# Childhood TB subgroup Summary of activities 2011-2012

Steve Graham

On behalf of Childhood TB Subgroup



# International Childhood Tuberculosis Meeting 2011

## Stockholm, 17-18 March 2011

Stop TB Partnership

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# CALL TO ACTION for CHILDHOOD TB

Read the Call in French, Read the Call in Russian

Sign the Call to Action

We, participants gathered at the 'International Childhood Tuberculosis Meeting' held March 17-18, 2011 in Stockholm, Sweden recognize that:

Signed by more than 1000 individuals/organisations

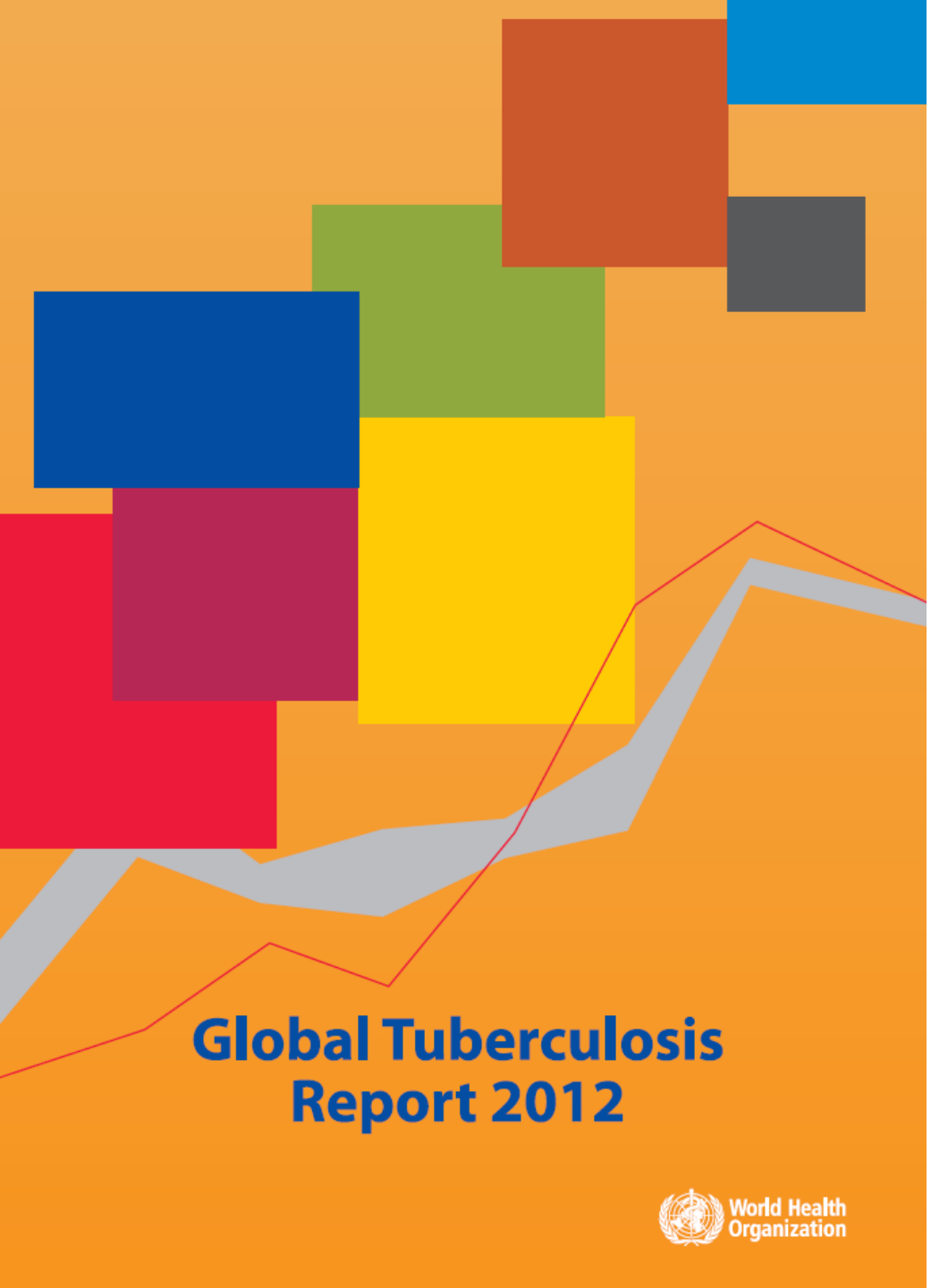
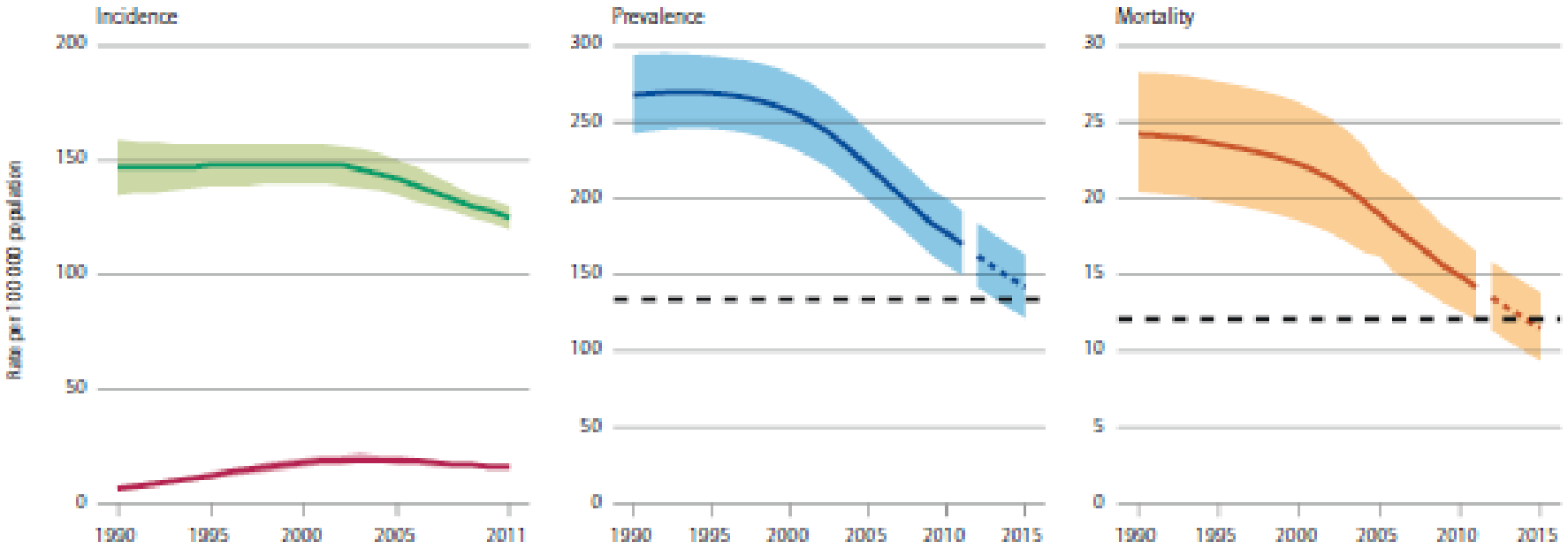

Global Tuberculosis
Report 2012
World Health
Organization

FIGURE 2.3 **Global trends in estimated rates of TB incidence, prevalence and mortality.** Left: Global trends in estimated incidence rate including HIV-positive TB (green) and estimated incidence rate of HIV-positive TB (red). Centre and right: Trends in estimated TB prevalence and mortality rates 1990–2011 and forecast TB prevalence and mortality rates 2012–2015. The horizontal dashed lines represent the Stop TB Partnership targets of a 50% reduction in prevalence and mortality rates by 2015 compared with 1990. Shaded areas represent uncertainty bands. Mortality excludes TB deaths among HIV-positive people.




# Global Tuberculosis Report 2012

World Health Organization

BOX 2.2

## The burden of TB disease among children

For many years, the prevention, diagnosis and treatment of TB among children have been relatively neglected. Greatest attention has been given to the detection and treatment of infectious cases, most of which occur in adults. The Stop TB Strategy launched by WHO in 2006 includes case-finding in high-risk or vulnerable groups such as children and prevention of TB in children who live in the same household as newly detected TB cases. To help to address the burden of TB in children (defined as those aged <15 years) and monitor progress, robust data on childhood TB are necessary. This is the first WHO report on global TB care and control to include estimates of the burden of TB disease among children, with best estimates of 490 000 cases and 64 000 deaths per year.[1] The reasons why it remains difficult to estimate the burden of TB disease in children, the methods used to produce this first set of estimates and the next steps needed to improve them are discussed below.

