Epidemiological science

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Child Lung Health
International Union Against Tuberculosis and Lung Disease
Paris
Child TB is common wherever TB is common – but how common?

Estimated TB incidence rates, 2011
Reported: range 1%-40%

Important factors:
Incidence of TB
Demographics - age
Effectiveness of case-finding and management
Prevalence of risk factors in children
BCG coverage

The percentage of the tuberculosis caseload made up by children <15 years of age in relation to the incidence of tuberculosis/100,000 population and the population pyramids typical of an (A) developed and a (B) developing community.
Risk of TB disease following infection by age

Expectations in high TB endemic setting

- 0-4 years > 5-14 years

- PTB: EPTB 2:1 to 3:1

- Smear-positive disease < 10%

- The younger the child, the more likely infected by a household contact
<table>
<thead>
<tr>
<th>Malawi NTP, 1998</th>
<th>numbers (proportion of childhood caseload)</th>
<th>proportion of total caseload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total caseload</td>
<td>22,982</td>
<td></td>
</tr>
<tr>
<td>Total childhood</td>
<td>2,739</td>
<td>11.9%</td>
</tr>
<tr>
<td>0-5 years</td>
<td>1,615 (58.9%)</td>
<td>7%</td>
</tr>
<tr>
<td>5-14 years</td>
<td>1,124 (41.1%)</td>
<td>4.9%</td>
</tr>
<tr>
<td>Smear-positive PTB</td>
<td>127 (4.6%)</td>
<td>1.3%</td>
</tr>
<tr>
<td>Smear-negative PTB</td>
<td>1,804 (65.9%)</td>
<td>21.3%</td>
</tr>
<tr>
<td>EPTB</td>
<td>808 (29.5%)</td>
<td>15.9%</td>
</tr>
</tbody>
</table>

Harries AD et al. IJTLD 2002
Child TB accounts for 33% of total TB case-load

<table>
<thead>
<tr>
<th>Pulmonary TB</th>
<th>1208 (61%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear positive</td>
<td>18</td>
</tr>
<tr>
<td>Smear negative</td>
<td>138</td>
</tr>
<tr>
<td>Smear not done</td>
<td>1052</td>
</tr>
<tr>
<td>EPTB</td>
<td>769 (39%)</td>
</tr>
<tr>
<td>Total</td>
<td>1977</td>
</tr>
</tbody>
</table>
### Types of childhood EPTB disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Malawi NTP, 1998</th>
<th>PNG, 2005-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPTB cases</td>
<td>808</td>
<td>1097</td>
</tr>
<tr>
<td>Lymphadenitis</td>
<td>331 (41%)</td>
<td>342 (31%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>101 (12%)</td>
<td>94 (9%)</td>
</tr>
<tr>
<td>Spinal</td>
<td>83 (10%)</td>
<td>41 (4%)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>60 (7%)</td>
<td>12 (1%)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>39 (5%)</td>
<td>173 (16%)</td>
</tr>
<tr>
<td>Miliary</td>
<td>34 (4%)</td>
<td>64 (6%)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>30 (4%)</td>
<td>257 (23%)</td>
</tr>
<tr>
<td>Bone disease</td>
<td>12 (1%)</td>
<td>15 (1%)</td>
</tr>
<tr>
<td>Not indicated/others</td>
<td>118 (14.6%)</td>
<td>99 (9%)</td>
</tr>
</tbody>
</table>

EPTB represented 30% and 39% of childhood TB cases in Malawi and PNG respectively.
**Revised TB recording and reporting forms and registers – version 2006**

### Quarter Report on TB Case Registration in Basic Management Unit

- **Name of BMU:**
- **Facility:**
- **Name of TB Coordinator:**
- **Signature:**

**Date of completion of this form:**

**Patients registered during**___ quarter of year___

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**Block 3: Laboratory activity - sputum smear microscopy**

<table>
<thead>
<tr>
<th>Sex</th>
<th>0-4</th>
<th>5-14</th>
<th>15-24</th>
<th>25-34</th>
<th>35-44</th>
<th>45-54</th>
<th>55-64</th>
<th>&gt; 65</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**New sputum smear microscopy positive TB**

<table>
<thead>
<tr>
<th>No. of TB suspects with positive sputum smear microscopy result</th>
<th>No. of TB suspects with positive sputum smear microscopy positive TB</th>
</tr>
</thead>
</table>

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**No. patients tested for HIV before or during TB treatment**

<table>
<thead>
<tr>
<th>New sputum smear microscopy positive TB</th>
</tr>
</thead>
</table>

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**No. patients HIV positive**

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1. Registration period is based on data registration of cases in the TB Register, following the start of treatment. 01: 1 January–31 March; 02: 1 April–30 June; 03: 1 July–30 September; 04: 1 October–31 December.

