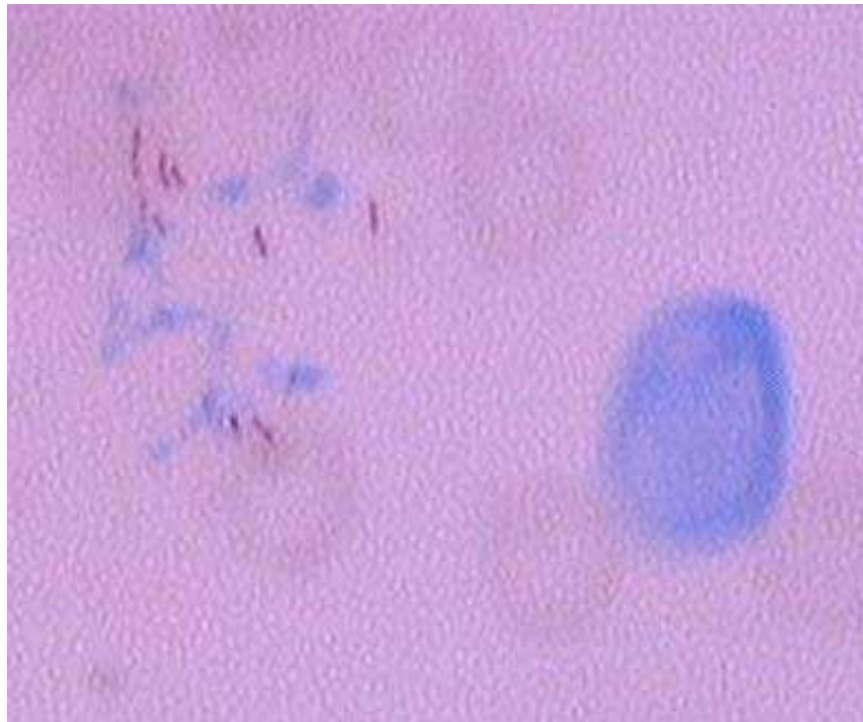


# Tuberculosis in Children: Burden, Management and Research Needs

**Soumya Swaminathan, MD**

Scientist G, National Institute for Research in Tuberculosis (formerly TRC), Chennai



# History

- 1956 - Tuberculosis Chemotherapy Centre
- ICMR, Madras Govt, BMRC, WHO
- 5 yr project to evaluate domiciliary Rx vs Sanatorium Rx
- Tuberculosis Research Centre – 1978
- HIV section in 2000
- NIH/International Centre for Excellence in Research in 2005
- National Institute for Research in Tuberculosis - 2011



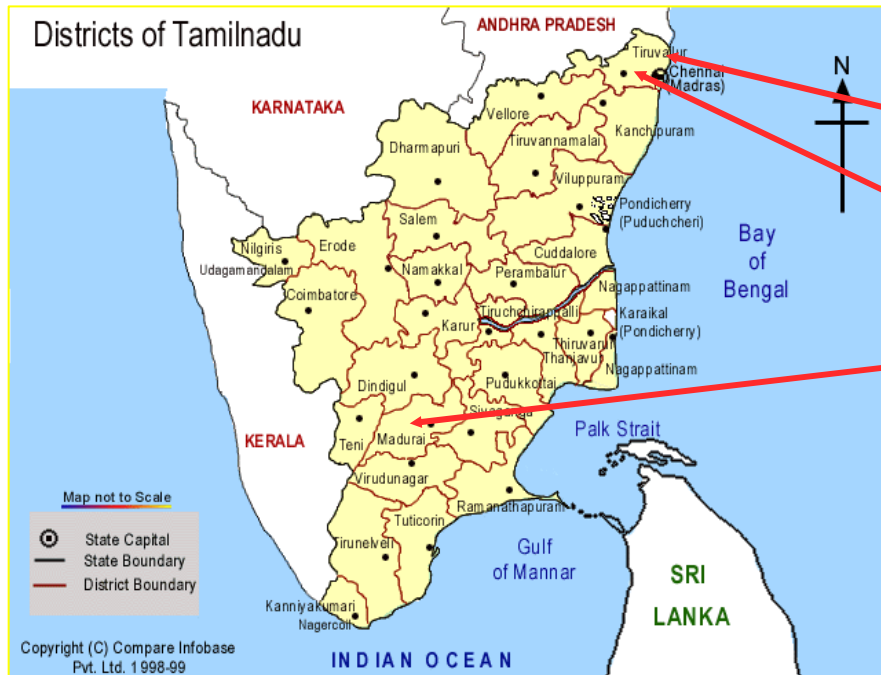
*Bull. Org. mond. Santé* } 1959, 21, 51-144  
*Bull. Wld Hlth Org.* }

## A Concurrent Comparison of Home and Sanatorium Treatment of Pulmonary Tuberculosis in South India

TUBERCULOSIS CHEMOTHERAPY CENTRE, MADRAS

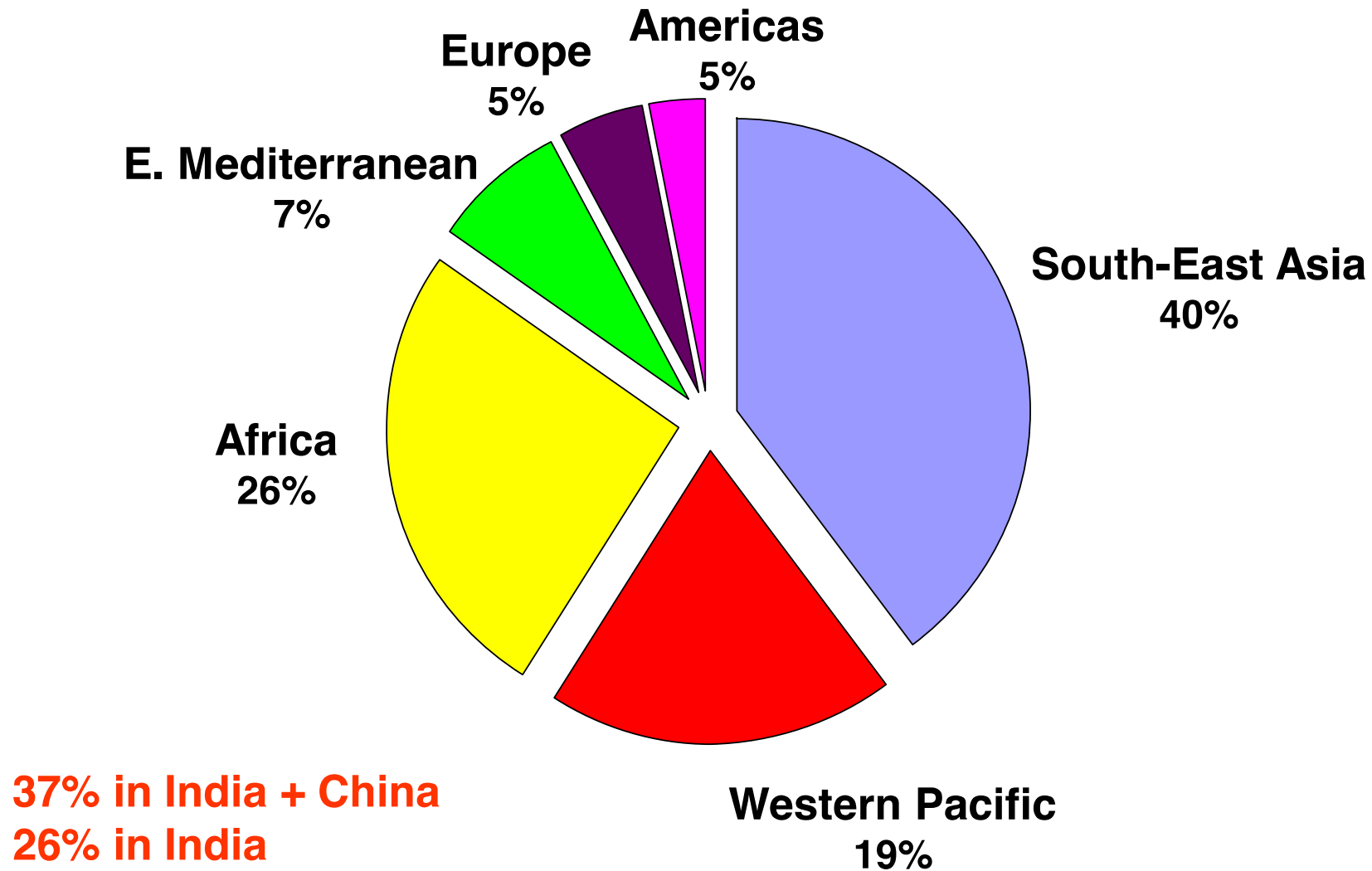
**In India, ... the TB problem is aggravated by an acute shortage of sanatorium beds. The number of active cases of TB ... estimated at 2½ million, but only 23,000 TB beds. ... In these circumstances great importance attaches to the possibility of applying mass domiciliary chemotherapy as a substitute for sanatorium treatment. The findings of this study, ..., show that despite the advantages of sanatorium care .... the merits of domiciliary chemotherapy are comparable, and that it would be appropriate to treat the majority of patients at home.....**

# Mission: Research for TB, HIV control

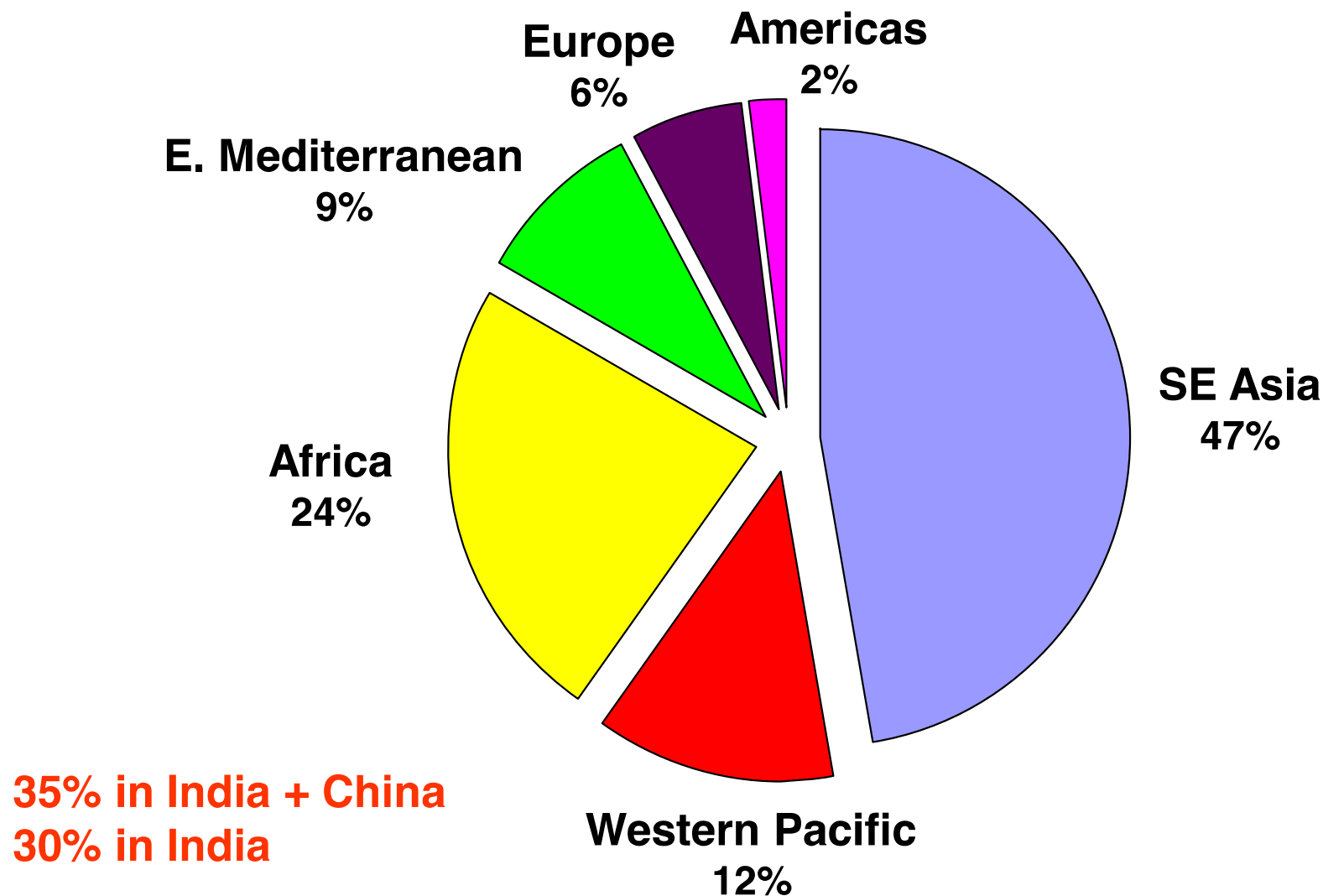


- ★ > 1,00,000 patients screened
- ★ > 15,000 patients enrolled in clinical trials
- ★ 40 RCTs for treatment and prevention of TB in HIV+ and HIV- adults and children
- ★ BCG Vaccine trial, HIV phase I vaccine trials
- ★ Clinical trials in leprosy & lymphatic filariasis
- ★ Socio-behavioural research in TB, HIV

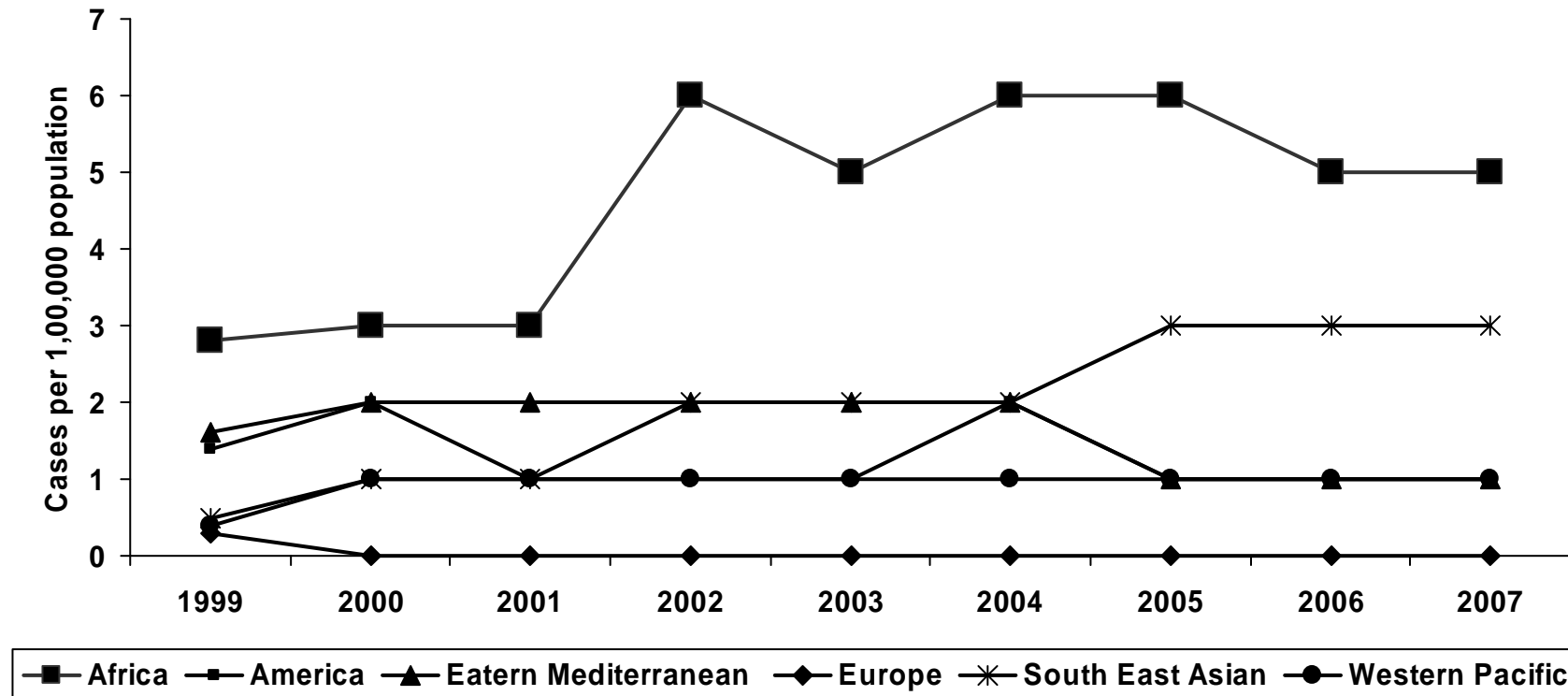
# Most TB cases in Asia and Africa



# Most TB deaths in Asia and Africa



## Trends in new smear positive notification rate among children 0-14 years per 1,00,000 population



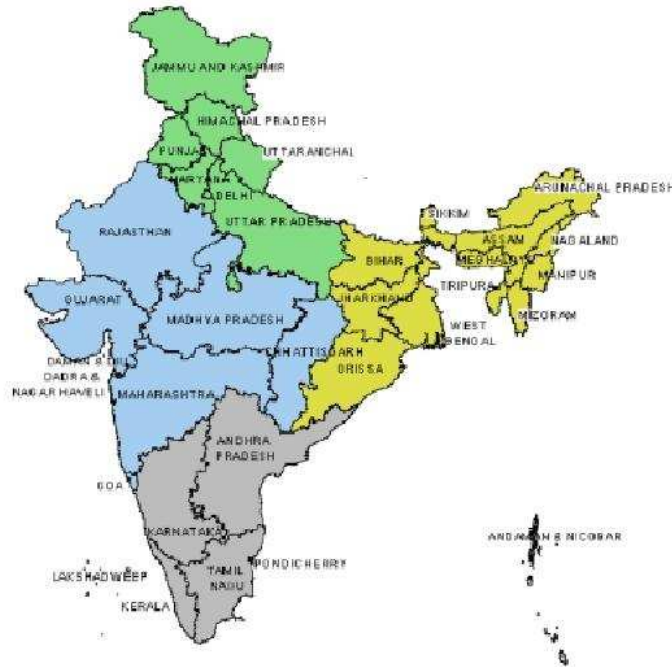
( Source – WHO reports 2001 – 2009)

# TB Epidemiology in India

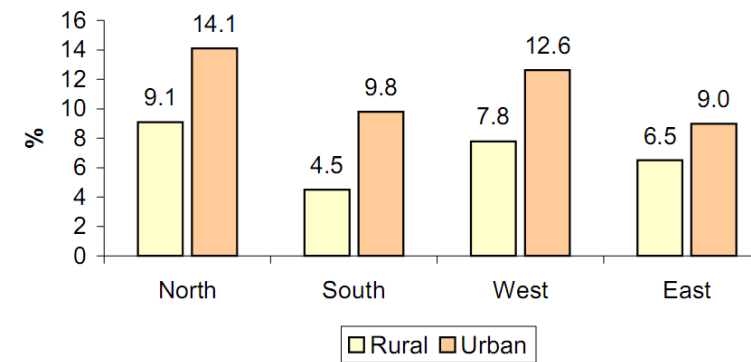
- > 50% of population has latent TB
- 1.52 million cases notified within the national TB control program (25% world's cases)
- 7% of notified cases in children
- Prevalence 256/100,000, mortality 26/100,000
- HIV prevalence in TB ~ 5%
- MDRTB 2.1% in new cases, 15% in re-treatment cases



