WHO TB burden estimation
An overview

Philippe Glaziou
Glion, March 2015
Outline

• History
  – 1990 Sudre et al.
  – 1999 Dye et al.
  – 2008, 2009 and 2010 Task Force reviews

• Incidence

• Mortality

• Prevalence
Best sources of data

• Incidence surveys impractical
• Best sources of data on TB burden are
  – **TB notifications** when data meet quality criteria and *under-reporting* low and documented
  – TB mortality from **Vital Registration with COD**
  – Prevalence from **national prevalence surveys**

• Data sources:
  – ARI (λ): surveys since 1975, low and high range of estimated ARI by WHO region
  – Case notifications compiled by EPI
  – Cause of death data from 62 countries

• Incidence smear pos \( I^+ \) (45% of total \( I \)):
  \[
  39.10^{-5} \, y^{-1} \leq \frac{I^+}{\lambda} \leq 45.10^{-5} \, y^{-1}
  \]

Mortality: CFR = 15% if cure <60%

<table>
<thead>
<tr>
<th></th>
<th>Number in 1990</th>
<th>Rate ($10^{-5} \cdot y^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notified (average 1980-1990)</td>
<td>2.5 million</td>
<td>52</td>
</tr>
<tr>
<td>Infected</td>
<td>1.7 billion</td>
<td>32 (%)</td>
</tr>
<tr>
<td>Infected, HIV+</td>
<td>3 million</td>
<td>38 (%)</td>
</tr>
<tr>
<td>Incident</td>
<td>8 million</td>
<td>152</td>
</tr>
<tr>
<td>Incident, HIV+</td>
<td>300,000</td>
<td>3.8 ($10^{-2} \cdot y^{-1}$)</td>
</tr>
<tr>
<td>Reported TB deaths</td>
<td>78,000</td>
<td>3</td>
</tr>
<tr>
<td>Mortality</td>
<td>2.6 – 2.9 million</td>
<td>46 - 55</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data sources</th>
<th>Main methods</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notifications (n=141) and Expert opinion</td>
<td>[ I = \frac{N}{1-U}, U \in [0 - 1] ]</td>
<td>( U ) under-reporting + ( U ) under-diagnosis</td>
</tr>
</tbody>
</table>
| Tuberculin surveys (n=24) | \[ I \approx \frac{\lambda S}{\sigma} \]
\[ p \approx \frac{L - (1 - e^{-\lambda L})}{\lambda L} \] | \( S \) Styblo ratio \( \sigma \) proportion smear pos (0.45) \( p \) prevalence of infection \( L \) life expectancy |
| Mortality (VR) | \[ I \approx \frac{M}{f} \] | \( f \) case fatality ratio |
| Prevalence survey (n=14) | \[ I \approx \frac{P}{d} \] | \( d \) disease duration \( d \in [0.8 - 1.5]y \) in DOTS \( d \in [1 - 3.5]y \) outside DOTS |

<table>
<thead>
<tr>
<th></th>
<th>Number* in 1997</th>
<th>Rate* (10⁻⁵.y⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notified</td>
<td>3.4 million</td>
<td>58</td>
</tr>
<tr>
<td>Infected</td>
<td>1.9 billion</td>
<td>32 (%)</td>
</tr>
<tr>
<td>Infected, HIV+</td>
<td>11 million</td>
<td></td>
</tr>
<tr>
<td>Incident</td>
<td>8 million</td>
<td>136</td>
</tr>
<tr>
<td>Incident, HIV+</td>
<td>640,000</td>
<td>8% of incident TB</td>
</tr>
<tr>
<td>Reported TB deaths</td>
<td>78,000</td>
<td>3</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.9 million</td>
<td>32</td>
</tr>
<tr>
<td>Prevalence</td>
<td>16 million</td>
<td>270</td>
</tr>
</tbody>
</table>

*Fractional error ±20%, country specific estimates available
Task Force sub-group on estimates