### Challenges in assessing the number of TB cases and deaths among children

There is no easy-to-use and accurate diagnostic test for TB in children. Most children have paucibacillary TB that is harder to diagnose with sputum smear microscopy and culture. Many children, especially younger children, are also not able to expectorate sputum. Diagnosis is usually made using a combination of clinical (as opposed to laboratory) criteria and a non-specific test for tuberculous infection, but there is no universally applied diagnostic algorithm. The definitive diagnosis of extrapulmonary TB requires specialized

similar results). WHO does not request age-disaggregated data for relapse cases or those reported as of unknown treatment history; the number of children in these categories was assumed to be zero.

To estimate TB incidence among children, it was assumed that the ratio of notified to incident cases at the global level in 2011 (best estimate 66%, range 64%–69%) was the same for adults and children. On this basis, TB incidence among children was estimated at 490 000 (range, 470 000–510 000) in 2011, equivalent to about 6% of the total number of 8.7 million incident cases.

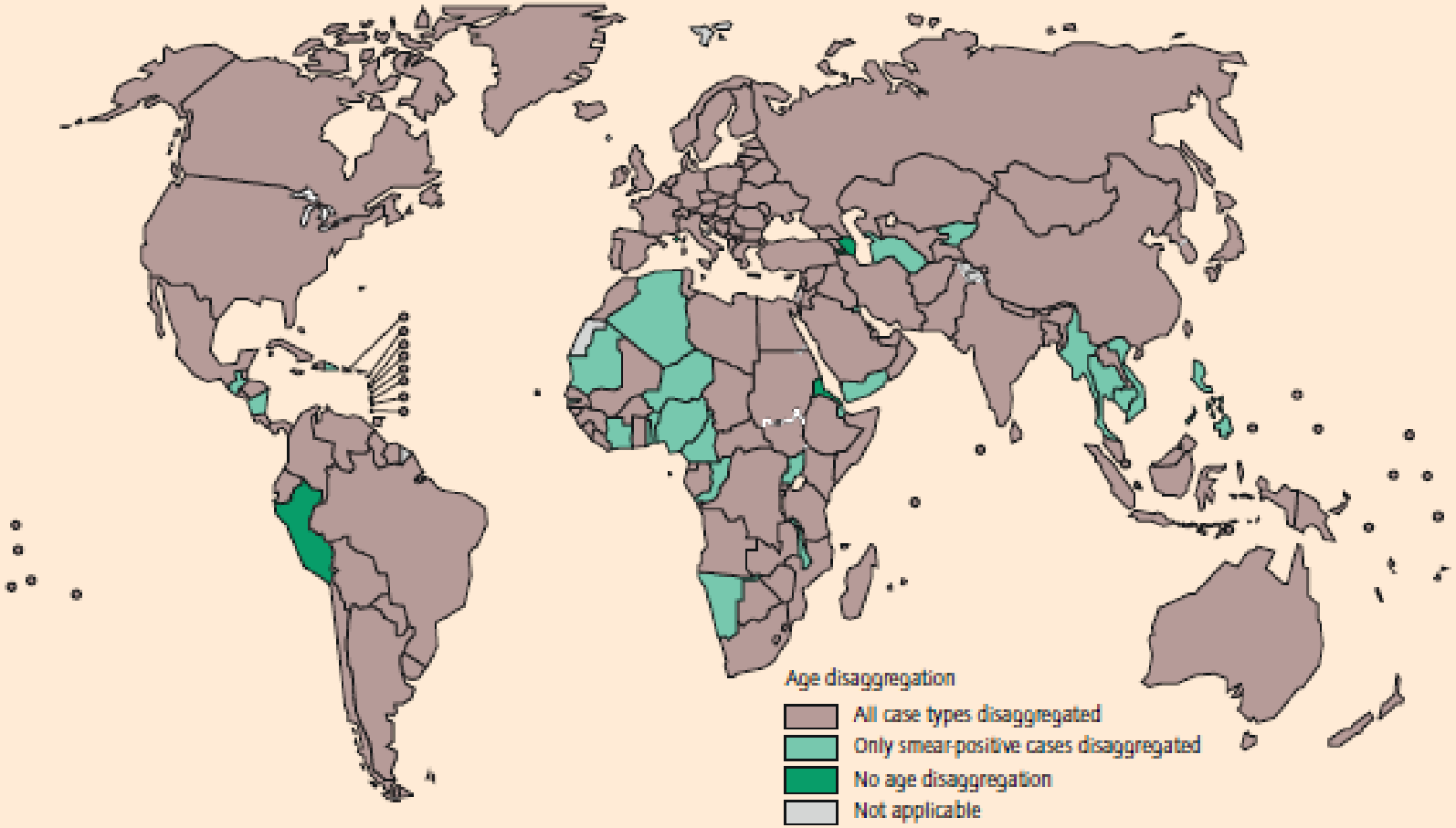
Limitations of the methods used include:

- The assumption that the ratio of notified to incident cases is the same for adults and children, in the absence of any data on levels of under-reporting of diagnosed cases for children and adults separately;
- The assumption that reported cases were true cases of TB. Misdiagnosis is possible, especially given the difficulties of diagnosing TB in children; and
- The proportion of cases among children may be different in countries for which age-disaggregated data are not available.

### Estimates of TB mortality in children in 2011 – methods and results

Mortality data disaggregated by age from VR systems that have been reported to WHO were analysed. TB death rates per 100 000

FIGURE B2.2.1
**Reporting of notification data disaggregated by age, 2011**




# Global Tuberculosis Report 2012

World Health Organization

# Revised TB recording and reporting forms and registers – *version 2006*

Tuberculosis Programme

Form 6

## Quarterly Report on TB Case Registration in Basic Management Unit

Name of BMU: _____ Facility: _____

Name of TB Coordinator: _____ Signature: _____

**Patients registered during**[1]

_____ **quarter of year** _____

Date of completion of this form: _____

**Block 1: All TB cases registered** [2]

| Pulmonary sputum smear microscopy positive | | | | New pulmonary sputum smear microscopy negative | | | Pulmonary sputum smear microscopy not done / not available | | | New extrapulmonary | | | Other previously treated [3] | TOTAL All cases |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| New cases | Previously treated: Relapses | Previously treated: After failure | Previously treated: After default | 0-4 yrs | 5-14 yrs | ≥ 15 yrs | 0-4 yrs | 5-14 yrs | ≥ 15 yrs | 0-4 yrs | 5-14 yrs | ≥ 15 yrs | | |
| | | | | | | | | | | | | | | |

**Block 2. New pulmonary sputum smear microscopy positive cases – Age group**

| Sex | 0-4 | 5-14 | 15–24 | 25–34 | 35–44 | 45–54 | 55–64 | ≥ 65 | Total |
|---|---|---|---|---|---|---|---|---|---|
| M | | | | | | | | | |
| F | | | | | | | | | |

**Block 3: Laboratory activity - sputum smear microscopy** [4]

| No. of TB suspects examined for diagnosis by sputum smear microscopy | No. of TB suspects with positive sputum smear microscopy result |
|---|---|
| | |

**Block 4: TB/HIV activities** [2]

| | No. patients tested for HIV before or during TB treatment [5] | No. patients HIV positive [5] |
|---|---|---|
| New sputum smear microscopy positive TB | | |
| All TB cases | | |

1 Registration period is based on date of registration of cases in the *TB Register*, following the start of treatment. Q1: 1 January–31 March; Q2:1 April–30 June; Q3: 1 July–30 September; Q4:1 October–31 December.

2 Transferred in' and chronic cases are excluded. In areas routinely using culture, a separate form for unit using culture should be used.

3 Other previously treated cases include pulmonary cases with unknown history of previous treatment, previously treated sputum smear microscopy negative pulmonary cases and previously treated extrapulmonary cases. 'Transferred in' and chronic cases are excluded.

4 Data collected from the TB *Laboratory Register* based on "Date specimen received" in the laboratory during the quarter, without including patients with examination because of follow-up.

5 Documented evidence of HIV tests (and results) performed in any recognized facility before TB diagnosis or during TB treatment (till end of the quarter) should be reported here.



