

Drug Resistant Tuberculosis in Children: Overview of Epidemiology

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Outline

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

Who carries the burden of tuberculosis?

...mostly, the most vulnerable

TB spreads in poor, crowded & poorly ventilated settings



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



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



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

Definitions

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

Definitions

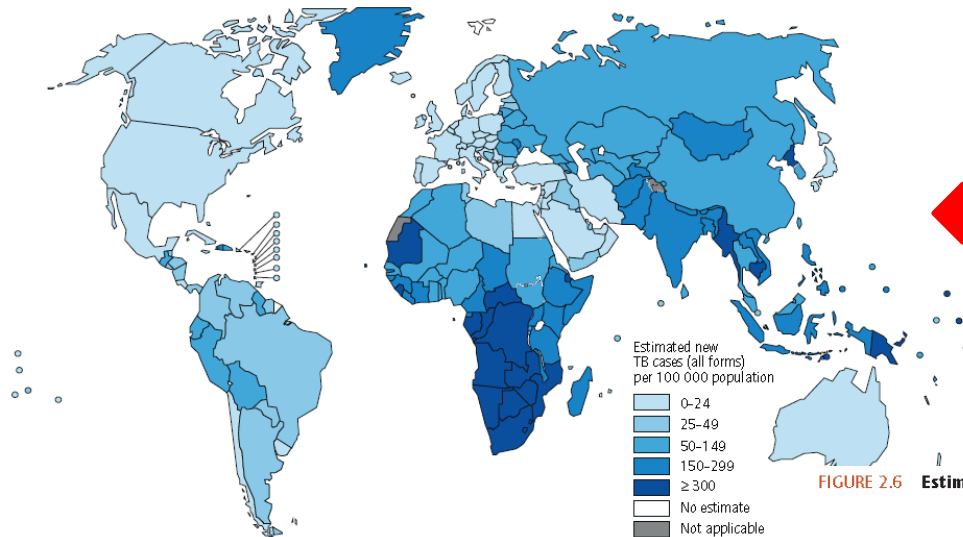
- “Pediatric” generally refers to children < 15 years of age
- Encompasses a variety of age groups, from neonates to adolescents
- These groups have varied epidemiology, disease presentation, diagnosis and treatment needs
- Consensus definition of various terms for research use developed and published

Consensus Statement on Research Definitions for Drug-Resistant Tuberculosis in Children. James A. Seddon et al on behalf of the Sentinel Project on Pediatric Drug-Resistant Tuberculosis. J Ped Infect Dis Society 2013 April

