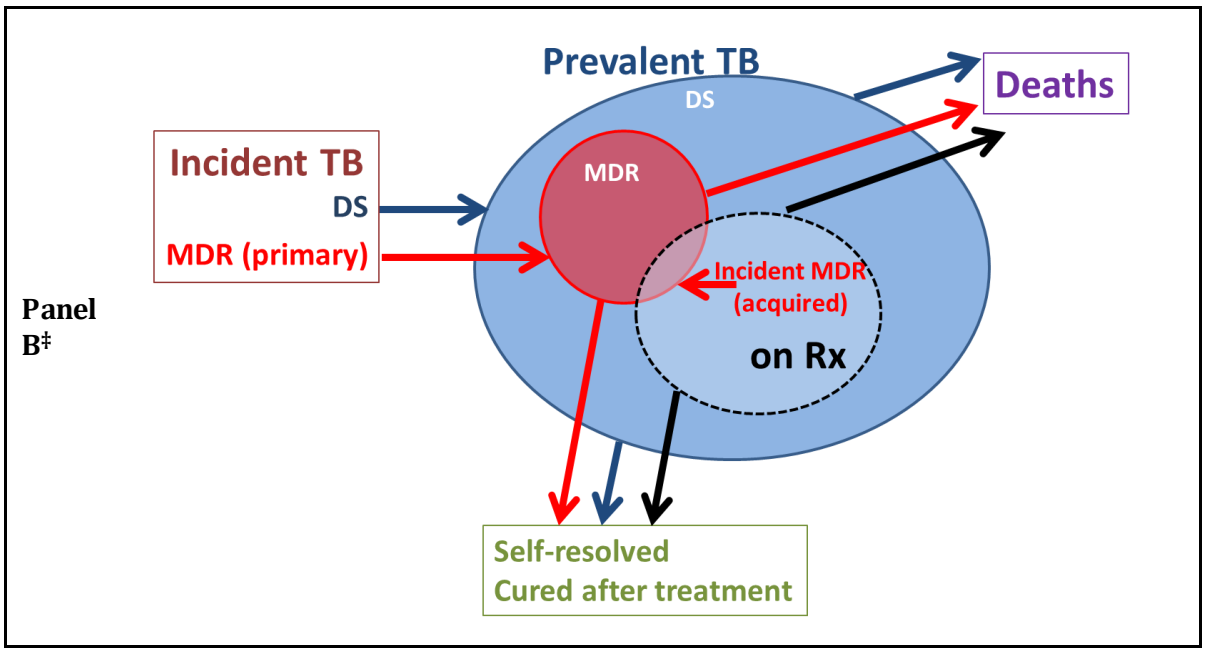
The key epidemiological dynamics and relationship between the indicators of incidence, prevalence and mortality for TB in general, as well as disaggregated by drug susceptibility status, are illustrated in **Figure 2**.

Incident (new) TB cases feed into the pool of prevalent (existing) TB cases, of which a proportion is on treatment (Rx) at any given point in time (**Panel A**). Prevalent cases die (with or without treatment), self-resolve without treatment, cure with treatment, or remain chronic prevalent cases.

TB dynamics disaggregated by drug susceptibility status (**Panel B**): incident TB cases: both drug susceptible to all first line anti-TB drugs (DS) and MDR (primary), feed into the pool of prevalent TB cases (DS and MDR respectively), of which a proportion is on Rx at any given point in time. From the cases on Rx, an additional sub-group of incident MDR-TB (acquired) feeds into the MDR-TB prevalent pool. Prevalent cases die (with or without treatment), self-resolve without treatment, cure with treatment, or remain chronic prevalent cases.

FIGURE 2. An overview of TB dynamics overall (Panel A) and disaggregated by drug susceptibility status (Panel B)



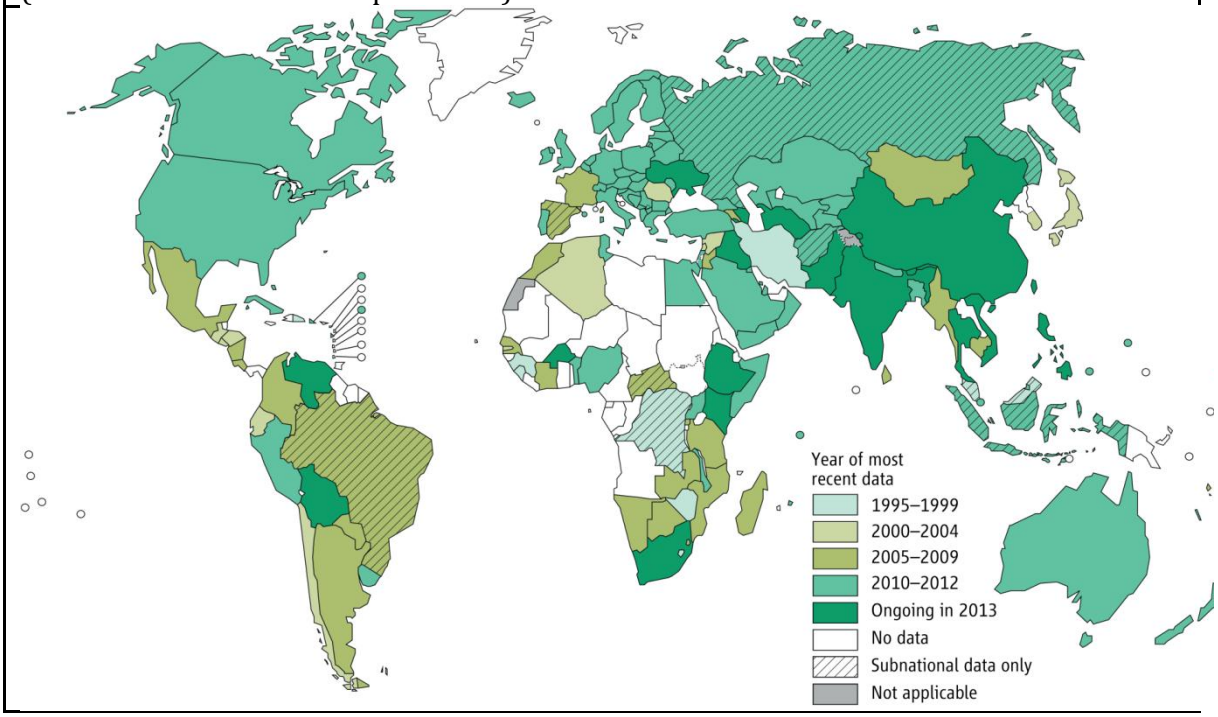


DS=drug-susceptible to all first-line anti-TB drugs; MDR=multidrug-resistant; Rx=first-line treatment

3. Surveillance of multidrug-resistant TB (MDR-TB)

The WHO Global Project on Anti-tuberculosis Drug Resistance Surveillance (DRS) was launched in 1994. Since then, data on drug resistance have been systematically collected and analysed from 136 countries worldwide (70% of WHO's 194 Member States). This includes 71 countries that have continuous surveillance systems based on routine diagnostic drug susceptibility testing (DST) of all TB patients and 65 countries that rely on special epidemiological surveys of representative samples of patients. Proportions of resistance to rifampicin and isoniazid are investigated separately for new and previously treated TB cases. All strains found with MDR-TB undergo second-line DST to the fluoroquinolones and injectable agents most commonly used in the country. The progress towards achieving global coverage of drug resistance data is shown in **Figure 3**. On average, 20 national surveys are implemented worldwide each year and an additional 20 are in the preparatory phase. Central and Francophone Africa continue to remain the regions for which drug resistance surveillance data are most lacking, largely as a result of the current weak laboratory infrastructure. Data on time trends in drug resistance are available from 88 countries and 10 territories worldwide for a total of 870 country-year data points. Drug resistance surveys should be conducted regularly, approximately every five years, to be able to monitor time trends in drug resistance. Molecular diagnostic technologies are now being incorporated in drug resistance surveys to simplify logistics, reduce laboratory workload and increase the frequency of surveys to improve understanding of time trends.

