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Contacts of Retreatment Tuberculosis Cases with a Prior Poor Treatment Outcome are at Increased Risk of Latent Tuberculosis Infection

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Abstract

\textbf{Objectives}—To estimate the prevalence of and risk factors for latent tuberculosis infection (LTBI) among contacts of index patients with tuberculosis (TB) with a prior history of active TB disease and TB treatment (retreatment cases).

\textbf{Methods}—A cross-sectional population-based study was conducted using data from the national TB contact surveillance program in the country of Georgia. Contacts of retreatment cases were investigated and tuberculin skin testing was offered. Bivariate and multivariable analyses were performed to calculate odds ratios and 95% confidence intervals for risk of LTBI among contacts.

\textbf{Results}—The prevalence of LTBI was significantly higher among contacts whose index TB patient had a prior unfavorable treatment outcome compared to those with a favorable outcome (OR=3.14). Contacts whose index TB case previously failed therapy (OR=6.43), was lost to follow-up (OR=5.63) or completed treatment (OR=3.33) had a significantly higher prevalence of LTBI compared to contacts of previously cured TB cases.

\textbf{Conclusions}—Among contacts of active TB retreatment cases, the risk of LTBI was related to the outcome of the index case’s previous TB treatment. Efforts aimed at reducing treatment loss to
follow-up should be emphasized to enhance TB control efforts and may also decrease LTBI and active TB among contacts.

**Keywords**

tuberculosis; georgia; TST; LTBI

**I. Background**

Tuberculosis (TB) remains a serious global public health problem, including in the country of Georgia. In 2014, the World Health Organization (WHO) reported the incidence rate of TB in Georgia was 106 cases per 100,000 persons. Georgia has high rates of multidrug-resistant (MDR) TB. Close contacts of persons with active TB disease are at increased risk of latent TB infection (LTBI) and active TB disease. Contact investigation of close contacts is a recommended control strategy for active TB case finding and for detecting individuals with LTBI who are at increased risk of progressing to active TB disease.

Contact investigations are commonly conducted in high-income, low TB incidence countries but are generally not part of routine TB control efforts in most low and middle-income countries (LMIC). Nonetheless, contact investigations are recommended by WHO in LMIC where the burden of TB disease is greatest. In 2012, the National Center for Disease Control and Public Health (NCDC) initiated a nationwide TB contact investigation program in the country of Georgia. Using data from this program, we aimed to estimate prevalence of and risk factors for LTBI among contacts of index patients with a prior history of treatment for active TB (retreatment cases).

**II. METHODS**

This cross-sectional study was conducted using surveillance data from the entire country of Georgia. We included only the close contacts of retreatment TB cases (index cases) who were sputum AFB smear positive at the time of diagnosis as a retreatment case identified between April and December 2012. Epidemiologists affiliated with the NCDC interviewed each index retreatment case to determine close contacts, defined as members of the same household and non-household contacts who had daily contact with index patient. Contacts were offered tuberculin skin testing; if they accepted, a tuberculin skin test (TST) was carried out using the Mantoux method with 0.1 ml tuberculin. An induration of ≥10 mm was defined as a positive TST. LTBI was defined as having positive TST (the first step of investigation) without symptoms of active TB disease. Contacts with a positive TST were referred to a TB physician for further evaluation but were not followed up as part of this study.

Analyses were performed using SAS version 9.3 (SAS Inc., Cary, NC USA). Bivariate analyses and a multivariable logistic regression analyses were used to calculate odds ratios and 95% confidence intervals for risk of LTBI among contacts. The primary exposure of interest was an index patient’s outcome of previous TB episode (cure, completion, loss to follow-up, failure). Treatment outcomes were defined based on WHO definitions. Model building and selection was based on purposeful selection of covariates strategy. A two-side...
p-value <0.05 was considered statistically significant for all analyses. The study was approved by Emory University and Georgian NCDC Institutional Review Boards.