WHO Report 2013

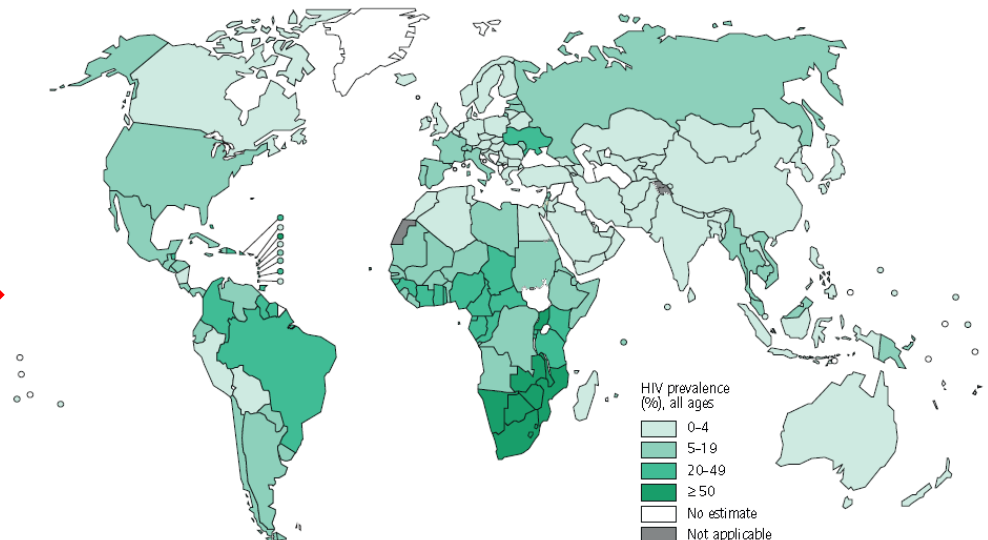
Global Tuberculosis Control

FIGURE 2.5 Estimated TB incidence rates, 2011



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

FIGURE 2.6 Estimated HIV prevalence in new TB cases, 2011

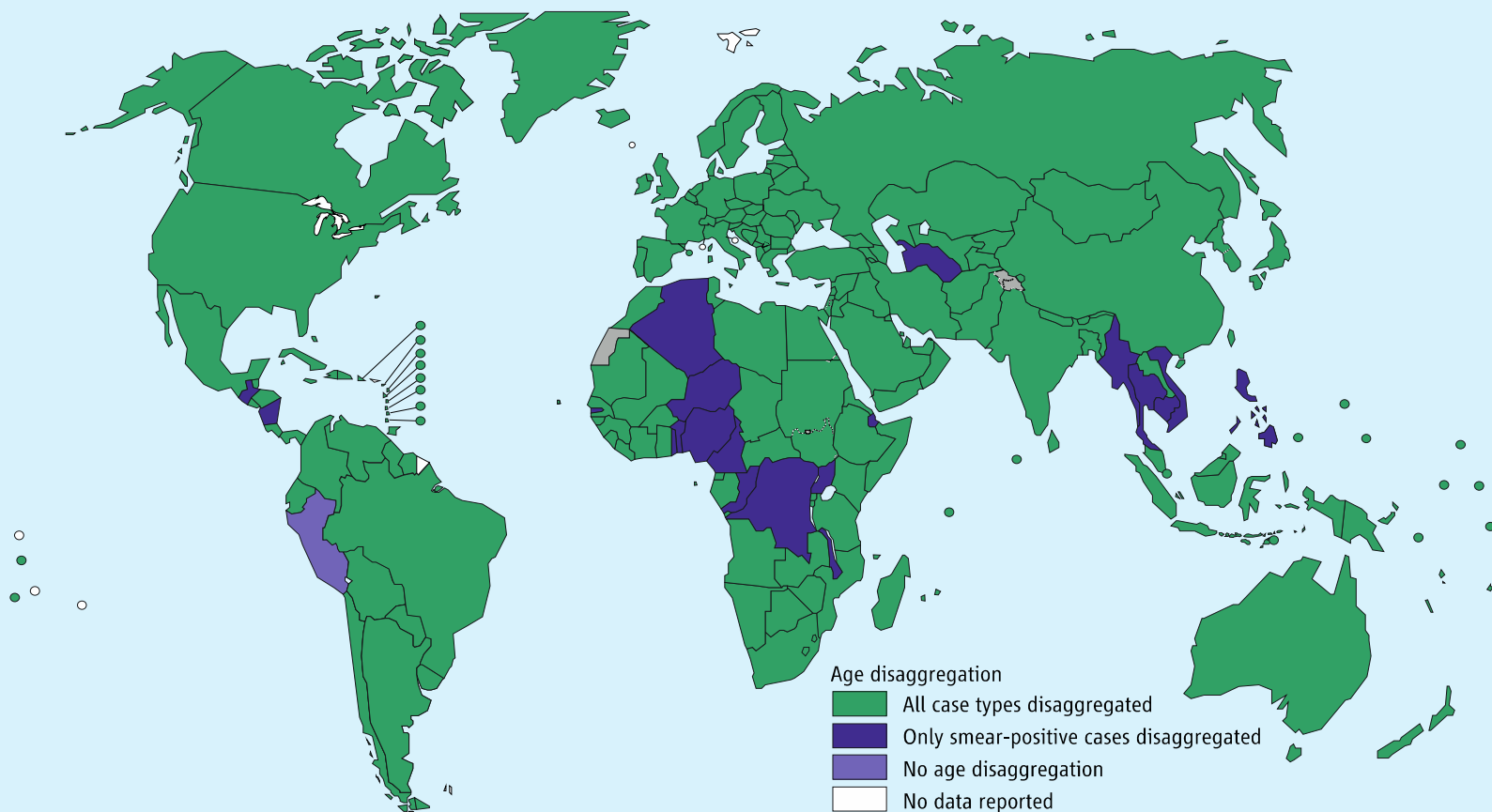


~1.13 million (13%)
HIV+TB cases;
320,000 HIV+TB deaths
in 2012

Countries Reporting TB Data Disaggregated by Age

FIGURE B2.2.3

Reporting of notification data disaggregated by age, 2012



Burden of TB in Children Estimated for First Time in 2011



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

Global TB Report 2013: Burden in Children

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

Epidemiology of Childhood TB in Select High Burden Countries, 2011

<u>Country</u>	<u>Childhood Cases</u>	<u>% Total Cases</u>
India	90,000	7
Afghanistan	17,540	25
Brazil	23,520	21
China	86,978	5
Pakistan	61,905	25
South Africa	35,449	16
Zimbabwe	12,267	16
Range		3 - 25
Total	327,659	9.6

Steps to Improve Estimation of TB Cases Among Children (WHO Report 2013)

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

Kiss of Death?

Case History

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

Global Concern about MDRTB



Risk Factors for Infection and Disease

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

TB Notifications by Age and HIV Status (Cape Town, 2009)

