PRINCIPLES OF TB EPIDEMIOLOGY IN CHILDREN INCLUDING CONTACT INVESTIGATION

ANNEKE C. HESSELING
DESMOND TUTU TB CENTRE
STELLENBOSCH UNIVERSITY
IMPAACT TB TRAINING
29 MAY 2017

International Maternal Pediatric Adolescent AIDS Clinical Trials Group

Estimates for TB in children have doubled since 2013
Only 1/3 of children with TB are reported to WHO

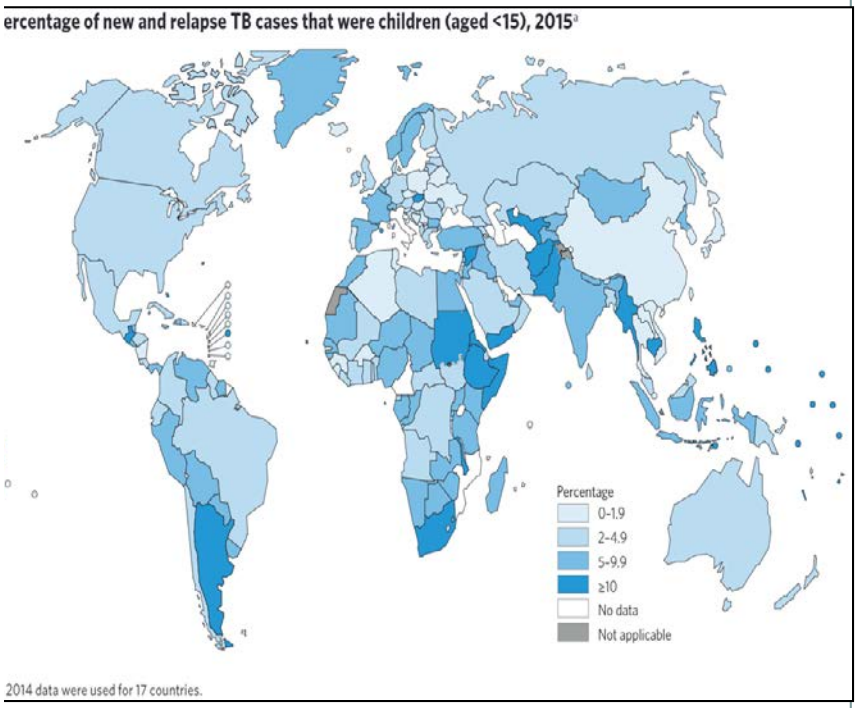
TB in children (0-14 yrs)
actual reported to WHO
2015 - 384,035 ↑ 7%
2014 - 358,956 ↑ 30%
2013 - 275,851

Best estimates:
2015 – 1 million cases and 210,000 deaths (HIV+ and HIV-)

2013 - 550,000 cases and 80,000 deaths (deaths only HIV negative)

Accounts for **10.5%** of the global caseload; higher in high-burden settings

"Know your epidemic"



GLOBAL TB PROGRAMME

World Health Organization

	Children younger than 5 years	Children aged 5–15 years
Number of children sharing household with an individual with tuberculosis*	5 354 128 (4 814 454–5 953 851)	9 969 007 (8 951 616–11 099 616)
Number of children infected with *Mycobacterium tuberculosis* in 2010†	2 645 968 (2 020 926–3 474 245)	4 946 152 (3 780 256–6 498 346)
Number of children infected with *M tuberculosis* at the end of 2010†	6 530 442 (4 993 555–8 518 986)	46 864 335 (36 110 021–60 525 588)
Number of children developing tuberculosis in 2010†	327 237 (205 206–494 575)	281 431 (134 237–526 014)

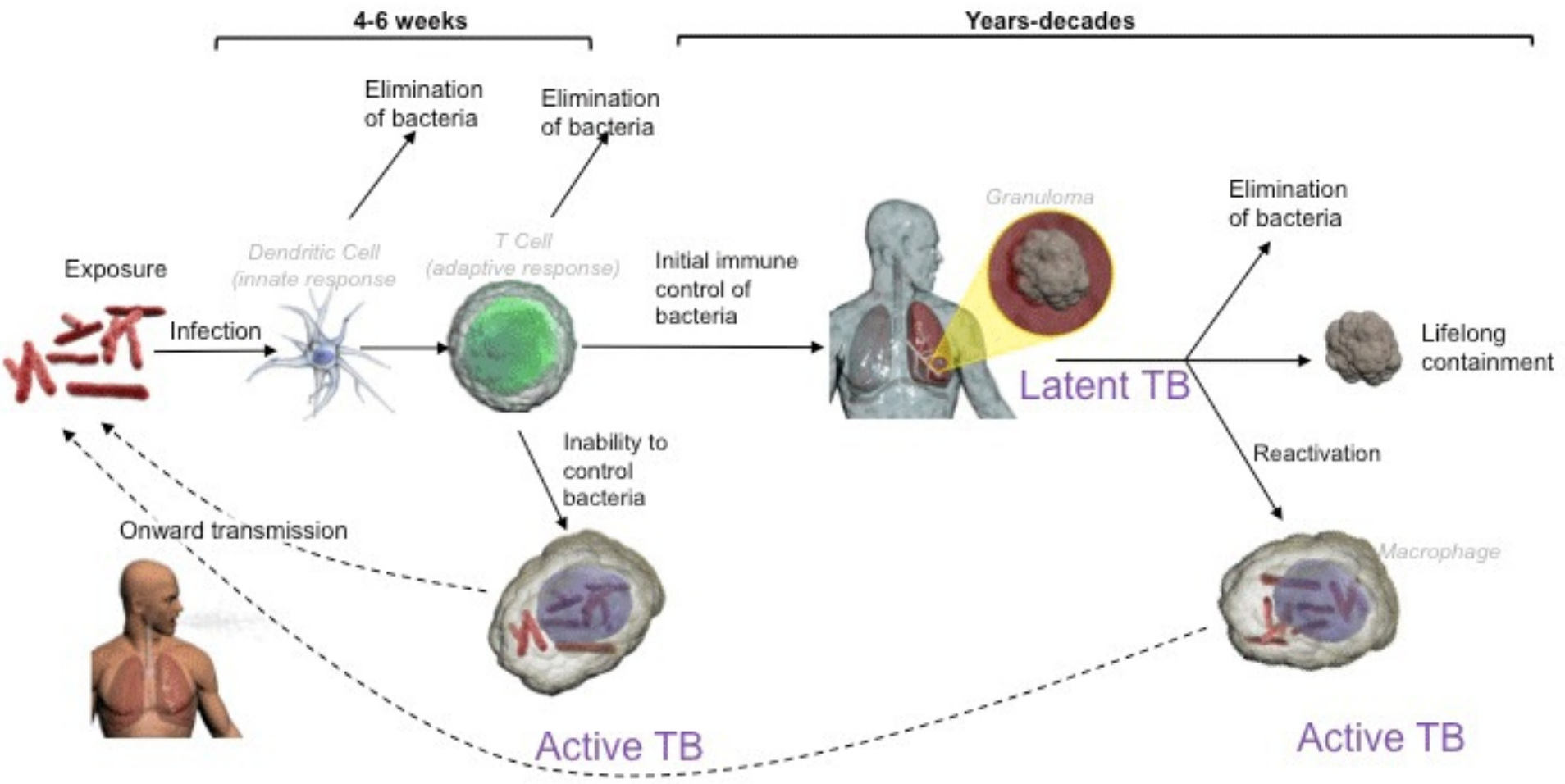
Data are median (IQR). *From household model. †From community model.

Table 1: Estimates of tuberculosis exposure, latent infection, and disease in children in 22 high-burden countries in 2010

"The incidence of paediatric TB is higher than the number of notifications, particularly in young children.
Estimates of current household exposure and cumulative infection suggest an enormous opportunity for preventive treatment."

