WHO TB diagnostic evaluation and policy development process: what is required from new tests?

GLOBAL TB PROGRAMME

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Outline

1. WHO TB diagnostic policy development process
2. Priority target product profiles (TPPs)
3. Evaluation framework for tests that predict progression from TB infection to active disease
4. Essential diagnostic list and pre-qualification for TB diagnostics – what does it mean for TB tests?
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.
## Prioritized need for TPPs

<table>
<thead>
<tr>
<th>Target product profiles for potential new TB diagnostic tests</th>
<th>Prioritization by key stakeholders</th>
<th>Impact</th>
<th>Market</th>
<th>Implementation and scalability</th>
<th>Score</th>
<th>Priority rank</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRIAGE, RULE OUT AND SYSTEMATIC SCREENING TEST</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Triage test for those seeking care</td>
<td>high</td>
<td>high</td>
<td>medium</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>B An HIVART clinic-based test to rule out active TB</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>low</td>
<td>high</td>
<td>high</td>
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<tr>
<td>C Systematic screening test for active case finding</td>
<td>high</td>
<td>medium-high</td>
<td>high</td>
<td>medium</td>
<td>medium</td>
<td>low</td>
</tr>
<tr>
<td><strong>RAPID TB DIAGNOSIS TEST (WITH OPTIONAL DRUG SUSCEPTIBILITY TESTING)</strong></td>
<td></td>
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<tr>
<td>D Rapid, sputum-based, cartridge-based, molecular test for microscopy center (with the option of add-on drug susceptibility testing cartridge)</td>
<td>medium-high</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
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<tr>
<td>E Rapid biomarker-based instrument-free test for non-sputum samples (which can also detect childhood and extrapulmonary TB)</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>low</td>
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<tr>
<td>F Multiplexed test for TB and other infectious diseases</td>
<td>high</td>
<td>medium-high</td>
<td>low</td>
<td>medium</td>
<td>medium-high</td>
<td>low</td>
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<tr>
<td><strong>NEXT-GENERATION DRUG SUSCEPTIBILITY TEST</strong></td>
<td></td>
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<tr>
<td>G Centralized, high-throughput, drug susceptibility test (incorporating new drugs to support the roll out of new TB treatment regimens post 2014)</td>
<td>medium</td>
<td>high</td>
<td>medium</td>
<td>low</td>
<td>medium</td>
<td>high</td>
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<tr>
<td><strong>TREATMENT MONITORING TEST</strong></td>
<td></td>
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<tr>
<td>H Treatment monitoring test (test for cure)</td>
<td>high</td>
<td>high</td>
<td>medium</td>
<td>low-med</td>
<td>low</td>
<td>19.5</td>
</tr>
<tr>
<td><strong>PREDICTIVE TEST FOR LATENT TB INFECTION</strong></td>
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<td></td>
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</tr>
<tr>
<td>I Predictive test for latent TB infection at high risk of active TB</td>
<td>high</td>
<td>high</td>
<td>medium</td>
<td>high</td>
<td>high</td>
<td>low</td>
</tr>
</tbody>
</table>

- **Kik S et al. ERJ 2014**
  - **Triage/rule-out test**
  - **Sputum-based, smear replacement**
  - **Biomarker-based, non-sputum**
  - **Rapid DST**
  - **Predictive tests**

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Diagnostic study dilemmas

What we want ...

Randomised trial
Target population

New test or strategy:
Triage
Replacement
Add-on

Test positive
True and false positives
Management
Outcomes important to patients

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

Test positive
True and false positives

New test negative
True and false negatives

Reference test

New test positive
True and false positives
Judgments about outcomes with new test

New test negative
True and false negatives
Judgments about outcomes with reference test

Schunemann et al. BMJ, 2008
WHO policy development process

WHO uses the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, and to develop and report recommendations.

Policy recommendations qualify their strength as well as the certainty of the evidence on which they are based.

A recommendation may be strong or conditional

<table>
<thead>
<tr>
<th>Strong recommendation</th>
<th>Conditional recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>All desirable consequences CLEARLY OUTWEIGH the undesirable consequences in most settings</td>
<td>Desirable consequences PROBABLY OUTWEIGH undesirable consequences in most settings</td>
</tr>
</tbody>
</table>

(And vice versa)

All TB diagnostics are evaluated only through the Global TB programme and are NOT INCLUDED in the WHO pre-qualification programme.
WHO’s recommended techniques for diagnosing LTBI

Either a tuberculin skin test TST or an interferon gamma release assay (IGRA) can be used to test for latent TB infection (LTBI).