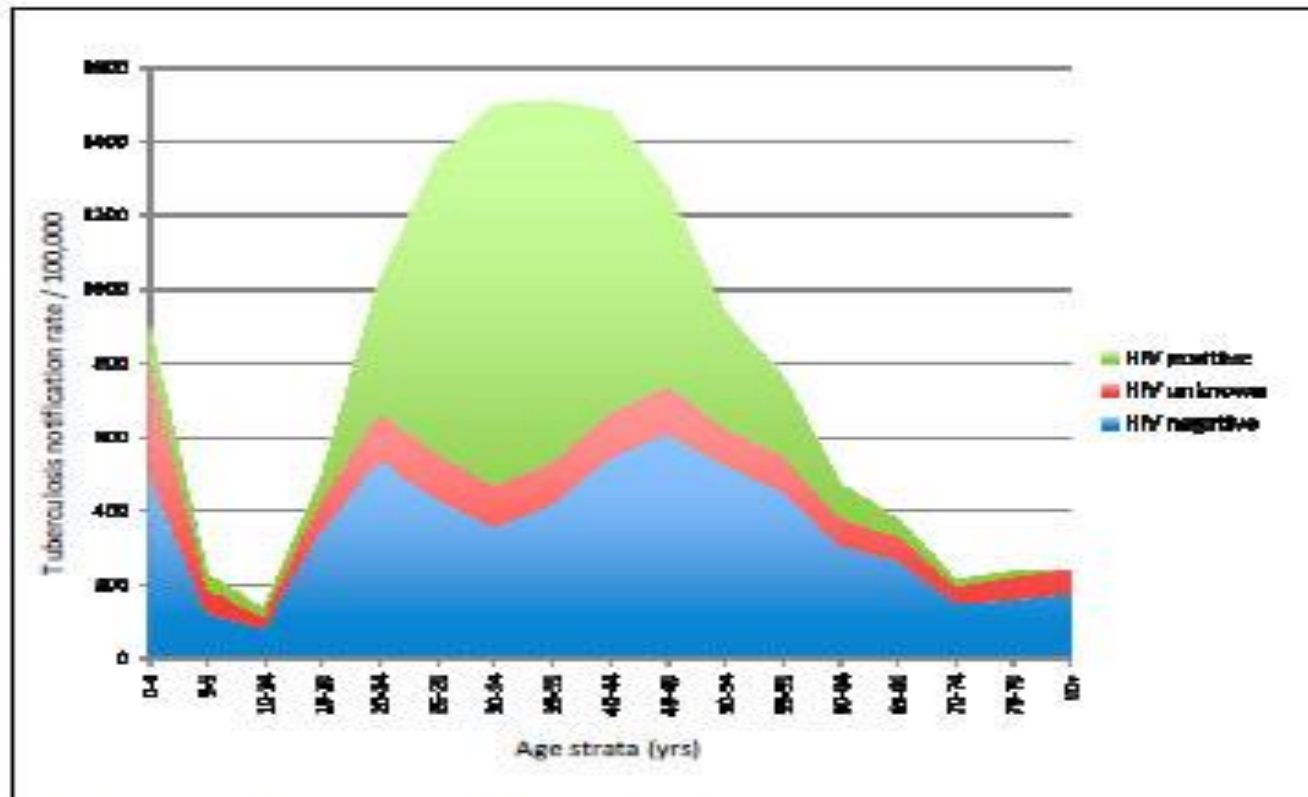
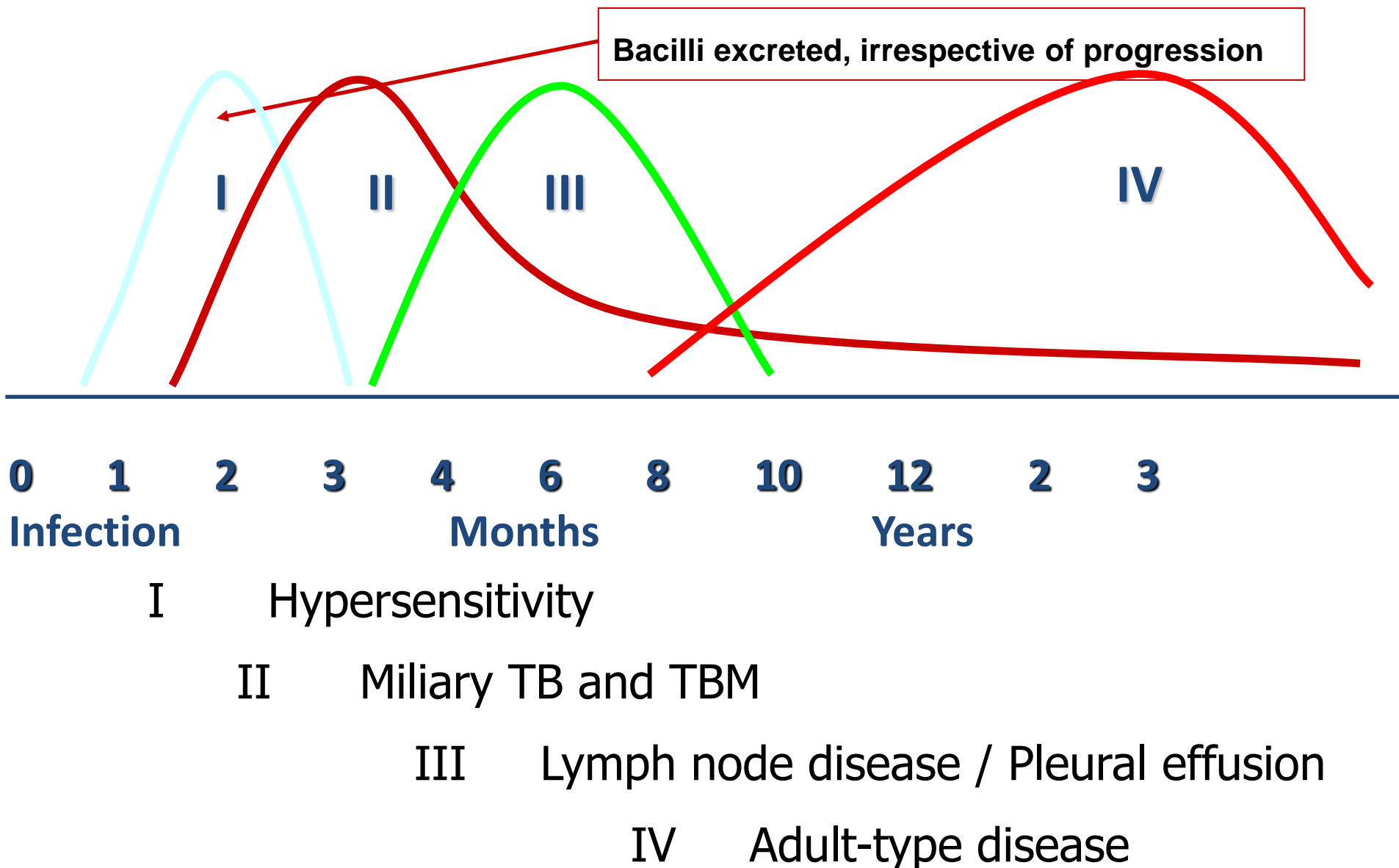
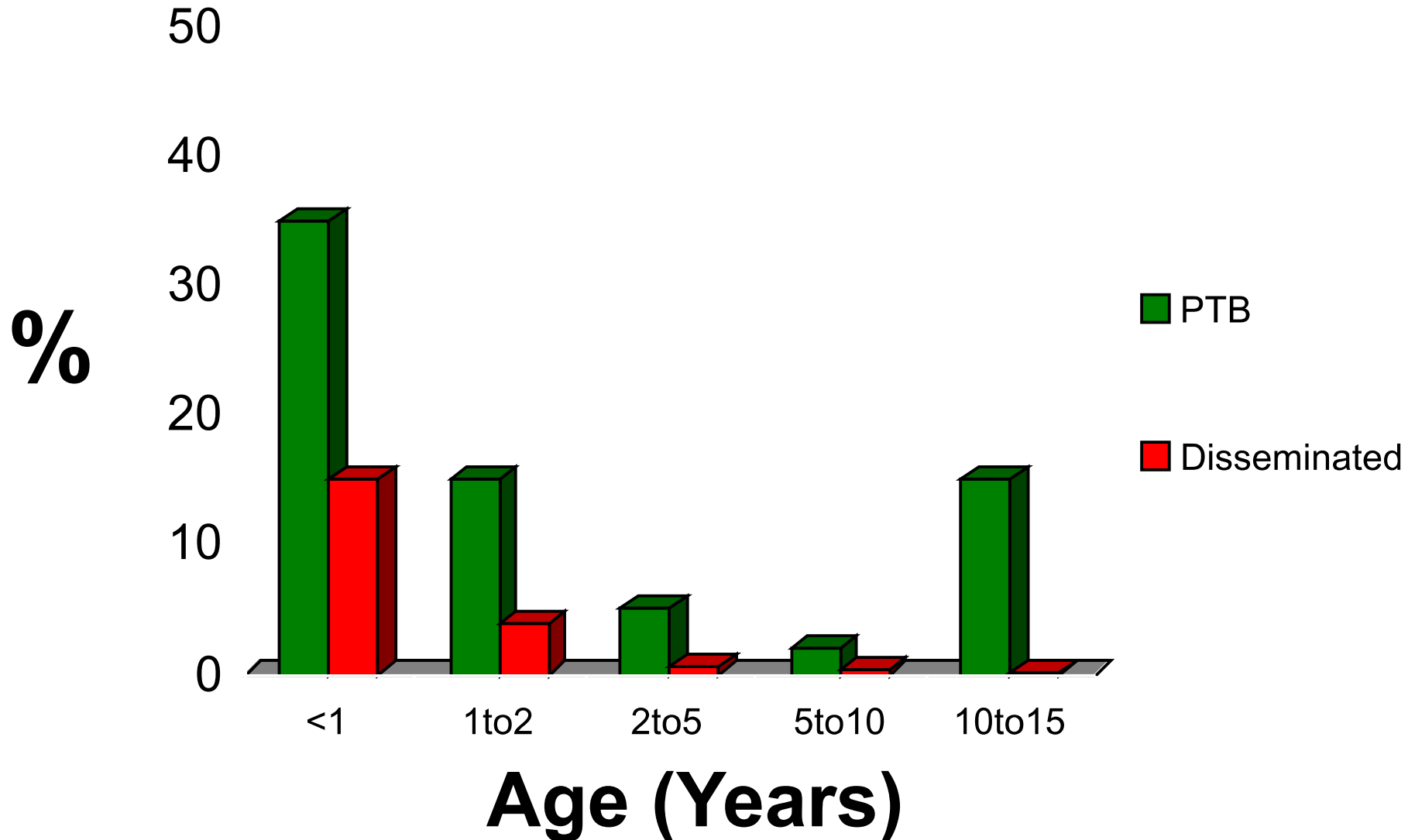


Fig. 1. TB notifications in 2009 for the City of Cape Town stratified by 5-year age groups and by provider-initiated HIV testing results. The denominators for age strata derived from National Department of Health/Health Information System Programme by disaggregating StatsSA district estimates (November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

