Current WHO methods used to estimate TB mortality

Global Task Force on TB Impact Measurement
3rd meeting of the TB estimates subgroup
Glion-sur-Montreux, 1 April 2015

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Carel Pretorius
Outline

• HIV-negative TB mortality
  – Current methods
    • Group 1. Vital registration and mortality surveys
    • Group 2. Case fatality ratio and incidence
  – Recently discontinued methods
    • Group 3. Ecological statistical modelling
    • Group 4. Bayesian modelling

• HIV-positive TB mortality
  – Current method
    • Group 1. Case fatality ratio and incidence
  – Recently discontinued method
    • Group 2. Bayesian modelling

• Implementation in Spectrum
Counting the dead and what they died from

- **Vital Registration (VR)** systems, ICD-10
- **Interim systems**
  - Sample VR (e.g. China)
  - Mortality surveys based on verbal autopsy (e.g. India)
  - Autopsy studies

1. Mathers CD. Bull World Health Organ 2005;83(3):171-7
HIV-NEGATIVE TB MORTALITY
Group 1. VR (n=124) and mortality studies (n=2)
Group 1. VR and mortality surveys (cont.)

- TB mortality \( (d_a) \) is measured as the number of deaths captured from the vital registration system \( (d) \) adjusted for coverage \( (c) \) and ill-defined causes \( (g) \):

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

- Coverage is estimated using UNPD life tables (drop if <50%)
- Ill-defined causes is an indicator of VR quality (drop if ≥20%)
- Uncertainty propagated using binomial exact calculation

Accounting for around 400,000 deaths, 36% of the global share for 2013
Example 1. Rise and fall in TB mortality in Russia

![Graph showing rise and fall in TB mortality in Russia](image-url)
Example 2. TB mortality in Thailand: under-resourced national VR
Limitations

• Coverage and quality of VR data
• Quality and representativeness of mortality survey data (e.g. India and Viet Nam)

Next steps

• Global attention to strengthening CRVS (post-2015 measurement and accountability roadmap)
• Other sources of mortality data (VA studies)
Group 2. Case fatality ratio (CFR) and incidence (n=91)
Group 2. CFR and incidence (cont.)

Implemented in Spectrum

\[ M = (I - T)F_U + TF_T \]

<table>
<thead>
<tr>
<th></th>
<th>HIV-negative TB mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>( M )</td>
<td></td>
</tr>
<tr>
<td>( I )</td>
<td>HIV-negative TB incidence</td>
</tr>
<tr>
<td>( T )</td>
<td>Case notifications adjusted for under-reporting</td>
</tr>
<tr>
<td>( F_U, F_T )</td>
<td>CFRs for untreated and treated cases respectively</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>( F_T )</th>
<th>Best estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.03</td>
<td>(0.00-0.07)</td>
</tr>
<tr>
<td>( F_U )</td>
<td>0.43</td>
<td>(0.28-0.53)</td>
</tr>
</tbody>
</table>

Accounting for around 700,000 deaths, 64% of the global share for 2013
Example. Indirect estimation more uncertain (in red) compared with VR measurement (in blue)
Group 3. Ecological statistical modelling (n=26)
Discontinued in 2014

- For countries without VR data
- Population-averaged negative binomial model (over-dispersion of TB deaths)
- Use countries with VR data as the test dataset to validate model
- Out-of-sample, goodness-of-fit, stepwise selection approach to identify predictors (n=10)
  - Infant mortality rate per 1000 live births
  - GDP per capita
  - HIV prevalence
  - Percentage of population aged more than 65 years
  - Etc.

