Technical Consultation Meeting on the Programmatic Management of Latent Tuberculosis Infection

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Venue: President Hotel, Seoul, Republic of Korea

LTBI diagnosis and target product profile

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Agenda and Disclosure

• Agenda
  – Introducing the concept of incipient TB
  – A Target Product Profile for a test to detect incipient TB
  – What we have now

• No conflict of interest

• A large share of presented material was prepared by FIND (Prathiba Seshadri and Claudia Denkinger, Samuel Shumacker) and by NDWG LTBI Task Force members, in particular Frank Cobelens, Sandra Kik, and Hanif Esmail
Guidelines on the management of latent tuberculosis infection
The testing and treatment algorithm

Ask for any symptoms of tuberculosis in individuals from the risk groups*

Yes ➔ TB and other disease investigations***

No ➔ TST or IGRA ➔ Positive ➔ Chest radiography ➔ Any abnormality

TST or IGRA ➔ Negative** ➔ No abnormality ➔ Treat for LTBI
Tuberculin Skin test (TST)

A crude mixture of proteins obtained from the sterile supernatant of liquid cultures of *M. tuberculosis*.

It is an in vivo assay that elicits a delayed type hypersensitivity reaction: the extent of cellular infiltrates correlates with a skin induration, which is quantified 48–72 h after intradermal tuberculin inoculation.
Interferon-Gamma Release Assays (IGRAs)

Whole-blood test used that utilizes *M. tuberculosis* specific antigens, mainly ESAT-6 and CFP-10.

It measures amount of IFN-γ released by blood cells in response to specific antigens

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>Nil*</th>
<th>TB Response†</th>
<th>Mitogen Response§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive‡</td>
<td>≤8.0</td>
<td>≥0.35 IU/ml and ≥25% of Nil</td>
<td>Any</td>
</tr>
<tr>
<td>Negative**</td>
<td>≤8.0</td>
<td>&lt;0.35 IU/ml or &lt;25% of Nil</td>
<td>≥0.5</td>
</tr>
<tr>
<td>Indeterminate††</td>
<td>≤8.0</td>
<td>&lt;0.35 IU/ml or &lt;25% of Nil</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td></td>
<td>&gt;8.0</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>

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* The interferon gamma (IFN-γ) concentration in plasma from blood incubated without antigen.
† The IFN-γ concentration in plasma from blood stimulated with a single cocktail of peptides representing early secretory antigenic target-6 (ESAT-6), culture filtrate protein-10 (CFP-10), and part of TB 7.7 minus Nil.
§ The IFN-γ concentration in plasma from blood stimulated with mitogen minus Nil.
‡ Interpretation indicating that *Mycobacterium tuberculosis* infection is likely.
** Interpretation indicating that *M. tuberculosis* infection is not likely.
†† Interpretation indicating an uncertain likelihood of *M. tuberculosis* infection.
Either TST or IGRA can be used to test for latent TB infection. IGRA should not replace TST in low and middle income countries\(^1\).

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

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How was evidence analyzed?

Measure of outcome

• Risk ratio (RR) for test positives compared to test negatives (cohort studies)

Selection of trials

• head-to-head studies (n=8), to minimize biases from heterogeneity of study setting and population
Pooled risk ratio for development of incident TB in 8 head to head studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Country_AB</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diel</td>
<td>2010</td>
<td>Germany</td>
<td>A</td>
<td>199.48 (12.11, 3285.58)</td>
</tr>
<tr>
<td>Harstad</td>
<td>2010</td>
<td>Norway</td>
<td>A</td>
<td>31.65 (1.79, 559.58)</td>
</tr>
<tr>
<td>Kik</td>
<td>2010</td>
<td>Netherlands</td>
<td>A</td>
<td>1.96 (0.40, 9.53)</td>
</tr>
<tr>
<td>Lee</td>
<td>2009</td>
<td>Taiwan</td>
<td>A</td>
<td>0.22 (0.01, 4.35)</td>
</tr>
</tbody>
</table>

Risk ratio comparable and very low, meaning that the vast majority of individuals positive to the test would be treated unnecessarily

SR performed by Rangaka M and Kik S, unpublished
### Recommendations on at-risk populations