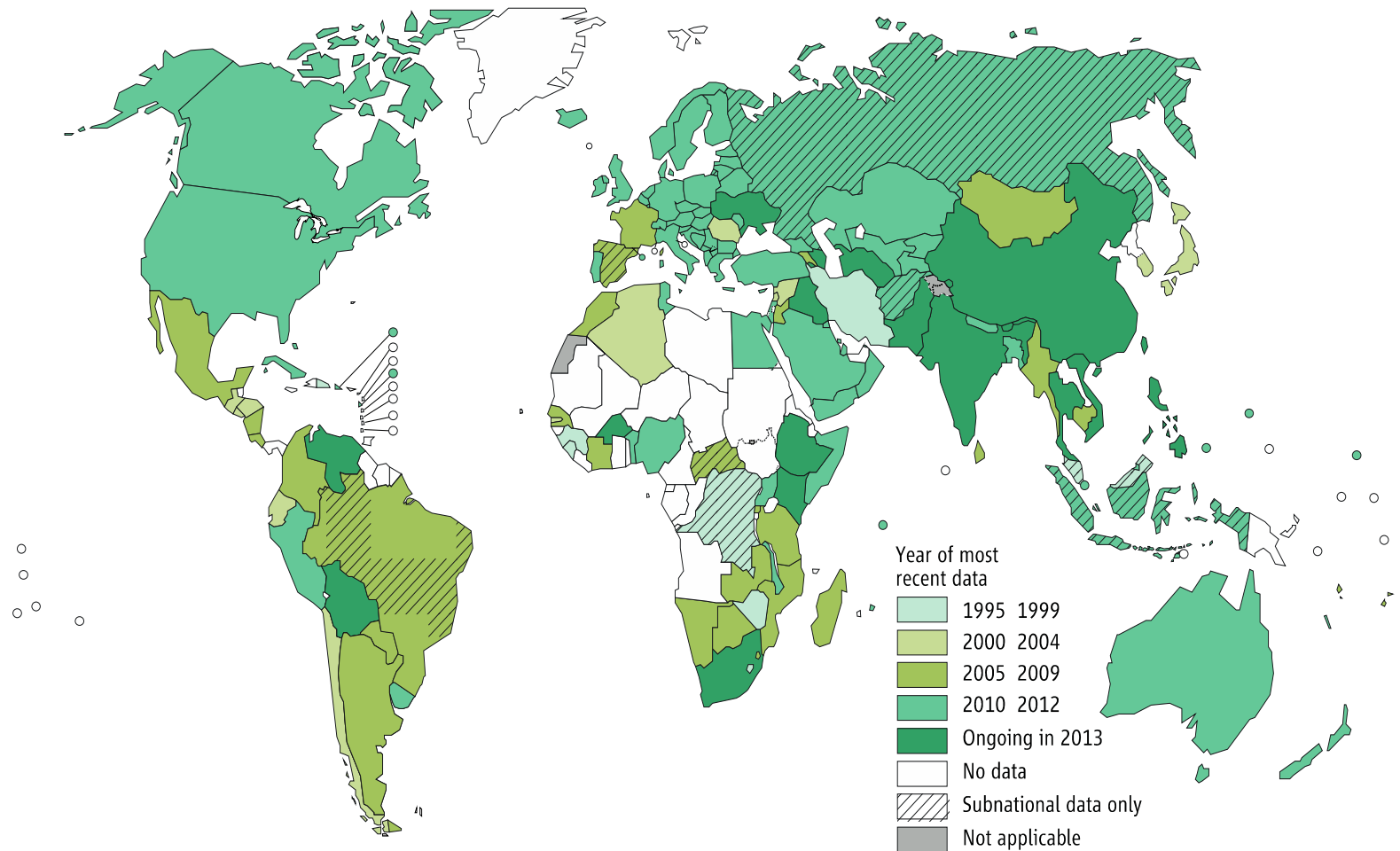
Wallgren's timetable: 90% of disease occurs in 1st year after infection