Dodd, Seddon. Lancet Global Health, 2014

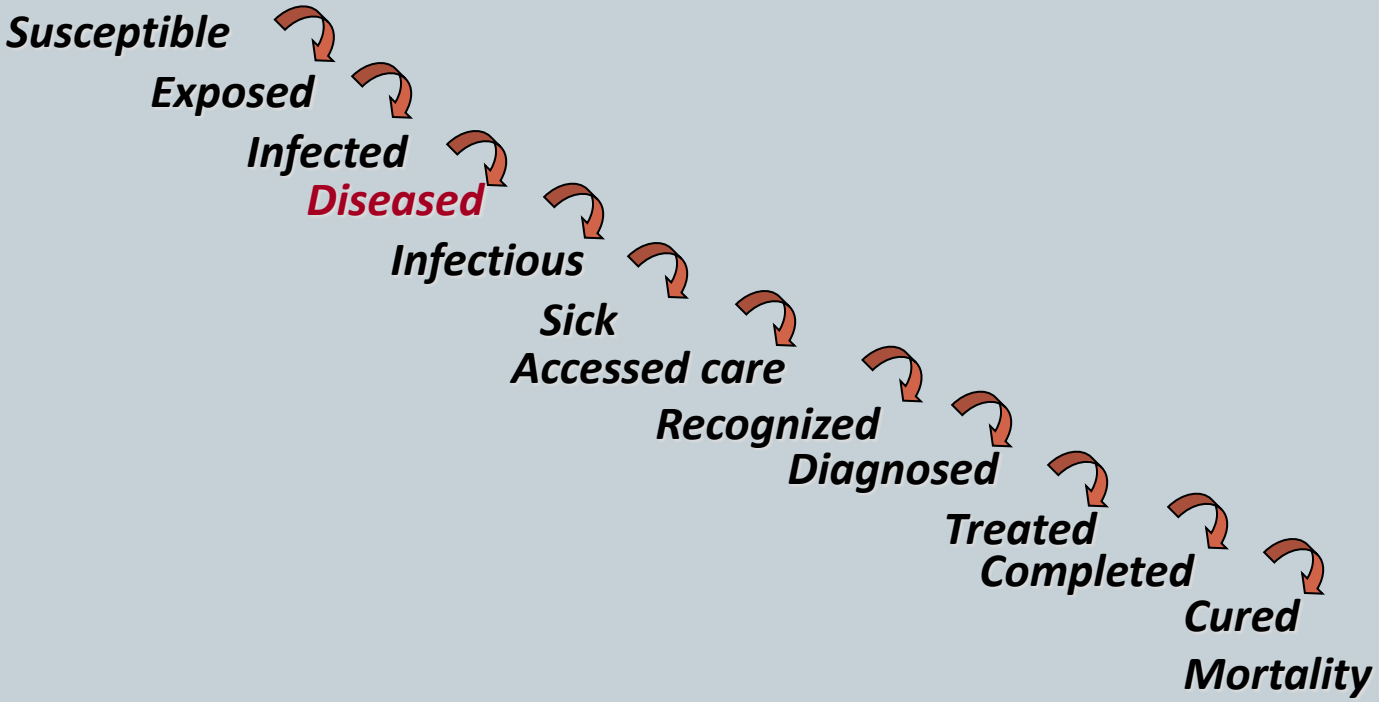
Natural history of *M.tb* infection



www.oxfordimmunotech.com Online

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

Key transitions in tuberculosis

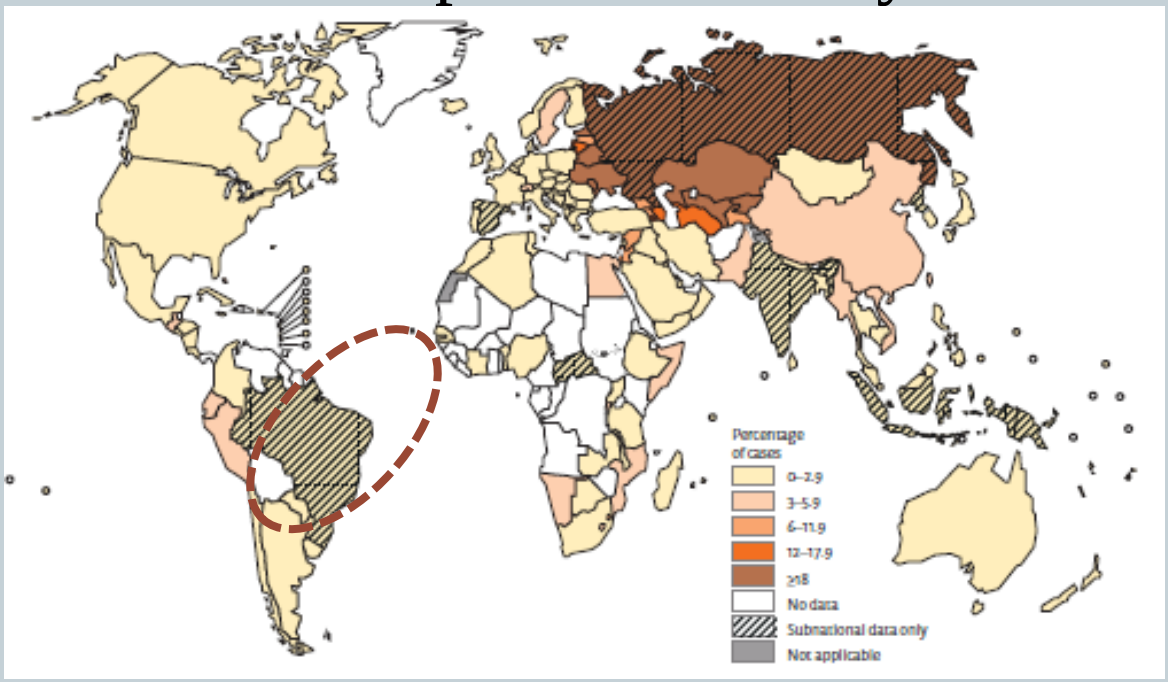


Don Enarson, The Union

Global MDR TB Burden

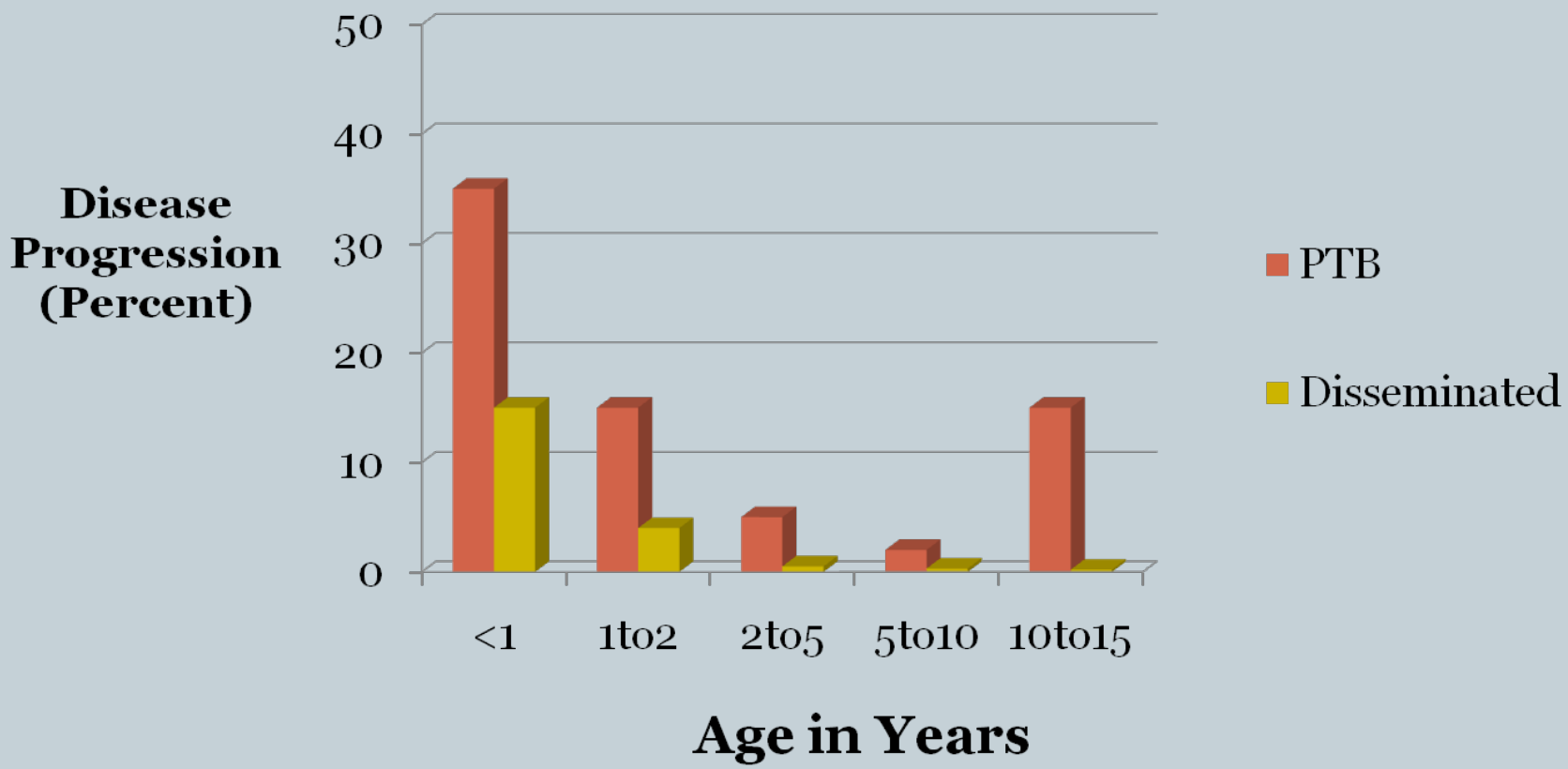
Globally >500 000 (MDR) TB cases in 2014

- 30 000 estimated paediatric MDR-TB cases annually
- At least 500 000 children exposed annually to MDR-TB



Percent of new TB cases with MDR TB: Global TB Report 2015

Age related TB disease risk in children



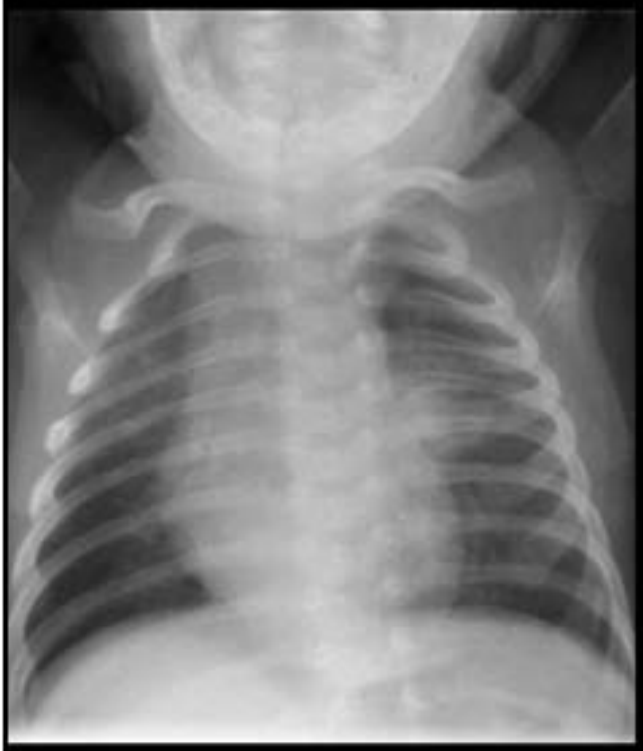
Marais et al. Int J Tuberc Lung Dis. 2004

