Module 9a

NTP MANAGEMENT AND CHILD TB

International Union Against Tuberculosis and Lung Disease

World Health Organization

Child TB and NTP

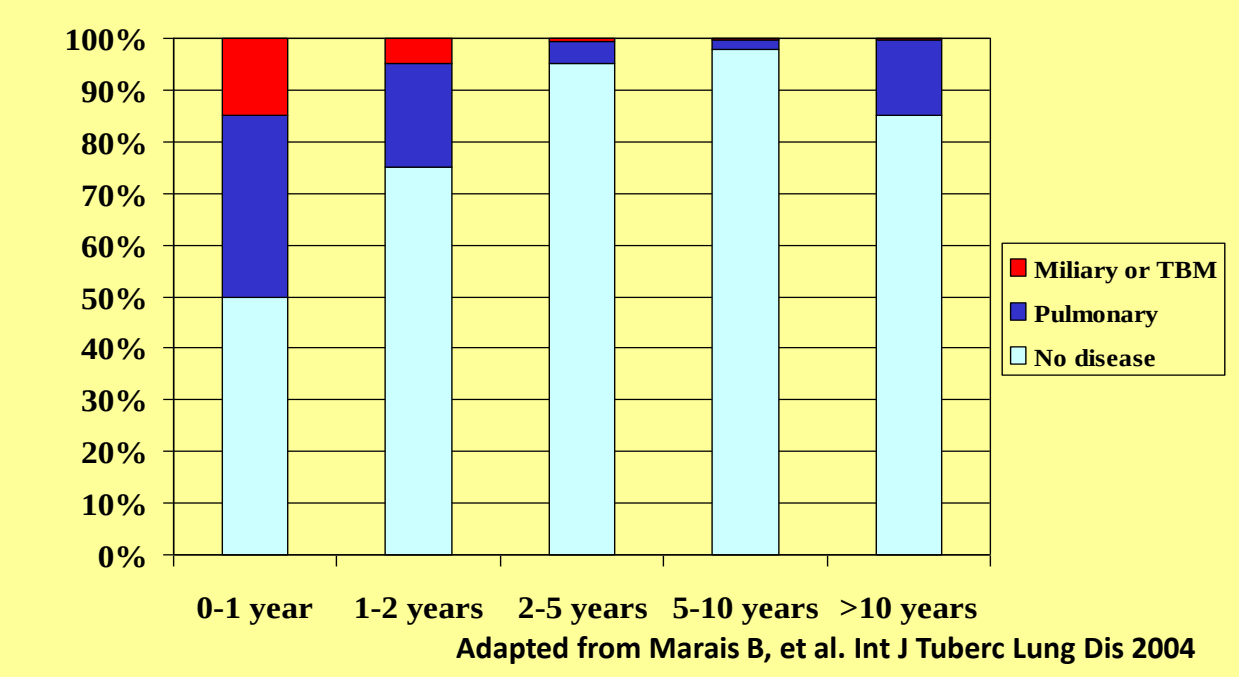
- What is the usual pattern of child TB cases
- What is impact of HIV on child TB
- What is important to know about treatment of TB in children
- Why it is important to register and report child TB cases routinely
- Why is contact screening and management important
- How to include child TB activities within NTP and improve child TB management

TB disease in children: clinical epidemiology

- Most cases occur in young children (<5years)
- Most disease occurs within 2 years after exposure/infection
  - The majority within 1 year

- Most cases in children are pulmonary TB
  - Smear negative or smear not done are the majority
  - Extrapulmonary TB is also common (around 25-35% of cases) and the type depends on age
  - Smear positive disease is usually in older children

Age specific risk for disease in children (pre-BCG)



The presentation of TB disease differs with age as older children have more mature and effective immune systems that eradicate or contain infection.

Infants and young children are particularly susceptible to severe, disseminated forms of TB as well as pulmonary TB.

The high risk of disease in young children is also the reason for contact screening and management.

