Treatment of childhood TB: issues and controversies

23rd PHILCAT Annual convention, Manila
19th August 2016

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Centre for International Child Health, University of Melbourne

International Union Against Tuberculosis and Lung Disease
(The Union)

Chair, Child TB sub-group, Stop TB Partnership
Outline

• Child TB in global framework

• Rationale for revised dosages

• Advantages of the new fixed-dose combination for children

• Update on diagnosis

• Strengthening links between paediatricians and NTP
Childhood tuberculosis: ending the neglect

JR Starke

In 1956, Katherine H K Hsu asked, “Should primary tuberculosis in children continue to be neglected?”¹ She noted that the advent of isoniazid made possible the successful treatment of early tuberculosis in children to prevent serious pulmonary and extra-pulmonary complications, and to prevent reactivation disease in adolescents and adults. Subsequent scientific study has shown that tuberculosis in childhood is frequent, with a substantial morbidity and mortality. The main deficiencies were: failure of treatment of latent tuberculosis infection in the child due to poor adherence to therapy; failure to treat children known to have been in contact with a case of tuberculosis before the child developed a positive tuberculin skin test (TST) or disease; and delays or inadequacies in the contact investigation of an
Putting child TB on the global public health agenda

Child TB subgroup of Stop TB Partnership formed 2003

Children recognised as a vulnerable group in need of increased case-finding: 2009

International Child TB Meeting, Stockholm, 2011

CALL TO ACTION for CHILDHOOD TB

Read the Call in French, Read the Call in Russian

Sign the Call to Action

We, participants gathered at the ‘International Childhood Tuberculosis Meeting’ held March 17-18, 2011 in Stockholm, Sweden recognize that:
67th World Health Assembly, Geneva, May 2014
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
TB in the context of maternal, neonatal, child and adolescent health

Increasing recognition that TB is an increasingly important cause of morbidity and mortality in infants and young children globally

Pregnancy-related TB – maternal and infant outcomes

Orphans due to TB – estimated to be around 9 million globally

Catastrophic economic costs of TB – families living with TB

TB in adolescents – uncertain burden and specific management issues

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.
“Know your epidemic”

**TB in children** (0-14 yrs)
358,521 reported in 2014
- 30% more than in 2013

“Best” estimates:
1,000,000 cases (UI: 900,000-1,100,000) or
10.4% of total caseload
140,000 deaths
Child TB burden in Philippines

WHO Global report 2014
Among 97,221 new cases:
2,065 (2%) cases children (<15 yrs)
M:F ratio: 2.3

WHO Global report 2015
Among 97,578 new and relapse cases:
12,191 (12%) cases children
M:F ratio: 1.8
Treatment
Treatment of TB in children

- Principles of treatment of TB in children are same as for adults – with similar regimens
- Most young children have paucibacillary disease which is why fourth drug is less critical in young children
- Children with TB usually respond well with symptomatic improvement during intensive phase and good outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Site</th>
<th>% EPTB</th>
<th>F/up period</th>
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<th>Mortality</th>
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<td>PNG</td>
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<tr>
<td>Reis FJ et al. Am Rev Resp Dis 1990</td>
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<td>Brazil</td>
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<td>Te Water Naude et al. PIDJ 2000</td>
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<td>South Africa</td>
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<td>18-36 mths</td>
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<tr>
<td>Al Dossary et al. PIDJ 2002</td>
<td>175</td>
<td>USA</td>
<td>9%</td>
<td>4 years</td>
<td>1</td>
<td>0%</td>
</tr>
</tbody>
</table>
TB treatment is well tolerated in children

- Adverse events are unusual and the most important is hepatotoxicity

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>N</th>
<th>Regimen</th>
<th>Adverse events</th>
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<tr>
<td>Te Water Naude et al. PEDJR Infect Dis J 2000</td>
<td>117</td>
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<td>2 R₂H₂Z₂ 4 R₂H₂</td>
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<tr>
<td>Al Dossary et al. PEDJR Infect Dis J 2002</td>
<td>175</td>
<td>2 RHZ 4 R₂H₂</td>
<td>1.2%</td>
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</tbody>
</table>
# Treatment adherence in children