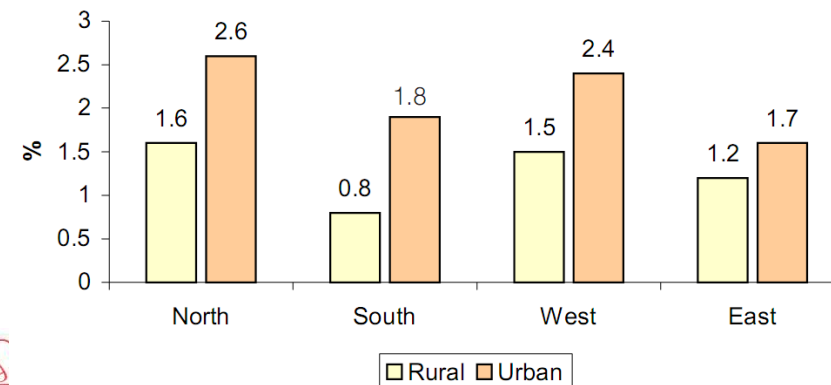
# Childhood TB in INDIA 2000-2003 (n=85,208)



Prevalence of infection among children 1-9 years of age by zone and stratum



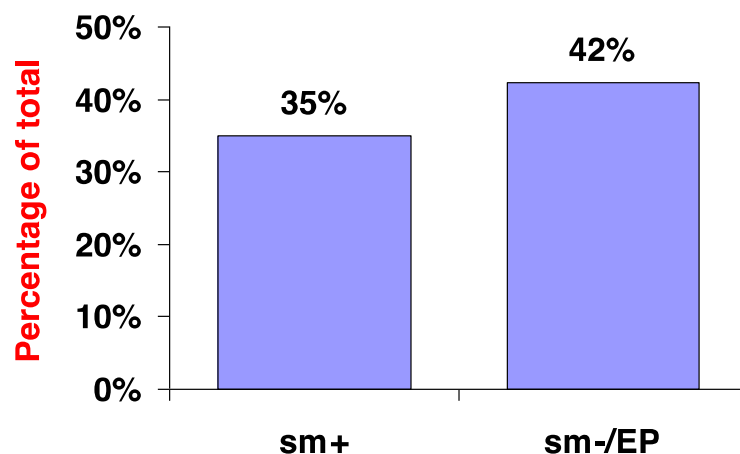
Annual Risk of Tuberculous infection (ARTI) by zone and stratum



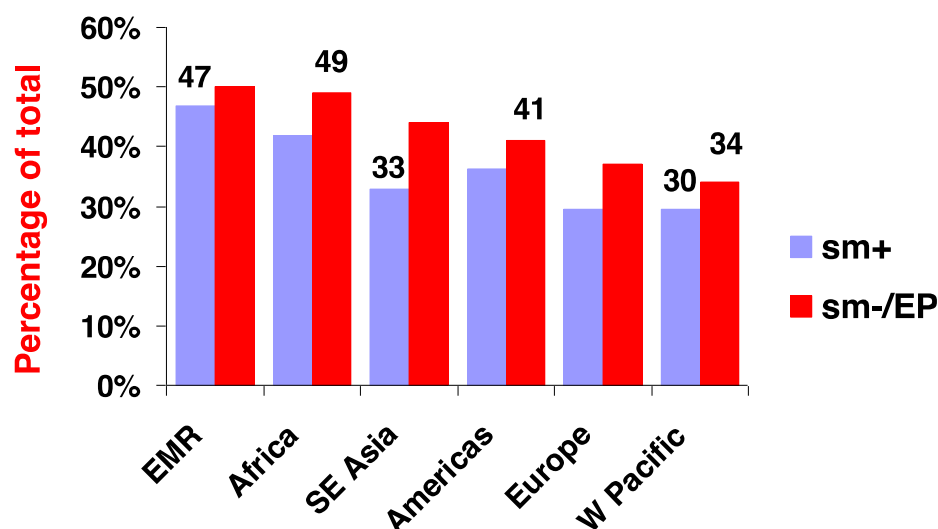
# Drug resistant TB in children in India

| Author, year              | Source                    | No. of children with M.tb positive cultures | Drug resistance                                 |
|---------------------------|---------------------------|---|---|
| Jawahar MS, TRC, 1990     | Lymph Node                | 96  | Isoniazid: 10%<br>Streptomycin: 2%              |
| Ramachandran P, TRC, 1992 | CSF                       | 88  | Isoniazid : 14%<br>Streptomycin : 8%<br>MDR: 2% |
| Swaminathan, TRC, 1996    | Sputum/Gast<br>ric Lavage | 201   | Isoniazid: 10%<br>Streptomycin: 9%<br>MDR: 3.5% |
| Singh, M, PGI             | Sputum/GL                 | 30  | MDR: 6%   |
| Singh S, AIIMS            | Induced<br>Sputum/GL      | -   | MDR: <1%  |

# Notifications among women, countries reporting cases disaggregated by sex, 2010

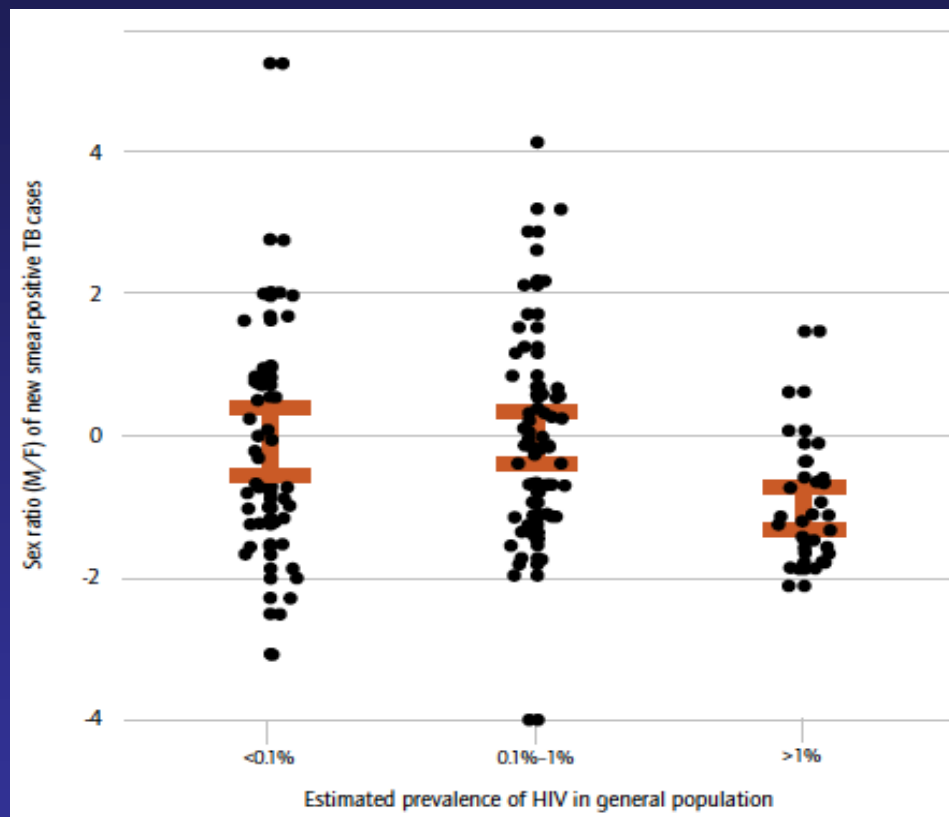


**~38% cases notified  
globally are among  
women**



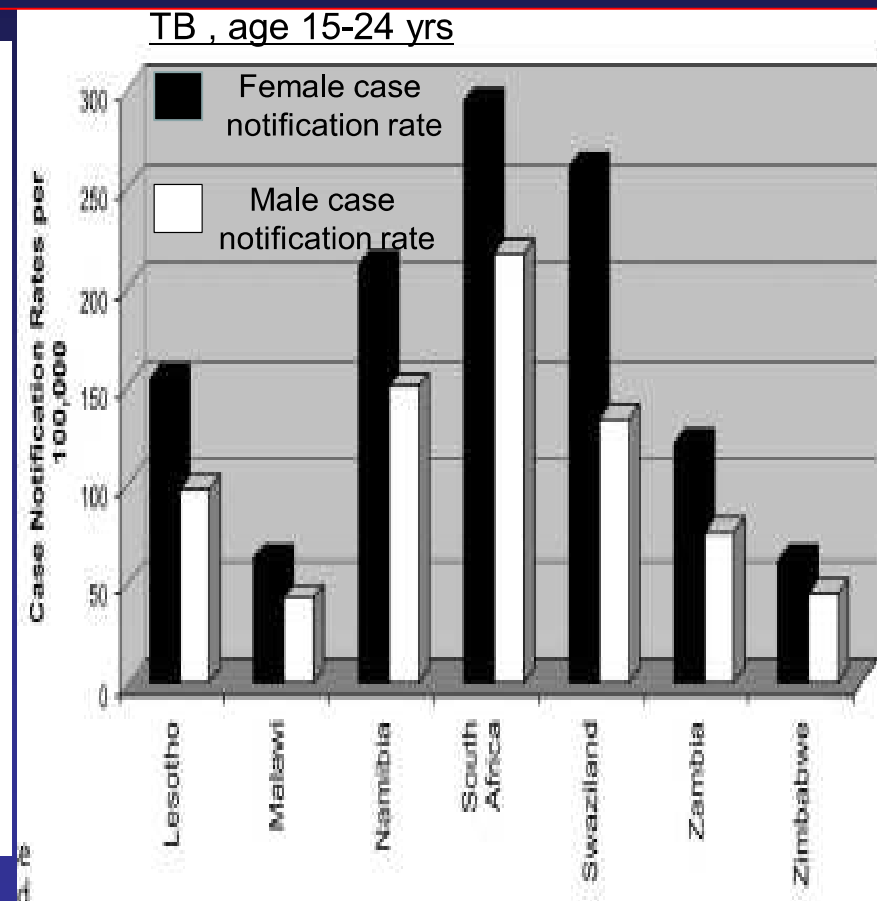
**Variation by region –  
higher percentage of  
cases among women in  
Africa and EMR**

# In areas high HIV prevalence, women in the 15-24 year age group have TB rates 1.5-2-fold higher than men



male:female sex ratio in smear + TB cases by HIV epidemic level

WHO global TB Report 2009



DeLuca A et al. JAIDS 2009;50:196-9

# TB and HIV in women

- HIV and TB are independent risk factors for maternal morbidity and mortality
  - 3.2 x higher death in TB/HIV than TB alone in Durban

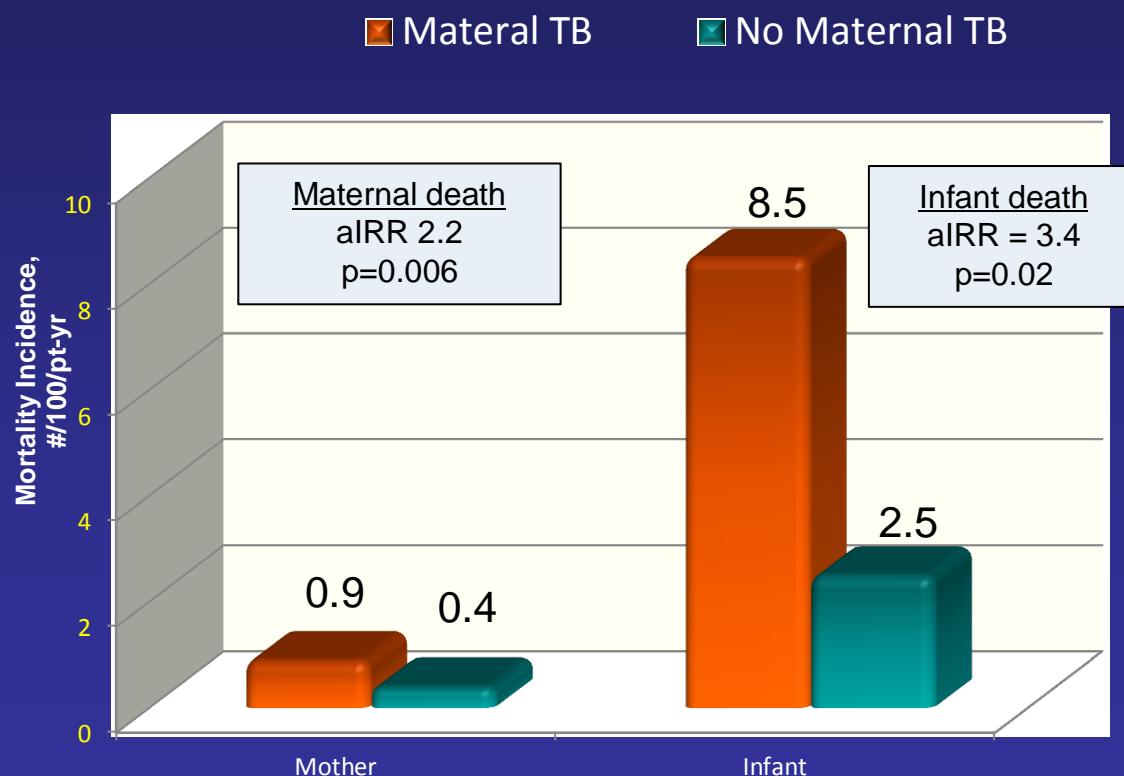
WHO Global TB report 2008; Khan AIDS 2001; Ahmed Int J Tub Lung Dis 1999; Mendendez PLOS One 2008

- TB/HIV in pregnancy
  - Both can be transmitted mother-to-child in utero, intrapartum, and postpartum
  - Maternal TB has negative consequences for
    - **Mom**: increased antenatal hospitalization, adverse pregnancy outcome (postpartum hemorrhage)
    - **infant**: increased prematurity, IUGR, low birth weight, mortality

Pillay IJTL D 2004; Pillay Lancet ID 2004; Jana NEJM 1999; Bjerkdal Scan J Resp Dis 1975; Lin IJOG 2010

# Maternal TB/HIV important risk factor for pediatric TB and mortality

- Maternal TB/HIV increased risk of postpartum mortality by 2.2 fold and probability of infant death by 3.4 fold.



715 HIV-infected pregnant women in Pune, India

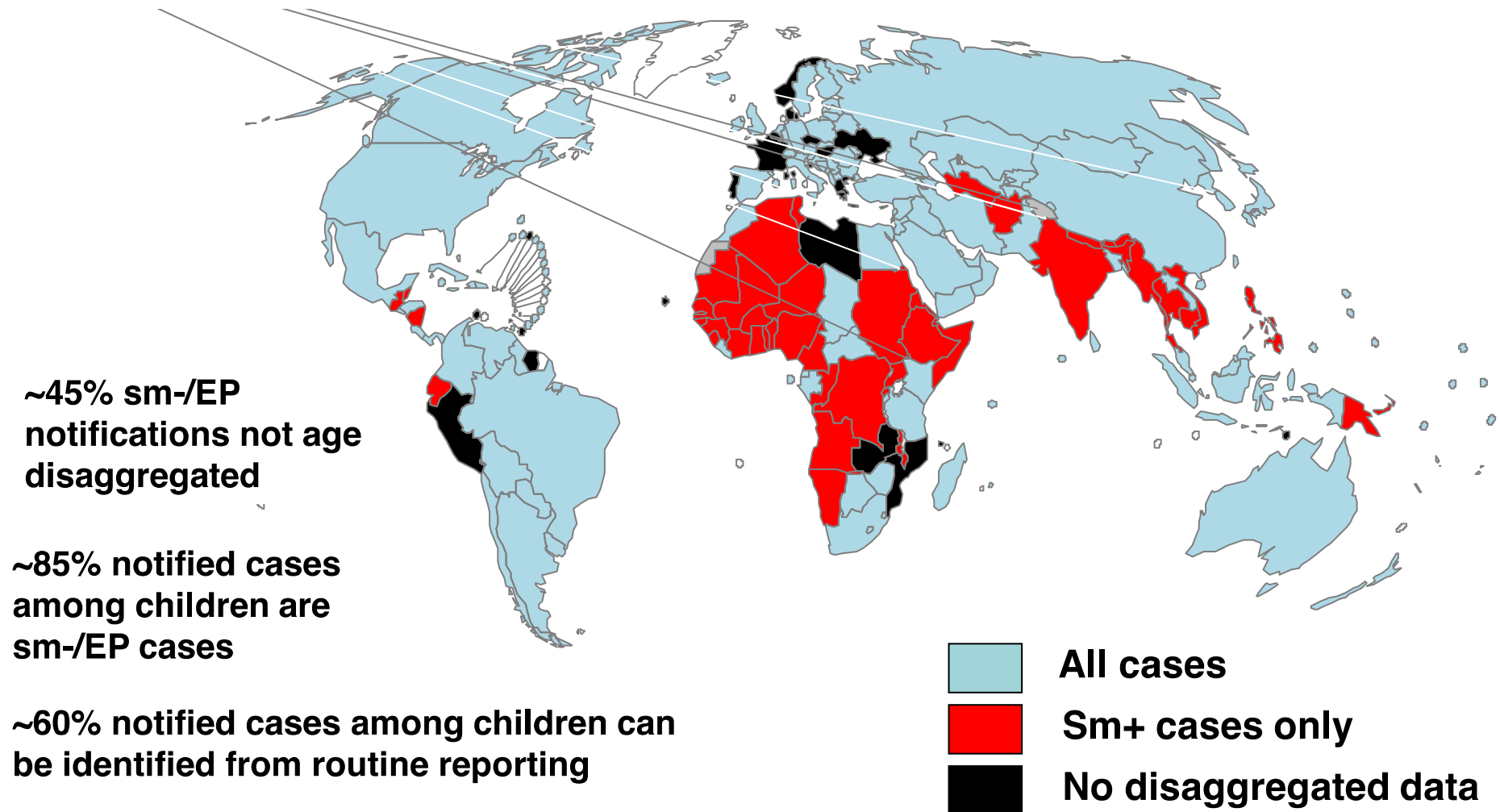
TB incidence 5/100 pt-yr (24 of 715 HIV+ women)

Sick mom=sick child

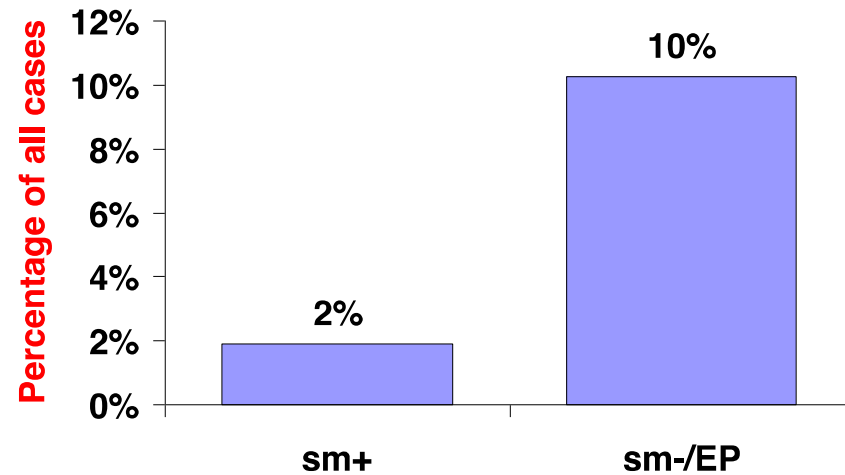
Gupta A et al. Clin Infect Dis 2007;45:241-9

