Estimating the global burden of LTBI

Rein Houben, Richard White

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Outline

• Why
• Change
• How
• Results
• Questions
Why picture

• Why
• Change
• How
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• Questions
Tuberculosis (TB)

Data and Statistics

Tuberculosis (TB) is one of the world’s deadliest diseases:

- One third of the world’s population is infected with TB.

It is estimated that one-third of the world’s population is infected with the TB bacterium, and that 16.2 million people currently have the disease.
Rationale

GEAR UP TO END TB

VISION

A WORLD FREE OF TB

END THE GLOBAL TB EPIDEMIC

GOAL

TARGETS

GETTING THERE: MILESTONES AND TARGETS

<table>
<thead>
<tr>
<th>MILESTONES</th>
<th>SDG</th>
<th>END TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>2025</td>
<td>2030</td>
</tr>
</tbody>
</table>

Reduction in number of TB deaths compared with 2015 (X):
- 35% 75% 90% 95%

Reduction in TB incidence rate compared with 2015 (X):
- 20% 50% 80% 90%

TB affected families facing catastrophic costs due to TB (X):
- 0% 0% 0% 0%

2 Billion at risk
Rationale

KEEP CALM AND GET PREPARED
Source of ‘one third’

- Originally?

Global Burden of Tuberculosis
Estimated Incidence, Prevalence, and Mortality by Country

Christopher Dye, DPhil
Suzanne Scheele, MS
Paul Dolin, DPhil
Vikram Pathania, MBA
Mario C. Raviglione, MD
for the WHO Global Surveillance and Monitoring Project

Objectives

To estimate infection and tuberculosis attributable to human infection.

Participants

A panel of countries was chosen by the Institute of Tuberculosis Research.

Evidence

Incidence of notification to the WHO (3) data on prevalence of tuberculosis.

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>Population, Thousands</th>
<th>Infection Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>611 604</td>
<td>35</td>
</tr>
<tr>
<td>The Americas</td>
<td>792 330</td>
<td>18</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>475 415</td>
<td>29</td>
</tr>
<tr>
<td>Europe</td>
<td>870 386</td>
<td>15</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>1 458 274</td>
<td>44</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1 641 179</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>5 849 188</td>
<td>32</td>
</tr>
</tbody>
</table>

Dye et al, JAMA 1999
• Why
• Change
• How
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What has changed?

955.8 million (1995)
India, Population (1995)

108.4 million (1995)

Year
1990
2000
2010
What has changed?

Prevalence of tuberculous infection and incidence of tuberculosis; a re-assessment of the Styblo rule

F van Leth, MJ van der Werf, & MW Borgdorff

Fig. 5. Number of tuberculosis infections per prevalent smear-positive TB cases

- China
- Philippines
- Republic of Korea
- Range with Styblo rule
What has changed?

### China

<table>
<thead>
<tr>
<th>High TB burden</th>
<th>High HIV burden</th>
<th>High MDR-TB burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population 2013</td>
<td>1 386 million</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimates of TB burden * 2013</th>
<th>Number (thousands)</th>
<th>Rate (per 100 000 population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (excludes HIV+TB)</td>
<td>41 (40–43)</td>
<td>3 (2.9–3.1)</td>
</tr>
<tr>
<td>Mortality (HIV+TB only)</td>
<td>0.67 (0.23–1.3)</td>
<td>0.05 (0.02–0.1)</td>
</tr>
<tr>
<td>Prevalence (includes HIV+TB)</td>
<td>1 300 (1 100–1 500)</td>
<td>94 (82–107)</td>
</tr>
<tr>
<td>Incidence (includes HIV+TB)</td>
<td>980 (910–1 100)</td>
<td>70 (66–77)</td>
</tr>
<tr>
<td>Incidence (HIV+TB only)</td>
<td>4.5 (4.3–9.9)</td>
<td>0.33 (0.31–0.72)</td>
</tr>
<tr>
<td>Case detection, all forms (%)</td>
<td>87 (79–93)</td>
<td></td>
</tr>
</tbody>
</table>

### Belarus

<table>
<thead>
<tr>
<th>High MDR-TB burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population 2013</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimates of MDR-TB burden * 2013</th>
<th>New</th>
<th>Retreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of TB cases with MDR-TB</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>MDR-TB cases among notified pulmonary TB cases</td>
<td>1 100 (1 100–1 200)</td>
<td>690 (660–730)</td>
</tr>
</tbody>
</table>
What has changed?