World Health Organization

WHO/HTM/TB/2006.373

WHO/HTM/TB/2006.37
WHO/FCH/CAH/2006.1

# Revised TB recording and reporting forms and registers – *version 2006*

WHO/HTM/TB/2006.365
WHO/FCH/CAH/2006.3

## Ethambutol efficacy and toxicity:

**literature review and recommendations for daily and intermittent dosage in children**

## Guidance for national tuberculosis programmes on the management of tuberculosis in children

WHO/HTM/TB/2007.381
WHO/FCH/CAH/07.02

## A research agenda for childhood tuberculosis

**Improving the management of childhood tuberculosis within national tuberculosis programmes:**

**research priorities based on a literature review**

## RAPID ADVICE

**Treatment of tuberculosis in children**

**Guidance for national tuberculosis and HIV programmes on the management of tuberculosis in HIV-infected children: Recommendations for a public health approach**

World Health Organization

International Union Against Tuberculosis and Lung Disease
*Health solutions for the poor*

World Health Organization

World Health Organization

# Childhood TB and control programmes

- Public health approach: Proper identification and treatment of infectious cases will prevent childhood TB

- Child TB historically afforded a low priority by NTPs:
  - Diagnostic difficulties
  - Usually not infectious
  - Limited resources
  - Lack of recording and reporting


But

- this disregards the impact of TB on childhood morbidity and mortality
- child TB reflects recent TB control

# Putting child TB on the global public health agenda

Child TB subgroup of WHO Stop TB Partnership formed
2003

WHO Stop TB strategy aims to increase case-finding:
2006

Children recognised as a vulnerable group in need of increased case-finding
2009

Opportunities to improve child TB activities
post-2015 strategy

# Putting child TB on the global public health agenda

Child TB subgroup of WHO Stop TB Partnership formed 2003

WHO Stop TB strategy aims to increase case-finding: 2006

Children recognised as a vulnerable group in need of increased case-finding: 2009

Opportunities to improve child TB activities provided by the post-2015 strategy

## …and taking the opportunities provided by challenges in TB control

| | |
|---|---|
| TB/HIV | New diagnostics |
| | Three I's |
| MDR TB | Culture facilities and Xpert |

# The fourth “I” – Integration Maternal/infant TB/HIV

TB in pregnancy or post-partum is common especially in HIV-infected women

Associated with maternal mortality

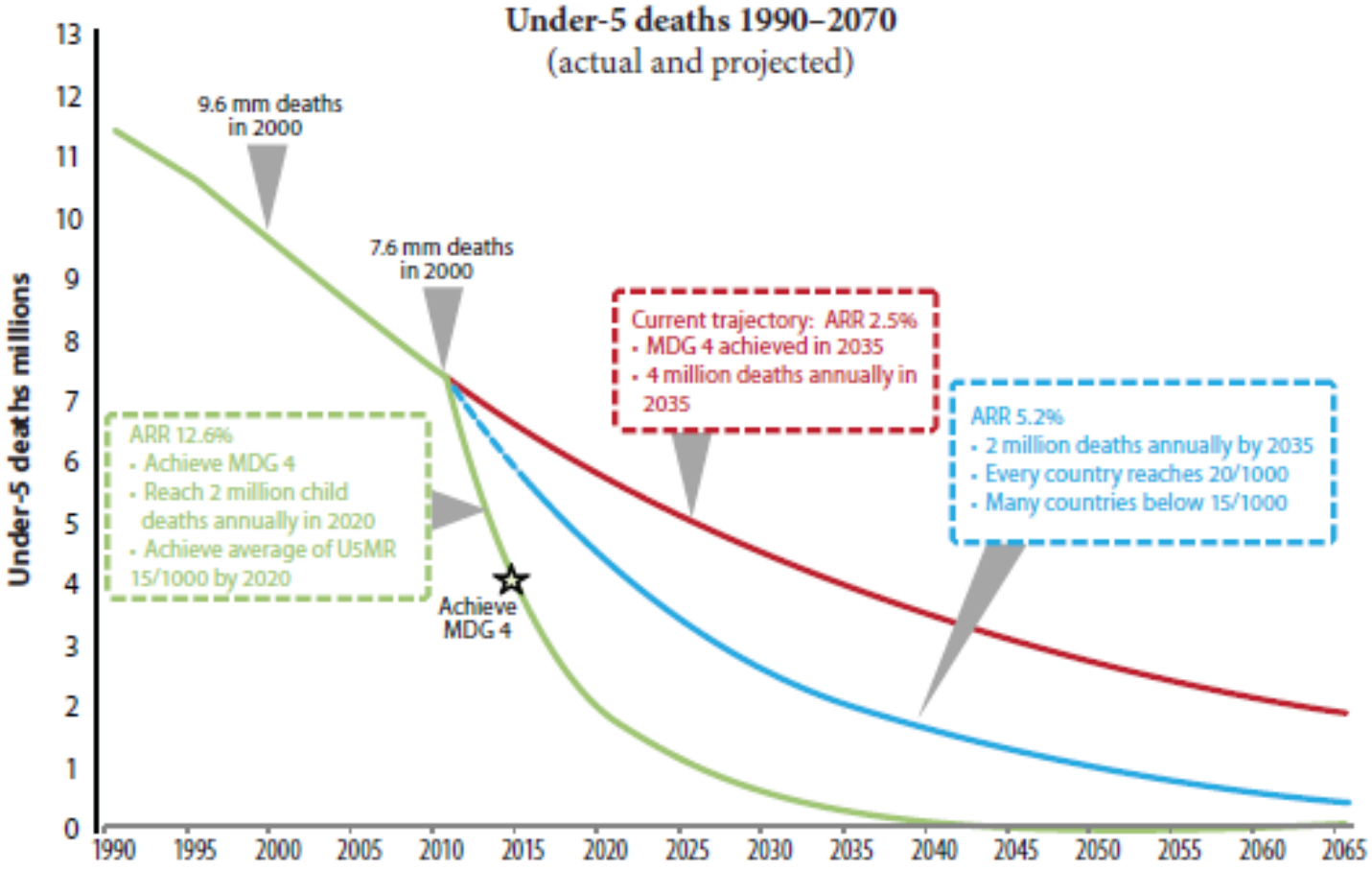
Associated with LBW and poorer infant outcomes

Associated with risk of TB and of HIV transmission

COMMITTING TO CHILD SURVIVAL
A PROMISE RENEWED

# Committing to Child Survival: A Promise Renewed

**Figure 2. Accelerating the progress on child survival – what can the world achieve if countries increase their annual rate of reduction?**




Source: UNICEF State of the World's Children 2012; The UN Inter-agency Group for Child Mortality Estimation, Levels and Trends in Child Mortality: Report 2011, 2011; Team analysis from 2035 onward based on straight-line ARR reduction from UNICEF numbers 1990-2035

CHILD SURVIVAL

**CALL to ACTION**

Ending Preventable Child Deaths

Child Survival: call to action. USAID/UNICEF, Washington, USA. June 14-15, 2012

# Putting child TB on the global public health agenda

Child TB subgroup of WHO Stop TB Partnership formed 2003

WHO Stop TB strategy aims to increase case-finding: 2006

Children recognised as a vulnerable group in need of increased case-finding: 2009

# …and taking the opportunities provided by global commitment to maternal and child health

**Renewed commitment to child survival - United Nations, 2011**

**Stop TB Symposium on "Meeting the unmet needs of women and children for TB prevention, diagnosis and care: expanding our horizons"**

Wednesday 26 October 2011 in Lille, France

Stop TB Partnership

World Health Organization




# Combating Tuberculosis in Children

## Quick Facts

- At least half a million children* become ill with tuberculosis (TB) each year.
- Up to 70 000* children die of TB every year.
- 70-80% of children with TB, have the disease in their lungs (pulmonary TB). The rest are affected by TB disease in other parts of the body (extrapulmonary TB).
- There were over ten million orphans due to parental TB deaths in 2010.

## Factors That Put Children At Risk

- Any child living in a setting where there are people with infectious TB can become ill with TB, even if they are vaccinated.
- TB illness in children is often missed or overlooked due to non-specific symptoms and difficulties in diagnosis, such as obtaining sputum from young children.
- Children with vulnerable immune systems, such as the very young, HIV-infected or severely malnourished, are most at risk for falling ill or dying from TB.
- Infants and young children are at increased risk of developing severe disseminated disease associated with high mortality, such as TB meningitis or miliary TB.
- Adolescents are at particular risk of developing adult-type disease, i.e. often sputum smear-positive and highly infectious.
- Children with TB are often poor and live in vulnerable communities where there may be a lack of access to health care.
- Newborn children of women with TB are at increased risk of contracting TB. Risks are very high for HIV-infected mothers and children.


