Drug Resistant Tuberculosis in Children: Overview of Epidemiology

Soumya Swaminathan, MD, FNASc, FASc, Director
National Institute for Research in Tuberculosis, Chennai
Outline

• Why knowing the burden is important
• Consider burden of exposed, infected and diseased children
• Review known epidemiology data
• Discuss limitations in known data
• Review newer approaches to estimating DR-TB burden in children
Who carries the burden of tuberculosis?

...mostly, the most vulnerable

TB spreads in poor, crowded & poorly ventilated settings

Half a million women and over 70,000 children die of TB each year; 10 million “TB” orphans

Migrants, prisoners, minorities, refugees face risks, discrimination & barriers to care

TB linked to HIV infection, malnutrition, alcohol, drug and tobacco use, diabetes
Definitions

- Drug-resistant TB (DR-TB): the presence of an *M. tuberculosis* strain with resistance to at least one antituberculous medication
- Multidrug-resistant TB (MDR-TB): the presence of an *M. tuberculosis* strain with resistance to at least INH and RIF
- Extensively drug-resistant TB (XDR-TB): the presence of an MDR *M. tuberculosis* strain with additional resistance to at least an injectable and a fluoroquinolone
- Primary/Transmitted: infected with a resistant strain
- Secondary/Acquired: acquisition of resistance during treatment
Definitions

• “Pediatric” generally refers to children < 15 years of age
• Encompasses a variety of age groups, from neonates to adolescents
• These groups have varied epidemiology, disease presentation, diagnosis and treatment needs
• Consensus definition of various terms for research use developed and published

WHO Report 2013
Global Tuberculosis Control

Worldwide, 8.6 million new incident cases of TB in 2012; 1.3 million TB deaths

~1.13 million (13%) HIV+TB cases; 320,000 HIV+TB deaths in 2012
Countries Reporting TB Data Disaggregated by Age

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
Burden of TB in Children Estimated for First Time in 2011

- Estimated at 490,000 cases and 65,000 deaths annually (6% of adults)
- Contribute 3-25% of total TB cases in various countries
- Challenges in estimating burden
  - Pauci-bacillary disease and inability to produce sputum
  - Extra-pulmonary TB needs specialized investigations
  - No universally applied diagnostic algorithm
  - Lack of linkages between pediatricians and national TB programs
  - Most national surveys do not include children
  - Most countries lack VR systems
  - Many assumptions used in calculations of burden
Global TB Report 2013: Burden in Children

- **Incidence:** 530,000 (510-550,000) – 6% of 8.6 million incident TB cases
- **Limitations** – assumption that CDR is 66% same as adults, misdiagnosis and age disaggregated data not available from some countries
- **Deaths:** 74,000 among HIV neg children
- **Limitations:** Many TB deaths could be misclassified as due to malnutrition, pneumonia, HIV-related etc
- **TB deaths in HIV+ children not known**
Epidemiology of Childhood TB in Select High Burden Countries, 2011

<table>
<thead>
<tr>
<th>Country</th>
<th>Childhood Cases</th>
<th>% Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>90,000</td>
<td>7</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>17,540</td>
<td>25</td>
</tr>
<tr>
<td>Brazil</td>
<td>23,520</td>
<td>21</td>
</tr>
<tr>
<td>China</td>
<td>86,978</td>
<td>5</td>
</tr>
<tr>
<td>Pakistan</td>
<td>61,905</td>
<td>25</td>
</tr>
<tr>
<td>South Africa</td>
<td>35,449</td>
<td>16</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>12,267</td>
<td>16</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td><strong>3 - 25</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>327,659</strong></td>
<td><strong>9.6</strong></td>
</tr>
</tbody>
</table>
Steps to Improve Estimation of TB Cases Among Children (WHO Report 2013)

• Global consultation to improve analytical methods and prioritize actions to obtain new data (Sep 2013)
• Promotion of case based electronic recording and reporting systems
• Nationwide inventory surveys to measure underreporting of childhood TB – recent study in Pakistan showed 10-78% under-reporting in 3 cities. Most children diagnosed in large private clinics and diagnostic facilities
• More contact tracing studies and integration of TB activities in MCH and child health services to find more cases
• Modelling – various approaches
Kiss of Death?

