Screening tests for active pulmonary tuberculosis in children & adolescents: a systematic review

Bryan Vonasek¹,², Tara Ness¹, Yemisi Takwoingi³, Alexander W Kay¹, Susanna van Wyk⁴, Laura Ouellette⁵, Ben J Marais⁶, Karen R Steingart⁷,a, Anna M Mandalakas¹,a

¹Global Tuberculosis Program, Baylor College of Medicine, Houston, Texas, USA
²University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA
³Test Evaluation Research Group, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
⁴Centre for Evidence-based Health Care, Epidemiology and Biostatistics, Department of Global Health, Organisation: Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
⁵Texas Medical Center Library, Houston, Texas, USA
⁶Marie Bashir Institute for Infectious Diseases and Biosecurity, University of Sydney, Sydney, Australia
⁷Honorary Research Fellow, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

ᵃThese authors contributed equally to this work
% of TB patients that are missed in different age groups

- TB reporting gap is biggest among younger children
- 69% of TB patients under 5 years are missed
- 40% of TB patients 5-14 years are missed
- 35% of TB patients All other ages combined are missed

- 31% of TB patients under 5 years are reported
- 60% of TB patients 5-14 years are reported
- 65% of TB patients All other ages combined are reported

TB missed (under-diagnosis and under-reporting)
TB reported
Background

Proportions of estimated 239,000 TB deaths in children aged <15 year in 2015
Primary Objective:

Determine the accuracy of screening tests for pulmonary tuberculosis in children & adolescents in high-risk groups
Differentiating Screening from Diagnosis

Close TB contacts

Living w/ HIV

Pneumonia Malnourished

Aged <5 years
Index Tests

1. One of multiple symptoms (symptom ‘clusters’)
2. Chest Radiography
   – Any abnormality
   – Abnormality suggestive of TB
3. Xpert MTB/RIF

Reference Standards

1. Microbiological (MRS): solid or liquid culture, Xpert MTB/RIF, or Xpert Ultra on a respiratory specimen
2. Composite (CRS):
   • Microbiological confirmation OR
   • Clinically diagnosed pulmonary TB
Reference Standards

Adapted from Drain PK, et al. 2019
TB in Children: Chest Radiography
TB in Children: Challenges in Diagnosis

• Respiratory infections in children are common
  – Much overlap with signs, symptoms, and radiographic findings of TB
• Many settings lack CXR or expertise for interpreting CXR
• Microbiological confirmation is complicated by:
  1. Young children can’t expectorate sputum
     – Typically rely on gastric lavage or induced sputum
  2. Paucibacillary disease: number of bacilli causing disease in children tends to be low
     – Even when culturing multiple specimens, typically less than half of child TB cases have microbiologic confirmation

Diagnosis of child TB:
Clinical >> Microbiological
Study Inclusion Criteria

• Study designs: cross-sectional, cohort (retrospective or prospective), RCTs
• Data available for individuals <20 years
• Index test(s) applied with screening, rather than diagnostic, intent
• Index test(s) reported against qualifying MRS or CRS
• If extrapulmonary TB described, must be <20% of cases
• With required reference standards implying pulmonary disease, studies not specifying “pulmonary” TB were included
PRISMA Diagram

Identification

Additional records identified through contacting the community of TB experts (n = 9)
Records identified through database searching (Medline OVID, Embase, Scopus, Cochrane Library) (n = 2135)
Records after duplicates removed (n = 2131)

Screening

Abstracts screened (n = 2131)
Records excluded as irrelevant (n = 1521)

Eligibility

Full-text articles assessed for eligibility (n = 610)
Full-text articles excluded (n = 594)
- Data not available for specific age (230)
- No included index tests (207)
- Full text not available (65)
- Wrong study design (51)
- No included reference test (33)
- Diagnostic study (5)
- Duplicate (2)
- Wrong outcomes (1)

Included

Studies included from database search (n = 16)
Overall studies included (n = 25)
## Characteristics of 25 Included Studies