FIGURE 3. Progress in global coverage of data on drug resistance surveillance, 1994-2013 (ref: Global Tuberculosis Report 2013)



4. Key epidemiological indicators

This section defines the four key epidemiological indicators that could be used for disease burden estimation, along the methods to estimate them and associated strengths and weaknesses (including data gaps). The notation used for parameters referred to throughout this section is shown in **Table 1**.

TABLE 1. Notation for parameters used in equations (1)-(5) for the estimation of MDR-TB disease burden for different indicators

Number of MDR-TB cases among notified pulmonary TB cases	
N	Number of MDR-TB cases among notified pulmonary TB cases
new	Number of all new notified pulmonary TB cases
ret	Number of all retreated notified pulmonary TB cases
p_n	Proportion of MDR-TB among new TB cases from DR surveys or continuous surveillance
p_r	Proportion of MDR-TB among retreated TB cases from DR surveys or continuous surveillance
MDR-TB incidence (method I)	
I	MDR-TB incidence
new	Number of all new notified TB cases
rel	Number of all relapse notified TB cases
ret_not_rel	Number of all retreatment notified TB cases that are not relapses
p_n	Proportion of MDR-TB among all new TB cases from DR surveys or continuous surveillance
p_r	Proportion of MDR-TB among all retreatment cases; assumed to follow a uniform distribution $\sim U(0,1)$
cdr	TB case detection ratio: (new + rel)/TB incidence, all forms
rr	Relative risk of MDR-TB among relapse vs. new cases, approximated by odds

	ratio
MDR-TB incidence (method II)	
I	MDR-TB incidence
m	MDR-TB mortality
f	MDR-TB case fatality ratio
p_t	Proportion of MDR-TB patients on treatment
f_t	Case fatality ratio among patients treated for MDR-TB
f_{un}	Case fatality ratio among untreated patients with MDR-TB
MDR-TB mortality	
m	MDR-TB mortality
M	Overall TB mortality
p	Overall proportion of MDR-TB among prevalent TB cases
rr	The relative risk of death among MDR-TB vs. non-MDR-TB patients
MDR-TB prevalence	
Pr	Overall TB prevalence
pr	MDR-TB prevalence
p	Overall proportion of MDR-TB among prevalent TB cases

4.1 Number of MDR-TB cases among notified pulmonary TB cases

The number of MDR-TB cases among notified pulmonary TB cases is an indicator monitored by WHO since 2010.[5]

This is calculated as the sum of estimated MDR-TB cases among new and retreated case notifications, which in turn are the product of: all new pulmonary case notifications, $\boldsymbol{new}$, multiplied by the proportion MDR-TB among new, $\boldsymbol{p_n}$, and all retreatment pulmonary case notifications, $\boldsymbol{ret}$, multiplied by the proportion MDR among retreatment cases, $\boldsymbol{p_r}$. (see **equation 1**).

$$\boldsymbol{N = (new * p_n) + (ret * p_r)} \quad (1)$$

For 2013, the best global estimate of the number of MDR-TB cases among notified pulmonary TB cases, along with the associated 95% confidence interval, was:

Best	Low	High
300 000	220 000	380 000

The main strengths of this burden indicator are:

- It is directly measureable at the national level and can be monitored on an annual basis with an established continuous DR surveillance system.
- It provides a pragmatic denominator for national TB programmes to monitor their progress towards diagnosing and treating MDR-TB cases among all notified TB cases.
- It provides a reliable number to use when forecasting drug procurement needs.

The main limitations are:

- It underestimates the number of MDR-TB patients in need of treatment especially when large numbers of TB cases are not diagnosed or reported to the national TB surveillance system.

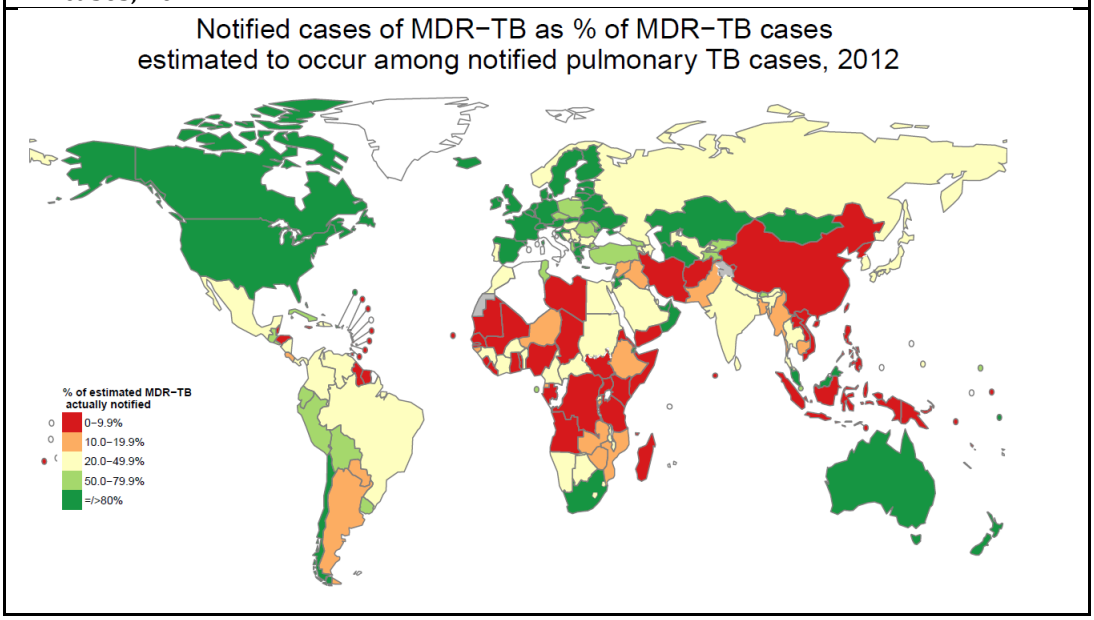
[5] http://www.who.int/tb/challenges/mdr/surveillance/en/index.html

- It does not include surviving MDR-TB patients from previous years who are still eligible for treatment, nor notified TB patients from previous years who were eligible for but did not undergo drug susceptibility testing.
- It does not include extra-pulmonary retreatment cases despite the availability of such data in a few countries (e.g. the UK).

