WHO methods used to estimate the burden of drug-resistant TB (MDR-TB, RR-TB, XDR-TB)

WHO Global Task Force on TB Impact Measurement
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Overview

A. Background

B. Methods for estimating MDR-TB incidence

C. Alternative suggestions for way forward
A. BACKGROUND
Why do we need DR-TB burden estimates?

• 6-month Rx not effective for RR/MDR-TB
• Treatment for RR/MDR-TB is much longer, highly toxic, at higher cost, and with poorer outcome
• Therefore, estimates extremely important for programmatic, planning and budgeting purposes
**DR-TB disease burden indicators considered**

- Historically five indicators considered:
  1. Proportion of MDR among new and previously treated TB cases
  2. Number of MDR among notified pulmonary TB cases
  3. Incidence
  4. Mortality
  5. Prevalence

- For the 2016 Global TB Report the focus from MDR-TB may be switched to RR-TB (about 10% higher)
  - RR-TB is basis for enrolment to 2\(^{nd}\) line Rx
  - Rollout of Xpert

- Estimation methods will be the same regardless MDR- or RR-TB outcome

- We are focusing on incidence for the rest of this presentation (soon to become obvious why)
MDR-TB burden incidence estimates published in WHO reports

- **2010**: country level incidence published in Global Report on MDR surveillance and reports (2008 estimates)
  - Dropped due to concerns from countries and some regional offices of unfairly representing their programmatic efforts (undetected cases)

- **2011 – 2013**: no published incidence estimates in WHO Global TB Reports, the focus was on estimated MDR among notified cases

- **2014 & 2015**: global level incidence published
  - following global MDR-TB stakeholder consultation in Paris
Key recommendations from Paris consultation

• MDR-TB cases among notified cases of pulmonary TB
  – This indicator should continue to be used for assessing programmatic performance at country level

• MDR-TB incidence
  – A global estimate is useful for advocacy

But demand for WHO to publish country level incidence estimates is intensifying...

- Especially from major funding agencies, Stop TB Partnership Secretariat and civil society
- Global Fund – disease burden formula, input for determining indicative funding allocation to countries
- USAID – reporting to Congress & the President’s National Action Plan for combating MDR-TB launched in Dec. 2015
- Civil society push for an indicator that also includes undetected TB cases
- WHO plans to publish country level estimates, following country review, in Global TB Report 2016
- Estimation methods, therefore, need to be reviewed
B. METHODS FOR ESTIMATING MDR-TB INCIDENCE
TB dynamics

- Incident TB
- Prevalent TB
  - on tx
  - Self-resolved
  - Cured after Rx
- Deaths
Two mechanisms for incident MDR-TB

Primary MDR-TB

Susceptible individual → progression → New drug-resistant case

Transmission

Drug-resistant case

Acquired MDR-TB

Susceptible individual → progression → TB treatment

New drug-susceptible case

Transmission

Drug-susceptible case

New drug-resistant case
TB dynamics disaggregated by drug susceptibility status

*Drug susceptible & non-MDR (DS), multidrug-resistant (MDR)*

- Incident TB
  - Drug susceptible (DS)
  - Multidrug-resistant (MDR)
  - (primary)

- Prevalent TB
- Deaths
  - Drug susceptible (DS)
  - Multidrug-resistant (MDR)

- On tx
  - + Incident MDR (acquired)
  - Cured after Rx
  - Self-resolved
Global coverage of RIF and INH data

Data source (DRS)

Directly measurable
MDR-TB incidence data requirements

Data requirements

1. TB incidence
2. Proportion of incident cases with primary MDR-TB
3. Number of people currently on first line treatment
4. Rate of acquisition of MDR while on treatment

Data (un)availability

1. ≠ case notifications
2. % MDR among new (DRS)
3. ≠ number notified, measured during prevalence surveys
4. ≠ % MDR among retreated (DRS)

*Indirect estimation is required instead*
MDR-TB incidence estimation (method I)

\[ I = a + b + c \]

\( I \) = approximate global MDR-TB incidence

\( a \) = incident MDR among new

\[ a = (new \times p_{new})/CDR \]

- \( new \) = all types, new notified cases
- \( p_{new} \) = prop. of MDR-TB among new cases (from DRS)
- \( CDR \) = global case detection rate

Assume levels of \( p_{new} \) from notified same as for all incident (excl. relapses) cases
MDR-TB incidence estimation (method I, cont.)

\[ I = a + b + c \]

\[ b = \text{incident MDR among relapses} \]

\[ = \frac{rel \times p_{rel}}{CDR} \]

- \( rel = \text{all notified relapse cases} \)
- \( p_{rel} = \text{prop. of MDR-TB among relapses} \approx RR \times p_{new} \)
- \( RR = \text{risk ratio} \approx \text{approximated by OR of MDR among relapse Vs. new cases} \)

\[ RR \text{ not representative, data only from Europe} \]

\[ CDR \text{ for relapses likely higher than for first episodes} \]

\[ \text{Misclassification of Rx history among notified cases} \]
MDR-TB incidence *estimation* (method I, cont.)

\[ I = a + b + c \]

\[ c = \text{incident MDR among retreated that are not relapses} \]

\[ = \frac{\text{ret}_{\text{notrel}} \times p_{\text{ret}}}{\text{CDR}} \]

- \text{ret}_{\text{notrel}} = \text{all notified retreated cases that are not relapses}
- \( p_{\text{ret}} = \text{prop. of MDR-TB among retreatment cases from DRS} \)
- \( p_{\text{ret}} = (w_1 \times p_{\text{rel}}) + (w_2 \times p_{\text{ret}_{\text{notrel}}}), (w_1 + w_2) = 1 \)

Double counting of primary MDR-TB among retreatments (unresolved TB episode counted in \( a \))

Misclassification of Rx history among notified cases

*CDR* for retreatments likely much higher than for first episodes
MDR-TB incidence *estimation* (method I, cont.)