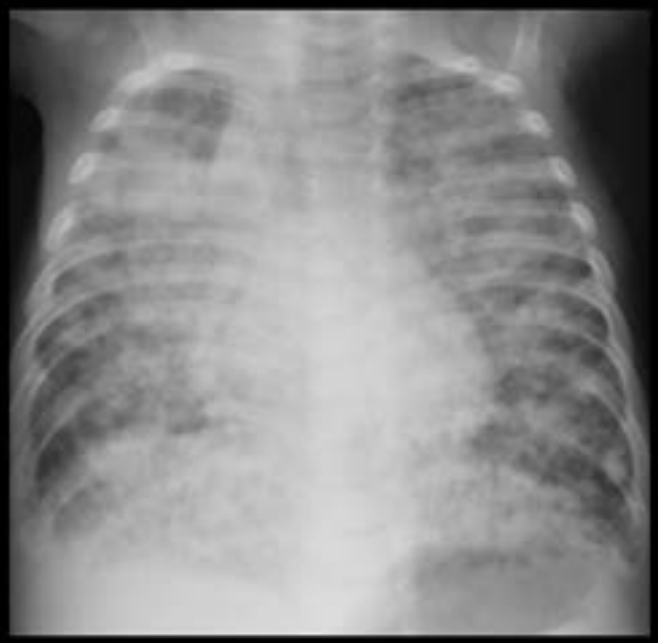
Historical public health approach to TB control and children

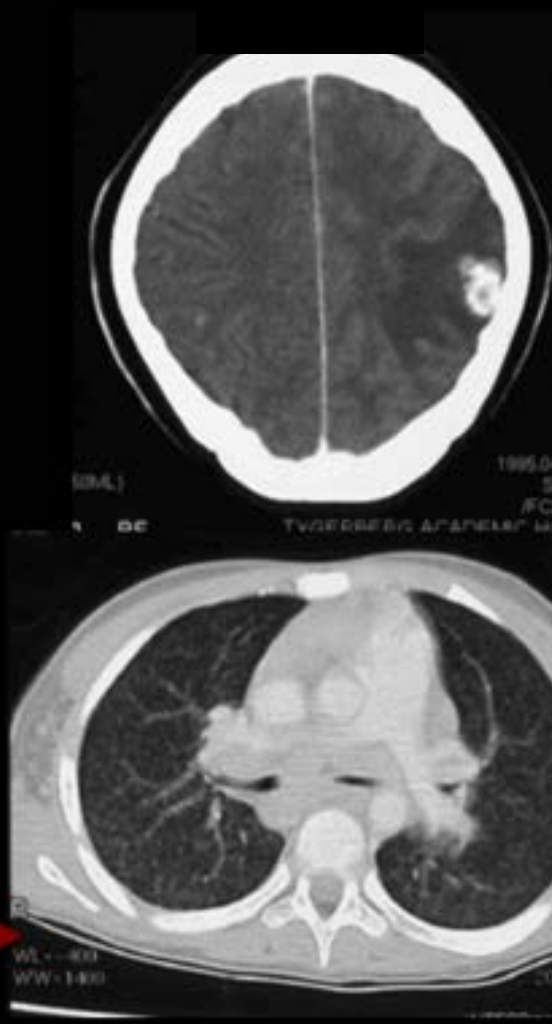
- Proper identification and treatment of infectious (adult) cases will also prevent childhood TB
- Childhood TB historically afforded low priority by NTP
  - Diagnostic challenges
  - Usually not infectious
  - Limited resources
  - Lack of recording and reporting
  - **Disregard for morbidity and mortality and opportunities for TB prevention**

NON-SEVERE TB

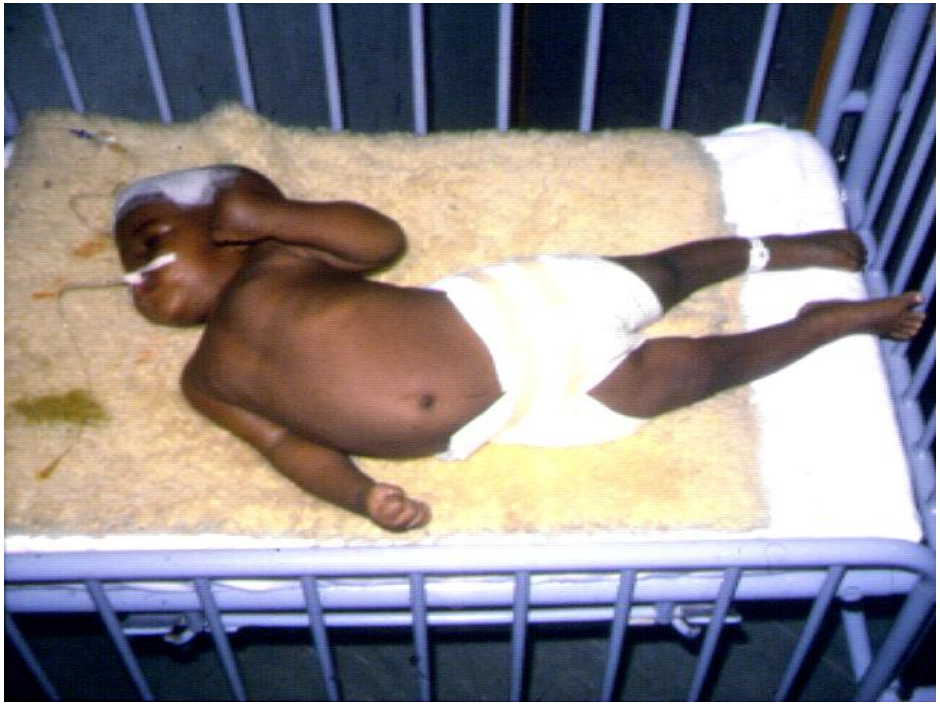
SEVERE TB (INCLUDING DISSEMINATED)







"A deterioration in the control of TB thus immediately hurts the youngest generation"



Rieder, 1997

Epidemiological relevance of TB in children

- Indication of epidemic control: failure of health systems
- Recent transmission: DS, DR-TB
- Unique spectrum and severity of disease especially in young
- Childhood TB is an epidemiological "sentinel event"

Children reflect TB transmission including MDR-TB

DST results	2003-05	2005-07	2007-09	2009-2011%
All cult+ cases	323 (%)	291 (%)	294 (%)	340 (%)
DSTs done*	320 (99.1)	285 (97.9)	292 (99.3)	340 (100)
Any DR	41 (12.8)	43 (15.1)	45 (15.4)	49 (14.4)
INH mono-R	22 (6.9)	22 (7.7)	15 (5.1)	19 (5.6)
RMP mono-R**	0	2 (0.7)	4 (1.4)	6 (1.8)
MDR-TB	19 (5.9)	19 (6.7)	26 (8.9)	24 (7.1)

Schaaf, IJTLD 2016

*Significant differences: RMR increase from 1st to 4th period: p = 0.03

Incomplete registration of hospital-diagnosed child TB cases: need for comprehensive surveillance

	Not registered n=101 (37.8%)	**Registered n=166 (62.2%**	**p-value**
Clinical factors			
Disseminated TB	29 (28.7)	27 (16.3)	0.015*
Miliary TB	12 (11.9)	16 (9.6)	0.562
TB Meningitis	22 (21.8)	13 (7.8)	0.001*
Deaths prior to referral	10 (9.9)	0 (0.0)	<0.001*
Type of consultation			
Outpatient	16 (15.9)	41 (24.7)	0.087
Inpatient	85 (84.2)	125 (75.3)	
Admission (days)	16 (5, 29)	3 (9, 20)	0.052