National TB control data

- *This slide could include recent data of TB control indicators from the National TB control programme*

Childhood TB caseload: the example of Malawi in 1998

Harries AD, et al. Int J Tuberc Lung Dis 2002

Malawi NTP, 1998	numbers (proportion of childhood caseload)	proportion of total caseload
Total caseload	22,982	
Total childhood	2,739	11.9%
0-5 years	1,615 (58.9%)	7%
5-14 years	1,124 (41.1%)	4.9%
Smear-positive PTB	127 (4.6%)	1.3%
Smear-negative PTB	1,804 (65.9%)	21.3%
EPTB	808 (29.5%)	15.9%

Types of childhood EPTB disease

	Malawi NTP, 1998	PNG, 2005-6
EPTB cases	808	1097
Lymphadenitis	331 (41%)	342 (31%)
Pleural effusion	101 (12%)	94 (9%)
Spinal	83 (10%)	41 (4%)
Pericarditis	60 (7%)	12 (1%)
Abdominal	39 (5%)	173 (16%)
Miliary	34 (4%)	64 (6%)
Meningitis	30 (4%)	257 (23%)
Bone disease	12 (1%)	15 (1%)
Not indicated/others	118 (14.6%)	99 (9%)

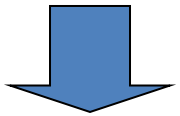
The diagnosis of TB can be made with confidence in the majority of children using careful clinical assessment

It is difficult to *confirm* diagnosis of TB in many children but it is usually not so difficult to *make a clinical diagnosis* of TB in a child

Child TB/HIV epidemiology

HIV epidemic

Large increase in TB cases in young adults



Increased number of child TB cases

HIV-infected children at risk of PTB because:

1. immune suppressed
2. more likely to be a contact of an adult with TB

HIV and TB in children

- HIV infected children at increased risk of exposure to TB
- HIV-infected at 20 times greater risk of TB disease than HIV-uninfected children
- Management of TB more complicated in HIV-infected children with significantly poorer outcomes
- Clinical diagnosis is more difficult especially for PTB as other HIV-related lung disease is common
- CPT and ART have a role in reducing TB-related death which is especially common within the first months following TB treatment

Treatment of TB in children

- Principles of treatment of TB in children are same as for adults
- Regimens are similar as for adults

- Children with TB usually respond well with symptomatic improvement during intensive phase and good outcome

- Dosages are calculated according to weight (not age)
- Weight is important for monitoring treatment response

- TB drugs are very well tolerated in almost all children
- The most important adverse event is hepatotoxicity
- Ethambutol can be safely used at recommended dosages in all ages including young children

- Register all children receiving anti-TB treatment
- Report treatment outcomes for children