Adherence for the full course of TB treatment is a challenge in children

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>No.</th>
<th>Poor adherence or defaulted</th>
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<tr>
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<td>USA</td>
<td>175</td>
<td>9% poor adherence</td>
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<tr>
<td>Biddulph J. PIDJ 1990</td>
<td>PNG</td>
<td>639</td>
<td>28% defaulted</td>
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<td>Te Water Naude et al. PIDJ 2000</td>
<td>South Africa</td>
<td>206</td>
<td>22% poor adherence</td>
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<td>Meissner PE et al. Int J TB Lung Dis 2002</td>
<td>Uganda</td>
<td>236</td>
<td>28% poor adherence</td>
</tr>
</tbody>
</table>
| Harries AD et al. Int J TB Lung Dis 2002 | Malawi        | 2,739 | 13% defaulted  
|                               |                |      | 21% unknown                 |

**SHINE trial** – commenced 2016

4 month regimen for non-severe TB in children using new FDC
Ethambutol in tuberculosis: time to reconsider?

S M Graham, H M Daley, A Banerjee, F M Salaniponi, A D Harries

- Ethambutol is recommended as fourth drug in intensive phase of first-line regimens
- Risk of toxicity is dose-related and related to duration of therapy
- The risk of toxicity is **negligible** for children of any age when ethambutol is used at recommended dosages – especially as duration is usually limited to 2 months
- Ethambutol can be safely used at recommended dosages in all ages
Pharmacokinetics of ethambutol in children and adults with tuberculosis


Very low Cmax (<1 mg/liter) for young children in studies in USA and Malawi –

target for ethambutol 2-6 mg/liter
Rationale for revised dosages

• Pharmacokinetic studies of first-line drugs for treatment of TB consistently showed:
  – lower levels in young children than in adults when using same mg/kg dosages, and
  – inadequate levels in young children when using recommended dosages at that time
Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children
Population Pharmacokinetic Modeling of Pyrazinamide in Children and Adults with Tuberculosis

Min Zhu, Ph.D., Jeffrey R. Starke, M.D., William J. Burman, M.D., Phillip Steiner, M.D.,
Jerry Jean Stambaugh, Pharm.D., David Ashkin, M.D., Amy E. Bulpitt, B.S.,
Shaun E. Berning, Pharm.D., and Charles A. Peloquin, Pharm.D.

Low Levels of Pyrazinamide and Ethambutol in Children with Tuberculosis and Impact of Age, Nutritional Status, and Human Immunodeficiency Virus Infection

S. M. Graham,1,2,4* D. J. Bell,1,3,4 S. Nyirongo,1 R. Hartkocrn,1 S. A. Ward,2 and E. M. Molyneux2
Malawi-Liverpool-Wellcome Trust Clinical Research Programme,1 Department of Paediatrics,1 and Department of Medicine,1
College of Medicine, Blantyre, Malawi, and Liverpool School of Tropical Medicine, University of Liverpool,
Liverpool, United Kingdom.

1
• Young children (<5 years) eliminate INH faster than older children and adults and require a higher mg/kg INH dosage to achieve serum concentrations comparable to adults

• Peak INH concentrations were <3 mg/liter in 70% of children receiving 4-6 mg/kg and 58% lower in children receiving 4-6 mg/kg compared to those receiving 8-10 mg/kg

• Receiving 10 (range 6-15) mg/kg of rifampin, mean 2-hour rifampin concentration in 54 children (mean age 4 years) of 3.9 (HIV-infected) and 4.8 (HIV-uninfected) mg/liter - considerably less than the suggested lower limit of 8 mg/liter
India on TB treatment thrice weekly:
INH 10 mg/kg; Rif 10 mg/kg; PZA 33 mg/kg