# Notifications disaggregated by age:

**available data, 2010**



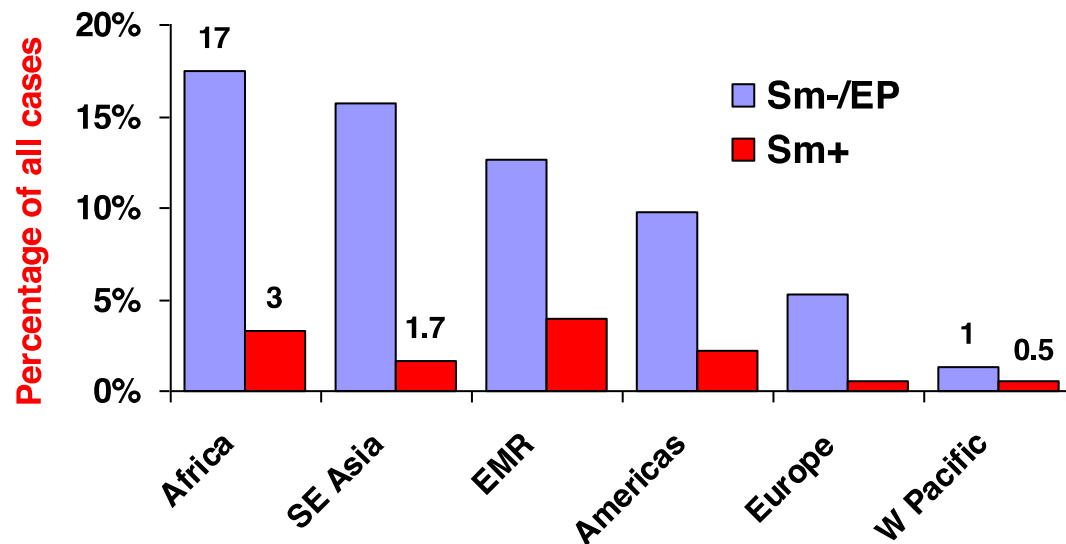
# Notifications among children, countries reporting age-disaggregated data, 2010



Estimated at least 6% of  
global notifications are  
among children

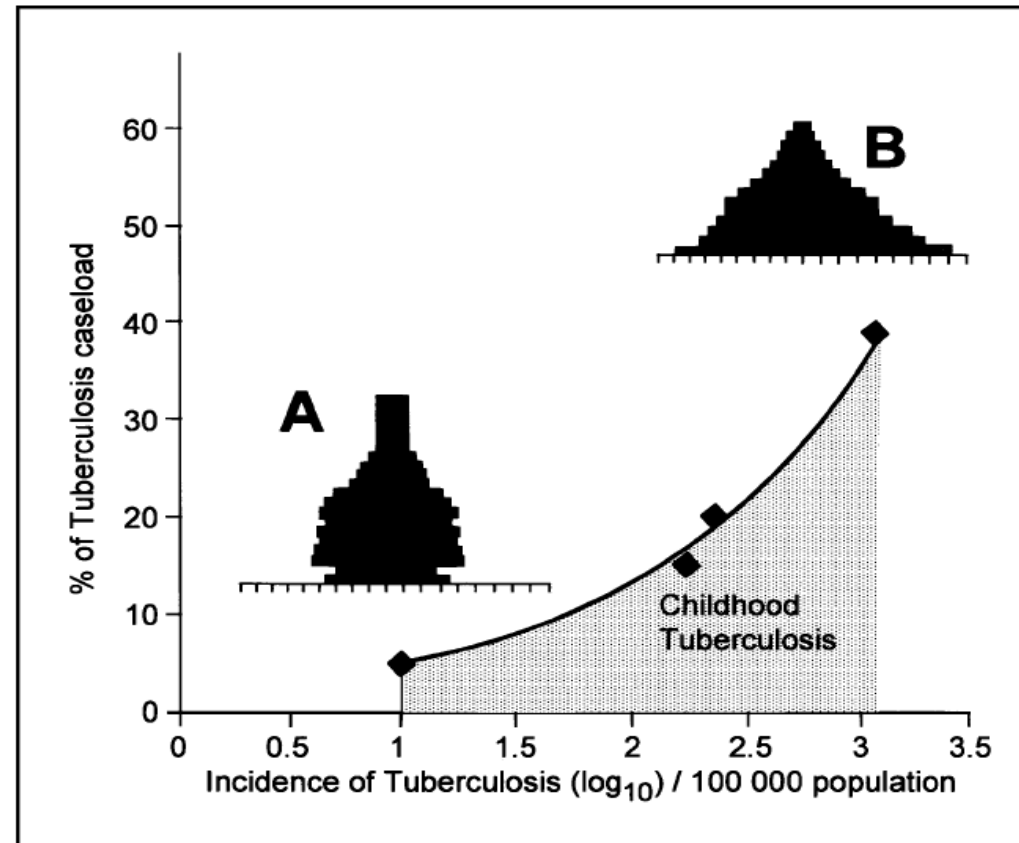


**BUT:** high levels of  
under-reporting of cases  
thought to exist e.g. due  
to lack of linkages  
between NTPs and  
paediatricians





# Proportion of TB caseload made up by children < 15 years in developed and developing country



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.

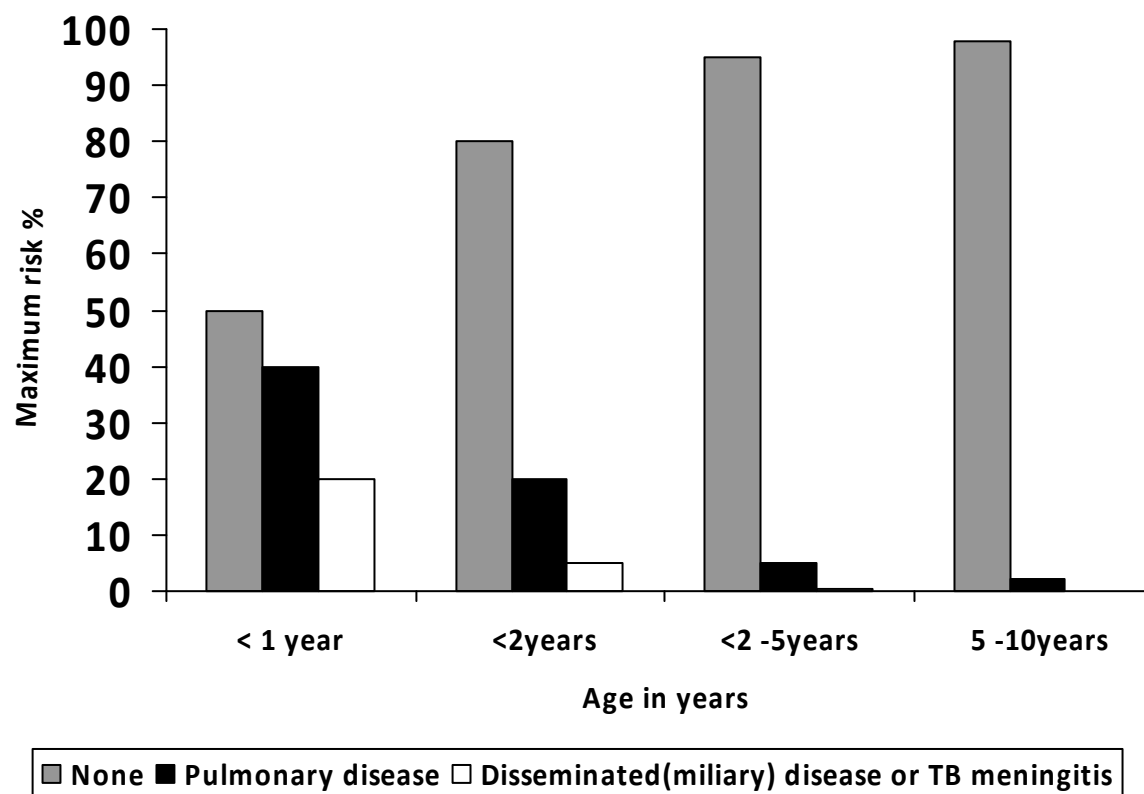
# Risk Factors for Infection and Disease

| Location, year    | No. of contacts | Proportion with LTBI or active TB | Risk factors  |
|-------------------|-----------------|-----------------------------------|---|
| Alaska, 1998      | 282             | 25% LTBI<br>10% TB                | Contact with smear pos, cavity<br>Younger age               |
| Zimbabwe, 2002    | 174             | 63% LTBI<br>40% xRay abnorm       | High load of AFB in index case                              |
| Gambia, 2003      | 384             | 26% LTBI                          | Geographic proximity<br>Household size<br>Duration of cough |
| Philippines, 2003 | 153             | 69% LTBI<br>4% TB                 | Age < 5 yrs for LTBI  |
| India, 2005       | 200 index cases | 34% LTBI<br>9 TB                  | Severe malnutrition<br>Passive smoking<br>Absence of BCG    |
| Malawi, 2006      | 195             | 45% LTBI<br>23% TB                | Female index case<br>Younger age                            |
| Laos, 2009        | 148             | 31% LTBI                          | Ethnic minorities   |

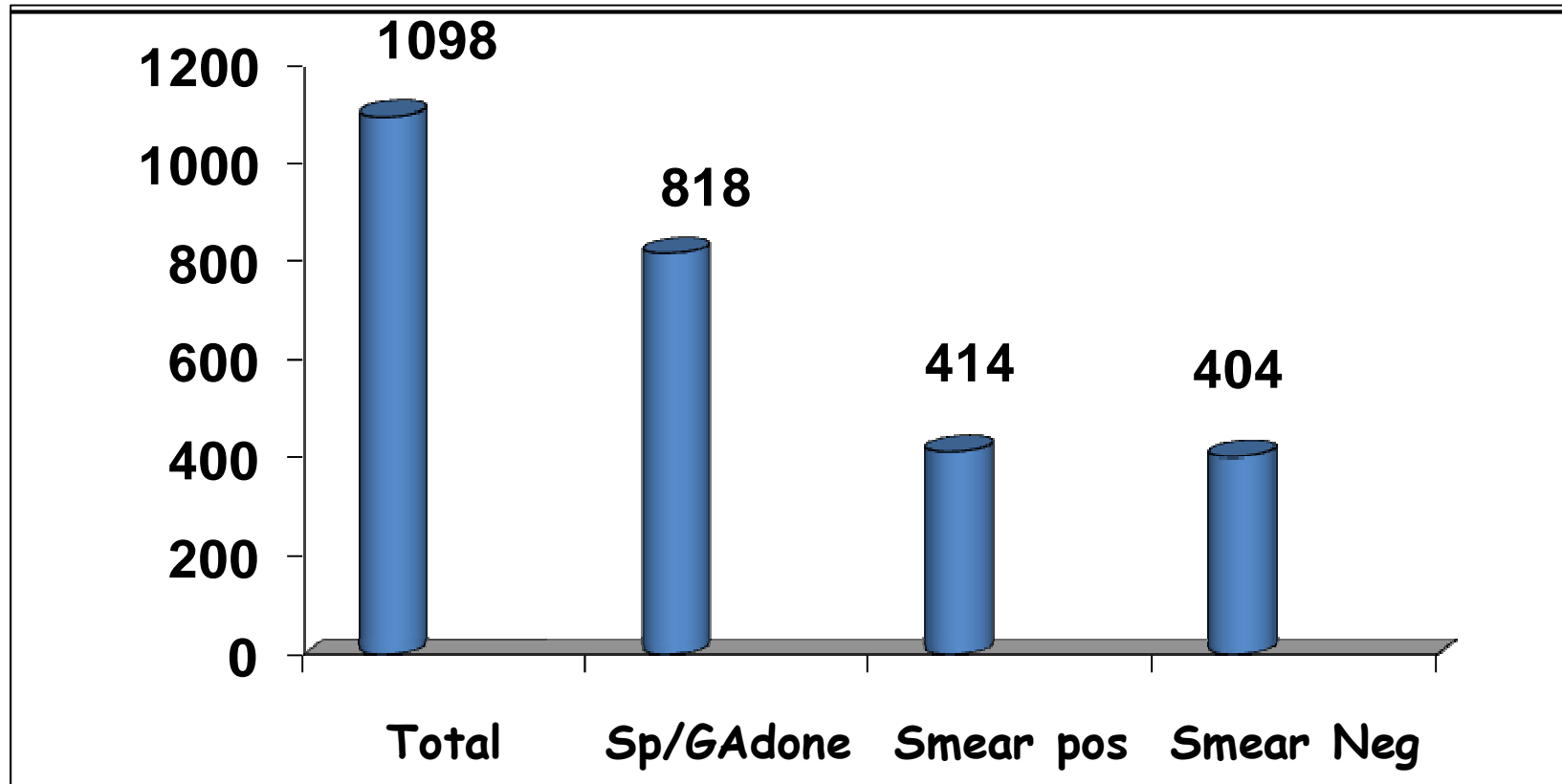
# Risk Factors for TB in Children

- Poverty
- Malnutrition
- HIV
- Exposure to indoor pollution/passive smoke
- Young age
- Maternal TB
- Orphans and vulnerable children

## Quantification of risk of progression from TB infection to disease - children <2 years at high risk

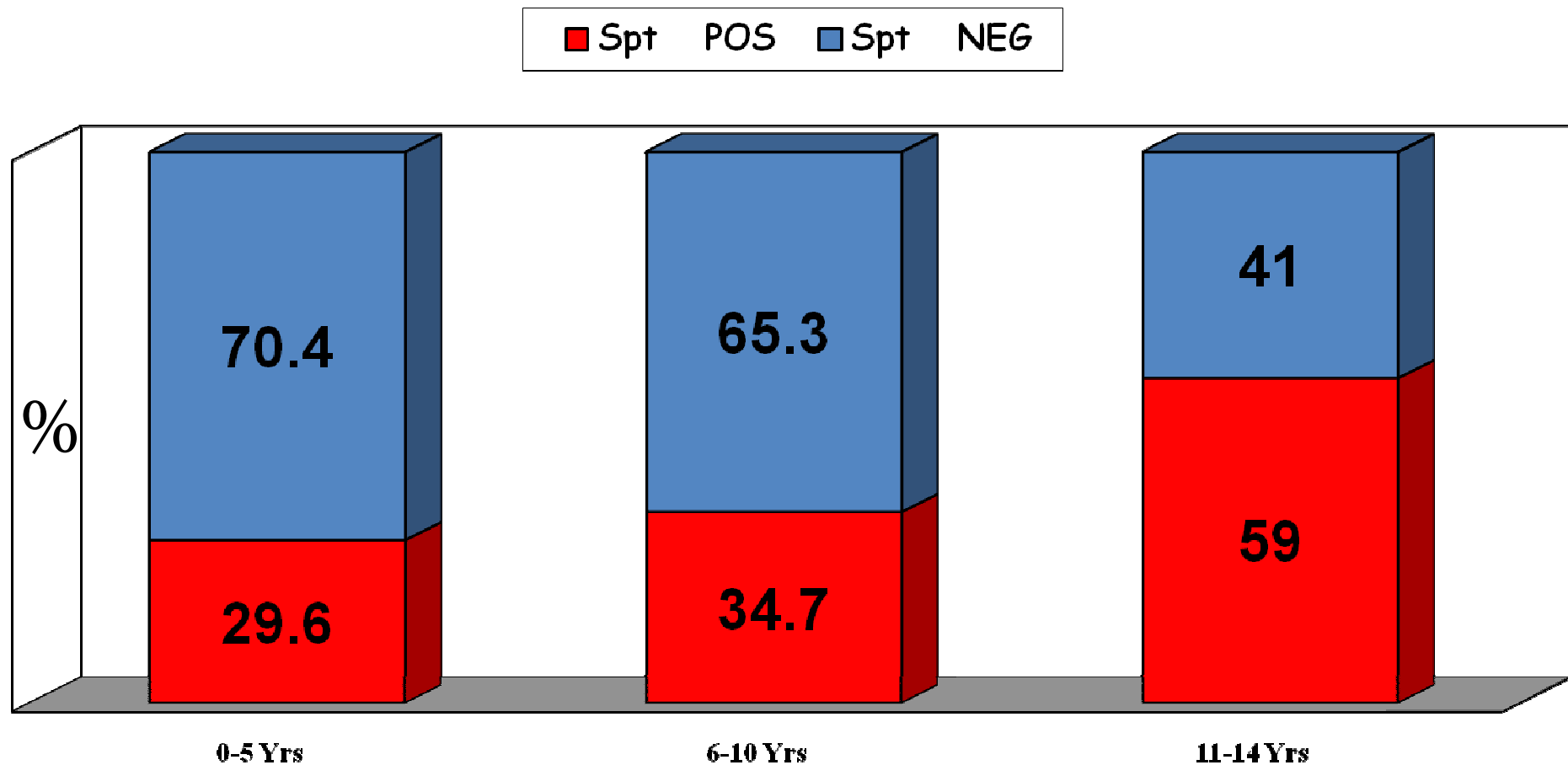


# Smear Positivity in Children



Sharma S, et al. *Int J Tuberc Lung Dis* 2008,12(1):74-80

# Age Stratification Of Smear Positive Children



# Why Worry About TB in Children?

- 1 million TB cases in children globally; in developing countries, pediatric TB constitutes 15-40% of cases.
- One in every 3 TB deaths occurs in children.
- Progression from primary infection to TB disease very high in infancy, miliary/meningitis TB common.
- TB in children reflects ongoing transmission in community
- Drug resistant TB in children is increasing – in Western Cape, MDR increased from 2% to 6% in 1994-97 to 7-15% in 2005-6
- TB major cause of morbidity/mortality in HIV-infected children.
- *Schaaf HS et al. Am J Pub Health 2009;99:1486-90, Hesselning AC et al. CID 2009;48:108-14, Hesselning AC et al. CID 2009;48:108-14*

# Implications

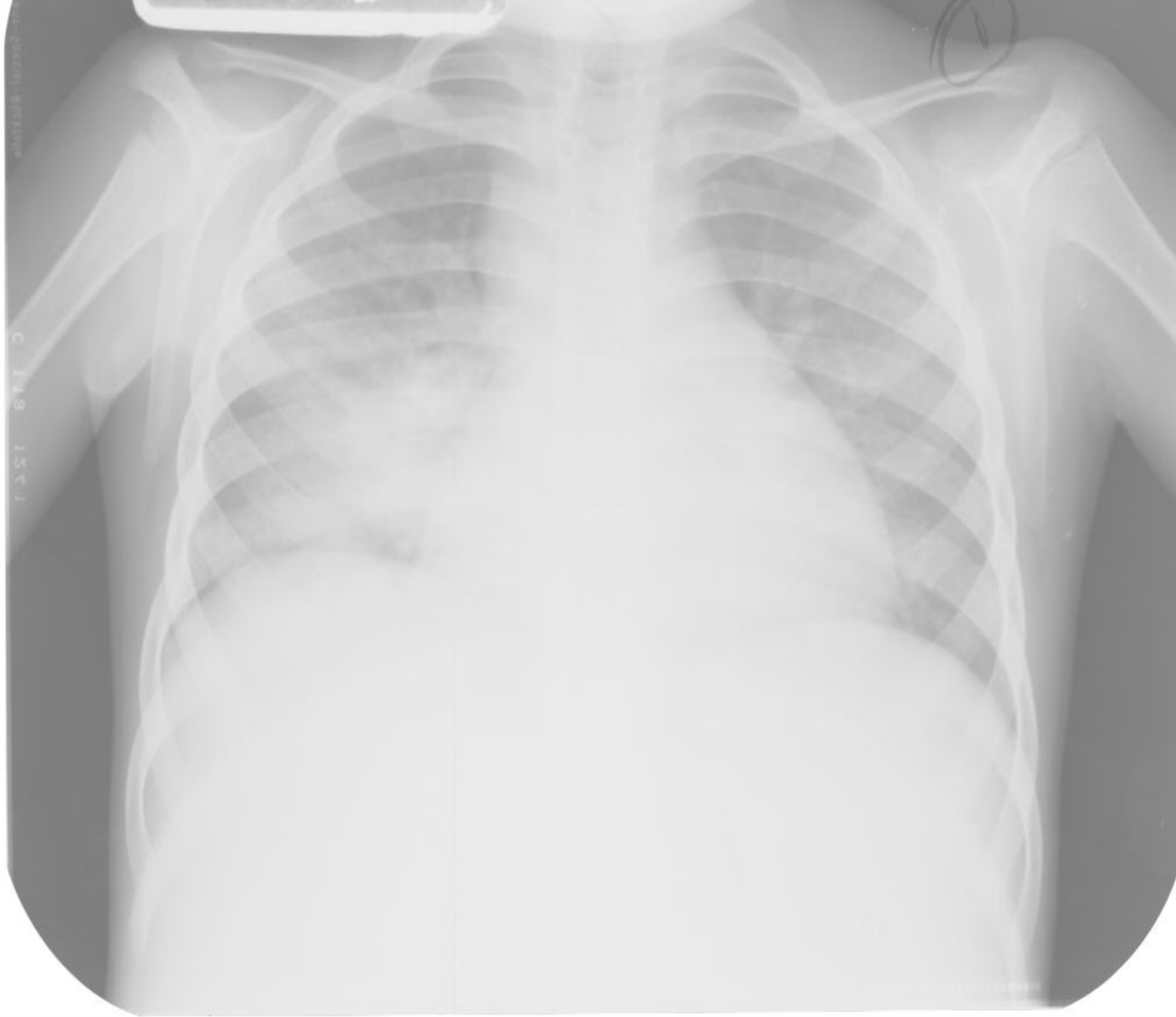
- TB in children reflects ongoing transmission in the community.
  - Because of more rapid progression after infection, in high-burden countries, pediatric TB major problem.
- Increasing drug resistance in children reflects resistance in the community
  - Critical need for data on pediatric dosing for 2nd line drugs (for which minimal to no data).
- HIV brings with it potential for multiple anti-HIV, anti-TB drug interactions that are crucial to evaluate.
  - Low drug levels bring risk for development of resistance and treatment failure (for HIV or TB).