Given the low specificity of the IGRA* and the TST**, and to avoid unnecessary treatment, neither test should be used to diagnose active TB disease.

*IGRAs: Interferon gamma release assay (IGRAs) for the diagnosis of latent TB infection (LTBI) Oxford Immunotec, UK; Qiagen, USA

**TST 5 tuberculin units (TU) of tuberculin PPD-S or 2TU of tuberculin PPD RT 23
What is needed for any new skin test or IGRA?

Any tuberculin skin test (TST) would need to be validated initially in guinea pigs for equivalence with the current PPD RT23.

Any new interferon gamma release assay (IGRA) to test for latent TB infection (LTBI) be evaluated for non-inferiority to existing assays.

Any TST or IGRA assay that proposes a new indication e.g. predicts progression to active TB, or a test of incipient TB, MUST undergo full clinical evaluation and public health impact studies and be assessed through a formal WHO Guideline Development Group process.
Characteristic of an incipient TB Test

• Negative in individuals never exposed to TB
• Negative in individuals who are infected with MTB but who have no incipient TB. They might have a persistent TB infection, have a positive LTBI test (TST or IGRA) but do not develop TB disease within the next 2 years.
• Negative in individuals who have been treated for LTBI.
• Positive in individuals who develop TB within a short period after the test was done (e.g. 2 years), and who do not have any indication of re-exposure after the test was performed.
• Positive in individuals with symptomatic TB disease.
• Negative in individuals who completed TB treatment and are considered cured.
Research questions

• What is the accuracy (sensitivity and specificity) of the test to predict incident active TB within a pre-specified period?
• What is the positive and negative predictive value of the test for incident active TB within a pre-specified period, and what are the corresponding number needed to screen to find a single positive test (NNS) and number needed to treat to prevent one incident TB case (NNT)?
• What is the relative risk (RR) of a positive compared to a negative test for incident active TB within a pre-specified period?
• What is the incident rate (IR) of TB after a positive and negative test, and what is the corresponding incidence rate ratio (IRR)?
Evidence needed for an incipient TB Test

Two key research questions need to be addressed:

The predictive ability of the test should be assessed in clinical evaluation studies that include the intended target population, although individuals should not receive preventive therapy.

Public health impact studies are necessary to evaluate the ITT under routine programmatic conditions and to assess the potential impact of the test on patient-important or health system-important outcomes.
Clinical evaluation of an ITT

Study enrollment

Prospective follow-up (>18-24 months)

Study outcomes

- Treatment efficacy
  - Incident cases

- Predictive utility of the test
  - Incident cases
  - RR, IR, IRR, sensitivity and specificity

Overall
- NNS and NNT
- Costs
- Cost effectiveness
Evaluation of Public Health Impact

**Study enrollment**

**Prospective follow-up (>18-24 months)**

- **Old test (i.e. TST and/or IGRA)**
  - Test +: Preventive treatment → # incident TB cases
  - Test -: No preventive treatment → # incident TB cases

- **New TBI test**
  - Test +: Preventive treatment → # incident TB cases
  - Test -: No preventive treatment → # incident TB cases

**Study outcomes**
- Δ Incident cases
- Δ AEs
- Δ Costs
- Δ NNS and NNT
- Cost effectiveness
Essential Diagnostic List

• Essential Medicine Lists (EML) are among the most valued tools developed by WHO. An Essential Diagnostics List (EDL) has a similar potential.

• The IVD field is growing rapidly (while still fragmented). Countries will need guidance for procurement decisions.

• There is strong support from the Global Health community for an EDL.

• First introducing limited number of IVDs (e.g. TB and malaria, already approved by the disease specific programmes) to validate the concept and then expanding it?

• Then, other IVDS for both infectious diseases and NCDs

• Process generally similar to the EMLs
Essential Diagnostic List and SAGE-IVD

The Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE IVD) will serve as a principal advisory group to the WHO Director-General on all aspects of IVDs.

A SAGE-IVD will oversee the EDL

- Scope, prioritization, inclusion criteria, process
- First meeting planned for September 2017
- The WHO Expert Committee on Selection and Use of Medicines could suggest IVDs for the EDL to be considered by the SAGE-IVD

EXCEPTION

Where policy and technical recommendations on IVD are provided through WHO established advisory mechanisms, such as for HIV, tuberculosis and malaria. For these, SAGE IVD would accept such recommendations without further review and incorporate such advice in its consideration of organization-wide policies.
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
THANK YOU

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