<table>
<thead>
<tr>
<th>Risk population groups</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• People living with HIV</td>
<td>Strong: systematic testing and treatment should be performed (Low to very low quality of evidence)</td>
</tr>
<tr>
<td>• Adult and child PTB contacts</td>
<td>Strong: systematic testing and treatment should be performed (Low to very low quality of evidence)</td>
</tr>
<tr>
<td>• Patients initiating anti-TNF treatment</td>
<td>Strong: systematic testing and treatment should be performed (Low to very low quality of evidence)</td>
</tr>
<tr>
<td>• Patients receiving dialysis</td>
<td>Strong: systematic testing and treatment should be performed (Low to very low quality of evidence)</td>
</tr>
<tr>
<td>• Patients preparing for transplantation</td>
<td>Strong: systematic testing and treatment should be performed (Low to very low quality of evidence)</td>
</tr>
<tr>
<td>• Patients with silicosis</td>
<td>Strong: systematic testing and treatment should be performed (Low to very low quality of evidence)</td>
</tr>
<tr>
<td>• Prisoners</td>
<td>Conditional: Systematic testing and treatment should be considered (Low to very low quality of evidence)</td>
</tr>
<tr>
<td>• Health workers</td>
<td>Conditional: Systematic testing and treatment should be considered (Low to very low quality of evidence)</td>
</tr>
<tr>
<td>• Immigrants from high burden countries</td>
<td>Conditional: Systematic testing and treatment should be considered (Low to very low quality of evidence)</td>
</tr>
<tr>
<td>• Homeless persons</td>
<td>Conditional: Systematic testing and treatment should be considered (Low to very low quality of evidence)</td>
</tr>
<tr>
<td>• Illicit drug user</td>
<td>Conditional: Systematic testing and treatment should be considered (Low to very low quality of evidence)</td>
</tr>
<tr>
<td>• Patients with diabetes</td>
<td>Conditional: Systematic testing and treatment is not recommended unless they belong in the upper two groups (Very low quality of evidence)</td>
</tr>
<tr>
<td>• People with harmful alcohol use</td>
<td>Conditional: Systematic testing and treatment is not recommended unless they belong in the upper two groups (Very low quality of evidence)</td>
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<tr>
<td>• Tobacco smokers</td>
<td>Conditional: Systematic testing and treatment is not recommended unless they belong in the upper two groups (Very low quality of evidence)</td>
</tr>
<tr>
<td>• Under-weight people</td>
<td>Conditional: Systematic testing and treatment is not recommended unless they belong in the upper two groups (Very low quality of evidence)</td>
</tr>
</tbody>
</table>
What is needed now for scale-up of LTBI programs

<table>
<thead>
<tr>
<th>COUNTRY GROUP</th>
<th>TESTING ALGORITHM</th>
<th>TREATING OPTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOW TB BURDEN</strong></td>
<td>• Exclude active TB using TB investigations according to national guidelines.</td>
<td>1. 6 months daily isoniazid</td>
</tr>
<tr>
<td></td>
<td>• A positive IGRA or TST result is required to diagnose LTBI.</td>
<td>2. 9 months daily isoniazid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. 3 months weekly rifapentine plus isoniazid</td>
</tr>
<tr>
<td>High-income and upper middle-income countries with an estimated TB incidence rate of less than 100 per 100 000 population</td>
<td></td>
<td>4. 3 to 4 months daily isoniazid plus rifampicin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. 3 to 4 months daily rifampicin</td>
</tr>
<tr>
<td><strong>HIGH TB BURDEN</strong></td>
<td>• Exclude active TB using TB investigations according to national guidelines.</td>
<td>1. 6 months daily isoniazid</td>
</tr>
<tr>
<td>Resource-limited and other high and middle-income countries with an estimated TB incidence rate of more than 100 per 100 000 population</td>
<td>• An LTBI test is not required prior to LTBI treatment, but is encouraged for people living with HIV.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IGRA should not replace TST.</td>
<td></td>
</tr>
</tbody>
</table>
Needs for tomorrow: better rule-in tests for LTBI

With current unfavorable risk/benefit trade-off, mass treatment is not at reach

Programmatic scale-up of LTBI diagnosis and treatment requires new diagnostic tools with much higher PPV for predicting incident TB.