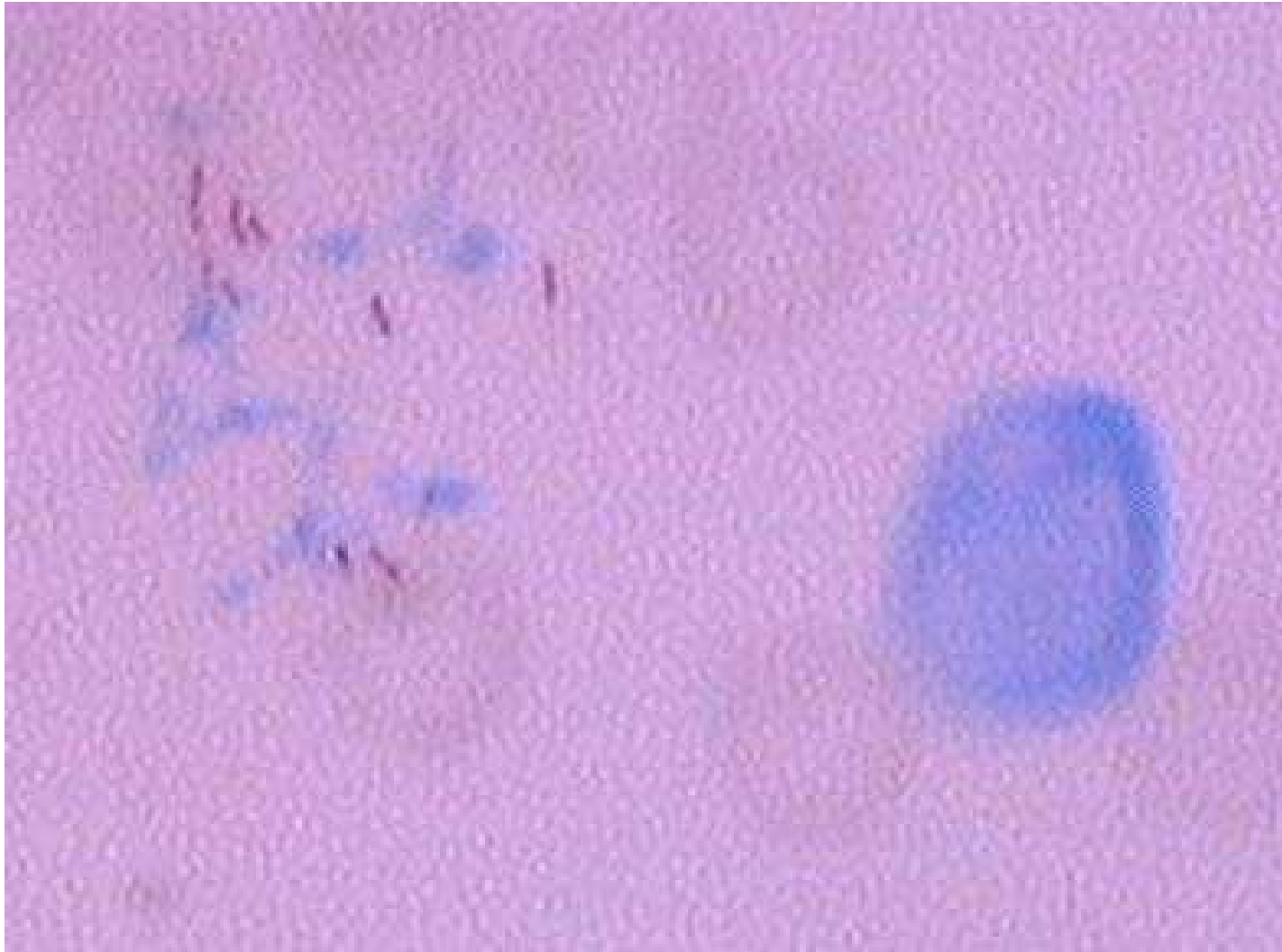
## **Yield of *Mycobacterium tuberculosis* in culture using various specimen collection methods**

| <b>Type of specimen</b>           | <b>Yield of <i>M.tb</i> in culture</b> | <b>Remarks</b>  |
|-----------------------------------|--|---|
| <b>Gastric lavage</b>             | <b>40% -92%</b>                        | Difficult, invasive procedure, increased yield in infants and extensive disease, 3 consecutive specimens required after overnight fasting. Can be done by trained nurses        |
| <b>Broncho-alveolar lavage</b>    | <b>4% - 43%</b>                        | Extremely invasive, requires tertiary care facilities. Useful if performed with diagnostic bronchoscopy   |
| <b>Naso-pharyngeal aspiration</b> | <b>24% - 30%</b>                       | Less invasive. Appropriate for low income countries with limited facilities   |
| <b>Laryngeal swab</b>             | <b>27% - 63%</b>                       | Useful in older children who are unable to expectorate  |
| <b>Induced sputum</b>             | <b>20% - 30%</b>                       | Yield comparable with gastric lavage and naso-pharyngeal aspiration. Requires training, can be done by nurses. Useful in hospital setting. Infection control procedures needed. |
| <b>String test</b>                | <b>Yet to be determined</b>            | Patients as young as 4 years tolerated the procedure well. Peak discomfort at the time of swallowing and mild during string retrieval. Further studies required.                |

4 yr old HIV+, sputum smear pos TB



## AFB in FNAC of lymph node



## Differential diagnosis of pulmonary TB in HIV infected children

|  | Age ranges                                    | Clinical features   | Radiological features   |
|--|---|---|---|
| <b>TB</b>  | All ages                                      | Subacute onset, <sup>a</sup> persistent and unremitting cough, Weight loss or failure to thrive, persistent fever | Lymph node enlargement, parenchymal infiltration, primary complex, miliary. |
| <b>Bacterial pneumonia</b>   | All ages                                      | Rapid onset, high fever, elevated leukocyte count, tachypnoea   | Bronchopneumonia or lobar consolidation                                     |
| <b>Viral pneumonia</b>   | More common in infants than in older children | Air trapping with wheezing, tachypnoea  | Diffuse interstitial infiltration, hyperinflation                           |
| <sup>a</sup> Onset can occasionally be acute, especially in immunocompromised infants. |   |   |   |

# Differential diagnosis of pulmonary TB in HIV infected children

|   | Age ranges                 | Clinical features  | Radiological features   |
|---|----------------------------|--|---|
| <b>Lymphoid interstitial pneumonitis</b>    | Older children (> 2 years) | Gradual onset, cough, mild hypoxia, generalized lymphadenopathy, parotid enlargement, finger clubbing                | Diffuse reticulonodular (miliary) pattern, lymph node enlargement |
| <b>Pneumocystis jiroveci pneumonia</b>      | Infants                    | Abrupt onset, tachypnoea, cough, severe hypoxia, fever $\pm$   | Diffuse interstitial infiltration, hyperinflation                 |
| <b>Bronchiectasis/ chronic lung disease</b> | Older children             | Gradual onset, cough productive of copious sputum (purulent, occasionally blood stained), halitosis, finger clubbing | Honeycombing, usually of lower lobes                              |

(WHO/HTM/TB/2006.362)

# Mantoux Test



# Latent TB tests

## TST

### Pros

- Inexpensive, low tech
- Been standard for decades

### Cons

- Requires return visit
- Operator dependent  
(placement and reading)
- Cross reactivity/false  
positive

## IGRAs

### Pros

- No return visit (result in 24 hrs)
- No cross reactivity with BCG
- No booster effect
- More likely positive in those recent MTB infection

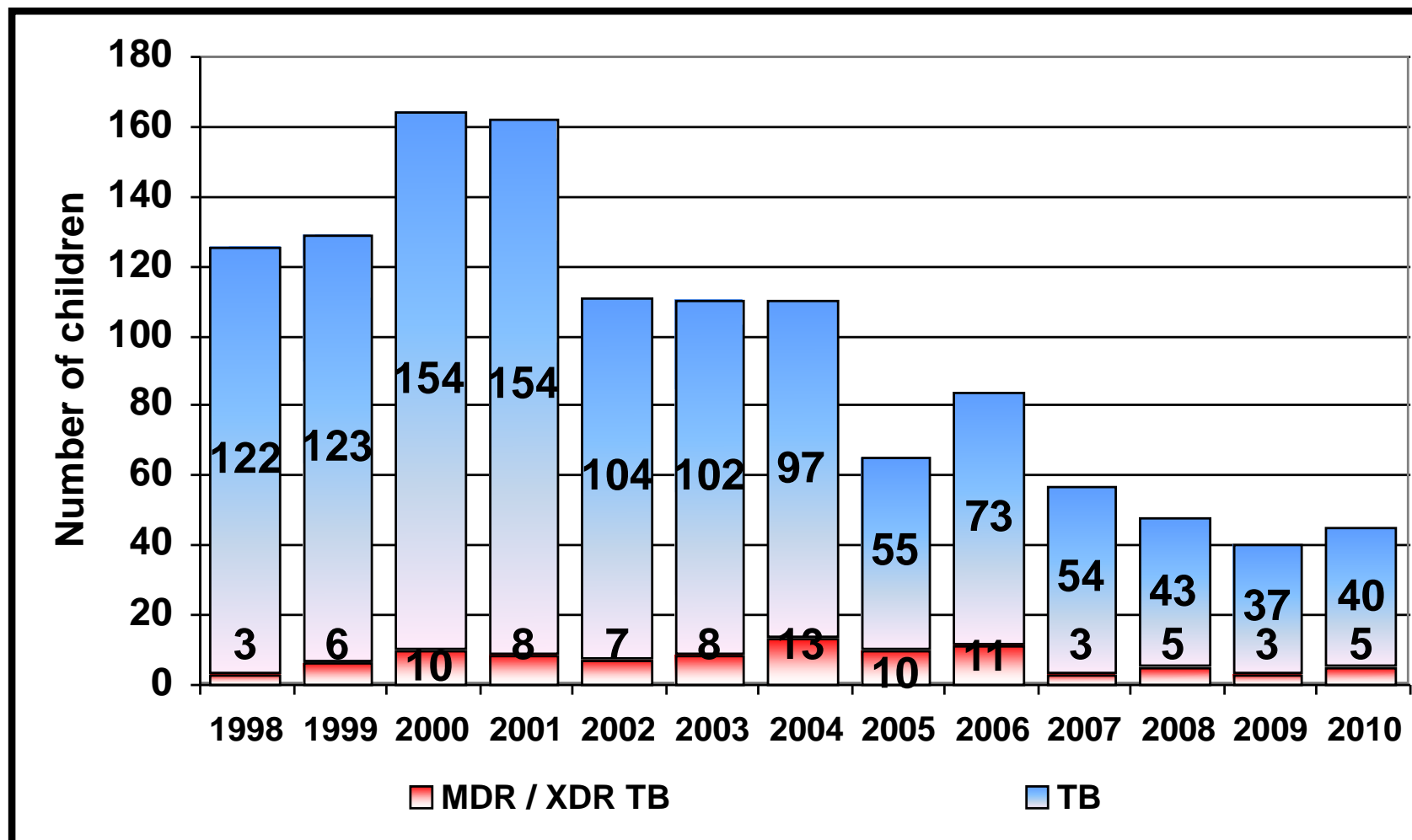
### Cons

- Fresh blood sample needed
- Expensive, needs a lab
- Cutoffs and interpretation

Neither test can distinguish between active disease or latent TB infection  
Both have false positives and false negatives and there is no gold standard

*CDC MMWR 2010 Updated IGRA guidelines*

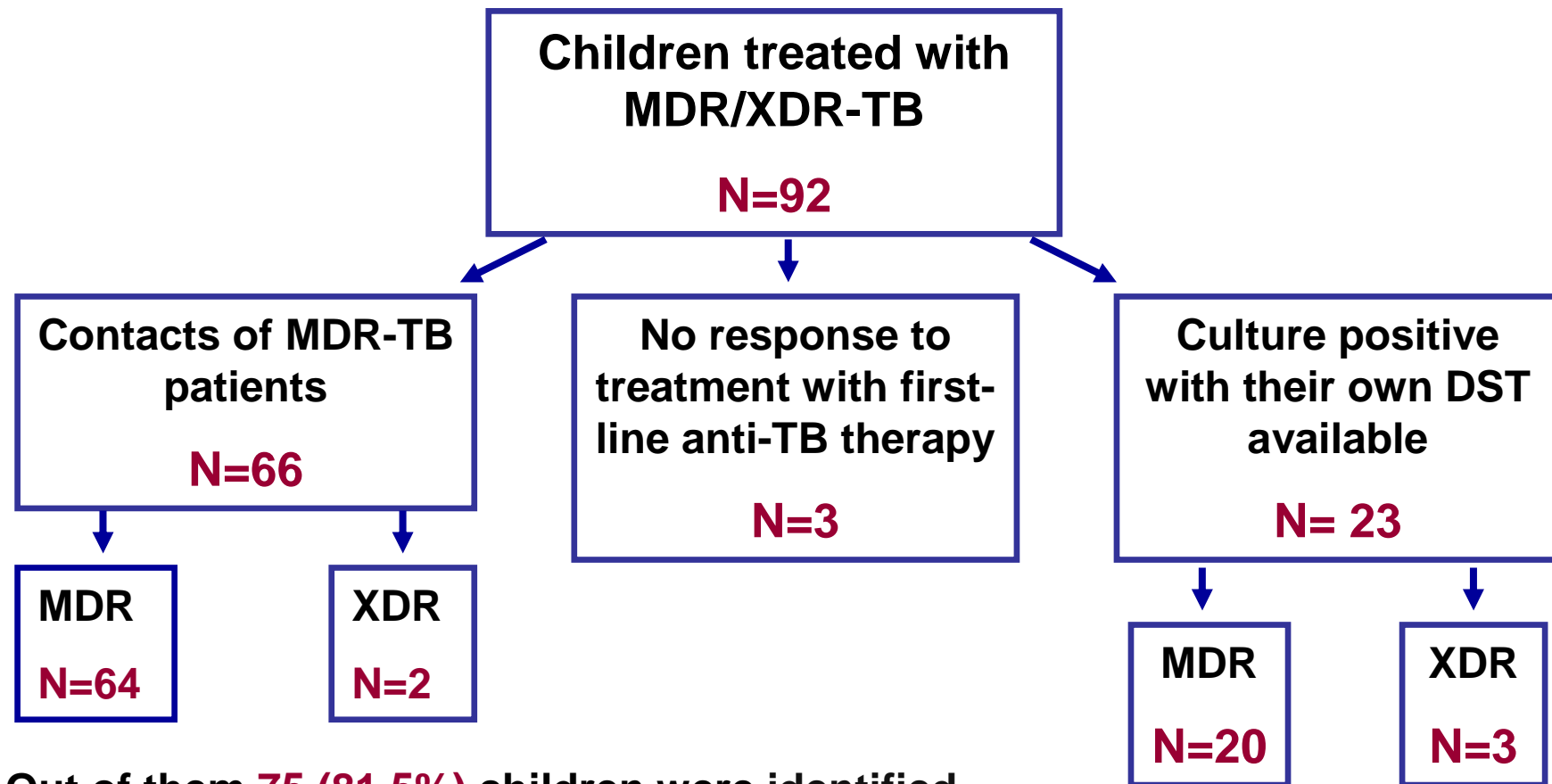
## Children under 15 years of age diagnosed with TB and MDR/XDR TB during 1998-2010, Latvia



Total **92 children** were treated with MDR/XDR TB, out of them **23 (25 %)** were culture positive for MT



## Children under 15 years of age treated with MDR/XDR-TB in Latvia (1998-2010)



Out of them **75 (81,5%)** children were identified through **contact** investigation in early stages of the disease

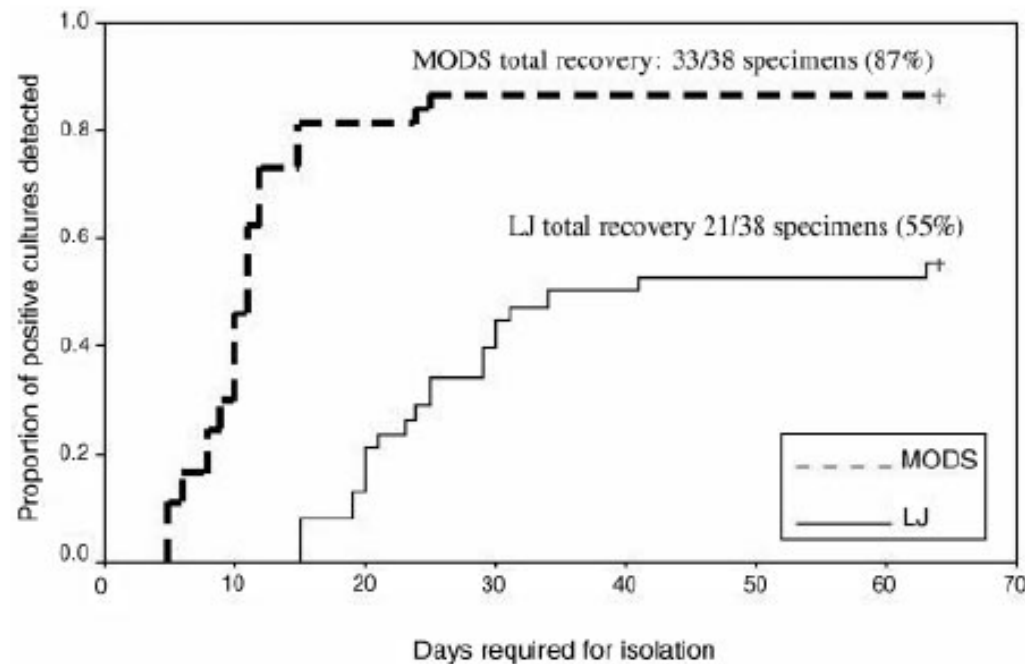
# Diagnosis of DRTB in Children

- Specimens – gastric aspirate, sputum (induced), nasopharyngeal aspirate, BAL, extrapulmonary specimens
- Specimen processing – decontamination protocols
- Transport – addition of Vancomycin, SKLM for LN, solid tissue
- Liquid culture – higher yield in pauci-bacillary specimens
- Yield of culture 20-40% depending on patient selection criteria

## Improved Recovery of *Mycobacterium tuberculosis* From Children Using the Microscopic Observation Drug Susceptibility Method