1. June 2006 – policy paper
2. June 2008, subgroup meeting, the Hague
   – Commissioned literature reviews (CFR, duration)
3. October 2009, Geneva, with recommendations endorsed by full TF in 2010
   – Simplified model
   – Use tuberculin surveys only for trends
   – Uncertainty framework
   – Systematic use of reported mortality data
     (VR, $n=89$, from $n=3$ previously)
2009 simplification

BEFORE

- Incident cases
  - HIV+ve
    - SS+ (45%)
      - DOTS
      - nonDOTS
      - untreated
    - SS- (55%)
      - DOTS
      - nonDOTS
      - untreated
  - HIV-ve
    - SS+ (35%)
      - DOTS
      - nonDOTS
      - untreated
    - SS- (65%)
      - DOTS
      - nonDOTS
      - untreated

AFTER

- Incident cases
  - HIV+ve
  - HIV-ve
    - Notified
    - Not Notified
    - Notified
    - Not Notified
Using tuberculin survey results

1 smear positive case remained infectious for 2 years and infected 10 people per year

\[ I^+ \approx \frac{\lambda \times 10^5}{2 \times 10} = 50 \left(10^{-5} y^{-1}\right), \lambda=0.01 \]
Using tuberculin survey results?

Nowadays, 1 smear-pos case remains infectious less than 2 years and infects less people / year

\[ I^+ > \frac{\lambda \times 10^5}{2 \times 10} = 50 \lambda (10^{-5} y^{-1}) \]

<table>
<thead>
<tr>
<th></th>
<th>ARI (%)</th>
<th>Incidence:Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA, white men*</td>
<td>1990</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* J Infect Dis 1997; 175(6):1535-7
Unpredictable performance of the PPD-test (e.g. Korea)

Clear-cut distributions  Sensitivity to distribution assumptions
Uncertainty about incidence derived from ARI (India 2010)

1. Positive PPD test (mixture, mirror, cut-off)
   ARI = 1.1%, measurement error = ±25%
2. Stratified cluster sampling, sampling error = ±20%
3. Styblo ratio (smear pos incidence / ARI)
   \[
   \frac{I^+}{\lambda} \sim U(40,150)
   \]
4. Percent incidence that is smear positive (45%), error ±20%
   Incidence (all) = 232 [61 – 407] \times 10^{-5} \text{ y}^{-1}

**Contribution to overall error:**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sampling</th>
<th>Styblo Ratio</th>
<th>% ss+</th>
</tr>
</thead>
<tbody>
<tr>
<td>15%</td>
<td>20%</td>
<td>55%</td>
<td>10%</td>
</tr>
</tbody>
</table>
Propagation of errors

• Plausible ranges (e.g. ~Uniform)
• Quantities bounded by 0 and 1: ~Beta
• Linearization of errors, where $f$ is a function of $k$ RVs $\beta$ and correlations are neglected

$$
\sigma_f^2 = \sum_k \left[ \left( \frac{\partial f}{\partial \beta_k} \right)^2 \sigma_{\beta_k}^2 \right]
$$

(otherwise, sims)
Eliciting expert opinion
( 6 regional workshops in 2009-2010)

- Data Quality
  - Reports complete
  - No dups, no misclassified
  - Data internally consistent
  - Data externally consistent

- Changes over time
  - Measure time-changes in notifications
  - Assess changes in case-finding
  - Assess changes in TB determinants

- Trends in Incidence
  - Trends in notifications reflect trends in incidence

- Incidence
  - capture re-capture onion model cross-validation
  - notifications ≈ incidence

- Entry point to evaluate IMPACT
- UPDATED estimates
- CERTIFIED

- IMPROVE surveillance system

Data Quality

Changes over time

Trends in Incidence

Incidence

Notifications complete
No dups, no misclassified
Data internally consistent
Data externally consistent

Measure time-changes in notifications
Assess changes in case-finding
Assess changes in TB determinants

Trends in notifications reflect trends in incidence

capture re-capture onion model cross-validation

notifications ≈ incidence
Ghana example

Data Quality
- Reports complete
- Data internally consistent

Changes over time
- Increase in EP due to HIV?
- Economic crisis 1997
- Stable determinants of notifications