## Key Challenges

- Attention to child TB activities rarely included in strategic plans and budgets of ministries of health.
- Need for better diagnostics that can detect TB in children.
- Lack of appropriate child-friendly fixed-dose combination drugs for treatment .
- Recommendations for provision of isoniazid preventive therapy (IPT) for children under 5 years of age rarely implemented.
- Systematic screening for TB not undertaken among children living in households affected by TB.
- Insufficient knowledge of health workers on child TB diagnosis and management issues.
- Current TB vaccine protects young children against the most severe forms of TB, such as meningitis and disseminated TB disease, but does not prevent transmission from an infectious contact.
- Need for increased collaboration between actors in TB and maternal and child health.
- Lack of community knowledge and advocacy.

# RESPONSE

## Reaching the MDGs

Millennium Development Goals 4 and 5 aim to reduce deaths among children and pregnant women, while MDG 6 focuses on turning around the TB, HIV and malaria epidemics. These goals cannot be achieved without additional efforts on TB diagnosis and treatment in children as well as pregnant women.

## What can be Done

- **Mobilize commitment** at global and national levels to address childhood TB.
- **Promote strategic partnerships** and **synergies** across the health system, especially between **TB, maternal and child health,** and **immunization** programmes and relevant stakeholders, to **prioritize** and **facilitate early detection** and management of children with TB.
- Advocate for increased **research** and **development** of **new diagnostics, drugs and vaccines** for childhood TB.
- Implement **contact investigation** and provide **IPT** to children under 5 years, through **training** and **awareness building** of health workers and the community on childhood TB.
- Advocate for **family-based approaches** to be integrated into TB and HIV activities.

## Roadmap: Key Actions to Address Childhood TB

| Short term (2012-15) | Medium term (2015-18) | Long term (2020) |
|---|---|---|
| Increased action in countries to prioritize childhood TB and implement activities such as contact investigation and IPT to detect and manage TB in children, in line with international standards | Improved prevention, detection, diagnosis and management of TB in children | Test for latent TB with ability to predict disease progression in children |
| High profile of childhood TB at the global and national levels | Integrated approaches implemented across the health system to address TB in children and pregnant women | Point of care test with good accuracy for childhood TB |
| Capacity building of health workers scaled up at all levels to detect and manage children with TB | Inclusion of children in trials on new diagnostics and drugs | Shorter, child-friendly regimens for both, infection and disease |
| Antenatal screening for TB, in tandem with HIV - detect, treat or prevent TB in mothers | Development of new diagnostics suitable for children | Vaccines to prevent infection and disease in children and adults |
| Research on new diagnostics, drugs and vaccines for childhood TB | | |
| Improved recording and reporting of data on childhood TB | | |

This roadmap is being developed by the World Health Organization and the Childhood TB Subgroup of the Stop TB Partnership. The document will be launched in November 2012. Please access www.who.int/tb/challenges/children for a related advocacy brochure. For more information please visit our websites: World Health Organization: www.who.int/tb; Stop TB Partnership: www.stoptb.org

Child TB up and running?

**World TB Day March 24 2012 – focus on child TB**

# Childhood TB and NTPs

# Childhood TB and NTPs

"Best Practices in Tuberculosis Control"
September 2010, Kigali, Rwanda

1. Develop and adapt child TB guidelines
2. Operationalise child TB guidelines
3. Identify child TB champion
4. Focal person for child TB at NTP – working group
5. Training – provide child TB training and incorporate into ongoing training related to TB and TB/HIV

6. Incorporate child TB into annual plans and 5-year strategic plan
7. Incorporate child TB into budget
8. Include child TB data in routine reporting and reviews
9. Operational research to determine constraints and barriers
10. Research aimed to improve child TB and contact management

# Childhood TB and NTPs

## Technical assistance

- Sudan – contact management guidelines 2011
- Zimbabwe – child TB review, guidelines revision and training 2011
- Indonesia – JEMM 2011
- Vietnam – 2011 situational analysis and guidelines revision
- Cambodia – 2012


# NATIONAL TB PROGRAM
# PAPUA NEW GUINEA

# MANUAL ON MANAGEMENT OF CHILDHOOD TUBERCULOSIS

**Jointly drafted by**
Pediatric Society of Papua New Guinea
National Department of Health
World Health Organization
University of Melbourne
2009

National TB Program Unit, Disease Control Branch, PO Box 807, Waigani, Port Moresby, Papua New Guinea
Telephones: Director (DCB) 3013738, NTP Manager 3013757, Fax: 3013604, 3250568

# Childhood TB and NTPs

## Training

- Training tools for WHO guidance
- Asia – Singapore Sept 2011
- Vietnam – September 2011
- Africa - Cape Town May 2012
- Africa – Nairobi Sept 2012


**Desk-guide for diagnosis and management of TB in children**

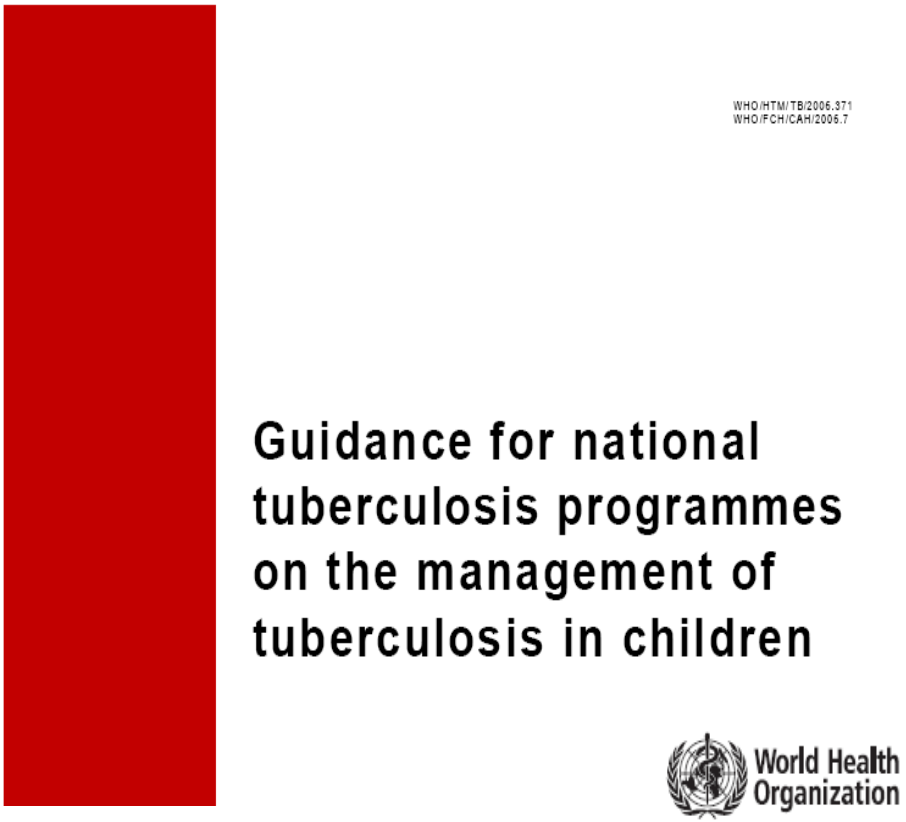
Training is a critical tool

- Identify national child TB champions
- Identify main management issues
- Identify operational research priorities
- Advocacy
- Implementation
- Monitoring progress

International Union Against Tuberculosis and Lung Disease
*Health solutions for the poor*

# Childhood TB and NTPs

- Revision of Guidance 2012
- Roadmap – 2011/12
- Framework – 2012 WHO AFRO




# Diagnostics

IGRA

Xpert

# BCG

Lack of GRC approved guidelines

BCG and HIV

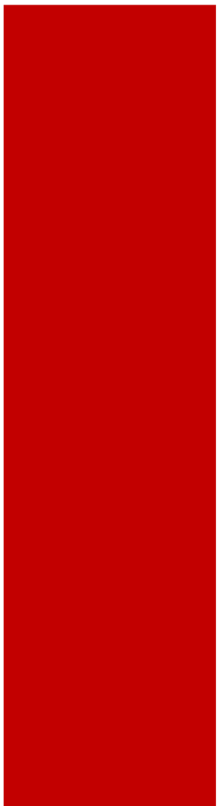
# Drug dosages

INH and FDCs

# IPT for HIV

Lack of evidence

More on MDR, TB/HIV and integration




# Definitions

Diagnostic – Xpert

Outcome –

Classification – PTB v EPTB

# Building consensus to support research

- Stop TB Partnership – DEWG – Child TB
- NDWG
- NIH
- TDR
- Many individual reserchers

National Institutes of Health
National Institute of Allergy and Infectious Diseases

**Workshop on TB and HIV Diagnostics in Adult and Pediatric Populations**
**June 28–30, 2011**

Silver Spring, Maryland

# Evaluation of TB diagnostics in children:

1. Proposed clinical case definitions for classification of intra-thoracic tuberculosis disease.

2. Methodological issues for conducting and reporting research evaluations of TB diagnostics for intrathoracic tuberculosis in children.

