GBD2013 Tuberculosis estimates of mortality, incidence and prevalence

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Tuberculosis estimation strategy

1) **Goal:** Use all available data on different outcomes and simultaneously estimate incidence, remission, excess mortality, prevalence, and cause-specific mortality

2) **Data:** annual case notifications, expert judgment on case detection rate, prevalence surveys, and cause of death data

3) **Tools:** DisMod-MR 2.0; the GBD 2013 Bayesian meta-regression environment
Case-notifications: improving over time

1) Detail by age and sex and form (smear-positive, smear-negative, extra-pulmonary), varies by country.

2) Much more detailed data in recent years. Notifications in the 1990s, e.g., in India, very poor with many TB suspects included.

3) Major variation across countries in percentage E-P not explained by HIV status

4) GBD 2013 used various regression methods to complete age-sex-clinical-type matrix, dealing with
   - Missingness age, sex, SN, EP
   - Redistribution of relapse cases & smear unknown
Expert judgment on case-detection rate

1) Major gap in tuberculosis epidemiology is the true incidence rate. Very few population cohort studies with active surveillance.

2) WHO and GBD 2013 used expert judgment on the case detection rate (with subjective uncertainty intervals) as an input into the estimation process.

3) Impossible to validate expert judgment....
National TB prevalence surveys

- Brunei Darussalam: 1986
- Botswana: 1956
- Eritrea: 2005
- Ethiopia: 2011
- Ghana: 1957
- Gambia: 2012
- Indonesia: 1980, 2004
- Japan: 1953, 1958
- Laos: 2010
- Lesotho: 1956
- Myanmar: 1972, 2009
- Mauritius: 1972, 2009
- Rwanda: 2012
- Saudi Arabia: 1993
- Thailand: 2012
- Tanzania: 2012
- Vietnam: 2006
TB prevalence surveys used in GBD2013

1) Excluded pre-1985 surveys

2) Used 27 national and 24 subnational prevalence surveys in 24 countries

3) Marked surveys by case ascertainment method:
   - Culture + (reference)
   - Smear +

4) In DisMod-MR 2.0 added ‘noise’ (greater non-sampling error) to subnational surveys

5) Adjusted prevalence data to account for extra-pulmonary TB using same inflation factors as for incidence data
Tuberculosis mortality

1) Mortality models based on nationally representative vital registration and verbal autopsy data

<table>
<thead>
<tr>
<th>Data type</th>
<th>Number of country- or site-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital Registration</td>
<td>2,731</td>
</tr>
<tr>
<td>Verbal autopsy</td>
<td>166</td>
</tr>
</tbody>
</table>

2) Cause of Death Ensemble modeling (CODEm): tests wide range of models with variations in quantity of interest (logit cause fraction or log rate), model function (space-time GPR, mixed effects) and predictive covariates.

3) Create combinations ‘ensembles’ of the best performing models.

4) Statistical tests of out-of-sample predictive validity all models

5) Select the best performing model or ensemble of models
<table>
<thead>
<tr>
<th>Covariate</th>
<th>Level</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol per capita</td>
<td>2</td>
<td>pos</td>
</tr>
<tr>
<td>Total cigarettes (5 year lag)</td>
<td>1</td>
<td>pos</td>
</tr>
<tr>
<td>Average fasting plasma glucose</td>
<td>1</td>
<td>pos</td>
</tr>
<tr>
<td>Average years of education</td>
<td>3</td>
<td>neg</td>
</tr>
<tr>
<td>health_system_access</td>
<td>1</td>
<td>neg</td>
</tr>
<tr>
<td>Lagged GDP</td>
<td>3</td>
<td>neg</td>
</tr>
<tr>
<td>% underweight (&lt;-2z)</td>
<td>1</td>
<td>pos</td>
</tr>
<tr>
<td>Prevalence indoor air pollution</td>
<td>1</td>
<td>pos</td>
</tr>
<tr>
<td>% Population density (500-1000/km²)</td>
<td>2</td>
<td>pos</td>
</tr>
<tr>
<td>% Population density (&gt;1000/km²)</td>
<td>2</td>
<td>pos</td>
</tr>
</tbody>
</table>
Tuberculosis mortality

1) ICD-10 has a code for HIV and mycobacterial infection (B30.0), but it is not used consistently; no code in ICD-9

2) Redistribute TB deaths to HIV in 52 countries by examining the relative age pattern of mortality by cause over time

3) …but for non-fatal estimation we use all TB mortality as incidence and prevalence data do not distinguish by HIV-status
Relative age pattern of tuberculosis mortality in South Africa
DisMod-MR 2.0

1. As previous versions of dismod, it ensures consistency between epidemiological estimates for a particular disease or sequela of a disease.

2. In order to evaluate all available info on a disease that passes inclusion criteria we use meta-regression to crosswalk data to reference values of critical characteristics such as case definition, case ascertainment method, representativeness.

