Child TB subgroup annual meeting

2016
Objectives

To share national and regional experiences in scaling up the response to childhood TB and to discuss next steps to move the agenda forward.

To discuss how to operationalize the End TB Strategy with a focus on childhood TB.

To give an update on the activities of the working group since the last annual meeting in Cape Town, South Africa.
Child TB subgroup of Stop TB Partnership formed 2003

WHO Guidance for NTPs on the management of TB in children 2006

International Child TB Meeting, Stockholm, 2011

First estimates of child TB in Global TB Report 2012

Roadmap for Childhood TB 2013

WHO Guidance for NTPs on the management of TB in children 2014

End TB Strategy (and SDGs) 2015
ROADMAP FOR CHILDHOOD TUBERCULOSIS

Include the needs of children and adolescents in research, policy development and clinical practices

- Collect and report better data, including data on prevention
- Develop training and reference materials for health care workers
- Foster local expertise and leadership
- Do not miss critical opportunities for intervention
- Engage key stakeholders
- Develop integrated family-centred and community-centred strategies
- Address research gaps
- Meet funding needs for childhood TB
- Form coalitions and partnerships to improve tools for diagnosis and treatment
The End TB Strategy: 3 pillars and 4 Principles

PILLAR 1
Integrated, patient-centered TB care and prevention

PILLAR 2
Bold policies and supportive systems

PILLAR 3
Intensified research and innovation

Government stewardship and accountability, with monitoring and evaluation

Building a strong coalition with civil society and communities

Protecting and promoting human rights, ethics and equity

Adaptation of the strategy and targets at country level, with global collaboration
SDG health goal 3 and its 13 targets by 2030

3.1 Reduce Maternal mortality

3.2 Reduce child and neonatal mortality

3.3 End the epidemics of AIDS, tuberculosis, malaria & neglected tropical diseases and combat hepatitis, water-borne and other communicable diseases

3.4 Reduce mortality due to NCD and improve mental health

3.5 Strengthen Prevention and treatment of substance abuse (narcotics, alcohol)

3.6 Reduce Mortality due to road traffic injuries

3.7 Universal access to sexual and reproductive health-care services

3.8 Achieve universal health coverage

3.9 Reduce deaths and illness due to pollution and contamination

3.1a Strengthen implementation FCTC (tobacco)

3.1b Access to affordable essential medicines and technologies

3.1c Increased health financing and health workforce in developing countries

3.1d Enhance capacity for early warning, risk reduction and management of national and global health risks
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TB in adolescents

Age Pyramid TB Casefinding 2012

- Males
- Females

“Know your epidemic”

TB in children (0-14 yrs)

Around 1,000,000 cases or 10% of total caseload
M:F ratio: 1.1-0.9
40% in SE Asia and 31% in Africa

169,000 deaths in HIV-uninfected
41,000 deaths in HIV-infected

Increasing case notifications to 6.3% of notified cases globally

Country specific data
Reporting disaggregated by age
Proportion of new and relapse TB that were children in 2015
The burden of MDR TB

It is estimated that 25,000 children developed MDR TB in 2014 although the vast majority (>95%) were not detected and treated.

Shorter course regimens and towards no injectables
New drugs (DLM/BDQ) for children

Preventive therapy for MDR TB contacts a major current issue
• RCTs commenced in 2016
• Observational evidence accumulates

• Harausz E, Garcia-Prats AJ, Seddon J et al. AJRCCM 2016
## Prevention of TB in children

<table>
<thead>
<tr>
<th><strong>Improved case-finding and management</strong></th>
<th>Early identification and effective treatment of infectious TB and MDR TB cases will reduce the burden of child TB and MDR TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCG</strong></td>
<td>The main benefit of neonatal BCG is protection against severe disseminated forms of TB in children. Recent global shortages: in 2015, 163 countries with &gt;90% coverage in 102 countries</td>
</tr>
<tr>
<td><strong>Contact screening and management</strong></td>
<td>Opportunity for active case detection of TB in contacts of all ages. Focus of LTBI management is on individuals infected with TB that have greatest likelihood of developing active TB disease following infection – this includes young children and HIV-infected children of any age. Widely recommended but uptake by families and implementation by NTP are poor.</td>
</tr>
<tr>
<td><strong>Infection control</strong></td>
<td>Lack of awareness of risk for children attending health facilities with carers – TB wards; TB clinics; HIV clinics</td>
</tr>
</tbody>
</table>
Available data on numbers of eligible child contacts that were started on preventive therapy in 2015