New LTBI tests should not be evaluated for their sensitivity and specificity for an LTBI state, but rather for their capacity to predict TB disease in the future.
Target Population
Narrow vs broad

Risk of exposure and/or progression

General population
- Community-level / mass screening

Moderate-risk individuals
- PLHIV
- Adult contacts
- People living in settings with very high transmission rates

High-risk individuals
- Childhood contacts
- Anti-TNF treatment, transplant patients etc.

Broad
- Low yield / efficiency
- Low cost-effectiveness
- High population impact

Narrow
- High yield / efficiency
- High cost-effectiveness
- Low population impact
Can the future be predicted?
*M. tuberculosis* exists in a dynamic state that ranges from infection to disease.

In particular, there is a preclinical phase when latency is broken and the disease has still to come.
Diagnostic tests for the identification of LTBI should be conceptually categorised as persistent infection tests versus incipient tuberculosis tests.
Can the future be predicted?

Yes we can; but ONLY for the near future.

We can predict that disease will happen because the disease is already there, only in its INCIPIENT form.
How tests that use memory immune cell response (TST, IGRA) work

- **a)** probability that infection is cleared spontaneously
- **b)** probability that infection leads to incipient TB
- **c)** probability that incipient TB leads to disease
- **d)** probability that infection existed before the (recent) exposure

![Diagram showing the process of TST and IGRA tests and their outcomes.](image-url)
Performance of a test for persistent infection

- **Infection cleared → no TB**
  - True negative
- **Persistent infection → no TB**
  - False positive
- **Subclinical TB → TB**
  - True positive
- **Halted progression → no TB**
  - False positive

Test result negative

Test result positive
Role of a test for persistent infection

Acts very well as rule-out test.

Whereas a positive result might not be very informative, a negative result provides confidence that the individual is unlikely to develop tuberculosis disease in the near future.
Performance of a test for incipient TB

- **Infection cleared → no TB**: True negative
- **Persistent infection → no TB**: True negative
- **Incipient TB → TB**: True positive
- **Halted progression → no TB**: False positive

Test result negative
Test result positive
Role of a test for incipient TB

Acts as rule-in test.

Provided that analytical performance is adequate, the specificity and PPV of an ITT will be high, population-independent, and determined primarily by the probability that asymptomatic progression is halted spontaneously.

Conversely, a negative test may provide limited information (timing may be wrong)
Best use of tests for incipient TB

Populations / individuals with an identified precipitating event:

⇒ Recent exposure as a household contact (i.e. adults in high incidence countries)
WHO Meeting Report of a Technical Expert Consultation: Development of a Target Product Profile (TPP) and a framework for evaluation for a test of progression from latent to active tuberculosis
Process for TPP development

Step 1: Drafted TPP by FIND and reviewed with experts

Step 2: Meeting May 2015 with experts organized by NDWG, WHO and FIND >> revised document

Step 3: Survey with a larger stakeholder group (May 2016)

Step 4: FU meeting of NDWG LTBI taskforce (July 2016) >> revised document on FIND website

Step 5: Final review in stakeholder meeting at WHO (Q1 2017) prior to finalization
Background
TPP purpose and scope

- Intent
  - Aid translation of science into products that benefit patients and populations
    - Clarify target condition, target population and performance expectations
    - A guide (not a rule or exact and absolute requirement)

- Time horizon
  - 5 years
  - Needs revisiting as science evolves

- “Meaning” of optimal/minimal targets
  - Optimal: aspirational, ambitious
  - Minimal: feasible but important improvement
## Predictive accuracy of TST/IGRA

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV*</th>
<th>NNTT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rangaka / Kik</td>
<td>TST</td>
<td>72% / 58%</td>
<td>41% / 64%</td>
<td>2.4% / 3.2%</td>
</tr>
<tr>
<td></td>
<td>IGRA</td>
<td>72% / 80%</td>
<td>50% / 56%</td>
<td>2.9% / 3.6%</td>
</tr>
</tbody>
</table>

- **Minimal target**
  - Increase PPV by factor of ~2 and (thus cutting NNTT by ~1/2) compared to IGRA

- **Optimal target**
  - Increase PPV by factor of ~5 and (thus cutting NNTT by ~1/5) compared to IGRA

*Based on 2% incidence*
What performance should we be aiming for?
PPV according to Sens/Spec for risk of progression

Note: Cumulative incidence of progression from TB infection to active TB: 2%
* Based on updated, unpublished SR/MA by Kik et al.

