LTBI management for children: where are the gaps?

Technical Consultation on the Programmatic Management of LTBI
Seoul, Republic of Korea, 1st September, 2017

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Outline

• Evidence and rationale

• Opportunity to address the policy practice gap

• Challenges

• Recent progress

• Research and implementation gaps
Risk of TB disease following infection by age

Why is LTBI management in children important?
Prevent child morbidity and mortality

- Estimated 239,000 (95% UI: 194,000-298,000) deaths in children (<15 years) due to TB in 2015 with 80% (191,000) of deaths in < 5 years
  Dodd PJ et al, Lancet Global Health 2017

- The prevalence of TB infection is high among child contacts

- Child household TB contacts had significant increase risk of all-cause mortality compared to children living in non-TB households in same community
  - If mother had TB, 8-fold increase: MRR 7.82 (95% CI 2.1-30)
    AF Gomes et al, Thorax 2011

- Missed opportunities for IPT were common (71%) in at-risk children that later presented with confirmed TB disease
  - 81% were <3 years of age, 25% had disseminated TB and 5% died
  - TB source case was the mother or father in 74/156 (47.4%) children
    K Du Preez et al, Ann Trop Paediatr 2011
TB in adolescents

Age Pyramid TB Casefinding 2012

- Males
- Females

Percentage of all TB with infectious TB by age

Kathryn Snow, PhD student – unpublished data
Evidence for over 50 years

• 420 children with positive TST in RCT
• IPT (5mg/kg) versus placebo
• TB meningitis: 1 child in IPT versus 6 children in placebo group
• EPTB: 6 children in IPT versus 25 in placebo group


• Observational study of 2,494 children received IPT
• 15,943 person years of observation
• No child < 5 years developed TB
• No reactivation during adolescence

Hsu K, JAMA 1984
“There are many contributions which the pediatrician can make to a TB control program.

First the negativism about tuberculosis so prevalent in pediatrics must be overcome…”

Edith Lincoln, 1961

Donald PR. Edith Lincoln, an American Pioneer of Childhood Tuberculosis. Pediatr Infect Dis J 2013
Contact investigation among child contacts in Uganda

- 761 Ugandan child household contacts with TB – half < 5 yrs

- TB confirmed in 7% of child contacts

More common in the young children - disease prevalence extremely high, equivalent to 16,400 per 100,000 young child contacts

Active case-finding identified 79 children with TB that had not been diagnosed previously

- Only two (<1%) of 483 eligible children developed TB while receiving IPT
Summary of the evidence for treatment of infection

Highly effective

Extremely safe

Low cost medication

Cost-effective

Does not increase the risk of resistant TB when disease is excluded
2.4 million young children (<5 years) and 5.1 million older children (5–14 years) living in households of adult patients with known TB

240,000 young children and 420,000 older children with active TB, or 10% and 8%, respectively

848,453 (or 39%) and 2,660,885 (or 57%) with LTBI
Available data on numbers of eligible child contacts that were started on preventive therapy in 2015
Closing the Policy-Practice Gap in the Management of Child Contacts of Tuberculosis Cases in Developing Countries

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Tropical Medicine and International Health
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Review

Preventive therapy in children exposed to Mycobacterium tuberculosis: problems and solutions

Merrin E. Rutherford\textsuperscript{1}, Philip C. Hill\textsuperscript{1}, Rina Triasih\textsuperscript{2}, Rebecca Sinfield\textsuperscript{3}, Reinout van Crevel\textsuperscript{4} and Stephen M. Graham\textsuperscript{5}

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Implementation challenges

- Site of screening
- Availability of tests for LTBI
- Rule out active TB
- Availability of preventive therapy
- Adherence to long regimens

- Engagement of maternal child health sector
- M&E tools: contact screening register and PT register
- Acceptability in caregivers & providers
- Barriers to delivery of treatment for LTBI
The management of infection with *M. tuberculosis* post-2015: an opportunity to close the policy-practice gap

Graham SM. Exp Rev Resp Med 2017

Political will

Decentralization and community-based integration

*Improved diagnostics*

Shorter, simpler and safer regimens

*Prevention of MDR TB in children*
Global Plan to End TB 2016-2020

Includes End TB goals for 2025..........
• 90% or more of children who have been exposed to TB receive preventive therapy
• 90% or more of people in close contact with all people diagnosed with TB should be evaluated for TB

“Top ten” indicators for monitoring implementation of the End TB Strategy include coverage of contact investigation and LTBI treatment

90% or more of children aged <5 years who are household contacts of TB cases started on treatment for LTBI
Decentralisation - Malawi

Using data for 1998 and 2014, estimated more than 7,000 young children eligible for preventive therapy each year