165 children < 12 yrs enrolled between April 2002 and February 2004 in Peru

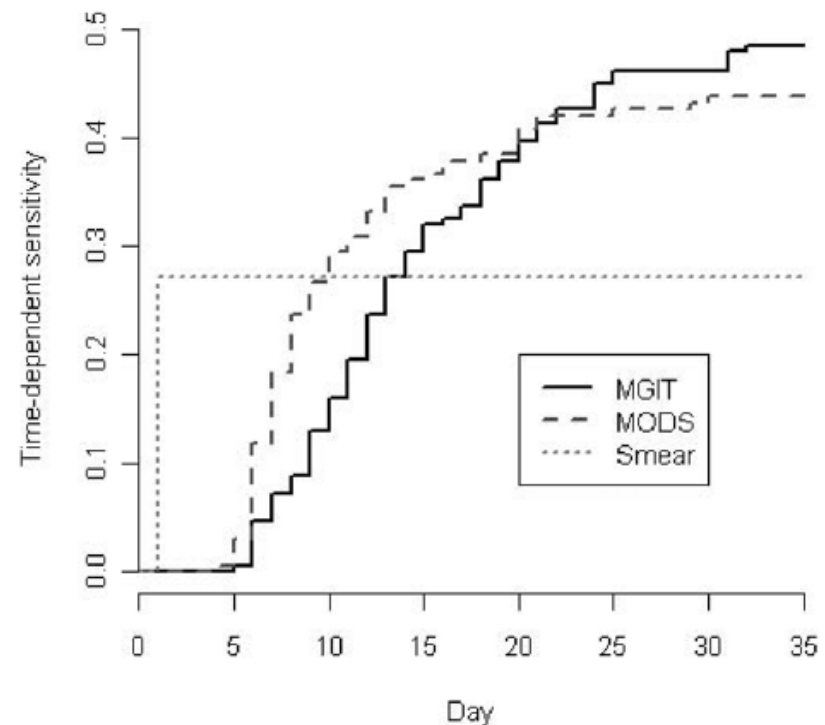
38 culture-positive specimens were obtained (22 gastric aspirate, 12 nasopharyngeal aspirates, and 4 stools)



# Microscopic Observation Drug Susceptibility Assay (MODS) for Early Diagnosis of Tuberculosis in Children

217 consecutive samples including sputum (n = 132), gastric fluid (n = 50), CSF (n = 32) and pleural fluid (n = 3) collected from 96 children with suspected TB in Vietnam

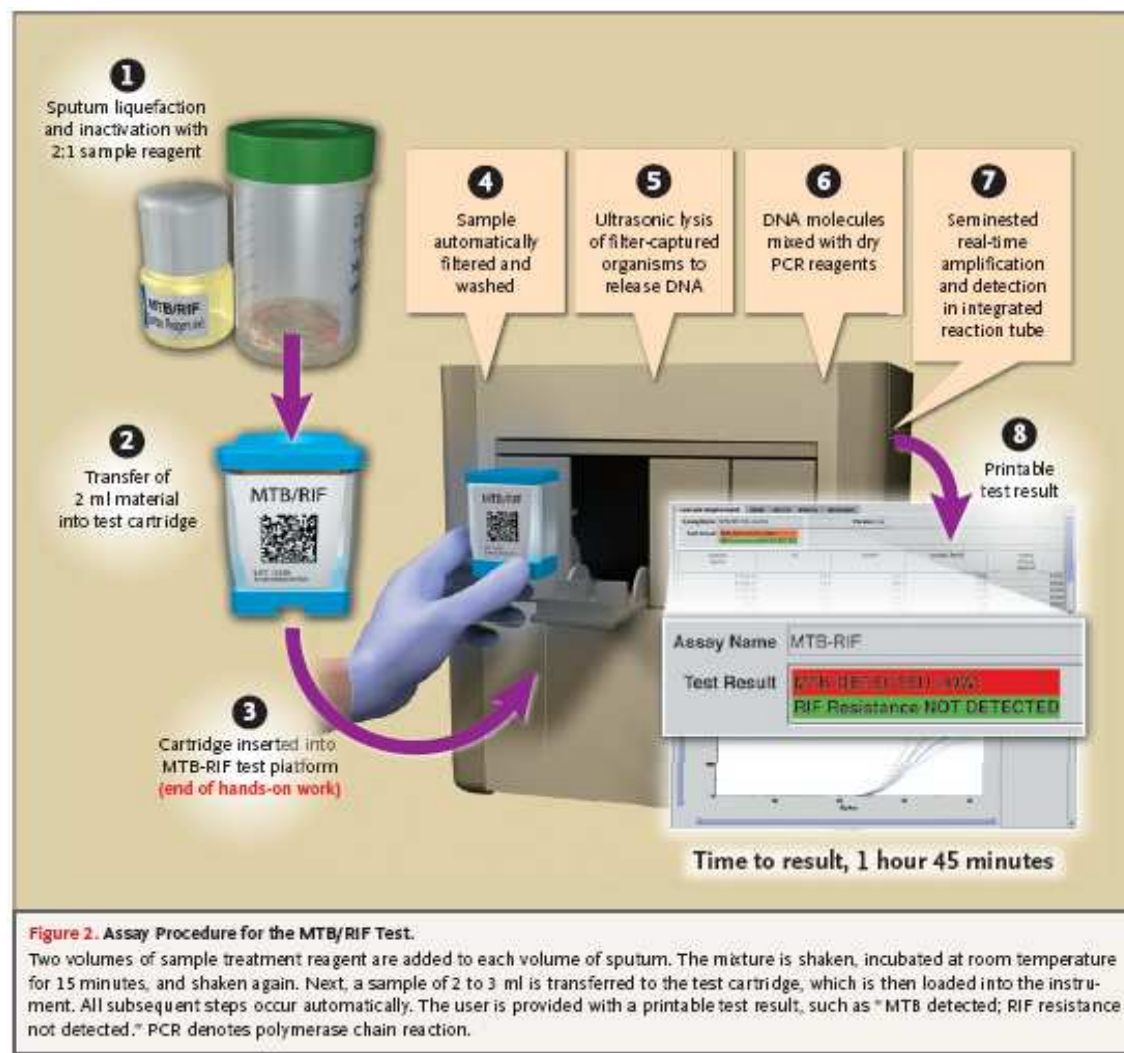
|       | Sensitivity | Specificity |
|-------|-------------|-------------|
| Smear | 28%         | 100%        |
| MODS  | 42%         | 100%        |
| MGIT  | 40%         | 94%         |



Ha DTM et al. Plos One 2009; 4(12): e8341

Time-dependent sensitivity of MODS higher than MGIT ( $P < 0.05$ )

# Automated molecular assay: Xpert™ MTB/RIF [Cepheid, USA]



## The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 9, 2010 VOL. 363 NO. 11

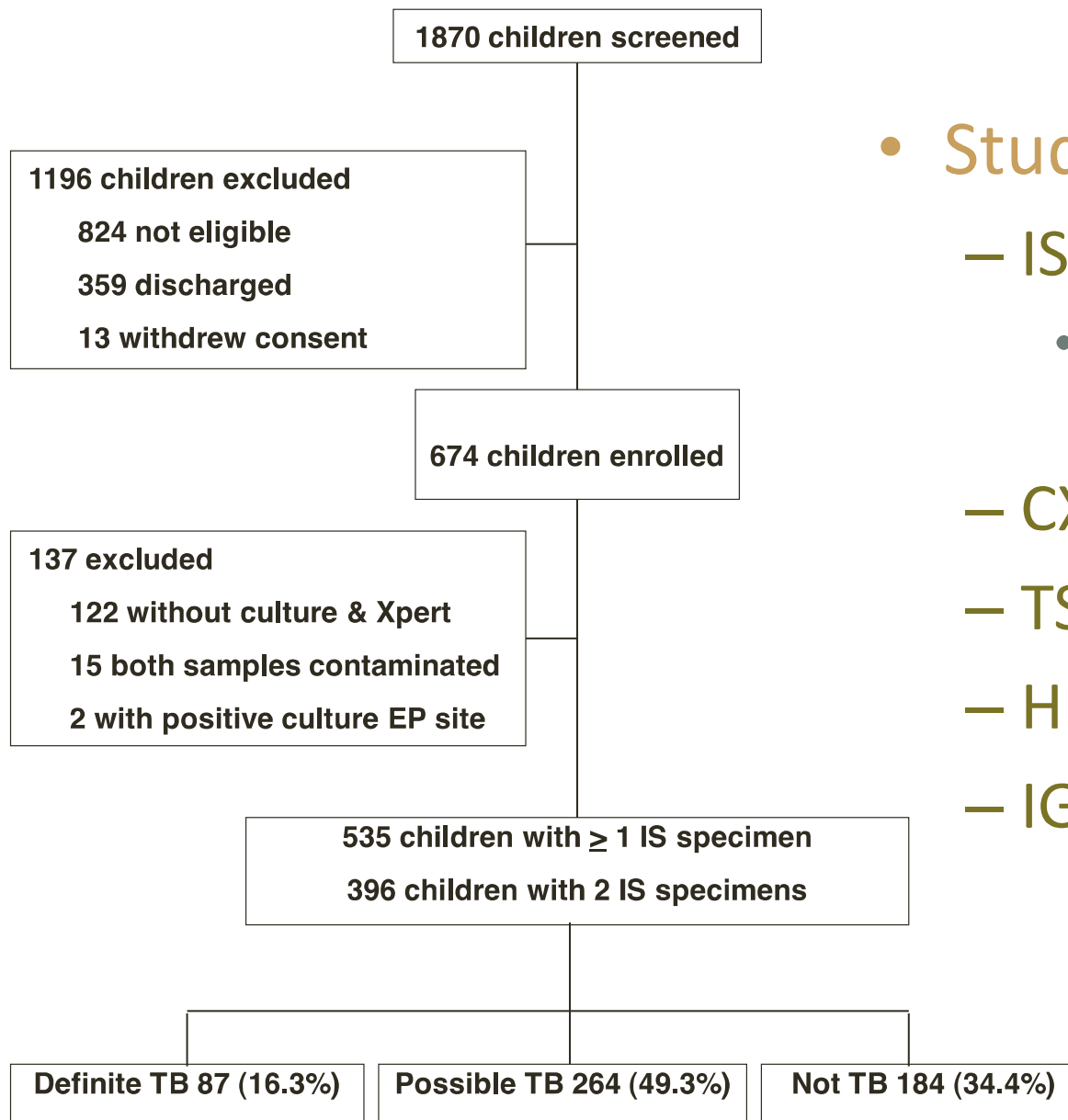
### Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark P. Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S., Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Geddes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.

- >98% sensitivity in S+/C+
- ~70% sensitivity in S-/C+
- >99% specificity in C-
- Rifampin resistance Y/N
- Results within 2 hours
- Recommended for diagnostic use in situations with high probability of drug resistance

# Xpert Mtb for the Diagnosis of TB

- Prospective study enrolling children with suspected TB at two hospitals in Cape Town
  - Cough >2 weeks plus one of:
    - Household contact with TB
    - Loss of weight or failure to gain weight
    - Positive TST
    - Suggestive CXR
- Definitions:
  - Definite TB = culture positive
  - Not TB = no TB treatment plus symptoms/signs resolve
  - Possible TB = all others



- **Study investigations**

- IS x2, NPA x2

- Xpert, smear, MGIT, (MODS)

- CXR

- TST

- HIV (plus CD4)

- IGRA

# Xpert for the diagnosis of TB in children

## Characteristics of subjects (n=535)

|                     | All              | Definite TB      | Possible TB      | Not TB           |
|---------------------|------------------|------------------|------------------|------------------|
| Age (months)        | 19.0 (11.2-38.3) | 21.1 (11.9-45.7) | 18.3 (11.2-34.8) | 18.4 (11.0-38.7) |
| Male (%)            | 294 (55.0)       | 51 (58.6)        | 142 (53.8)       | 101 (54.9)       |
| HIV infection (%)   | 117 (21.9)       | 15 (17.2)        | 65 (24.6)        | 37 (20.1)        |
| Prior TB (%)        | 56 (10.4)        | 6 (6.9)          | 28 (10.6)        | 22 (12.0)        |
| CXR suggests TB (%) | 333 (67.4)       | 55 (73.3)        | 167 (69.0)       | 111 (63.4)       |
| TB treatment (%)    | 273 (51.4)       | 87 (100)         | 185 (70.1)       | 0 (0)            |
| WAZ score < -2 (%)  | 68 (15.6)        | 17 (29.3)        | 33 (15.5)        | 18 (10.9)        |
| TST positive (%)    | 191 (39.2)       | 62 (74.7)        | 111 (47.2)       | 18 (10.7)        |



# Performance of Xpert and smear microscopy

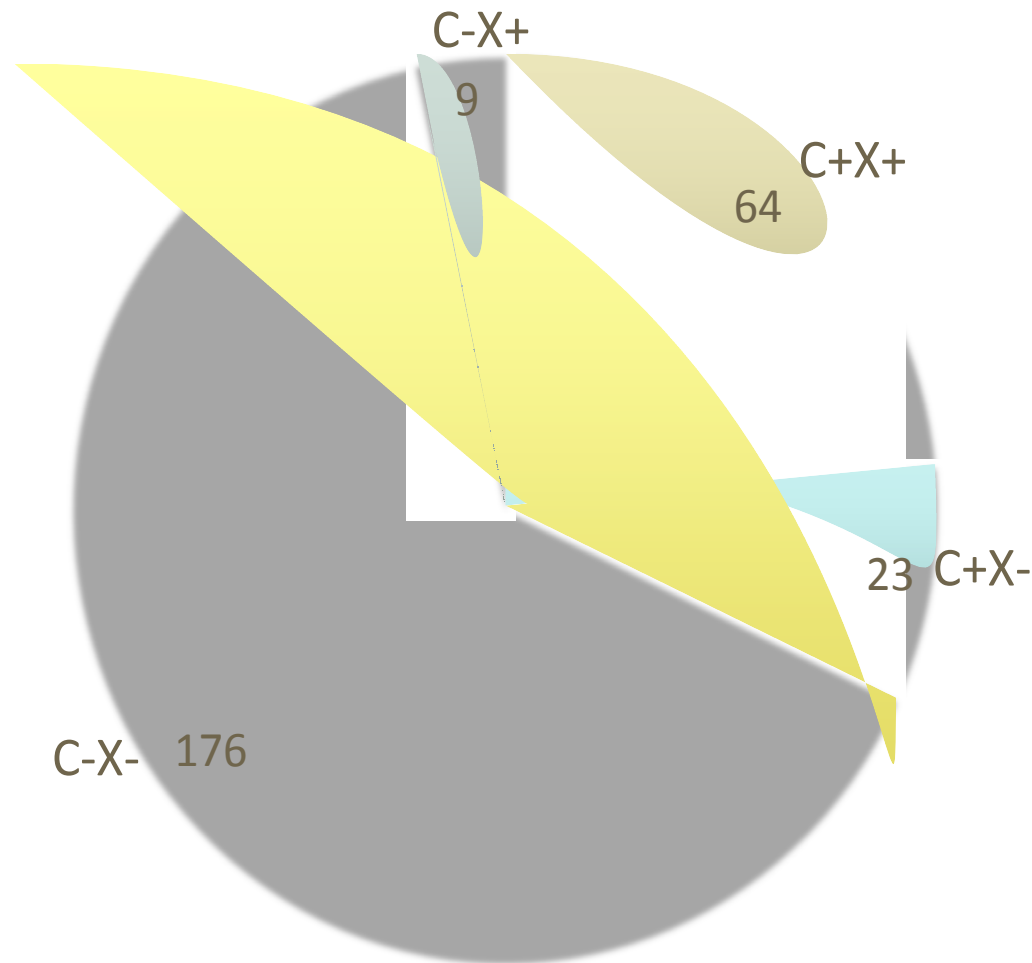
|  | Sensitivity      | Specificity      | PPV  | NPV  | Sensitivity in<br>smear-positive | Sensitivity in<br>smear-negative |
|--|------------------|------------------|------|------|----------------------------------|----------------------------------|
| <i>All children with complete results from at least one specimen (n=535)</i> |                  |                  |      |      |                                  |                                  |
| <b>Xpert</b>   |                  |                  |      |      |                                  |                                  |
| All  | 64/87            | 443/448          | 92.8 | 95.1 | 29/30                            | 35/57                            |
|  | 73.6 (64.1-83.0) | 98.9 (97.9-99.9) |      |      | 96.7 (89.9-100)                  | 61.4 (48.4-74.4)                 |
| HIV infected   | 14/15            | 102/102          | 100  | 99.0 | 9/9                              | 5/6                              |
|  | 93.3 (79.0-100)  | 100 (96.4-100)   |      |      | 100 (66.4-100)                   | 83.3 (40.5-100)                  |
| HIV uninfected   | 50/72            | 340/345          | 90.9 | 93.9 | 20/21                            | 30/51                            |
|  | 69.4 (58.5-80.3) | 98.6 (97.3-99.8) |      |      | 95.2 (85.3-100)                  | 58.8 (44.8-72.8)                 |

# Summary of Performance for TB Detection

- Sensitivity twice that of smear microscopy (33%)
  - 1 Xpert 57% (smear negative: 36%)
  - 2 Xpert 71% (smear negative: 57%)
- Specificity excellent
  - 99% for children with 2 negative cultures
  - 1/184 in “not TB” group false positive (99.5%)

# Xpert: Experience in Children

Culture and Xpert results in children started on TB treatment  
n=272



27% Xpert positive

32% Culture positive

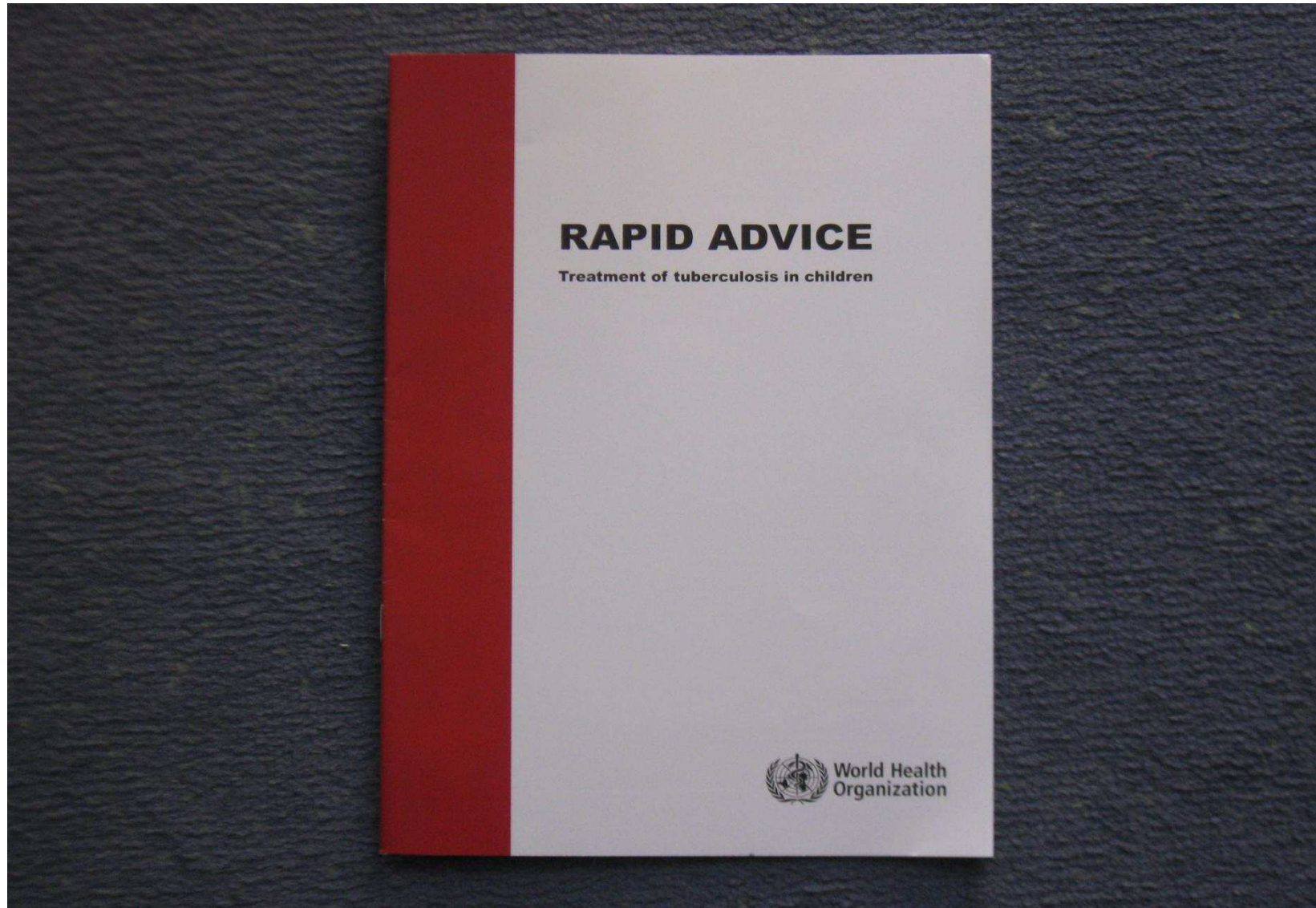
65% Both negative

Difference in yield of Xpert  
vs. culture = 14 cases (5%)