<table>
<thead>
<tr>
<th>First Author</th>
<th>Publication Year</th>
<th>Country or Countries of Sampling</th>
<th>Sampling in High Burden TB Country?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggerbeck</td>
<td>2018</td>
<td>South Africa</td>
<td>Yes</td>
</tr>
<tr>
<td>Arscott-Mills</td>
<td>2014</td>
<td>Botswana</td>
<td>No</td>
</tr>
<tr>
<td>Birungi</td>
<td>2018</td>
<td>Rwanda</td>
<td>No</td>
</tr>
<tr>
<td>Chiappini</td>
<td>2019</td>
<td>Italy</td>
<td>No</td>
</tr>
<tr>
<td>Clemente</td>
<td>2017</td>
<td>Italy</td>
<td>No</td>
</tr>
<tr>
<td>Dorjee</td>
<td>2018</td>
<td>India</td>
<td>Yes</td>
</tr>
<tr>
<td>Dreesman</td>
<td>2017</td>
<td>Belgium</td>
<td>No</td>
</tr>
<tr>
<td>Jaganath</td>
<td>2013</td>
<td>Uganda</td>
<td>No</td>
</tr>
<tr>
<td>Kruk</td>
<td>2008</td>
<td>South Africa</td>
<td>Yes</td>
</tr>
<tr>
<td>LaCourse</td>
<td>2014</td>
<td>Malawi</td>
<td>No</td>
</tr>
<tr>
<td>Mahomed</td>
<td>2013</td>
<td>South Africa</td>
<td>Yes</td>
</tr>
<tr>
<td>Malik</td>
<td>2018</td>
<td>Pakistan</td>
<td>Yes</td>
</tr>
<tr>
<td>Marais</td>
<td>2006</td>
<td>South Africa</td>
<td>Yes</td>
</tr>
<tr>
<td>Portevin</td>
<td>2014</td>
<td>Tanzania</td>
<td>Yes</td>
</tr>
<tr>
<td>Rose</td>
<td>2012</td>
<td>Tanzania</td>
<td>Yes</td>
</tr>
<tr>
<td>Sawry</td>
<td>2018</td>
<td>South Africa</td>
<td>No</td>
</tr>
<tr>
<td>Schwoebel</td>
<td>2020</td>
<td>Benin, Burkina Faso, Cameroon, &amp; CAR</td>
<td>Only one of four (CAR)</td>
</tr>
<tr>
<td>Tieu</td>
<td>2014</td>
<td>Thailand</td>
<td>Yes</td>
</tr>
<tr>
<td>Togun</td>
<td>2016</td>
<td>The Gambia</td>
<td>No</td>
</tr>
<tr>
<td>Togun</td>
<td>2015</td>
<td>The Gambia</td>
<td>No</td>
</tr>
<tr>
<td>Triasih</td>
<td>2015a</td>
<td>Indonesia</td>
<td>Yes</td>
</tr>
<tr>
<td>Triasih</td>
<td>2015b</td>
<td>Indonesia</td>
<td>Yes</td>
</tr>
<tr>
<td>Ustero</td>
<td>2017</td>
<td>Eswatini (Swaziland)</td>
<td>Yes</td>
</tr>
<tr>
<td>Vonasek</td>
<td>2019</td>
<td>Botswana, Eswatini, Lesotho, Malawi, Tanzania, &amp; Uganda</td>
<td>Two of six</td>
</tr>
</tbody>
</table>

Range: 2006 to 2020

**Sub-Saharan Africa: 17 studies**
- Asia: 5 studies
- Europe: 3 studies

High-Burden Countries: 15 studies
<table>
<thead>
<tr>
<th>Population</th>
<th>Index Test/Screen</th>
<th>Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>TB close contact</td>
<td>Composite</td>
</tr>
<tr>
<td>General population</td>
<td>Cough</td>
<td>Composite</td>
</tr>
<tr>
<td>All risk groups</td>
<td>Nutrition status</td>
<td>Composite</td>
</tr>
<tr>
<td>Accessing healthcare</td>
<td>Xpert MTB/RIF</td>
<td>Microbiological</td>
</tr>
<tr>
<td>Accessing healthcare</td>
<td>Nutrition status</td>
<td>Microbiological</td>
</tr>
<tr>
<td>Accessing healthcare &amp; &lt; 5 y/o</td>
<td>Suggestive CXR</td>
<td>Composite</td>
</tr>
<tr>
<td>Accessing healthcare &amp; &lt; 5 y/o</td>
<td>Cough, fever, or decreased playfulness</td>
<td>Composite</td>
</tr>
<tr>
<td>TB close contacts</td>
<td>Abnormal CXR</td>
<td>Composite</td>
</tr>
<tr>
<td>TB close contacts</td>
<td>Suggestive CXR</td>
<td>Composite</td>
</tr>
<tr>
<td>TB close contacts</td>
<td>Nutrition status</td>
<td>Composite</td>
</tr>
<tr>
<td>TB close contacts</td>
<td>Cough, fever, or poor weight gain</td>
<td>Composite</td>
</tr>
<tr>
<td>HIV outpatients</td>
<td>ICF symptom screen</td>
<td>Composite</td>
</tr>
<tr>
<td>Active pneumonia &amp; &lt;5 y/o</td>
<td>Abnormal CXR</td>
<td>Microbiological</td>
</tr>
</tbody>
</table>
Index Test: Chest radiography with any abnormality
Reference Standard: composite
Population: children and adolescent close TB contacts

8 studies, 3513 individuals
Prevalences: 2% to 25%
Pooled sensitivity: 0.87 (0.75 to 0.93)
Pooled specificity: 0.98 (0.68 to 1.00)
Index Test: WHO-recommended four-symptom screen

Reference Standard: composite

Population: children and adolescents living with HIV

Adults and adolescents living with HIV and screened for TB with a clinical algorithm and who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases.

*Strong recommendation, moderate quality of evidence*

Children living with HIV who have any one of the following symptoms – poor weight gain*, fever, current cough or contact history with a TB case – may have TB and should be evaluated for TB and other diseases.

*Strong recommendations, low quality of evidence*

2 studies; 20,926 individuals; 203,135 screens

Prevalences: 3% and 7%

Pooled sensitivity: 0.61 (0.58 to 0.64)

Pooled specificity: 0.94 (0.86 to 0.98)
Going Forward

- Ongoing dissemination of findings
- WHO TB Screening guideline update
- Systematic review of TST & IGRA to screen for active TB
- Overall limited research evaluating TB screening in children; future studies should:
  - Use both composite & microbiologic reference standards
  - Apply the reference standard to all, not just those with positive screens
  - Assess sequential and parallel strategies utilizing complementary strategies (eg. symptom screen→CXR)
Acknowledgements

• Support from:
  o Liverpool School of Tropical Medicine
  o Department for International Development (DFID)
  o WHO Global TB Programme
• Vittoria Lutje of the Cochrane Infectious Disease Group
• Annemieke Brands, Dennis Falzon, Tamara Kredo, Cecily Miller, and Sabine Verkuijl of the WHO
• Child and Adolescent TB Working Group