- HIV-uninfected (n=84): children < 3 years had significantly lower RMP, INH and PZA concentrations than older children and 90% of all children had sub-therapeutic C_{max} for Rifampicin
  

- HIV-infected children (n=77): children < 5 years had lower C_{max} and exposure for INH and PZA than older children

- Unfavourable outcomes associated with lower C_{max} of Rif (p=0.002) and PZA (p=0.45)
  
• Cmax for pyrazinamide significantly lower in young children <5 years compared to older children
  Graham SM, et al. AAC 2006

• Peak PZA concentrations at 1 month in 34 children (mean age 3 years) receiving median dose of 23 mg/kg were < 35 mg/kg in the majority
Anti-TB drug-induced hepatotoxicity in children

Donald PR. Pediatric Reports 2011

• Review of 12,708 children receiving preventive therapy (mainly isoniazid alone): 1 (0.06%) jaundice and 110 (8%) abnormal LFTs
• Review of 8984 children treated for TB: 75 (0.83%) jaundice and 380 (9.9%) abnormal LFTs

• Rifampicin dosages used ranged from 10-20 mg/kg
• Isoniazid dosages used ranged from 10-20 mg/kg - extremely low risk with isoniazid dosages <15 mg/kg
Revised dosages for children:

- Rif: 15 (10-20) mg/kg/day was 10 (8-12)
- INH: 10 (10-15) mg/kg/day was 5 (4-6)
- PZA: 35 (30-40) mg/kg/day was 25 (20-30)
- Eth: 20 (15-25) mg/kg/day was 15 (10-20)

Revisions based on pharmacokinetic data not clinical outcome
Age, nutritional status and INH acetylator status affect pharmacokinetics of anti-tuberculosis drugs in children

G. Ramachandran,* A. K. Hemanth Kumar,* P. K. Bhavani,* N. Poorana Gangadevi,* L. S. Vijayasekaran,* V. V. Banu Rekha,* S. Ramesh Kumar,* N. Ravichandran,* G. Mathevan,* S. Swaminathan*

Pharmacokinetics of isoniazid, rifampicin, pyrazinamide and ethambutol in Indian children

Aparna Mukhesjee1, Thirumurthy Velparidilan, Mohit Singla1, Kunwar Kantiya3, Sushil K Kabra1 and Rakesh Lodha1

Pharmacokinetics of Isoniazid, Rifampin, and Pyrazinamide in Children Younger than Two Years of Age with Tuberculosis: Evidence for Implementation of Revised World Health Organization Recommendations

S. Thee, J. A. Seddon1, P. R. Donald1, H. I. Seifart, C. J. Werely, A. C. Hesselings, B. Rosenkranz, S. Roll, K. Magdorczyk, and H. S. Schaff

Tropical Medicine and International Health

doi:10.1111/tmi.12003

Pharmacokinetics of anti-tuberculosis drugs in Venezuelan children younger than 16 years of age: supportive evidence for the implementation of revised WHO dosing recommendations


Pharmacokinetics of anti-TB drugs in Malawian children: reconsidering the role of ethambutol

R. Mlotha1, D. Waterhouse1, F. Dzingalama3, A. Ardrey3, E. Molyneux1, G. R. Davies4 and S. Ward3
Recent PK studies from South Africa, India and Malawi support revised dosages.
PK study in less than 2 years using previous and updated dosages
Thee S, et al AAC 2011

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cmax</th>
<th>Previous Dosage mg/kg</th>
<th>Updated dosage mg/kg</th>
<th>Recommended target concentrations</th>
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<tbody>
<tr>
<td>Rifampicin</td>
<td></td>
<td>6.36</td>
<td>11.69</td>
<td>8-24</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>17.78</td>
<td>36.95</td>
<td></td>
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<tr>
<td>Isoniazid</td>
<td></td>
<td>3.19</td>
<td>8.11</td>
<td>3-6</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>8.09</td>
<td>20.36</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td></td>
<td>29.94</td>
<td>47.11</td>
<td>20-50</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>118.0</td>
<td>175.2</td>
<td></td>
</tr>
</tbody>
</table>
These are the revised dosages (WHO 2014) for children up to 25 kgs:

Rifampicin 15 (7-20) mg/kg/day
Isoniazid 10 (7-15) mg/kg/day
Pyrazinamide 35 (30-40) mg/kg/day
Ethambutol 20 (15-25) mg/kg/day

From 25 kgs, can change to adult dosages and preparations

Note also other revisions to recommendations:

1. Four drugs (RHZE) in intensive phase for new cases in HIV endemic setting
2. No intermittent regimens in HIV-endemic setting
3. 12-month regimens for TBM and osteo-articular TB
4. Streptomycin (or Cat II regimen) no longer recommended for children
Survey of NTPs and revised dosage recommendations

34 countries from 5 regions
Dec 2011-Feb 2012
10 TB high-burden countries

Obstacles to implementation relate to awaiting update of guidelines, need for training, and that available FDCs do not match dosage guidelines.

Preventive therapy not implemented and shortages and stock outs of single isoniazid (H100) preparation

Informal consultation on the development of new paediatric fixed-dose formulations
Stellenbosch, May 2012

• New additions and preferably dispersable or crushable
  – RHZ 75/50/150
  – RH 75/50

• Do not include Ethambutol in FDC

• Retain following products and add that prefer dispersible
  – H 50 & H 100 tablet
  – E 100 tablet
  – Z 150 tablet

• Cut-off for child dosages as < 25 kg

• Revise range for isoniazid to 7-15 mg/kg
In Dec. 2015, first manufacturer Macleods made available new child-friendly correctly-dosed fixed-dosed combinations of the generic drugs used to treat TB:

- 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)
Availability of Child-friendly FDCs

- Market now more responsive to children with TB
- Procurement available through the Global Drug Facility and using Global Fund grants.
- WHO Prequalification of Macleods FDCs anticipated in 2016
- Macleods is pursuing additional regulatory filings across HBCs to ensure broad market access
- Development underway of dispersible isoniazid and ethambutol
<table>
<thead>
<tr>
<th>Weight bands</th>
<th>Numbers of tablets</th>
<th>Numbers of tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive Phase</td>
<td>Continuation Phase</td>
</tr>
<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>
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<tr>
<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 For example: 2 RHZE 150/75/400/275</td>
<td></td>
</tr>
<tr>
<td>Body Weight (Kgs.)</td>
<td>Isoniazid (200mg/5ml)</td>
<td>Rifampicin (200mg/5ml)</td>
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<td>-------------------</td>
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<td>10mg/kg</td>
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<td>Weight bands</td>
<td>Numbers of tablets</td>
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<td></td>
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<td>RHZ</td>
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<tr>
<td>4-7kg</td>
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<td>75/50/150</td>
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<tr>
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<tr>
<td>25 kg+</td>
<td>Go to adult dosages and preparations</td>
<td>For example: 2 RHZE 150/75/400/275</td>
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</tbody>
</table>

Table No. 14 - Drug Administration According to Kg Body Weight for Children

<table>
<thead>
<tr>
<th>Body Weight (Kgs.)</th>
<th>Weight bands</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>
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<tbody>
<tr>
<td></td>
<td></td>
<td>ml</td>
<td>ml</td>
<td>ml</td>
<td>Tablet</td>
<td>ml</td>
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<tr>
<td>2.1-3</td>
<td>1</td>
<td>0.75</td>
<td>1.00</td>
<td>1.75</td>
<td>1/8*</td>
<td>0.18</td>
</tr>
<tr>
<td>3.1-4</td>
<td>1</td>
<td>1.00</td>
<td>1.50</td>
<td>2.50</td>
<td>0.24</td>
<td></td>
</tr>
</tbody>
</table>