Note that a test with Se/Sp 99/99 would yield PPV=67%

NNT=17
Treat 2,600/10,000

NNT=28
Treat 4,472/10,000
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-test probability of 0.1%</th>
<th>Pre-test probability of 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives (TPs)</td>
<td>8 (8)</td>
<td>75 (80)</td>
</tr>
<tr>
<td>False negatives (FNs)</td>
<td>3 (2)</td>
<td>25 (20)</td>
</tr>
<tr>
<td>True negatives (TNs)</td>
<td>7,493 (5,594)</td>
<td>7,425 (5,544)</td>
</tr>
<tr>
<td>False positives (TPs)</td>
<td>2,498 (4,396)</td>
<td>2,475 (4,356)</td>
</tr>
<tr>
<td>Number needed to test and treat to prevent one case of active TB (100% treatment efficacy)</td>
<td>334 (550)</td>
<td>34 (55)</td>
</tr>
<tr>
<td>Number needed to test and treat to prevent one case of active TB (60% treatment efficacy)</td>
<td>557 (917)</td>
<td>57 (92)</td>
</tr>
</tbody>
</table>
THEORY

PRACTICE
The c-tb skintest

C-Tb combines the simplicity and low cost of the skin test with the diagnostic accuracy of the IGRA tests.

Generium - Diaskin test

QuantiFERON-TB Gold Plus

- Nil
- TB1
- TB2
- Mitogen
To construct and validate a prognostic correlate of risk (COR), based on messenger ribonucleic acid (mRNA) expression signatures, which discriminates between TB cases and healthy controls (in the 2 month after testing – HIV uninfected)
Prognostic COR—step 1

• Follow-up (two years) of the Adolescent Cohort Study in South Africa, to derive (retrospective cohort) a signature of risk from whole blood RNA sequencing data by comparing participants who developed active TB (progressors) with those who remained healthy (matched controls).

• Between July 6, 2005, and April 23, 2007, 6363 adolescents enrolled, 46 progressors and 107 matched controls

• A 16 gene signature of risk identified.

The signature predicted TB progression with a sensitivity of 66·1% (95% CI 63·2–68·9) and a specificity of 80·6% (79·2–82·0) in the 12 months preceding TB diagnosis.

Zak et al Lancet 2016
Adaptation of the signature to multiplex quantitative real-time PCR (qRT-PCR)

Use the signature to predict TB in untouched adolescent samples and in samples from independent cohorts of South African and Gambian adult progressors and controls (household contacts of adults with active pulmonary TB).

4,466 adults enrolled

The signature was highly predictive of TB in the 12 months preceding the disease (p values <0.0001 by qRT-PCR) with a sensitivity of 53.7% (42.6–64.3) and a specificity of 82.8% (76.7–86)
What is the potential use of such a test?

- Rule in test for treatment of LTBI among adult contacts in high burden countries
- Exclude active TB in children starting LTBI treatment with a rifamycin-containing regimen in high burden countries
- ............
What next

• The CORTIS trial

• Cost-effectiveness model with assessment of how impact may vary depending on test accuracy and assessment of what cost a test would need to be to be cost-effective
  – TIME model by the LSHTM
  – LTBI specific model from Erasmus University
CORTIS trial
A Randomized, Partially-blinded, Clinical Trial of Isoniazid and Rifapentine (3HP) Therapy to Prevent Pulmonary TB in High-risk Individuals Identified by a Transcriptomic Correlate of Risk

First prospective evaluation of the COR test

**Primary Aims**
1. Test whether preventive therapy (3HP) reduces the rate of incident TB disease, compared to standard of care (active surveillance), in COR+ persons.
2. Test whether COR status differentiates persons with cumulative prevalent or incident TB disease from persons without TB disease.

**Secondary Aims**
1. Estimate whether COR status differentiates persons at high risk for incident TB disease from persons at low risk for incident TB disease
Conclusions – LTBI diagnostic research

- The changing paradigm of LTBI implies that two complementary types of test with different purposes are needed: a test for persistent infection and a test for incipient TB.

- Two research pipelines should be in place, guided by relevant TPP and by the Framework of Evaluation for the ideal study design for clinical and public health impact evaluation.

- A 'screen & treat' strategy, based on serial mass campaigns to provide targeted, short-course preventive therapy only to individuals with positive incipient TB test, may offer the solution for durable, community-wide protection in high TB burden countries.