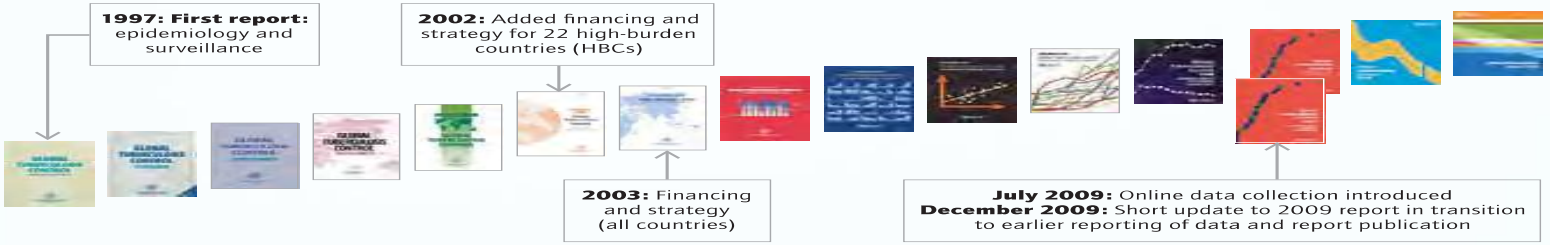
Research Priorities for Drug Resistant Tuberculosis in Children: Progress and Future Needs

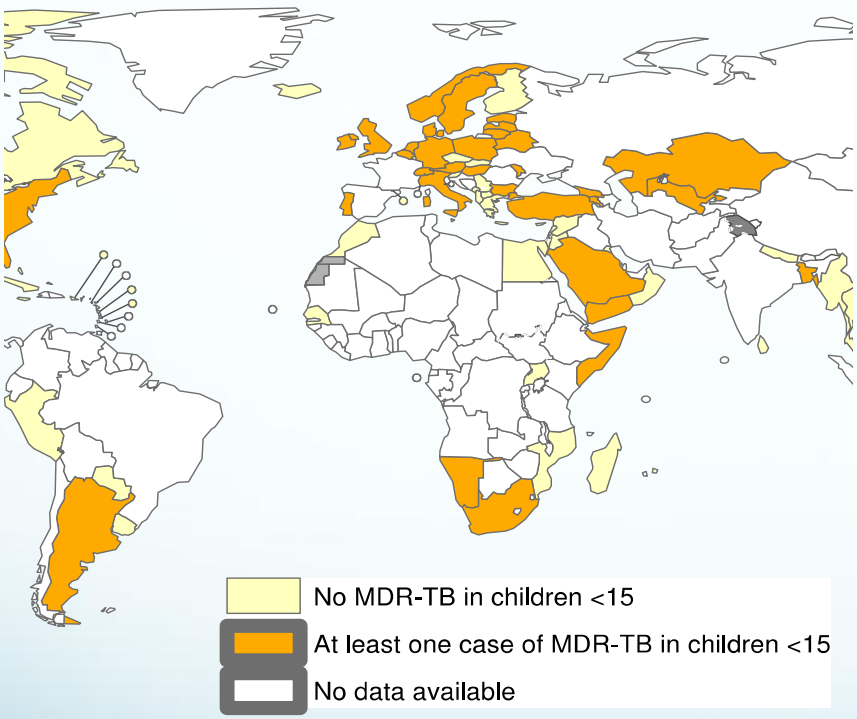
Soumya Swaminathan, MD, FIAP, FNASc
Director,
National Institute for Research in TB
Chennai, India
For the Sentinel Project subgroup

Burden of TB in Children Estimated for First Time in 2011



- Estimated at 490,000 cases and 65,000 deaths annually (6% of adults)
- 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 in which TB deaths are disaggregated by age
  - Many assumptions used in calculations of burden

MDRTB in Children



- Estimated 350,000 MDR among notified pulmonary TB patients in 2011, only 60,000 reported to WHO
- India, China and Russia account for 60%
- < 10% of MDR patients detected in India, China
- In 37 countries, children accounted for 1-13% of patients reported
- 6% of 350,000 = 21,000 conservative estimate

Why Children are not included in prevalence surveys (WHO's Global Task Force on TB Impact Measurement)

- Few bacteriologically confirmed cases
- Ethical considerations with mass X-ray screening
- Tests of TB infection and broad criteria for "abnormal" xRay would lead to invasive procedures to obtain specimens from young children
- Referral hospitals needed for diagnostic confirmation
- Logistics – double the cost of prevalence surveys

Drug Susceptibility Test Results for the 3 Surveys in the Western Cape Province of South Africa

