Mathematical modelling approach to estimating TB burden in children

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Health Economics & Decision Science
School of Health & Related Research
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Overview

Goal:

Circumvent potential shortcomings in paediatric notification data by mathematical modelling starting from adult data. **Global estimate** (c.f. 22 HBCs in published article.)

Two modelling steps:

1. Relate adult prevalence to infection risk
2. Model progression from infection to disease

Uncertainty in knowledge of each ingredient included.
Bird's eye view

Ovals = models; diamonds = data inputs; squares = numbers.
Data for these results from 2013, for all countries reported.
Data for these results from 2013, for all countries reported.

_data: WHO_
A model of community infection, via an updated Styblo's rule mainly based on a review by Bourdin Trunz et al.
Progression

Diagram:
- Demography
- TB prevalence
- HIV
- ARI data
- Latitude
- BCG
- Numbers at risk
- Model of exposure
- Infection incidence
- Probability of progression to disease
- Incident EPTB by age
- Incident PTB by age
- Total TB incidence

Flow:
1. Input from Demography
2. Input from TB prevalence
3. Changes in HIV
4. Changes in ARI data
5. Changes in Latitude
6. Changes in BCG
7. Input from Numbers at risk
8. Model of exposure
9. Infection incidence
10. Probability of progression to disease
11. Incident EPTB by age
12. Incident PTB by age
13. Total TB incidence

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### Progression

Age-dependent risks of disease following infection

Separated by 5 age groups and type of disease:

<table>
<thead>
<tr>
<th>age</th>
<th>quantity</th>
<th>median</th>
<th>LQ</th>
<th>UQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>probability of disease</td>
<td>0.500</td>
<td>0.298</td>
<td>0.702</td>
</tr>
<tr>
<td>1</td>
<td>probability of disease</td>
<td>0.215</td>
<td>0.108</td>
<td>0.360</td>
</tr>
<tr>
<td>2-4</td>
<td>probability of disease</td>
<td>0.016</td>
<td>0.002</td>
<td>0.064</td>
</tr>
<tr>
<td>5-9</td>
<td>probability of disease</td>
<td>0.001</td>
<td>0.000</td>
<td>0.013</td>
</tr>
<tr>
<td>10-14</td>
<td>probability of disease</td>
<td>0.110</td>
<td>0.043</td>
<td>0.219</td>
</tr>
<tr>
<td>0</td>
<td>probability disease is EP</td>
<td>0.255</td>
<td>0.112</td>
<td>0.451</td>
</tr>
<tr>
<td>1</td>
<td>probability disease is EP</td>
<td>0.295</td>
<td>0.107</td>
<td>0.557</td>
</tr>
<tr>
<td>2-4</td>
<td>probability disease is EP</td>
<td>0.060</td>
<td>0.017</td>
<td>0.145</td>
</tr>
<tr>
<td>5-9</td>
<td>probability disease is EP</td>
<td>0.085</td>
<td>0.029</td>
<td>0.183</td>
</tr>
<tr>
<td>10-14</td>
<td>probability disease is EP</td>
<td>0.000</td>
<td>0.000</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Distributions based on Marais *et al.*, 2004 review of the pre-chemotherapy literature.
HIV

Crude approach

- UNAIDS under-15 HIV prevalence, not disaggregating by age, ART-status or CD4 count.
- Single IRR based on a few South African papers:

<table>
<thead>
<tr>
<th>quantity</th>
<th>median</th>
<th>LQ</th>
<th>UQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRR: TB given HIV infection</td>
<td>20.000</td>
<td>10.118</td>
<td>39.261</td>
</tr>
</tbody>
</table>
### BCG

**Effect**

- Potential variation in efficacy by latitude (up to 41% of efficacy)
- Greater protection against extrapulmonary disease (Rodrigues et al., Colditz et al.)

<table>
<thead>
<tr>
<th>quantity</th>
<th>median</th>
<th>LQ</th>
<th>UQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>protection for PTB</td>
<td>54%</td>
<td>38%</td>
<td>69%</td>
</tr>
<tr>
<td>protection for EPTB</td>
<td>70%</td>
<td>52%</td>
<td>84%</td>
</tr>
</tbody>
</table>

**Data**

- Coverage as WHO BCG vaccination coverage estimates from 2013.
- Country latitudes as barycentre of country.
Countries included

Figure: Countries included with WHO estimates of per capita TB incidence, 2013.

