WHAT'S IN A NUMBER? TWO RECENT REPORTS ESTIMATING CHILDHOOD TB CASES.

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www.drtbnetwork.org
Two 2014 reports & accompanying commentaries


How many children get sick with MDR-TB every year?
How many children get sick with DR-TB every year?
Childhood TB is different from adult TB

- Extrapulmonary disease
- Bacterial burden
- Testable sputum
Accounting for under diagnosis with smear microscopy

Percent Smear Positive

Age-Groups

~50-60%

~10%
Data inputs and outputs

- WHO smear positive notifications by age (for ~70% of countries)
- Scaled up using Murray et al. 1990 (smear positive percentages)
- Percentage of TB cases that are in children (70% of countries)
Can we estimate proportion of all cases that are in children?

Donald P.
“Childhood TB: Out of control?”
Curr Opinion Pulm Med 2002

Figure 1. Percentages of the tuberculosis caseload

The percentage of the tuberculosis caseload made up by children <15 years of age in relation to the incidence of tuberculosis/100,000 population and the population pyramids typical of an (A) developed and a (B) developing community.
Data inputs and outputs

- Percentage of TB cases that are in children + WHO estimated total TB incidence per 100,000
- Fit regression curve as in Donald 2002
- Percentage of TB cases that are in children for all countries
Logistic regression using our scaled-up TB incidence estimates shows exponential increase consistent with Donald 2002.
Data inputs and outputs

WHO TB incidence per 100,000 estimates
  * UN population numbers
  * Percentage of TB cases in children

Number of incident active childhood TB cases in one year

999,792 (95% CI: 937,877 – 1,055,414) child TB cases
Estimating the risk of MDR-TB in child TB cases

Systematic review resulting in 31 papers quantifying the risk of MDR in child TB cases and adult treatment-naïve TB cases

\[ Y = -0.00261 + 1.0691X \]

Jenkins et al. Lancet 2014
Number of incident active childhood MDR-TB cases in one year

31,948 (95% CI: 25,594 – 38,663) childhood MDR-TB cases
What does this mean?

• We now understand the magnitude of the discrepancy better and can better predict resources needed:
  o 3 x annual notified child TB of 349,000
  o 2 x WHO recent global estimates of 540,000
  o Slightly higher than Dodd et al. of ≈ 800,000 (global)
  o reports of MDR-TB in the literature (across 40 years) ~2% of total burden (in one year!)
• Most of this morbidity (and mortality) is preventable
• We need more investment in diagnostics and treatment
• In the meantime we need to use tools available to us (eg. contact tracing, preventive treatment…)
Acknowledgements

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Estimating the burden of paediatric tuberculosis through mathematical modelling

Pete Dodd (University of Sheffield)
& James Seddon (Imperial College London)

Thursday, 9 October 2014

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

Goal:
*Circumvent potential shortcomings in paediatric notification data by mathematical modelling* starting from adult data. Applied to the **22 HBCs**.

Two modelling steps:

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

Uncertainty in knowledge of each ingredient must be included.

*mechanistic vs. phenomenological*
The canonical picture

- deaths : incidence : prevalence in ratio
  1 : 2 : 4 for smear positive TB
  i.e. CFR ≈ 50% & duration ≈ 2 years

- ARI of 1% corresponds with
  smear+ incidence 50/100,00 per year
  \( \beta \approx \frac{1\%/y}{(2y \times 50 \times 10^{-5}/y)} = 10 \text{ y}^{-1} \)

- With a 10% lifetime risk of disease, 50% of it smear positive
  1 smear+ case → 20 infections → 2 cases = 1 smear+ case
  i.e. Stable situation, \( R_n = 1 \)

**Figure:** Karel Styblo, 1921-1998: the ‘father of TB control’
Ovals = models; diamonds = data inputs; squares = numbers.
Demography

Data: UN ESA
TB prevalence

data: WHO
Infection

Introduction
A Model
Overview
Infection
Progression
Factors
Results
Under-reporting
Overall Numbers
By country
Pattern by incidence
Conclusion
## Two approaches:

1. A model of community infection, via an updated Styblo's rule.
   - data on ARI/prevalence ratios (see left)

2. A household (only) infection model from:
   - detailed data on household make-up
   - data informing risks of household infection
Progression

