Available approaches to prevent TB in children

<table>
<thead>
<tr>
<th>Improved case-finding and management</th>
<th>Early identification and effective treatment of infectious TB cases will reduce the burden of child TB</th>
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**Available approaches to prevent TB in children**

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<th>Improved case-finding and management</th>
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</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 |
Effectiveness of BCG is variable

- BCG more protective against disseminated TB and TBM than pulmonary TB
- BCG has a role in prevention of leprosy
- BCG effectiveness to protect from TB also depends on:
  - BCG strain used
  - Age it is given
  - Region
BCG protects against disseminated TB in children

Summary Efficacy
Miliary Tuberculosis 77%

Summary Efficacy
Tuberculous Meningitis 73%


<table>
<thead>
<tr>
<th>Publication date</th>
<th>Efficacy (%, 95% CI)</th>
<th>Publication date</th>
<th>Efficacy (%, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tuberculous meningitis</strong></td>
<td></td>
<td><strong>Miliary tuberculosis</strong></td>
<td></td>
</tr>
<tr>
<td>Buenos Aires, Argentina</td>
<td>1988</td>
<td>98% (70 to 100)</td>
<td>Buenos Aires, Argentina</td>
</tr>
<tr>
<td>Bahia, Brazil</td>
<td>1991</td>
<td>91% (78 to 97)</td>
<td>Yangon, Burma</td>
</tr>
<tr>
<td>São Paulo, Brazil</td>
<td>1990/93</td>
<td>87% (72 to 94)</td>
<td>Papua New Guinea*</td>
</tr>
<tr>
<td>São Paulo, Brazil</td>
<td>1990/93</td>
<td>92% (65 to 98)</td>
<td>Djakarta, Indonesia</td>
</tr>
<tr>
<td>Belo Horizonte, Brazil</td>
<td>1988</td>
<td>81% (47 to 93)</td>
<td>Summary efficacy</td>
</tr>
<tr>
<td>Belo Horizonte, Brazil</td>
<td>1988</td>
<td>65% (17 to 86)</td>
<td></td>
</tr>
<tr>
<td>Yangon, Burma</td>
<td>1987</td>
<td>52% (13 to 73)</td>
<td></td>
</tr>
<tr>
<td>Nagpur, India</td>
<td>1996</td>
<td>87% (70 to 94)</td>
<td></td>
</tr>
<tr>
<td>Chennai, India</td>
<td>1996</td>
<td>77% (63 to 86)</td>
<td></td>
</tr>
<tr>
<td>Delhi, India</td>
<td>1996</td>
<td>64% (30 to 81)</td>
<td></td>
</tr>
<tr>
<td>Delhi, India</td>
<td>1989</td>
<td>84% (69 to 97)</td>
<td></td>
</tr>
<tr>
<td>Lucknow, India</td>
<td>1999</td>
<td>47% (-6 to 74)</td>
<td></td>
</tr>
<tr>
<td>Papua New Guinea*</td>
<td>1980</td>
<td>58% (-36 to 87)</td>
<td></td>
</tr>
<tr>
<td>Delhi, India</td>
<td>1993</td>
<td>56% (-49 to 87)</td>
<td></td>
</tr>
<tr>
<td>Summary efficacy</td>
<td></td>
<td>73% (67 to 79)</td>
<td></td>
</tr>
</tbody>
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## Available approaches to prevent TB in children

<table>
<thead>
<tr>
<th>Improved case-finding and management</th>
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| **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** | This has huge potential to reduce the burden of TB in children  
Focus 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 children of any age  
Widely recommended but uptake by families and implementation by NTP are poor |
Risk of TB disease following infection by age


![Risk of TB disease following infection by age graph](image-url)
Studies of child contacts in African communities

- One-third to two-thirds of child household contacts of TB cases have evidence of TB infection i.e. TST positive
- Incidence of TB disease among household contacts is very high – reported as >1,000 cases/100,000 population
- Likelihood of infection is related to closeness/proximity of contact to and sputum smear positivity of index case
- Risk of infection greatest when the index case is the child’s carer e.g. mother, grandmother
- HIV-infected children are at increased risk of exposure to TB

### Studies of child contacts in Asian countries

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>No. of child contacts</th>
<th>Proportion with TB infection</th>
<th>Proportion with TB disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrew et al</td>
<td>India</td>
<td>398</td>
<td>39 %</td>
<td>5.5 %</td>
</tr>
<tr>
<td>Narain et al</td>
<td>India</td>
<td>790</td>
<td>24 %</td>
<td>NR</td>
</tr>
<tr>
<td>Kumar et al</td>
<td>India</td>
<td>142</td>
<td>NR</td>
<td>3 %*</td>
</tr>
<tr>
<td>Singh et al</td>
<td>India</td>
<td>281</td>
<td>34 %*</td>
<td>3 %*</td>
</tr>
<tr>
<td>Rathi et al</td>
<td>Pakistan</td>
<td>151</td>
<td>27 %</td>
<td>NR</td>
</tr>
<tr>
<td>Salazar et al</td>
<td>Philippines</td>
<td>153</td>
<td>69 %</td>
<td>3 %</td>
</tr>
<tr>
<td>Tornee et al</td>
<td>Thailand</td>
<td>500</td>
<td>47 %</td>
<td>NR</td>
</tr>
<tr>
<td>Nguyen et al</td>
<td>Lao PDR</td>
<td>148</td>
<td>31 %</td>
<td>NR</td>
</tr>
<tr>
<td>Okada et al</td>
<td>Cambodia</td>
<td>217</td>
<td>24 %*</td>
<td>9 %*</td>
</tr>
</tbody>
</table>

