LETTER TO THE EDITOR

Tuberculosis and leprosy infections in the Marshallese population of Arkansas, USA

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Summary The cross-immunity between tuberculosis and leprosy is unknown. The aim of this pilot study was to evaluate the occurrence of Mycobacterium tuberculosis and M. leprae infection in Marshallese adult volunteers in Springdale, Arkansas, U.S.A., a population that experiences high rates of leprosy and tuberculosis. We used immunodiagnostic testing for tuberculosis and leprosy infection and found significant prevalence of latent tuberculosis infection (19.0%), and asymptomatic Mycobacterium leprae infection (22.2%). We found a negative association between presence of antibodies to Mycobacterium leprae and a positive interferon-γ release assay for Mycobacterium tuberculosis infection, prevalence odds ratio = 0.1 (95% CI = 0.0, 0.9). Although these findings require confirmation on a larger scale, they are supportive of the existence of cross-immunity.


**Introduction**

The Marshallese population in Arkansas, USA, tripled from 1996 to 2012. According to records available to the Arkansas Department of Health (ADH), the age-adjusted reported incidence of tuberculosis (TB) in 2009–2012 among the Marshallese in Washington County, Arkansas was 248.7 per 100,000 compared to three per 100,000 for the US. The corresponding rate of newly diagnosed cases of leprosy in 2009–2012 in Marshallese living in Washington County, Arkansas was 77 per 100,000 compared to 0.05 per 100,000 for the entire country.

The existence of cross-immunity across mycobacterial species was postulated by Chaussinand and Fernandez. Actual data on populations in which both markers of tuberculosis or latent TB infection (LTBI), and leprosy or asymptomatic *M. leprae* infection is sparse. Here, we present data on markers of both mycobacterial infections among Marshallese in Arkansas.

**Aims**

To assess *M. tuberculosis* and *M. leprae* infections in a sample of Marshallese adults in Arkansas.

**Methods**

Our study protocol was reviewed and approved by IRB of University of Arkansas for Medical Sciences (Protocol 202692). Adult volunteers were recruited through the ADH Joseph Bates outreach clinic in Springdale. Fifteen of the volunteers were known cases of TB (*n* = 7), LTBI (*n* = 1) or leprosy (*n* = 7). In 25 of these subjects we obtained blood samples to test for *Mycobacterium leprae* infection using the Leprosy Detect™ fast ELISA (InBios International, Seattle, WA) which detects antibodies to phenolic glycolipid I and the LID-1 fusion protein. This test has been found to have a sensitivity of 96% and a specificity of 93% to detect multibacillary leprosy. Specimens were submitted for an enzyme-linked immunospot assay (T.SPOT) which detects T-lymphocytes sensitised to early secretory antigenic target-6 and culture filtrate protein 10 antigens specific to *Mycobacterium tuberculosis*, which are absent in BCG and environmental mycobacteria.

**Results**

To assess the prevalence asymptomatic *M. leprae* infection we excluded people that came into the study with leprosy (*n* = 7). Among the remaining participants the prevalence of antibodies to *M. leprae* was 22.2% or (4/18) (Mid-P 95% CI: 7.4%, 45.3%) and was unrelated to age. Upon clinical examination none of the people with positive Leprosy Detect™ fast ELISA had changes in skin sensitivity to temperature or skin lesions suggestive of leprosy. Thus, among Marshallese in Springdale, Arkansas, we found that about a fifth had antibodies to *M. leprae* at levels suggestive of latent infection. Excluding participants who were known to have TB or LTBI, four of 21 participants examined tested positive to the T.SSPOT test, indicating a prevalence of LTBI of 19.0% (Mid-P 95% CI: 6.4%, 39.8%). This seemed to
increase by age but the differences by age were not statistically significant (Table 1). All subjects that tested positive to T.SPOT subsequently received standard treatment.

To assess co-infections, we restricted the analysis to the subset of 25 subjects with complete data on T.SPOT and the Leprosy Detect™ fast ELISA (Table 2), including known HD and TB or LTBI patients.