Introduction

A Model
- Overview
- Infection
- Progression
  - Factors

Results
- Under-reporting
- Overall Numbers
- By country
- Pattern by incidence

Conclusion
Age-dependent progression

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>
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<tbody>
<tr>
<td>0</td>
<td>probability of disease</td>
<td>0.500</td>
<td>0.298</td>
<td>0.702</td>
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<tr>
<td>1</td>
<td>probability of disease</td>
<td>0.215</td>
<td>0.108</td>
<td>0.360</td>
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<td>2-4</td>
<td>probability of disease</td>
<td>0.016</td>
<td>0.002</td>
<td>0.064</td>
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<td>5-9</td>
<td>probability of disease</td>
<td>0.001</td>
<td>0.000</td>
<td>0.013</td>
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<td>10-14</td>
<td>probability of disease</td>
<td>0.110</td>
<td>0.043</td>
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<td>0.255</td>
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<td>0.295</td>
<td>0.107</td>
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<td>0.060</td>
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<td>0.085</td>
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<td>0.000</td>
<td>0.000</td>
<td>0.008</td>
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distributions based on Marais *et al.*, 2004 review of the pre-chemotherapy literature.
Other factors influencing progression

**BCG vaccination**

- Greater protection against extrapulmonary disease
- Potential variation in efficacy by latitude

**HIV infection**

Scant data on the effect of HIV on TB progression in children
Results
Comparison with notifications

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<tr>
<th>Country</th>
<th>0-5</th>
<th>5-15</th>
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Number of new paediatric tuberculosis cases per year (log scale)

Suggests a CDR of 35% (IQR 23% - 54%)
Overall Numbers

Remember: data from 2010; estimates for 22 HBCs

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<th>median</th>
<th>LQ</th>
<th>UQ</th>
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</thead>
<tbody>
<tr>
<td>cohabit w/ TB case</td>
<td>15,300,000</td>
<td>13,800,000</td>
<td>17,100,000</td>
</tr>
<tr>
<td>incident <em>M. tb</em> infections</td>
<td>7,600,000</td>
<td>5,800,000</td>
<td>9,970,000</td>
</tr>
<tr>
<td>prevalent <em>M. tb</em> infections</td>
<td>53,200,000</td>
<td>41,000,000</td>
<td>69,000,000</td>
</tr>
<tr>
<td>incident TB cases</td>
<td>651,000</td>
<td>425,000</td>
<td>983,000</td>
</tr>
</tbody>
</table>

**Table:** For children (<15 years) the 22 HBCs in 2010.

- large uncertainty
- other model variants ...
highest. The average age at infection, when risks of progression are also noted that a high force of infection leads to a younger correlation with younger-skewed demographics. He pointed out that increased proportions would be expected in countries where overall burden is highest, because of reporting up to 39% of the burden in children. The proportion of tuberculosis burden occurring in children has frequently been used to estimate probable burden in children vary widely, with some investigators exist. As with any model, our approach involved assumptions and has limitations. The limiting assumptions were present and accumulated result of a failure to identify contacts would probably substantially reduce the disease after household exposure should be thought to have developed preventable tuberculosis; screening of individuals sharing a household with an adult who has been diagnosed with tuberculosis and treatment of child have a higher proportion of global paediatric tuberculosis, which is probably a result of its large size, and lower than the value of 1 million numbers predicted by our model also represent the. The comparison; rTingmkr ekD=lneml \[\text{dr}=\text{Democratic Republic.}\]

Our model has identified large populations that could from preventive treatment, although not all the latest HBCs. The comparison of notifications and model estimates suggests under-reporting up to 39% of the burden in children. In view of the efficacy of isoniazid preventive therapy, children would be eligible. In view of the extrapolation of our approach would suggest a global burden that is up to 25% higher than our prediction for the 22 HBCs. Our model reproduces this expected trend, somewhat higher than those in the 2012 WHO report, and has limitations. The limiting assumptions were:

- Direct measurements do not exist.
- Local estimates for the proportion of tuberculosis burden occurring in children were not available.
- The proportion of tuberculosis burden occurring in children has frequently been used to estimate probable numbers predicted by our model also represent the median number of new paediatric tuberculosis cases per year.
Pattern by incidence

Recall Helen's slide...
Conclusion

Summary & comments

- We presented a mathematical modelling approach to estimating the burden of paediatric TB starting from adult prevalence data.
- Pros and cons:
  - More assumptions needed (→ more uncertainty, more frailty).
  - Highlights important areas of relative ignorance
  - A richer set of estimates
  - Can be used to model interventions
- Substantial burden of disease in children, with large numbers targetable for preventive therapy.
Impact of Global TB Estimates for Clinicians: Measuring the Chasm
Chasms

**LTBI**
- Not reportable
- 1/3 of global population (?)
- Few recent national-level data
- Data from certain cohorts not generalizable

