Programmatic management of LTBI: a two pronged approach for ending the TB epidemic

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What is latent TB infection?

A state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB.
Estimated LTBI prevalence in general population

- Americas: 15%
- Africa: 31%
- SE Asia: 46%
- European: 14%
- EMR: 27%
- West Pacific: 32%

Global estimate: 30%

Corbett et al, 2003
LTBI represent the TB reservoir

- 95% of the population have latent TB infection
- 5% develop active disease within 15 years

- 2 billion population with latent TB infection
- 9.6 million TB cases /year
End TB Strategy

TARGETS: 90% reduction of deaths and 80% reduction in incidence by 2030

1. Integrated, patient-centered TB care and prevention
   - Early diagnosis of TB including universal drug-susceptibility testing and systematic screening of contacts and high-risk groups

2. Bold policies and supportive systems
   - Treatment of all people with TB including drug-resistant TB, and patient support

3. Intensified research and innovation
   - Collaborative TB/HIV activities, and management of co-morbidities

4. Preventive treatment of persons at high risk and vaccination of children
Dye et al, 2013

- **Baseline**
- **① Treat active TB**
- **② Prevent infection**
- **③ Mitigate risk factors**
- **④ Treat latent TB**
- **⑤ Treat active and latent TB**

**Cases (per million per year)**

**Year**

- 2000
- 2010
- 2020
- 2030
- 2040
- 2050
LTBI management is one of the priority actions for TB elimination.
Approach for programmatic management of LTBI

1. Identify and prioritize high risk population groups as targets for LTBI management
   - Assess TB risk in different population groups based on prevalence of infection and risk of progression

2. Select and test individuals with high risk of progression to active TB
   - Assess TB risk in individuals based on diagnostic tests, clinical assessment including personal risk exposure (selective algorithmic approach to rule-in LTBI and rule-out TB)

3. Initiate treatment
   - Define standard treatment options and include in national policy
   - Address concurrent risk factors for LTBI
   - Implement interventions to ensure adherence

4. Complete treatment
   - Monitor adverse events

5. Establish follow up mechanism to monitor the development of active TB during and after completion of LTBI treatment

Provide programmatic support: algorithm-based national guidelines targeting high risk population groups; proper documentation, reporting and monitoring of people receiving LTBI treatment; functional supply system for diagnostic tests, drugs and other treatments; promote implementation and basic science research to develop service delivery models and scale up novel evidence based interventions.
Principles of LTBI treatment and diagnosis

- Individual benefits should outweigh the risk
- Public health approach with individual benefit
- Complement active TB case finding activities
Considerations for recommendations

- Balance of benefits and harms
- Values and preferences of clients and healthcare providers
- Resource considerations
## Two sets of countries for global LTBI response

### High-TB burden
- Estimated TB incidence >100 per 100,000
- LICs and LMICs
- Risk groups
  - PLHIV
  - Household child contacts (<5y)

### Low-TB burden
- Estimated TB incidence <100 per 100,000
- UMICs and HICs
- Risk groups
  - PLHIV
  - Child and adult contacts
  - Clinical indications
    - Transplant
    - Dialysis
    - Anti-TNF
    - Silicosis
Primary targets for LTBI guidelines (low TB burden)

113 high or upper middle income countries with an estimated TB incidence rate of less than 100 per 100,000 population
# LTBI treatment recommendations for low-TB burden

## Risk population groups

- Prisoners
- Health workers
- Immigrants from high burden countries
- Homeless persons
- Illicit drug user

## Strength of recommendation

Conditional: Systematic testing and treatment should be considered *(Low to very low quality of evidence)*

## Additional recommendations

- Patients with Diabetes
- People with harmful alcohol use
- Tobacco smokers
- Under-weight people

Conditional: systematic testing and treatment is not recommended unless they belong in the upper two groups *(Very low quality of evidence)*
Two sets of countries for global LTBI response