Model was dropped due to instability
Group 4. Bayesian modelling (n=68)

Discontinued in 2013

- Priors ~ Gamma

<table>
<thead>
<tr>
<th>CFR(SD)</th>
<th>High-income</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notified</td>
<td>0.039 (0.042)</td>
<td>0.074 (0.03)</td>
</tr>
<tr>
<td>Non-notified</td>
<td>0.12 (0.042)</td>
<td>0.32 (0.13)</td>
</tr>
</tbody>
</table>

- The models used normal errors and Gibbs sampling:
  \[ y = (I - N)\beta_1 + N\beta_2 + \varepsilon, \varepsilon \sim N(0, \sigma^2) \]

<table>
<thead>
<tr>
<th>( y )</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>y</td>
<td>TB mortality from VR</td>
</tr>
<tr>
<td>I</td>
<td>TB incidence excluding PLHIV</td>
</tr>
<tr>
<td>N</td>
<td>TB notifications excluding PLHIV</td>
</tr>
<tr>
<td>( \beta_1 )</td>
<td>CFR in non-notified</td>
</tr>
<tr>
<td>( \beta_2 )</td>
<td>CFR in notified</td>
</tr>
</tbody>
</table>

Move to implementation in Spectrum
HIV-POSITIVE TB MORTALITY
Contributory causes of AIDS deaths
6 cohort studies

- TB leading cause in 5 out of 6 studies
- High rate of loss to follow-up leading to under-reporting
- High proportion of unknown cause
- TB 16-51%

1. Severe P. NEJM 2005
2. Lawn SD. AIDS 2005;19:2141
3. Zachariah R. AIDS 2006;20:2355
4. Etard AIDS 2006;20:1181
5. Moore, CROI 2007;#34
Autopsy study
England, 1983-2005 (n=115) \(^1\)

- Autopsies change the underlying cause of death by 70%
- 36% of all opportunistic infections are missed
- 100% of TB is missed

Review of pre-ART autopsy studies in Sub-Saharan Africa¹

- 593 HIV+ adults, **20 studies in 10 countries**
- Not nationally-representative, geographical heterogeneity
- Mostly hospital-based
- TB was the leading contributory cause of death in between **32%-45%**

Variation in TB mortality risk ratio on/off ART

Thailand, $n=667$

Hazard Ratio 0.16 [0.07–0.36]
Varma JK. BMC Infect Dis 2009;9:42

Ethiopia, $n=365$

Hazard Ratio 0.35 [0.19–0.63]
Jerene D. AIDS Res Ther. 2006;3:10
Group 1. CFR and incidence (n=217)

Implemented in Spectrum

\[ M_i = (I_i - T_i)F_{U_i} + T_iF_{T_i} \]

| \( M \) | HIV-negative TB mortality |
| \( I \) | HIV-negative TB incidence |
| \( T \) | Case notifications adjusted for under-reporting |
| \( F_{T_i}, F_{U_i} \) | CFRs for treated and untreated cases respectively |
| \( i \) | not on ART, on ART for \( \leq 1 \) year, on ART for >1 year |

<table>
<thead>
<tr>
<th>CFR (95%CI)</th>
<th>Not on ART</th>
<th>ART for ( \leq 1 ) year</th>
<th>ART for &gt;1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>( F_T )</td>
<td>0.09 (0.03-0.15)</td>
<td>0.06 (0.01-0.13)</td>
<td>0.04 (0.00-0.10)</td>
</tr>
<tr>
<td>( F_U )</td>
<td>0.78 (0.65-0.94)</td>
<td>0.62 (0.39-0.86)</td>
<td>0.49 (0.31-0.70)</td>
</tr>
</tbody>
</table>

CFR estimates from systematic review from TB MAC
Group 2. Bayesian modelling
Discontinued in 2013

- **Prior ~ Beta**
  37% [32-45] of AIDS deaths (UNAIDS) with TB as a contributory cause (pooled pre-art autopsy studies)

- **Likelihood**
  \[ \text{Inc} X \text{prob}(HIV|TB) X \text{CFR} \]
  - \( \text{CFR} = 50\% \text{ (SD 5\%)} \) in low and middle income,
  - \( 20\% \text{ (SD 2\%)} \) in high-income
  - \( \text{HR on ART} 50\% \text{ (SD 5\%)} \)