**Consensus from an Expert Panel***

# Evaluation of Tuberculosis Diagnostics in Children: 1. Proposed Clinical Case Definitions for Classification of Intrathoracic Tuberculosis Disease. Consensus From an Expert Panel

Stephen M. Graham,[1,2] Tahmeed Ahmed,[3] Farhana Amanullah,[4] Renee Browning,[5] Vicky Cardenas,[6] Martina Casenghi,[7] Luis E. Cuevas,[8] Marianne Gale,[9] Robert P. Gie,[10] Malgosia Grzemska,[11] Ed Handelsman,[12] Mark Hatherill,[13] Anneke C. Hesseling,[14] Patrick Jean-Philippe,[5] Beate Kampmann,[15,16] Sushil Kumar Kabra,[17] Christian Lienhardt,[11] Jennifer Lighter-Fisher,[18] Shabir Madhi,[19] Mamodikoe Makhene,[20] Ben J. Marais,[21] David F. McNeeley,[22] Heather Menzies,[23] Charles Mitchell,[24] Surbhi Modi,[25] Lynne Mofenson,[26] Philippa Musoke,[27] Sharon Nachman,[28] Clydette Powell,[29] Mona Rigaud,[18] Vanessa Rouzier,[30] Jeffrey R. Starke,[31] Soumya Swaminathan,[32] and Claire Wingfield[33]

# Evaluation of Tuberculosis Diagnostics in Children: 2. Methodological Issues for Conducting and Reporting Research Evaluations of Tuberculosis Diagnostics for Intrathoracic Tuberculosis in Children. Consensus From an Expert Panel[a]

Luis E. Cuevas,[1] Renee Browning,[2] Patrick Bossuyt,[3] Martina Casenghi,[4] Mark F. Cotton,[5] Andrea T. Cruz,[6] Lori E. Dodd,[7] Francis Drobniewski,[8] Marianne Gale,[9] Stephen M. Graham,[10] Malgosia Grzemska,[11] Norbert Heinrich,[12] Anneke C. Hesseling,[13] Robin Huebner,[14] Patrick Jean-Philippe,[2] Sushil Kumar Kabra,[15] Beate Kampmann,[16,17] Deborah Lewinsohn,[18] Meijuan Li,[19] Christian Lienhardt,[11] Anna M. Mandalakas,[20] Ben J. Marais,[21] Heather J. Menzies,[22] Grace Montepiedra,[23] Charles Mwansambo,[24] Richard Oberhelman,[25,26] Paul Palumbo,[27] Estelle Russek-Cohen,[28] David E. Shapiro,[23] Betsy Smith,[29] Giselle Soto-Castellares,[30] Jeffrey R. Starke,[6] Soumya Swaminathan,[31] Claire Wingfield,[32] and Carol Worrell[33]

**published in J infect Dis 2012**

# Making an IMPAACT

Tuberculosis Scientific Committee, IMPAACT, National Institutes of Health

- Objectives: novel research on diagnostics, therapeutics and vaccines

- Chair: Anneke Hesseling
- Co-vice chairs: Amita Gupta and Steve Graham

**RAPID ADVICE**

**Treatment of tuberculosis in children**

Revised dosages for children up to 30 kgs:

| | |
|---|---|
| Rifampicin | 15 (10-20) mg/kg/day |
| Isoniazid | 10 (10-15) mg/kg/day |
| Pyrazinamide | 35 (30-40) mg/kg/day |
| Ethambutol | 20 (15-25) mg/kg/day |

Note also other revisions to recommendations in 2010:

1. **Four drugs (RHZE)** in intensive phase for all new cases in HIV endemic setting
2. **No intermittent regimens** in HIV-endemic setting
3. Streptomycin no longer recommended for first-line therapy
4. 12-month regimens for TBM and osteo-articular TB

World Health Organization

# Recent revision of recommended drug dosages: rationale and challenges

- The 2006 guidelines listed regimens and drug dosages for children that were consistent with those used in adults.
- Rationale for change
  - Consistent evidence that serum levels of drug are low in young children when these dosages (mg/kg) are used.
  - Poor outcomes in some child TB cases (e.g. HIV-infected) raised possibility (theoretical, no evidence) that higher levels might mean better outcomes
  - Extensive review established that risk of toxicity remained very low if higher dosages are used
- Challenges
  - Current FDC preparations are not ideal for the new dosages – esp need for added isoniazid
  - Most FDCs have a ratio of R:H of 2:1 (e.g. R/H of 60/30) when it would be better to have 3:2 ratio

# Population Pharmacokinetic Modeling of Pyrazinamide in Children and Adults with Tuberculosis

Min Zhu, Ph.D., Jeffrey R. Starke, M.D., William J. Burman, M.D., Phillip Steiner, M.D., Jerry Jean Stambaugh, Pharm.D., David Ashkin, M.D., Amy E. Bulpitt, B.S., Shaun E. Berning, Pharm.D., and Charles A. Peloquin, Pharm.D.

Pharmacotherapy 2002

INT J TUBERC LUNG DIS 8(11):1360–1367


# Pharmacokinetics of ethambutol in children and adults with tuberculosis

M. Zhu,* W. J. Burman,† J. R. Starke,‡ J. J. Stambaugh,§ P. Steiner,¶ A. E. Bulpitt,* D. Ashkin,§ B. Auclair,* S. E. Berning,** R. W. Jelliffe,*** G. S. Jaresko,***‡‡ C. A. Peloquin,*#§§

ADC ONLINE

# Isoniazid pharmacokinetics in children treated for respiratory tuberculosis

H S Schaaf, D P Parkin, H I Seifart, C J Werely, P B Hesseling, P D van Helden, J S Maritz and P R Donald

*Arch. Dis. Child.* 2005;90;614-618
doi:10.1136/adc.2004.052175

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2006, p. 407–413
0066-4804/06/$08.00+0 doi:10.1128/AAC.50.2.407–413.2006

Vol. 50, No. 2

# Low Levels of Pyrazinamide and Ethambutol in Children with Tuberculosis and Impact of Age, Nutritional Status, and Human Immunodeficiency Virus Infection

S. M. Graham,[1,2,3]* D. J. Bell,[1,3,4] S. Nyirongo,[1] R. Hartkoorn,[3] S. A. Ward,[3] and E. M. Molyneux[2]

*Malawi-Liverpool-Wellcome Trust Clinical Research Programme,[1] Departments of Paediatrics,[2] and Departments of Medicine,[4] College of Medicine, Blantyre, Malawi, and Liverpool School of Tropical Medicine, University of Liverpool, Liverpool, United Kingdom[3]*

**BMC Medicine**

BioMed Central

Research article

Open Access

# Rifampin pharmacokinetics in children, with and without human immunodeficiency virus infection, hospitalized for the management of severe forms of tuberculosis

Hendrik Simon Schaaf*[1], Marianne Willemse[1], Karien Cilliers[2], Demetre Labadarios[2,6], Johannes Stephanus Maritz[3], Gregory D Hussey[4], Helen McIlleron[5], Peter Smith[5] and Peter Roderick Donald[1,3]

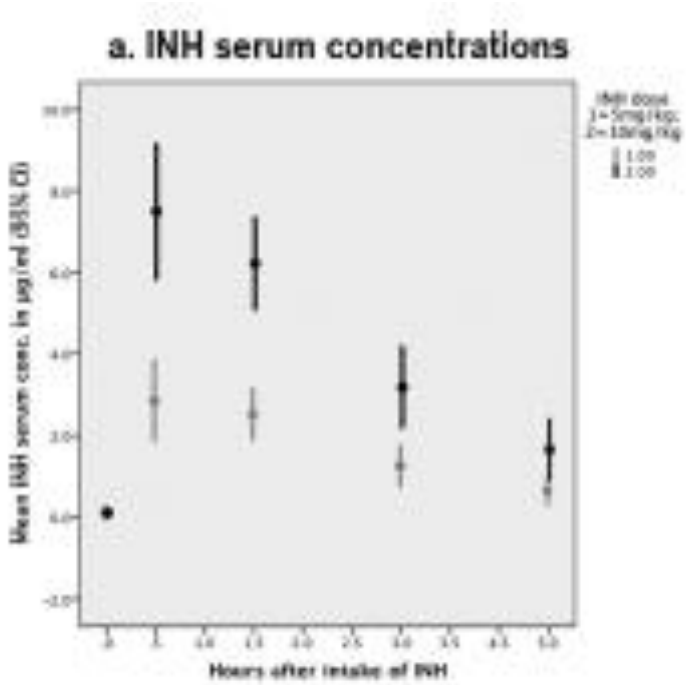
# Isoniazid Plasma Concentrations in a Cohort of South African Children with Tuberculosis: Implications for International Pediatric Dosing Guidelines