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

World Health Organization

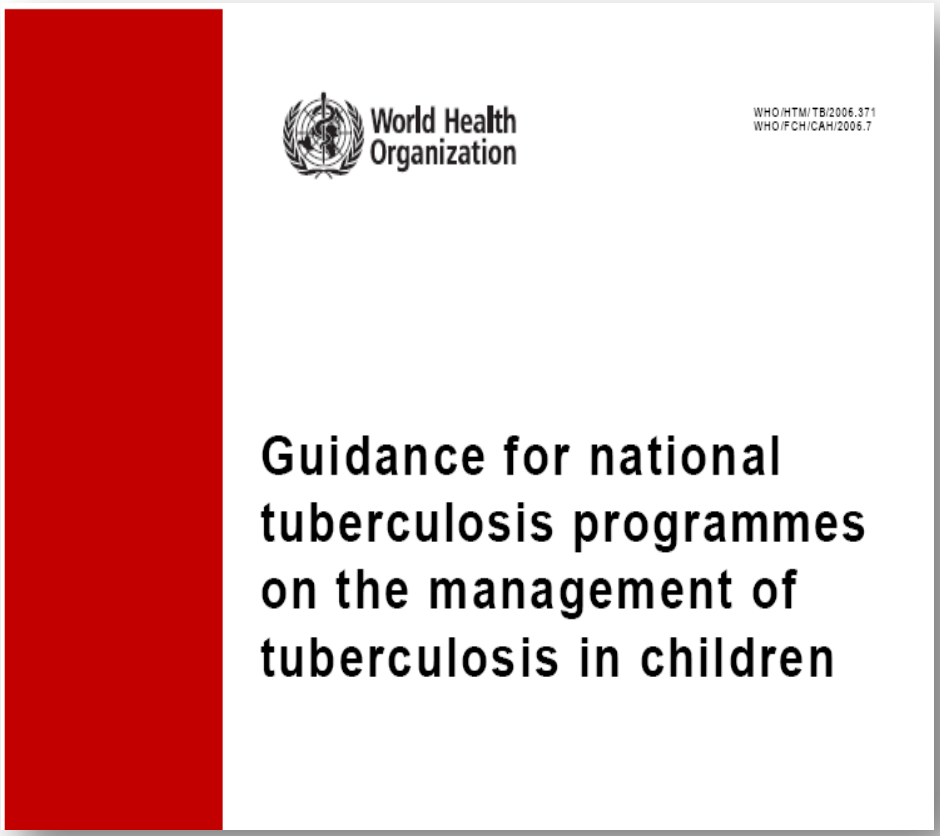
Use of ethambutol in children

- Ethambutol is recommended as fourth drug in intensive phase of first-line regimens in HIV and MDR endemic settings
- Risk of toxicity is dose-related and related to duration of therapy
- The risk of toxicity is **negligible** for children of any age when ethambutol is used at recommended dosages – especially when duration is limited to 2 months (as in first-line regimens)
- **Ethambutol can be safely used at recommended dosages in all ages**

The 2006 guidelines listed regimens and drug dosages for children that were consistent with those used in adults.

There is increasing and consistent evidence that serum levels of drug are often low when these dosages in mg/kg are used.

Therefore, in 2010, drug dosages for children were revised.



RAPID ADVICE

Treatment of tuberculosis in children

These are the 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

- Rationale for change
  - Consistent evidence that dosages need to be higher in mg/kg in young children (especially < 5 years) to achieve similar levels in the blood as for adults – and to achieve blood levels of drug considered high enough to provide optimal therapeutic effectiveness
  - 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

Recommended drug dosages should be consistent with national guidelines

Insert drug regimens and dosages according to national guidelines

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

WHO also now recommends that all cases of child TB should be registered and reported within age bands: 0-4 years and 5-14 years

rogramme

Form 6

Quarterly Report on TB Case Registration in Basic Management Unit

_____ Facility:_____

rdinator:_____ 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			0-4 yrs	5-14 yrs	≥ 15 yrs	0-4 yrs	5-14 yrs	≥ 15 yrs	0-4 yrs	5-14 yrs	≥ 15 yrs		
	Relapses	After failure	After default											

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.