# Questions still to be answered

- Other respiratory samples
  - Gastric washings, NPA...
    - NPA may offer alternative where IS not available
    - Promising early results
- Extra-pulmonary TB
  - FNA looks very promising
    - 97% sensitivity in adult patients
      - (Ligthelm et al. J Clin Microbiol 2001, Epub Aug 31)
- Children with less severe illness (not hospitalized)
  - Studies currently underway in Cape Town
- Performance in larger group of HIV-infected children

# WHO Treatment Guidelines Revised 2010



# Scope of revision – in the "Rapid Advice"

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## Literature review

- **Dosing** of 3 first line medicines: isoniazid, rifampicin and pyrazinamide
- **Hepatotoxicity** of anti-TB drugs
- Efficacy and safety of **intermittent treatment regimens** of TB in children
- Efficacy, safety and pharmacokinetics of the first line TB medicines in **children less than 3 months of age**
- Efficacy and safety of the first-line TB medicines in the **treatment of TB meningitis**
- Efficacy and safety of the first-line TB medicines in the **treatment of osteo-articular TB**
- The choice of **fluoroquinolones** for treatment of TB in children, including a review of safety



THE  
**STOP TB**  
DEPARTMENT

# Recommendations at a glance

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- Given the risk of drug-induced hepatotoxicity, WHO recommends the following dosages of anti-tuberculosis medicines for the treatment of tuberculosis in children:
  - Isoniazid (H) – **10 mg/kg** (range 10–15 mg/kg); maximum dose 300 mg/day
  - Rifampicin (R) – **15 mg/kg** (range 10–20 mg/kg); maximum dose 600 mg/day
  - Pyrazinamide (Z) – **35 mg/kg** (30–40 mg/kg)
  - Ethambutol (E) – **20 mg/kg** (15–25 mg/kg)



## Other Recommendations

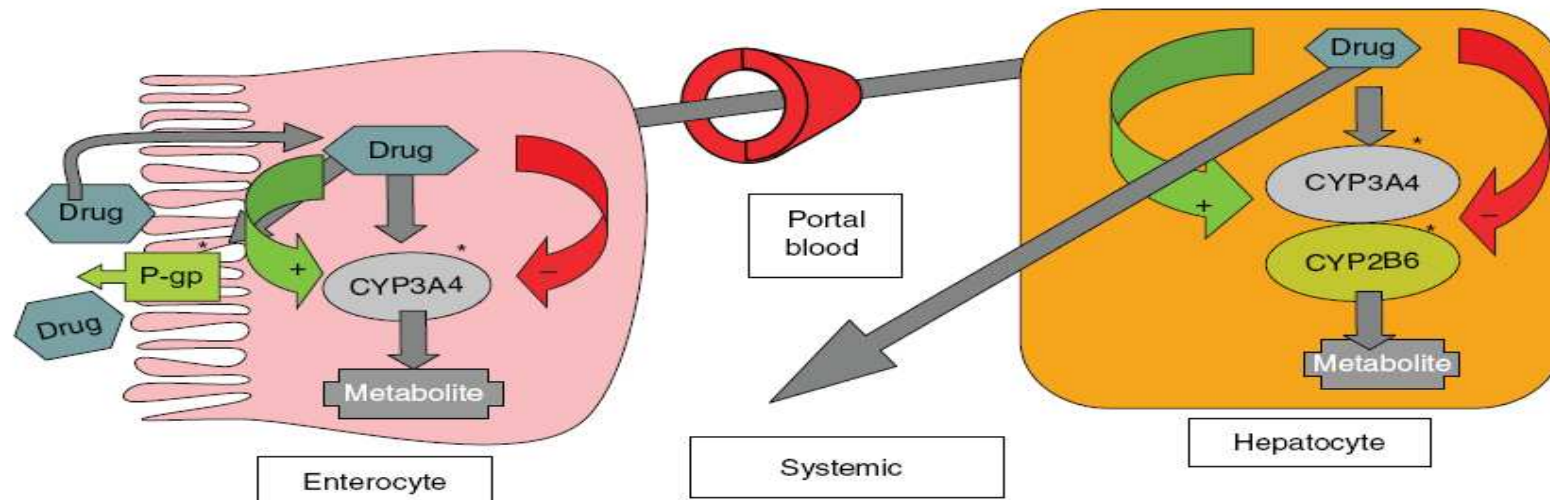
- Use 6 month regimen **2EHRZ/4RH** for all children with TB living in areas with high HIV or Isoniazid resistance
- Thrice-weekly treatment in continuation phase in HIV uninfected children only
- Avoid Streptomycin in first line regimen
- For meningitis and bone and joint TB: use **2EHRZ/10HR** (12 months regimen)
- Infants 0-3 months with TB should be promptly treated – may need dose adjustment
- Fluoroquinolones can be used for MDR treatment



# Antiretroviral Therapy for TB/HIV

- Any child with active TB disease should begin TB treatment immediately, and start ART as soon as tolerated in the first 8 weeks of TB therapy, irrespective of CD4 count and clinical stage.
- The preferred first-line ARV regimen when taking a rifampicin- containing regimen for TB
  - for infants and children less than 3 years of age - 2 NRTIs + NVP or a triple NRTI regimen
  - for children more than 3 years of age - 2 NRTIs + EFV
  - for infants and children less than 2 years of age, who have been exposed to NVP - triple NRTI regimen

# Influence of induction or inhibition of enzymes or transporters on systemic drug exposure



- Rifampin is a potent inducer and the NNRTIs and PIs are themselves inducers and/or inhibitors of CYP enzymes or P-glycoprotein transporter.
- Modulation of these systems may cause altered metabolism and drug concentrations when inducers and/or inhibitors are used concurrently with enzyme substrates.

# Drug Interactions

- Factors affecting Nevirapine levels:
  - Age (< 3 yrs lower levels)
  - pharmacogenetics (Cyp2B6 TT genotype higher levels)
  - Rifampicin and other enzyme inducers lower levels
  - ? Malnutrition
- If NVP used with Rif, should be dosed at max of 200 mg/sqm/day

# Reasons for lower success rates

- poor compliance and non-completion of treatment
- late presentation by patients and delay in diagnosis by health workers
- incorrect diagnosis
- high early mortality in children with advanced HIV
- malabsorption of anti-tuberculosis drugs in HIV-infected
- severely malnourished children
- MDR-TB

# Pharmacokinetics of anti-TB Drugs in Children – NIRT study

- To study the impact of age and nutritional status on the PK of RMP, INH & PZA in children receiving anti-TB treatment as per RNTCP guidelines in India
- To correlate blood levels of first line anti-TB drugs with TB outcomes

# Study Population

- ❖ Aged 1 to 12 years
- ❖ Receiving TB treatment as per RNTCP for minimum 15 days
- ❖ Clinically stable
- ❖ HIV negative
- ❖ Not suffering from severe hematological or biochemical abnormality
- ❖ Obtained informed, written consent from parent/guardian in all cases & assent from children >7 years

# Recruitment sites

- ❖ Institute of Child Health, Chennai
- ❖ Govt Hospital of Thoracic Medicine, Chennai
- ❖ Kilpauk Medical College & Hospital, Chennai
- ❖ Govt Rajaji Hospital, Madurai

# INH acetylator status

*Indian Pediatr 1990; 27: 134 - 42*

- ❖ Test undertaken after a washout period of 72h
- ❖ INH syrup - 2.5mg/kg dose given & time noted
- ❖ ~1 ml saliva collected at 5 h after INH admin
- ❖ Estimation of salivary INH by HPLC
- ❖ INH conc  $\leq 0.3\mu\text{g/ml}$  – rapid acetylator



# Conduct of PK study

- ❖ PK study done at Institute of Child Health
- ❖ Blood draws at pre-dosing, 2, 4, 6 & 8h after directly observed administration of drugs
- ❖ Anthropometric measurements on study day & at end of ATT
- ❖ D-xylose absorption test (2g) during PK study
- ❖ Repeat blood draw at end of IP & end of treatment (2h – post dose only)

# Assessment of Nutritional Status

- ❖ Classification of PEM using WHO growth standards for children, 2000
- ❖ Children classified as wasted, under weight or stunted based on z scores
- ❖ z score  $< -2$  denotes moderate &  $< -3$  denotes severe malnutrition

# Estimations & Analysis

- ❖ Plasma RMP, INH & PZA by HPLC

*Indian J Pharmacol 2004; 36: 231-3; J. Chromatogr. B Analyt. Techonol. Biomed. Life Sci. 2002; 766: 181*

- ❖ D-xylose in whole blood (at 1.5 hours)

- ❖ PK variables calculated

- ❖ Statistical analysis using SPSS, version 14

- ❖ Age stratification:1-3, 3.1-6, 6.1-9, 9.1-12 years

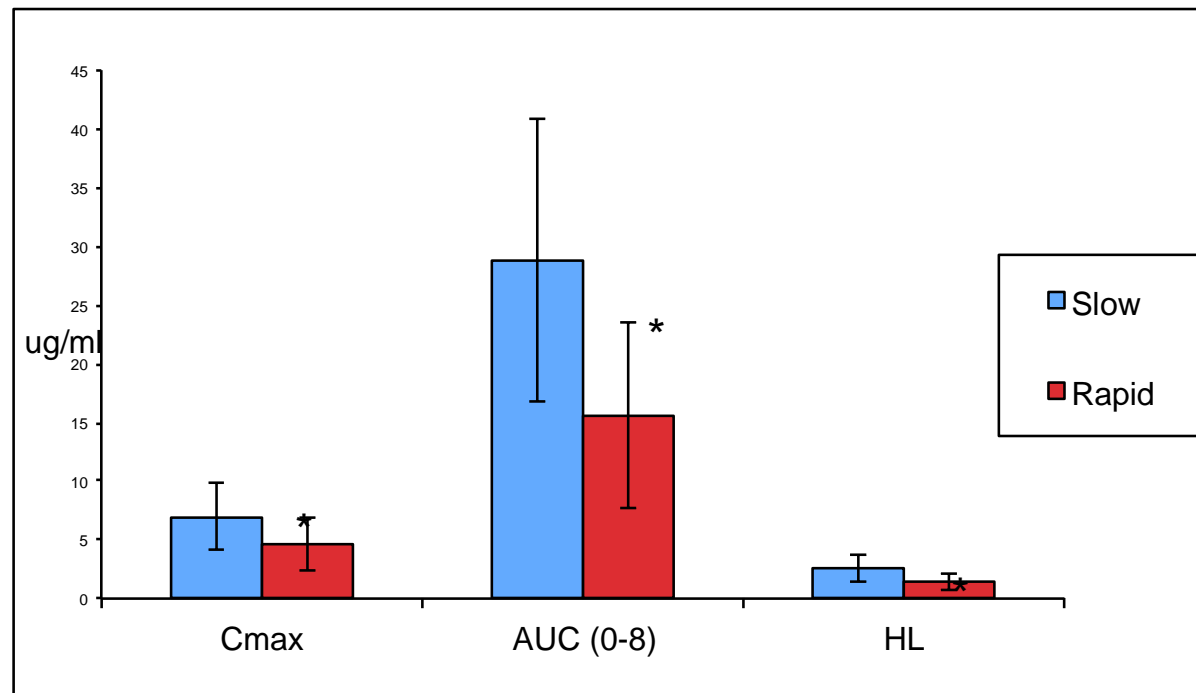
## Baseline characteristics (n = 84)

| Details                      | Mean $\pm$ SD  |
|------------------------------|----------------|
| Age (years)                  | 7.1 $\pm$ 3.3  |
| Males (n)                    | 40             |
| Body wt (kg)                 | 18.8 $\pm$ 7.2 |
| HAZ (Stunting)               | -1.2 $\pm$ 1.3 |
| WAZ (Underweight)            | -1.7 $\pm$ 1.0 |
| WHZ (Wasting)                | -1.2 $\pm$ 1.1 |
| Serum albumin (g/dl)         | 4.0 $\pm$ 0.5  |
| Rapid acetylators of INH (n) | 27             |

## TB treatment details

| Details  | Mean $\pm$ SD                                    |
|--|--|
| Dose mg/kg<br>RMP<br>INH<br>PZA                          | 9.7 $\pm$ 2.2<br>9.7 $\pm$ 2.2<br>32.0 $\pm$ 8.9 |
| Duration of ATT (months)                                 | 0.8 $\pm$ 0.3                                    |
| Regimen (n)<br>Category I<br>Category II<br>Category III | 48<br>3<br>33                                    |
| Type of TB (n)<br>Pulmonary<br>Extrapulmonary<br>Both    | 19<br>63<br>2                                    |

# Comparison of PK between slow & rapid acetylators of INH



Values are Mean; Vertical bars denote SD

\* Denotes  $p < 0.05$  vs Slow acetylators

## PK of RMP, INH & PZA among different age groups

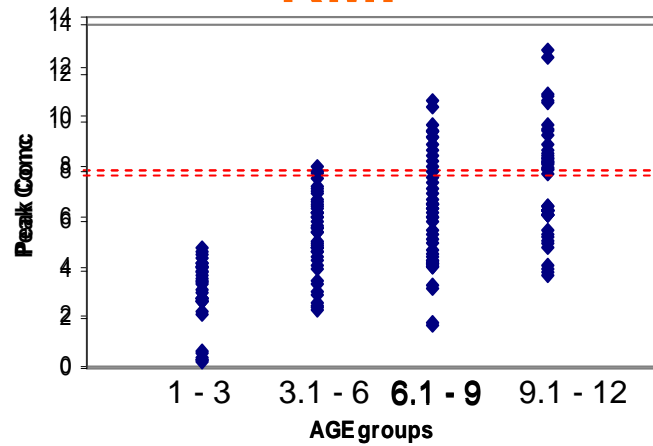
| Drugs      | PK Variables | Age Groups (years)   |                  |                   |                    |
|------------|--------------|----------------------|------------------|-------------------|--------------------|
|            |              | 1 – 3<br>n = 17      | 3.1 – 6<br>n =22 | 6.1 – 9<br>n = 22 | 9.1 – 12<br>n = 23 |
| <b>RMP</b> | Cmax         | <b>2.9 ± 1.4*</b>    | 5.4 ± 1.6        | 6.3 ± 2.2         | 5.8 ± 2.4          |
|            | AUC(0-8)     | <b>13.6 ± 6.9*</b>   | 25.5 ± 10.0      | 29.4 ± 11.3       | 28.1 ± 12.7        |
| <b>INH</b> | Cmax         | <b>3.3 ± 1.2*</b>    | 6.7 ± 3.4        | 6.4 ± 2.4         | 7.5 ± 2.3          |
|            | AUC(0-8)     | <b>14.0 ± 6.7*</b>   | 27.5 ± 14.8      | 22.8 ± 9.0        | 30.7 ± 11.4        |
| <b>PZA</b> | Cmax         | <b>28.4 ± 7.2*</b>   | 38.6 ± 14.8      | 42.1 ± 8.6        | 38.0 ± 10.3        |
|            | AUC(0-8)     | <b>156.6 ± 41.8*</b> | 219.2 ± 66.3     | 232.5 ± 48.8      | 220.3 ± 55.8       |

Cmax – Peak concentration; AUC – Exposure

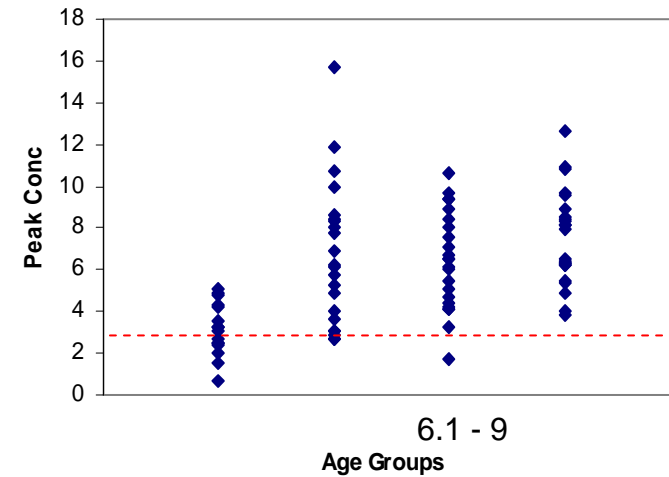
Values are Mean ± SD; \* denotes p < 0.05 vs. other age groups

# Peak concentration of drugs among different age groups

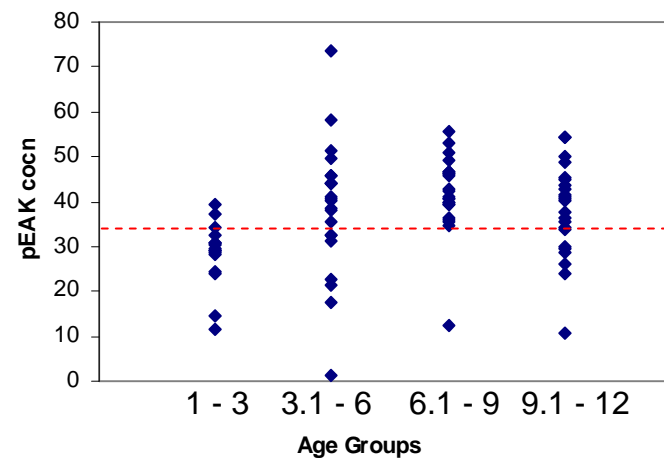
**RMP**



**INH**



**PZA**





# Sub-therapeutic peak levels by age

- ❖ **RMP (< 8.0 µg/ml)**
  - < 3 years: 17 / 17 (100%)
  - ≥ 3 years: 59 / 67 (88%)
- ❖ **INH (< 3.0 µg/ml)**
  - < 3 years: 7 / 17 (41%)
  - ≥ 3 years: 4 / 67 (6%)\*
- ❖ **PZA (< 35.0 µg/ml)**
  - < 3 years: 15 / 17 (88%)
  - ≥ 3 years: 17 / 67 (25%)\*

\* P < 0.001

## PK of RMP, INH & PZA among stunted & non-stunted children

| Drugs      | PK variables | Stunted<br>(n = 23) | Normal<br>(n = 61) |
|------------|--------------|---------------------|--------------------|
| <b>RMP</b> | Cmax         | 4.3 $\pm$ 1.8*      | 5.6 $\pm$ 2.4      |
|            | AUC(0-8)     | 20.4 $\pm$ 9.9*     | 26.6 $\pm$ 12.3    |
| <b>INH</b> | Cmax         | 5.3 $\pm$ 2.2       | 6.5 $\pm$ 3.0      |
|            | AUC(0-8)     | 21.1 $\pm$ 9.7      | 25.7 $\pm$ 13.1    |
| <b>PZA</b> | Cmax         | 33.2 $\pm$ 12.3*    | 38.9 $\pm$ 11.1    |
|            | AUC(0-8)     | 180.7 $\pm$ 66.2*   | 221.9 $\pm$ 63.5   |

