Guidance document for the evaluation of TB prediction tests to inform WHO endorsement

An update

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<thead>
<tr>
<th>Affiliation / financial interest</th>
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</thead>
<tbody>
<tr>
<td>Tobacco-industry and tobacco corporate affiliate related conflict of interest</td>
<td></td>
</tr>
<tr>
<td>Grants/research support (to myself, my institution or department):</td>
<td>Qiagen is donating Quantiferon Plus testkits for the WHIP3TB trial on which i am a co-investigator</td>
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Why need an evaluation framework?

1. To set a standard for *admissible evidence* for WHO endorsement (GRADE process)

2. To inform test manufacturers, researchers and research funders about the types of studies that are required for WHO endorsement
Which test should we concentrate on?

<table>
<thead>
<tr>
<th>Test</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexposed</td>
</tr>
<tr>
<td>“LTBI test” (TST, current IGRA?)</td>
<td>-</td>
</tr>
<tr>
<td>Persistent infection test</td>
<td>-</td>
</tr>
<tr>
<td>Incipient TB test</td>
<td>-</td>
</tr>
<tr>
<td>Active TB test</td>
<td>-</td>
</tr>
</tbody>
</table>

+ = test is positive; - = test is negative; +/- = test is sometimes positive, sometimes negative

Concentrate on a **test for incipient TB** as this is expected to have high predictive value for incident TB disease (**rule-in test**).
Test for incipient TB

Predicts clinical TB occurring within 12-18 months

May have low sensitivity depending on when the test is done → may need to be repeated

May be combined with a test for persistent infection

**Rule-out** progression to TB disease

**Rule-in** progression to TB disease
Evaluation phases

1. Analytical evaluation
   evaluation of different subsets of well characterized (banked) samples

2. Clinical evaluation
   evaluate the test in the intended target population
   in a controlled setting with high quality standards
   (compare the results of the new test against a reference standard)

3. Evaluation for (public) health impact
   evaluate the test under routine conditions
   for impact on patient-important or health system-important outcomes
   (comparison against a reference standard not necessary)
For targeting preventive treatment we are not interested in latent TB infection as such, but in predicting disease.

→ WHO endorsement must be ultimately based on prediction of disease.

→ Some designs as used in evaluation of IGRA will be non-informative:

  • studies comparing test results with that of IGRA or TST as ‘reference’ standard (beyond very early stages of test evaluation – candidate selection)

  • studies that analyze test results along a *M. tuberculosis* exposure gradient

  • Cross-sectional studies (= without follow-up)
Purpose
Establish the predictive ability of the test in the absence of preventive treatment

Research questions:
1. What is the accuracy (sensitivity and specificity) of the test to predict incident active TB within a specified period?
2. What is the positive and negative predictive value of the test for incident active TB within a specified period, and what is the corresponding number needed to screen to find 1 positive test (NNS) and number needed to treat to prevent one incident TB case (NNT)?
3. What is the incidence rate (IR) of active TB after a positive test? What is the incidence rate after a negative test? What is the corresponding incidence rate ratio (IRR) of the test?
Clinical evaluation - designs

Key questions:
1. Is the test positive in persons who develop active TB over 12-18 months?
2. Is the test negative in persons who remain without active TB over same period?

Design:
Follow-up studies of persons with high likelihood of recent exposure or otherwise at high risk of developing TB

Options:
1. Cohort designs
2. Nested case-control designs
Clinical evaluation - cohort designs

Follow tested individuals actively over 12-18 months
Active ascertainment of incident TB, stratified by test result

**Essential requirements:**
Probability of being included as a TB case should be independent of test result
TB case ascertainment should be blinded with regard to test result
TB diagnosis should have high specificity (bacteriological confirmation)
## Clinical evaluation – design challenges (1)

<table>
<thead>
<tr>
<th>Design challenge</th>
<th>Low incidence country</th>
<th>High incidence country</th>
<th>Potential effect</th>
<th>Possible mitigation strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of preventive therapy</td>
<td>Present for majority of suitable study populations</td>
<td>Present for some study populations, but not all</td>
<td>Bias of accuracy estimates (if included) or limiting enrolment (if excluded)</td>
<td>Choose study population in which IPT is not given (MDR-contacts, ineligible per country guidelines, declining IPT, non-adherent to IPT) Include individuals assigned to non-intervention arm in RCT of e.g. TB preventive therapy or post-exposure vaccines trials RCT, comparing LTBI test and treat strategy with new TB-PT test and treat strategy</td>
</tr>
</tbody>
</table>
### Clinical evaluation – design challenges (2)

<table>
<thead>
<tr>
<th>Design challenge</th>
<th>Low incidence country</th>
<th>High incidence country</th>
<th>Potential effect</th>
<th>Possible mitigation strategy</th>
</tr>
</thead>
</table>
| Follow-up time long    | Present               | Present                | Long study duration, loss to follow-up (potential for new infection as discussed above) | Use shorter follow-up time (e.g. 12 months) or analyze results for different lengths of follow-up (6, 12, 18 months)  
  Compare RR and IRR to determine how differential loss to follow-up may have affected study outcomes |
Clinical evaluation – design challenges (3)