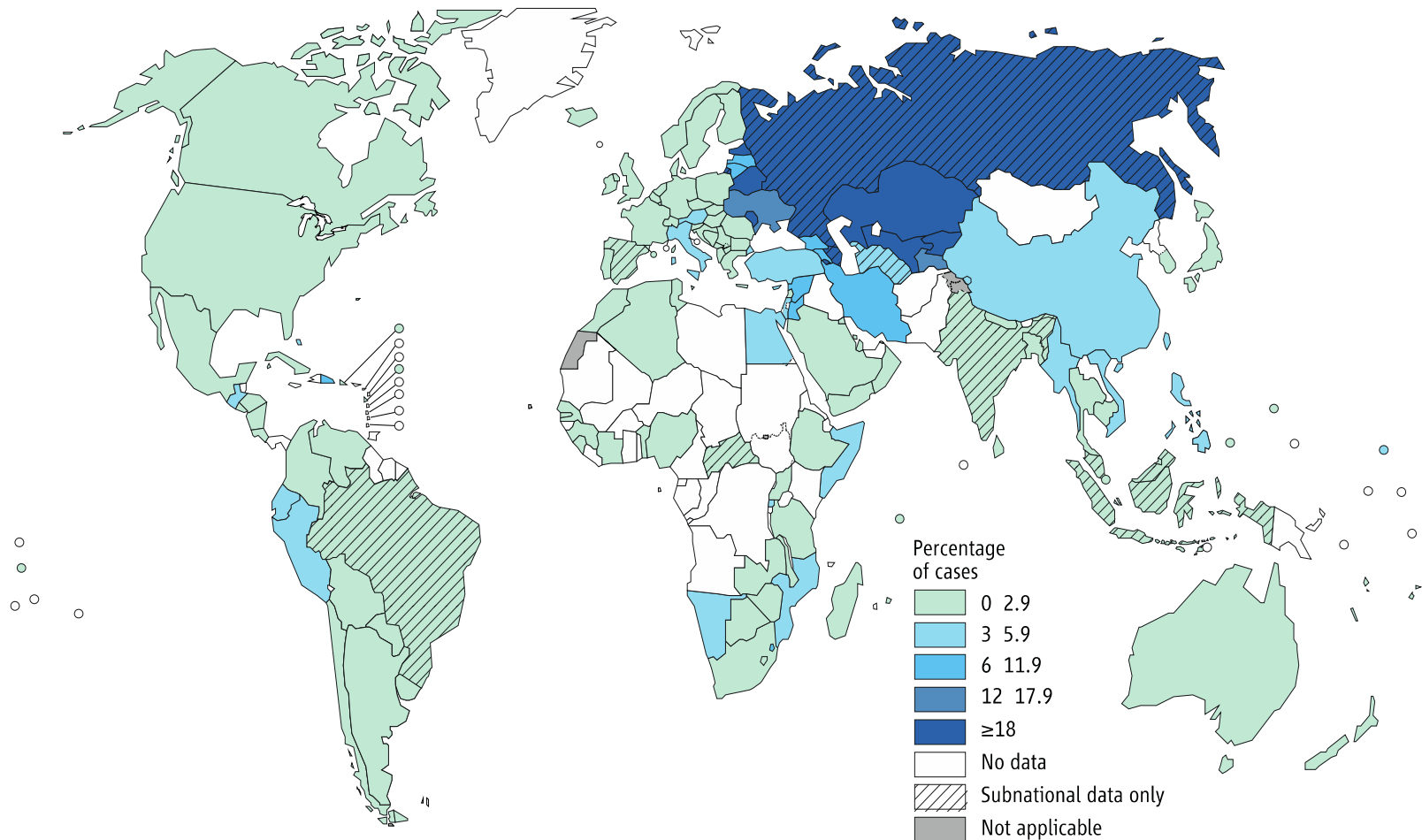
Age and risk – modified by HIV



Progress in Global coverage of drug resistance surveillance data 1994-2013

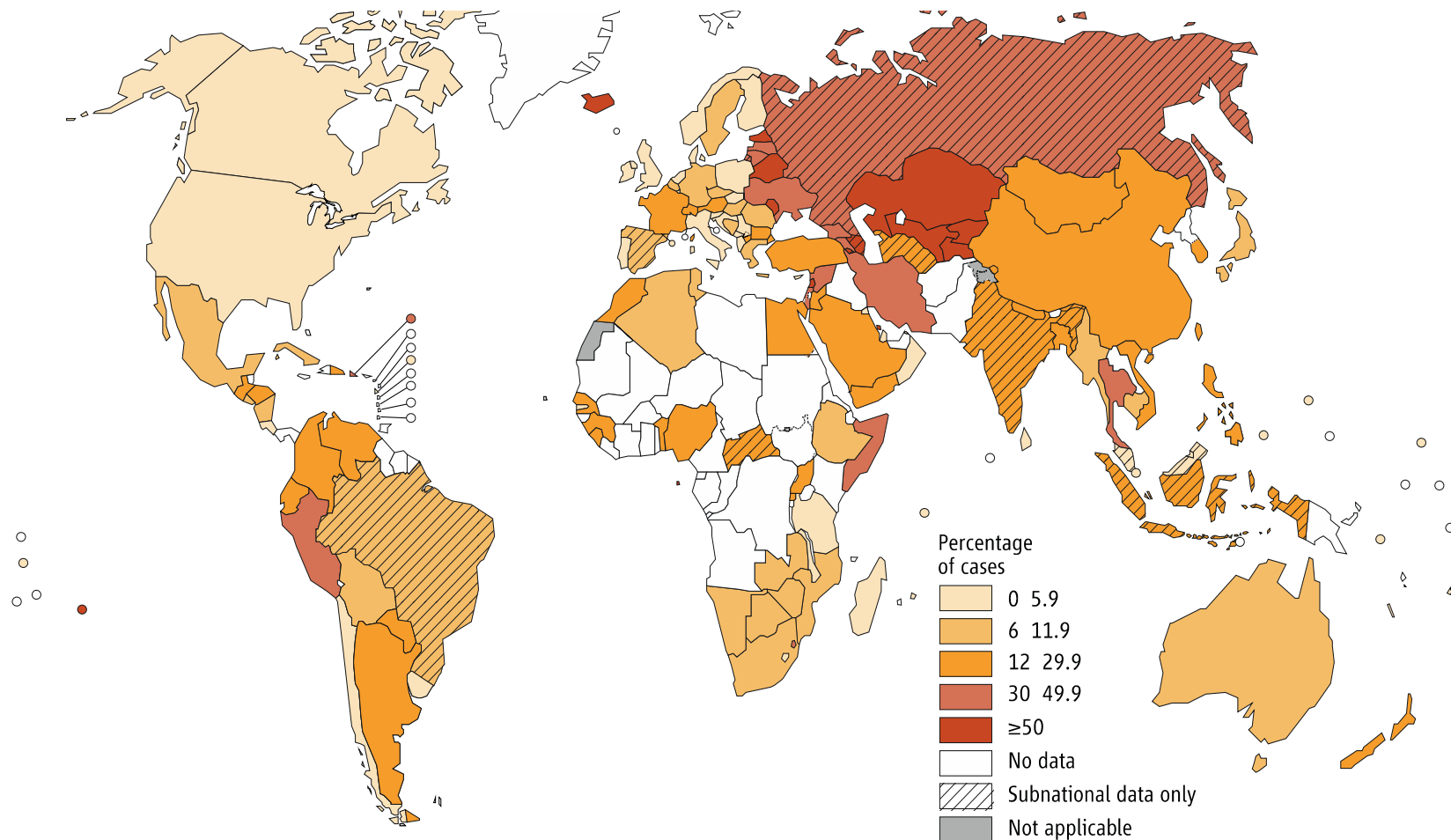


Prevalence of MDRTB among new cases (global average 3.6 (2.1- 5.1)%



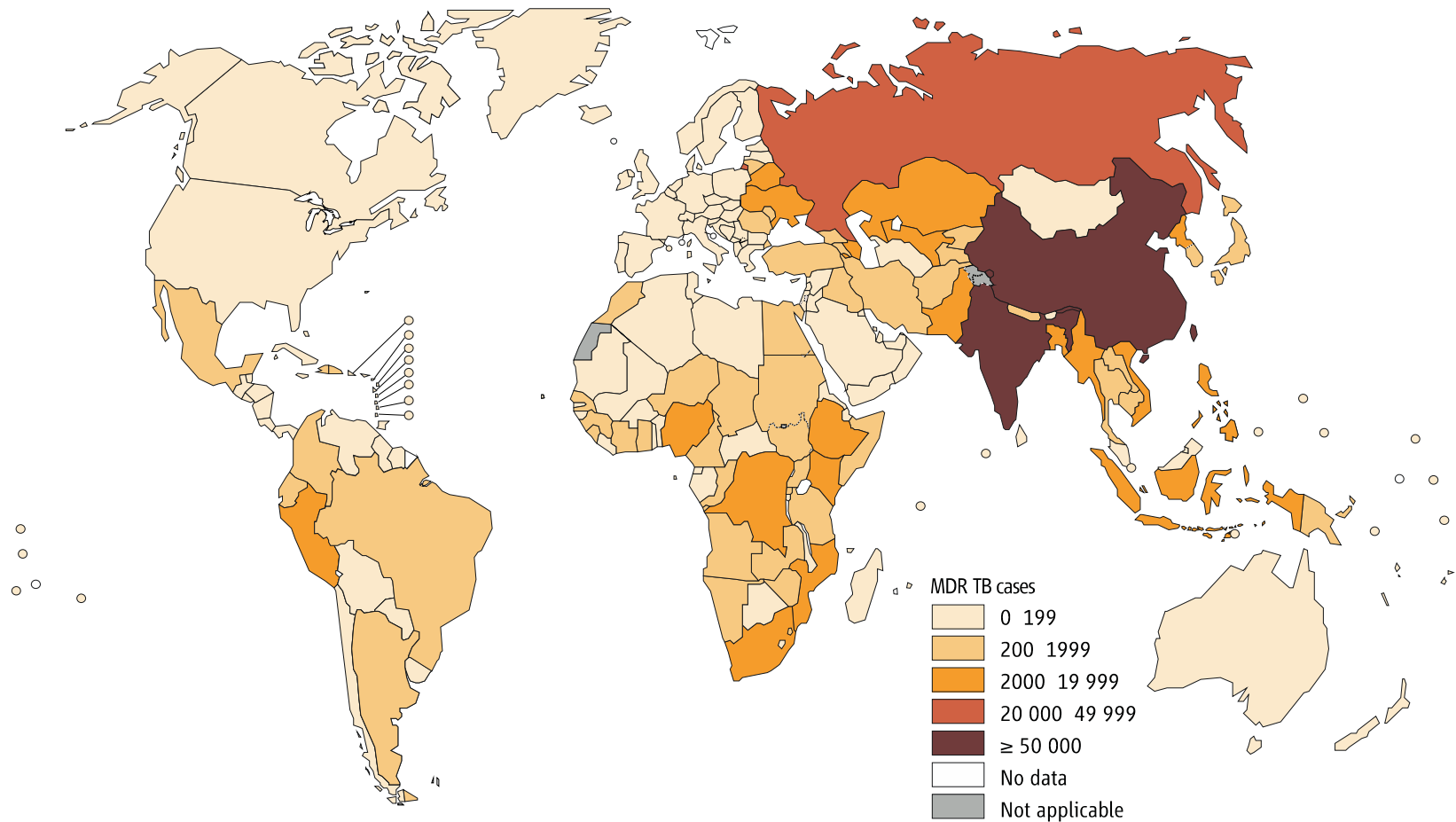
^a Figures are based on the most recent year for which data have been reported, which varies among countries.