24.1-25 | 6.25 | 9.50 | 15.00 | 1.5  | 1.56  | 1.62  | 1.68  | 1.74  | 1.8  |
25.1-26 | 6.50 | 9.75 | 15.50 | 1.5  | 1.56  | 1.62  | 1.68  | 1.74  | 1.8  |
26.1-27 | 6.75 | 10.00 | 16.00 | 1.5  | 1.56  | 1.62  | 1.68  | 1.74  | 1.8  |
27.1-28 | 7.00 | 10.50 | 16.75 | 1.5  | 1.56  | 1.62  | 1.68  | 1.74  | 1.8  |
28.1-29 | 7.25 | 11.00 | 17.50 | 1.5  | 1.56  | 1.62  | 1.68  | 1.74  | 1.8  |
29.1-30 | 7.50 | 11.25 | 18.00 | 1.5  | 1.56  | 1.62  | 1.68  | 1.74  | 1.8  |
30.1-31 | 7.75 | 11.50 | 18.50 | 1.5  | 1.56  | 1.62  | 1.68  | 1.74  | 1.8  |
Advantages of new fixed dose combination

• Can be used for all first-line regimens (i.e. +/-E)
• Ratio of drugs, especially rifampicin: isoniazid allow use of revised recommended dosages in young children
• No breaking of tablets required
• Dispersible – easier to swallow
• Flavoured
• Inexpensive
• Solid preparations simple for transport and storage

• Challenge is to ensure co-availability of single drug preparations for use as preventive therapy (e.g. IPT) or MDR treatment (e.g. PZA)
Diagnosis
Clinical challenges are the diagnostic challenges

- Young age
- Acute severe pneumonia
- HIV-infected
- Malnourished
- MDR TB
Risk of TB disease following infection by age

Diagnosing Childhood Tuberculosis - What do we have?

History

Tuberculin-Skin Test (1890)

Chest X-ray (1896)

Bacteriology (1882)

- Indicator of infection with limitations
- Low Specificity
- Low Sensitivity

Ozuah (2001) JAMA

High negative predictive value
Diagnostic accuracy of chest radiography in detecting mediastinal lymphadenopathy in suspected pulmonary tuberculosis

G H Swingler, G du Toit, S Andronikou, et al.

Arch Dis Child 2005 90: 1153-1156

Sensitivity = 67%
Specificity = 59%

Observer variation in detecting lymphadenopathy on chest radiography

G. Du Toit, G. Swingler, K. Iloni

School of Child and Adolescent Health, Red Cross Children’s Hospital and University of Cape Town, Cape Town, South Africa

Inter-observer agreement = 0.33
Intra-observer agreement = 0.55
What about Xpert?


• Xpert is more sensitive and specific than smear
• Xpert compared to culture has:
  – Sensitivity 66%
  – Specificity 98%
• Xpert provides more rapid result than culture
• Xpert provides rifampicin resistance data

• Introduction of Xpert-ultra in 2017

• Challenge remains to provide a sample
Xpert MTB/RIF should be used as the initial diagnostic test in children:

suspected of having MDR TB or HIV associated TB
– strong recommendation, very low quality of evidence

suspected of TB (incl extrapulmonary TB)
– conditional recommendation acknowledging resource implications, very low quality of evidence

from Boehme CC et al, NEJM 2010
Diagnostic yield 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

Desk-guide for diagnosis and management of TB in children

Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide

International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

Childhood TB for Healthcare Workers: an Online Course
Prevention
## Available approaches to prevent TB