<table>
<thead>
<tr>
<th>High-TB burden</th>
<th>Low-TB burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No TST or IGRA required</td>
<td>• TST or IGRA required</td>
</tr>
<tr>
<td>• INH 6 months recommended</td>
<td>• Multiple regimens</td>
</tr>
<tr>
<td></td>
<td>▪ 6 months isoniazid (6H)</td>
</tr>
<tr>
<td></td>
<td>▪ 9 months isoniazid (9H)</td>
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<tr>
<td></td>
<td>▪ 3 months weekly rifapentine plus isoniazid (3HP)</td>
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<tr>
<td></td>
<td>▪ 3 to 4 months isoniazid plus rifampicin (3-4HR)</td>
</tr>
<tr>
<td></td>
<td>▪ 3 to 4 months rifampicin alone (3-4R)</td>
</tr>
</tbody>
</table>
Diagnosis of LTBI: Tuberculin Skin Test

- Mix of several Antigens
- Cross reactivity with BCG
- Low specificity
- Anergy (e.g. PLHIV)

Operational challenges
- Return visit (48-72 hr)
- Cold chain and dark room
- Trained personnel to read
- Reading problems (Under-reading and reader variability)
IGRAs: target MTB specific antigens (ESAT-6; CFP-10; TB7.7)

IGRAs are more costly and technically complex
Head-to-head comparison of TST and IGRA for prediction of future TB disease

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Country_AB</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td><strong>IGRA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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, TSpotTB</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>
<tr>
<td>Leung</td>
<td>2010</td>
<td>China</td>
<td>A</td>
<td>7.15 (0.95, 54.09)</td>
</tr>
<tr>
<td>Mahomed</td>
<td>2011</td>
<td>South Africa</td>
<td>B</td>
<td>2.89 (1.55, 5.41)</td>
</tr>
<tr>
<td>Shanaube</td>
<td>2013</td>
<td>Zambia</td>
<td>B</td>
<td>1.59 (0.83, 3.05)</td>
</tr>
<tr>
<td>Yang</td>
<td>2013</td>
<td>Taiwan</td>
<td>A</td>
<td>77.20 (4.18, 1422.68)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td></td>
<td>4.94 (1.79, 13.65)</td>
</tr>
</tbody>
</table>

| **TST**      |      |                |            |                      |
| Diel         | 2010 | Germany        | A          | 3.74 (1.54, 9.07)     |
| Harstad      | 2010 | Norway         | A          | 5.69 (1.16, 27.88)    |
| Kik          | 2010 | Netherlands    | A          | 3.42 (0.20, 57.84)    |
| Lee          | 2009 | Taiwan         | A          | 0.60 (0.04, 8.73)     |
| Leung        | 2010 | China          | A          | 1.74 (0.55, 5.49)     |
| Mahomed      | 2011 | South Africa   | B          | 2.71 (1.42, 5.15)     |
| Shanaube     | 2013 | Zambia         | B          | 1.86 (1.05, 3.29)     |
| Yang         | 2013 | Taiwan         | A          | 43.60 (2.36, 805.18)  |
| **Subtotal** |      |                |            | 2.58 (1.72, 3.88)     |
LTBI tests adopted by countries
(Survey among 74 low TB burden countries)
Ask for any symptoms of tuberculosis in individuals from the risk groups*

Yes

TB and other disease investigations***

Any abnormality

No abnormality

Treat for LTBI

No

TST or IGRA

Positive

Chest radiography

Negative**

No abnormality
Rifapentine/INH (12 doses) for LTBI treatment

- FDA approval for LTBI: done and EML: ongoing
- Included in WHO essential medical list and expression of Interest for manufacturers
- Fixed dose combination of HP developed: 300H/300P (adults) and 150H/150P (for children and solvable)
- Studies show no interaction with Efavirenz
- It is efficacious both in adults and children (>2y)
Challenge: Gap between policy and practice
(Survey among 74 low TB burden countries)

- National policy on LTBI exists
- Testing and treatment for LTBI being provided for people living with HIV and/or child contacts
Challenge: Not all LTBI activities are recorded and reported (Survey among 74 low TB burden countries)
Conclusion

• Programmatic management of LTBI is an integral part of End TB Strategy

• It has relevance for both high and low TB burden countries

• Efforts should intensify for the programmatic management of LTBI globally including M and E