Case History

- 4 month old baby with fever, weight loss 1 mo
- RUL pneumonic patch, anemic, underweight
- Had aunt with TB on chronic treatment who was very ill and visited baby shortly before she died, 2 months prior to this episode
- Baby started on 1st line treatment – no improvement after 1 month
- Gastric lavage culture - MDRTB
# Risk Factors for Infection and Disease

<table>
<thead>
<tr>
<th>Location, year</th>
<th>No. of contacts</th>
<th>Proportion with LTBI or active TB</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alaska, 1998</td>
<td>282</td>
<td>25% LTBI 10% TB</td>
<td>Contact with smear pos, cavity. Younger age</td>
</tr>
<tr>
<td>Zimbabwe, 2002</td>
<td>174</td>
<td>63% LTBI 40% xRay abnor</td>
<td>High load of AFB in index case</td>
</tr>
<tr>
<td>Gambia, 2003</td>
<td>384</td>
<td>26% LTBI</td>
<td>Geographic proximity. Household size. Duration of cough</td>
</tr>
<tr>
<td>Philippines, 2003</td>
<td>153</td>
<td>69% LTBI 4% TB</td>
<td>Age &lt; 5 yrs for LTBI</td>
</tr>
<tr>
<td>India, 2005</td>
<td>200 index cases</td>
<td>34% LTBI 9 TB</td>
<td>Severe malnutrition. Passive smoking. Absence of BCG</td>
</tr>
<tr>
<td>Malawi, 2006</td>
<td>195</td>
<td>45% LTBI 23% TB</td>
<td>Female index case. Younger age</td>
</tr>
<tr>
<td>Laos, 2009</td>
<td>148</td>
<td>31% LTBI</td>
<td>Ethnic minorities</td>
</tr>
</tbody>
</table>
TB Notifications by Age and HIV Status
(Cape Town, 2009)

Fig. 1. TB notifications in 2009 for the City of Cape Town stratified by 5-year age groups and by provider-initiated HIV testing results. The denominators for age strata derived from National Department of Health/Health Information System Programme by disaggregating StatsSA district estimates (November 2009) using data from the 'Small Area Layer' (StatsSA, 2004).
Wallgren's timetable: 90% of disease occurs in 1st year after infection

I  Hypersensitivity
II  Miliary TB and TBM
III  Lymph node disease / Pleural effusion
IV  Adult-type disease
Age and risk – modified by HIV

Percentage distribution of PTB and disseminated cases by age group:

- <1 year: 30% PTB, 10% disseminated
- 1 to 2 years: 20% PTB, 5% disseminated
- 2 to 5 years: 10% PTB, 2% disseminated
- 5 to 10 years: 5% PTB, 1% disseminated
- 10 to 15 years: 5% PTB, 1% disseminated
Progress in Global coverage of drug resistance surveillance data 1994-2013
Prevalence of MDRTB among new cases (global average 3.6 (2.1- 5.1)%)

* Figures are based on the most recent year for which data have been reported, which varies among countries.
MDRTB among previously treated patients – average 20 (13-27)%

*Figures are based on the most recent year for which data have been reported, which varies among countries. The high percentages of previously treated TB cases with MDR-TB in Bahrain, Bonaire – Saint Eustatius and Saba, Cook Islands, Ireland, San Tome and Principe, and Lebanon refer to only a small number of notified cases (<10).*
Number of MDRTB Cases Among Notifed TB Cases, 2012 – only 28% being detected
Diagnostic DST for rifampicin and isoniazid

DST coverage for new (red) and retreated (blue) TB patients, by region and globally 2011
<table>
<thead>
<tr>
<th>WHO Region</th>
<th>2012 Estimated</th>
<th>2012 Reported</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>African</td>
<td>38,000</td>
<td>18,129</td>
<td>48%</td>
</tr>
<tr>
<td>American</td>
<td>7,100</td>
<td>2,967</td>
<td>42%</td>
</tr>
<tr>
<td>East Med.</td>
<td>18,000</td>
<td>2,236</td>
<td>12%</td>
</tr>
<tr>
<td>European</td>
<td>74,000</td>
<td>36,708</td>
<td>50%</td>
</tr>
<tr>
<td>S-E Asian</td>
<td>90,000</td>
<td>19,202</td>
<td>21%</td>
</tr>
<tr>
<td>West Pacific</td>
<td>74,000</td>
<td>4,473</td>
<td>6%</td>
</tr>
<tr>
<td>Global</td>
<td>300,000</td>
<td>83,715</td>
<td>28%</td>
</tr>
</tbody>
</table>
Global Burden of Pediatric MDR-TB
MDRTB in Children – Global Report

