Challenging Paradigms in Pediatric Tuberculosis: Where Does Transmission Occur

Leonardo Martinez
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Enthusiasm & Energy

Children with TB: neglected no more . . .

Between 2011 and 2015, the world spent US$80 million on pediatric TB research – just 40% of the US$200 million target outlined in the Roadmap for Childhood Tuberculosis.6 Global elimination of TB will only occur as we develop better treatments and improved diagnostics for children. To achieve that, greater investment in pediatric TB research is

Counting children with tuberculosis: why numbers matter


Importance of tuberculosis control to address child survival

Tuberculosis commonly affects young children (<5 years) in countries that have high rates of child mortality.1 The WHO, vital registration data cannot be used to estimate the number of deaths and not contributory causes to WHO, vital

Reid and Goosby, IJTLD, 2016; Seddon et al, IJTLD, 2015; Graham et al, Lancet, 2014
Global and Regional Pediatric Tuberculosis and MDR-Tuberculosis Incidence

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated number of child tuberculosis cases (95% CI)</th>
<th>Estimated number of child multidrug-resistant tuberculosis cases (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African region</td>
<td>279,825 (250,187–308,717)</td>
<td>4,736 (2,829–6,848)</td>
</tr>
<tr>
<td>Eastern Mediterranean region</td>
<td>71,162 (60,320–83,193)</td>
<td>2,417 (339–5,087)</td>
</tr>
<tr>
<td>European region</td>
<td>43,224 (39,572–47,242)</td>
<td>5,645 (4,206–7,463)</td>
</tr>
<tr>
<td>Region of the Americas</td>
<td>27,199 (24,935–29,635)</td>
<td>606 (374–854)</td>
</tr>
<tr>
<td>South-East Asia region</td>
<td>397,040 (350,615–447,474)</td>
<td>10,000 (4,993–15,568)</td>
</tr>
<tr>
<td>Western Pacific region</td>
<td>179,515 (159,246–202,626)</td>
<td>8,349 (5,639–11,610)</td>
</tr>
<tr>
<td>Total</td>
<td>999,792 (937,877–1,055,414)</td>
<td>31,948 (25,594–38,663)</td>
</tr>
</tbody>
</table>

These regions correspond to those defined by WHO.

*Table 2: Estimated number of incident cases of tuberculosis disease and multidrug-resistant tuberculosis disease in children by WHO region, 2010*
Global and Regional Pediatric Tuberculosis and MDR-Tuberculosis Incidence

Smear-positive notifications in children → Estimated number of all paediatric TB cases → Estimated number of all adult TB cases → Estimated proportion of TB cases in all ages that occur in children

Inflation by the age-specific proportion of cases expected to be smear-positive

Seddon et al, *IJTLD 2015*
Pediatric Tuberculosis in 22 High-Burden Countries

Figure 4: Numbers of new paediatric tuberculosis cases in 2010, by country
Estimates were calculated with the community model. Error bars show IQRs. DR=Democratic Republic.

Global Pediatric Mortality Due to Tuberculosis

Dodd et al, The Lancet Global Health, 2017
Pediatric Tuberculosis is a Global Problem
Pediatric Tuberculosis is a Global Problem

Historically Neglected
Pediatric Tuberculosis is a Global Problem

Historically Neglected

Long Held Beliefs Remain Unchallenged
Widely Held Belief: Vast majority of tuberculosis transmission to children occurs from a source inside the child’s household in high-burden settings

“Most transmission in young children occurs in the household”

“....young children more likely to have been infected by a household member”

“A household contact is often found to be the source of infection in children under 5 years of age with TB; infants and young children are especially likely to have contracted TB at home”
What proportion of tuberculosis transmission to children is attributable to household tuberculosis exposure?
Beginning to Question

Systematic Reviews and Meta- and Pooled Analyses

Transmission of *Mycobacterium Tuberculosis* in Households and the Community: A Systematic Review and Meta-Analysis

Leonardo Martinez*, Ye Shen, Ezekiel Mupere, Allan Kizza, Philip C. Hill, and Christopher C. Whalen

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Initially submitted December 3, 2015; accepted for publication June 2, 2016.