Next steps that could be taken to improve the estimation of this indicator are:

- Proactively engage with and expand the TB surveillance system coverage to the private sector, prisons, army forces, corporate and other non-NTP health facilities, and ensure these are included in national DR surveys or continuous surveillance.
- Promote the use of additional measures to improve case detection, such as through patient awareness to self-present for TB diagnosis.
- Promote up-to-date and robust country-level MDR-TB estimates through surveys or continuous surveillance.
- Promote the move towards universal drug susceptibility testing of all notified pulmonary TB cases.

FIGURE 4. Number of MDR-TB cases estimated to occur among notified pulmonary TB cases, 2012[6]



4.2 MDR-TB incidence

As described in **Section 2.1,** incident MDR-TB comprises incident TB for which the strain is MDR (*primary MDR-TB*) and incident MDR-TB occurring among prevalent TB cases whose strains have acquired MDR characteristics through exposure to first-line treatment (*acquired MDR-TB*). **Table 2** shows the parameters for which data are required to directly measure MDR-TB incidence (also see **section 2.4**), and the data which are currently available for the indirect estimation of this indicator.

[6] WHO. Global TB Report, World Health Organization. Geneva, 2013

TABLE 2. Data requirements for the direct measurement of incident MDR-TB, and data available for its indirect estimation

Data required for direct measurement	***Available direct measurements***	***Inherent uncertainty***
TB incidence	TB case notifications	Case notifications come from the pool of prevalent cases. Bias of unknown magnitude may exist, depending on the level of under-reporting and under-diagnosis
Prevalence of primary MDR-TB among incident TB	Proportion of MDR-TB among new cases, drawn from DR surveys or continuous surveillance	Biased when patients tested in DRS are not representative of all incident new TB cases
Number of people currently on first line anti-TB treatment	1. Number of TB cases notified to national surveillance systems 2. A few national TB prevalence surveys	1. Biased when not all cases on treatment are notified (e.g. private sector) 2. Imprecise due to small numbers
Rate of acquisition of MDR-TB while on treatment	Using the upper limit of the proportion MDR-TB among retreatment cases from DR surveys or continuous surveillance as the maximum possible rate of acquisition.	*Biased*: not all MDR-TB among retreatment cases have acquired MDR-TB; some have primary (previously undetected) MDR-TB

Given the obvious data gaps for the direct measurement of MDR-TB incidence, two different methods for its indirect estimation and associated results are provided below.

Method I (**equation 2**) approximates total MDR-TB incidence by summing the estimated number of MDR-TB cases among three distinct types of TB case notifications (new all forms $\boldsymbol{new}$, relapse all forms $\boldsymbol{rel}$, and all retreatments that are not relapse forms $\boldsymbol{ret\_not\_rel}$) inflated upwards by the estimated amount of incident cases not identified by the surveillance system, for all forms of TB. It should be noted that the case detection rate, $\boldsymbol{cdr}$, in the denominator of (2) is assumed to be the same for all three groups of cases ($\boldsymbol{new}$, $\boldsymbol{rel}$, $\boldsymbol{ret\_not\_rel}$); this is an assumption that is unlikely to hold in practice. For instance, $\boldsymbol{rel}$ cases may be more likely to be detected and reported again if they were previously reported as $\boldsymbol{new}$, as a result of their previous treatment history. The $\boldsymbol{cdr}$ for $\boldsymbol{ret\_not\_rel}$ is also likely to be different from the $\boldsymbol{cdr}$ for $\boldsymbol{new}$ cases because $\boldsymbol{ret\_not\_rel}$ cases are drawn from the pool of prevalent notified cases on treatment. If the $\boldsymbol{cdr}$ for $\boldsymbol{new}$ is indeed lower than for the other two categories of cases, then the estimate of $\boldsymbol{I}$ will be biased towards higher values.

$$\boldsymbol{I} = \frac{(\boldsymbol{new} * \boldsymbol{p_n}) + (\boldsymbol{rel} * \boldsymbol{p_n} * \boldsymbol{rr}) + (\boldsymbol{ret\_not\_rel} * \boldsymbol{p_r})}{\boldsymbol{cdr}} \quad (2)$$

Method II (**equation 3**) estimates MDR-TB incidence as the ratio of the number of MDR-TB deaths $\boldsymbol{m}$ (also see **section 6**) divided by the MDR-TB case fatality rate $\boldsymbol{f}$ (expressed as a proportion). We have allowed the probability of death among MDR-TB patients to vary

according to whether the patient is on second-line treatment f_t (parameterisation informed from treatment outcome data collected from MDR-TB patient cohorts) or not f_{un} (assumed to follow an uninformative uniform distribution). The proportion of MDR-TB patients on treatment p_t is approximated by the proportion of enrolled MDR-TB patients on treatment among those estimated to exist among notified TB patients with pulmonary TB.

$$I = \frac{m}{f} = \frac{m}{p_t * f_t + (1 - p_t) * f_{un}} \quad (3)$$

For 2013, the best global estimates of the incidence of MDR-TB, along with the associated 95% confidence intervals for each of the two methods, were estimated to be:

	Best	Low	High
Method I	450 000	300 000	600 000
Method II	430 000	240 000	630 000

The main strengths of this burden indicator are:

- It has strong advocacy potential, especially at the global level, for highlighting the urgency of taking action against MDR-TB.
- The estimation method is relatively simple and transparent.

Limitations include:

- There are important data gaps and a number of required approximations that need to be made for the indirect estimation of incident MDR-TB.
- The incidence of MDR-TB does not describe actual needs for MDR-TB treatment, which are equal to the estimated number of prevalent MDR-TB cases.
- Estimates of CDR are highly imprecise.
- It is assumed that MDR-TB levels are the same among TB cases notified to the NTP and TB cases treated in the health sector not reporting to the NTP (e.g. private sector).
- The proportion of MDR among new pulmonary TB estimated from DR surveys or continuous surveillance is assumed to be the same as the proportion of MDR-TB among all new TB case types (i.e. extra-pulmonary TB).
- There are as yet very little empirical data published on the emergence of MDR-TB among patients on treatment. Those that are available are based on cases in former Soviet Union countries and show considerable variation depending on pre-existing non-MDR resistance patterns (e.g. H+S resistance) at the start of treatment.[7,8] As a result, the approximation above uses a value chosen from between 0 to the upper limit of the proportion of MDR observed among retreatment cases in surveys.

[7] Cox HS, Niemann S, et al. Risk of acquired drug resistance during short-course directly observed treatment of tuberculosis in an area with high levels of drug resistance. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2007 Jun 1;44(11):1421–7.

[8] Gelmanova I, Keshavjee S, et al. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. *Bull World Health Organ*. 2007 Sep;85(9):703–11.