• Data from drug resistance surveillance reported to WHO from 1994-2012 was analyzed
• 376,292 TB patients with known age and DST – odds ratios derived by logistic regression
• A child with TB was as likely as an adult to have MDRTB
• 94,000 MDRTB cases reported in 2012, children are a handful
• Children should be included in DR surveys and household contact investigations of MDRTB patients must be strengthened

Isoniazid Resistant TB: Systematic Review
(Yuen etal. Ped Infect Dis J 2013 May)

• 95 studies, 8351 children included
• Median proportion of children with INH resistance 8% (0-18% IQR)
• In adults, 14% and 45% TB patients (in European region) have H resistance
• They are at higher risk of treatment failure and amplification of drug resistance if treated with standard regimens
• More research is needed for effective treatment and prevention regimens in children
Expansion of DST Capacity in Countries, but Children Being Left Out

Increase in MDRTB Diagnosis in India 2008-12

<table>
<thead>
<tr>
<th>Year</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>308</td>
</tr>
<tr>
<td>2009</td>
<td>1660</td>
</tr>
<tr>
<td>2010</td>
<td>2967</td>
</tr>
<tr>
<td>2011</td>
<td>4237</td>
</tr>
<tr>
<td>2012</td>
<td>16</td>
</tr>
</tbody>
</table>

Reasons For Very Few Children

- Low awareness that children can have DRTB
- Specimens not obtained or not sent for culture and DST
- Negative culture – paucibacillary specimens
- DST Capacity still limited and centralized
Probable MDRTB – Proposed Definition

• Children with signs and symptoms of active TB diseases who in addition have the following risk factors should be considered as having “probable” MDR-TB and started on MDR-TB treatment, even in the absence of bacteriological confirmation:
  – Close contact with a known case of MDR-TB;
  – Close contact with a person who died whilst on TB treatment;
  – Close contact with a person who failed TB treatment;
  – Failure of a first-line regimen, recognizing that both bacteriological and clinical definitions of failure should be used;
  – Previous treatment with second-line medications
• All patients considered to have "probable" MDR-TB should be presented to and discussed with a DR TB Centre Committee, and a decision to treat made. This consideration of initiation of SLD ATT therapy without bacteriological confirmation does not replace the need for a thorough and ongoing diagnostic evaluation, including consideration of non-tuberculous causes, prior to the initiation of the SLD ATT.

• Children with central nervous system disease and/or those with other life-threatening manifestations who meet the criteria for “probable” MDR-TB should be initiated on therapy immediately given the high risk of mortality if treatment initiation is delayed whilst awaiting the confirmation of the DR TB Centre Committee to initiate treatment.

• More detailed and specific operational criteria regarding the points above are necessary for implementation in the field.
## Drug resistant TB in children (Africa)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Source</th>
<th>No. of children with M.tb positive cultures</th>
<th>Drug resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. Kassa-Kelembho, 2004</td>
<td>PTB</td>
<td>165 (HIV+ 21%)</td>
<td>Isoniazid : 9.1% MDR: 0.6%</td>
</tr>
<tr>
<td>Schaaf et al, 2006</td>
<td>PTB &amp; EPTB</td>
<td>306 (HIV+ 8 %)</td>
<td>Isoniazid : 12.8% MDR: 2.3%</td>
</tr>
<tr>
<td>Schaaf, 2007</td>
<td>PTB &amp; EPTB</td>
<td>596 (HIV+ 22%)</td>
<td>Isoniazid : 7.3% MDR: 3.7%</td>
</tr>
<tr>
<td>Failee, 2011</td>
<td>PTB &amp; EPTB</td>
<td>148 (HIV+ 53%)</td>
<td>Isoniazid : 14.2% MDR : 8.8%</td>
</tr>
</tbody>
</table>
Drug Susceptibility Test Results for the 3 Surveys in the Western Cape Province of South Africa