2. Other previously treated cases include previous smear microscopy positive pulmonary cases and previously treated extrapulmonary cases transferred from the TB Laboratory Register. Data from TB Laboratory Register based on “Date specimen received” in the laboratory during the quarter, without patients’ examination because of follow-up.

3. NEW evidence of HIV test (results) performed in any recognized facility before TB diagnosis or during TB treatment (end of the quarter) should be reported here.
FIGURE B2.2.3
Reporting of notification data disaggregated by age, 2012

Age disaggregation:
- All case types disaggregated
- Only smear-positive cases disaggregated
- No age disaggregation
- No data reported

No data reported in the following countries:
- Afghanistan
- Angola
- Chad
- China
- Congo (Brazzaville)
- Congo (Kinshasa)
- Eritrea
- Ethiopia
- Gabon
- Gambia
- Ghana
- Guyana
- Iraq
- Jordan
- Kenya
- Kyrgyzstan
- Lebanon
- Libya
- Madagascar
- Malawi
- Mali
- Mongolia
- Morocco
- Namibia
- Nepal
- Nicaragua
- Niger
- Nigeria
- Pakistan
- Palau
- Panama
- Peru
- Philippines
- Russia
- Saudi Arabia
- Sierra Leone
- Somalia
- Sudan
- Syrian Arab Republic
- Tajikistan
- Timor-Leste
- Togo
- Tonga
- Turkmenistan
- Turkmenistan
- Tuvalu
- Ukraine
- United States
- Uruguay
- Uzbekistan
- Vanuatu
- Yemen
- Zambia
- Zimbabwe
Limitations of child TB data

Reported burden of child TB ranges from <2% to 40%

**Under-recognition**

Recent prevalence survey in Laos:
Culture-positive TB was 606 per 100,000
Only 78 children treated for TB in 2012 i.e. <5 per 100,000 children


**Under-reporting**

Recent study from Java, Indonesia:
Only 1.6% of 4,821 TB cases in children were registered with NTP

Increased attention to Child TB

<table>
<thead>
<tr>
<th>Year</th>
<th>New PTB+ (0-14)</th>
<th>Primary Complex (PTB)</th>
<th>Hilary lymphadenopathy</th>
<th>TB Meningitis</th>
<th>Total child TB</th>
<th>Total TB</th>
<th>% Child TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>298</td>
<td>3 111</td>
<td>1 387</td>
<td>64</td>
<td>27 960</td>
<td>128 739</td>
<td>22%</td>
</tr>
<tr>
<td>2009</td>
<td>282</td>
<td>8 521</td>
<td>4 244</td>
<td>175</td>
<td>32 540</td>
<td>134 023</td>
<td>24%</td>
</tr>
<tr>
<td>2010</td>
<td>302</td>
<td>9 334</td>
<td>4 527</td>
<td>370</td>
<td>32 471</td>
<td>137 403</td>
<td>24%</td>
</tr>
<tr>
<td>2011</td>
<td>308</td>
<td>10 234</td>
<td>5 585</td>
<td>256</td>
<td>37 734</td>
<td>143 164</td>
<td>26%</td>
</tr>
<tr>
<td>2012</td>
<td>338</td>
<td>13 367</td>
<td>4 411</td>
<td>163</td>
<td>42 434</td>
<td>147 984</td>
<td>29%</td>
</tr>
</tbody>
</table>
Child health in high TB endemic setting

• High under 5 mortality

• Young age a risk for respiratory disease, malnutrition, meningitis, HIV

• TB is a disease of poverty
Diagnostic challenges

TB in context of child survival

• Severe pneumonia

Autopsy studies: TB in 9% of children dying with respiratory disease –

Clinical studies: 6% culture confirmed plus 13% clinical TB in 270 Ugandan children with acute severe pneumonia –
*Nantango JM, et al BMC Pediatr 2013*

• Severe malnutrition and respiratory disease

23-24% clinical TB and 4-6% microbiologically confirmed TB

• HIV

Changing epidemiology

• Meningitis

In TB endemic settings, *M. tuberculosis* is common cause of meningitis with poor outcome –
Diagnosis – well-defined symptoms