<table>
<thead>
<tr>
<th>Improved case-finding and management</th>
<th>Early identification and effective treatment of infectious TB cases will reduce transmission of infection and therefore disease</th>
</tr>
</thead>
</table>
| **BCG**                             | Neonatal BCG immunisation is used widely but efficacy is variable  
The main proven benefit of neonatal BCG is protection against severe disseminated forms of TB in children |
| **Contact screening and management** | Focus of preventive therapy is on individuals infected with TB that have greatest likelihood of developing active TB disease following infection – this includes infants, young children and HIV-infected persons of any age  
Widely recommended but uptake by eligible groups and implementation by NTP are poor in TB endemic settings |
| **Infection control**               | Reduce infection risk at health facilities – TB wards; TB clinics; HIV clinics |


Global Plan to Stop TB 2016-2020

Included 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
Policy Forum

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

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

Tropical Medicine and International Health

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. Graham⁵

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

doi:10.1111/j.1365-3156.2012.03053.x

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Barriers to preventive therapy

- Screening includes investigations – TST and CXR
- Facility-based implementation – travel and waiting
- Lack of understanding of rationale
- Time required by health workers
- Lots of myths and misperceptions
- Lack of suitable preparations
- Adherence a common challenge - long regimens
- Transport costs
- Medication costs
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
Shorter, simpler preventive therapy regimens

- Standard regimen is 9H or 6H
- Dosage in young children 10 mg/kg daily
- INH + Rifapentine (3HP) versus 9H –
  - Weekly (12 dosages) versus daily (270 dosages)
  - Meet non-inferiority criteria: 7 TB cases/3986 3HP versus 15/3745 9H (cumulative rate 0.43%) Sterling TR, et al. NEJM 2011
  - Meet non-inferiority criteria in 2-17 years of age: 0/471 3HP v 3/434 9H (cumulative rate 0.74%) Villarino ME, et al. JAMA Pediatr 2015
  - Less hepatotoxic 0.4% (3HP) versus 1.8% (9H) Bliven-Sizemore EE, et al. IJTL 2015
- Now US recommendations except < 2 years, PLHIV on ART, pregnancy, presumptive infection with DR TB
- 3RH routinely used in UK
- Pyrazinamide containing e.g. 2RZ, unacceptable frequency of hepatotoxicity – observations in adults
Currently available options for preventive therapy in young children

The Union Deskguide – third edition, 2016

**Table 4a - H50 or H100 tablets daily for 6 months duration (IPT – 6H)**

<table>
<thead>
<tr>
<th>Weight bands</th>
<th>Isoniazid (mgs)</th>
<th>H50 tablet</th>
<th>H100 tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-7kg</td>
<td>50</td>
<td>1</td>
<td>1/2</td>
</tr>
<tr>
<td>8-11kg</td>
<td>100</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>12-15kg</td>
<td>150</td>
<td>3</td>
<td>1 1/2</td>
</tr>
<tr>
<td>16-24 kg</td>
<td>200</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 4b – RH 75/50 FDC daily for 3 months (3RH)**

<table>
<thead>
<tr>
<th>Weight bands</th>
<th>RH 75/50 tabs</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-7kg</td>
<td>1</td>
</tr>
<tr>
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</tr>
<tr>
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<td>3</td>
</tr>
<tr>
<td>16-24 kg</td>
<td>4</td>
</tr>
</tbody>
</table>

For children that are 25 kg and above, use adult preparations: one tablet of H300mg or two RH150/75.
Management of MDR TB contacts

• No current guidelines or recommendations

• Observational studies suggest that preventive therapy regimen that is determined by drug susceptibility of index case is effective

• Randomised placebo-controlled trials of levofloxacin for MDR contacts to start in 2015 in South Africa and Viet Nam
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 healthcare 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
Framework for child TB and NTP

Figure. Interventions that target stages of the continuum in children from susceptibility to disease and outcome.
Importance of data of TB in children by NTP

• Value of audit to identify challenges/barriers
  – Situational analysis
  – Case management and outcome
  – Background data and potential focus for operational research

• Improved child-related NTP data and activities
  – Allocation of resources for child TB activities
  – Drug procurement
  – Focus for training
  – Advocacy

• Monitoring & evaluation
“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