<table>
<thead>
<tr>
<th>Drug Susceptibility Test Results</th>
<th>1994-1998 (n=338), No. (%)</th>
<th>2003-2005 (n=323), No. (%)</th>
<th>2005-2007 (n=291), No. (%)</th>
<th>( p^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug susceptibility test available</td>
<td>306 (90.5)</td>
<td>319 (98.8)</td>
<td>285 (97.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Drug susceptible(^b)</td>
<td>285 (93.1)</td>
<td>278 (87.1)</td>
<td>242 (84.9)</td>
<td>.005</td>
</tr>
<tr>
<td>Any resistance(^b)</td>
<td>21 (6.9)</td>
<td>41 (12.9)</td>
<td>43 (15.1)</td>
<td>.005</td>
</tr>
<tr>
<td>Isoniazid mono resistance</td>
<td>14 (4.6)</td>
<td>23 (7.2)</td>
<td>22 (7.7)</td>
<td>.24</td>
</tr>
<tr>
<td>Rifampin mono resistance</td>
<td>0</td>
<td>0</td>
<td>2 (0.7)</td>
<td>.24</td>
</tr>
<tr>
<td>Multidrug resistance(^a)</td>
<td>7 (2.3)</td>
<td>18 (5.6)</td>
<td>19 (6.7)</td>
<td>.03</td>
</tr>
</tbody>
</table>

\( ^a \)\( p \) values compare differences among all 3 groups.
\( ^b \)Difference between last 2 surveys was not significant.

- previously treated children had significantly more drug resistance than did new TB cases (19 of 66 [28.8%] vs 24 of 225 [10.7%]; odds ratio = 3.39
- HIV infection not significantly associated with drug resistance

## Drug resistant TB in children in India

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Source</th>
<th>No. of children with M.tb positive cultures</th>
<th>Drug resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jawahar MS, TRC, 1990</td>
<td>Lymph Node</td>
<td>96</td>
<td>Isoniazid: 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Streptomycin: 2%</td>
</tr>
<tr>
<td>Ramachandran P, TRC, 1992</td>
<td>CSF</td>
<td>88</td>
<td>Isoniazid: 14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Streptomycin: 8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MDR: 2%</td>
</tr>
<tr>
<td>Swaminathan, TRC, 1996</td>
<td>Sputum/Gastric Lavage</td>
<td>201</td>
<td>Isoniazid: 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Streptomycin: 9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MDR: 3.5%</td>
</tr>
<tr>
<td>Singh, M, PGI</td>
<td>Sputum/GL</td>
<td>30</td>
<td>MDR: 6%</td>
</tr>
<tr>
<td>I Shah, Mumbai</td>
<td>Induced Sputum/GL</td>
<td>500</td>
<td>MDR: 5%</td>
</tr>
</tbody>
</table>
Children under 15 years of age diagnosed with TB and MDR/XDR TB during 1998-2010, Latvia

Total 92 children were treated with MDR/XDR TB, out of them (25 %) were culture positive for MT
Children under 15 years of age treated with MDR/XDR-TB in Latvia (1998-2010)

Children treated with MDR/XDR-TB
N=92

Contacts of MDR-TB patients
N=66

MDR
N=64

XDR
N=2

No response to treatment with first-line anti-TB therapy
N=3

Culture positive with their own DST available
N=23

MDR
N=20

XDR
N=3

Out of them 75 (81.5%) children were identified through contact investigation in early stages of the disease
Pediatric TB: The Litmus Test for TB Control

• Harris County, Texas: prospective population based active surveillance and molecular epi project (2000-4)
• Genotyped all pediatric TB cases by IS 6110 and spoligotyping and compared with source case
• 103 children, 59% had source case identified
• 60% of genotypes matched with known source case
• Among children with no known source, 69% clustering
• Clustering increased over time
• Conclusions: High degree of clustering indicates recent transmission. Contact tracing not being done comprehensively

