Treatment-decision algorithms for childhood pulmonary TB: Review of individual-patient data (IPD)

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Annual meeting of the Child and Adolescent TB Working Group
Disclosures & Conflicts of Interest

• Agreement for Performance of Work from WHO
• The reviewer team led development of the Gunasekera et al., 2021 Algorithm that is evaluated
• The reviewer team has had scientific input from individuals involved in development of other algorithms being evaluated in this review (Marcy et al., 2019, Marais et al., 2006)
Diagnostic challenges for child pulmonary TB (PTB) contribute to child mortality

% TB missed by age group

- 0-4 years: 65% missed, 35% reported
- 5-14 years: 49% missed, 51% reported
- All <15 years: 56% missed, 44% reported
- All >15 years: 25% missed, 75% reported

Box 1. Guidance on approach to diagnosis of TB in children
- Careful history (including history of TB contact and symptoms consistent with TB)
- Clinical examination (including growth assessment)
- Tuberculin skin testing
- Chest X-ray (if available)
- Bacteriological confirmation whenever possible
- Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB
- HIV testing

WHO 2020
Scores/algorithms standardize rapid treatment decision-making

A Treatment-Decision Score for HIV-Infected Children With Suspected Tuberculosis

Marcy et al. Pediatrics. 2019

Development of a Treatment-decision Algorithm for Human Immunodeficiency Virus–uninfected Children Evaluated for Pulmonary Tuberculosis

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Clinical history/physical evaluation
Chest radiography
Bacteriology

Gunasekera et al. Clin Infect Dis 2021
ESTABLISH A LARGE, GEOGRAPHICALLY DIVERSE DIAGNOSTIC EVALUATIONS DATASET OF CHILDREN BEING EVALUATED FOR PTB

1. Evaluate existing scores/algorithms
2. Develop a data-driven algorithm
ASSEMBLE INDIVIDUAL PARTICIPANT DATA OF CHILDREN BEING EVALUATED FOR PTB
Data reflects population of children brought to healthcare with PTB symptoms

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Clinical evaluation</th>
<th>Diagnostic tests and imaging</th>
<th>Reference classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Sex HIV-status Weight Height</td>
<td>Cough (duration) Fever (duration) Lethargy Weight loss Known contact w/ TB Temperature Heart rate Respiratory rate Etc.</td>
<td>Chest X-Ray <em>Features seen on chest X-ray</em> Rapid molecular test</td>
<td>TB (confirmed and unconfirmed) <em>OR</em> Unlikely TB</td>
</tr>
</tbody>
</table>
Total size: 4811

% TB: 38%

Age (months) median [IQR]: 26 [13.4-58.25]

% HIV-positive: 20%

% Severely acutely malnourished: 14%

Study population included
Reasonable attempts to handle imperfect data

### Missing data

<table>
<thead>
<tr>
<th>Study</th>
<th>Cough</th>
<th>CXR-nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) A</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2) A</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>3) B</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>4) B</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>5) B</td>
<td>1</td>
<td>NA</td>
</tr>
</tbody>
</table>

### Heterogeneous definitions

- i.e., weight loss:
  - Failure to thrive
  - Caregiver-reported weight loss
  - $<-2$ standard deviations below mean weight-for-age Z-score

### MICE: Multiple Imputation by Chained Equations

### Collapsed heterogeneous definitions where reasonable
1. EVALUATE EXISTING SCORES/ALGORITHMS
Selected key algorithms/scores to evaluate ability to discriminate TB vs. non-TB

<table>
<thead>
<tr>
<th>Algorithms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Union Desk Guide</td>
</tr>
<tr>
<td>2) Uganda National TB/Leprosy Control Program Algorithm</td>
</tr>
<tr>
<td>3) Brazilian Ministry of Health Child PTB Scoring System (cutoff of at least 30)</td>
</tr>
<tr>
<td>4) Gunasekera et al., 2021 Algorithm (HIV-negative children)</td>
</tr>
<tr>
<td>5) Keith Edward Score</td>
</tr>
<tr>
<td>6) Marcy et al., 2019 Algorithm (children living with HIV)</td>
</tr>
<tr>
<td>7) Stegen-Toledo Score (cutoff of at least 5)</td>
</tr>
<tr>
<td>8) Marais et al., 2006 Criteria</td>
</tr>
</tbody>
</table>
Modifications to scores/algorithms if IPD data not available