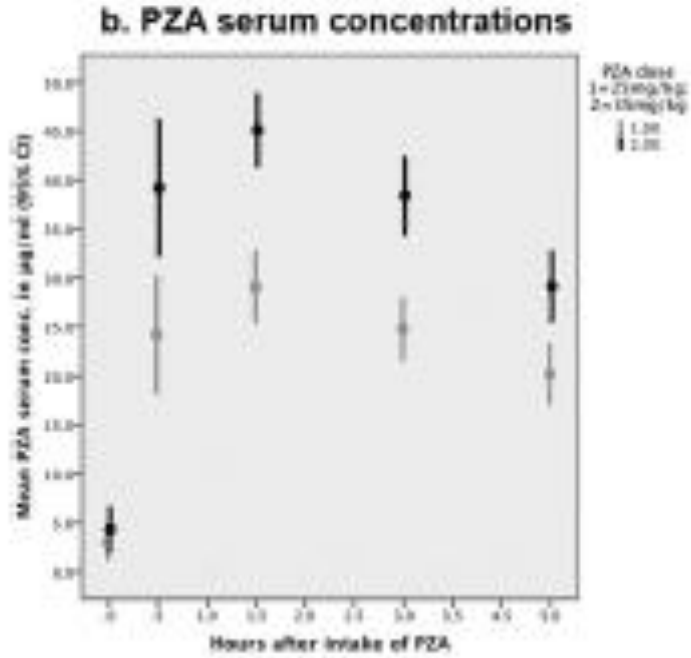
**Helen McIlleron,[1] Marianne Willemse,[4,5] Cedric J. Werely,[6,7] Gregory D. Hussey,[2,3] H. Simon Schaaf,[4,5] Peter J. Smith,[1] and Peter R. Donald[4,5]**

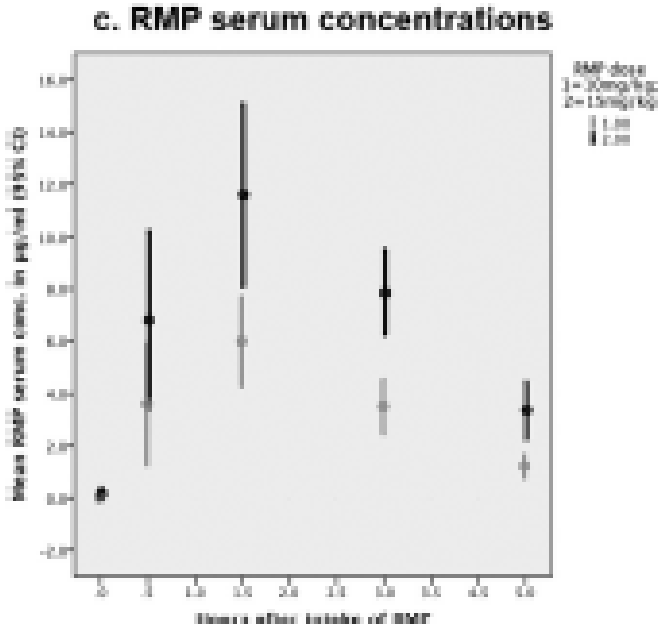
[1]Division of Clinical Pharmacology, Department of Medicine, [2]Institute of Infectious Diseases and Molecular Medicine, and [3]School of Child and Adolescent Health, University of Cape Town, and [4]Tygerberg Children's Hospital, Cape Town, and [5]Department of Paediatrics and Child Health, [6]Division of Molecular Biology and Human Genetics, and [7]Medical Research Council Centre for Molecular and Cellular Biology, Faculty of Health Sciences, University of Stellenbosch, Stellenbosch, South Africa

Clin Infect Dis 2009

| | WHO 2006[*2] | WHO 2010[1] |
|---|---|---|
| **Isoniazid** | 5 (4-6)[**]<br>max. 300 mg/day | 10 (10-15)<br>max 300 mg/day |
| **Rifampicin** | 10 (8-12) | 15 (10-20)<br>max 600 mg/day |
| **Pyrazinamide** | 25 (20-30) | 35 (30-40) |
| **Ethambutol** | 20 (15-25) | 20 (15-25) |




Pharmacokinetics of Isoniazid, Rifampin, and Pyrazinamide in Children Younger than Two Years of Age with Tuberculosis: Evidence for Implementation of Revised World Health Organization Recommendations[v]

Thee S et al, AAC 2011

# Recent challenges for implementation of dosages and regimens

- Current FDC preparations are not ideal for the new dosages – esp need for added isoniazid
- Recommended dosage for INH is at bottom of range 10-15 mg
- Recommended four drugs (RHZ**E**) in intensive phase for HIV endemic settings adds to pill burden
- Availability of FDC has affected availability of INH alone preparation

# Recent issues and challenges for implementation


## Report of an informal consultation on missing priority medicines for children

14-15 July 2011, WHO HQ, Geneva, Switzerland

Table 1.A. : Interim recommendation for intensive phase using dispersible FDCs (rifampicin, isoniazid, pyrazinamide: 60+30+150 and rifampicin, isoniazid: 60+60)

| Weight (kg) | Rifampicin, isoniazid, pyrazinamide *dispersible* (60,30,150) | Rifampicin, isoniazid *dispersible* (60,60) | Rifampicin (mg/kg) | Isoniazid (mg/kg) | Pyrazinamide (mg/kg) |
|---|---|---|---|---|---|
| 5 | 1 | 1 | 24.0[∞] | 18[∞] | 30.0 |
| 6 | 1 | 1 | 20.0 | 15.0 | 25.0[r] |
| 7 | 1 | 1 | 17.1 | 12.9 | 21.4[r] |
| 8 | 2 | 1 | 22.5[∞] | 15.0 | 37.5 |
| 9 | 2 | 1 | 20.0 | 13.3 | 33.3 |
| 10 | 2 | 1 | 18.0 | 12.0 | 30.0 |
| 11 | 2 | 1 | 16.4 | 10.9 | 27.3[r] |
| 12 | 2 | 1 | 15.0 | 10.0 | 25.0[r] |
| 13 | 2 | 1 | 13.8 | 9.2[r] | 23.1[r] |
| 14 | 2 | 1 | 12.9 | 8.6[r] | 21.4[r] |
| 15 | 3 | 2 | 20.0 | 14.0 | 30.0 |
| 16 | 3 | 2 | 18.8 | 13.1 | 28.1[r] |
| 17 | 3 | 2 | 17.6 | 12.4 | 26.5[r] |
| 18 | 3 | 2 | 16.7 | 11.7 | 25.0[r] |
| 19 | 3 | 2 | 15.8 | 11.1 | 23.7[r] |
| 20 | 3 | 2 | 15.0 | 10.5 | 22.5[r] |

World Health Organization

Dosing instructions for the use of currently available fixed-dose combination TB medicines for children

# Survey of NTPs and current recomendations

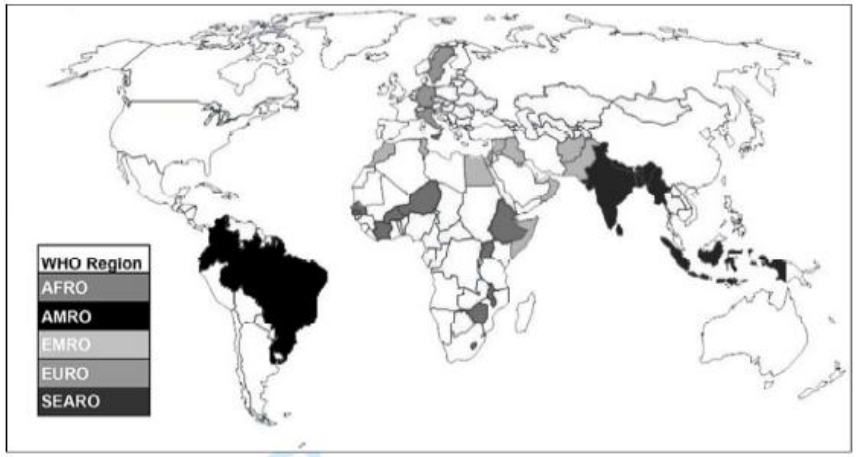
34 countries from 5 regions

Dec 2011-Feb 2012

10 TB high-burden countries

14 low-middle income

11 low income countries




12 use 2006 dosage guidelines and 19 use 2010 dosage guidelines

Majority recommend RHZ (some add E in older children > 10 years)

