Prevalence and Incidence of tuberculosis infection and disease among household contacts of multidrug-resistant (MDR) TB cases


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AIDS 2020
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MDR TB in Household Contacts (HHCs)

- MDR TB contact investigation is poorly implemented globally
- Studies of HHCs of MDR TB cases have largely been single site retrospective studies
- High quality data on prevalence and incidence of TB infection and disease needed to inform programs, epidemiologic models and trials of preventive therapies/vaccines

Cain KP et al. Int J Tuberc Lung Dis
PHOENIx Feasibility Study Objectives

- **PHOENIx Feasibility study (A5300/I2003)**
  - 2 US NIH-funded HIV clinical trials networks, ACTG and IMPAACT
  - 8 high TB burden countries at 16 sites
  - Prepare for a large multisite cluster randomized interventional trial of delaminid vs isoniazid for prevention of TB in high risk HHCs

- **Objectives**
  - Main
    - To describe feasibility of identifying, recruiting, and characterizing adults MDR TB index cases and their HHCs
    - Prevalence of TB infection, TB Disease, and HIV infection among HHCs
  - This analysis
    - To describe incidence of TB infection and disease 1 year later

Gupta CID 2019
Suryavanshi CID 2019
Swindells IJTL 2018
Kim CROI 2020
Key Inclusion Criteria

Sites
- ACTG and IMPAACT sites with ability to enroll 10 MDR TB cases in a 16-week period

Population
- **Index Cases:**
  - An adult (18+ years) with pulmonary RR/MDR TB by genotypic or phenotypic testing
  - Started on TB treatment within past 6 months
  - Willing to allow access to their households

- **Household contacts:**
  - Residing in same dwelling unit or plot of land with shared housekeeping arrangements as the index case
  - Reported exposure within 6 months prior to index case starting MDR TB treatment
Methods

- **Outcomes**
  - **Incident TB Infection**: HHC ≥ 5 years IGRA-negative or indeterminate at baseline and positive repeat IGRA at 1 year using QuantiFERON Gold-in-tube
  - **Incident TB Disease**: Negative symptom screen, chest radiography, mycobacteriology at baseline and positive at follow-up (routine program or via study)
  - Confirmed, probable, possible TB categories based on microbiology, clinical adjudication

- **High-risk groups** defined as:
  - Children <5 years
  - HIV-infected
  - TBI by either TST or IGRA

- **Statistical Analysis**: Cumulative incidence proportions and 95% CI estimated using Generalized Estimating Equations because of correlation within households
Flow Diagram for incident TB Disease

**Step 1**
305 Index Cases with Pulmonary MDR-TB Enumerated HHs

1016 HHCs from 284 HHs Enrolled and Evaluated

130 prevalent TB
  9 already diagnosed
  121 (12%) newly diagnosed
    17 (2%) confirmed,
    33 (3%) probable,
    71 (7%) possible  (all children)

**Step 2**
Median 51.4 weeks
850 HHCs from 247 HH enrolled to Step 2 or died (n=6, 0.6%, 2 TB-related)

108 prevalent TB from Step 1
  25 confirmed
  22 probable
  61 possible

742 HHCs from 243 HH at risk of incident TB disease

Gupta CID 2019
Flow Diagram for incident TB Infection

Step 1

1016 HHCs from 284 HHs Enrolled and Evaluated

IGRA + prevalence
- 43/102 (42%) IGRA+ age <5
- 588/905 (58%) IGRA+ and age ≥5
- 1/102 (1%) indeterminate age <5
- 43 (4%) Step 1 IGRA not available