While most subjects (68% or 17/25) were positive to the leprosy ELISA or the T.SPOT test, only one subject was positive to both, and seven were negative in both assays (Fisher’s exact two-tailed P-value = 0.04). Those with elevated antibodies to *M. leprae* were less likely to have a positive T.SPOT test (odds ratio = 0.1; 95% CI = 0.0, 0.9). Thus, as determined by levels of antibodies to highly specific *M. leprae* glycolipid I and the LID-1 fusion protein and *in vivo* reactivity to *M. tuberculosis* using an interferon-γ release assay, we found a negative association between *M. leprae* and *M. tuberculosis* infections. When the known cases of TB, LTBI and leprosy cases were excluded, we found none of the subjects had both infections, three had *M. leprae* infection, and four had LTBI, and six had neither (Fisher’s exact two-tailed P-value = 0.5).

**Discussion**

As expected based on morbidity reports to the ADH, the Marshallese in Arkansas experienced high prevalence of leprosy and tuberculosis. In comparison, serum antibodies to phenolic glycolipid I were found in only three (0.7%) among 426 subjects of Chicago.\(^6\) Also, for comparison, only 5.2% of 2,418 US healthcare workers tested positive to a T.SPOT test,\(^7\) which were consistent with estimates of the prevalence of LTBI from the NHANES which used the tuberculin skin test for US adults (5.0% to 6.5%).\(^8\)

### Table 1. Prevalence of latent tuberculosis infection and asymptomatic *M. leprae* infection among adult Marshallese volunteers, Springdale, Arkansas, 2014

<table>
<thead>
<tr>
<th>Age Groups (yrs.)</th>
<th>Latent TB Infection</th>
<th>Asymptomatic <em>M. leprae</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tested*</td>
<td>Positive (%)</td>
</tr>
<tr>
<td>18–29</td>
<td>7</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>30–39</td>
<td>6</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>40–72</td>
<td>8</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>4 (19.1)</td>
</tr>
</tbody>
</table>

*following exclusion of known cases of TB or LTBI; **following exclusion of known HD

### Table 2. Prevalence of antibodies to *M. leprae* and interferon-γ release assay results among adult Marshallese volunteers, Springdale, Arkansas, 2014

<table>
<thead>
<tr>
<th>Anti-<em>M. leprae</em> Antibodies (row %)</th>
<th>T.SPOT Interferon-γ release assay</th>
<th>Total (column %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Present</td>
<td>1 (10.0)</td>
<td>9</td>
</tr>
<tr>
<td>Absent</td>
<td>8 (53.3)</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>9 (36.0)</td>
<td>16</td>
</tr>
</tbody>
</table>

Odds ratio = 0.1 (95% CI = 0.0, 0.9) Fisher’s Exact P-value = 0.04
The study documents a high burden of these infections in a US population. Simulations predicted screening and treatment of LTBI among the foreign-born could result in achieving the eradication goals for this group 20 years earlier.\textsuperscript{9–10} It should also be noted that leprosy from imported cases has not resulted in local transmission in the US,\textsuperscript{11} while LTBI among foreign born results mostly in cases among close contacts.\textsuperscript{12} Universal screening for LTBI and \textit{M. leprae} infection in this population followed-up by examination and treatment for these infections might be appropriate. These data is also relevant to the Marshall Islands, a state in free association with the United States. Research is urgently needed to assess the feasibility and cost-effectiveness of those interventions.

**Limitations**

Our study was small, enriched by known cases of leprosy and TB or LTBI and was not done on a probability sample.

**Acknowledgements**

We are thankful to Ms. Wanna Bing and Mr. Kenny Boaz, the other two dedicated and well trained professionals with the Arkansas Department of Health who also conducted interviews, examinations, measurements and phlebotomies. We appreciate the support of Minority Health Commissioner Ms. Melissa Laelan for her leadership and translation of the informed consent forms. We also want to thank the Republic of the Marshall Islands Consul in Springdale, AR, Ms. Carmen Chung-Gum for her support.

**References**