Obstacles to implementaion relate to awaiting update of guidelines, need for training, that available FDCs do not match dosage guidelines, the need for change not accepted by local experts, and quantity of pills required is increased

Preventive therapy not implemented and shortages and stock outs of H100

Detjen A, et al Pub Health Action 2012 (in press)

# Informal consultation on the development of new paediatric fixed-dose formulations
# 5 May 2012, Stellenbosch, South Africa

- Ethambutol – part of FDC or not
- Isoniazid dosage range
- Ratio and composition of “ideal” FDC
- At which weight to switch from paediaric to adult dosing and formulation
- Interim advice to countries
- Discussion on preparations
- Discussion on PQ EoI process
- Agreement on products to request for EoI

# Selecting the priority first-line FDC for children

| RHZE | RHZ+E |
|---|---|
| Reduce pill burden and so improve adherence | Limited to specific settings – not necessary in most settings |
| Consistency with adult regimens and usage | No additional efficacy in majority |
| Low risk of toxicity | Very limited protective effect against increased prevalence of resistance |
| | Additional size of FDC |
| | Ongoing concerns about toxicity |
| | Longevity – likely to be replaced |
| | Falling TB/HIV in children |

# Informal consultation on the development of new paediatric fixed-dose formulations
# 5 May 2012, Stellenbosch, South Africa

- New additions and preferably dispersable or crushable
  - RHZ 75/50/150
  - RH 75/50
- Retain following products and add that prefer dispersible or crushable
  - H 50 & H 100 tablet
  - E 100 tablet
  - Z 150 tablet
- Remove
  - Liquid formulations: oral liquid E 25 mg/ml and Z 30 mg/ml
  - H 150 tablet

# Interim guidelines for treatment of TB in young children using currently available FDCs and dosages achieved per weight

| Weight in kilograms | Number of tablets | Actual mg/kg dosage received when using number of tablets containing dosages listed for that weight band | | |
|---|---|---|---|---|
| | | Rifampicin 60 mg | Isoniazid 30 mg | Pyrazinamide 150 mg |
| 4 | 1 | 15.0 | 7.5 | 37.5 |
| 5 | 1 | 12.0 | 6.0 | 30.0 |
| 6 | 1 | 10.0 | 5.0 | 25.0 |
| 7 | 2 | 17.1 | 8.6 | 42.9 |
| 8 | 2 | 15.0 | 7.5 | 37.5 |
| 9 | 2 | 13.3 | 6.7 | 33.3 |
| 10 | 2 | 12.0 | 6.0 | 30.0 |
| 11 | 3 | 16.4 | 8.2 | 40.9 |
| 12 | 3 | 15.0 | 7.5 | 37.5 |
| 13 | 3 | 13.9 | 6.9 | 34.6 |
| 14 | 3 | 12.9 | 6.4 | 32.1 |
| 15 | 4 | 16.0 | 8.0 | 40.0 |
| 16 | 4 | 15.0 | 7.5 | 37.5 |
| 17 | 4 | 14.1 | 7.1 | 35.3 |
| 18 | 4 | 13.3 | 6.7 | 33.3 |
| 19 | 4 | 12.6 | 6.3 | 31.6 |
| 20 | 5 | 15.0 | 7.5 | 37.5 |
| 21 | 5 | 14.3 | 7.1 | 35.7 |
| 22 | 5 | 13.6 | 6.8 | 34.1 |
| 23 | 5 | 13.0 | 6.5 | 32.6 |
| 24 | 5 | 12.5 | 6.3 | 31.3 |

**Guidelines for treatment of TB in young children (less than 25 kgs) using proposed new FDCs (not yet available in 2012) and dosages achieved per weight**

| | | R 75 mg | H 50 mg | Z 150 mg |
|---|---|---|---|---|
| (kg) | | 10-20 mg/kg | 7-15 mg/kg | 30-40 mg/kg |
| | tabs | 75 | 50 | 150 |
| | | | | |
| 4 | 1 | 18.75 | 12.50 | 37.50 |
| 5 | 1 | 15.00 | 10.00 | 30.00 |
| 6 | 1 | 12.50 | 8.33 | 25.00 |
| 7 | 1 | 10.71 | 7.14 | 21.43 |
| 8 | 2 | 18.75 | 12.50 | 37.50 |
| 9 | 2 | 16.67 | 11.11 | 33.33 |
| 10 | 2 | 15.00 | 10.00 | 30.00 |
| 11 | 2 | 13.64 | 9.09 | 27.27 |
| 12 | 3 | 18.75 | 12.50 | 37.50 |
| 13 | 3 | 17.31 | 11.54 | 34.62 |
| 14 | 3 | 16.07 | 10.71 | 32.14 |
| 15 | 3 | 15.00 | 10.00 | 30.00 |
| 16 | 4 | 18.75 | 12.50 | 37.50 |
| 17 | 4 | 17.65 | 11.76 | 35.29 |
| 18 | 4 | 16.67 | 11.11 | 33.33 |
| 19 | 4 | 15.79 | 10.53 | 31.58 |
| 20 | 4 | 15.00 | 10.00 | 30.00 |
| 21 | 4 | 14.29 | 9.52 | 28.57 |
| 22 | 4 | 13.64 | 9.09 | 27.27 |
| 23 | 4 | 13.04 | 8.70 | 26.09 |
| 24 | 4 | 12.50 | 8.33 | 25.00 |

| | | E 100 mg |
|---|---|---|
| (kg) | | 15-25 mg/kg |
| | tabs | 100 |
| | | |
| 4 | 1 | 25.00 |
| 5 | 1 | 20.00 |
| 6 | 1 | 16.67 |
| 7 | 1 | 14.29 |
| 8 | 2 | 25.00 |
| 9 | 2 | 22.22 |
| 10 | 2 | 20.00 |
| 11 | 2 | 18.18 |
| 12 | 3 | 25.00 |
| 13 | 3 | 23.08 |
| 14 | 3 | 21.43 |
| 15 | 3 | 20.00 |
| 16 | 4 | 25.00 |
| 17 | 4 | 23.53 |
| 18 | 4 | 22.22 |
| 19 | 4 | 21.05 |
| 20 | 4 | 20.00 |
| 21 | 4 | 19.05 |
| 22 | 4 | 18.18 |
| 23 | 4 | 17.39 |
| 24 | 4 | 16.67 |

Use of currently available FDC and proposed revised dosages 2012

| Weight bands | Numbers of tablets | | |
|---|---|---|---|
| | Intensive Phase | | Continuation Phase |
| | RHZ | E | RH |
| | 60/30/150 | 100 | 60/30 |
| 4-6kg | 1 | 1 | 1 |
| 7-10kg | 2 | 2 | 2 |
| 11-14kg | 3 | 2 | 3 |
| 15-19 kg | 4 | 3 | 4 |
| 20-24kg | 5 | 4 | 5 |

Use of recently recommended FDC and proposed revised dosages 2012

| Weight bands | Numbers of tablets | | |
|---|---|---|---|
| | Intensive Phase | | Continuation Phase |
| | RHZ | E | RH |
| | 75/50/150 | 100 | 75/50 |
| 4-7kg | 1 | 1 | 1 |
| 8-11kg | 2 | 2 | 2 |
| 12-15kg | 3 | 3 | 3 |
| 16-24 kg | 4 | 4 | 4 |

# Progress and ongoing challenges

- New suggested FDC has WHO PQ and one EoI

- Small market and very limited suitable manufacturers or prequalified suppliers
- Procurement issues for NTP

- PK studies for second-line agents and small sub-groups e.g. newborns
- Very difficult to go beyond PK to clinical outcome without improved diagnostic
- Shorter regimens for children

# Policy-practice gap

# EVERYONE

TELLS ME TO MOVE ON

NO ONE TELLS ME HOW

WHO/HTM/TB/2006.373

WHO/HTM/TB/2006.37
WHO/FCH/CAH/2006.1

# Revised TB recording and reporting forms and registers – *version 2006*

WHO/HTM/TB/2006.365
WHO/FCH/CAH/2006.3

## Ethambutol efficacy and toxicity:

**literature review and recommendations for daily and intermittent dosage in children**

## Guidance for national tuberculosis programmes on the management of tuberculosis in children

WHO/HTM/TB/2007.381
WHO/FCH/CAH/07.02

## A research agenda for childhood tuberculosis

**Improving the management of childhood tuberculosis within national tuberculosis programmes:**

**research priorities based on a literature review**

## RAPID ADVICE

**Treatment of tuberculosis in children**

**Guidance for national tuberculosis and HIV programmes on the management of tuberculosis in HIV-infected children: Recommendations for a public health approach**

