The Bacteriologic Yield in Children with Intrathoracic Tuberculosis

B. J. Marais,1,2 A. C. Hesseling,1,2 R. P. Gie,1,2 H. S. Schaaf,1,2 D. A. Enarson,2 and N. Beyers1,2
1Desmond Tutu TB Centre and 2Department of Paediatrics and Child Health, Tygerberg Children’s Hospital, Stellenbosch University, Cape Town, South Africa; and 3International Union Against Tuberculosis and Lung Disease, Paris, France

This report documents the bacteriologic yield in children who received treatment for intrathoracic tuberculosis in an area where it is highly endemic. A total of 307 children were included in the study, and bacteriologic confirmation was achieved in 122 (62.2%) of 196 children from whom specimens were collected. The lowest bacteriologic yield was recorded for the 69 children with uncomplicated lymph node disease (24 [34.8%] had bacteriologic confirmation). The high overall bacteriologic yield indicates the need to reassess the value of bacteriology-based approaches to diagnosis of intrathoracic tuberculosis in children, particularly in areas of endemicity where they frequently present with advanced disease.

The diagnosis of childhood tuberculosis is complicated by the absence of a practical gold standard test due to the difficulty of collecting bacteriologic specimens and the reportedly low bacteriologic yield [1]. It has been reported that *M. tuberculosis* is isolated from 10%–15% [2, 3].

Bacteriologic confirmation is rarely attempted in children, particularly in areas where tuberculosis is highly endemic, because of resource limitations and the expected low yield. However, bacteriologic confirmation may have particular value in these areas, where epidemiologic indicators such as known exposure to and/or proven infection with *M. tuberculosis* contribute little diagnostic value. In addition to providing a definitive diagnosis, isolation of *M. tuberculosis* offers opportunities for drug susceptibility testing and molecular investigation. The aim of this study was to document the proportion of children given treatment for intrathoracic tuberculosis in an area of high endemicity who had bacteriologic confirmation.

**Methods.** A prospective, community-based, observational study was conducted from 1 February 2003 through 31 October 2004 in Cape Town, South Africa. Five primary health care clinics, all using the same referral hospital (Tygerberg Children’s Hospital, Cape Town), were selected. The people living in the study area rarely access private medical services, and children who receive a diagnosis of tuberculosis are routinely referred to their local primary health care clinic for treatment. Pediatric services are only accessible to children who are <13 years old.

All children (aged <13 years) from the study area who initiated antituberculosis treatment during the study period were screened by the investigator. The investigator visited each clinic on a weekly basis to evaluate children who received antituberculosis treatment at the primary health care clinic, whereas a study nurse documented those who received antituberculosis treatment in the hospital. The chest radiographs of all children were reviewed, and children with radiographic signs suggestive of intrathoracic tuberculosis were included in the study.

All children underwent standard anteroposterior and lateral chest radiography. Chest radiographs were reviewed by the same 2 independent experts. Findings were documented on a standard report form. All children with radiographic signs suggestive of intrathoracic tuberculosis (even if indicated by only 1 of the 2 independent experts) were included. Disease classification was done on the basis of the most severe disease entity reported, by use of a recently proposed radiological classification system for childhood intrathoracic tuberculosis [4]. Children without any radiographic signs suggestive of intrathoracic tuberculosis were excluded.

For all children, an attempt was made to collect at least 1 respiratory specimen for mycobacterial culture. However, for children whose tuberculosis was diagnosed at the referral hospital, multiple specimens were collected as part of a separate hospital-based study that aimed to compare the bacteriologic yield achieved with different specimen-collection methods. Specimens collected included gastric aspirates, nasopharyngeal aspirates, induced and uninduced sputum, and pleural fluid aspirates. Samples were routinely inoculated into liquid broth by use of either the Bactec or the MGIT system (Becton Dickinson). *M. tuberculosis* was confirmed by PCR speciation.

Routine specimens were defined as the first 2 gastric aspirates and/or uninduced sputum specimens collected. Bacteriologic
confirmation was defined as culture confirmation of *M. tuberculosis* or the presence of acid-fast bacilli on sputum microscopy.

Parents gave separate written informed consent for study participation and HIV testing. Ethics approval was obtained from the Institutional Review Board of Stellenbosch University, from the City of Cape Town Health Department, and from local health care committees.

**Results.** During the study period, 439 children received antituberculosis treatment (data on the complete cohort are described elsewhere [5]), 307 of whom had radiographic signs suggestive of intrathoracic tuberculosis. The sex distribution was equal (152 boys [49.5%]). The age distribution was as follows: 230 (74.9%) of the children were <5 years old, 53 (17.3%) were 5–9 years old, and 24 (7.8%) were ≥10 years old. The majority of children (211 [68.7%]) were tested for HIV, and 17 (8.1%) were found to be infected with HIV.

Table 1 reflects the intrathoracic disease manifestations documented and the proportion with bacteriologic confirmation. Uncomplicated lymph node disease was the most frequently documented intrathoracic disease manifestation (147 [47.9%] of 307). Adult-type disease was documented in 14 (4.6%) of the children, and all 14 had bacteriologic confirmation. This was the only group that included children who had sputum smears tested; 7 (70%) of the 10 children for whom sputum smear microscopy was performed had positive test results.

