TB in children

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Robert Koch 1843-1910
Discovered *M. Tuberculosis* 1882
Web of causation

Mycobacterium tuberculosis

Exposure

Infection

Disease

Crowding

HIV

Poverty

Tobacco smoke

Diabetes mellitus

Malnutrition
Child TB
“spill over” host

Adult TB
maintenance host

POVERTY / HIV

Exposure
Vulnerability
Increasing TB/HIV Burden

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of TB notifications</th>
<th>Population size</th>
<th>TB notification rate, cases/100,000 persons</th>
<th>TB re-treatment rate, %</th>
<th>Estimated prevalence of HIV infection, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>32</td>
<td>5518</td>
<td>580</td>
<td>3</td>
<td>6.3</td>
</tr>
<tr>
<td>1997</td>
<td>42</td>
<td>6429</td>
<td>653</td>
<td>21</td>
<td>8.9</td>
</tr>
<tr>
<td>1998</td>
<td>67</td>
<td>7339</td>
<td>913</td>
<td>7</td>
<td>11.6</td>
</tr>
<tr>
<td>1999</td>
<td>74</td>
<td>8250</td>
<td>897</td>
<td>20</td>
<td>14.2</td>
</tr>
<tr>
<td>2000</td>
<td>90</td>
<td>9161</td>
<td>982</td>
<td>17</td>
<td>16.5</td>
</tr>
<tr>
<td>2001</td>
<td>142</td>
<td>10,071</td>
<td>1410</td>
<td>15</td>
<td>18.4</td>
</tr>
<tr>
<td>2002</td>
<td>150</td>
<td>10,982</td>
<td>1366</td>
<td>18</td>
<td>19.9</td>
</tr>
<tr>
<td>2003</td>
<td>175</td>
<td>11,892</td>
<td>1472</td>
<td>22</td>
<td>21.1</td>
</tr>
<tr>
<td>2004</td>
<td>188</td>
<td>12,803</td>
<td>1468</td>
<td>24</td>
<td>21.9</td>
</tr>
</tbody>
</table>

\( ^a \) \( P = .007 \), by test for trend.
\( ^b \) \( P = .073 \), by test for trend.
TB - Age & Gender shift

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?

- **Rare** (not true)
  
  Estimated contribution globally 15-20%
  
  Cape Town, SA
  
  ALL TB incidence children 407/100 000/yr (adults 845)
  
  Marais, IJTL 2006;10:259-63

- **Limited disease only** (not true)
  
  Autopsy study Zambia, as common a cause of death as acute bacterial pneumonia
  
  Chintu, Lancet 2002; 360: 985-90

- **Pose no transmission risk** (not true)
  
  Adolescents frequently as infectious as adults
  
  Marais, PIDJ 2005; 24: 743-44
### Lung Disease Identified At Necropsy In Zambian Children

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HIV positive N=180</th>
<th>HIV negative N=84</th>
<th>Odds ratio (95%C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyogenic pneumonia</td>
<td>41%</td>
<td>50%</td>
<td>0.7 (0.4- 1.2)</td>
</tr>
<tr>
<td>PCP</td>
<td>29%</td>
<td>7%</td>
<td>5.3 (2.1-15.7)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>18%</td>
<td>26%</td>
<td>0.6 (0.3- 1.2)</td>
</tr>
<tr>
<td>CMV</td>
<td>22%</td>
<td>4%</td>
<td>7.7 (2.3-40.0)</td>
</tr>
<tr>
<td>Interstitial pneumonitis</td>
<td>8%</td>
<td>18%</td>
<td>0.4 (0.2-0.96)</td>
</tr>
<tr>
<td>Other</td>
<td>24%</td>
<td>16%</td>
<td>-</td>
</tr>
</tbody>
</table>

**M. tb** 2nd Most Common Pathogen identified in Children with CAP who Failed Empirical Antibiotic Therapy


Among children who failed to respond to AB Rx:

- **<1yr of age:** *M. tb* in 18% HIV+ / 29% HIV-
- **>1yr of age:** *M. tb* in 39% HIV+ / 57% HIV-

Table 5: Organisms isolated from children who were investigated for failing to respond by HIV status and age

## Under 5 mortality Kolkata, India rate / 1000 person yrs by age grp

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>&lt;1yr</th>
<th>1-4yrs</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory infections</td>
<td>2.97</td>
<td>0.86</td>
<td>1</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1.98</td>
<td>0.52</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoeal diseases</td>
<td>1.98</td>
<td>0.34</td>
<td>3</td>
</tr>
</tbody>
</table>

- Verbal autopsy study covering slum areas 29 & 30
- Death surveillance May 2003 - October 2004

Accurate baseline demographic data / numbers small

Kanungo S et. al. Bull WHO 2010; 88: 667-74
Millennium Development Goal 4: Reduce Child Mortality

REDUCE CHILD MORTALITY

Under-Five Child Mortality
Global distribution of cause-specific mortality among children under five years of age:

- Pneumonia: 19%
- Diarrhoea: 17%
- Malaria: 8%
- Neonatal: 37%
- Measles: 4%
- HIV/AIDS: 3%
- Injuries: 3%
- Other: 10%

Note: The global distribution of under-five deaths by cause does not sum to 100% due to rounding.


January 2007
Millennium Development Goals

1. Eradicate extreme poverty and hunger
2. Achieve universal primary education
3. Promote gender equality and empower women
4. Reduce child mortality
5. Improve maternal health
6. Combat HIV/AIDS, malaria and other diseases
7. Ensure environmental sustainability
8. Global partnership for development

Round peg in a square hole
Focus mainly on epidemic control
Relative contribution

- Vaccine preventable diseases,
- HIV/AIDS (PCP, CMV),
- Diarrhoea / malnutrition
- Malaria

[Graph showing relative contribution over time with increased TB transmission from 2020 onwards]
Call on UNICEF and other global agencies involved in maternal & child health (MDG 4 & 5) to take child TB on board
Inhalation

T cell priming

T cell expansion

T cell migration back to the lung via blood

Migration to LN via lymph ducts

Ag uptake

Alveolar Mφ activation by T cells

granuloma formation

Courtesy Willem Hanekom
Understanding the Natural History of Disease & Determinants of risk

Major transitions

Exposure → Infection → Disease
Age-related risk

Immune compromised

Age in Years

PTB
Disseminated

%
**Time-related risk**

### Phase of disease

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>II</td>
<td>Miliary TB and TBM</td>
</tr>
<tr>
<td>III</td>
<td>Lymph node disease / Pleural effusion</td>
</tr>
<tr>
<td>IV</td>
<td>Adult-type disease</td>
</tr>
</tbody>
</table>

**HIV-infected - PERSISTENT RISK OF REACTIVATION DISEASE**
DIVERSITY OF DISEASE

Manifestations of intra-thoracic TB in children
Complicated Ghon focus
Fig. 8.—Distribution of the tracheobronchial lymph nodes. (Semidiagrammatic drawing after W. Snow Miller: *The Lung*, Springfield, Ill., 1937, Charles C Thomas.)
Cardiac Catheterization
Complicated lymph node disease
TB caseating / expansile pneumonia
Pleural effusion
Disseminated (miliary) disease
Adult-type disease
Different age-related patterns

Immune compromised

Complicated Ghon focus
Miliary TB
Lymph node disease
Pleural effusion
Adult-type disease

Age in years
INH preventive Rx

It works

- Up to 90% TB reduction with good adherence
- Focus on the most vulnerable children with documented close exposure
WHO – IPT in children

• Close contact with an infectious TB source case (pulmonary TB)
  – All children <5 years of age
  – All HIV-infected children
    • Likelihood of TB infection is high
    • Risk of TB disease progression is high

Asymptomatic for TB – provide IPT

No TST or CXR required prior to commencing
If TB is suspected, investigate as per guidelines
‡ unless the child is HIV-infected (in which case INH 6/12)
TB treatment
TB deaths in England and Wales