3. All countries are evaluated in a Bayesian framework implemented as a cascade from global to 7 super-regions to 21 regions, 188 countries and subnational units for selected countries (China, Mexico and UK in GBD2013).
DisMod-MR 2.0

**Inputs:**

1) Adjusted WHO tuberculosis case notifications
2) Prevalence surveys
3) Tuberculosis mortality estimates
4) Remission estimates
5) Excess mortality estimates

**Outputs:**

DisMod-MR 2.0

1) Incidence, remission and excess mortality are the primary hazards
2) Prevalence is a ‘derived’ quantity
3) Cause-specific mortality rate (CSMR) from CODEm is equivalent to excess mortality rate / prevalence
4) That means that dismod is underspecified when we feed in incidence, prevalence and CSMR only
5) → we made pre-dismod estimates of remission and excess mortality to ‘guide’ the calculations
Excess mortality rates

1) Excess mortality from case notification data and TB deaths from 70 countries (743 country year observations) where incidence and death notifications are believed to be (near) complete; 1980 onwards for most countries but supplemented with 1950-1980 data from AUS, GBR, DLD, CAN, USA & JAP

2) Regression of logit ratio incidence to mortality, lagged GDP and country random effects
1) Remission from incidence to prevalence ratios for country/year combinations for which we had prevalence surveys: simple regression with dummies for age and sex and random effects on geography

\[ p = i \times av\ dur \]

and

\[ remission + exc\ mort = \frac{1}{av\ dur} \]
Tuberculosis: simultaneous estimation of incidence, prevalence, and death

*Figure 5: Bayesian meta-regression estimates for tuberculosis prevalence (A), incidence (B), remission (C), excess mortality (D), and cause-specific mortality (E) for male individuals in Kenya, 2013*
Estimating HIV-free TB morbidity

- Tuberculosis all forms incidence and prevalence estimates generated by DisMod-MR 2.0
- Reviewed the literature and used meta-regression to estimate RR of TB incidence in HIV+ individuals in the absence of ARTs
- Since RR is a function of CD4 count and ART – parsed out the ratios using additional studies

<table>
<thead>
<tr>
<th>ART Status</th>
<th>CD4 count</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>On ART</td>
<td>All</td>
<td>1.7 (1.2 – 2.3)</td>
</tr>
<tr>
<td>No ART</td>
<td>All</td>
<td>8.7 (5.9 – 11.7)</td>
</tr>
<tr>
<td></td>
<td>&lt;200</td>
<td>15.7 (10.6 – 21.1)</td>
</tr>
<tr>
<td></td>
<td>200-350</td>
<td>10.8 (7.3 – 14.5)</td>
</tr>
<tr>
<td></td>
<td>&gt;350</td>
<td>3.2 (2.2 – 4.3)</td>
</tr>
</tbody>
</table>

- Computed population attributable fractions (PAF) for each category using estimates of HIV prevalence for each category; aggregated these to get a single PAF
Global tuberculosis deaths: 1990-2013

Deaths (millions)

Year


GBD 2013 (all tuberculosis)
GBD 2013 (HIV-negative tuberculosis)
WHO 2013 (HIV-negative tuberculosis)
Global tuberculosis deaths in 2013: more in men than women
Age-standardized TB incidence (no HIV): 2013

Rates per 100,000 population
Age-standardized TB mortality (no HIV): 2013

Rates per 100 000 population

- Dark purple: <0.60
- Dark blue: 0.60-1.7
- Green: 1.7-3.3
- Orange: 3.3-6.9
- Red: 6.9-18
- Bright red: >18

Map showing TB mortality rates per 100,000 population across the world.
Global annualized percent change

- Tuberculosis, all forms

<table>
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<tr>
<th>Parameter</th>
<th>1990-2000</th>
<th>2000-2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>0.55 (0.36 to 0.72)</td>
<td>-0.67 (-0.78 to -0.58)</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0.83 (0.70 to 0.98)</td>
<td>-1.35 (-1.44 to -1.25)</td>
</tr>
<tr>
<td>Mortality</td>
<td>-2.85 (-3.59 to -2.20)</td>
<td>-3.66 (-4.32 to -2.99)</td>
</tr>
</tbody>
</table>

- Tuberculosis, no TB-HIV

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<th>2000-2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>0.03 (-0.18 to 0.24)</td>
<td>-0.59 (-0.71 to -0.48)</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0.40 (0.22 to 0.58)</td>
<td>-1.28 (-1.39 to -1.17)</td>
</tr>
<tr>
<td>Mortality</td>
<td>-3.30 (-4.08 to -2.59)</td>
<td>-3.66 (-4.36 to -2.94)</td>
</tr>
</tbody>
</table>
Understanding age-specific relationships incidence, prevalence, and mortality

1) Bayesian meta-regression points to the markedly different relationship between incidence, prevalence, and death with age. More direct studies on this would help narrow the range of plausible relationships.

2) Prevalence surveys with linkage to incidence registries with identifiers could allow more direct quantification of duration.
Tuberculosis in India

1) Large share of cases and deaths in 2013 are in India.

2) Huge uncertainty in the epidemiology of tuberculosis, particularly at younger ages in India.

3) More locality-specific verbal autopsy, registration, and prevalence data will be essential to resolving global epidemiological questions.
Spatial analysis of tuberculosis

1) As with other diseases, e.g., malaria, spatially detailed analysis of tuberculosis may help narrow the uncertainty in the TB incidence, prevalence, and death estimates.

2) Tuberculosis likely spatially heterogeneous, substantial data from notifications combined with prevalence surveys could be analyzed.