WHO support to the evolving TB Diagnostic Landscape

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Content

• Diagnostic techniques recommended by WHO
• WHO policy development process for new TB diagnostics
• Target product profiles and support to diagnostic developers
• Planned work on diagnostic policy development
WHO’s recommended techniques for diagnosing TB

- **Microscopy**
  - Conventional light microscopy
  - Light-emitting diode fluorescent microscopy

- **Culture**
  - Culture on solid media
  - Commercial liquid culture systems and rapid speciation

- **Drug-susceptibility testing**
  - DST first-line anti-TB agents
  - DST for second-line anti-TB agents
  - Non-commercial methods

- **Molecular testing**
  - LPA (first and second-line)
  - TB-LAMP
  - Xpert MTB/RIF assay (Ultra)

- **LF-LAM Urine test for PLHIV**
Interest in TB is at an all time high and the pipeline of technologies is robust

- Majority of technologies developed for the intermediate and central level laboratories
- More technologies suitable for the peripheral level as are replacement for microscopy are needed
- Greater investment in conducting the field evaluation and demonstration studies in high burden setting is needed
WHO’s process for developing policies on TB diagnostics

Policy development process

• The developers of diagnostic tests are encouraged to engage in early discussions with WHO to ensure that the new technology will be appropriate for the end-users.

• Priority target product profiles (TPP) for new diagnostics, developed following a consensus building process, are described in the TPP meeting report.
## Prioritizing the Products

### Product Ideas

<table>
<thead>
<tr>
<th>Target product priorities for potential new TB diagnostics/therapies</th>
<th>Prioritization by key stakeholders</th>
<th>Impact</th>
<th>Market</th>
<th>Implementation and scalability</th>
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<tr>
<td>A</td>
<td>Triage rule-out and systematic screening test</td>
<td>high</td>
<td>high</td>
<td>medium</td>
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<td>B</td>
<td>Rapid DST at the peripheral level</td>
<td>high</td>
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</tbody>
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**Evaluation Criteria**

- **Impact**
  - High
  - Medium
  - Low

- **Market**
  - High
  - Medium
  - Low

- **Implementation and scalability**
  - High
  - Medium
  - Low

### Prioritized Need for TPPs

- **Triage/rule-out test**
- **Sputum-based, smear replacement**
- **Biomarker-based, non-sputum**
- **Rapid DST at the peripheral level**
- **Test of progression**

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Kik S et al. ERJ 2014
WHO supporting manufacturers’ to bring products to the market

Manufacturers are encouraged to engage with WHO early in the development process to ensure that once a design-locked product is developed it can be properly evaluated to meet WHO requirements

- Reference standards are appropriate
- Appropriate samples are tested
- Ensure study design appropriate with statistical power
- Evaluations are performed in different epidemiological and geographical settings
- FIND as a WHO collaborating centre can facilitate independent evaluation

*Much greater investment in the field evaluation studies is needed to expedite new tests from the pipeline*
Diagnostic study dilemmas

What we want ...

Randomised trial
Target population

New test or strategy:
- Triage
- Replacement
- Add-on

Test positive
- True and false positives

Test negative
- True and false negatives

Management
Outcomes important to patients

What we have ...

Accuracy study
Target population

New test or strategy:
- Triage
- Replacement
- Add-on

Reference test

New test positive
- True and false positives

New test negative
- True and false negatives

Judgments about outcomes with new test
Judgments about outcomes with reference test

Schunemann et al. BMJ, 2008

*Grades of Recommendation Assessment, Development and Evaluation
Desirable vs undesirable consequences

**Effect x value**

- **For**:
  - ↑ Accuracy
  - ↑ Robustness
  - ↓ Morbidity
  - ↓ Death

- **Against**:
  - ↑ Resources
  - ↑ Biosafety
  - ↑ QA
  - ↑ Training

- **Conditional**
  - Strong
Essential considerations

Since no diagnostic test has perfect accuracy...

Assessing the use of a diagnostic needs to consider the sensitivity and specificity of the test, the level of the health system, the target population and the prevalence of the condition being detected
Lateral flow-Urine Lipoarabinomannin assay (LF-LAM)

Not recommended by WHO for TB screening or diagnosis of active TB disease in most population groups

Recommended to help with the diagnosis of TB in two specific population groups:

- People living with HIV who have signs or symptoms of TB and a CD4 cell count less than or equal to 100 cells/μL
- People living with HIV who are “seriously ill” regardless of CD4 count or if the CD4 count is unknown.
Future work on diagnostics

1. Review of critical concentrations for performing DST and establish methods for new and re-purposed drugs
   WHO Technical Expert Group April 24-26 2017

2. Evaluation of the use of sample transport solutions for improved recovery of MTB from culture or detection using molecular methods
   WHO Technical Expert consultation planned for May 29 2017

3. Review of centralized high-throughput platforms for the detection MTBC and drug resistance
   Guideline Development Group Meeting planned for Q4 2017
GeneXpert Omni and Xpert Ultra

- Small and Portable
- Durable
- Low Power Consumption
- Automatic Connectivity
- Solid State
- Integrated Battery

Expert MTB/RIF Ultra has been evaluated in a non-inferiority diagnostic accuracy study as a replacement for the Xpert MTB/RIF cartridge – Guidance available 24th March 2017

Evaluation the Omni instrument delayed until end of 2017
THANK YOU

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