Drug Susceptibility Test Results	1994–1998 (n = 338), No. (%)	2003–2005 (n = 323), No. (%)	2005–2007 (n = 291), No. (%)	P[a]
Drug susceptibility test available	306 (90.5)	319 (98.8)	285 (97.9)	<.001
Drug susceptible[b]	285 (93.1)	278 (87.1)	242 (84.9)	.005
Any resistance[b]	21 (6.9)	41 (12.9)	43 (15.1)	.005
Isoniazid monoresistance	14 (4.6)	23 (7.2)	22 (7.7)	.24
Rifampin monoresistance	0	0	2 (0.7)	
Multidrug resistance[a]	7 (2.3)	18 (5.6)	19 (6.7)	.03

[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

Schaaf et al. Am J Public Health. 2009 ;99(8):1486-90.

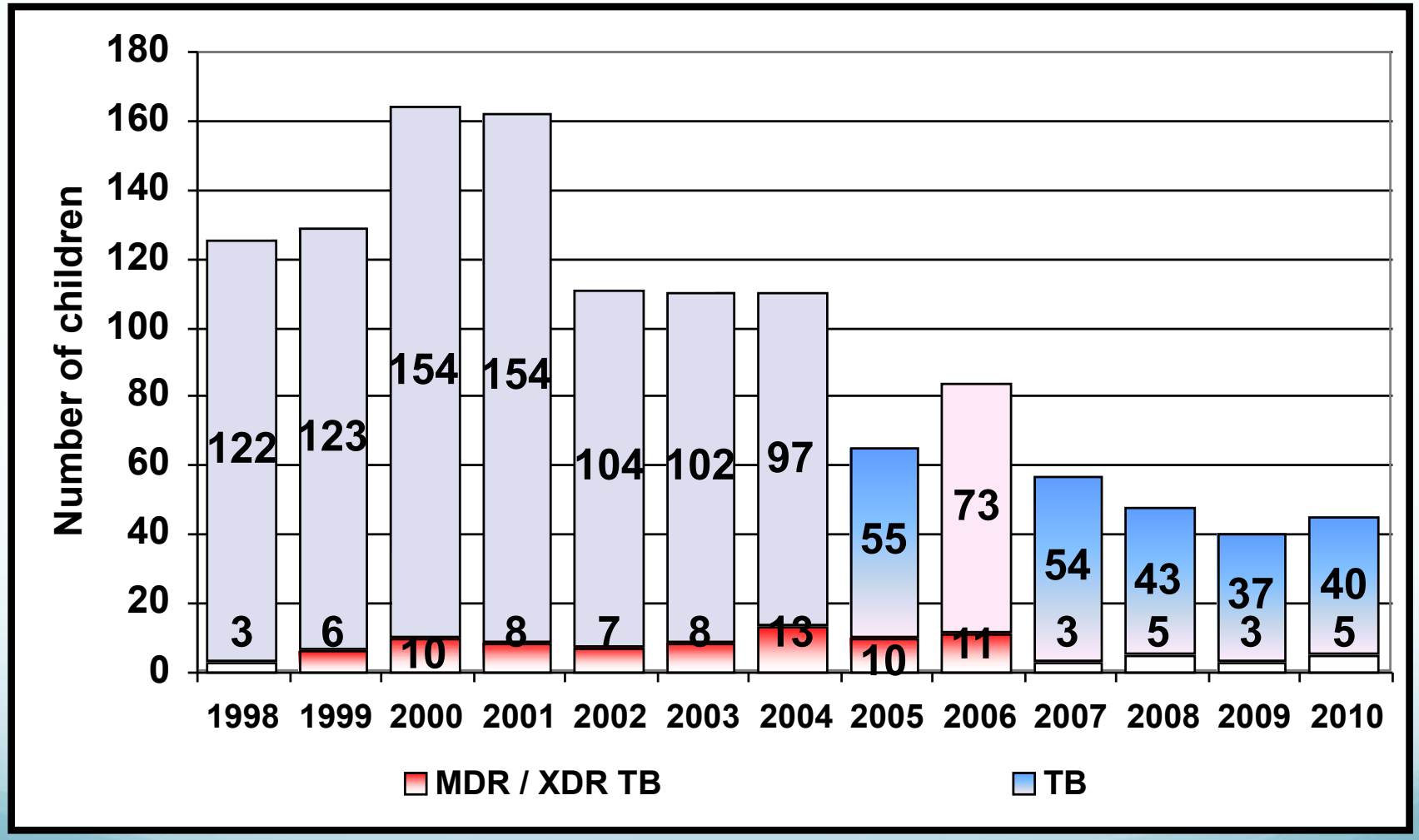
Drug resistant TB in children (Africa)