<table>
<thead>
<tr>
<th>Global values 2015</th>
<th>Absolute numbers</th>
<th>Share of total incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a$</td>
<td>274,852</td>
<td>58%</td>
</tr>
<tr>
<td>$b$</td>
<td>127,135</td>
<td>27%</td>
</tr>
<tr>
<td>$c$</td>
<td>70,197</td>
<td>15%</td>
</tr>
</tbody>
</table>
MDR-TB incidence *limitations*

- Global estimate is plagued by serious limitations *(used for advocacy purposes)*
  - Important data gaps
  - Non-representativeness of key parameters
  - Double counting
  - Assume data from DRS applies to all incident TB cases (detected and undetected)
  - Assume CDR is the same for all case types

- Additional limitations for country-level estimates *(to be used for programmatic purposes!)*
  - Some parameters do not have country level values
**MDR-TB incidence estimation (method II)**

To triangulate results from method I, a complementary method II was used for a global estimate

\[ I = \frac{m}{f} \]

Where:
- \( I \) = global MDR-TB incidence
- \( f \) = global MDR-TB case fatality rate
- \( m \) = global MDR-TB mortality

\[ m = Mpr \]

Where:
- \( M \) = global TB mortality
- \( p \) = prop. MDR-TB among prevalent TB cases
  - Approximated by weighted average of \( p_{new} \) & \( p_{ret} \) (DRS)
- \( r \) = \( RR \) of dying among MDR-TB Vs. non-MDR-TB patients
  - Literature review (n=25 studies)
**MDR-TB incidence estimation (method II, cont.)**

\[ f = p_t \times f_t + (1 - p_t) \times f_{unk} \]

- \( p_t \) = proportion treated
  - approximated by the proportion of enrolled MDR-TB patients on Rx out of those estimated among notified TB
- \( f_t \) = case fatality rate among treated patients of MDR-TB
  - treatment outcome data for MDR-TB patient cohort
- \( f_{unk} \) = case fatality rate among untreated patients of MDR-TB
  - assume same as for untreated TB

**Wide uncertainty intervals of key parameters**
Global estimates (2014)

Number of MDR-TB cases

Increased uncertainty

Notified Among notified Inc. (method I) Inc. (method II)

95% confidence interval

Number of MDR-TB cases

- Notified: 122618
- Among notified: 300000
- Inc. (method I): 480000
- Inc. (method II): 540000

Global estimates (2014)

Increased uncertainty
C. SUGGESTED UPDATES TO EXISTING METHODS AND ALTERNATIVE SUGGESTIONS FOR WAY FORWARD
Suggested updates to method I

• $RR$ value for MDR in relapses Vs. new: update literature review
• Stop dividing by $CDR$ for part $c$ but rather $(1 - \text{under-reporting})$
• Double-counting (?)
Alternative suggestion 1

Estimate MDR incidence in two groups only: primary (previously $a$) and acquired (previously $b+c$)

**Primary:** $I_p = I \times p_{new}$
- $I$ TB incidence
- $p_{new}$ estimated from DRS – notifications and not incident cases

**Acquired:** $I_a = \rho \times T \times (1 - p_T)$

**No direct measurement YET for any of the parameters**
- $\rho$ rate of acquisition of resistance during 1st line treatment
- $T$ person-time on Rx during the period considered for measuring incidence
- $p_T$ proportion of $T$ with primary MDR

**BUT cohort studies with sequential testing GX could inform $\rho$ of Rif. resistance incidence**
Alternative suggestion 2

Estimate MDR incidence in two groups only: primary (previously a) and acquired (previously b+c)

Dynamic model to fit estimates of TB incidence and DRS data by country

Uncertainty in resulting estimates
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Questions to the Task Force

1. What methodological approach would you recommend for producing country-specific estimates of MDR(or RR)-TB incidence to be published in WHO's 2016 global TB report?

2. For the two major approaches presented in the document for the estimation of MDR(or RR)-TB incidence, are there any specific improvements that you would recommend that could be implemented by July 2016?

3. Are there other approaches (alternatives to methods I and II) that you think should be explored in the next 1-2 years?
Feedback from group work and plenary discussion
Suggestions from the Task Force

1. & 2. What methodological approach would you recommend for producing country-specific estimates of MDR(or RR)-TB incidence to be published in WHO's 2016 global TB report?

General principle not to make a dramatic shift in method for 2016, and therefore:

a. Use method I with the following refinements

- $RR$ value for MDR in relapses Vs. new: update literature review
- Mitigate problem with $CDR$ for part $b, c$
  - (1 - under-reporting) if inventory study data are available
  - If not use a distribution bounded by CDR and 1
- Use DRS data to
  - Cross-check the relative share of relapse/retreatments from notification
  - $p_{new}$ and $p_{ret}$ from PPM sites to check hypothesis of private sector having higher levels of MDR

b. Produce country level estimates using method II and compare
Suggestions from the Task Force

3. Are there other approaches (alternatives to methods I and II) that you think should be explored in the next 1-2 years?

Commission dynamic model (Pete to do, funding TME/DRS)
Other issues

• Advance communication with all member states that country specific estimates of MDR-TB incidence will appear in WHO Global TB Report
  – TME plans to send estimates with customised communication as appropriate by end of June
  – This will include a specific request to let us know if any additional data are available to inform the estimate

• Small working group: Ted, Pete, Philippe, Draurio, Matteo, William

• Grading for country estimates depending on data quality