Characteristics of cough: persistent (>2 weeks), unremitting and unresponsive to antibiotics

Fatigue, reduced playfulness

Documented weight loss, failure to thrive (in preceding 3 months)

Well characterized symptoms improve diagnostic accuracy

≥ 3 years: specificity: 98.9%; PPV: 85.1%

Less useful in young

< 3 years: specificity: 82.6%; PPV: 88.6%

Performed poorly in HIV-infected

Assessment of a symptomatic child
8 years and older suspicious of having TB at Township and District Hospitals

Symptomatic
Physical Examination

Pulmonary TB
Sputum examination
Sputum Sm. Neg or Non productive cough
CXR
CXR+
Treat TB
CXR-
Follow up

Extra-pulmonary TB
Cervical glands
Biopsy/FNAC
Treat TB
Other EPTB
Refer to appropriate Centre for further Investigations

Revised National Guideline on Management of Tuberculosis in Children, 2012, Myanmar
CXR important tool for child TB diagnosis
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%

Very low inter-observer and intra-observer agreement
Very poor agreement between reviewers on the assessment of hilar adenopathy
Triasih R, et al. unpublished data

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th></th>
<th>Hilar lymphadenopathy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kappa</td>
<td>95% CI</td>
<td>kappa</td>
<td>95% CI</td>
</tr>
<tr>
<td>R1 – R2</td>
<td>0.25</td>
<td>0.12 – 0.37</td>
<td>0.11</td>
<td>0.07 – 0.28</td>
</tr>
<tr>
<td>R1 – R3</td>
<td>0.34</td>
<td>0.22 – 0.45</td>
<td>0.25</td>
<td>0.06 – 0.43</td>
</tr>
<tr>
<td>R1 – R4</td>
<td>0.46</td>
<td>0.35 – 0.57</td>
<td>-0.03</td>
<td>-0.13 – 0.06</td>
</tr>
<tr>
<td>R2 – R3</td>
<td>0.33</td>
<td>0.21 – 0.46</td>
<td>0.18</td>
<td>0.00 – 0.36</td>
</tr>
<tr>
<td>R2 – R4</td>
<td>0.33</td>
<td>0.21 – 0.45</td>
<td>-0.02</td>
<td>-0.13 – 0.08</td>
</tr>
</tbody>
</table>
Is there an easier way?

16 studies in children to date

Sensitivity 66% compared to culture
Specificity >98% compared to culture

TBXpert Project

The TBXpert Project will provide approximately 1.4 million Xpert MTB/RIF test cartridges and over 220 GeneXpert Instruments for the rapid detection of TB and rifampin resistance in 21 recipient countries in 2013-2015 (see map and list of recipient countries below). The USD25.9 million TBXpert Project is funded by UNITAID and executed by the WHO Stop TB Department and the Stop TB Partnership. To ensure country absorptive capacity and effective use of the technology, the TBXpert Project links a broad network of partners and existing initiatives for TB laboratory strengthening and innovative approaches to expand access to vulnerable populations in both the public and private sector. TBXpert Project partners include the Global Laboratory Initiative (GLI), TB REACH, the Global Drug Facility (GDF), the EXPAND-TB Project, Interactive Research and Development (IRD) and the African Society for Laboratory Medicine (ASLM).

Recipient countries:
Bangladesh, Belarus, Cambodia, Congo, Ethiopia, India, Indonesia, Kenya, Kyrgyzstan, Malawi, Mozambique, Myanmar, Nepal, Pakistan, Philippines, Republic of Moldova, Swaziland, Uganda, United Republic of Tanzania, Uzbekistan, Viet Nam
Context of case-finding

Active versus passive – early versus late disease

What can we learn from vaccine trials
  - young
  - symptoms
  - investigations

What do we learn from child contact studies

What could be the effect of child contact screening
<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 2011
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
Framework for child TB and NTP

Figure. Interventions that target stages of the continuum in children from susceptibility to disease and outcome.
Global consultation on Paediatric Tuberculosis: Disease Burden Estimation and Quantification of its Drug Market
New York, September 25-26th

1. Strengthening surveillance: bringing the non-NTP sector into routine surveillance

2. Studies to address identified data gaps to improve estimates

3. Further data and analyses to improve estimates
Thank you