![Graph showing the decrease in TB deaths over time from 1838 to 1960](image)

- **1838**: Tubercle bacillus identified
- **1940**: Chemotherapy
- **1960**: BCG Vaccination

Death rate (per million)
Main objectives in TB Rx

• Rapidly kill most bacilli
  - stop disease progression
  - terminate ongoing transmission

• Effect cure and prevent relapse (eliminate dormant bacilli)

• Minimal adverse events

• Prevent emergence of drug-resistance
A current perspective of the cell envelope of *Mycobacterium tuberculosis*, 2006
Current First-Line Regimen

Bacterial intensive phase
INH, RMP
PZA (EMB, SM)

Sterilising continuation phase
INH, RMP

85–95% Sputum culture negative

Percentage organisms killed

Percentage patients cured

Time (months)
## Early Bactericidal Activity

<table>
<thead>
<tr>
<th>Drug</th>
<th>EBA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>0.5-0.6</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>0.2</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>0.2</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>0.04</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Dose related response of INH
Donald PR et al. Am J Respir Crit Care Med 1997; 156: 895-900
RMP: Dose-ranging EBA
Isoniazid PK vs EBA
2-hr INH concentration vs. dose.

concentration associated with the EBA90 is 2.2 µg/ml
## Doses of 1st-line TB drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended daily dose in mg/kg</th>
<th>Previous</th>
<th>New</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (H)</td>
<td>5 (4-6)</td>
<td></td>
<td>10 (5-15)</td>
</tr>
<tr>
<td>Rifampicin (R)</td>
<td>10 (8-12)</td>
<td></td>
<td>15 (10-20)</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>25 (20-30)</td>
<td></td>
<td>35 (30-40)</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>not given</td>
<td></td>
<td>20 (15-25)</td>
</tr>
<tr>
<td>Streptomycin (S)</td>
<td>15 (12-18)</td>
<td></td>
<td>15 (12-18)?</td>
</tr>
</tbody>
</table>
**Drug resistant TB**

**MDR TB** - resistant to at least INH and RMP

**XDR TB** – MDR with additional resistance to any fluoroquinolone AND any second-line injectable (amikacin, kanamycin, capreomycin)

TB with **any** drug resistance

[Diagram showing MDR TB and XDR TB]
ETH & INH cross resistance

**ETH**
- **KatG**
  - INH resistance
- **EthA**
  - ETH resistance

**INH**
- **InhA**
  - INH & ETH resistance

**Mycolic acid synthesis**

Usually high-level INH resistance

Usually low-level INH resistance

Schaaf HS et. al. IJTLD 2009
Discovery of TB Drugs


Development of Regimens

1943* Streptomycin (S)
1948 PAS
1951 Thiacetazone
1952 Isoniazid (H)
1954 Pyrazinamide (Z)
1955 Cycloserine
1960 Ethionamide
1961 Ethambutol (E)
1963 Capreomycin
1970
1982 Ofloxacin
1990
2000
2010

1982s – S replaced by Z: H/R/Z/E 6-8 months, oral therapy?
2010s – Potential New Regimen 2-4 months, oral therapy?

1952 – First regimen: S/PAS/H 24 months of therapy
1956 – First randomized trial: S Monotherapy led to S resistance
1960s – PAS replaced by E: S/H/E 18 months of therapy
1970s – Addition of R: S/H/R/E 9-12 months of therapy

Ma Z et al. Lancet TB series 2010
DNA

mRNA

Reactive
Species

Peptide

\[ H^+ \]

\[ ADP \rightarrow ATP \]

DNA Gyrase

- PA-824
- OPC-67683
- Gatifloxacin
- Moxifloxacin

RNA Polymerase

- Rifapentine

Ribosome

- Linezolid
- PNU-100480

Cell-Wall Synthesis

- SQ109

ATP Synthase

- TMC-207

Ma Z et al. Lancet TB series 2010
Questions?