Only 9 of 30 high burden countries reported data. Afghanistan and Bangladesh reported the largest number: around 10,000. WHO African region reported 28% of total.
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

A “top ten” indicator for monitoring implementation of the End TB Strategy

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

87,000 children started on “preventive treatment” or 7% of estimated 1.2 million young child household contacts of bacteriologically confirmed TB cases in 2015

Recommendations for high TB burden setting
- TB incidence rate ≥100 per 100,000 population

**Strong recommendations for at-risk populations:**
- People living with HIV
- Children under 5 years of age who are household contacts of pulmonary TB cases

**Global and national indicators**
- Proportion of children who are household contacts who have completed evaluation for TB
- Proportion of those eligible for prevention that have started treatment
- Proportion that have completed
Numbers for LTBI management in children

Estimates in 2014: 2.4 million young children (<5 years) and 5.1 million older children (5-14 years) living in households of patients with TB
Of these, around 240,000 (10%) young children and 420,000 (8%) older children will have TB
Of the remaining 2.16 million young child contacts and 4.68 million older child contacts without TB, it was estimated that 848,453 (or 39%) and 2,660,885 (or 57%) were infected.

Therefore, the global target of 90% or more of exposed children translates to:
• at least 6.2 million child contacts of all ages treated with preventive therapy if screening did not include testing for LTBI
• around 2 million if preventive therapy was limited to young child contacts.

Detection of LTBI

• Current major shortages of tuberculin solution
• A novel skin test C-Tb developed at Statens Serum Institut, Copenhagen uses specific *M. tuberculosis* antigens (ESAT-6 and CFP-10) with cut-point of 5 mm induration established
• C-Tb is more specific than TST as not affected by prior BCG
• When evaluated in patients with active TB, sensitivity lower than for TST and reduced in PLHIV with marked immunosuppression as measured by CD4 count (as for TST)
• Compared to IGRA, C-Tb does not require a laboratory and is likely to be low-cost

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).
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6H, or
9H, or
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3RH

(Strong recommendation, moderate to high quality of evidence).
Closing the Policy-Practice Gap in the Management of Child Contacts of Tuberculosis Cases in Developing Countries

Philip C. Hill¹*, Merrin E. Rutherford¹, Rick Audas², Reinout van Crevel³, Stephen M. Graham⁴,⁵

¹Centre for International Health, Department of Preventive and Social Medicine, University of Otago School of Medicine, Dunedin, New Zealand, ²Department of Preventive and Social Medicine, University of Otago School of Medicine, Dunedin, New Zealand, ³Department of Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, ⁴Centre for International Child Health, Department of Paediatrics, University of Melbourne, Melbourne, Australia, ⁵International Union Against Tuberculosis and Lung Disease, Paris, France

Tropical Medicine and International Health
doi:10.1111/j.1365-3156.2012.03053.x

VOLUME 17 NO 10 PP 1264–1273 OCTOBER 2012

Review

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

Merrin E. Rutherford¹, Philip C. Hill¹, Rina Triasih², Rebecca Sinfield³, Reinout van Crevel⁴ and Stephen M. Graham³

¹Centre for International Health, Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand
²Department of Pediatrics, Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia
³Mersey Deanery, Liverpool, UK
⁴Department of Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands
⁵Centre for International Child Health, University of Melbourne, Department of Paediatrics and Murdoch Children’s Research Institute, Royal Children’s Hospital, Melbourne, Vic., Australia
WHO symptom based screening