* Data only for < 5 years; NR: not recorded

From Triasih R et al, J Trop Med 2012
Proportion of children with TB infection (positive TST) by degree of smear positivity of the source case

Kenyon TA et al, Int J Tuberc Lung Dis 2002
Increased risk of TB exposure among young children in HIV-endemic countries

Tanzania NTLP / IUATLD. Progress Report 1996;No. 36

From: Reider HL. Interventions for TB control and elimination. IUATLD publication 2002
More evidence to support screening of child contacts of TB cases: if not now, then when?
Graham SM, Triasih R. Clin Infect Dis 2013

• Evidence that informs the rationale for screening child TB contacts available for over 50 years

• Policy universally accepted but rarely implemented

• Contact screening has two main roles:
  – to identify at-risk contacts such as young or HIV-infected children that require preventive therapy
  – to identify contacts of any age that have tuberculosis i.e. active case-finding.
Why is child contact screening important? 
Prevent child morbidity and mortality

• The prevalence of TB infection is high among child contacts
  Triasih R et al, J Trop Med 2012

• 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
Why is contact screening important? Increased case-finding

• The prevalence of TB infection and disease is high among contacts
  
  
  – All TB cases 4.5% (95% CI 4.3-4.8)
  – Confirmed cases 2.3% (95% CI 2.1-2.5)
  – Latent TB infection 51.4% (95% CI 50.6-52.2)

• TB prevalence significantly higher by active case finding in household contacts (1735/100,000) than with passive case finding (191/100,000)
  

• Incidence of TB disease among contacts was 603 per 100,000 (95% CI 370-830)
  
  PC Hill et al, PLoS ONE 2008

  and in same community, prevalence of TB cases was 1518 per 100,000 among 2174 contacts of 317 adults with smear-positive PTB

Contact investigation for active TB among child contacts in Uganda

- 761 Ugandan child household contacts with TB – half 0-5 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
Early evidence from USA

- 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
IPT reduces the risk of TB disease by around 60% among infected contacts of all ages  

Large observational studies suggest that the efficacy may be higher (80-90%) in child contacts

From: Reider HL. Interventions for TB control and elimination. IUATLD publication 2002
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

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

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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

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
Symptom-based screening is also recommended in the WHO guidance.

Guidance for national tuberculosis programmes on the management of tuberculosis in children.
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

More than 5 years

Symptomatic

If becomes symptomatic

Well

No treatment

Note that contact screening has two important roles
1. Active case-finding
2. Preventive therapy for at-risk contacts without TB
Management of child contacts

- **Decentralise**: symptom-based screening provides opportunity to undertake an integrated family-based approach in the community around the source case receiving DOT rather than requiring referral to health facility for all cases.

- **Adherence**: to IPT for 6 months is a major challenge.

- **Enhanced case-finding**: Note that symptom-based screening also aims to identify symptomatic contacts of any age for investigation for possible TB disease.
Management of child contacts

List close contacts

- What is the age of the contact?
- Is the contact HIV-infected?
- Does the contact have any symptoms suggestive of TB?

Checklist of main symptoms

- Persistent cough for more than 2 weeks
- Weight loss or failure to gain weight
- Persistent fever for more than 1 week and/or night sweats
- Fatigue, reduced playfulness, less active
Management of child contacts

Criteria for contacts to receive IPT

- No active TB disease – no symptoms suggestive of TB
- At high risk of disease following TB exposure
  - < 5 years
  - HIV-infected

<table>
<thead>
<tr>
<th>Management of contacts</th>
<th>Response</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>TB treatment</td>
<td>Register</td>
</tr>
<tr>
<td>Sputum smear positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Refer for further assessment</td>
<td>Fill referral form for patient to take Fill referral register which stays at health facility</td>
</tr>
<tr>
<td>Sputum smear-negative or not available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic and high risk</td>
<td>IPT</td>
<td>IPT register</td>
</tr>
<tr>
<td>Asymptomatic and not high risk</td>
<td>No treatment</td>
<td>Advise to return if symptoms develop</td>
</tr>
</tbody>
</table>
## Sample IPT register

### Isoniazid Preventive Treatment Register

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

**Year:**

<table>
<thead>
<tr>
<th>No.</th>
<th>Name of TB contact treated with IPT</th>
<th>Age</th>
<th>Sex</th>
<th>HIV-infected (Y/N)</th>
<th>IPT started on (date)</th>
<th>IPT completed (Y/N)</th>
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Average age specific risk for disease development following primary infection (pre-BCG)

Average age specific risk for disease development following primary infection with BCG
Average age specific risk for disease development following primary infection: BCG and IPT

High BCG coverage

Contact screening and preventive therapy
## Available approaches to prevent TB in children

| **Improved case-finding and management** | Early identification and effective treatment of infectious TB cases will reduce the burden of child TB |
| **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 |
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Focus 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 children of any age  
Widely recommended but uptake by families and implementation by NTP are poor |
| **Infection control** | Lack of awareness of risk for children attending health facilities with carers – TB wards; TB clinics; HIV clinics |
Summary of prevention

• The main effectiveness of neonatal BCG is prevention of severe, disseminated disease in infants and young children

• Child contact screening and management has huge potential to reduce the burden of child TB

• Child contact screening and management can be instituted at the peripheral facility level on the basis of symptom-based screening

• Community-based child contact screening and management is a means of case-finding suspected TB cases of any age

• IPT must be given for at least 6 months to be effective and a major challenge for effectiveness of IPT is adherence and follow-up is critical

• Contact screening and management has huge potential for operational research