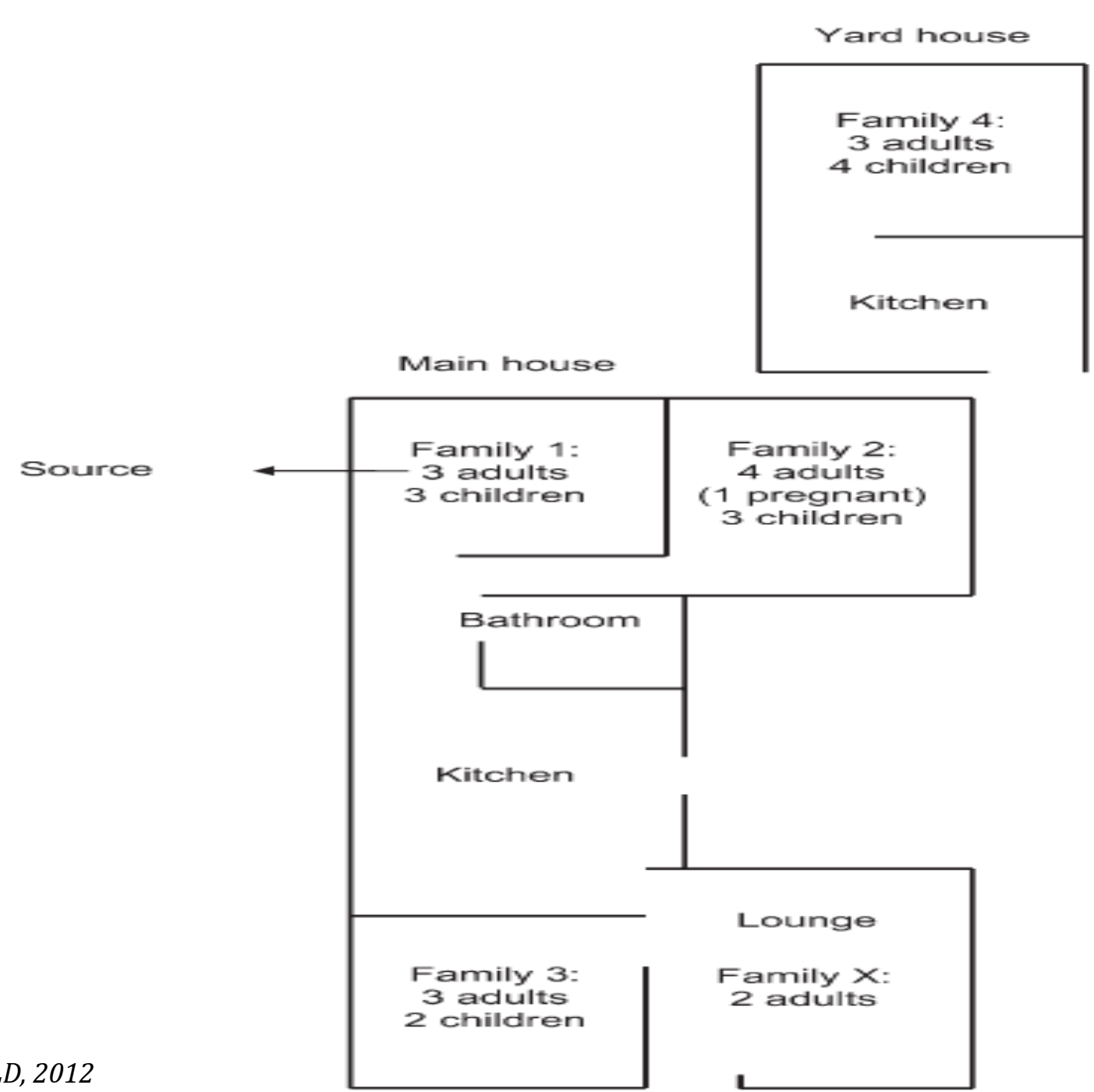
Du Preez, PHA, 2012

TUBERCULOSIS

YOUR KISS OF AFFECTION
THE GERM OF INFECTION

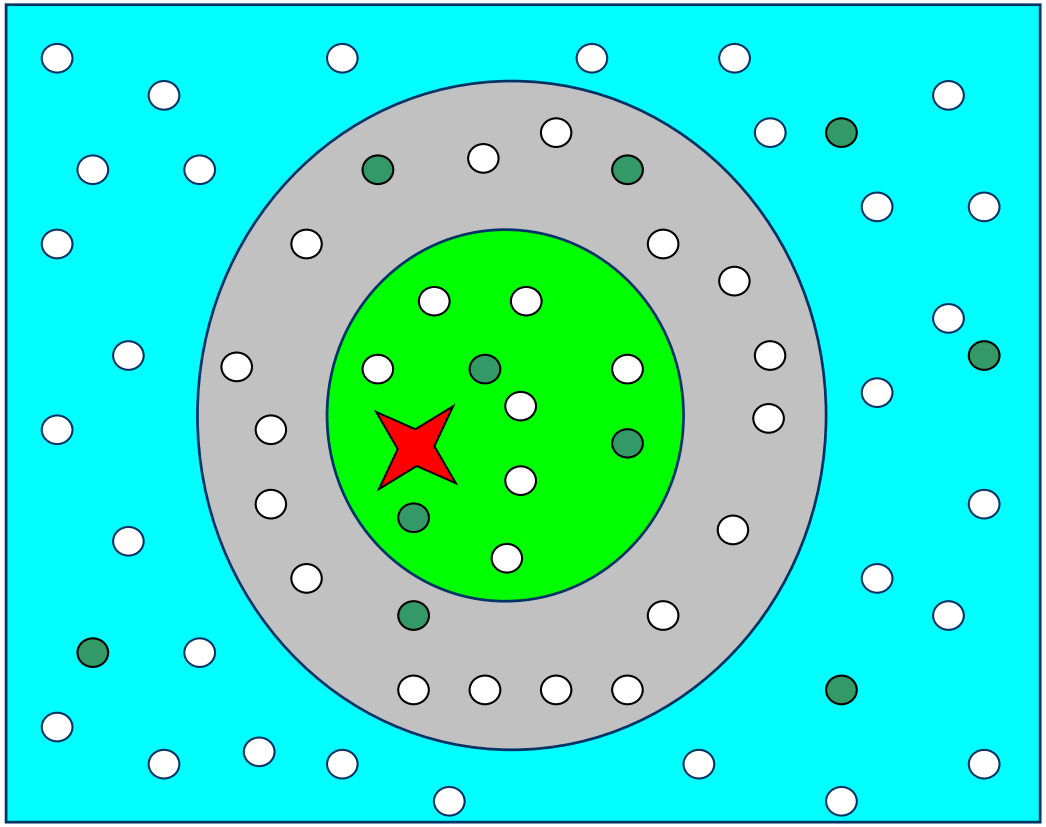
TOWN OF HEMPSTEAD, W.H. RUNCIE MD. HEALTH OFFICER
WPA FEDERAL ART PROJECT DISTRICT 4


ORIGINAL



Van Wyk, IJTLD, 2012

Key Transitions in TB : Who gets infected?