Trends in Incidence
- Trends in notifications reflect trends in incidence
- Introduce case-based eRR
- Introduce culture
- Plan prevalence survey

NOTES
- YES
- UPDATED estimates
- NO

Incidence
- capture re-capture onion model cross-validation
- notifications ≈ incidence
Eliciting expert opinion, con’t
(6 regional workshops in 2009-2010)

<table>
<thead>
<tr>
<th>Source</th>
<th>DHS</th>
<th>Capture-recapture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not have access to health care</td>
<td>Survey</td>
<td></td>
</tr>
<tr>
<td>Have access but do not seek care</td>
<td>Survey</td>
<td></td>
</tr>
<tr>
<td>Seek care but not diagnosed</td>
<td>Survey</td>
<td></td>
</tr>
<tr>
<td>Diagnosed but not reported</td>
<td>Inventory study</td>
<td></td>
</tr>
</tbody>
</table>
Non TB data

• Used to inform opinion on trends
  – Prevalence of selected comorbidities
    • HIV (UNAIDS)
    • Smoking
    • Type 2 diabetes
    • Undernourished
  – Macro-economic indicators (GDP/capita)
  – Performance of health systems (U5MR, LE, out of pocket expenditures for health/THE, density of health services)
# AFRO workshop

**Changes in CDR (%)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Previous</th>
<th>Revised</th>
<th>Previous</th>
<th>Revised</th>
<th>Revised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>89 (74–100)</td>
<td>71 (59–89)</td>
<td>62 (51–76)</td>
<td>46 (31–59)</td>
<td>68 (59–76)</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>11 (9.4–14)</td>
<td>8.5 (7.1–11)</td>
<td>14 (12–17)</td>
<td>27 (23–46)</td>
<td>32 (27–47)</td>
</tr>
<tr>
<td>Burundi</td>
<td>34 (28–42)</td>
<td>25 (21–32)</td>
<td>25 (21–31)</td>
<td>50 (40–60)</td>
<td>56 (46–65)</td>
</tr>
<tr>
<td>Côte d'Ivoire</td>
<td>30 (25–37)</td>
<td>22 (18–27)</td>
<td>27 (22–33)</td>
<td>45 (35–57)</td>
<td>50 (40–62)</td>
</tr>
<tr>
<td>DR Congo</td>
<td>36 (30–45)</td>
<td>35 (29–44)</td>
<td>45 (38–56)</td>
<td>17 (8–25)</td>
<td>34 (26–41)</td>
</tr>
<tr>
<td><strong>Kenya</strong></td>
<td><strong>45 (38–56)</strong></td>
<td><strong>62 (51–77)</strong></td>
<td><strong>85 (70–100)</strong></td>
<td><strong>73 (67–78)</strong></td>
<td><strong>77 (72–82)</strong></td>
</tr>
<tr>
<td>Malawi</td>
<td>48 (40–60)</td>
<td>49 (41–61)</td>
<td>49 (41–60)</td>
<td>38 (32–44)</td>
<td>50 (40–60)</td>
</tr>
<tr>
<td>Mali</td>
<td>17 (14–22)</td>
<td>13 (11–16)</td>
<td>16 (13–19)</td>
<td>27 (21–33)</td>
<td>53 (48–58)</td>
</tr>
<tr>
<td>Mozambique</td>
<td>38 (31–47)</td>
<td>32 (26–40)</td>
<td>46 (38–57)</td>
<td>22 (10–45)</td>
<td>28 (15–44)</td>
</tr>
<tr>
<td>Namibia</td>
<td>110 (92–140)</td>
<td>93 (77–100)</td>
<td>76 (63–92)</td>
<td>63 (53–72)</td>
<td>68 (59–76)</td>
</tr>
<tr>
<td>Nigeria</td>
<td>6.7 (5.6–8.4)</td>
<td>10 (8.4–13)</td>
<td>19 (16–24)</td>
<td>10 (2–40)</td>
<td>18 (4–39)</td>
</tr>
<tr>
<td>Uganda</td>
<td>40 (33–50)</td>
<td>39 (33–49)</td>
<td>44 (36–54)</td>
<td>25 (15–45)</td>
<td>44 (29–58)</td>
</tr>
<tr>
<td>Zambia</td>
<td>NA (NA–NA)</td>
<td>74 (61–92)</td>
<td>80 (66–98)</td>
<td>54 (49–59)</td>
<td>78 (72–83)</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>67 (56–84)</td>
<td>52 (43–64)</td>
<td>46 (38–56)</td>
<td>63 (51–74)</td>
<td>53 (41–63)</td>
</tr>
</tbody>
</table>