Overall, 122 (62.2%) of the 196 children from whom specimens were collected had bacteriologic confirmation; 102 (55.7%) of 183 children had bacterial confirmation when only routine specimens were included in the analysis. In children with intrathoracic disease manifestations other than uncomplicated lymph node disease, 98 (77.2%) of 127 had bacteriological confirmation, which was significantly higher than the yield in those with uncomplicated lymph node disease (22 [34.8%] of 69) (OR, 6.3; 95% CI, 3.2–12.8). The significance persisted when only routine specimens were included in the analysis (81 [71.0%] of 114 vs. 21 [30.4%] of 69) (OR, 5.6; 95% CI, 2.8–11.4).

**Discussion.** The majority of children given treatment for intrathoracic tuberculosis in this area where it is highly endemic had bacteriologic confirmation. Possible reasons for this unexpected high yield are (1) the selection criteria that were applied, as children without any radiographic sign suggestive of intrathoracic tuberculosis were excluded; (2) the diligence with which specimens were collected and cultured, as the high yield persisted despite the exclusion of nonroutine specimens from the analysis; (3) the community-based approach, as hospital-based studies tend to accumulate more children with alternative diagnoses and radiographic signs that are difficult to interpret; and (4) the fact that many children presented with advanced intrathoracic disease, as <50% were classified as having uncomplicated lymph node disease.

Although uncomplicated lymph node disease (often considered the typical manifestation of childhood tuberculosis) was the most common disease entity, it was documented in only 47.9% of children. The fact that the bacteriologic yield was the lowest in this group may explain the low bacteriologic yields reported from areas of nonendemicity where active contact-tracing programs are usually well established. Therefore, the majority of children receive diagnoses at a very early stage (i.e., when they have uncomplicated lymph node disease [6]), and few present with advanced disease.

To our knowledge, the bacteriologic yield in children treated for intrathoracic tuberculosis in an area of high endemicity has not been reported before. However, similar and even higher bacteriologic yields have been described in select patient groups, such as children with lymph node disease complicated by expansile tuberculous pneumonia [7] and infants who frequently develop rapidly progressive disease [8, 9]. These studies support the observation that the bacteriologic yield is primarily influenced by the type of radiographic disease manifestation recorded. Radiographic disease manifestations show clear age-related patterns in children [10]. In this study, the bacteriologic yield did differ according to age, but the age-related effect disappeared when the specific radiologic disease manifestation was taken into account, which illustrates the importance of accurate disease classification [4].

The main study limitations were the fact that bacteriologic

<table>
<thead>
<tr>
<th>Disease manifestation</th>
<th>No. (%)</th>
<th>Proportion (%)</th>
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<tbody>
<tr>
<td>Ghon focus</td>
<td>4 (1.3)</td>
<td>4/4 (100)</td>
</tr>
<tr>
<td>Primary (Ghon) complex</td>
<td>15 (3.6)</td>
<td>5/9 (55.6)</td>
</tr>
<tr>
<td>Lymph node disease</td>
<td></td>
<td></td>
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<tr>
<td>Uncomplicated</td>
<td>147 (47.9)</td>
<td>24/69 (34.7)</td>
</tr>
<tr>
<td>Complicated</td>
<td>17 (5.6)</td>
<td>9/17 (52.9)</td>
</tr>
<tr>
<td>Airway compression</td>
<td>25 (8.1)</td>
<td>10/18 (55.6)</td>
</tr>
<tr>
<td>Parenchymal consolidation</td>
<td>62 (20.6)</td>
<td>40/49 (81.6)</td>
</tr>
<tr>
<td>Pleurisy</td>
<td>24 (7.8)</td>
<td>10/17 (58.8)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1 (0.3)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Disseminated (miliary) disease</td>
<td>15 (4.9)</td>
<td>14/15 (93.3)</td>
</tr>
<tr>
<td>Adult-type disease</td>
<td>14 (4.6)</td>
<td>14/14 (100)</td>
</tr>
<tr>
<td>All</td>
<td>307 (100)</td>
<td>122/196 (62.2)</td>
</tr>
</tbody>
</table>

* The numerator is the number of children who had bacteriologic confirmation (a positive culture result for *Mycobacterium tuberculosis* or the presence of acid-fast bacilli in sputum), and the denominator is the number of children from whom specimens were collected. The percentage with bacteriologic confirmation is in parentheses.

* Three of these 14 children had positive results for sputum smears only, as no cultures were performed.
confirmation was not attempted with equal vigor in all children. The multiple specimens collected at the referral hospital may have introduced sampling bias. We attempted to correct for possible sampling bias by restricting the analysis to routine samples only. However, a more rigorous evaluation of the association between disease severity and bacteriologic yield and a comparison between different specimen collection methods will require accurate disease classification and standardized procedures for specimen collection.

In this area of high endemicity, an unexpectedly high proportion of children treated for intrathoracic tuberculosis had bacteriologic confirmation. This finding indicates a need to reassess the value of bacteriology-based approaches to diagnosis of intrathoracic tuberculosis in children, particularly in areas of endemicity where children frequently present with advanced disease.

Acknowledgments

We thank Dr. Carl Lombard from the Medical Research Council of South Africa (MRC), for assistance with the statistical analysis, and the primary health care clinics, the patients, and their parents, for their participation. The study was done in partial fulfillment of a Ph.D. thesis.

Financial support. MRC and the US Agency for Aid and International Development.

Potential conflicts of interest. All authors: no conflicts.

References