Gamma Interferon Release Assays for Detection of *Mycobacterium tuberculosis* Infection

Madhukar Pai, a Claudia M. Denkinger, a,b Sandra V. Kik, a Molebogeng X. Rangaka, c Alice Zwerling, d Olivia Oxlade, e John Z. Metcalfe, f Adithya Cattamanchi, f David W. Dowdy, d Keertan Dheda, g Niaz Banaei h

McGill International TB Centre and Department of Epidemiology & Biostatistics, McGill University, Montreal, Canada; Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; Institute of Infectious Diseases and Molecular Medicine and Centre for Infectious Diseases and Epidemiology Research, University of Cape Town, Cape Town, South Africa; Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA; Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, University of California, San Francisco, San Francisco, California, USA; Department of Medicine and UCT Lung Institute, University of Cape Town, Cape Town, South Africa; Department of Pathology and Medicine, Stanford University School of Medicine, Palo Alto, California, USA

Pending on when and how often BCG is given, the sensitivity for the T-SPOT.TB assay appears to be higher than that for the QFT assay or TST (approximately 90%, 80%, and 80%, respectively). IGRA sensitivity is diminished by HIV infection and in children (see later discussion) (22, 23).
What has changed?

Gao at al 2015, Lancet ID
Courtesy of Rebecca Harris (LSHTM)
• Why
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What do we want?
Latent tuberculosis may be defined for convenience as that which is unaccompanied by symptoms and physical signs, causes no obvious disturbance and is not recognised by the physician. There is no sharp distinction between latent and manifest tuberculosis, and in some instances latent tuberculosis is more extensive than that which is recognisable. Ability to distinguish between latent and manifest disease will vary with the means available for diagnosis. (Opie & McPhedran 1926 [14, p. 347])
A model should be as simple as possible, but no simpler

Albert Einstein
Method - model
Global Burden of Tuberculosis
Estimated Incidence, Prevalence, and Mortality by Country

Objective
To estimate the risk and prevalence of Mycobacterium tuberculosis (MTB) infection and tuberculosis (TB) incidence, prevalence, and mortality, including disease attributable to human immunodeficiency virus (HIV), for 212 countries in 1997.

Participating countries were identified through national reports and surveys.

Evidence
Data from surveillance and notification systems (3) data sources.

Fig. 5. Number of tuberculosis infections per prevalent smear-positive TB cases

- China
- Philippines
- Republic of Korea
- Range with 95% CI
Statistical model (2)

- Cohort model --> Reconstruct (assumed) historical prevalence (from ~1930).
- Change Styblo rule correlated to treatment availability

Fig. 5. Number of tuberculosis infections per prevalent smear-positive TB cases

- China
- Philippines
- Republic of Korea
- Range with Styblo rule
Dynamic Transmission
Data/Inputs

• Prevalence
  – including pre-1990 scenarios (for option 2: cohort)

• Notifications
  – Including pre-1990 scenarios (for option 3: dynamic transmission model)

• LTBI prevalence across ages
  – Review of old LTBI surveys (to restrict model runs)
  – Gao study + new ARI/Infection prevalence studies
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LTBI estimates from existing dynamic transmission models

Note: only final model was set up to estimate size of LTBI population
Note: results unpublished, do not distribute
Results from dynamic transmission models

LTBI prevalence in 2015 = 26% (24-31%)
Pros and Cons

1. JAMA 1999 method + new Styblo:
   - Pro: Very simple, updated with Styblo rule
   - Con: no time trend, constant ARI over time and age, not suited for e.g. MDR

2. Cohort model:
   - Pro: Relatively simple few parameters and assumptions, maps change in Styblo rule
   - Con: Not linked to all data, no projections/counterfactual

3. Dynamic trans model
   - Pro: internally consistent with notification and prevalence, independent of Styblo rule, can provide projections and counterfactual
   - Con: more parameters and assumptions (natural history)
Outline

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Questions for discussion

• Should we re-estimate LTBI burden?

• Method:
  1. JAMA 1997 method + new Styblo
  2. Cohort
  3. Dynamic transmission?

• Outcomes: MDR, Age, HIV/ART?

• Data: can LTBI survey data inform modelling? How adjust for sens/spec? What test? Should we collect more data?

• Granularity: world, region, country?
Acknowledgements

• LSHTM TB Modelling Group
  – Rebecca Harris
  – Tom Sumner
Thank you

Any questions?