**Disease**
- Reportable (but reporting gaps)
- 2012: disaggregated pediatric data
- #s don’t correspond to population structure
- Few HIV/TB data in children

**MDR-TB**
- Reporting obstacles if linked solely to microbiologic confirmation
- Few disaggregated pediatric data
- Diagnostic limitations in HBCs
Clinical impact: how the #s help

• While we knew we were under-reporting disease in children, we had few prior estimates of infection
• Raises awareness of prevention opportunities
• Opportunity to benchmark
  – Impossible to benchmark what’s not currently measured
• Allows for estimates of resource allocation
Infection Prevalence

• Prior estimate: 1/3 of global population
  – If accurate, should have many more cases of TB disease
• Not reportable in most settings
• U.S. estimates:
  – Non-generalizable cohorts (e.g., military recruits, nurses)
  – Recent immigrants
  – Single-center studies
Infection Incidence

• Estimated that $\frac{1}{2}$ of lifetime risk of progression to disease is within first 1-2 years of infection

• Better #s:
  – Identify a cohort of children who would benefit most from preventive therapy
  – Allow for potential risk-stratification in resource-limited settings where IPT may not be able to be operationalized across the pediatric age spectrum
MDR-Infection

• No current estimates
• Few data on optimal treatment regimens
  – Efficacy
  – Tolerability
• Few children with MDR-TBI treated
  – Heterogeneous regimens preclude comparison
• Could data from Jenkins & Dodd papers be used to model MDR-TBI?
  – Impetus for clinical trials?
Prevention Opportunities

• Many HBCs may be overwhelmed by disease, which is measurable

• TB infection seems invisible.. until it is not.

• Most data on prevention come from low-incidence nation, where lessons learned may seem to be difficult to generalize across the resource gradient
How did high-incident countries become low-incident countries (pre-HIV)

• Societal infrastructure changes
• Active surveillance
• Emphasizing prevention
Figure 1—The Scheme for Tuberculosis Contact Investigation

Findings 693 households of index patients with MDR tuberculosis were enrolled in the study. In 48 households, the *Mycobacterium tuberculosis* isolate from the index patient was XDR. Of the 4503 household contacts, 117 (2.60%) had active tuberculosis at the time the index patient began MDR tuberculosis treatment—there was no difference in prevalence between XDR and MDR tuberculosis households. During the 4-year follow-up, 242 contacts developed active tuberculosis—the frequency of active tuberculosis was nearly two times higher in contacts of patients with XDR tuberculosis than it was in contacts of patients with MDR tuberculosis (hazard ratio 1.88, 95% CI 1.10–3.21). In the 359 contacts with active tuberculosis, 142 (40%) had had isolates tested for resistance against first-line drugs, of whom 129 (90.9%, 95% CI 85.0–94.6) had MDR tuberculosis.

Interpretation In view of the high risk of disease recorded in household contacts of patients with MDR or XDR tuberculosis, tuberculosis programmes should implement systematic household contact investigations for all patients identified as having MDR or XDR tuberculosis. If shown to have active tuberculosis, these household contacts should be suspected as having MDR tuberculosis until proven otherwise.
Disease Estimates

- ~ 1/3 reported
  - Reporting barriers?
- Even more underestimated in countries reliant upon smear microscopy
- Better #s help quantify unmet needs for diagnosis & treatment
  - Education for clinicians
  - Augmented laboratory support:
    - Sputum induction, gastric aspirates
    - Molecular modalities
TB/HIV in Children

• Even harder to measure than TB in immunocompetent children
• Historically has gone unmeasured
• With current IPT guidelines, most of these children represent preventable cases
• Better #s:
  – Benchmark IPT
  – Trials: minimizing adverse events; shorter-course regimens
MDR-TB Estimates

• Disparities in reporting:
  – Underreporting if no cultures obtained (TB)
  – Over-reporting if no culture obtained (NTM)
• No disaggregated pediatric data
• Better #s:
  – Improved contact tracing
  – Trials: duration of therapy, pharmacokinetic information, # of drugs needed
  – Pediatric-friendly formulations
How to Operationalize?

• Add childhood contacts to TB case card
  – Actually implement IPT for at-risk child contacts
  – Allows for linkages to source case susceptibilities

• Integrate into existing maternal/child health services
  – Venues where children already seeking care
  – Decentralize from national tuberculosis programs
Conclusions

• The estimates may differ; however, they still serve as estimates for something which had been suboptimally measured previously

• Better numbers help us make the case for:
  – Increasing programmatic resources
    • Infection
    • Disease
  – Augmenting pediatric-friendly drug formulations
  – Enabling countries to benchmark what they are currently doing and setting future goals
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