- The number of incident MDR-TB cases missed by the surveillance system is assumed to be the same as that for drug susceptible TB, and does not vary according to retreatment categories.
- The estimation of the relative risk (that approximates the odds ratio of MDR-TB among relapse cases versus MDR-TB among new cases) is based on a small number of (mostly European) countries for which data are available.
- There is a lack of country-level data for some of the parameters required for the estimation, meaning that pooled global data must be used for country-level calculations.

The next steps that could be taken to improve the estimation of this indicator are:

- Investigate mathematical modelling approaches to identify the most important data gaps that need to be addressed to reduce the uncertainty of indirect estimation.

4.3 MDR-TB mortality

Data sources to directly inform the measurement of MDR-TB mortality are available, but not yet fully developed to capture nationally representative and robust data.

One of these possible sources is the cause of death (COD) data produced from national systems that monitor vital statistics (such as death). The current 10th revision of the International Classification of Diseases (ICD-10) does not have standardised COD codes assigned specifically to death from MDR-TB. However, user-defined codes can be assigned and monitored by countries themselves. The South African example is presented in **Table 3**. Despite national coverage of the vital registration (VR) system, these data are not being used; the coverage of DST among pulmonary TB cases means that reported deaths from MDR-TB in South Africa are an underestimate of the true number of deaths from MDR-TB.

TABLE 3. Number of deaths from MDR- and XDR-TB from the national ICD-10 vital registration system of South Africa, 2006–2010, and national DST coverage among cases of pulmonary TB. User-defined COD codes: U51 for an MDR- and U52 for an XDR-TB death.

Data source: Statistics SA	**2006**	**2007**	**2008**	**2009**	**2010**
U51	604	597	712	1184	856
U52	3	84	135	151	171
DST coverage among pulmonary TB	Not available	Not available	27%	10%	12%

MDR-TB=multidrug-resistant TB; XDR-TB=extensively drug-resistant TB

Another source of information on deaths from MDR-TB is the patient cohort data on treatment outcomes of registered MDR-TB cases. However, these are not representative of all existing MDR-TB cases (e.g. MDR-TB patients not in the NTP cohort are not included), nor is every registered treatment outcome of death due to MDR-TB or even TB. For these reasons, MDR-TB treatment outcome cohort data do not constitute a robust and nationally representative data source that can be used for the direct estimation of national MDR-TB mortality.

Therefore, indirect methods to estimate MDR-TB mortality are being used instead. The number of deaths from MDR-TB $\boldsymbol{m}$ can be estimated as the product of overall deaths from TB $\boldsymbol{M}$, the overall proportion of TB cases that have MDR-TB $\boldsymbol{p}$ (approximated by the weighted

average of the proportion of new and retreated cases that have MDR-TB, as calculated from DR surveys or continuous surveillance), and the relative risk $\boldsymbol{rr}$ of dying among people with MDR-TB compared with those without MDR-TB (estimated from a systematic review that included data from twenty-five studies).

$$\boldsymbol{m = M * p * rr} \quad (4)$$

For 2013, the best global estimate of the number of deaths due to MDR-TB, along with the associated 95% confidence interval, was:

Best	Low	High
170 000	100 000	240 000

The strengths of this burden indicator are:

- It has strong advocacy potential, especially at the global level, to highlight the urgency of taking action against MDR-TB.

Limitations include:

- It is assumed that the proportion of MDR-TB among the prevalent TB cases in the general population is the same as the proportion of MDR-TB estimated from DR surveys or continuous surveillance.
- Given the lack of country-level data on the relative risk $\boldsymbol{rr}$, country-level values cannot be reliably calculated.

The next steps that could be taken to improve the estimation of this indicator are:

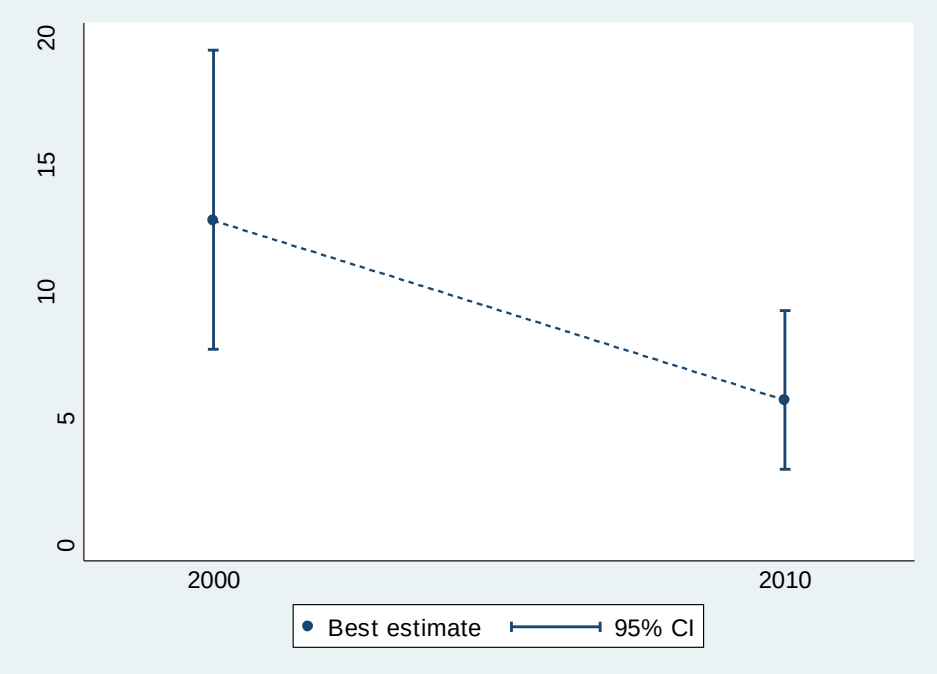
- Focus on high MDR-TB burden countries with already established VR systems and universal DST coverage to promote the inclusion of a specific code for MDR-TB as a cause of death (since mortality is a disease burden indicator that can be measured directly for MDR-TB through the advocacy for and promotion of national VR systems).
- Further refinement of the measurement of the relative risk $\boldsymbol{rr}$ based on the actual cause of death (TB vs. non-TB).
- Proactive engagement with and expansion of the TB surveillance system to cover the private sector, prisons, army forces, corporate and other non-NTP health facilities, and ensuring that these are part of the sampling frame of national DR surveys.

4.4 MDR-TB prevalence

Pulmonary TB prevalence is an indicator that can be directly measured among the general population through population-based prevalence surveys. Drug susceptibility testing of all bacteriologically-confirmed TB cases identified in the survey provides an unbiased estimate of pulmonary MDR-TB prevalence among the general population, but usually with very low precision because of the small numbers of cases identified through these prevalence surveys. Typically, only about 100-200 prevalent TB cases are identified through these prevalence surveys, of which only a handful of MDR-TB cases may be identified; in some instances there is even a reasonable likelihood that none will be detected. **Figure 5** shows time trends in MDR-TB prevalence in China as estimated by repeat prevalence surveys in 2000 and 2010. In the 2000 survey, of the 375 599 eligible individuals, there were 263 pulmonary TB cases identified of which 20 (7.6%) had MDR-TB. In the 2010 survey, of the 263 281 eligible individuals, there were 241 pulmonary TB cases identified of which 13 (5.4%) had MDR-TB.