Move to implementation in Spectrum
Over to Carel

IMPLEMENTATION IN SPECTRUM
Estimation with cubic splines

- Widely used for time-dependent data, e.g. EPP for estimating HIV incidence
- Present trend as sum of $k$ cubic-splines:
  \[ I(x) = \sum_{i=1}^{k} \beta_i B^m_i(x) \]
- We use 10 cubic-splines spanning the projection time interval
General form of objective function

- Minimize sum of squares:

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

- \( \lambda \) is a smoothness penalty
- \( \beta \)s are the spline coefficients
- \( S \) is a ‘difference’ matrix and the term \( \lambda \beta^T S \beta \) is proportional to smoothness
Bootstrapped uncertainty

- Find residuals of fit
- Use variance of residuals w.r.t to data as variance of zero mean Gaussian function
- Create new datasets by adding this Gaussian noise to data
- Estimating resulting cubic-spline curves
- Use 2.5%, 50% and 97.5% percentiles for 95% plausibility UA interval
TB-HIV incidence disaggregation

- Based on idea of B. Williams that RR for TB increases by 70% per 100/uL CD4 decline

- A regression model in TIME uses this assumed relationship

- First estimate ‘Force of Infection’ for HIV negative cases

  \[ F(\text{HIV-negative}) = \frac{I^-}{P} \]

  \[ F(c) = F(\text{HIV-negative}) \cdot p(1) \cdot p(2)^{dc} \]

  where \( c \) a CD4 category and \( dc \) a unit of 100 CD4 decline
TB-HIV incidence disaggregation

Regression model for TB-HIV disaggregation:

\[ I_h(t) = \sum_c P_{h,c} \times F(t) \times A_{h,c} \times B_{h,c} \]

- \( F(t) \) is the risk of TB for HIV-negative cases.
- \( h \) is a label for HIV status: HIV-negative (\( h=1 \)), HIV-positive not on ART (\( h=2 \)), HIV-positive TB cases on ART for 0 to 6 months (\( h=3 \)), 7 to 12 months (\( h=4 \)) and more than one year (\( h=5 \)).
- \( c \) is a label for the seven CD4 categories of each HIV-positive state (\( h>=2 \)).
- \( P_{h,c} \) is the population size of group \( h, c \).
- \( A_{h,c} = p(1) \times p(2)^{dc} \) for \( h>=2 \) and \( c=1 \) to 7 (1 otherwise) and \( B_{h,c} = 0.35 \) for \( h>=4 \) (1 otherwise).
Global TB-HIV incidence:
1,074,902/8,520,298 = 12.6%
TB-HIV mortality

- Based on Case Fatality Ratio (CFR):
  \[ \text{TB mortality} = \text{TB incidence} \times \text{CFR} \]
- CFR was defined as the “fraction of individuals with active TB that will die due to TB, during that TB episode, regardless of the duration of that episode”
- \[ M = (I-N)F_u + NF_n \]
  where \( M \) represents TB mortality, \( I \) incident TB cases, \( N \) cases that are notified, \( (I-N) \) cases that are not notified and \( F \) represents CFRs for distinct TB categories
## HIV-TB Mortality

<table>
<thead>
<tr>
<th></th>
<th>Non-notified</th>
<th>Notified</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV-</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of triangular</td>
<td>0.45</td>
<td>0.07</td>
</tr>
<tr>
<td>distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIV+ not receiving ART</strong></td>
<td>0.85</td>
<td>0.25</td>
</tr>
<tr>
<td>Mode of triangular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Receiving ART for less than one year</strong></td>
<td>0.75</td>
<td>0.17</td>
</tr>
<tr>
<td>Mode of triangular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Receiving ART for more than one year</strong></td>
<td>0.60</td>
<td>0.08</td>
</tr>
<tr>
<td>Mode of triangular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>distribution</td>
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</tbody>
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CFR estimates from systematic review from TB MAC
Global TB-HIV mortality:
321,014/1,507,089 = 21.3%