Cmax – Peak concentration; AUC – Exposure

Values are Mean & SD; \* Denotes  $p < 0.05$  vs. normal children

## PK of RMP, INH & PZA among children with low weight for age (underweight) and normal weight for age

| Drugs      | PK variables | Under weight<br>(n=32) | Normal<br>(n=52) |
|------------|--------------|------------------------|------------------|
| <b>RMP</b> | Cmax         | 4.3 $\pm$ 2.0          | 5.8 $\pm$ 2.3    |
|            | AUC(0-8)     | 20.3 $\pm$ 10.5        | 27.7 $\pm$ 12.0  |
| <b>INH</b> | Cmax         | 5.5 $\pm$ 2.3          | 6.6 $\pm$ 3.1    |
|            | AUC(0-8)     | 21.8 $\pm$ 9.6         | 26.1 $\pm$ 13.7  |
| <b>PZA</b> | Cmax         | 34.0 $\pm$ 12.1*       | 39.4 $\pm$ 11.0  |
|            | AUC(0-8)     | 188.3 $\pm$ 68.3*      | 224.5 $\pm$ 62.1 |

Cmax – Peak concentration; AUC – Exposure

Values are Mean & SD; \* Denotes  $p < 0.05$  vs. normal children

## PK of RMP, INH & PZA among children with low weight for height (wasting) and normal weight for height

| Drugs      | PK Variables | Wasted<br>(n = 16) | Normal<br>(n = 51) |
|------------|--------------|--------------------|--------------------|
| <b>RMP</b> | Cmax         | 5.1 $\pm$ 2.0      | 5.3 $\pm$ 2.5      |
|            | AUC(0-8)     | 24.9 $\pm$ 11.1    | 24.3 $\pm$ 12.6    |
| <b>INH</b> | Cmax         | 6.6 $\pm$ 3.2      | 5.6 $\pm$ 2.8      |
|            | AUC(0-8)     | 25.3 $\pm$ 13.3    | 22.3 $\pm$ 11.9    |
| <b>PZA</b> | Cmax         | 40.0 $\pm$ 9.2     | 36.3 $\pm$ 12.3    |
|            | AUC(0-8)     | 222.4 $\pm$ 50.1   | 204.2 $\pm$ 51.5   |

Cmax – Peak concentration; AUC – Exposure  
Values are Mean & SD;

# Correlation

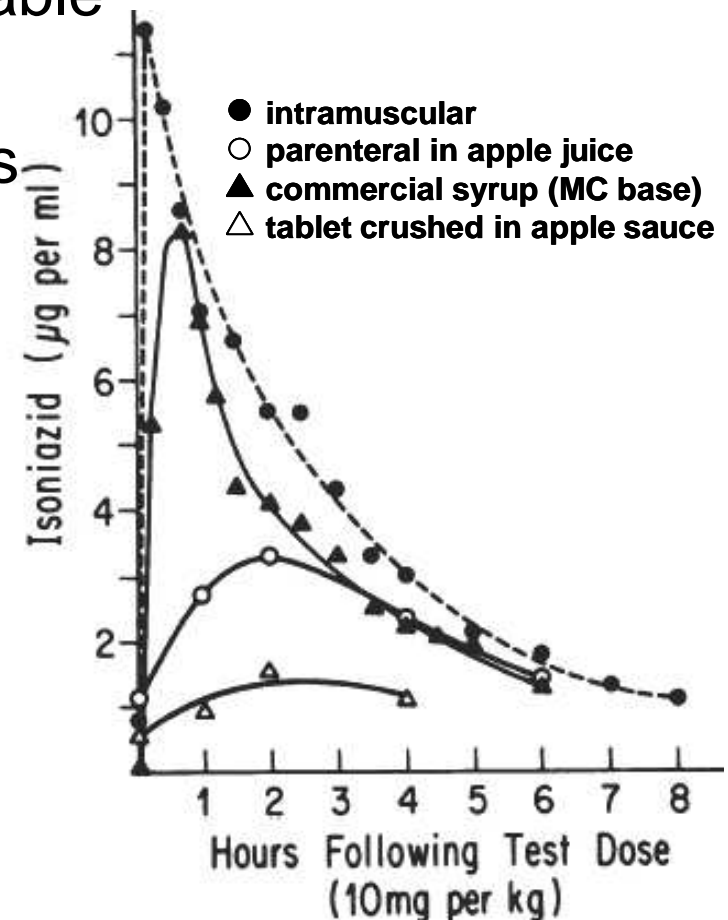
- ❖ Significant correlation between
  - C<sub>max</sub> & AUC of RMP, INH & PZA
  - mg/kg dose with C<sub>max</sub> & AUC of RMP & PZA
- ❖ No correlation between blood D-xylose & drug levels

# TB treatment outcome

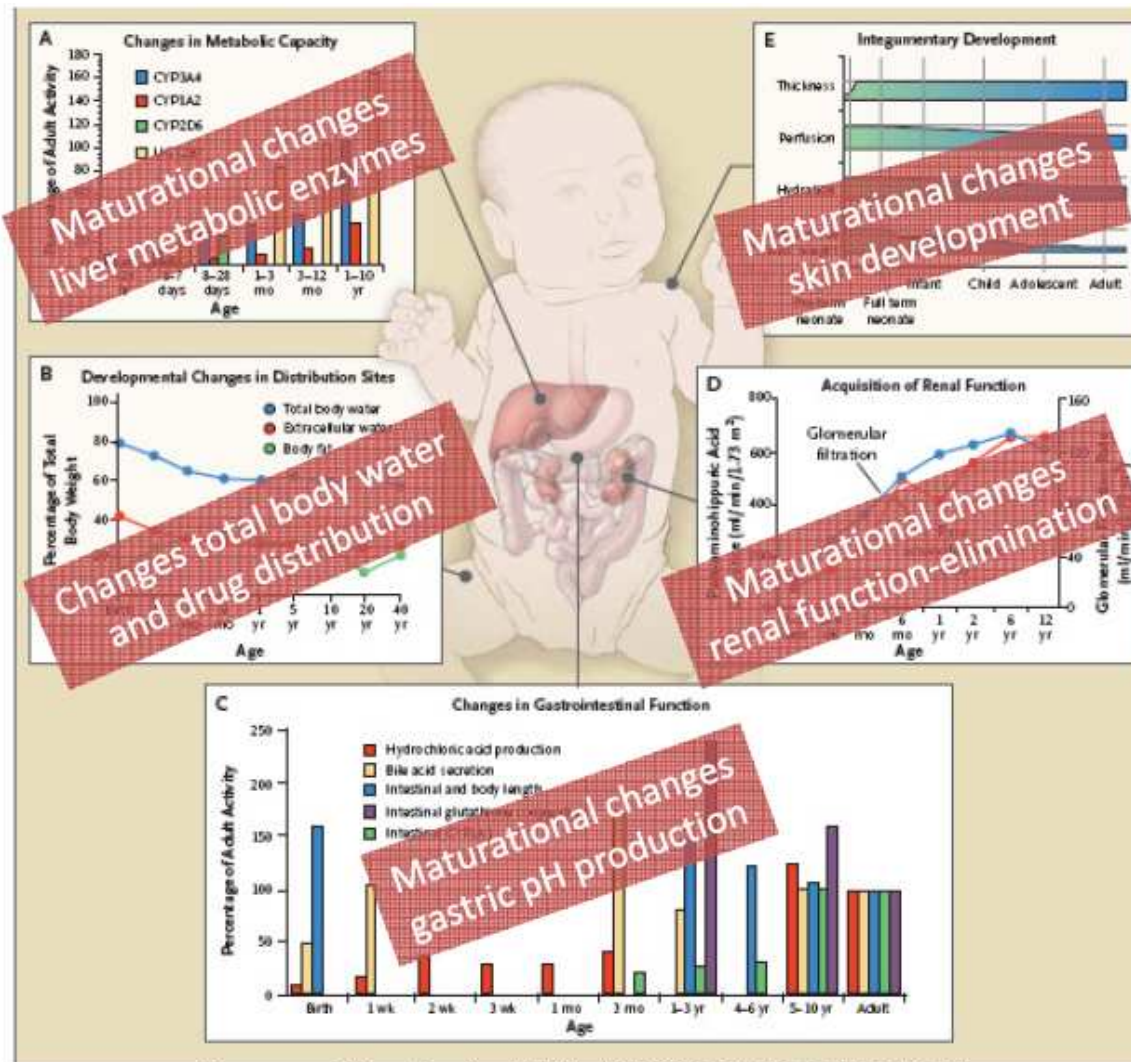
- TB treatment outcome known in 64 patients
  - Favourable outcome: 57 (89%)
- Multiple Logistic Regression
  - Age independently correlated with peak and exposure of RMP, INH and PZA
  - No significant influence of age, Cmax, HAZ, WAZ on TB treatment outcome

# Factors Contributing to Sub-therapeutic Drug Concentrations

- poor adherence
- inadequate regimen/dose
- drug unavailable/sporadically available
- substandard/counterfeit generics
- drug-drug/drug-disease interactions
- genetics
- diet/nutritional status
- age
- extemporaneous compounding



# Why is Pediatric Drug Dosing So Difficult? Multiple Age-Related Physiologic Developmental Changes Influence Drug Disposition



- Age-related changes in drug metabolism and disposition mean that we cannot just extrapolate pediatric dosing from adults dosing modified by body weight.



Proposed Dosing Schedule for a New Pediatric FCD for  
Tuberculosis: Rif-80mg; INH-70mg; PZA - 200 mg and  
ETH - 110 mg

| Body Weight (kg) | Number of Tablets per Day (single bolus) |
|------------------|--|
| 5 to 7           | 1  |
| 8 to 14          | 2  |
| 15 to 20         | 3  |
| 21 to 25         | 4  |
| 26 to 30         | 5  |

*from Prof. B. Fourie, 2010*

## Proposed dosing strategy for a single FDC

| Product |           | INH      | Rifampin | Pyrazinamide |
|---------|-----------|----------|----------|--------------|
|         |           | 150 mg   | 200 mg   | 400 mg       |
| Weight  | Dose      |          |          |              |
| 5 kg    | ½ pill    | 15 mg/kg | 20 mg/kg | 40 mg/kg     |
| 6 kg    | ½ pill    | 12.5     | 16.7     | 33.3         |
| 7 kg    | ½ pill    | 10.7     | 14.3     | 28.5         |
| 8 kg    | ½ pill    | 9.4      | 12.5     | 25           |
| 9 kg    | ½ pill    | 8.8      | 11.1     | 22           |
| 8 kg    | 1 pill    | 18.7     | 25       | 50           |
| 9 kg    | 1 pill    | 16.7     | 22.2     | 44           |
| 10 kg   | 1 pill    | 15       | 20       | 40           |
| 11 kg   | 1 pill    | 13.5     | 18       | 36.4         |
| 12 kg   | 1 pill    | 12.5     | 16.6     | 33.3         |
| 13 kg   | 1 pill    | 11.5     | 15.4     | 30.1         |
| 14 kg   | 1 pill    | 10.7     | 14.3     | 28.6         |
| 15 kg   | 1 pill    | 10       | 13.3     | 26.6         |
| 16 kg   | 1 ½ pills | 14.1     | 18.8     | 37.5         |
| 17 kg   | 1 ½ pills | 13.2     | 17.6     | 35.3         |
| 18 kg   | 1 ½ pills | 12.6     | 16.6     | 33.3         |
| 19 kg   | 1 ½ pills | 11.8     | 15.8     | 31.6         |
| 20 kg   | 1 ½ pills | 11.2     | 15       | 30           |
| 21 kg   | 1 ½ pills | 10.7     | 14.3     | 28.5         |
| 21 kg   | 2 pills   | 14.8     | 19       | 38           |
| 22 kg   | 2 pills   | 13.6     | 18.2     | 36.4         |
| 23 kg   | 2 pills   | 13       | 17.4     | 34.8         |
| 24 kg   | 2 pills   | 12.5     | 16.6     | 33.3         |
| 25 kg   | 2 pills   | 12       | 16       | 32           |
| 26 kg   | 2 pills   | 11.5     | 15.4     | 30.1         |
| 27 kg   | 2 pills   | 11.1     | 14.8     | 29.6         |
| 28 kg   | 2 pills   | 10.7     | 14.3     | 28.5         |
| 29 kg   | 2 pills   | 10.4     | 13.8     | 27.5         |
| 30 kg   | 2 pills   | 10       | 13.3     | 26.6         |

# Formulations needed for developing countries.....

- Affordable, commercially viable
- Stable
- Accurately divisible
  - One dose form for all is ideal
- Transportable and low bulk/weight
- Minimal administration frequency
- Minimum, non-toxic excipients
- Convenient, easy, reliable administration
  - Palatable
  - Minimal manipulation
- Confirmatory studies
  - Relative bioavailability
  - Additional PK data
  - Exposure – response data



## When to suspect drug resistant TB in a child? Need a programmatic definition

- The child is in contact with a known case of drug resistant TB
- The child's adult contact has been on chronic irregular treatment and continues to be sputum positive
- The adult contact died after taking irregular treatment; or
- The child shows initial improvement to ATT and then deteriorates (clinically and radiologically)

# Management of MDR –TB in children

- **A child contact of an adult DR-TB source case should receive treatment according to the adult's DST result if no *M. tuberculosis* isolate is obtained from the child.**
- At least three or preferably four or more drugs to which the child's or adult source case's isolate is susceptible or naïve should be administered
- Growth and development need to be monitored and drug dosages should be adjusted for weight gain
- The patient/parent/care giver should receive counselling about adverse effects, treatment duration and importance of adherence to treatment at every visit.
- Early primary (hilar adenopathy or contained primary pulmonary [Ghon] focus) MDR-TB in children could probably be treated for 12–15 months only.
- Microbiological monitoring in children is important, but follow-up cultures are often difficult to obtain and are more often negative. Clinical and chest radiographic monitoring during follow-up is helpful.

Chang CY et al. INT J TUBERC LUNG DIS 2010; 14(6):672–682

Schaaf et al. S Afr Med J 2007; 97: 995–997., Arch Dis Child 2003; 88: 1106–1111.

## Pediatric Dosing of second-line antituberculosis drugs

| <b>DRUG</b>           | <b>DAILY DOSE<br/>(mg/kg)</b> | <b>FREQUENCY</b>      | <b>MAXIMUM<br/>DAILY DOSE</b> |
|-----------------------|-------------------------------|-----------------------|-------------------------------|
| Streptomycin          | 20-40                         | Once daily            | 1 g                           |
| Kanamycin             | 15-30                         | Once daily            | 1 g                           |
| Amikacin              | 15-22.5                       | Once daily            | 1 g                           |
| Capreomycin           | 15-30                         | Once daily            | 1 g                           |
| Ofloxacin             | 15-20                         | Twice daily           | 800 mg                        |
| Levofloxacin          | 7.5-10                        | Once daily            | 750 mg                        |
| Moxifloxacin          | 7.5-10                        | Once daily            | 400 mg                        |
| Ethionamide           | 15-20                         | Twice daily           | 1 g                           |
| Protonamide           | 15-20                         | Twice daily           | 1 g                           |
| Cycloserine           | 10-20                         | Once or Twice daily   | 1 g                           |
| p-aminosalicylic acid | 150                           | Twice or thrice daily | 12 g                          |

(WHO/HTM/TB/2008.402)

# MDRTB Diagnostic delay, Rx outcome

- 39 children, South Africa, median age 4.5 years at first TB diagnosis and 6.2 years on MDR culture confirmation
- Delay in starting appropriate MDR treatment after TB diagnosis was a median of 2 days if MDR TB source cases were taken into account, but 246 days if DST of the source case was not considered.
- Correlation between the drug susceptibility results of the child's and adult source case's isolates was 68%.
- Obtaining a detailed contact history is essential as a delay in starting appropriate MDR antituberculosis treatment has potentially serious consequences

*Schaaf et al . Arch Dis Child 2003;88:1106-1111*

# Outcome of Community-Based MDRTB Treatment for Children in Peru

- Children with suspected or proved MDRTB 38 treated with supervised, individualized regimens
- 18-24 months treatment with  $\geq 5$  drugs
- 45% had malnutrition/anemia
- 45% required initial hospitalization
- Adverse events for 42%, none required termination of drugs
- Cure rate 95%

**Second-line TB treatment is well tolerated by children**

Drobac PC et al. Pediatrics 2006; 116:2022-28



# **Lala Ram Sarup Hospital, New Delhi**

## **Experience (January 2000 – December 2004)**

- **Total – 36**
- **Sex ratio – M : F = 8 : 28**
- **Average Age – 12.7 yrs.**
- **Mean S/m duration – 18.6 months**
- **Mean duration of prior ATT – 13.2 months**
- **$1^0 : 2^0 = 2 : 34$** 
  - **All  $2^0$  pt. had taken 1<sup>st</sup> line drug and 3 had taken 2<sup>nd</sup> line**

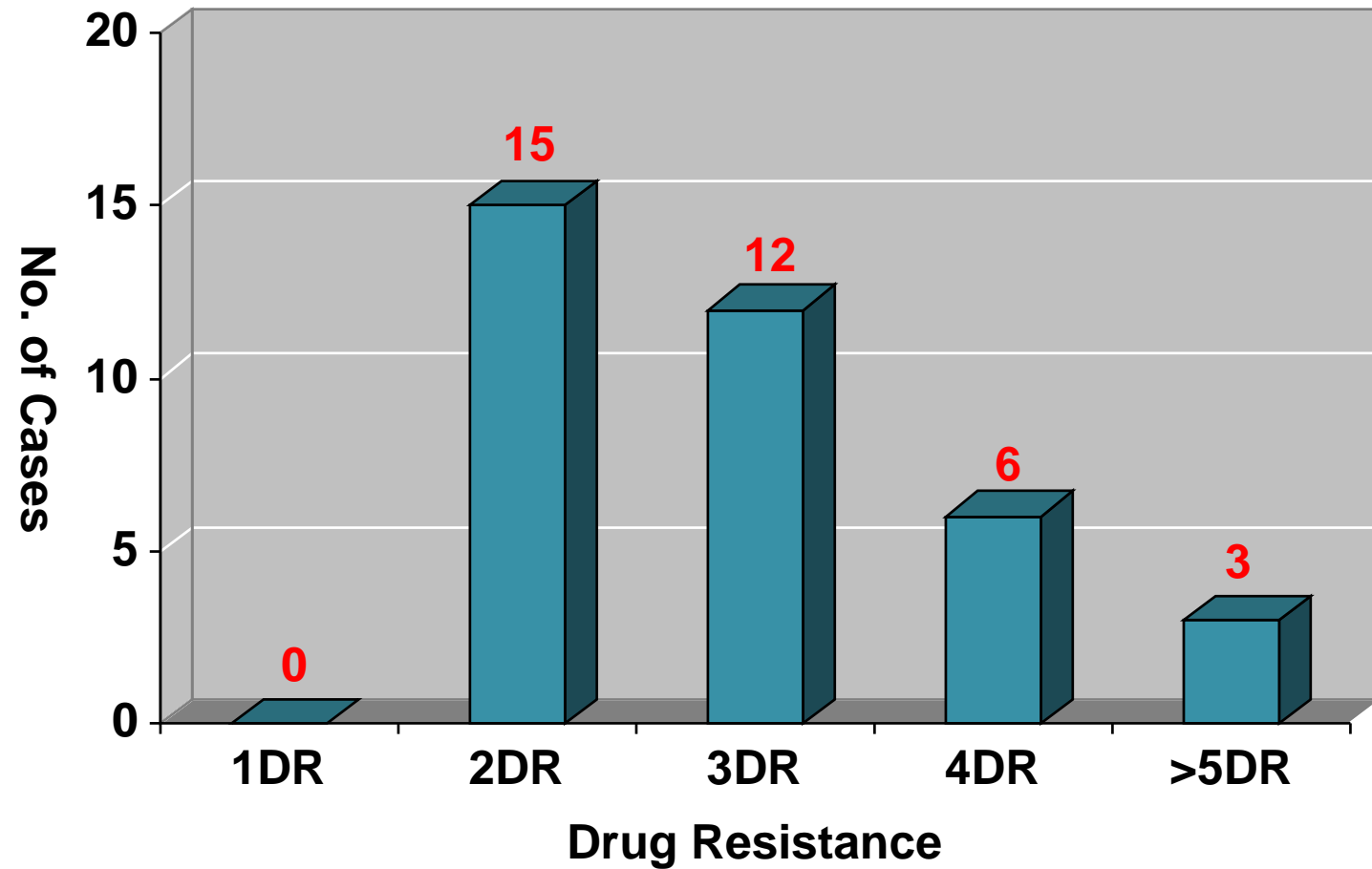
**Sharma S. (Unpublished data)**  
**Sharma S. Infection in Children 2003**