Given the overlap in confidence limits this observation does not show a statistically significant change, but could still inform public health decisions based on other probabilistic statements calculated from the overlap of density functions of the two estimates of MDR-TB prevalence, and their uncertainty, from the 2000 and 2010 surveys.

FIGURE 5. Prevalence rate of MDR-TB per 100 000 general population was estimated through repeat population-based TB prevalence surveys in China (2000 and 2010). These are unbiased, but imprecise, estimates that could provide.



Therefore, indirect estimation of MDR-TB prevalence is instead used. The number of prevalent MDR-TB cases $\boldsymbol{pr}$ can be estimated as the product of the overall TB prevalence $\boldsymbol{Pr}$ and the overall proportion of TB cases that have MDR-TB $\boldsymbol{p}$ (approximated by the weighted average of the proportion of new and retreated cases that have MDR-TB).

$$\boldsymbol{pr} = \boldsymbol{Pr} * \boldsymbol{p} \tag{5}$$

For 2013, the best global estimate of the prevalence of MDR-TB , along with the associated 95% confidence interval was:

Best*	Low	High
600 000	460 000	740 000

*Unpublished estimate for 2012

The main strength of this burden indicator is:

- It reflects the estimated number of people in need of MDR-TB treatment among the general population.

Limitations include:

- The proportion of MDR-TB among the prevalent TB cases in the general population is assumed to be the same as the proportion of MDR-TB estimated from DR surveys or continuous surveillance among self-presenting TB cases.

- The estimates of TB prevalence are highly imprecise, especially in countries with no national TB prevalence survey.
- Prevalence is not a suitable indicator for detecting rapid changes in burden.

The next steps that could be taken to improve the estimation of this indicator are:

- Proactive engagement with and expansion of the TB surveillance system to the private sector, prisons, and other non-NTP health facilities.
- Ensuring that the private sector, prisons, army forces, corporate and other non-NTP health facilities are part of the sampling frame of national DR surveys or continuous surveillance.
- Improve the reporting of TB cases.

5. Country examples

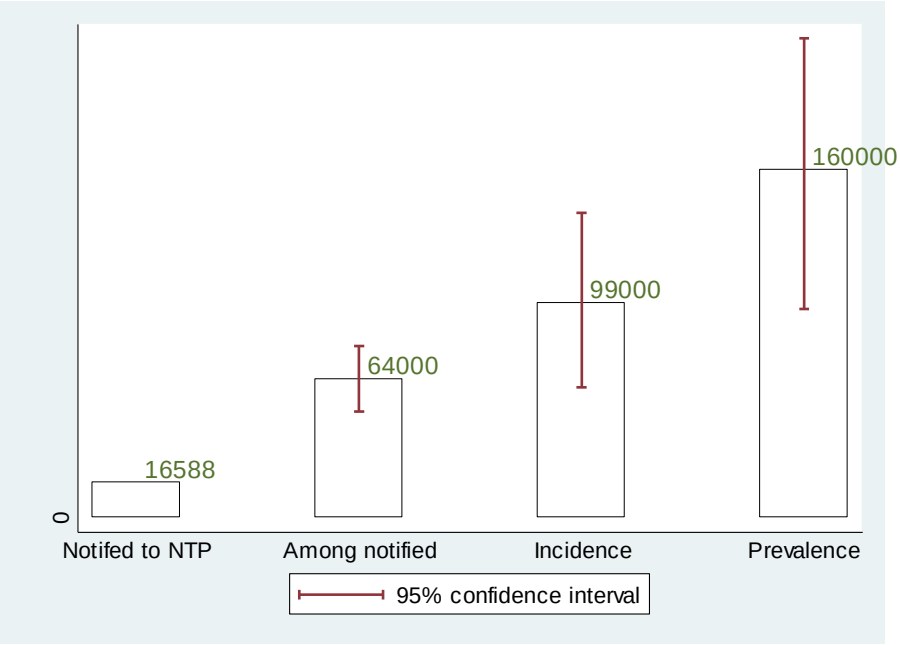
In this section, we estimate and discuss the accuracy and precision of country-level estimates for (i) the number of MDR-TB cases among pulmonary TB cases, (ii) the number of incident MDR-TB cases and (iii) the number of prevalent MDR-TB cases. We use three country examples based on 2013 data from India, Kazakhstan and South Africa, and produce estimates calculated according to the methods described in **sections 4**, **5** (*method I*), and **7**.

5.1 India

16 588 MDR-TB cases were notified to the NTP in India in 2012. The best estimate of the number of MDR-TB cases for each of the three indicators, along with their 95% confidence intervals, were calculated (see table below).

Number of MDR-TB cases	Best	Low	High
(i) Among notified	64 000	49 000	79 000
(ii) Incidence	99 000	60 000	140 000
(iii) Prevalence	160 000	96 000	220 000

Due to the data gaps in the country-level parameters necessary for the estimation of each of the indicators, the relative uncertainty increases significantly in the direction of (i)<<(iii)<<(ii), making it difficult to draw meaningful conclusions with regards to progress in scale-up and treatment coverage using incidence and prevalence compared to the number among notified.

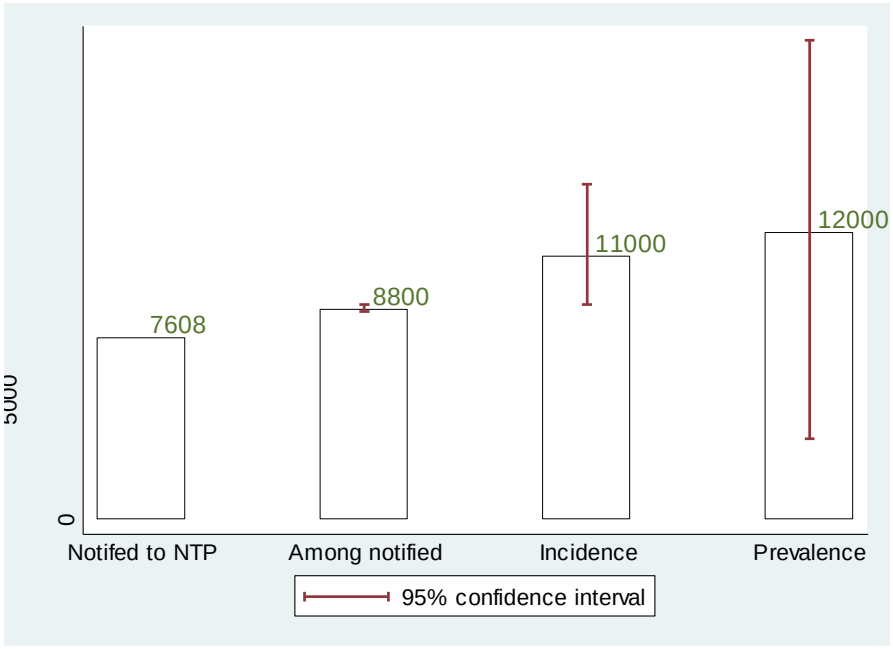


5.2 Kazakhstan

7 608 MDR-TB cases were notified to the NTP in Kazakhstan in 2012. The best estimates of the number of MDR-TB cases for each of the three indicators, along with their 95% confidence intervals, were calculated (see table below).