MDRTB among previously treated patients – average 20 (13-27)%



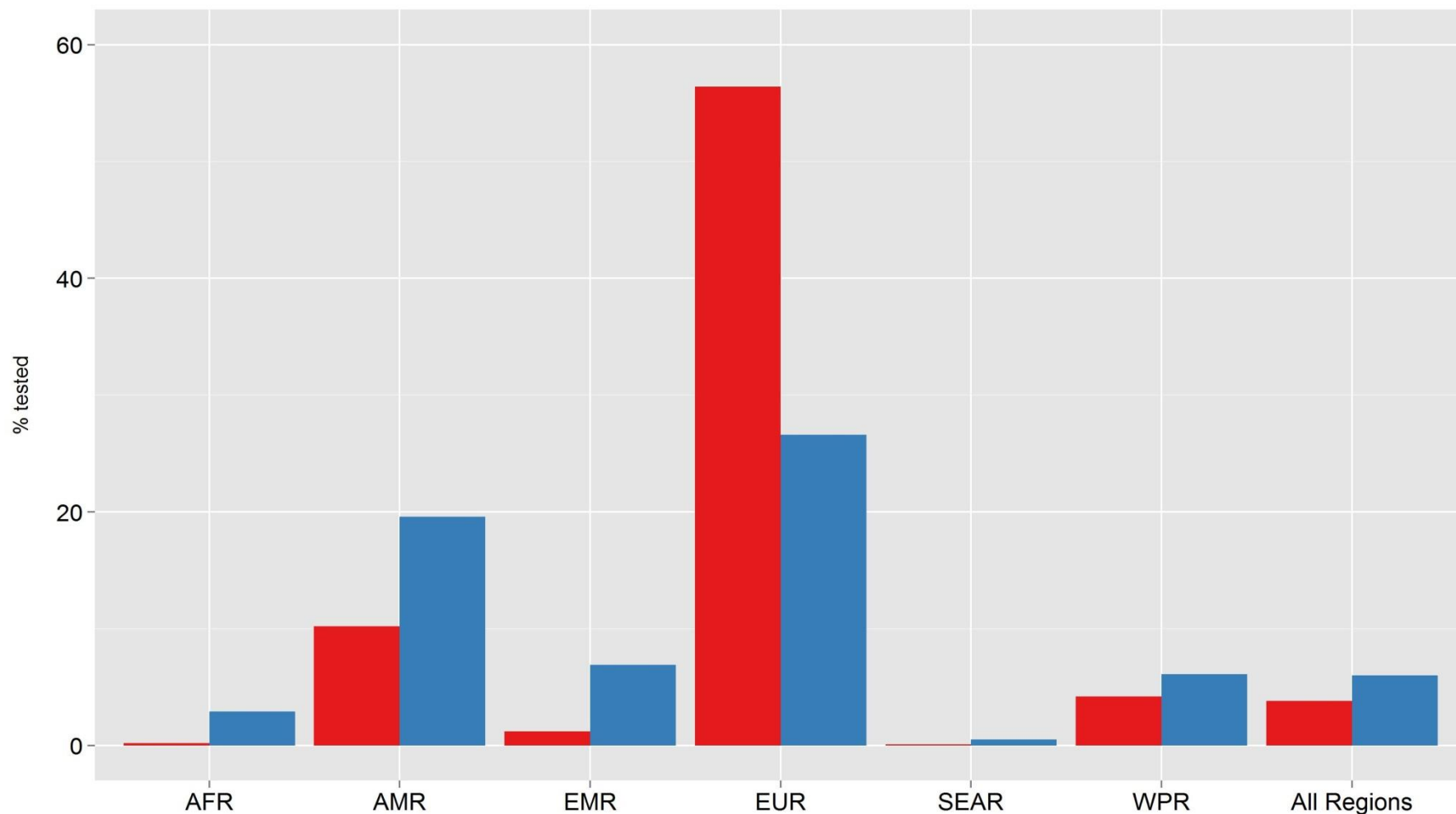
^a Figures are based on the most recent year for which data have been reported, which varies among countries. The high percentages of previously treated TB cases with MDR-TB in Bahrain, Bonaire – Saint Eustatius and Saba, Cook Islands, Iceland, Sao Tome and Principe, and Lebanon refer to only a small number of notified cases (< 10).

Number of MDRTB Cases Among Notified TB Cases, 2012 – only 28% being detected



Diagnostic DST for rifampicin and isoniazid

DST coverage for new (red) and retreated (blue) TB patients,
by region and globally 2011



MDR-TB notification and enrolment

MDR cases reported vs estimated among notified TB, 2012

WHO Region	2012		
	Estimated	Reported	Ratio
African	38,000	18,129	48%
American	7,100	2,967	42%
East Med.	18,000	2236	12%
European	74,000	36,708	50%
S-E Asian	90,000	19,202	21%
West Pacific	74,000	4,473	6%
Global	300,000	83,715	28%

Global Burden of Pediatric MDR-TB



MDRTB in Children – Global Report

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

^a Zignol et al. Multidrug-resistant tuberculosis in children: evidence from global surveillance. *European Respiratory Journal* 2013; 42:701–7.

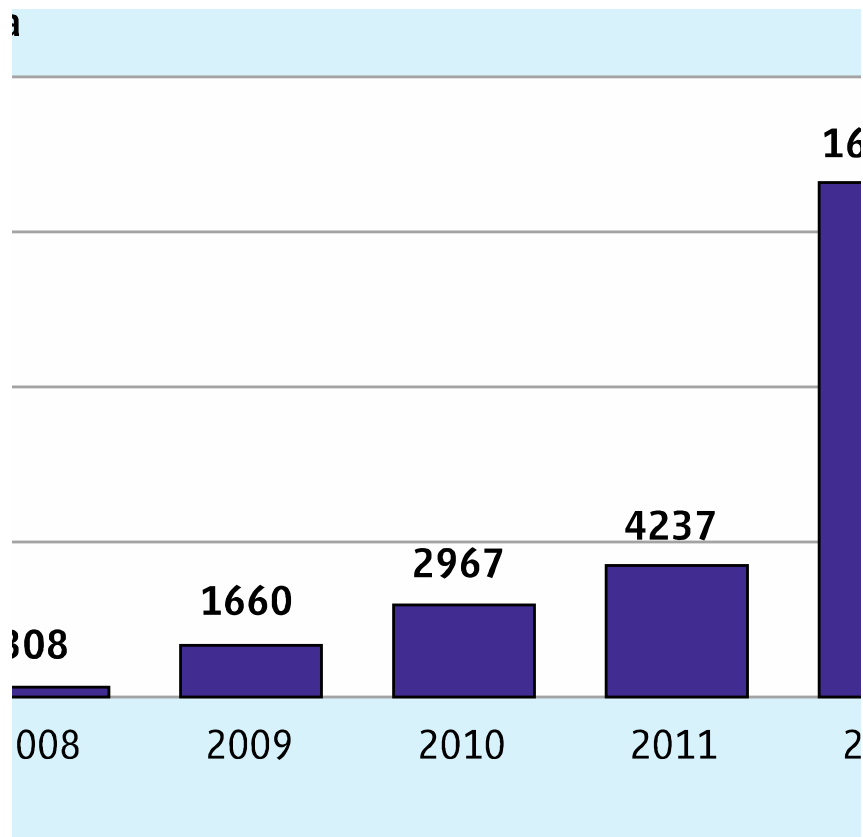
Isoniazid Resistant TB: Systematic Review

