Diagnostic Algorithms to Improve Case Detection

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Presentation overview

- Background
  - Goals of screening for active TB
  - Systematic screening guidelines
  - Diagnostic algorithms
  - Clinical Epidemiology

- Systematic literature review of symptom and CXR screening

- Modelling the yield of 12 diagnostic algorithms

- Rule-out algorithm LTBI guidelines

- Discussion
Goals of systematic screening for active TB (=active case finding)

I. To detect active TB early, and initiate effective treatment
   1. reducing the risk of poor treatment outcomes, health sequelae, adverse social and economic consequences of TB for the individual.
      -> reduces suffering, the prevalence of TB, and death from TB.
   2. reducing TB transmission by shortening of the duration of infectiousness.
      -> reduces incidence of TB infection and consequently incidence of TB disease (weak evidence)

II. Rule out active TB to help identify persons eligible for treatment of latent TB infection

III. Identify persons at increased risk of developing TB in the future.

General principles include: do no harm
   • Avoid unnecessary treatment / overtreatment and stigma


Systematic screening for active tuberculosis: principles and recommendations

WHO has developed guidelines on systematic screening for active tuberculosis (TB) based on a thorough review of available evidence. Early detection of TB is essential to further improve health outcomes for people with TB, and to reduce TB transmission more effectively. Systematic screening in high risk groups is a possible complement to efforts to improve the patient-initiated pathway to TB diagnosis (that is, diagnosing TB among people who actively seek care with TB symptoms, also called “passive case-finding”).

Systematic screening for active TB =

- the systematic identification of people with suspected active TB,
- in a predetermined target group,
- using tests, examinations or other procedures that can be applied rapidly.
Reasons for (s)low case detection

→ Important for strategy to improve case detection

- Patient related barriers
  - Financial
  - Distance
  - Knowledge, beliefs

→ Which populations to target for screening for active TB?

- Health system related
  - Patients with signs and symptoms of active TB are not recognized / not examined

→ Where?

- Recognition of infectious tuberculosis disease
  - In population prevalence surveys: high proportion of asymptomatic TB cases
  - TB≠prolonged cough

→ Which diagnostic algorithm?

Background – Diagnostic Algorithms

Screening tool(s) + Confirmatory test(s)

Symptoms; CXR
Smear microscopy, Xpert MTB/RIF, culture

1 screening tool

2 screening tools

parallel

sequential

Diagram showing different screening algorithms with 1 and 2 screening tools.
Background - Clinical Epidemiology

**Number needed to screen** = the number of persons that need to undergo screening in order to diagnose one person with active TB.

**Sensitivity of a test** = the proportion of people known to have the disease, who test positive for it.
- Low sensitivity $\rightarrow$ missed TB cases $\rightarrow$ low case detection

**Specificity** = the proportion of healthy patients known not to have the disease, who will test negative for it.
- Low specificity $\rightarrow$ high proportion false-positives $\rightarrow$ require confirmatory test or receive unnecessary treatment

Systematic review of symptom and CXR screening

- Evidence to inform choice of screening tools for different settings
  - Protocol: Cochrane library
Number of Screens and included studies by Population

<table>
<thead>
<tr>
<th>Population</th>
<th>Screen</th>
<th>No of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population n=11</td>
<td>1. CXR any abnormality</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2. CXR abnormalities suggestive of TB</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>3. CXR and symptom screening in parallel</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>4. CXR as a 2nd screen</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>5. Prolonged cough</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>6. Cough of any duration</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>7. Any TB Symptom</td>
<td>8</td>
</tr>
<tr>
<td>Asia and sub Saharan Africa</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Prolonged cough</td>
<td>8</td>
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<tr>
<td>Special populations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCT n=2</td>
<td>Cough</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Any Symptom</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>CXR</td>
<td>1</td>
</tr>
<tr>
<td>Homeless n=1</td>
<td>Cough</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Any Symptom</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>CXR</td>
<td>1</td>
</tr>
<tr>
<td>Migrants n=1</td>
<td>CXR</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Any Symptom</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>CXR</td>
<td>1</td>
</tr>
<tr>
<td>Outpatient n=1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupational – Gold Miners n=1</td>
<td>Cough</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Any Symptom</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>CXR</td>
<td>1</td>
</tr>
</tbody>
</table>

- High TB prevalence in study populations (Lowest: 90/100 000 smear+ in Eritrea)
- Few studies from high or middle income countries

Prolonged Cough (≥2 or ≥3 weeks)

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>HIVprev</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>den Boon 2008 (1)</td>
<td>14</td>
<td>34</td>
<td>12</td>
<td>2171</td>
<td>High</td>
<td>0.54 [0.33; 0.74]</td>
<td>0.87 [0.86; 0.89]</td>
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<td></td>
</tr>
<tr>
<td>vanH Hoog 2012</td>
<td>64</td>
<td>2200</td>
<td>1283</td>
<td>18243</td>
<td>High</td>
<td>0.52 [0.43; 0.61]</td>
<td>0.82 [0.78; 0.86]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corbett 2010</td>
<td>37</td>
<td>312</td>
<td>42</td>
<td>8598</td>
<td>High</td>
<td>0.47 [0.36; 0.58]</td>
<td>0.90 [0.86; 0.95]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ayea 2009</td>
<td>34</td>
<td>750</td>
<td>145</td>
<td>7415</td>
<td>High</td>
<td>0.43 [0.32; 0.53]</td>
<td>0.93 [0.83; 0.94]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MoH Cambodia 2005</td>
<td>105</td>
<td>1396</td>
<td>167</td>
<td>20492</td>
<td>Low</td>
<td>0.39 [0.33; 0.45]</td>
<td>0.94 [0.93; 0.94]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoa 2012</td>
<td>71</td>
<td>1429</td>
<td>190</td>
<td>59360</td>
<td>Low</td>
<td>0.28 [0.21; 0.32]</td>
<td>0.95 [0.35; 0.56]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MoH Ghanam 2012</td>
<td>60</td>
<td>1373</td>
<td>244</td>
<td>49830</td>
<td>Low</td>
<td>0.20 [0.15; 0.25]</td>
<td>0.97 [0.97; 0.97]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Datta 2001</td>
<td>18</td>
<td>391</td>
<td>108</td>
<td>15500</td>
<td>Low</td>
<td>0.14 [0.09; 0.22]</td>
<td>0.98 [0.97; 0.98]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pooled estimate