Number of MDR-TB cases	Best	Low	High
(i) Among notified	8 800	8 700	9 000
(ii) Incidence	11 000	9 000	14 000
(iii) Prevalence	12 000	3 400	20 000

Each of the indicators could be used as the denominator against which one could monitor the progress towards finding and treating MDR-TB cases in the country. However, the best estimates of each of the indicators provide different targets for countries to reach with increasing (and more difficult) denominators (i)<(ii)<(iii). Therefore, for a country like Kazakhstan that does well with finding MDR-TB cases among notified TB cases and putting them on treatment (86% on treatment), it would seem preferable to use MDR-TB incidence as the denominator (69% on treatment) rather than MDR-TB prevalence (63% on treatment).

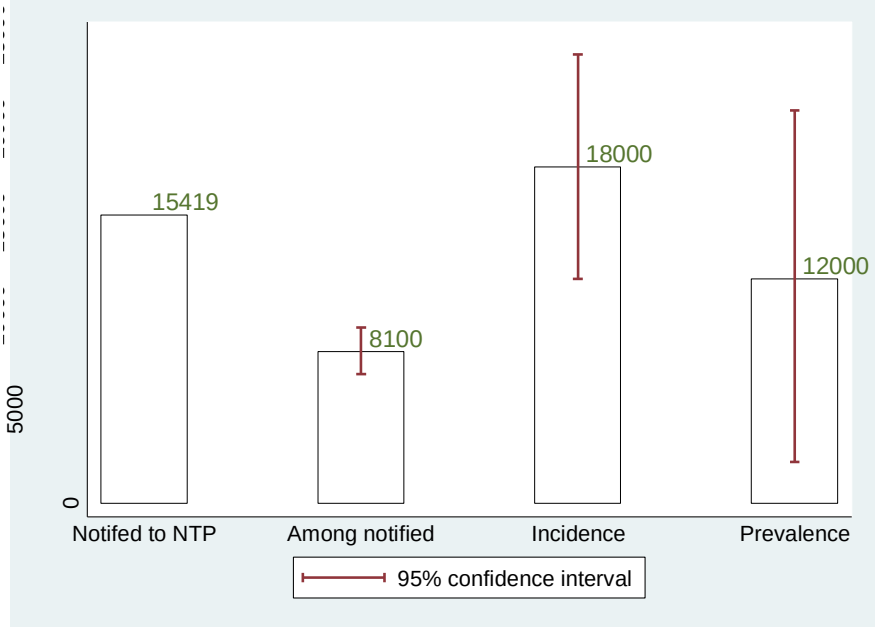


5.3 South Africa

15 419 MDR-TB cases were notified to the NTP in South Africa in 2012. Best estimates of the number of MDR-TB cases for each of the three indicators, along with their 95% confidence intervals, were calculated (see table below).

Number of MDR-TB cases	Best	Low	High
(i) Among notified	8 100	6 900	9 400
(ii) Incidence	18 000	12 000	24 000
(iii) Prevalence	12 000	2 200	21 000

The estimated number of MDR-TB cases among notified TB cases is much lower than the actual number of MDR-TB cases notified to the NTP. This is most probably due to: a) duplicate TB case notifications and/or b) outdated data (the last national DR survey was completed in 2002; a repeat survey implemented in 2013 and 2014 will provide up-to-date data).



6. Recommendations

In preparation for the global MDR-TB stakeholders meeting, a summary table was prepared as the basis for group discussions. For each of the four burden indicators discussed above, the summary table (**Appendix 1**) summarized the data sources currently used for estimation and included a pre-assessment of whether the indicator was suitable (Yes/No response) for the following four purposes: a) monitoring of progress in diagnostic and treatment coverage b) planning/budgeting and allocation of funding c) advocacy and d) assessment of trends in the epidemic of MDR-TB. Explanatory comments were also included where these were thought necessary to explain the Yes/No response indicated. During group discussions, each of the four groups discussed the table and updated it (including the Yes/No assessment) or added comments as appropriate. The updated version based on the group discussions is the version shown in **Appendix 1**.

The main recommendations based on the four-page summary table in **Appendix 1** are:

- **MDR-TB cases among notified cases of pulmonary TB**. This indicator should continue to be used for assessing programmatic performance in diagnostic and treatment coverage, at country and global levels. It is also appropriate for planning and budgeting purposes. In some instances it may be useful for advocacy purposes, especially at country level.
- **MDR-TB incidence**. A global estimate is useful for global advocacy. Country-specific numbers become increasingly relevant as a) overall detection of TB cases approaches 100% and b) treatment coverage among notified TB cases approaches 100%.
- **MDR-TB prevalence**. A global estimate is useful for global advocacy. Since incidence and prevalence can be confused, global publications should focus on only one of these two indicators (for example, in abstracts, executive summaries of global reports and advocacy brochures). Prevalence numbers are not appropriate at the country level unless prevalence has been directly measured in a national TB prevalence survey (e.g. China).
- **MDR-TB mortality**. A global estimate is useful for global advocacy. Country-specific estimates are only appropriate for countries in which there is a vital registration system of high quality and coverage *and* there is a specific code for MDR-TB as a cause of death.

- **Proportion of new and previously treated TB cases with MDR-TB**. This indicator is useful for monitoring trends in levels of drug resistance at global and country levels.

Appendix I. Consolidated and updated post-meeting version of discussion document on MDR-TB burden

DISCUSSION DOCUMENT ON MDR-TB BURDEN INDICATORS : POST-MEETING, CONSOLDATED AND UPDATED VERSION BASED ON GROUP WORK AND FEEDBACK (MDR-TB stakeholders' meeting, Paris, 28 October 2013)						
Indicator	**Data sources used in current estimation**	**Potential application**[1]				**Explanatory comments**
		Monitoring of diagnosis & treatment coverage	*Planning and funding allocation*	*Advocacy*	*Impact assessment of the epidemic*	
Number of MDR among notified pulmonary TB	DR surveys or continuous surveillance TB case notifications	Yes	Yes	Yes *One of the four groups was not convinced this indicator was useful for advocacy.	No/Yes *The original "default answer was "Yes". However, two groups (2 and 3) felt this was not a suitable indicator for assessing impact. Groups 1 and 2 strongly recommended that the best indicator for measuring impact is the % of new cases with MDR-TB, and that this should be used in preference to the number of MDR-TB cases among notified TB patients.	Provides the number of MDR-TB that would be found if all notified pulmonary TB cases were tested for drug susceptibility (using WHO recommended diagnostics). Underestimates number in need of treatment especially when large numbers of TB cases are not diagnosed or reported or large numbers of MDR-TB cases are on waiting lists. Advocacy potential, especially during early treatment rollout when the gap between treatment enrolment and estimated patients in need of treatment is large. Requires up-to-date DR surveys or continuous surveillance for estimates that are relevant and usable.