Each district hospital would need to provide preventive therapy for an average of around 300 young child contacts per year compared to around 15 per year if this was managed at the primary health centre level.
Symptom-based screening approach to child contact management – if LTBI test unavailable

Children in close contact with a case of sputum smear-positive TB

Less than 5 years
- Well: Preventive therapy
- Symptomatic: Evaluate for TB disease
  - If becomes symptomatic

More than 5 years
- Symptomatic: Evaluate for TB disease
  - If becomes symptomatic
- Well: No treatment
The outcome of symptom based screening in Indonesian children

269
All child contacts

108
Children < 5 yrs

161
Children > 5 yrs

71
well

37
symptomatic

61
symptomatic

99

9

9

12

149

4

IPT

No IPT

• 530 CXRs of 265 child contacts
• Four independent readers: 2 radiologists and 2 paediatricians

• No asymptomatic child contact had TB disease diagnosed by CXR
• Commonest abnormality reported was hilar lymphadenopathy in 6-16%
• Poor agreement on abnormalities between readers: K= -0.03 to 0.25
Scale up childhood TB management

- **2012-2013**: 4 pilot provinces
- **2013**: 3 provinces (Nam dinh, Hung yen and Khanh hoa)
- **2014**: 3 provinces (Hai phong, Dong nai, Binh thuan)
- **2015**: 3 provinces (Hai duong, Bac giang, Da nang)
- **2016**: 3 provinces (Thai nguyen, Ninh binh, Quang nam)

Scale up child contact screening and management: Q1/2015 countrywide (registers, INH and guidance available in all communes (10,732))
12,750 posters

554,400 leaflets
Job aides and free on-line training
Setting Numbers eligible Numbers (%) uptake Numbers (%) complete Health system level

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<th>Setting</th>
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<th>1615</th>
<th>Health extension workers</th>
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<td>Uganda</td>
<td>910</td>
<td>670</td>
<td>569</td>
<td>Village health teams</td>
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Community-based screening and IPT

Previous facility-based studies consistently low uptake of screening and IPT (<20%) and low treatment completion of 6H (<50%)
Rapid development of diagnostics

- **History**: 1882
- **Bacteriology**: 1890
- **Tuberculin Skin Test**: 1890
- **Chest X-ray**: 1896
Treatment options recommended for LTBI include:
6H, or
9H, or
3HP weekly rifapentine plus isoniazid, or
3RH

Strong recommendation, moderate to high quality of evidence

Ideal test for infection
Point-of-care with high degree of accuracy
Distinguishes between infection and disease
Blood-based biomarker with immediate result
Applicable at primary care or household level

Tebruegge M, et al. AJRCCM 2015
Treatment options recommended for LTBI include: 3RH (75mg/50mg)
Child contacts of MDR TB cases are at high-risk for infection and disease due to MDR *M. tuberculosis*

WHO: “clinicians can consider individually tailored treatment regimens based on the drug susceptibility profile of the index case, particularly for child contacts below 5 years of age, when benefits can outweigh harms with reasonable confidence.”

RCTs in progress (including children) but results unavailable until 2020.

Limited observational evidence suggests effectiveness and cost-effectiveness of preventive therapy.
Benefit outweighs harm with reasonable confidence

- Consequences of developing MDR TB
  - Mortality
  - Sequelae – permanent deafness, chronic lung disease
  - Cost to health service
  - Cost to families

- Regimen and duration

- Major (but unwarranted) concerns
  - Safety
  - Propagation of resistance
Need for M & E tools for contact management: collapsed cascade of care for children

• Number contacts screened
• Numbers (%) diagnosed with TB
• Numbers (%) eligible for preventive therapy
• Numbers (%) received preventive therapy
• Numbers (%) completed preventive therapy
Programmatic needs

• Available preventive therapy
• Epidemiology – when to include test for infection
• Integrated approach – training and health systems strengthening
• Community and health worker education
• Improve child TB diagnosis
• Funding and inclusion in budgets
• Guidance on MDR contact management
Research priorities

• Accurate point-of-care and low cost test that distinguishes between not infected and infected and active disease: rule in and rule out

• Test that determines “cure” of infection or sterilisation

• Effective preventive therapy regimen that is
  – Short duration: 2 months weekly or 1 month daily
  – Effective for contacts of DS and DR TB cases
  – Excellent safety profile with few exclusion criteria
  – Compatible with other treatments e.g. ART

• Interventions to prevent infection in adolescents and disease
Research priorities

• Evidence of optimal integrated family-based/community-based models of care

• Implementation models with cascade of care including follow-up

• Impact of interventions on child TB burden

• Cost and cost-effectiveness
Thank you

Global Consultation on the Programmatic Management of Latent Tuberculosis Infection

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