Example: Uganda National TB/Leprosy Control Program Algorithm

- Excluded
  - Antibiotic treatment history
  - Acute/recurrent pneumonia
  - Spinal deformity
TB is suspected on basis of typical and persistent symptoms

Sputum smear/Xpert negative or not done

Sputum smear or Xpert positive

- Positive contact history
- Physical signs suggestive of PTB*
- Chest radiograph (CXR) suggestive of PTB

If only one or none of the features are present

Make a diagnosis of TB if two or more of these features are present

IF CHILD SICK, ADMIT TO HOSPITAL FOR FURTHER INVESTIGATION

IF CHILD WELL, REVIEW AFTER 2-4 WEEKS

TREAT FOR TB
Performance against the Union Desk Guide is varied
2. DEVELOP A DATA-DRIVEN ALGORITHM

1. Prediction modeling in algorithm development
2. Improve prediction in primary care/peripheral health centers
Prediction modeling in data-driven algorithm development

<table>
<thead>
<tr>
<th>Clin Eval + Testing Model</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough Duration</td>
<td></td>
</tr>
<tr>
<td>Cough &lt; 1 week</td>
<td>0.62</td>
</tr>
<tr>
<td>Cough 1-2 weeks</td>
<td>1.29</td>
</tr>
<tr>
<td>Cough 2-3 weeks</td>
<td>1.35</td>
</tr>
<tr>
<td>Cough &gt; 3 weeks</td>
<td>2.48</td>
</tr>
<tr>
<td>Fever</td>
<td>1.69</td>
</tr>
<tr>
<td>Failure to Thrive</td>
<td>1.80</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1.68</td>
</tr>
<tr>
<td>History of TB Exposure</td>
<td>6.99</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>1.18</td>
</tr>
<tr>
<td>CXR</td>
<td>9.38</td>
</tr>
<tr>
<td>Xpert</td>
<td>90.41</td>
</tr>
</tbody>
</table>

Example from Gunasekera et al., Clin Infect Dis 2021

Scale odds ratio to score
>100 is TB at 90% sensitivity
Considerations in selecting model sensitivity/specificity threshold

<table>
<thead>
<tr>
<th>Decision</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
</table>
| **More sensitive threshold** | • Reduce mortality due to TB disease progression | • Delayed/missed non-TB diagnosis  
• Unnecessary treatment |
| **More specific threshold** | • Pursue non-TB diagnosis | • Mortality due to TB disease progression  
• Lost to follow-up |
Differences between model development and model application populations

Model Development

- Tertiary/Referral
  - ↑ TB Prevalence

Model Application

- Tertiary/Referral
  - ↑ TB Prevalence

- Primary/Peripheral
  - ↓ TB Prevalence
Model performance expected to be consistent in high-TB prevalence, tertiary/referral care setting.
Model performance may be worse in low-TB prevalence, primary/peripheral care setting.

Model Development

- Tertiary/Referral
  - ↑ TB Prevalence

Model Application

- Primary/Peripheral
  - ↓ TB Prevalence

- Tertiary/Referral
  - ↑ TB Prevalence
Adding a triage step to delay treatment for children at low risk of TB-mortality may improve prediction.

Model Development

Children at low-risk of TB mortality only enter model after 1-2 weeks follow-up.

Model Application

↑ TB Prevalence

Tertiary/Referral

↑ TB Prevalence

Primary/Peripheral (w/ triage)

↑ TB Prevalence
Triage

Prediction Model

Assess for danger signs

Stratify by risk of progression of TB
- Higher risk, proceed
- Lower risk, follow-up before entering model

Prediction model to classify TB vs. non-TB
Need to be humble about algorithm sensitivity/specificity expectations on implementation.
Limitations

1. Imperfect reference standard
2. Heterogeneous inclusion criteria, variable definitions
3. Missing data
4. No external validation

Strengths and future work

1. Evidence-based approach to treatment decision-making
2. Framework for future
   1. Better reference standard
   2. POC biomarkers
3. Future: External validation
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IPD treatment-decision algorithm development

Assembled large, geographically diverse cohort

Estimated the performance of existing scores/algorithms

Developing a prediction model to include in data-driven algorithm to guide childhood pulmonary TB treatment decision-making

Total size: 4811
% TB: 38%
Age (months) median [IQR]: 26 [13.4-58.25]
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