Author, year	Source	No. of children with M.tb positive cultures	Drug resistance
E. Kassa-Kelembho, 2004	PTB	165 (HIV+ 21%)	Isoniazid : 9.1% MDR: 0.6%
Schaaf et al, 2006	PTB & EPTB	306 (HIV+ 8 %)	Isoniazid : 12.8% MDR: 2.3%
Schaaf, 2007	PTB & EPTB	596 (HIV+ 22%)	Isoniazid :7.3% MDR: 3.7%
Fairlie, 2011	PTB & EPTB	148 (HIV+ 53%)	Isoniazid : 14.2% MDR : 8.8%

Drug resistant TB in children in India

Author, year	Source	No. of children with M.tb positive cultures	Drug resistance
Jawahar MS, TRC,1990	Lymph Node	96	Isoniazid: 10% Streptomycin: 2%
Ramachandran P, TRC, 1992	CSF	88	Isoniazid : 14% Streptomycin : 8% MDR: 2%
Swaminathan, TRC,1996	Sputum/Gastric Lavage	201	Isoniazid: 10% Streptomycin: 9% MDR: 3.5%
Singh, M, PGI	Sputum/GL	30	MDR: 6%
I Shah, Mumbai	Induced Sputum/GL	500	MDR: 6%

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 23 (25 %) were culture positive for MT

Pediatric TB: The Litmus Test for TB Control

Marquez L et al Pediatr Infect Dis J. 2012 Nov;31(11):1144-7

- 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

Epidemiology, Burden: Priorities

- Incidence of DRTB in children – pattern, risk factors, geographic variation, impact of HIV
- Transmission of DRTB from adults to household contacts (compared to transmission of DSTB) – rate, risk factors
- Document current practices at DOTS Plus sites and proportion of children diagnosed and treated for MDRTB
- Future DR prevalence surveys to systematically include children
- Post mortem studies – TB and DRTB as a cause of mortality in children (HIV+ and neg)

Next Steps to Improve Estimates of TB cases and deaths in children

- Systematic reviews of existing data on incident childhood TB, under-reporting and misdiagnosis
- Global consultation to develop analytic methods and to define actions needed to obtain new data
- Promotion of case-based electronic recording and reporting systems
- Nationwide inventory surveys to measure under-reporting of childhood TB
- Improve VR systems in countries – for mortality
- Mortality surveys in high-burden countries
- **More contact tracing and integration of TB services in maternal, newborn and child health would help find children with TB**

Diagnosis: Progress

- Microbiologic confirmation achieved only in ~ 25% of cases
- Better yield with multiple specimens, different collection methods, combination of lab assays
- Xpert MTB/Rif evaluated in children: sensitivity ~70%, specificity ~99%. False pos Rif resistance needs study
- Line probe assay: in smear positive disease
- Research Definitions for DRTB: provides definitions when bacteriology is negative
- Field guide: guidance on diagnosis, management and prevention (algorithms) in the field

Bates et al. Lancet Nov 5,2012, Seddon et al. JPIDS in press

Diagnosis: Research Priorities

- Validate the consensus case definition for DRTB in children – in various settings
- Evaluate newer methods of diagnosis of TB infection eg using more specific antigens
- Evaluate newer methods of diagnosis for active DRTB disease eg Xpert MTBRif, LPA and other molecular tests, in different settings
- Compare various specimen collection methods
- Drug resistance diagnosis in extra-pulmonary TB

Treatment Outcomes for Children with MDRTB: Systematic Review and Meta-analysis

Ettehad et al Lancet Infect Dis Feb 2012

- 8 studies, 315 patients
- Time to appropriate treatment 2 days - 46 months
- Duration of treatment: 6 to 34 months
- Pooled estimate of treatment success: 82% (95%CI 54-91)
- 6% died, 6% defaulted,
- 39% had AE (nausea, vomiting, hearing loss, hypothyroidism, psychiatric effects)
- Treatment of pediatric DRTB has been neglected, but outcomes as good or better than adults

Caring for children with DR-TB: recent guidance

- **Seddon et al. Caring for children with DR-TB: practice based recommendations. AJRCCM, Sept 2012**
- **Furin et al. Field Guide, Nov 2012**

Multidrug-Resistant Tuberculosis in Children: A Field Guide

USAID FROM THE AMERICAN PEOPLE TB CARE II

Sentinel Project on pediatric drug-resistant tuberculosis

Factors influencing PK of TB drugs in children

Factor	Effect
Acetylator status	Reduced INH exposure in rapid than slow acetylators Schaaf 2005; McIlleron 2009; Jeena et al 2011
Drug transporter polymorphisms	Significant effect of *SLCO1B1* polymorphism on RMP exposure (adult study) Weiner 2010
Age	Lower plasma RMP, INH, PZA & EMB levels in younger children Schaaf 2005, 2009; McIlleron 2009; Thee 2010; Jeena et al 2011; Graham 2006
Drug interactions	Low RMP exposure in presence of EMB Thee 2009
Drug-food interactions	Food reduces peak conc of RMP, INH & EMB Lin 2010
Nutritional status	Plasma PZA & EMB lower in malnourished Graham 2006
HIV infection	Low RMP, PZA in HIV-infection Schaaf 2009