# DST Results (36/36)

| 2DR   |       | 3DR    |       | 4DR   |       | >5DR   |       |
|-------|-------|--------|-------|-------|-------|--------|-------|
| Drugs | Cases | Drugs  | Cases | Drugs | Cases | Drugs  | Cases |
| RH    | 12    | SRH    | 7     | RHZE  | 2     | SRHZE  | 2     |
| SR    | 1     | RHZ    | 2     | SRHE  | 4     | Others | 1     |
| HE    | 1     | SRThia | 1     |       |       |        |       |
| SH    | 1     | RHThia | 2     |       |       |        |       |
| Total | 15    |        | 12    |       | 6     |        | 3     |

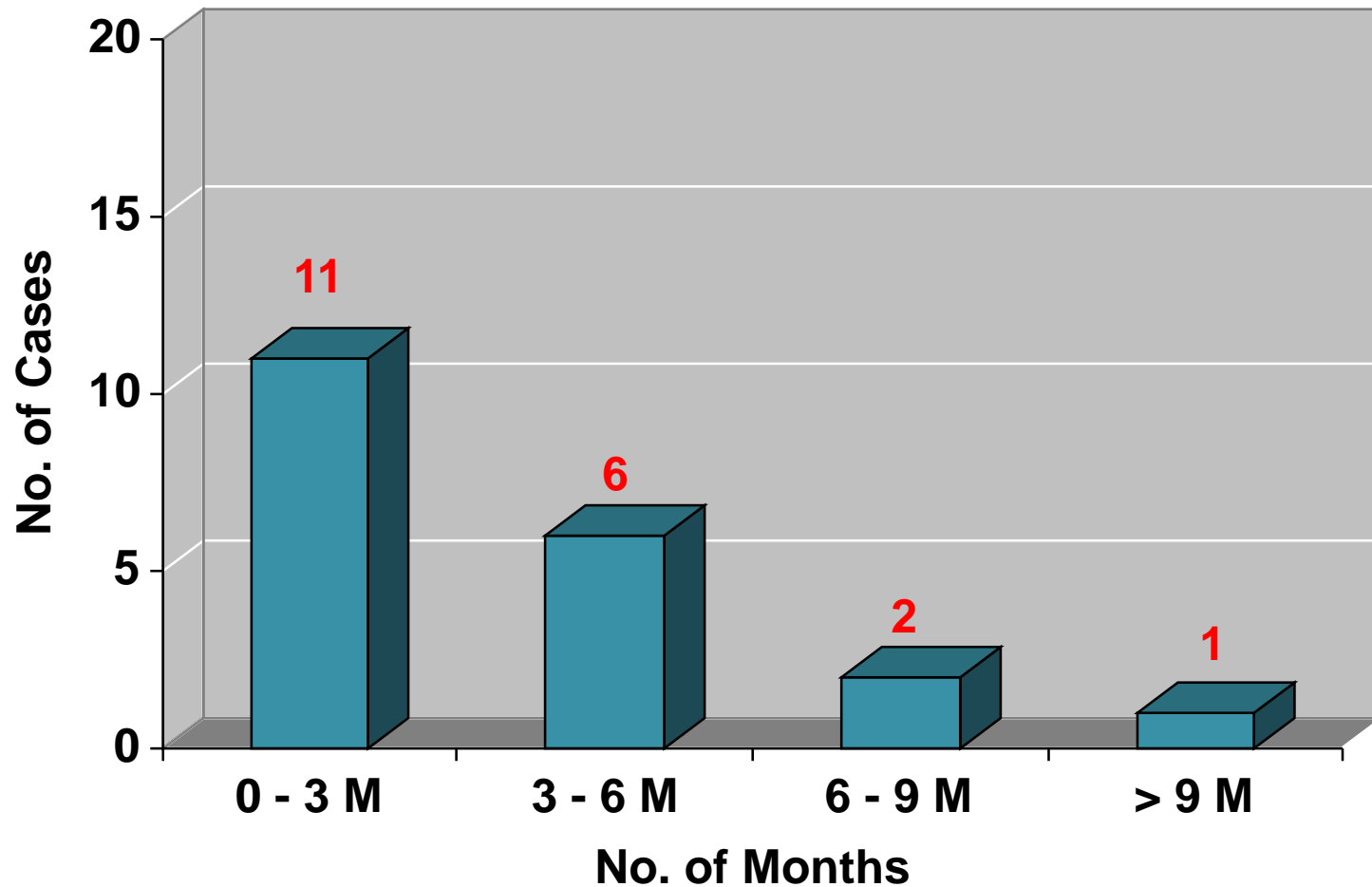
Sharma S. Infection in Children 2003  
Sharma S. (Unpublished data)

# DST Results



Sharma S. Infection in Children 2003  
Sharma S. (Unpublished data)

# Sputum conversion (20/36)

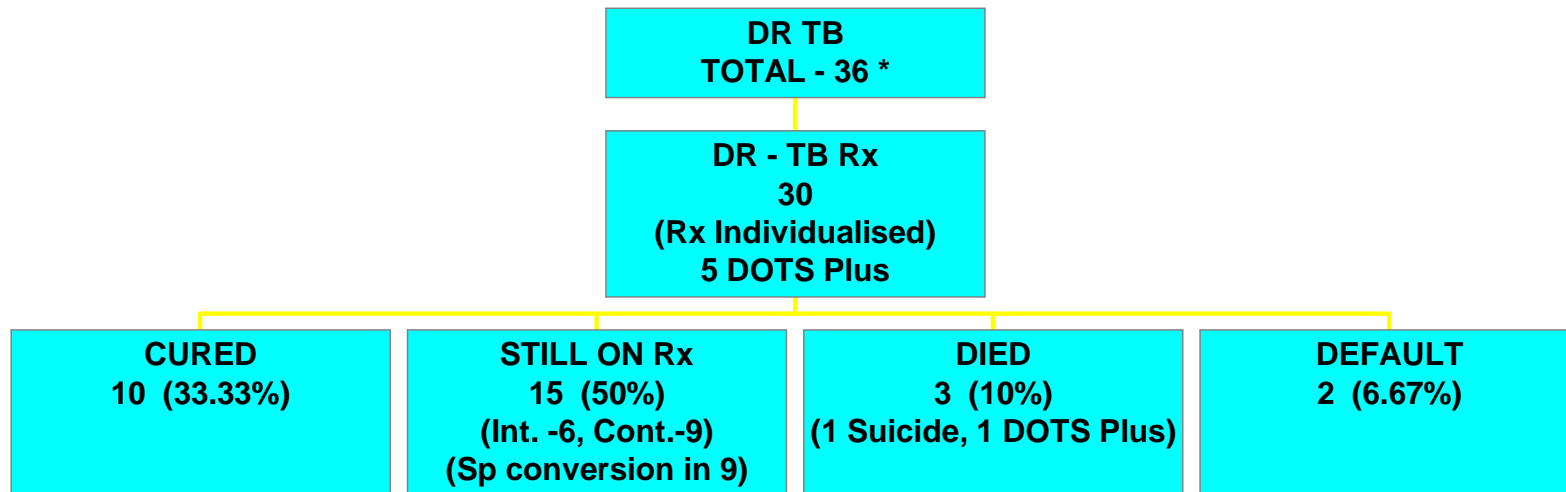


Sharma S. Infection in Children 2003  
Sharma S. (Unpublished data)

# **LRS Experience**

- **Minor deviation in Regimen**
  - **R Sensitive – 1 case**
  - **O Resistance – 1 case → E**
- **Major Deviation in Regimen**
  - **> 5 DR - 3**
  - **Drug complication –3**
    - **Suicide – 1**
    - **Ac. Psychosis – 1**
    - **Hypothyroidism – 1**
- **Overall tolerance good**

# LRS Experience

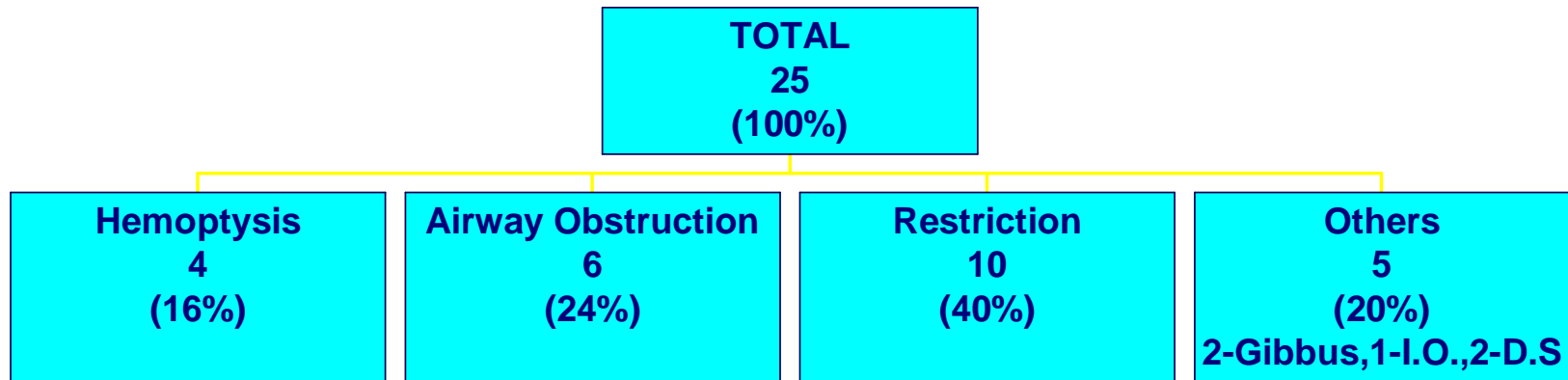


- \* PT - 31, EPT - 5
- \* 3 Died before Rx could be initiated.
- \* 3 Rx could not be initiated.
- \* Overall Drug Tolerance good.
- (January 2000 - December 2004)

Sharma S. Infection in Children 2003  
Sharma S. (Unpublished data)

# LRS Experience

## MORBIDITY



(January 2000 - December 2004)

Sharma S. Infection in Children 2003  
Sharma S. (Unpublished data)

# Management of pediatric MDR and LTBI

- Retrospective study of children <15 years of age treated for MDR-TB or MDR-latent TB infection (LTBI) from 1995 to 2003 in New York
- Twenty subjects with MDR-TB (mean age 2.7 years) and 51 with MDR-LTBI (mean age 9.8 years)
- The most commonly used second-line TB drugs were cycloserine, quinolone agents, and ethionamide, which were used in 70%, 69%, and 54% of subjects, respectively.
- Sixteen (80%) of 20 MDR-TB and 38 (75%) of 51 MDR-LTBI cases completed treatment.
- A greater proportion of subjects receiving care at a Dept. of Health (DOH) clinic completed treatment for LTBI (36/41, 88%), when compared with subjects treated at non-DOH sites [(2/9, 22%)  $P < 0.001$ ].
- Review of the TB registry indicated that no subjects had recurrent disease or progression of LTBI to active disease during the study period and for 2 years thereafter.
- **CONCLUSIONS:** Children with MDR-TB and LTBI were best cared for in public health settings. A multicenter registry for pediatric MDR-TB and MDR-LTBI would be desirable to obtain accurate rates of toxicity and cure.  
Feja K et al. Pediatr Infect Dis J. 2008;27(10):907-12.



# Prevention of TB in Children

- Intensive case finding
- Isoniazid preventive therapy
- Infection control
- Integration

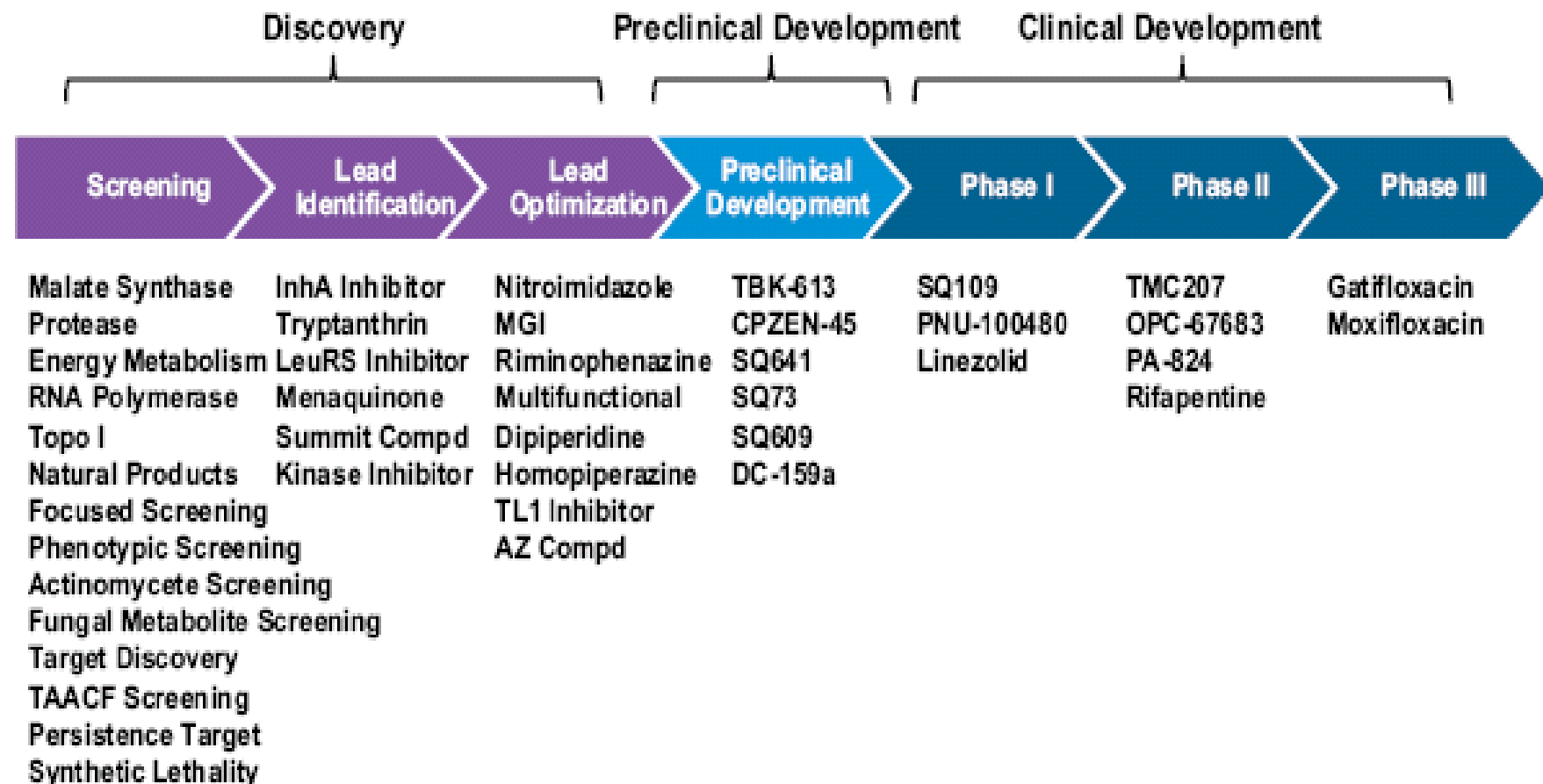
# New drugs in clinical development

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

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

IOM/INSA/ICMR Forum on Drug Resistant  
TB, New Delhi, 18-19 April 2011

# Portfolio of new TB drugs in development: children need to be included in clinical trials



# Involvement of Children in TB Drug Development

Burman WJ et al Plos Med 2008

| Barrier   | Ways to Overcome   |
|---|--|
| Difficulty in diagnosis                                 | Use validated case definitions for TB  |
| Lack of PK data   | Methods using low volume ?LCMS   |
| Complacency about efficacy of treatment in drug susc TB | PK and tolerability of new drugs in children when efficacy in adults under trial |
| Trial design issues                                     | Collaboration with pediatric trialists   |
| Concern about Regulatory issues                         | Incentives by funding and regulatory authorities                                 |
| Concern about SE  | Appropriate monitoring   |
| Funding concerns  | Advocacy to ↑ funding for TB research  |

# 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 2 <sup>nd</sup> 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 |

# Pediatric TB Drug Research Needs

- Multiple factors including age, nutritional status, HIV coinfection, and genetics (rapid vs slow acetylators) impact drug exposure for 1st line TB drugs in children.
- Other factors may be important – exploration of pharmacogenetic factors that influence PK need further study in children, along with gene expression variations with maturation.
- Understanding of relation between PK parameters established in adults and treatment outcomes for TB in children is incomplete.
- Need more data relation of drug levels and TB treatment outcome, and impact of sub-therapeutic drug levels on treatment failure and emergence drug-resistant TB strains.

# Pediatric TB Drug Research Needs

- Infant dosing information
- PK data on 2nd line drugs in children.
- PK studies in HIV+ children.
- TB-HIV drug-drug interactions in HIV+ children and effect on outcomes (TB and HIV).
- Effect of malnutrition on TB drug metabolism
- randomized trial of different lengths of treatment of tuberculous meningitis
- optimal preventive chemotherapy in children in contact with a confirmed source case of multidrug-resistant tuberculosis.

# **The Sentinel Project on Pediatric Drug-Resistant TB**

**Harvard Medical School and the National  
Institute for Research in Tuberculosis  
(formerly TRC) in Chennai, India**

- invite you to join a global research and learning network**
- that aims to develop and disseminate strategies to prevent child deaths from drug-resistant TB**



# **The Sentinel Project: Goals**

- 1. Connect us as a virtual community**
- 2. Share experiences, concerns**
- 3. Identify areas of mutual interest**
- 4. Collaborate on priority projects**
- 5. \*\* Focus attention on preventable deaths \*\***

# **The Sentinel Project: Year 1 priority activities**

- **To be defined (and effected) by network participants**
- **$\geq 6$  network calls by April 1, 2012**
- **Online virtual community**
- **Assess results by October 1, 2012**

# Expressed interest

- Global Health Committee
- Indus Hospital
- National Child Health Institute of Peru
- Desmond Tutu TB Centre of Stellenbosch Univ.
- Children's TB Clinic of Baylor College of Medicine
- TBRU at Case Western Reserve Univ.
- Treatment Action Group
- Médecins Sans Frontières
- Partners In Health

**You are all cordially invited to join...**

**Let us work together toward  
zero child deaths from DR TB**

**To join this network:**

**<http://ghsm.hms.harvard.edu/sentinel/>**

**Or via email:**

**[sentinel\\_project@hms.harvard.edu](mailto:sentinel_project@hms.harvard.edu)**

WE ASPIRE TO A WORLD WITH  
**ZERO TB DEATHS**