(Yuen et al. Ped Infect Dis J 2013 May)

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

Expansion of DST Capacity in Countries, but Children Being Left Out

Increase in MDRTB Diagnosis in India 2008-12



Reasons For Very Few Children

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

Probable MDRTB – Proposed Definition

- Children with signs and symptoms of active TB diseases who in addition have the following risk factors should be considered as having “probable” MDR-TB and started on MDR-TB treatment, even in the absence of bacteriological confirmation:
 - Close contact with a known case of MDR-TB;
 - Close contact with a person who died whilst on TB treatment ;
 - Close contact with a person who failed TB treatment ;
 - Failure of a first-line regimen , recognizing that both bacteriological and clinical definitions of failure should be used;
 - Previous treatment with second-line medications

- All patients considered to have "probable" MDR-TB should be presented to and discussed with a DR TB Centre Committee, and a decision to treat made. This consideration of initiation of SLD ATT therapy without bacteriological confirmation does not replace the need for a thorough and ongoing diagnostic evaluation, including consideration of non-tuberculous causes, prior to the initiation of the SLD ATT.
- Children with central nervous system disease and/or those with other life-threatening manifestations who meet the criteria for "probable" MDR-TB should be initiated on therapy immediately given the high risk of mortality if treatment initiation is delayed whilst awaiting the confirmation of the DR TB Centre Committee to initiate treatment.
- More detailed and specific operational criteria regarding the points above are necessary for implementation in the field .

Drug resistant TB in children (Africa)

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

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

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

^a*P* values compare differences among all 3 groups.

^bDifference between last 2 surveys was not significant.

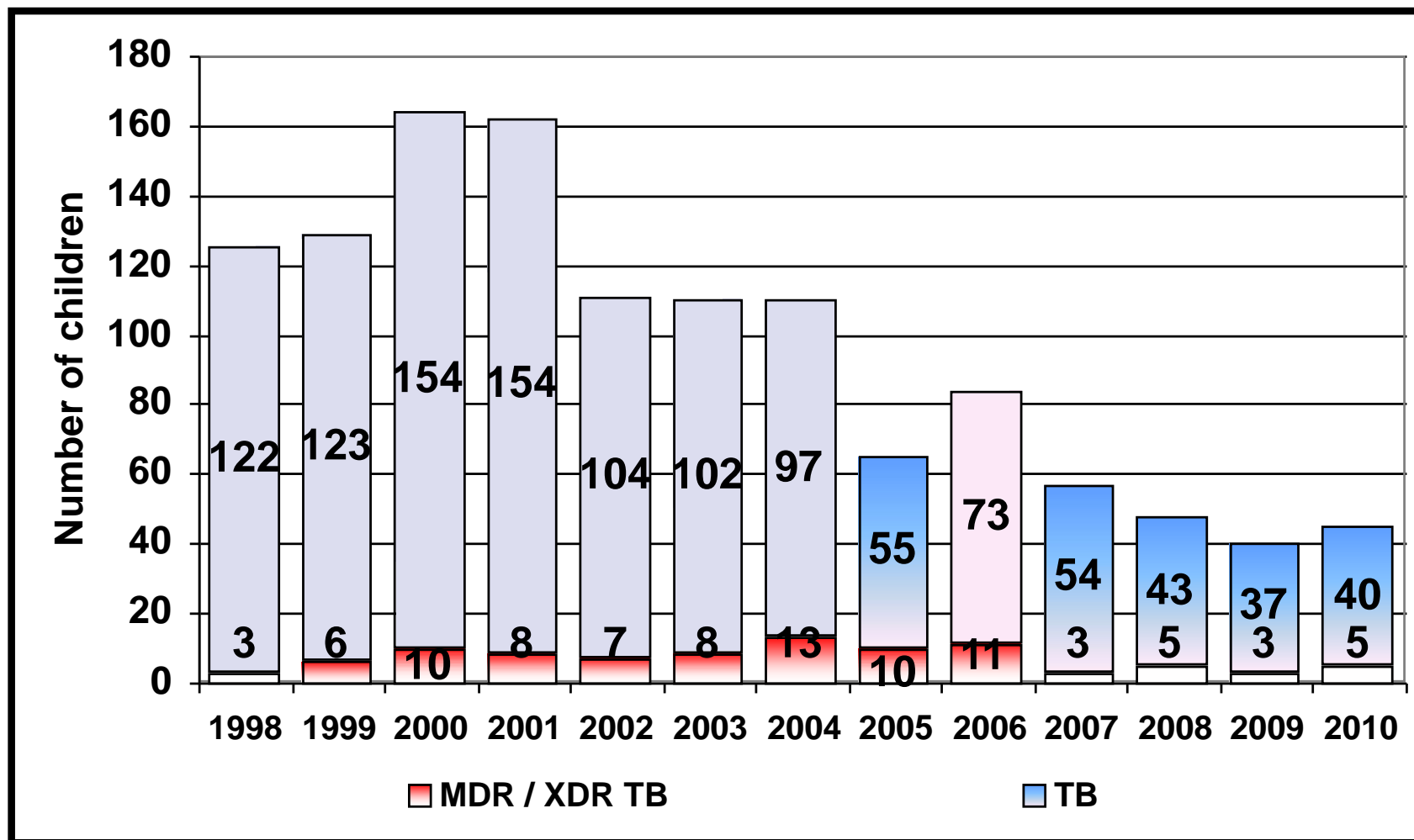
- previously treated children had significantly more drug resistance than did new TB cases (19 of 66 [28.8%] vs 24 of 225 [10.7%]; odds ratio = 3.39)
- HIV infection not significantly associated with drug resistance