The individual- and population-level impact of household tuberculosis exposure on transmission is unclear but may have implications for the effectiveness and implementation of control interventions. We systematically searched for and included studies in which latent tuberculosis infection was assessed in 2 groups: children exposed and unexposed to a household member with tuberculosis. We also extracted data on the smear and culture status of index cases, the age and bacillus Calmette-Guérin vaccination status of contacts, and study design characteristics. Of 6,176 citations identified from our search strategy, 26 studies (13,999 children with household exposure to tuberculosis and 174,097 children without) from 1929–2015 met inclusion criteria. Exposed children were 3.79 (95% confidence interval (CI); 3.01, 4.78) times more likely to be infected than were their community counterparts. Meta-regression demonstrated higher infection among children aged 0–4 years of age compared with children aged 10–14 years (ratio of odds ratios = 2.24, 95% CI: 1.43, 3.51) and among smear-positive versus smear-negative index cases (ratio of odds ratios = 5.45, 95% CI: 3.43, 8.64). At the population level, we estimated that a small proportion (~20%) of transmission was attributable to household exposure. Our results suggest that targeting tuberculosis prevention efforts to household contacts is highly effective. However, a large proportion of transmission at the population level may occur outside the household.

Abbreviations: CI, confidence interval; OR, odds ratio.
Cohort Studies

What is the prevalence of household tuberculosis exposure?

Follow-up Time

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<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Years</th>
<th>Age, yrs</th>
<th>Setting</th>
<th>Study Design (Sample Size)‡</th>
<th>Conclusions</th>
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<tr>
<td>Martinez, 2018</td>
<td>2012–2017</td>
<td>0-5</td>
<td>South Africa</td>
<td>Prospective cohort (N=915), tuberculin conversion</td>
<td>11% of conversions occurred in households with a tuberculosis case in the last year</td>
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<tr>
<td>Andrews, 2017</td>
<td>2009–2012</td>
<td>0-2</td>
<td>South Africa</td>
<td>Prospective cohort (N=2512), QuantiFERON conversion</td>
<td>19% of conversions occurred in households with a tuberculosis case</td>
</tr>
<tr>
<td>Khan, 2018</td>
<td>2012–2015</td>
<td>&lt;6</td>
<td>Malawi</td>
<td>Prospective cohort (N=3066), tuberculin conversion</td>
<td>11% of conversions lived a distance &lt;200 meters from a known tuberculosis case</td>
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</tbody>
</table>
## Cohort Studies

### What is the Prevalence of Household Tuberculosis Exposure?

- **General Population Sample**
- **No Active Tuberculosis**
- **Developed Active Tuberculosis**

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### Disease Progression Studies

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<td>South Africa</td>
<td>Prospective cohort (N=915)</td>
<td>19% of children developing tuberculosis were exposed to tuberculosis in the home</td>
</tr>
<tr>
<td>Nachman, 2011</td>
<td>2004–2008</td>
<td>0-3</td>
<td>South Africa</td>
<td>Prospective trial data of HIV-exposed infants (N=1329)</td>
<td>45 children developed tuberculosis; 28% were exposed to tuberculosis in the home*</td>
</tr>
</tbody>
</table>
## Tuberculosis Infection Surveys

All tested for Tuberculosis Infection

- **Positive**
- **Negative**

### What is the Prevalence of Household Tuberculosis Exposure?

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<td><strong>Cross-Sectional Surveys</strong></td>
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<tr>
<td>Martinez, 2017</td>
<td>1931–2015</td>
<td>&lt;15</td>
<td>14 countries</td>
<td>Systematic review of tuberculin surveys (N=170615)</td>
<td>Household exposure at the population-level was low; &lt;25% of transmission occurred in households</td>
</tr>
<tr>
<td>Khan, 2016</td>
<td>2012</td>
<td>2-4</td>
<td>Malawi</td>
<td>Tuberculin survey (N=3170)</td>
<td>&lt;10% transmission occurred in households with a tuberculosis case</td>
</tr>
<tr>
<td>Dorjee, 2018</td>
<td>2017–2018</td>
<td>13†</td>
<td>Tibet</td>
<td>Tuberculin survey (N=5234)</td>
<td>&lt;10% of childhood infections were attributable to recent household exposure</td>
</tr>
<tr>
<td>Cranmer, 2014</td>
<td>1999–2002</td>
<td>0.5</td>
<td>Kenya</td>
<td>T-SPOT.TB survey (N=128)</td>
<td>14% of infants with a positive T-SPOT.TB were exposed to a parent with active tuberculosis</td>
</tr>
<tr>
<td>Lule, 2015</td>
<td>2002–2005</td>
<td>5</td>
<td>Uganda</td>
<td>T-SPOT.TB survey (N=886)</td>
<td>20% of T-SPOT.TB positive children were exposed to a tuberculosis case</td>
</tr>
<tr>
<td>Ganmaa, 2018</td>
<td>2015–2017</td>
<td>6–13</td>
<td>Mongolia</td>
<td>QuantIFERON-TB survey (N=9810)</td>
<td>13.1% of tuberculosis infections were attributable to household tuberculosis exposure</td>
</tr>
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</table>
Molecular Studies