- 25 studies evaluated a median of 111 household contacts of DRTB cases
- The pooled yield for active TB was 7.8% (95CI: 5.6-10.0%) and for latent TB infection was 47.2% (95CI: 30.0-61.4%).
- Among children – 4% had active TB and 27% LTBI
- Majority of secondary cases detected within a year of primary diagnosis
- > 50% had concordant DST
Time for targets

We need to:

1. Estimate global burden

2. Identify (so we can begin to monitor) treatment gap
Time for targets

Children infected with DR-TB at home point us to 3 targets
Target 1

Start from: # new MDR-TB patients dx in place Z

How many kids in their homes?
(use estimate of average hh size X % <15 y)

Answer = Target 1

ALL should be: enumerated AND evaluated
Target 2

Start from Target 1: # kids in MDR-TB hhs

How many expected with active TB
*(use estimates from lit, other sources)*

(a) at time of MDR pt dx ?
(b) during some follow-up i.e. 12 mo ?

\[ a+b = \text{Target 2} \]
Target 3

Start again from Target 1:
# kids in MDR-TB hhs

How many expected to have LTBI
*(use estimates from lit, other sources)*

(a) at time of MDR pt dx
(b) during some follow-up i.e. 12 mo

a+b = Target 3
3 targets: child contacts in MDR hhs

Target 1: # kids to enumerate & evaluate

Target 2: # kids who require treatment for active TB

Target 3: # kids who require treatment for LTBI, or ‘watch & wait’ (& actually watch)
Parameters to get started

1. average # of <15 y in household
   2, but 1 in China

2. % active TB in <15 y in 12 months
   2.5%

3. % LTBI in <15 y in 12 months
   23.5%

*Can be refined, of course.*
Example: India

99000 incident MDR-TB patients (2011 estimated)

Multiply 99000 by 2 (av # of <15 yo in hh) =
Target 1: 1,98,000 children

Multiply 1,98,000 by 2.5% (active TB in 12 mo) =
Target 2: 4950 children

Multiply 1,98,000 by 23.5% (LTBI in 12 mo) =
Target 3: 46530 children
First pass – to be refined

(where av # kids/hh = 2; active TB = 2.5%; LTBI = 23.5%

<table>
<thead>
<tr>
<th>Region</th>
<th># MDR inc cases 2008</th>
<th>TARGET 1</th>
<th>TARGET 2</th>
<th>TARGET 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEARO</td>
<td>136,129</td>
<td>272,258</td>
<td>3,403</td>
<td>31,990</td>
</tr>
<tr>
<td>WPRO</td>
<td>124,207</td>
<td>148,414</td>
<td>3,105</td>
<td>29,189</td>
</tr>
<tr>
<td>EURO</td>
<td>80,530</td>
<td>161,060</td>
<td>2,013</td>
<td>18,925</td>
</tr>
<tr>
<td>AFRO</td>
<td>63,100</td>
<td>126,200</td>
<td>1,578</td>
<td>14,829</td>
</tr>
<tr>
<td>EMRO</td>
<td>22,488</td>
<td>44,976</td>
<td>562</td>
<td>5,285</td>
</tr>
<tr>
<td>AMRO</td>
<td>8,676</td>
<td>17,352</td>
<td>217</td>
<td>2,039</td>
</tr>
<tr>
<td>TOTAL</td>
<td>435,130</td>
<td>770,260</td>
<td>10,878</td>
<td>102,256</td>
</tr>
</tbody>
</table>

Treatment gap
Forum on Drug Discovery, Development, and Translation
Institute of Medicine USA

Washington, DC USA
Nov. 2008

Pretoria, South Africa
March 2010

Moscow, Russian Federation
May 2010

Delhi, India
April 2011
The Sentinel Project on Pediatric Drug-Resistant Tuberculosis

Pediatric drug-resistant tuberculosis is both a preventable and treatable disease. Every child who dies with drug-resistant tuberculosis is a sentinel for both ongoing transmission and inadequate treatment delivery systems.

The Sentinel Project on Pediatric Drug-Resistant Tuberculosis is a global partnership of researchers, caregivers, and advocates aiming to develop and deploy evidence-based strategies to prevent child deaths from this treatable disease. We are a learning network committed to generating and disseminating knowledge and data for immediate action.