Matching across all datasets leaves 180 countries, total population > 7 billion.
By type & age

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By type & age
TB incidence, total

<table>
<thead>
<tr>
<th>LAT</th>
<th>median</th>
<th>LQ</th>
<th>UQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>lat</td>
<td>828,560</td>
<td>549,402</td>
<td>1,243,878</td>
</tr>
<tr>
<td>nolat</td>
<td>593,140</td>
<td>379,758</td>
<td>912,563</td>
</tr>
</tbody>
</table>
TB incidence, by age

<table>
<thead>
<tr>
<th>age</th>
<th>LAT</th>
<th>median</th>
<th>LQ</th>
<th>UQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>lat</td>
<td>423,585</td>
<td>270,191</td>
<td>635,439</td>
</tr>
<tr>
<td>0-4</td>
<td>nolat</td>
<td>289,245</td>
<td>177,650</td>
<td>459,425</td>
</tr>
<tr>
<td>5-14</td>
<td>lat</td>
<td>352,835</td>
<td>171,139</td>
<td>657,833</td>
</tr>
<tr>
<td>5-14</td>
<td>nolat</td>
<td>254,302</td>
<td>118,603</td>
<td>489,681</td>
</tr>
</tbody>
</table>
TB incidence, by country

data: WHO
Proportion in children

\[
\text{odds} = \frac{1}{50} \times \text{incidence}^{1/4}
\]
### M. tb infection

<table>
<thead>
<tr>
<th>M. tb infection</th>
<th>age group</th>
<th>median</th>
<th>LQ</th>
<th>UQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>prevalence</td>
<td>0-14</td>
<td>62,896,959</td>
<td>48,897,936</td>
<td>80,649,253</td>
</tr>
<tr>
<td>incidence</td>
<td>0-14</td>
<td>8,997,410</td>
<td>6,936,881</td>
<td>11,696,688</td>
</tr>
<tr>
<td>prevalence</td>
<td>0-4</td>
<td>7,861,145</td>
<td>6,080,713</td>
<td>10,173,695</td>
</tr>
<tr>
<td>incidence</td>
<td>0-4</td>
<td>3,191,801</td>
<td>2,459,671</td>
<td>4,145,840</td>
</tr>
<tr>
<td>prevalence</td>
<td>5-14</td>
<td>55,063,579</td>
<td>42,804,117</td>
<td>70,500,851</td>
</tr>
<tr>
<td>incidence</td>
<td>5-14</td>
<td>5,809,956</td>
<td>4,477,617</td>
<td>7,553,058</td>
</tr>
</tbody>
</table>
Comparison with notifications

Overall CDR ≈ 37%
Discussion

Limitations

- Adult TB estimates used as starting point - all limitations inherited.
- Homogeneous mixing assumption - especially poor where TB is rare.
- BCG efficacy data difficult to interpret.
- Crude treatment of HIV.

& others ...
Discussion

Ongoing work

- systematic review of evidence around effects of HIV/ART
- drug resistance
- mortality & morbidity
- interventions
- uncertainty
Discussion

Summary

- Mechanistic model of TB infection and disease in children
- Provides results by age on incidence & prevalence of infection & incidence of disease (by type):

<table>
<thead>
<tr>
<th>quantity</th>
<th>measure</th>
<th>median</th>
<th>LQ</th>
<th>UQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>infection</td>
<td>incidence/yr</td>
<td>9.0 million</td>
<td>6.9 million</td>
<td>11.7 million</td>
</tr>
<tr>
<td>infection</td>
<td>prevalence</td>
<td>62.9 million</td>
<td>48.9 million</td>
<td>80.6 million</td>
</tr>
<tr>
<td>disease (lat)</td>
<td>incidence/yr</td>
<td>827,000</td>
<td>549,000</td>
<td>1,245,000</td>
</tr>
<tr>
<td>disease (nolat)</td>
<td>incidence/yr</td>
<td>593,000</td>
<td>379,000</td>
<td>914,000</td>
</tr>
</tbody>
</table>

Table: Global model estimates for 2013.