General Population Sample → All Culture Positive Cases (Adults and Children) → Molecular Genotyping → Children with Culture Positive Tuberculosis → Adults with Culture Positive Tuberculosis

What Proportion have a Matching Genotype in their Household?

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<td>Schaaf, 2003</td>
<td>1993–1998</td>
<td>≤15</td>
<td>South Africa</td>
<td>Population-based; all culture-confirmed pediatric cases (N=35)</td>
<td>34% of diseased children were part of a cluster with a household tuberculosis case</td>
</tr>
<tr>
<td>Guthrie, 2018</td>
<td>2005–2014</td>
<td>&lt;18</td>
<td>British Colombia</td>
<td>Population-based; all culture-confirmed pediatric cases (N=49)</td>
<td>70% of transmission occurred either in a foreign country or locally but outside the household</td>
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Mathematical Modeling Studies

Andrews et al, JID 2014
Mathematical Modeling Studies

Andrews et al, *JID* 2014
So, what proportion of tuberculosis transmission to children is attributable to household tuberculosis exposure?

Population-attributable fraction =
\[
\frac{(\text{Prevalence of exposure} \times [\text{relative risk} - 1])}{(\text{Prevalence of exposure} \times [\text{relative risk} - 1]) + 1}
\]
Prevalence of children having a household tuberculosis exposure at the population level

+ Prospective cohort (outcome is progression to disease)
+ Tuberculosis infection survey
○ Prospective cohort (outcome is TST/QFT conversion)
■ Systematic review of tuberculin surveys
Prevalence of children having a household tuberculosis exposure at the population level

Relative risk of transmission to a child due to household exposure

- + Prospective cohort (outcome is progression to disease)
- ♦ Tuberculosis infection survey
- ○ Prospective cohort (outcome is TST/QFT conversion)
- ■ Systematic review of tuberculin surveys

Martinez et al, Lancet Resp Med 2019
Where in the Community Then?

- Almost no field intervention studies outside the household for pediatric tuberculosis
- Where outside the household?
- Entry points?

Picture: Kumar, Lancet 2019
Where in the Community Then?

Andrews et al, *JID* 2014

![Bar chart showing proportion transmitted by location and age group.](chart_image)
A before-and-after implementation study from Uganda evaluated the effect of strengthening diagnosis, treatment, and prevention of paediatric tuberculosis at peripheral health facilities.

After implementation, a 140% increase in paediatric case notification was recorded, almost entirely driven by health-care facility interventions.
Most Tuberculosis Transmission to Children Occurs Outside the Household

- Between 10% to 20% of tuberculosis transmission to children occurs in the household.

- Household contact tracing, when done perfectly at 100% implementation, may have limited impact.

- A comprehensive approach that combines a set of public health, community-based screenings, in combination to household contact tracing, is necessary.
Dogma

Most transmission in young children occurs in the household, with up to 60% of children with tuberculosis having a reported household or close contact.

"...young children more likely to have been infected by a household member"

A household contact is often found to be the source of infection in children under 5 years of age with TB; infants and young children are especially likely to have contracted TB at home.

Differing Study Design Show Consistent Results

Where transmission is occurring needs work

>70% of Tuberculosis Transmission Outside Households

Prevalence of children having a household tuberculosis exposure at the population level

Relative risk of transmission to a child due to household exposure

Population-attributable fraction of transmission to children due to household exposure

Guidance for national tuberculosis programmes on the management of tuberculosis in children

Second edition

Conversion Studies

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Jason R. Andrews
Olivia Cords
Nathan C Lo

Baylor University, School of Medicine
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Alexander Kay

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Heather Zar

University of Otago
Philip C. Hill

Boston University
Bob Horsburgh

London School of Hygiene & Tropical Medicine
Palwasha Khan

SATVI
Mark Hatherill
Thank you for listening.
Questions?
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>70% of Tuberculosis Transmission Outside Households

Where transmission is occurring needs work