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

Less than 5 years

- Well
  - Preventive therapy
    - If becomes symptomatic

- Symptomatic
  - Evaluate for TB disease
    - If becomes symptomatic

More than 5 years

- Symptomatic
  - Evaluate for TB disease
    - If becomes symptomatic

- Well
  - No treatment
Need for M & E tools for contact management

• Numbers screened
• Numbers (%) diagnosed with TB
• Numbers (%) eligible for preventive therapy
• Numbers (%) received preventive therapy
• Numbers (%) completed preventive therapy
Sample Contact Screening Register

<table>
<thead>
<tr>
<th>No.</th>
<th>Date of contact screen</th>
<th>Name of index case</th>
<th>Name of contact</th>
<th>Age</th>
<th>Sex</th>
<th>Symptom screen</th>
<th>HIV status</th>
<th>Management</th>
<th>Date and sign when complete</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. Well</td>
<td>1. Positive</td>
<td>1. IPT</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Symptomatic</td>
<td>2. Negative</td>
<td>2. TB treatment</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4. Did not seek care</td>
<td>4. Did not seek care</td>
<td>4</td>
</tr>
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</table>
# Isoniazid Preventive Treatment Register

**PHC centre/Hospital TB control Unit:**

**Year:**

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Age</th>
<th>Sex (M/F)</th>
<th>HIV-infected (Y/N/U)</th>
<th>IPT started (date)</th>
<th>Monthly follow-up Insert weight and tick if collected IPT</th>
<th>Outcome</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>1 2 3 4 5 6</td>
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</tr>
</tbody>
</table>
Introduction of the new FDCs in 2016

- Rifampicin 75 mg + Isoniazid 50 mg + Pyrazinamide 150 mg (two-month intensive phase)
- Rifampicin 75 mg + Isoniazid 50 mg (four-month continuation phase)

- Product attributes: Correct, WHO-recommended doses, Dispersible in liquid, Palatable fruit flavors
- The average treatment costs is $15.54 through the Global Drug Facility (GDF)
- First introduced in Kenya and PNG
- UNITAID funding to scale-up
<table>
<thead>
<tr>
<th>Body Weight (Kgs.)</th>
<th>Isoniazid (200mg/5ml)</th>
<th>Rifampicin (200mg/5ml)</th>
<th>Pyrazinamide (250mg/5ml)</th>
<th>Ethambutol (400mg/tab)</th>
<th>Streptomycin* (1g/2ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10mg/kg</td>
<td>15mg/kg</td>
<td>30mg/kg</td>
<td>20mg/kg</td>
<td>Tablet</td>
</tr>
<tr>
<td>2.1-3</td>
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<td>1.00</td>
<td>1.75</td>
<td>1/8*</td>
<td>0.18</td>
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<tr>
<td>3.1-4</td>
<td>1.00</td>
<td>1.50</td>
<td>2.50</td>
<td></td>
<td>0.24</td>
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<tr>
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<td>3.00</td>
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<td></td>
<td></td>
<td>1+1/2</td>
<td>1.8</td>
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*Dosages are based on WHO guidelines.
<table>
<thead>
<tr>
<th>Weight bands</th>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
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<tbody>
<tr>
<td></td>
<td>RHZ 75/50/150</td>
<td>E 100</td>
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<tr>
<td>4-7kg</td>
<td>1</td>
<td>1</td>
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<td>8-11kg</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>12-15kg</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>16-24 kg</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>25 kg+</td>
<td>Go to adult dosages and preparations</td>
<td>For example: 2 RHZE 150/75/400/275</td>
</tr>
</tbody>
</table>
Rapid development of diagnostics

History

- Tuberculin Skin Test: 1890
- Bacteriology: 1882

Bacteriology

- 1882
- Very low sensitivity

High negative predictive value but poor specificity

Tuberculin Skin Test

- 1890
- Indicates infection with limitations of sensitivity and specificity

Chest X-ray

- 1896
- Low specificity
Clinical challenges are the diagnostic challenges

- Young age
- Acute severe pneumonia
- HIV-infected
- Malnourished
- MDR TB
Diagnostic yield from Xpert for pulmonary TB comparing children to adults