Step 2

720 not eligible for Step 2 IGRA testing

41 eligible but not enrolled in Step 2

242 HHCs from 131 HH at risk for incident TB infection and evaluated

Gupta CID 2019
## HHC Characteristics evaluated in Step 2 follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HHC (N=844)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (interquartile range)</td>
<td>25 (11,43)</td>
</tr>
<tr>
<td>Female</td>
<td>497 (59%)</td>
</tr>
<tr>
<td>Countries (# sites)</td>
<td></td>
</tr>
<tr>
<td>Botswana (1)</td>
<td>36 (4%)</td>
</tr>
<tr>
<td>Brazil (1)</td>
<td>17 (2%)</td>
</tr>
<tr>
<td>Haiti (1)</td>
<td>39 (5%)</td>
</tr>
<tr>
<td>India (2)</td>
<td>188 (22%)</td>
</tr>
<tr>
<td>Kenya (1)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Peru (2)</td>
<td>181 (21%)</td>
</tr>
<tr>
<td>South Africa (7)</td>
<td>345 (41%)</td>
</tr>
<tr>
<td>Thailand (1)</td>
<td>28 (3%)</td>
</tr>
<tr>
<td>Risk group</td>
<td></td>
</tr>
<tr>
<td>Group 1: &lt; 5 years old</td>
<td>87 (10%)</td>
</tr>
<tr>
<td>Group 2: &gt;=5 years and HIV+</td>
<td>48 (6%)</td>
</tr>
<tr>
<td>Group 3: &gt;=5 years and HIV-/unknown and LTBI+</td>
<td>501 (59%)</td>
</tr>
<tr>
<td>Not in groups 1-3</td>
<td>200 (24%)</td>
</tr>
<tr>
<td>Active TB prior to Step 1</td>
<td>8 (1%)</td>
</tr>
</tbody>
</table>
Significant differences in age-specific incidence of TB disease among household contacts

Higher TB incidence in <15 years compared to those older, p=0.023

<table>
<thead>
<tr>
<th>Age Group</th>
<th>N</th>
<th>TB Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 years</td>
<td>57</td>
<td>7.0%</td>
</tr>
<tr>
<td>5 - 14 years</td>
<td>129</td>
<td>3.9%</td>
</tr>
<tr>
<td>15 - 45 years</td>
<td>376</td>
<td>1.3%</td>
</tr>
<tr>
<td>45+ years</td>
<td>180</td>
<td>1.1%</td>
</tr>
<tr>
<td>Overall</td>
<td>742</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Notes:
- Confirmed/Probable
- Possible

Graph: Bar chart showing the percentage of confirmed/probable and possible TB cases across different age groups.
Cumulative incidence of TB Disease significantly differs by risk group

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<th>TB Disease</th>
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</thead>
<tbody>
<tr>
<td>Age &lt; 5 years (N=57)</td>
<td></td>
<td>7.0%</td>
</tr>
<tr>
<td>HIV+ Age ≥5 (N=46)</td>
<td></td>
<td>6.8%</td>
</tr>
<tr>
<td>TST/IGRA+ Age ≥5 HIV− (N=450)</td>
<td></td>
<td>1.8%</td>
</tr>
<tr>
<td>Not in High Risk Group (N=189)</td>
<td></td>
<td>0.5%</td>
</tr>
<tr>
<td>Overall (N=742)</td>
<td></td>
<td>2.3%</td>
</tr>
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High risk groups overall 2.7% compared to 0.5%, p=0.006

Only 26 (5%) of 553 high-risk HHCs were on preventive therapy.
Increasing age-specific incidence of TB infection (IGRA conversion) at 1 year of follow-up among household contacts of RR/MDR TB cases

Comparing age 5-<15 to ≥ 15, p=0.007
No observed difference in incident TB infection (IGRA conversion) by HIV status

<table>
<thead>
<tr>
<th></th>
<th>HIV-positive (N=18)</th>
<th>HIV-negative/unknown (N=224)</th>
<th>Overall (N=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGRA+</td>
<td>22.1%</td>
<td>21.5%</td>
<td>21.6%</td>
</tr>
</tbody>
</table>

*p=0.95*
Cumulative incidence of TB Infection by risk group

- HIV+ Age ≥5 (N=18) 22.1%
- TST/IGRA+ Age ≥5 HIV− (N=44) 24.6%
- Not in High Risk Group (N=180) 20.9%
- Overall (N=242) 21.6%
Summary

- Cumulative TB disease incidence was 2.7% in high risk HHCs compared to 0.5% not in high risk group
  - Highest in younger age but many were not confirmed microbiologically
  - Higher in HIV+ vs HIV- but small numbers so statistically non-significant
- Cumulative TB infection incidence high: 21% converted
  - Increased by age
  - No difference by HIV status
- Only 5% of high risk HHCs on preventive therapy
- Novel TB prevention strategies are urgently needed
Acknowledgments

Study Participants, Site Community Advisory Boards

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Thank you