Pediatric TB research
Barriers and progress

Ben Marais
## Global Burden of TB - 2012

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Estimated Incidence</th>
<th>Estimated number of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>All forms of TB</td>
<td>8.6 million (8.3–9.0 million)</td>
<td>940 000 (1.3–1.6 million)</td>
</tr>
<tr>
<td>HIV-associated TB</td>
<td>1.1 million (13%) (1.0–1.2 million)</td>
<td>320,000 (300,000–340,000)</td>
</tr>
<tr>
<td>Multidrug-resistant TB</td>
<td>450,000 (300,000–600,000)</td>
<td>170 000 (100 000 – 240 000)</td>
</tr>
</tbody>
</table>

### Disease burden in children

~1 million children with TB every year

*Excluding deaths attributed to HIV/TB*

Source: WHO Global Tuberculosis Report 2013

Global Burden of TB - 2012

Jenkins HE et al. Lancet 2014
Epidemic spread of MDR-TB
Children are affected

Marais BJ et. al. JCM 2013; 51: 1818-25

Solid lines show a single loci-MIRU change, while dotted lines show 2 (black coloured) or more (grey coloured) changes. Circles show 12-loci MIRU international type (MIT) numbers and the color of the circles reflects the number of clinical isolates identified (N=71), illustrating unique (sky-blue) versus clustered isolates (deep blue, 2 to 5 strains; dark blue, 5 to 10 strains; brown, 10 to 20 strains; red, 20 strains and more). Additional colour groups demonstrate likely clusters with minimal strain variation.

~ 32 000 children develop MDR-TB every year
All cases ever reported <2% of estimated annual burden

Jenkins HE et.al. Lancet 2014

www.sentinel-project.org
www.treatmentactiongroup.org/tb/publications/2013/we-can-heal
The diagram illustrates the relationship between the incidence of tuberculosis and the percentage of tuberculosis caseload. The x-axis represents the incidence of tuberculosis in logarithmic scale (log10) per 100,000 population, while the y-axis shows the percentage of tuberculosis caseload. Two distinct sections are labeled as A and B, with section B showing a higher incidence and percentage compared to section A. The shaded area indicates the childhood tuberculosis.
Incidences of All TB / 100 000 Population: 1990-2004

Nunn P et al. JID 2007; Suppl 196: S5:14
HIV prevalence in general population:

- 3-4% 0-9y
- 25% 20-39y

Lawn SD et al. CID 2006; 42: 1040-7
Child TB - Why bother?

- Morbidity / disease burden
  Estimated contribution globally ~8-12% of all TB cases
  ~1 million children with TB every year
  Jenkins HE et.al. Lancet 2014

- Mortality / cause of death
  TB is a common, but unrecognized, cause of death in children from TB endemic countries
  Graham S et.al. Lancet 2014

- Epidemic control
  Children >10yrs of age with adult-type disease, are highly infectious and contribute to ongoing transmission

TB is treatable
TB and child survival/mortality

Grossly underestimated among deaths from
- pneumonia
- malnutrition
- meningitis
- HIV

Relative importance likely to increase
- widespread vaccine roll-out (Hib, pneumo, rota)
- rise in DR-TB
Transitions in TB

Susceptible
Exposed
Infected
Diseased
Infectious
Sick
Accessed care
Recognized
Diagnosed
Treated
Completed
Cured
Major transitions

Exposure → Infection → Disease
Fig. 8.—Distribution of the tracheobronchial lymph nodes. (Semidiagrammatic drawing after W. Snow Miller: The Lung, Springfield, Ill., 1937, Charles C Thomas.)
DIVERSITY OF DISEASE

Highly variable clinical severity / relevance

Intra- & extra-thoracic
Age-related risk

Immune compromised

Marais. IJTL 2004
Phase of disease

I  Hypersensitivity
II Miliary TB and TBM
III Lymph node disease / Pleural effusion
IV Adult-type disease

HIV-infected - PERSISTENT RISK OF REACTIVATION DISEASE
## Bacteriologic yield is variable

<table>
<thead>
<tr>
<th>Disease manifestation</th>
<th>Total (%)</th>
<th>Bacteriologic yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not TB</strong></td>
<td>85 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Intra-thoracic TB</td>
<td>307 (69.9)</td>
<td>120/195 (61.5)</td>
</tr>
<tr>
<td>Uncomplicated LN</td>
<td>147 (47.9)</td>
<td>22/64 (34.4)</td>
</tr>
<tr>
<td>ALL other</td>
<td>160 (52.1)</td>
<td>98/131 (74.5)</td>
</tr>
<tr>
<td>Extra-thoracic TB</td>
<td>72 (16.4)</td>
<td>31/46 (67.4)</td>
</tr>
<tr>
<td>Cervical adenitis</td>
<td>35 (48.6)</td>
<td>27/27 (100)</td>
</tr>
<tr>
<td>TBM</td>
<td>14 (19.4)</td>
<td>1/10 (10.0)</td>
</tr>
<tr>
<td>Other</td>
<td>23 (31.9)</td>
<td>5/9 (55.6)</td>
</tr>
</tbody>
</table>