<table>
<thead>
<tr>
<th>Design challenge</th>
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<th>High incidence country</th>
<th>Potential effect</th>
<th>Possible mitigation strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression rare</td>
<td>Present</td>
<td>Present</td>
<td>Large sample size needed</td>
<td>Focus on highest risk groups</td>
</tr>
</tbody>
</table>
## Clinical evaluation – design challenges (4)

<table>
<thead>
<tr>
<th>Design challenge</th>
<th>Low incidence country</th>
<th>High incidence country</th>
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</tr>
</thead>
</table>
| Re-infection     | Absent                | Present                | Biased estimates:  
|                  |                       |                        | ↓ sensitivity    | Use shorter follow-up      |
|                  |                       |                        | = specificity    | time (e.g. 6 months)      |
|                  |                       |                        | ↑ PPV            | Focus on populations      |
|                  |                       |                        | ↓ NPV            | with a lower risk of      |
|                  |                       |                        |                 | exposure to ongoing       |
|                  |                       |                        |                 | transmission in           |
|                  |                       |                        |                 | community (e.g. young      |
|                  |                       |                        |                 | children)                 |
Clinical evaluation - nested case-control design

Follow tested individuals passively over defined period (passive cohort)
Passive ascertainment of incident TB
Test status among incident TB cases compared to that of random subset of non-TB cases
Allows for larger sample sizes

Requirements and design challenges:
As for cohort studies

Additional challenges:
Incomplete TB case ascertainment: no bias, but sample size trade-off
Clinical evaluation – subgroups

Of interest for stratified/subgroup analysis:

- history previous TB disease
- children
- gender
- BCG vaccination status
- comorbidities: e.g. HIV, diabetes, malnutrition
Evaluation of (public) health impact - *admissible evidence*

The new test may identify the same absolute number of persons who develop TB disease as TST or IGRA but with much higher PPV ( = lower number-needed-to-treat)

→ Comparative studies cannot just have effectiveness endpoints but must also have **cost-benefit endpoints**

Cost-benefit should entail:
- Individual patient benefits
- Public health benefits
- Health system monetary costs
- Patient monetary costs
- Additional costs, e.g. adverse events
Evaluation of health impact – research questions

Purpose
Assess the impact of the assay on patient important outcomes and its public health impact when used to guide preventive treatment decisions under routine conditions.

Research questions:
1. What is the effectiveness of the test for reducing incident TB when combined with a strategy to offer preventive treatment upon a positive test?
2. Is the test combined with a preventive treatment a cost-effective strategy to reduce incident TB in individuals for whom testing and preventive treatment is currently not recommended?
3. Is the test combined with preventive treatment a more effective and cost-effective strategy compared to alternative LTBI test and treat strategies using TST and/or IGRA?
4. What is the effect of the test combined with preventive treatment on the occurrence of adverse effects (e.g. hepatotoxicity), when compared to alternative LTBI test and treatment strategies (e.g. based on TST and/or IGRA)?
5. What is the effect of the test combined with preventive treatment on the uptake and acceptance of preventive treatment?
6. Which treatment regimen (monodrug or multidrug preventive treatment) is most effective when used for individuals with a positive test?
Key questions:
1. Does the test when used in routine settings improve health outcomes?
2. Does the test when used in routine settings improve cost-effectiveness?

Design:
Comparative designs, ideally randomized trial (individual/group):
• Randomize individuals with a positive test for treatment vs no treatment
• Randomize individuals for old test & treat strategy vs new test & treat strategy
**Health impact evaluation**

_Trial randomizing individuals with positive test_

- **Preventive treatment**
- **No preventive treatment**

**Study enrollment**

- New TBI test
- **Randomize**

**Prospective follow-up 12-18 months**

- # incident TB cases
- # incident TB cases
- # incident TB cases

**Study outcomes**

- **Treatment efficacy**
  - \( \Delta \) Incident cases
  - RR, IR, IRR, sensitivity and specificity

- **Predictive utility of the test**
  - \( \Delta \) Incident cases
  - NNS and NNT
  - Costs
  - Cost effectiveness

\( \Delta = \) difference, \( IR = \) incidence rate, \( IRR = \) incidence rate ratio, \( NNS = \) number of individuals needed to screen to find a positive test, \( NNT = \) number of individuals needed to treat to prevent one incident TB case, \( RR = \) risk ratio, \( TBI = \) tuberculosis infection.

Based on the CORTIS study
Only in target groups that currently not eligible for preventive treatment
In target groups for which preventive treatment is currently indicated
Conclusions

What we’re looking for is a test for incipient TB

This requires a different evaluation approach than used for IGRA thus far

Endorsement should ultimately be based on predictive power (of incident TB)
→ follow-up studies

Cohort studies with relatively short follow-up are needed for clinical evaluation
Nested case-control studies may be useful alternative

Randomized trials are ideally done to show impact on patient/health system-important outcomes

For such trials, number-needed-to-treat, adverse events and cost-effectiveness are important endpoints
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