III. RESULTS

Among 583 close contacts of an index patient with active TB with a prior history of TB (i.e., retreatment case), 139 (24%) received a TST and were included in this analysis. The overall prevalence of LTBI among these contacts was 33% (46/139). The prevalence of LTBI was significantly higher among those contacts whose index TB case had an unfavorable treatment outcome (failed or lost to follow-up) during their prior treatment episode compared to those whose index patients had favorable outcome (cured or completed) (OR 3.14, 95% CI 1.48–6.70). Further analysis showed that contacts whose index TB case failed, was lost to follow-up or completed treatment had significantly higher prevalence of LTBI compared to contacts of TB cases who were previously cured (Table 1). In multivariable analysis controlling for sex of contact and type of contact, independent risk factors for LTBI included being a contact of an index TB case that completed treatment, (aOR 3.25, 95% CI 1.20–8.78), was lost to follow-up (aOR 3.67, 95% CI 1.13–11.89) or failed treatment (aOR 7.75, 95% CI 2.05–29.32) as compared to contacts of TB cases with a prior outcome of cure (Table 2).

IV. DISCUSSION

To our knowledge, our investigation is the first to report that contacts of index patients with active TB disease who were retreatment cases had a significantly higher risk of having LTBI based on a prior unfavorable treatment outcome among the index TB case. The risk of LTBI appeared to be dose-dependent based on the outcome of the index TB case’s previous TB treatment. This novel result highlights the importance of completing TB treatment regimens and curing patients, especially in countries like Georgia, where the loss to follow-up rate among MDR-patients is high. Index cases whose initial treatment regimen was not successful were likely to remain infectious for prolonged periods of time resulting in a greater risk of transmission of Mycobacterium tuberculosis among their contact. Therefore, efforts aimed at reducing treatment loss to follow-up should enhance TB control efforts and may also decrease LTBI and active TB among contacts.

Acknowledgements

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<table>
<thead>
<tr>
<th>Highlights</th>
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<tbody>
<tr>
<td>- Risk of LTBI in contacts depends on the outcome of index case’s previous treatment.</td>
</tr>
<tr>
<td>- Prevalence of LTBI is higher in contacts of index patients with unfavorable outcome.</td>
</tr>
<tr>
<td>- More efforts should be aimed at reducing patient loss to follow-up.</td>
</tr>
</tbody>
</table>
Table 1

Association of index case previous TB treatment outcome and prevalence of LTBI among their contacts

<table>
<thead>
<tr>
<th>Index TB case outcome of previous TB treatment</th>
<th>Contacts with \textsuperscript{a} LTBI (%) N=46</th>
<th>Contacts without LTBI (%) N=93</th>
<th>OR\textsuperscript{b} (95% CI\textsuperscript{c})</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>8 (15.1)</td>
<td>45 (84.9)</td>
<td>1.00</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Completed</td>
<td>16 (37.2)</td>
<td>27 (62.8)</td>
<td>3.33 (1.26–8.82)</td>
<td>0.01</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>14 (50.0)</td>
<td>14 (50.0)</td>
<td>5.63 (1.96–16.16)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Failure</td>
<td>8 (53.3)</td>
<td>7 (46.7)</td>
<td>6.43 (1.81–22.72)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Latent tuberculosis infection

\textsuperscript{b}Odds ratio

\textsuperscript{c}Confidence interval
Table 2

Prevalence of latent tuberculosis infection (LTBI) among contacts of index tuberculosis (TB) retreatment cases based on the index patient’s prior TB treatment outcome.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(aOR^a) (N=131)</th>
<th>95% CI(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome Completed vs Cured</td>
<td>3.25</td>
<td>1.20–8.78</td>
</tr>
<tr>
<td>Outcome loss to follow-up vs Cured</td>
<td>3.67</td>
<td>1.13–11.89</td>
</tr>
<tr>
<td>Outcome Failure vs Cured</td>
<td>7.75</td>
<td>2.05–29.32</td>
</tr>
<tr>
<td>Household vs Non-household contact</td>
<td>3.03</td>
<td>0.76–12.08</td>
</tr>
<tr>
<td>Male contacts vs Female contacts</td>
<td>1.57</td>
<td>0.69–3.55</td>
</tr>
</tbody>
</table>

\(^a\) Adjusted odds ratio. The model included all variables in the table.

\(^b\) Confidence interval