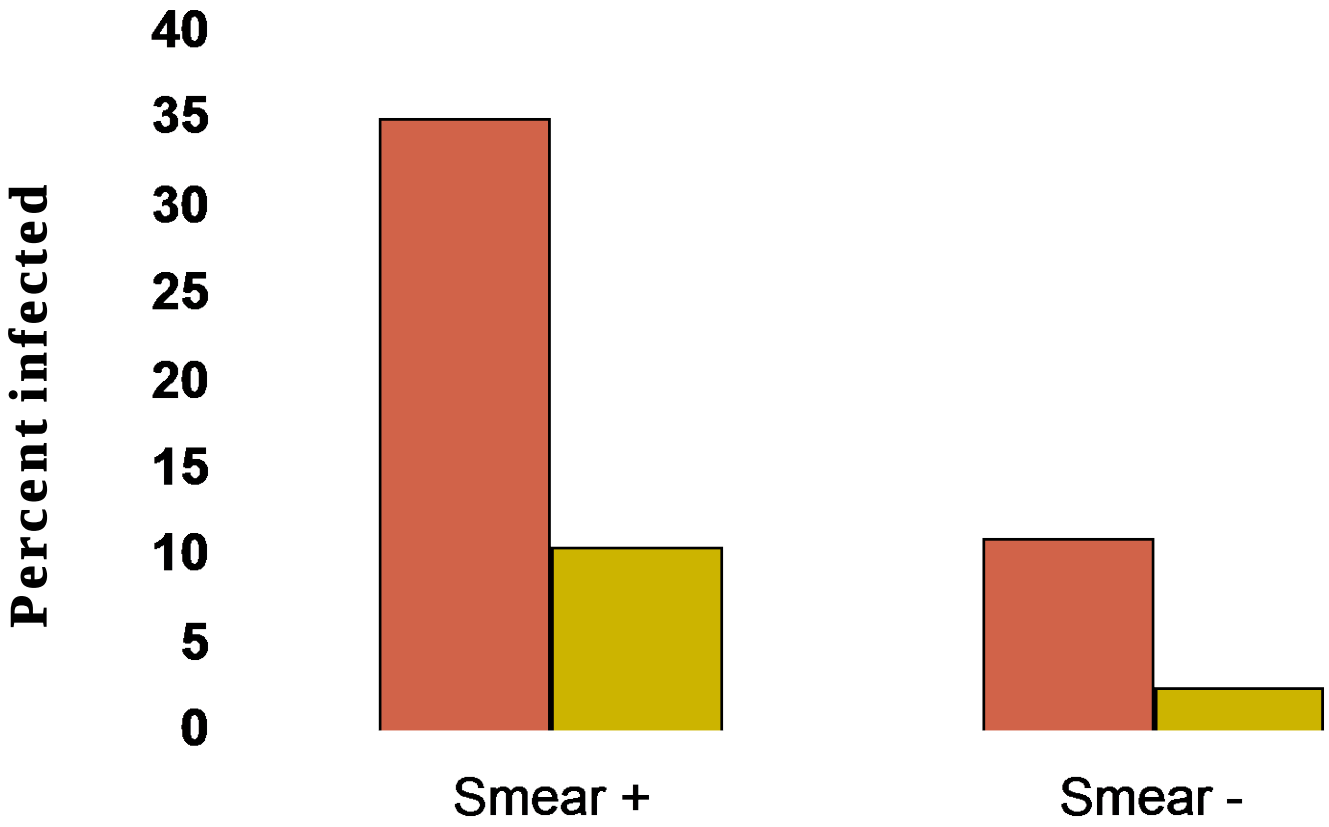
Casual

Intermediate

Close

From: Rieder Epidemiologic Basis of Tuberculosis Control

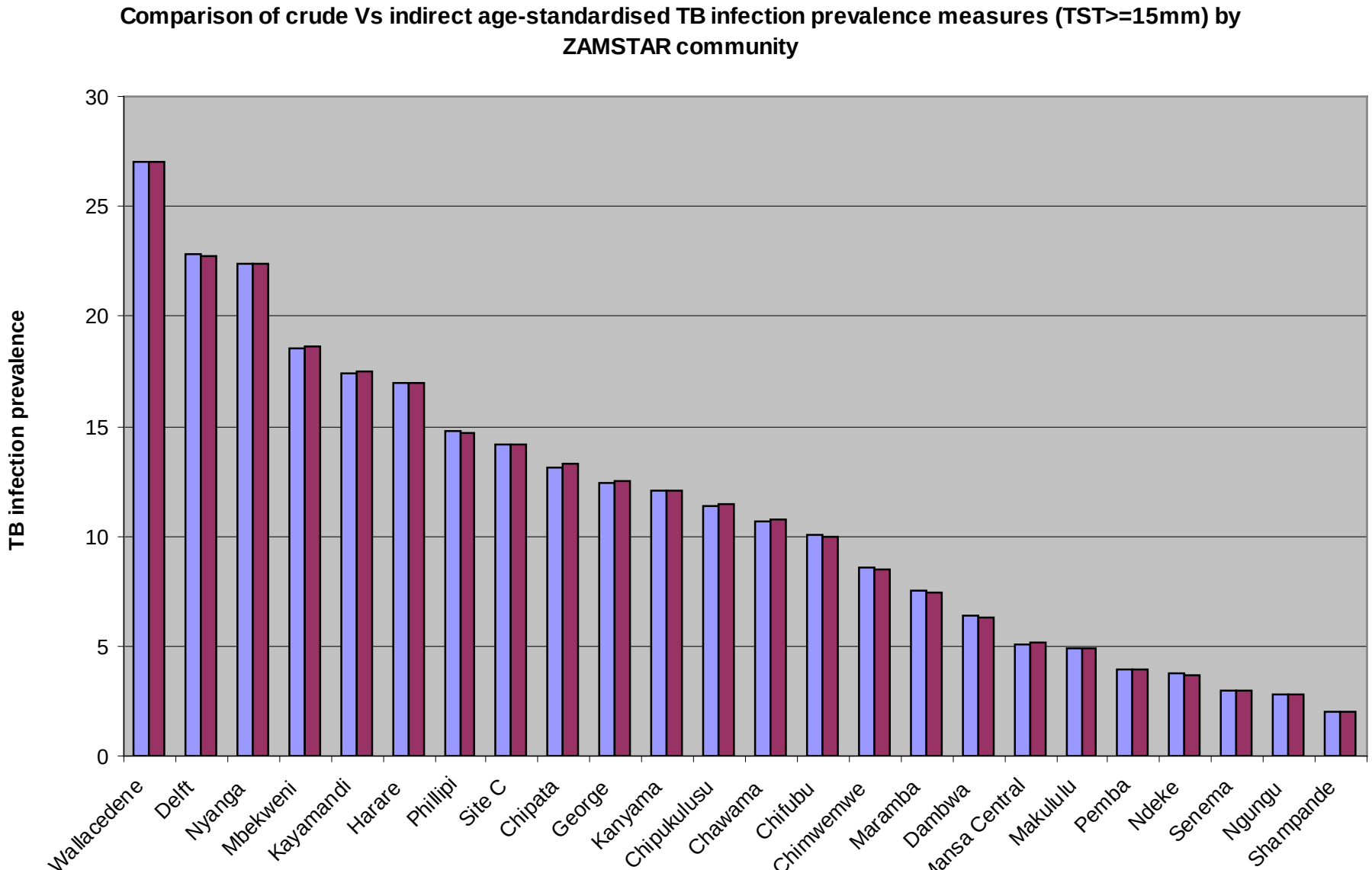
Risk of TB infection



Tuberculous Infection Among Children by Type of Contact and Bacteriologic Status of Index Case, British Columbia and Saskatchewan, 1966 - 1971

Grzybowski S. Bull Int Union Tuberc 1975

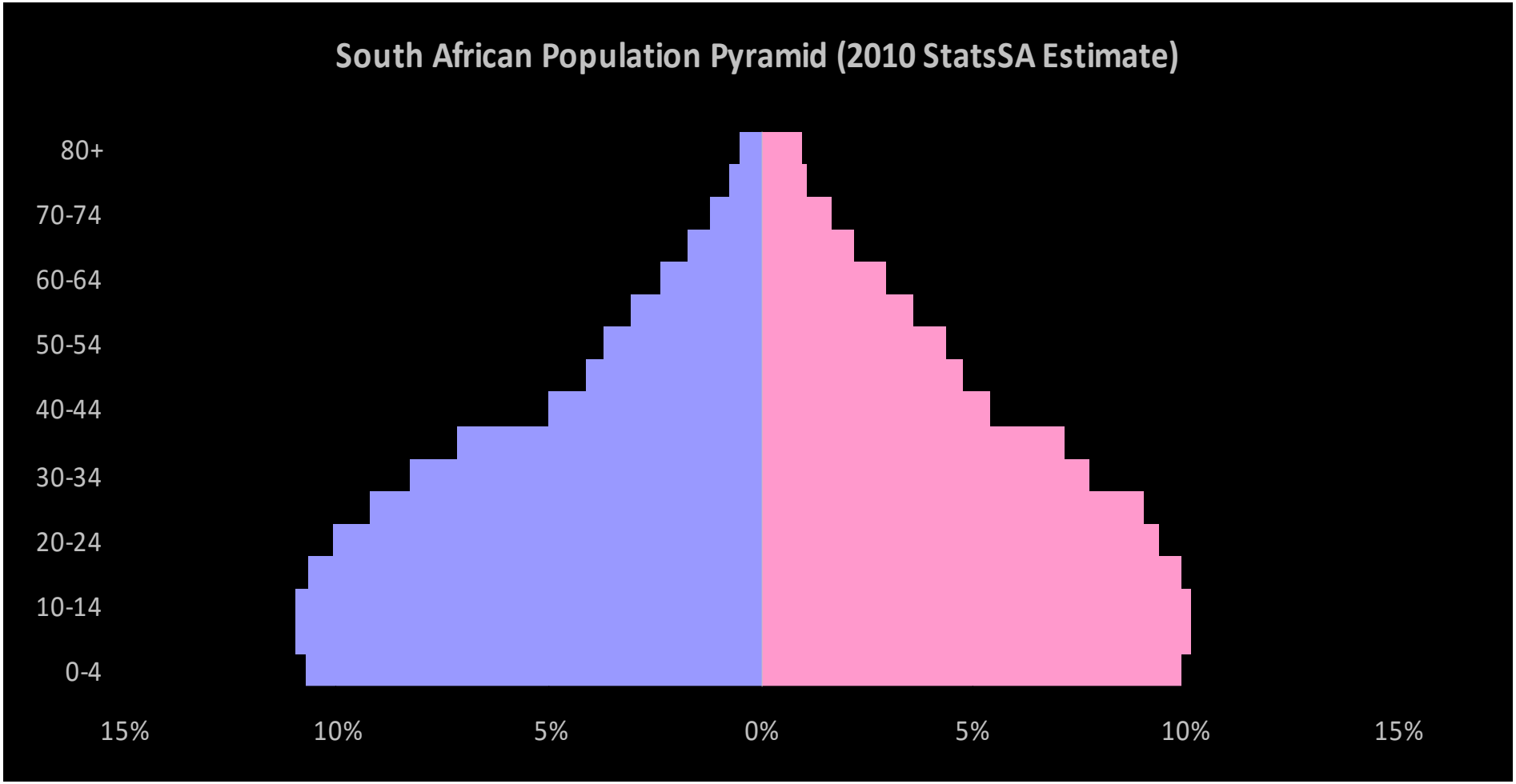
Age standardised prevalence of *M.tb* infection in children (Mantoux test done n=25 048, read n= 22 563)