[1]Country, region, global

IMPORTANT NOTE: THE GROUP DISCUSSION AND FEEDBACK SHOWED THAT THERE WAS STRONG AGREEMENT WITH MOST OF THE ORIGINAL "DEFAULT" VALUES (I.E. YES/NO) THAT WERE PROVIDED IN THE TABLE AS THE BASIS FOR DISCUSSION. IN THIS CONSOLIDATED DOCUMENT PREPARED ACCORDING TO THE FEEDBACK FROM THE FOUR GROUPS, ALL YES/NO RESPONSES ON WHICH THERE WAS STRONG AGREEMENT WITH THE DEFAULT ASSESSMENT (THREE OF FOUR OUT OF THE FOUR GROUPS AGREED WITH IT) ARE SHOWN IN BLACK. DEFAULT VALUES ON WHICH THERE WAS NOT STRONG AGREEMENT (AT LEAST TWO OF THE FOUR GROUPS DISAGREED WITH THE DEFAULT VALUES) ARE HIGHLIGHTED IN YELLOW ALONGSIDE EXPLANATORY COMMENTS. EXPLANATORY COMMENTS ARE ALSO PROVIDED IF ONE GROUP EXPRESSED A DIFFERENT OPINION COMPARED TO THE DEFAULT VALUE OR HAD A SPECIFIC COMMENT. ALL EXPLANATORY COMMENTS ARE SHOWN IN RED.

Indicator	Data sources used in current estimation	Potential application[1]				Explanatory comments
		Monitoring of diagnosis & treatment coverage	*Planning and funding allocation*	*Advocacy*	*Impact assessment of the epidemic*	
MDR-TB incidence	DR surveys or continuous surveillance TB case notifications Global TB disease burden estimates on incidence	No *One group noted that this would depend on treatment coverage. If overall TB case detection is high and scale-up of MDR-TB diagnosis and treatment is already relatively good, then MDR incidence could be a suitable denominator (it would also not be very different to estimated cases among notified TB patients if the overall case detection rate is high, as for example in many high MDR-TB countries in Europe).	No/Yes *The "default" answer was "No". Two groups agreed with this. However, Group 3 considered the answer to be "Yes". Group 2 also felt that MDR-TB incidence could be useful for *long-term planning* in settings where the gap between notified MDR-TB cases and the estimated number of MDR-TB cases among notified TB patients is small (e.g. Kazakhstan)	Yes *Group 2 stressed the importance of this indicator for advocacy at all levels - global, regional, country	No *One group said "Yes" on the condition that it was monitored over time.	Estimates could be heavily biased and imprecise, esp. at country level. With current tools and methods it is not possible to directly measure the number of new MDR-TB cases (primary and acquired) emerging each year. Important data gaps include: • Incidence of primary MDR depends on the quality of estimates of TB incidence, which are typically uncertain when there is likely to be under-reporting of diagnosed cases and limitations in access to health care mean that a proportion of incident cases are not diagnosed. No country has ever directly measured TB incidence through a population-based survey. • Incidence of acquired MDR emerging among patients on treatment (new or retreated) requires data on the number of ALL TB patients on treatment (including in the private sector). This is often unknown. Estimates may change substantially in certain countries with old or no previous DRS data (e.g. South Africa) and/or when estimates of TB incidence are revised in view of new data such as from inventory studies, prevalence or mortality surveys (e.g. Pakistan, Nigeria). Using incident MDR-TB for planning and funding purposes may not be appropriate, especially when large numbers of TB cases are not diagnosed or reported, and would require additional active case finding interventions. Overestimation of MDR-TB incidence may occur due to double-counting of retreatment cases in a calendar year. Advocacy potential, especially at global level, to highlight need for urgent action on MDR-TB.

[1]Country, region, global

Indicator	Data sources used in current estimation	Potential application[1]				Explanatory comments
		Monitoring of diagnosis & treatment coverage	*Planning and funding allocation*	*Advocacy*	*Impact assessment of the epidemic*	
MDR-TB prevalence	DR surveys or continuous surveillance TB case notifications Global TB disease burden estimates of prevalence	No *One of the four groups thought prevalence might be a useful denominator and was the most understandable at the country level.	No *One of the four groups felt that for smaller countries specifically, prevalence may be the best and most precise denominator to use.	Yes	No	Estimates of TB prevalence are relatively imprecise (e.g. compared with incidence) at country level. Only a relatively small number of countries are conducting national TB prevalence surveys and they are conducted only around every 10 years. DRS data provide a proxy for percentage of prevalent TB cases with MDR, through the weighted average of MDR-TB in new and retreated cases. This is not the same and should not be confused with the number of MDR among notified cases indicator. • MDR-TB prevalence calculation provides the number of MDR-TB patients in need of treatment in the general population at one point in time. • MDR-TB prevalence estimates could be biased, as they assume that the TB patient profile in a DRS survey is the same as that in the general population. An alternative MDR-TB prevalence calculation would require drug susceptibility testing of all TB cases found from a population-based pulmonary TB prevalence survey. This estimate would be highly imprecise due to the small number of survey TB cases likely to be found.

[1]Country, region, global

Indicator	Data sources used in current estimation	Potential application[1]				Explanatory comments
		Monitoring of diagnosis & treatment coverage	*Planning and funding allocation*	*Advocacy*	*Impact assessment of the epidemic*	
MDR-TB mortality	DR surveys or continuous surveillance Systematic review of the literature (Relative Risk of dying from MDR-TB Vs. non-MDR-TB) MDR-TB case fatality ratios Global TB disease burden estimates of mortality	No *Group 3 thought that the answer should be "Yes" and Group 4 thought that mortality *might* be useful for monitoring diagnosis and treatment coverage.	No *One group (Group 3) thought that the answer should be "Yes".	Yes (global) *Group 2 emphasized the importance of using MDR-TB mortality for advocacy purposes at the country and regional levels as well, while recognizing that this was not yet possible in many countries or all regions because of the need to strengthen vital registration and DST coverage.	No *One group (Group 3) thought that the answer should be "Yes".	Provides the indirectly estimated number of deaths due to MDR-TB at global level. Country-level estimates based on indirect estimation could be heavily biased and imprecise due to current data gaps. In the future, country level directly measured MDR-TB mortality may provide an option for impact assessment but would require: • A well-developed vital registration system with high coverage and standardised MDR-TB ICD codes, • routine drug susceptibility testing, with high coverage.