- High HIV prevalence population / SSA (n=4) 49.2% [38.9; 59.7] 92.3% [89.1; 95.6]
- Low HIV prevalence population / Asia (n=4) 24.7% [17.6; 31.7] 96.3% [94.7; 97.9]
- Low and high HIV combined (n=8) 35.2% [24.4; 45.7] 94.7% [92.5; 96.8]
Screens - Sensitivity and Specificity Summary

- CXR screening: higher sensitivity and greater accuracy compared to symptom screening
- Symptom Screening: considerable heterogeneity

Modelling yield of 12 diagnostic algorithms

True positive TB cases detected and False positive TB diagnoses

<table>
<thead>
<tr>
<th>#</th>
<th>Screening method</th>
<th>Confirmatory test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
<td>Second (if 1st positive)</td>
</tr>
<tr>
<td>1</td>
<td>Prolonged Cough*</td>
<td>SSM</td>
</tr>
<tr>
<td>2</td>
<td>Prolonged Cough</td>
<td>Xpert</td>
</tr>
<tr>
<td>3</td>
<td>Prolonged Cough</td>
<td>CXR‡</td>
</tr>
<tr>
<td>4</td>
<td>Prolonged Cough</td>
<td>CXR‡</td>
</tr>
<tr>
<td>5</td>
<td>Any TB Symptom†</td>
<td>SSM</td>
</tr>
<tr>
<td>6</td>
<td>Any TB Symptom</td>
<td>Xpert</td>
</tr>
<tr>
<td>7</td>
<td>Any TB Symptom</td>
<td>CXR‡</td>
</tr>
<tr>
<td>8</td>
<td>Any TB Symptom</td>
<td>CXR‡</td>
</tr>
<tr>
<td>9</td>
<td>CXR abnormality suggestive of TB</td>
<td>SSM</td>
</tr>
<tr>
<td>10</td>
<td>CXR abnormality suggestive of TB</td>
<td>Xpert</td>
</tr>
<tr>
<td>11</td>
<td>Any CXR abnormality</td>
<td>SSM</td>
</tr>
<tr>
<td>12</td>
<td>Any CXR abnormality</td>
<td>Xpert</td>
</tr>
</tbody>
</table>

SSM= Sputum smear microscopy; CD= clinical diagnosis; XP= Xpert MTB/RIF; TB=tuberculosis; CXR= chest X-ray

*Cough for 2-3 weeks or longer  † Any one out of 4-7 symptoms suggestive of TB
§The proportion of persons who receive a clinical diagnosis depends on the negative predictive value of the prior algorithm, as shown in Table 2.

**All persons with a negative first confirmatory test receive a clinical diagnosis.
Choosing algorithms for TB screening: a modelling study to compare yield, predictive value and diagnostic burden

Anna H van’t Hoog1,2*, Ikushi Onozaki3 and Knut Lonnroth3

TB case detection and requirements for screening chest X-rays and confirmatory tests of each algorithm, assuming 1% TB prevalence in the screened population.
Number needed to screen to find one true case of active TB value of each algorithm at different levels of TB prevalence.

A. NNS to find one TP case

Positive predictive value of each algorithm at different levels of TB prevalence.

B. PPV
Effect of uncertainty in the accuracy of screening and diagnostic tests and assumptions about clinical diagnosis on the NNS (panel A) and PPV (panel B), assuming 1% TB prevalence

The symbols represent the point estimates and the vertical bars the range due to uncertainty in the model parameter, as specified in Table 1. The specific scenarios are listed in Text box 2.

CXR=chest X-ray for screening ; SSM=sputum smear microscopy ; XP=Xpert MTB/RIF ; PE=point estimate used in primary analysis
1=first screen ; 2=second screen if first is positive. SSA=sub Saharan Africa ;

The next step towards implementation - expected:

Systematic Screening for Active TB:
An Operational Guide

- Includes a Tool for screening prioritization
  - Based on:
    - Size of the risk group
    - Relative risk of TB in the specific group
    - Choice of diagnostic algorithm
    - Expected participation / coverage
  - Being developed by WHO/UCSF and partners
- Guidance on implementation and monitoring and evaluation
- Available by?
Rule-out algorithm for active TB when identifying individuals to be treated for LTBI

WHO Guidelines (2014) on the management of latent tuberculosis infection

- Individuals should be asked about symptoms of TB before being tested for LTBI.
- Chest radiography can be done if efforts are intended also for active TB case finding.
- Individuals with TB symptoms or any radiological abnormality should be investigated further for active TB and other conditions.

*(Strong recommendation, very low quality of evidence)*

Conclusions and discussion

- Diagnostic algorithms for systematic screening for active TB
  - Prolonged cough: low sensitivity and high NNS
  - CXR screening has greater accuracy compared to symptom screening
  - Confirmatory test with high sensitivity and specificity preferred, especially in low prevalence setting
    - Confirm with culture?
- Evaluate if algorithm performs according to expectations
- Better screening test desired
  - Promising candidates? Biomarkers?
  - Computer assisted reading of digital CXRs?
Thank you!

Questions?