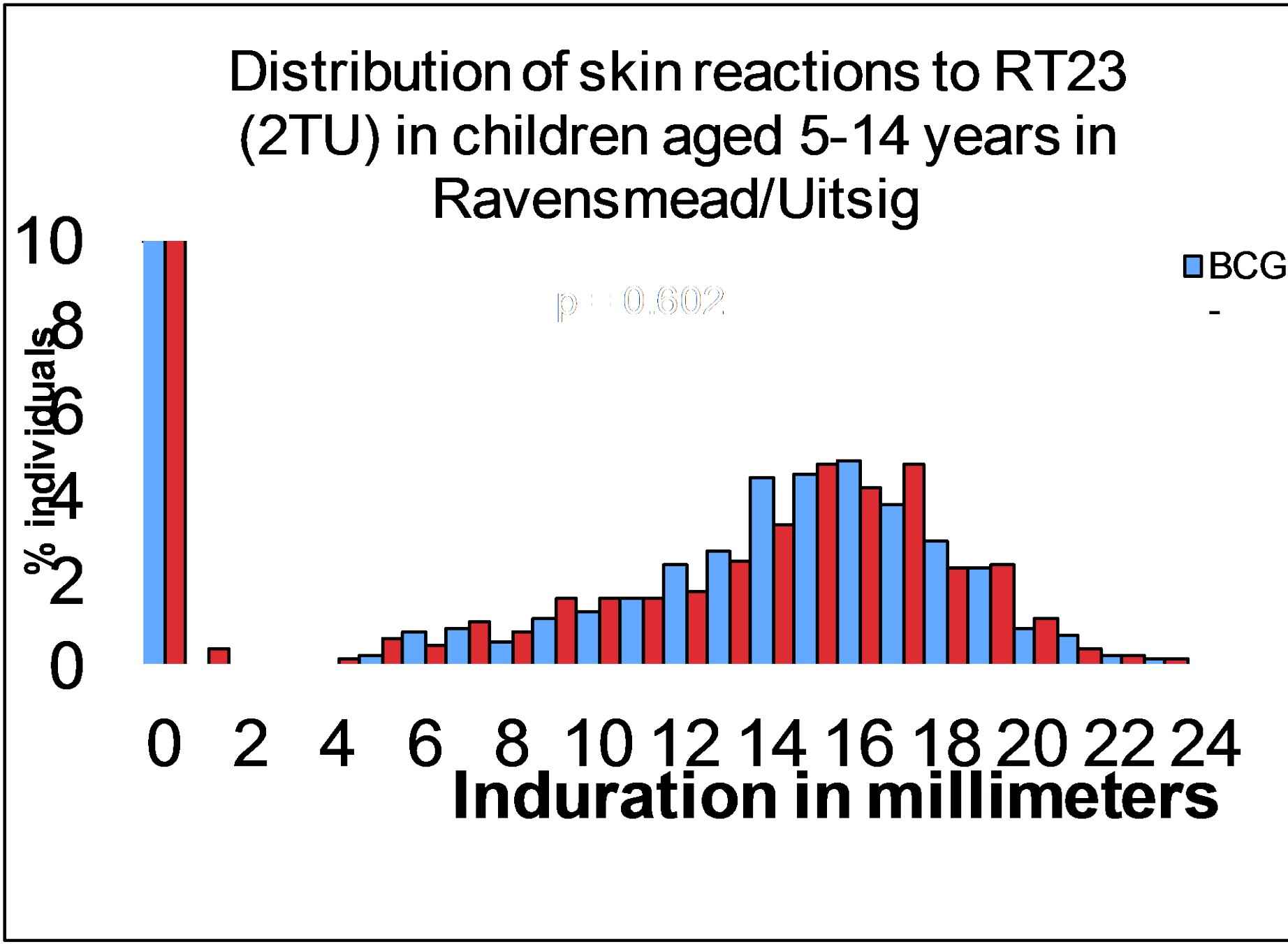


Annual risk of TB infection (ARTI)

- Zambia: 2.8%
- South Africa: 4.2%

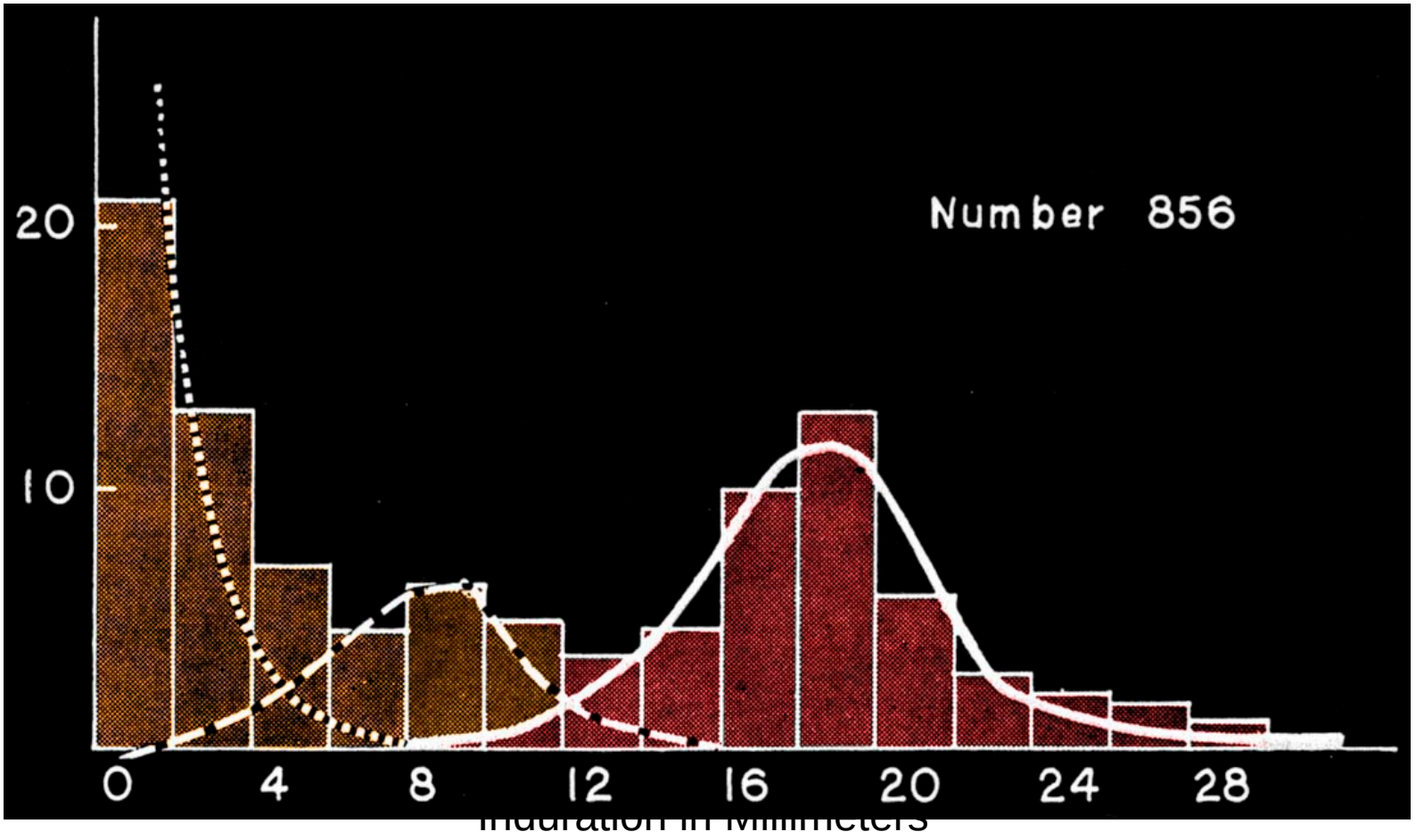
Shanaube, PLOS One, 2010


South African Population Pyramid (2010 StatsSA Estimate)
80+
70-74
60-64
50-54
40-44
30-34
20-24
10-14
0-4
15%
10%
5%
0%
5%
10%
15%


Distribution of skin reactions to RT23 (2TU) in children aged 5-14 years in Ravensmead/Uitsig
p = 0.602
BCG
-
% individuals
10
8
6
4
2
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Induration in millimeters

Verteilung der Indurationsdurchmesser nach 5 TU PPD (RT):

Schulkinder, Oberer Nil, Sudan (n=856)