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

Drug resistant TB in children in India

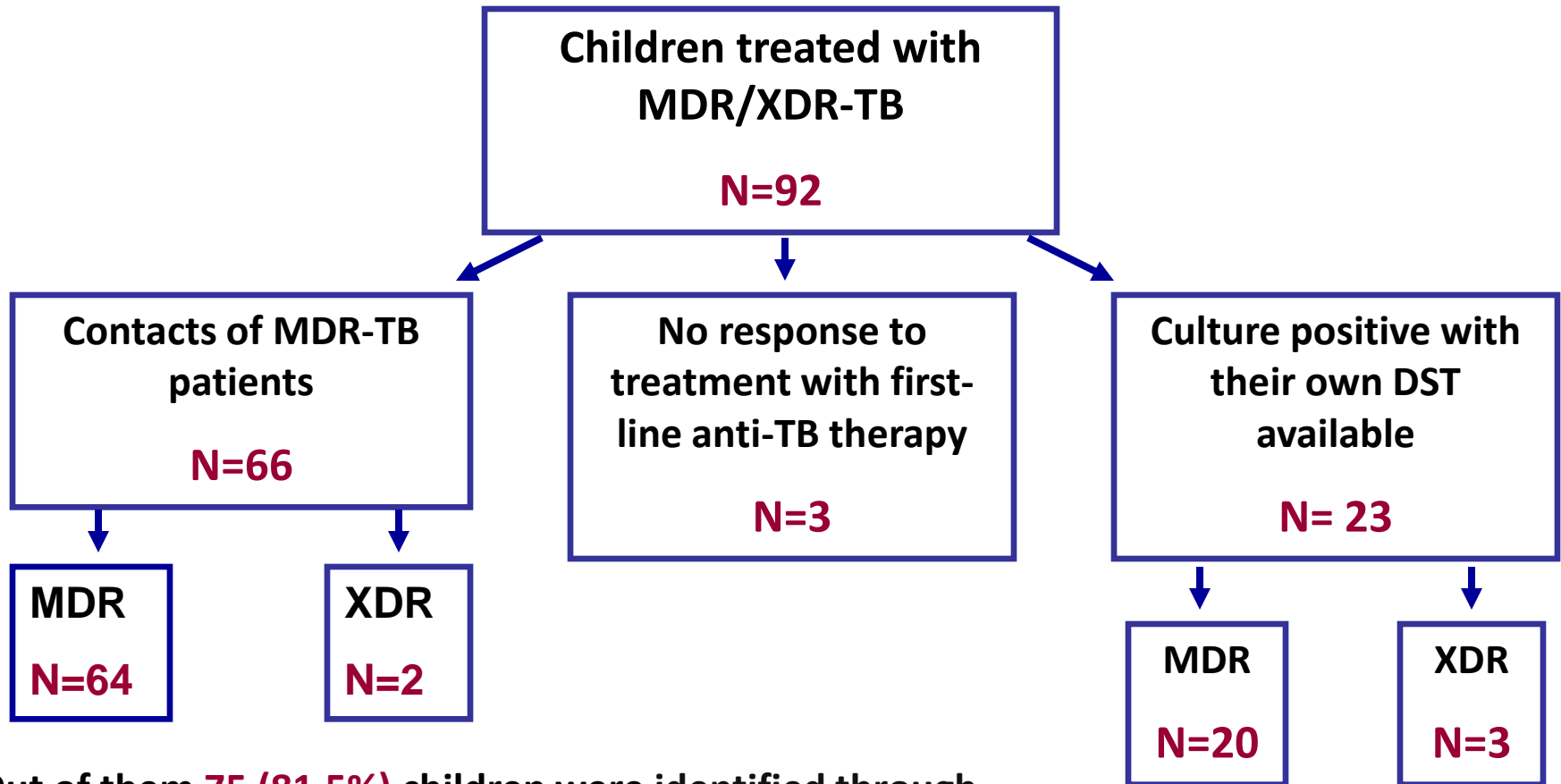
Author, year	Source	No. of children with M.tb positive cultures	Drug resistance
Jawahar MS, TRC, 1990	Lymph Node	96	Isoniazid: 10% Streptomycin: 2%
Ramachandran P, TRC, 1992	CSF	88	Isoniazid : 14% Streptomycin : 8% MDR: 2%
Swaminathan, TRC, 1996	Sputum/Gast ric Lavage	201	Isoniazid: 10% Streptomycin: 9% MDR: 3.5%
Singh, M, PGI	Sputum/GL	30	MDR: 6%
I Shah, Mumbai	Induced Sputum/GL	500	MDR: 5%

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



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

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



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

Pediatric TB: The Litmus Test for TB Control

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

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

Contacts of MDRTB Patients: Systematic Review (Shah et al. Clin Infect Dis in press)

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

Time for targets

We need to:

- 1. Estimate global burden**
- 2. Identify (so we can begin to monitor) treatment gap**

Time for targets

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

Target 1

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

How many kids in their homes?

(use estimate of average hh size X % <15 y)

Answer = Target 1

**ALL should be:
enumerated AND evaluated**

Target 2

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

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

(a) at time of MDR pt dx ?

(b) during some follow-up i.e. 12 mo ?

$a+b = \text{Target 2}$

Target 3

Start again from Target 1:

kids in MDR-TB hhs

How many expected to have LTBI

(use estimates from lit, other sources)

(a) at time of MDR pt dx

(b) during some follow-up i.e. 12 mo

$a+b = \text{Target 3}$

3 targets: child contacts in MDR hhs

Target 1: # kids to enumerate & evaluate

**Target 2: # kids who require treatment
for active TB**

**Target 3: # kids who require treatment
for LTBI, or
'watch & wait' (& actually watch)**

Parameters to get started

1. **average # of <15 y in household**
2, but 1 in China
2. **% active TB in <15 y in 12 months**
2.5%
3. **% LTBI in <15 y in 12 months**
23.5%

Can be refined, of course.

Example: India

99000 incident MDR-TB patients (2011 estimated)

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



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

**Multiply 1,98,000 by 23.5% (LTBI in 12 mo) =
Target 3: 46530 children**

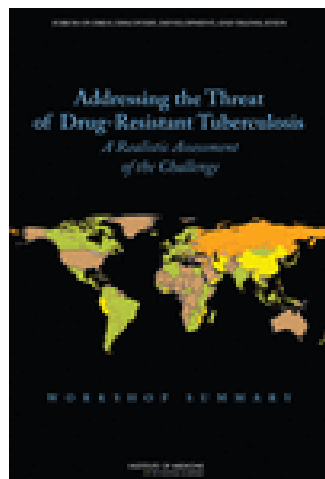
First pass – to be refined

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

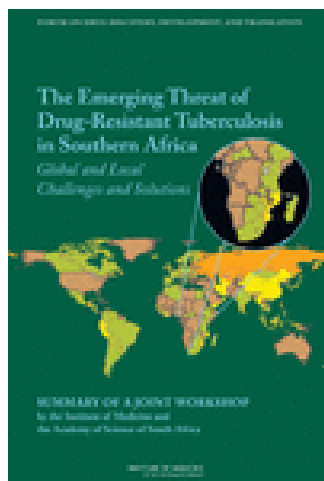
Region	# MDR inc cases 2008	TARGET 1	TARGET 2	TARGET 3
SEARO	136,129	272,258	3,403	31,990
WPRO	124,207	148,414	3,105	29,189
EURO	80,530	161,060	2,013	18,925
AFRO	63,100	126,200	1,578	14,829
EMRO	22,488	44,976	562	5,285
AMRO	8,676	17,352	217	2,039
TOTAL	435,130	770,260	10,878	102,256

 
Treatment gap

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



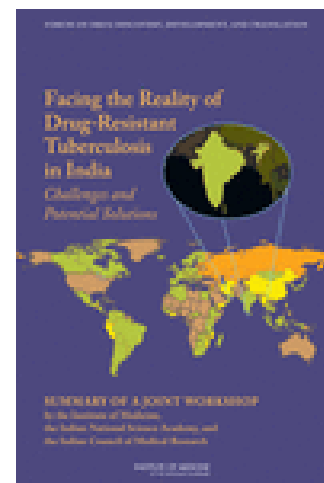
Washington, DC
USA
Nov. 2008



Pretoria,
South Africa
March 2010



Moscow,
Russian Federation
May 2010



Delhi, India
April 2011



» The Sentinel Project on Pediatric Drug-Resistant Tuberculosis



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

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

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