Xpert cannot be used to rule out TB

Xpert needs research on implementation to inform optimal usage in children
Experience of Xpert yield for presumptive TB in children in programmatic conditions

- Diagnostic yield twice as high as smear microscopy in Indian children with presumptive TB
- 12970 presumptive with 1,107 (8.5%) TB diagnosed
- Of these, 143 (13%) with Rif resistance

- Similar yield from induced sputum (5%), gastric lavage (6%) and CSF (7%) – higher yield (36%) from FNA

- Lower sensitivity (42%) from Xpert in outpatients versus inpatients and from presumptive cases from contact screening
Job aides
• Membership increased by around 30% to 284 members

• New members of core group in 2016
  o Mandy Slutsker, WHO Civil Society Task Force
  o High burden country/regional representation: WPRO – Telly How stepped down and replaced by Dr Sally Gatchalian (Philippines Pediatric Infectious Disease Society)

• Core group conference calls in 2016: February 23, July 19
• Core group F2F meeting: Oct 27

• New chair elected for 2017
Technical assistance and training

- Sri Lanka
- Nepal
- Viet Nam
- The Philippines
- Kenya
- Indonesia
- Myanmar
- PNG
TB meetings and conferences

- Annual WHO STAG TB meeting, Geneva
- NTP managers meeting, Geneva
- Pan African Thoracic Society meeting, Nairobi
- Annual PhilCAT Convention, Manila
- The Union European, Bratislava
- PNG Paediatric Society, Port Moresby
- Western Pacific Regional NTP manager’s meeting, Manila
- IMCI meeting, Geneva
- Unicef meeting in collaboration with WHO and TB Alliance, New York.
- A 3-day interactive seminar on ‘Where is TB in Maternal and Child Health’ held on the MSH LeaderNet platform
- American Society of Tropical Medicine and Hygiene annual meeting, Atlanta
- Union World conference on Lung Health, Liverpool
Contribution to TB guidelines

• NTP guidelines updated
• WHO consolidated guidelines on LTBI management
• WHO MDR TB guidelines
• WHO new drugs in children
• WHO Chest radiography in TB detection
• NIH SOPs for diagnostics
New (and old) diagnostics including biomarkers

New (and old) preventive therapy – DS and DR

Shorter treatment regimens

Shorter LTBI management regimens

Second line and new drugs – PK and safety

Implementation research

The full report is available here: http://www.pipelinereport.org
2016 TB R&D Resource Tracking Report

TAG started tracking *pediatric* TB R&D spending in 2010

The *Global Plan to End TB* includes some pediatric TB R&D funding targets: currently at about 50% of $200M targeted for 2011-2015 in Childhood TB Roadmap

2011-2015 pediatric TB R&D investments make up about 3% of total TB R&D spending and most is on drug development (60%)

**2016 TB R&D Resource Tracking Report Findings**

In 2015, $26.7M invested in pediatric TB R&D

- 60% drugs
- 17% diagnostics
- 8% basic science
- 7% vaccines
- 7% operational research

Pediatric TB R&D Funding by Research Category, 2015
Total: $26,700,543

- **Diagnostics**: $4,446,229 (17%)
- **Vaccines**: $1,893,253 (7%)
- **Basic Science**: $2,184,371 (8%)
- **Operational Research**: $1,757,335 (7%)
- **Drugs**: $16,139,836 (60%)
- **Infrastructure/Unspecified**: $279,520 (1%)
2016 Pipeline Report

- Tracks pipeline for pediatric TB treatment studies and formulation development
- And now also includes special section tracking pediatric TB diagnostics research
- Includes recommendations for researchers, regulators, policy makers, and donors to help fill critical knowledge gaps, expedite development, and facilitate access

• WHO Global TB Programme
  • Malgosia Grzemska
  • Annemieke Brands

• Core members of Child TB sub-group

• NTP managers and Regional WHO TB programmes

• TB Alliance

• USAID