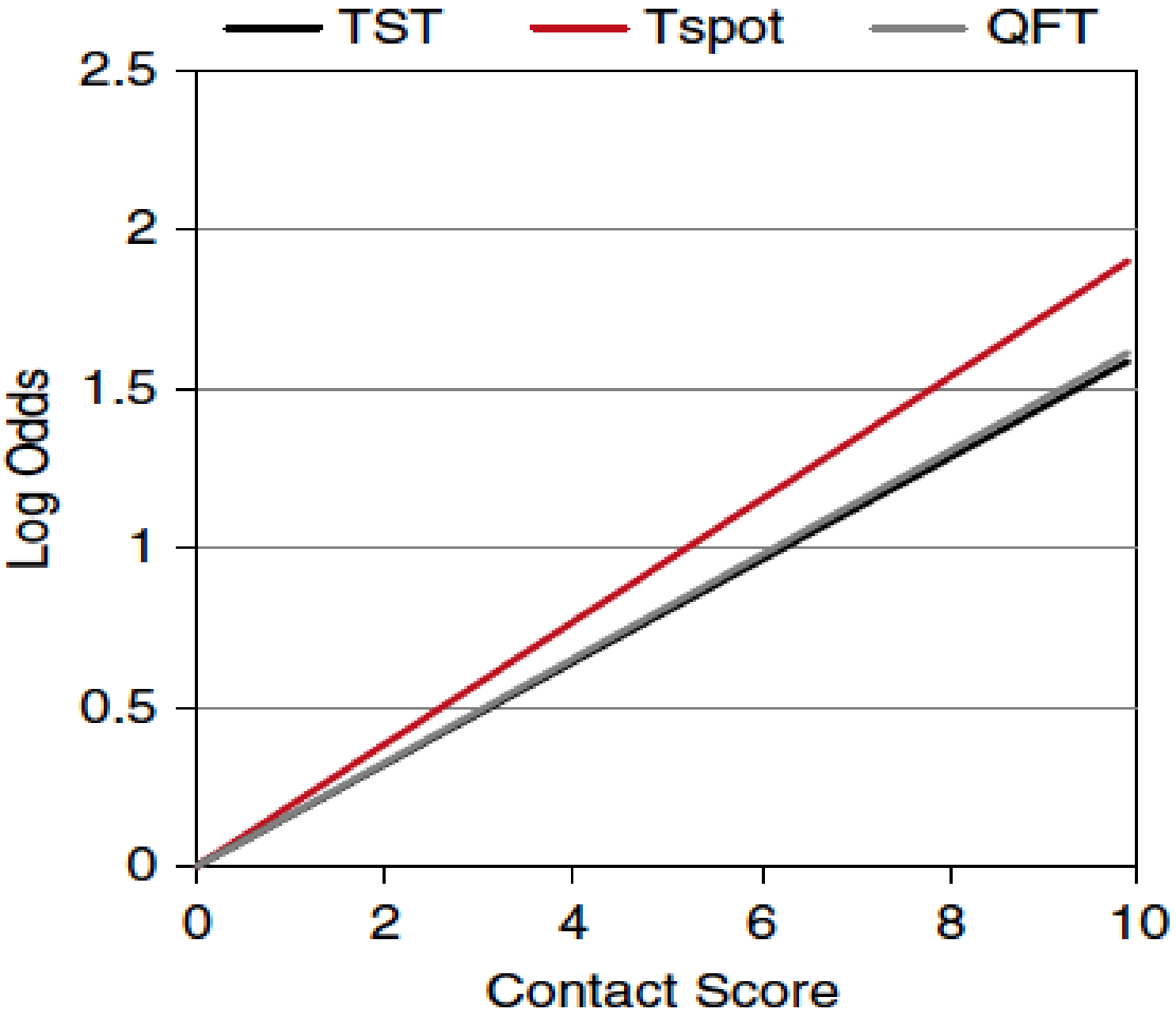


WHO Tuberculosis Research Office, 1955 und 1956

IGRA diagnostic accuracy for definite/probable TB

Index test	Sensitivity		Specificity	
	Participants (studies)	**Sensitivity (95%CI)**	Participants (studies)	**Specificity (95%CI)**
TST 5 mm	265 (13)	**91 (84-98)**	217 (4)	**70 (17-100)**
TST 10 mm	321 (15)	**84 (75-93)**	276 (5)	**88 (62-100)**
TST 15 mm	389 (11)	**67 (50-83)**	131 (3)	**92 (71-100)**
QFT-G	74 (5)	**92 (82-100)**	82 (1)	**35 (0-80)**
QFT-IT	393 (13)	**77 (65-88)**	568 (6)	**92 (86-100)**
QFT-G/QFT-IT combined	431 (17)	**83 (75-92)**	323 (7)	**91 (78-100)**
T-SPOT	336 (9)	**84 (63-100)**	143 (4)	**94 (87-100)**

Detjen, CID, 2016



Mandalakas, Hesseling, AJRCCM 2015

Risk factors for TB infection

Proximity, Duration, Intensity of M.tb exposure

- 10 simple factors predict 70% of TST and/or IGRA+ children 0-5 years of age with household TB exposure

Mandalakas, Hesseling, Thorax, 2012

Risk factors for TB infection

Proximity, Duration, Intensity of M.tb exposure

Mandalakas, Hesseling, Thorax, 2012

Rationale for TB contact management

1. Detection of *M. tuberculosis* exposure/ infection
   - "Relevant disease" in young children
   - Relevant disease in immune compromised children (HIV, malnutrition)
   - Effectively contained through preventive therapy

2. Detection of active (prevalent) TB in children and other high-risk contacts (HIV+, adolescents, DM)

3. Other household health opportunities (HIV)

Summary of contact management yield

•The overall yield for all TB (bacteriologically confirmed and clinically diagnosed) was 4.5% (95% CI 4.3-4.8, I(2)=95.5%) of contacts investigated; for cases with bacteriological confirmation the yield was 2.3% (95% CI 2.1-2.5, I(2)=96.6%).

•*M.tb* infection was found in 51.4% of contacts investigated.

•"Contact investigation merits serious consideration as a means to improve early case detection and decrease transmission of *M tuberculosis* in high-incidence areas".

Morrison, Lancet Infect Dis 2008

More evidence to support screening of child contacts of TB cases: if not now, then when?

- 761 children from 351 households
- 79 TB cases
- 10% prevalent TB
- 71% bacteriologically confirmed

Evidence that informs the rationale for screening of children who are close contacts of a case of tuberculosis and for providing preventive therapy for this high-risk group has been available for >50 years [1, 2]. The policy is almost universally accepted, being included in global and almost all national tuberculosis control program guidelines [3]. However, in practice it is rarely implemented except in low-tuberculosis-burden, resource-rich settings [4]. Contact screening has 2 main roles. One is to identify at-risk contacts such as young or human immunodeficiency virus (HIV)–infected children who require preventive therapy. The other is to identify contacts of any age who have tuberculosis, that is, active, case finding.

Jaganath D, Clin Infec Dis 2013
Graham SM, Triasih R. Clin Infect Dis. 2013

Using TB contact management as quantification of paediatric disease burden

- Quantify number at-risk children (community, facility) – indirect estimate of childhood TB burden
- Estimate number infected and diseased (who should be attending)
- Document who attended and TB prevention offered
- Earlier diagnosis and less severe TB disease detected

Contact investigation study: children with a documented TB source case less likely to have severe TB disease than those without (21% vs. vs. 44%; OR: 0.34, 95%CI: 0.12; 1.01, p=0.025)”

Wiseman, IJTLD 2015

MDR-TB: Micronesia outbreak

- MDR TB outbreak in the Federated States of Micronesia, HH contacts treated with 12 months moxi or LVF, with or without ethambutol or ethionamide
- Of 119 infected contacts, 15 refused; 104 began treatment
- Of 104 who initiated treatment, 93 (89%) completed treatment
- 4 contacts discontinued due to adverse effects.
- None of the 104 contacts who tool preventive therapy of any duration developed MDR-TB disease
- 3 of 15 contacts who refused and 15 unidentified contacts developed MDR-TB
- Preventive regimens were safe and well tolerated.

Bamrah S, IJTLD 2014

Risk of infection, disease and MDR-TB in South African children

- 228 MDR-TB-exposed children <5 years of age enrolled
- 45% were TST positive
- 6.6% had prevalent TB at enrolment.
- Children without TB received a regimen of INH (15-20mg/kg), ofloxacin (15-20mg/kg) and ethambutol (20-25mg/kg) daily for 6 months. Ofloxacin was available at the time; LFX now used in children < 8 years.
- Children were monitored for clinical outcomes and adverse events, resulting in >200 patient years of follow-up. No SAEs detected

Seddon. Clin Infect Dis. 2013

TB Among HH Contacts Exposed to MDR TB Patients in High & Middle Burden Countries

Author / Year	Population	Rate of TB (per 100 person-years)[a]	% MDR TB
Vella, 2011*	KZN,SA	4.0	43.8%
Grandjean, 2011	Lima, Peru	2.4	72%
Becerra, 2011	Lima, Peru	1.5	90.9%
Becerra, 2013	Lima, Peru	2.1 (children) 2.6 (adults)	91%
Leung, 2013	Hong Kong	0.2	9.1%
Singla, 2011	Delhi, India	5.3%	12.5%

*% HH contacts exposed to MDR TB & XDR TB cases that died was 14% & 52% respectively

Shah et al CID 2014

Characteristics in children 0-5 with household MDR-TB vs. DS-TB exposure

	DS-TB exposure (n=316) N (%) or median (IQR)	MDR-TB exposure (n=228) N (%) or median (IQR)
Child factors		
<1yr	48 (15.2)	50 (21.8)
1 yr	66 (20.9)	41 (17.9)
2 yrs	71 (22.5)	44 (19.2)
3 yrs	73 (23.1)	56 (24.5)
4 yrs	58 (18.4)	38 (16.6)
Male	162 (51.3)	119 (52.2)
Black African (vs. mixed race)	52 (16.5)	101 (44.1)***
HIV-positive	1 (0.3)	8 (3.7)**
BCG scar/vaccination documented	310 (98.1)	181 (81.2)***
Previous TB treatment	8 (2.5)	21 (9.2)**
WFA z-score <-2	32 (10.1)	23 (10.1)
Sleeps in same room as TB source case	79 (25.3)	34 (15.0)***
Sleeps in same bed as TB source case	20 (6.4)	57 (25.2)***
Adult source case /household factors		
Source case sputum acid-fast bacilli smear-positive	181 (62.9)	180 (80.0)***
Household tobacco smoke exposure	245 (80.4)	145 (63.3)***
Mean socioeconomic index (x/11), n, SD	4.0 (2.6)	4.1 (2.5)
Children's TB status		
Exposure no infection	205 (65.7)	125 (61.3)
Infection no disease (TST+)	80 (25.6)	86 (38.1)**
TB disease	27 (8.7)	15 (6.6)

	Total	Infected N (%)	AOR (95% CI)
Child factors			
Age <2 years	203	64 (31.5%)	ref
Age ≥2 years	335	144 (43%)	**1.61 (1.09, 2.37)**
Female	259	96 (37.1%)	ref
Male	278	112 (40.3%)	1.02 (0.70, 1.47)
Mixed race / other ethnicity	390	161 (41.3%)	ref
Black African ethnicity	148	47 (31.8%)	0.54 (0.33, 0.88)
HIV-negative	518	202 (39%)	ref
HIV-positive	9	3 (33.3%)	0.66 (0.15, 2.94)
No BCG scar /no vaccination documented	45	16 (35.6%)	ref
BCG scar/vaccination documented	487	191 (39.2%)	1.62 (0.80, 3.29)
No prior TB treatment	509	189 (37.1%)	ref
Prior TB treatment	29	19 (65.5%)	**2.36 (1.03, 5.39)**
Weight for age (z-score) ≥-2	482	186 (38.6%)	ref
Weight for age (z-score) <-2	54	21 (38.9%)	1.04 (0.56, 1.92)
Sleeps in different room to TB source case	348	132 (37.9%)	ref
Sleeps in same room as TB source case	113	40 (35.4%)	0.85 (0.53, 1.36)
Sleeps in same bed as TB source case	77	36 (46.8%)	1.05 (0.60, 1.82)
Adult source case/household factors			
DS-TB source case	312	107 (34.3%)	ref
MDR-TB source case	226	101 (44.7%)	**2.05 (1.34, 3.12)**
No household tobacco smoke exposure	144	50 (34.7%)	ref
Household tobacco smoke exposure	394	158 (40.1%)	1.22 (0.76, 1.94)