[1]Country, region, global

Appendix II. List of meeting participants

Name	Institution/ Country
Session co-chairs	
Katherine Floyd	WHO/HQ
Karin Weyer	WHO/HQ
Group facilitators	
Ted Cohen	Harvard Medical School
Dennis Falzon	WHO/HQ
Paula Fujiwara	The Union
Agnes Gebhard	KNCV
Philippe Glaziou	WHO/HQ
Salman Keshavjee	PIH
Charalampos (Babis) Sismanidis	WHO/HQ
Matteo Zignol	WHO/HQ
Invited commentaries	
Frank Cobelens	KNCV
Ted Cohen	Harvard Medical School
Dr Maureene Kamene	Kenya
Michael Kimmerling	Bill and Melinda Gates Foundation
YaDiul Mukadi	USAID
Dr Tran Ngoc Buu	Viet Nam
Mr Anshu Prakash	India
Dr Mao Tan Eang	Cambodia
Mohammed Yassin	Global Fund
Rest of meeting participants	
Martha Benezet	ABT Associates
Jeff Takle	Abt Associates/ Bethesda
Gerald Friedland	Academia/ Yale school of Medicine
Karapet Davtyan	Armenia
Dr Natavan Alikhanova, NTP	Azerbaijan
Dr Md. Nuruzzaman Haque	Bangladesh
Dr Abdul Kalam Mohammed Manzurul Alam	Bangladesh
Dr Alena Skrahina	Belarus
Daniel Chin	Bill and Melinda Gates Foundation
Andrew Jones	Bill and Melinda Gates Foundation
Mahfuza Rifat	BRAC
Sarder Tanzir Hossain	BRAC
Khann Sokhan	Cambodia
Desire Nolna	Cameroon/NTP
Jerome Singh	Caprisa
Eugene McCray	CDC
Wanda Walton	CDC
Ekaterina Kurbatova	CDC
Tom Shinnick	CDC
Niki Alami	CDC

Paul Jensen	CDC
A Petes	CDC
Harkesh Dabas	CHAI
M. Macfarlane	CHAI
Charles Kasipo	Clinton Health Access
Lucy Chesire	community representative
Khurshid Talukder	CWCH, Bangladesh
Constatino Voniatis	Cyprus
Michael Voniatis	Cyprus
Dr Georges Bakaswa	DR Congo
Manfred Danilovits	Estonia
Henny Phiri	FHI 360/ TBCARE1
C.N. Paramasivan	FIND
Daniel Orozco	FIND
Jesse Wambugu	FIND
Heidi Abert	FIND
Joel Keravec	GDF/TBP
Silas Holland	GF
Nii Nortey Hanson	Ghana
Mercedes Becerra	Harvard Medical School
Rick O'Brien	Independent consultant
Marl Mantala	Independent consultant
Paul Nunn	Independent consultant
Dyah Erti Mustikawati	Indonesia
Gini Williams	International Council of Nurses
Dr Mahshid Nasehi	Iran
Aamir Khan	IRD Research Pakistan
Uzma Khan	IRD Research Pakistan
Saira Khan	IRD Research Pakistan
Kamidah Hussain	IRD Research Pakistan
Fauzia Putri	IRD Research Pakistan
Lara Wolfson	Janssen, Belgium
Vivam Canon	Janssen, Belgium
Jeroen van Gorkom	KNCV
Kitty van Weezenbeek	KNCV
Nguyen Thien Huong	KNCV/ Vietnam
Gidado Mustafa	KNCV/TBCARE
Dr Dinara Saginbaeva, Minister of Health	Kyrgyzstan
Maral Martin	Kyrgyzstan
David Moore	LSHTM TB Centre
Willy Morose	LSHTM TB Centre
Vijay Agarwal	Macleods Pharmaceuticals
Rawan Ababneh	MENA
Dr Riziki Michael Kisonga	Ministry of Health and Social Welfare
Andrew Nunn	MRC Clinical Trials Unit
Francis Varaine	MSF
David Collins	MSH

Catherine Mundy	MSH
Andre Zagorski	MSH
D. B. Gima	MSH
Dr Muluken Melese	MSH, Ethiopia
Dr Thandar Lwin	Myanmar
Dr Mar Mar Htay	Myanmar
Boniface Makumbi	Namibia
Charles Daley	NJHealth/USA
Numzzam Haque	NTP Bangladesh
Triya Novita Dinihari	NTP Indonesia
Razia Fatima	NTP Pakistan
Eric Adam	Otsuka
Margarette Bury	PAHO
Dr. Ejaz Qadeer	Pakistan
Andrei Mosneaga	PAS Center/Moldova (rGLC EUR)
Dr Anna Marie Celina Garfin	Philippines
Michael Rich	PIH
Mr Dorin Rotaru,	Republic of Moldova
Takashi Yoshiyama	Research institute of tuberculosis, JATA
Essam Elmoghazy	rGLC EMR chair
Rohit Sarin	rGLC SEAR chair
Lee Reichman	rGLCWPR chair
Teresa Kasaeva	Russia
Irina Vasilyeva	Russia
Lyalya Gabbasova	Russia
Daniela Cirillo	SNRL/ Italy
Elisa Tagliani	SNRL/ Italy
Emanuele Borroni	SNRL/ Italy
Somsak Rienthong	SNRL/ Thailand
Dhanida Rienthong	SNRL/ Thailand
Dr. Norbrt Ndjeka,	South Africa
Bruno Lab	Swiss tropical and Public Health Institute
Dr Klaus Reither	Swiss tropical and Public Health Institute
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Dr Davlatbekov Saidbek,	Tajikistan
Dr Bobokhojaev Octam, NTP Manager	Tajikistan
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Heena Narotam	TB Proof
Arne von Delft	TB Proof
Dalene von Delft	TB Proof
Helene Mari van der Wsthuizen	TB Proof
Koot Kotze	TB Proof
Jurgens Peters	TB Proof
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William Wells	USAID
Alexander Golubkov	USAID
Meghan Hololan	USAID
Jacqueline Firth	USAID
Thomas Chiang	USAID
Amy Bloom	USAID
Cheri Vincent	USAID
T Odusute	USAID
Tillyashaykhov Mirzagaleb	Uzbekistan
Parpieva Nargiza	Uzbekistan
Dr Sokhan Khann	WHO CO Cam
Maria Regina	WHO CO Ino
Erwin Cooreman	WHO CO Myn
Dr Woojin Lew	WHO CO Phl
Patrick Hazangwe	WHO CO Zw
Ayodele Awe	WHO Nigeria
Daniel Kibuga	WHO/AFRO
Dr Nicolas NKIERE, NPO/TUB	WHO/AFRO
Fabio Scano	WHO/China
Abera Bekele	WHO/Eto
Martin van den Boom	WHO/EURO
Ogtay Gozalov	WHO/EURO
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Fraser Wares	WHO/HQ
Wayne van Gemert	WHO/HQ
Chris Gilpin	WHO/HQ
Vineet Bhatia	WHO/HQ
Linh Nguyen	WHO/HQ
Fuad Mirzayev	WHO/HQ
Ernesto Jaramillo	WHO/HQ
Lynne Harrop	WHO/HQ
Setiawan jati Laksono	WHO/INO
Mirtha del Granado	WHO/PAHO
Tauhid Islam	WHO/WPRO
K Osuga	WHO/WPRO
Sheela Shenoy	Yale university
Ralph Brooks	Yale university
Dr Mkhokheli Ngwenya	Zimbabwe