Optimizing Treatment: Drug Combinations and Duration

- Pharmacokinetic studies of 2nd line drugs
- Shortening treatment regimens: 9-12 months adequate?
- Fully oral regimens – role of inhaled Capreomycin
- Evaluate surrogate markers for treatment response
- Management of adverse events
- Psychosocial issues and adherence
- Work with pharma to develop better formulations
- Trials with new TB drugs

New drugs in clinical development

	Drug	Mode of action	Manufacturer
Quinolone	Moxifloxacin,	DNA gyrase	Bayer
Rifampicin	Rifapentine	RNA polymerase	Aventis
Oxazolidinones	Linezolid PNU-100480 AZD-5847	Ribosome	Pfizer Pfizer Astra Zeneca
Diarylquinolene	TMC207	ATP synthase	Tibotec
Nitroimidazoles	PA-824 OPC-67683	Many Targets ? Bio-reduction	TB Alliance Otsuka
Ethylene-diamines	SQ-109	? Cell wall synthesis inhibitor	Seqella

***Modified from Lancet* 2010; 375: 2100–09**

Types of Research Activity Among Children by Stage of Clinical Trial Efforts among Adults for a New Drug

Burman WJ et al Plos Med 2008

Clinical trial phase adults	**Suggested research activities among children**
I PK and tolerability among healthy adults	None
IIa EBA and PK in TB patients	Initial work on possible formulations for children
IIb Sputum culture conversion at 2nd month	Initial PK among children with TB
III RCT with TB outcomes as primary endpoint	RCT of new drug/regimen with PK and tolerability as primary endpoint
IV Further evaluation of effective regimen	Additional studies among subgroups eg < 3 yrs, validation of selected dosages

Contact Tracing and Chemoprophylaxis

- Recommended by WHO and most national TB programs
- We performed a situational analysis in 4 TUs of TamilNadu – only 14% of child contacts were screened for TB and 19% of < 5yrs initiated on IPT
- After training and implementation of an IPT card and register, rates increased to 75%
- Ongoing observational study in Cape Town, of 227 child contacts of MDRTB patients: 41% were TST+ and 6% had TB
- Received high dose INH, ethambutol and ofloxacin for 6 months – 2% developed TB and I died
- PLoS One. 2011;6(7):e22500, Int J Tuberc Lung Dis. 2009 Dec;13(12):1507-12, IJTLD (in press), Anneke Hesseling (personal communication).

Management of Contacts of MDRTB: Two Systematic Reviews

- > 2000 references reviewed, only 3 studies included
- One study: no contacts developed TB
- Other 2 showed non-significant risk differences of 4% and 5% in favour of chemoprophylaxis
- Available evidence of low quality, not sufficient to support or reject preventive treatment
- Adverse events and rates of discontinuation of treatment high (58-100%)
- DST pattern of child's isolate matches adult HH contact in 46-86%; in high burden countries, infection can occur outside household

van der Werf et al, IJTLD 2012; 16: 288, Becerra et al Lancet 2011; 377: 147–152, Kritski et al Am J Respir Crit Care Med 1996; 153: 331–335, Texeira et al Int J Tuberc Lung Dis 2001; 5: 321–328.

Management of Contacts: Priorities

- Optimal preventive therapy regimen for child contacts of MDRTB patients (drug combination, duration): efficacy and safety in HIV+ and HIV-, various age groups.
- Evaluate new TB drugs for prevention
- Explore other methods to prevent transmission – at household, community, health facility

Private sector Involvement

- What is the current role of private sector in managing TB and MDRTB in children, in high burden countries? Documenting current practice, knowledge and gaps
- How best to involve private general practitioners, pediatricians, pediatric associations etc in providing optimal care to children with suspected TB?

Programmatic Issues

- Screening criteria for children to have access to MDRTB diagnostics
- Strategies to improve adherence - role of family in management of DRTB
- Strengthening Pharmacovigilance

Role of Nutritional Support and other Adjunctive Therapies for TB

- Can macronutrient supplementation improve treatment outcomes?
- Can improving nutritional status prevent TB infection or disease?
- Role of micronutrients in improving outcomes, reducing toxicity
- Role of Immunotherapy