Characteristics associated with TB disease in child contacts: DS-TB vs. MDR-TB exposure

	Total	Disease N (%)	OR (95% CI)	AOR (95% CI)
Child factors				
Age<2 years	64	20 (31.3%)	ref	ref
Age ≥2 years	144	22 (15.3%)	0.40 (0.20, 0.80)	**0.32 (0.15, 0.71)****
HIV negative	202	40 (19.8%)	ref	ref
HIV positive	3	2 (66.7%)	8.10 (0.72, 91.57)	**23.0 (1.11, 477.86)***
No BCG scar / no vaccination documented	16	3 (18.8%)	ref	ref
BCG scar / vaccination documented	191	39 (20.4%)	1.11 (0.30, 4.09)	1.14 (0.21, 6.20)
Weight for age (z-score) ≥-2	186	34 (18.3%)	ref	ref
Weight for age (z-score) <-2	21	7 (33.3%)	2.24 (0.84, 5.96)	2.17 (0.72, 6.55)
Adult source case factors				
DS-TB	107	27 (25.2%)	ref	ref
MDR-TB	101	15 (14.9%)	0.52 (0.26, 1.04)	**0.43 (0.19, 0.97)***
Smear-negative source case	43	4 (9.3%)	ref	ref
Smear-positive source case			2.84	

Risk of TB disease progression in children

- Young age
  - 43% of infants (children < 1year)
  - 25% of children aged one to five years
  - 15% of adolescents
- Recent infection (1-2 years) children with close contact (e.g. household)
- Malnutrition
- HIV

Marais et al. Int J Tuberc Lung Dis. 2004

WHO/HTM/TB/2006.371
WHO/FCH/CAH/2006.7

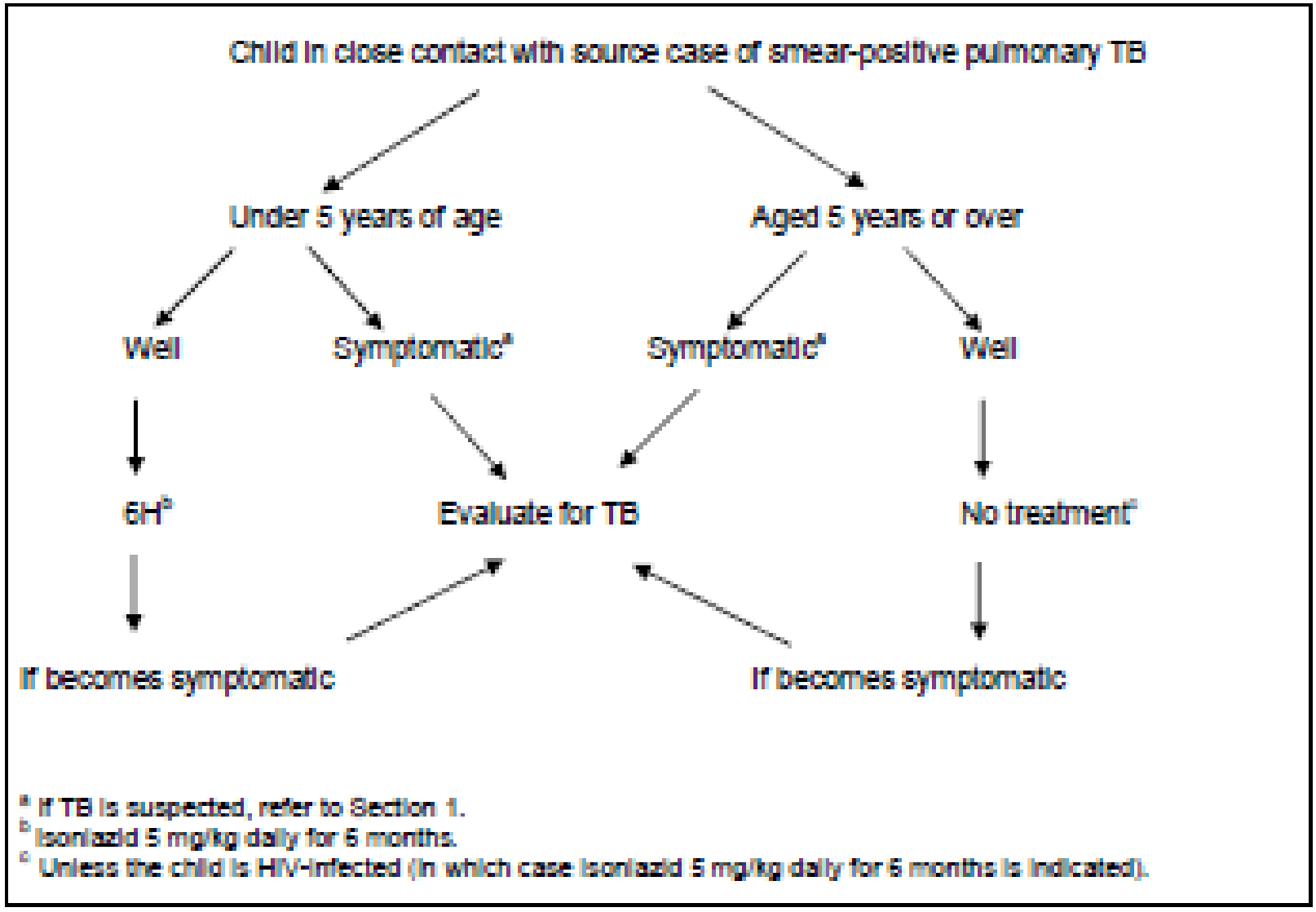
Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children

Box 5 Definitions used in contact screening

Source case	A case of pulmonary TB (usually sputum smear-positive) which results in infection or disease among contacts
Contacts for screening	All children aged under 5 years (whether sick or well) and children 5 years or older if symptomatic, who are in close contact with a source case
Close contact	Living in the same household as a source case (e.g. the child's caregiver) or in frequent contact with a source case

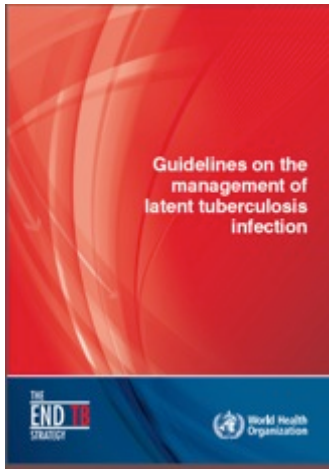
World Health Organization

Figure 1 Approach to contact management when chest X-ray and tuberculin skin test are not readily available



[a] If TB is suspected, refer to Section 1.
[b] Isoniazid 5 mg/kg daily for 6 months.
[c] Unless the child is HIV-infected (in which case isoniazid 5 mg/kg daily for 6 months is indicated).

WHO 2014 guidelines for preventive therapy for MDR TB contacts



- Treatment of presumptive MDR TB infection not recommended
  - Quality of evidence seriously limited
- Recommend strict clinical observation and close monitoring for TB disease for at least two years
- Clinicians as part of sound clinical practice can consider individually tailored preventive treatment
- Urgent need for high-quality data

	TB-CHAMP	V-QUIN	PHOENIx (A5300/I2003)
Intervention	LVF (novel paediatric dispersible formulation) vs. placebo daily for 6 months	LVF vs. placebo daily for 6 months	**DLM vs standard dose INH daily for 26 weeks**
Design	Cluster randomized; superiority Community-based	Cluster randomized; superiority Community-based	**Cluster randomized; superiority** **Community-based**
Target Population	• 0-5 y regardless of TST or HIV status	• All ages • Paediatric enrolment currently on hold • TST +	• **HIV +** • **Children 0-5 yrs** • **TST/IGRA + > 5 y**
Assumptions	LVF decreases TB incidence from 7 to 3.5% 80% power	LVF decreases TB incidence by 70% from 3% untreated 80% power	**DLM decreases TB incidence by 50% from 5% to 2.5%** **90% power**
Sample size	778 Households 1556 contacts	1326 Households 2785 contacts	**1726 Households** **3452 contacts**
Sites	South Africa	Viet Nam NTP	**ACTG & IMPAACT sites**
Timelines to open	Q1 2017 (lead-in)	Open (Q1 2016)	**Q1 2018**
Funder, PI	BMRC/Wellcome Trust/DFID, SA MRC SHIP; Hesseling, Seddon	Australian MRC Fox, Nguyen	**DAIDS, ACTG/IMPAACT** **Churchyard, Gupta, Hesseling, Swindells**

Phoenix: Lessons learnt

- Importance of paediatric TB expertise at non-IMPAACT sites and integration with other child health services
- Appropriate sampling of children for TB confirmation (gastric aspirates, sputum) to ensure adequate number confirmed cases (efficacy trial): paucibacillary disease
- Inadequate enrollment of children 0-5 years
- Importance of central CXR review (case definitions); majority of children (70%) will have clinically diagnosed TB
- Importance of clinical follow-up for diagnosis

FAMILY- BASED APPROACHES TO TB CONTACT MANAGEMENT

PT

(evidence based needed)

Intensified Case Finding

Infection Control

Integration

EPI

IMCI

Summary: key principles

- Childhood TB is a sentinel event
- Indicator of ongoing (recent) transmission: DS and DR-TB
- TB burden in children varies by in-country TB incidence
- Children may be exposed in and outside of the household but household key opportunity
- Improved surveillance of TB in children important: diagnosis, treatment, recording and reporting
- Rigorous evidence based need for MDR-TB prevention

“A generation of children free of tuberculosis”