Marais et.al. IJTLD 2006;10:732-738

Bacteriologic yield is variable.
EXPECTED

1) Disease burden
2) Geographic spread
3) Age spectrum
4) Case mix
Child TB Notifications since 2005

>75% cases clinically Dx cervical adenitis

Kindly provided by the Cambodian NTP
Geographic clustering
Provincial Breakdown of child TB cases

N = 5 375 (2011)

- 60% of cases diagnosed in 3 provinces
- Almost 30% in 1 province alone

Majority of cases 5-10yrs of age

Kindly provided by the Cambodian NTP
### Calculated risk of distant/disseminated BCG disease in HIV-infected children

<table>
<thead>
<tr>
<th>Risk scenarios of disseminated BCG disease</th>
<th>Cases/year 2002</th>
<th>Cases/year 2003</th>
<th>Cases/year 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual cases/year</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Risk of disseminated BCG disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case scenario 1, assuming 5% total vertical HIV infection</td>
<td>$\frac{2}{571}=\frac{350}{100000}/\text{year}$</td>
<td>$\frac{2}{608}=\frac{329}{100000}/\text{year}$</td>
<td>$\frac{3}{719}=\frac{417}{100000}/\text{year}$</td>
</tr>
<tr>
<td>Case scenario 2, assuming 10% total vertical HIV infection</td>
<td>$\frac{2}{1142}=\frac{175}{100000}/\text{year}$</td>
<td>$\frac{2}{1217}=\frac{164}{100000}/\text{year}$</td>
<td>$\frac{3}{1439}=\frac{208}{100000}/\text{year}$</td>
</tr>
<tr>
<td>Case scenario 3, assuming 15% total vertical HIV infection</td>
<td>$\frac{2}{1713}=\frac{117}{100000}/\text{year}$</td>
<td>$\frac{2}{1825}=\frac{110}{100000}/\text{year}$</td>
<td>$\frac{3}{2158}=\frac{139}{100000}/\text{year}$</td>
</tr>
</tbody>
</table>

Hesseling et al, Vaccine 2007
New vaccines

Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

Michele D Tameris*, Mark Hatherill*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hussey, Willem A Hanekom, Hassan Mahomed†, Helen McShane†, and the MVA85A 020 Trial Study Team

Interpretation MVA85A was well tolerated and induced modest cell-mediated immune responses. Reasons for the absence of MVA85A efficacy against tuberculosis or *M tuberculosis* infection in infants need exploration.
The culture conundrum

Dodd LE et. al. Lancet 2012
### Xpert MTB/Rif in children

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Sm+</th>
<th>Xpert +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicol (2011) Cape Town</td>
<td>2x Induced sputa</td>
<td>39% (21/87)</td>
<td>74% (52/70)</td>
</tr>
<tr>
<td>Zar (2012) Cape Town</td>
<td>1x NPA 1x IS</td>
<td>24% (21/87) 32% (28/87)</td>
<td>56% (49/87) 74% (64/87)</td>
</tr>
<tr>
<td>Rachow (2012) Tanzania</td>
<td>2-3x sputa or IS</td>
<td>25% (7/28)</td>
<td>75% (21/28)</td>
</tr>
<tr>
<td>Bates (2012) Zambia</td>
<td>1x sputum 1x GA</td>
<td>30% (3/10) 25% (12/48)</td>
<td>90% (9/10) 69% (33/48)</td>
</tr>
</tbody>
</table>
Tuberculous meningitis: a uniform case definition for use in clinical research

Suzaan Marais, Guy Thwaites, Johan F Schoeman, M Estée Török, Usha K Misra, Kameshwar Prasad, Peter R Donald, Robert J Wilkinson, Ben J Marais
Treatment

Old drugs
- No pharmacokinetic (Pk) data in children
- Extrapolated pediatric doses from adult mg/kg dosages

New drugs
- Development cost / ethical barriers / small market
- Nearly impossible to establish efficacy
- Major risk / Minimal potential benefit

Need to separate the issues
1) No reason why efficacy cannot be inferred from adult data
2) Safety and Pk profile must be established separately

Accepted in principle by FDA/EMA
- NIH workshop consensus document in press