World Health Organization

International Union Against Tuberculosis and Lung Disease
*Health solutions for the poor*

World Health Organization

World Health Organization

# From guidelines to implementation: addressing the policy-practice gap

| Issue | Response |
|---|---|
| Understanding child TB epidemiology | |
| The challenge of diagnosis<br>Clinical approach<br>Perceptions and misperceptions | |
| Contact screening and management<br>Understanding of rationale<br>Challenges for implementation | |
| NTP management issues for children differ from adults<br>Classification of cases<br>Drug dosages | |

# From guidelines to implementation: addressing the policy-practice gap

| Issue | Response |
|---|---|
| Understanding child TB epidemiology | Training<br>NTP data |
| The challenge of diagnosis<br>Clinical approach<br>Perceptions and misperceptions | Training<br>Operational research |
| Contact screening and management<br>Understanding of rationale<br>Challenges for implementation | Training<br>Operational research |
| NTP management issues for children differ from adults<br>Classification of cases<br>Drug dosages | Training<br>NTP data |

# From guidelines to implementation: addressing the policy-practice gap

Safdar et al. BMC Health Services Research 2011, 11:187
http://www.biomedcentral.com/1472-6963/11/187


RESEARCH ARTICLE Open Access

## Childhood tuberculosis deskguide and monitoring: An intervention to improve case management in Pakistan

Nauman Safdar[1,2*], Sven Gudmund Hinderaker[2,4], Noor Ahmed Baloch[3], Donald A Enarson[4], Muhammad Amir Khan[1] and Odd Morkve[2]

Lestari *et al. BMC Public Health* 2011, **11**:784
http://www.biomedcentral.com/1471-2458/11/784

BMC Public Health

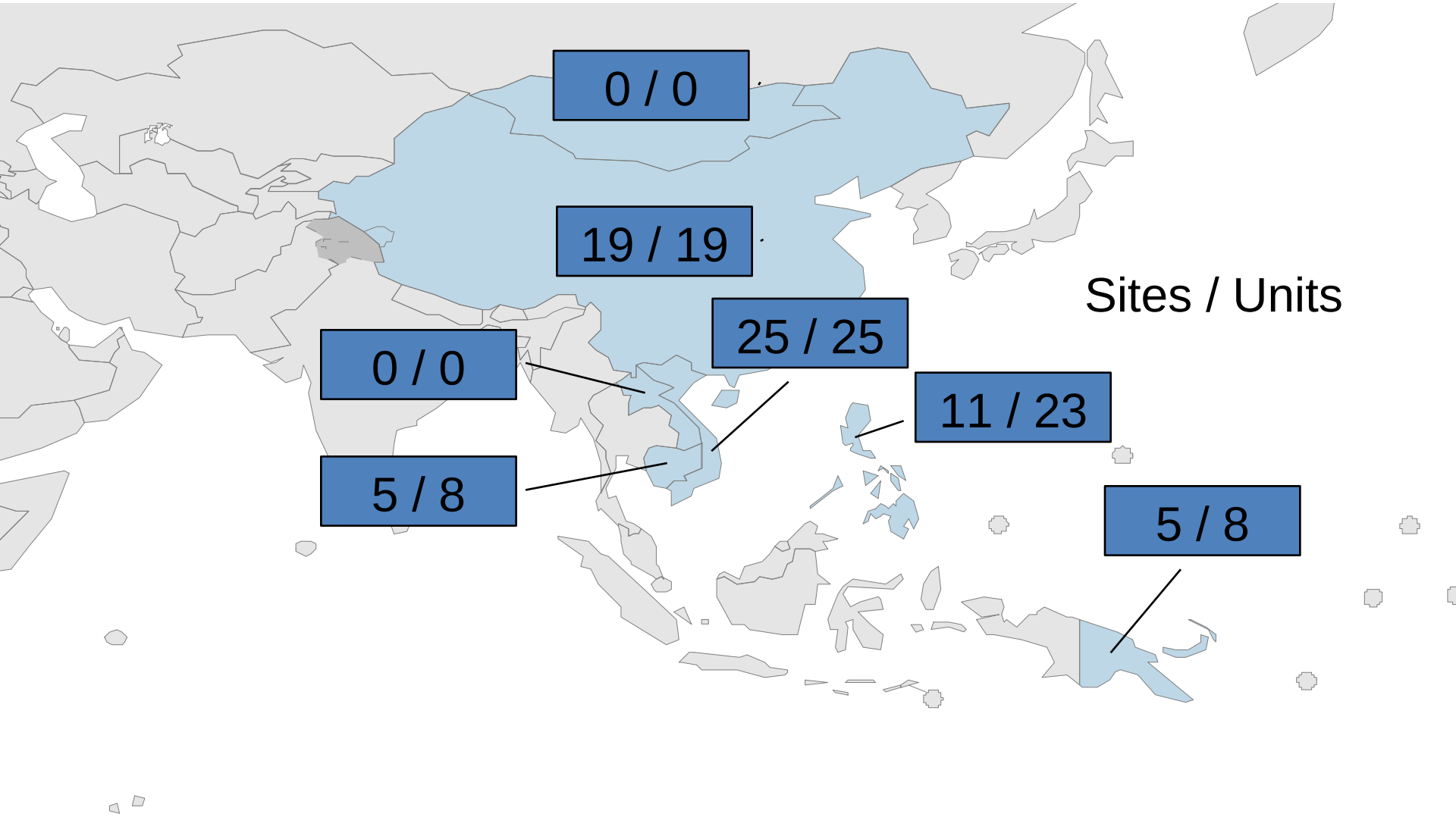
RESEARCH ARTICLE Open Access

# High caseload of childhood tuberculosis in hospitals on Java Island, Indonesia: a cross sectional study

Trisasi Lestari[1*], Ari Probandari[2], Anna-Karin Hurtig[3] and Adi Utarini[1]

**Only 1.6% of 4,821 cases in children were registered with NTP**

# GeneXpert



# Xpert MTB/RIF in children

| | South Africa<br>Nicol M et al Lancet Infect Dis 2011 | Tanzania<br>Rachow A et al Clin Infect Dis 2012 | Zambia<br>Bates M et al Lancet Infect Dis 2012 |
|---|---|---|---|
| Numbers | 452 | 164 | 930 |
| Median age | 19.4 months | 5.8 years | 2 years |
| HIV prevalence | 24 % | 51 % | 31 % |
| Smear positive | 27 (6%) | 7 (4%) | 15 (1.6%) |
| Culture positive | 70 (15%) | 28 (17%) | 58 (6.2%) |
| Xpert sensitivity | 74 % | 75 % | 72 % |
| Xpert specificity | 98 % | 100 % | 99 % |
| Median time to result | 1 day | 2 days | |

STAG TB WHO – 2012

TAG WPRO – 2012

including children increasingly

post-2015 strategy


WHO
WHAT
WHERE
WHEN
WHY
HOW
QUESTIONS
ANSWERS

# Roadmap Goals and Objectives

- Summarize key developments and achievements in childhood TB
- Highlight critical challenges and gaps
- Outline potential opportunities to accelerate progress
- Identify critical needs, priorities and way forward in the short and longer-term
- Place TB in broader context of maternal, newborn and child health and engage broad group of stakeholders in addressing childhood TB

# Key Stakeholders

- Global policy makers
- National policy makers/TB Programs
- Related health care and other sectors
- Private providers/health systems
- CBOs/CSOs/NGOs
- Advocacy organizations
- Families and communities

# Innovative approaches to TB care

# Innovative approaches to TB care

# Community-based integrated approach

Innovative approaches to TB care

Community-based integrated approach

Wider health sector

Innovative approaches to TB care

Community-based integrated approach

Wider health sector

Preventive therapy

Innovative approaches to TB care

Community-based integrated approach

Wider health sector

Preventive therapy

Operational research


Innovative approaches to TB care

Community-based integrated approach

Wider health sector

Preventive therapy

Operational research

# CHILD TB


Leadership

Technical expertise

High burden representation

# CHILD TB

Thank you

Child TB core subgroup

Malgosia Grzemska

Annemieke Brands