*Completed prevalence survey*
TB surveillance checklist used (March 2015)
Vietnam example
Case notification rate in Vietnam

All forms

Smear positive
Contribution of PPM + active case finding in prisons
Trends in case notifications (log scale)

Underlying trends in incidence

NTP minus PPM and active case finding in prisons

Rate per 100,000/year (log scale)

$h = HIV$ prevalence in general population (UNAIDS, 2012)
$\rho = TB$ incidence rate ratio
$t = HIV$ prevalence in TB (NTP 2012)
Assumptions about trends in incidence

- Notifications $N$ over 2007-2011 minus PPM run parallel to incidence on a log scale
  - Basis: standards and benchmarks assessment
- Incidence *not attributable to HIV* in exponential decline
  - Exponential decline in u5MR (1990-2011)
  - Exponential increase in GDP/capita (1990-2011)
Assumptions about level in incidence (2007)

• **Under-reporting** \( R \) from 2007 prevalence survey [1]
  – \( R \) uncertainty range (7.1% - 20.3%)

• **Under-diagnosis** \( D \) values within plausible range for higher income countries with similarly good health indicators, e.g. Brazil
  – \( D \) uncertainty range (5.6% - 35%)

• Incidence = \( N / (R + D) \)

1. Nguyen B Hoa et al. IED 2011;17:502-4
Estimated incidence rate 1990-2011

Slight deceleration in the decline due to increasing HIV
Moving away from expert-opinion based estimates

Incidence derived from:

– results of prevalence surveys ($n=13$)
– capture-recapture modelling ($n=5$)
– inventory studies (8 completed, 6 planned)
– ecological modelling?
– dynamic modelling?
TB mortality

+ Indonesia sample CRVS (April 2015 update)
Mortality, 2013

1. From VR \((n=126)\)

2. \(M = \sum_{i,j} I_{i,j} \times f_{i,j}\)
   \[i \in \{treated, untreated\}, j \in \{HIV+, HIV-\}\]

CFR HIV+ TBMac
Mortality HIV-neg validation (VR countries 2013)
Prevalence, 2013

1. National surveys, error in $P \pm 25\%$

2. $P = \sum_{i,j} I_{i,j} \times d_{i,j}$
   
   $i \in \{treated, untreated\}, j \in \{HIV+, HIV-\}$

   High uncertainty of $d_{i,j}$, error in $P \pm 50\%$
Uncertainty in prevalence estimates, Myanmar example

Updated prevalence rate (population-based survey)

Uncertain prior prevalence rate (incidence * duration)
Validation: pre- vs. post-survey prevalence estimates
# Data sources in 2013

<table>
<thead>
<tr>
<th>Data source</th>
<th>% of global burden</th>
<th>Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>VR and mortality surveys ($n=126$)</td>
<td>36</td>
<td>Mortality HIV-</td>
</tr>
<tr>
<td>Prevalence surveys ($n=13$)</td>
<td>43/42</td>
<td>Prevalence Incidence</td>
</tr>
<tr>
<td>Capture recapture ($n=5$)</td>
<td>0.5</td>
<td>Incidence</td>
</tr>
<tr>
<td>Epi reviews</td>
<td>57.5</td>
<td>Incidence</td>
</tr>
<tr>
<td>Case notifications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expert opinion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB/HIV surveillance</td>
<td>95/89</td>
<td>HIV+ incidence HIV+ mortality</td>
</tr>
<tr>
<td>Repeat tuberculin surveys ($n=3$ countries)</td>
<td>22</td>
<td>Trends in incidence</td>
</tr>
</tbody>
</table>