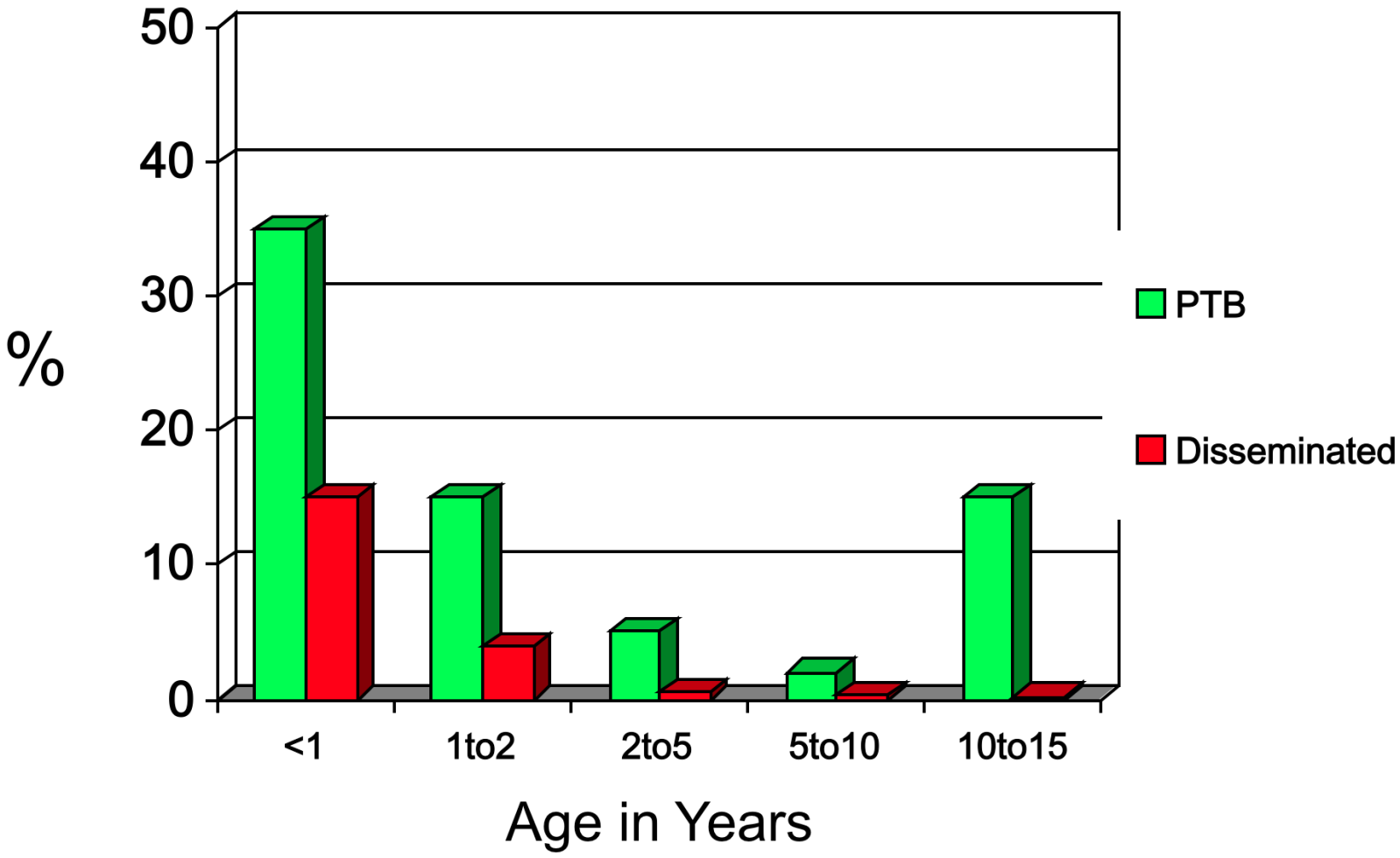
5 Documented evidence of HIV tests (and results) performed in any recognized facility before TB diagnosis or during TB treatment (till end of the quarter) should be reported here.

Treatment outcomes in children with TB

- Treatment outcomes should be routinely recorded and reported for child TB cases
- Outcome categories are the same as for adult cases (although few child TB cases would meet the criteria for “cured”)
- Treatment outcomes are important data for monitoring & evaluation
- There are few NTP data of treatment completion – but often poor in children

Available approaches to prevent TB in children	
Improved case-finding and management	Early identification and effective treatment of infectious TB cases will reduce the burden of child TB
BCG	Neonatal BCG immunisation is used widely but efficacy is variable The main proven benefit of neonatal BCG is protection against severe disseminated forms of TB in children
Contact screening and management	This has huge potential to reduce the burden of TB in children Focus is on individuals infected with TB that have greatest likelihood of developing active TB disease following infection – this includes infants, young children and HIV-infected children of any age Widely recommended but uptake by families and implementation by NTP are poor The usual form of preventive therapy used for at-risk TB exposed individual without active disease is isoniazid preventive therapy or IPT

Risk of TB disease following infection by age



Adapted from Marais B, et al. Int J Tuberc Lung Dis 2004

Studies of child contacts in Asian countries

Study	Location	No. of child contacts	Proportion with TB infection	Proportion with TB disease
Andrew et al	India	398	39 %	5.5 %
Narain et al	India	790	24 %	NR
Kumar et al	India	142	NR	3 %*
Singh et al	India	281	34 %*	3 %*
Rathi et al	Pakistan	151	27 %	NR
Salazar et al	Philippines	153	69 %	3 %
Tornee et al	Thailand	500	47 %	NR
Nguyen et al	Lao PDR	148	31 %	NR
Okada et al	Cambodia	217	24 %*	9 %*

* Data only for < 5 years; NR: not recorded

From Triasih R et al, J Trop Med 2012

Studies of child contacts in African communities

One-third to two-thirds of child household contacts of TB cases have evidence of TB infection i.e. TST positive

Incidence of TB disease among household contacts is very high – reported as >1,000 cases/100,000 population

Likelihood of infection is related to closeness/proximity of contact to and sputum smear positivity of index case

Risk of infection greatest when the index case is the child's carer e.g. mother, grandmother

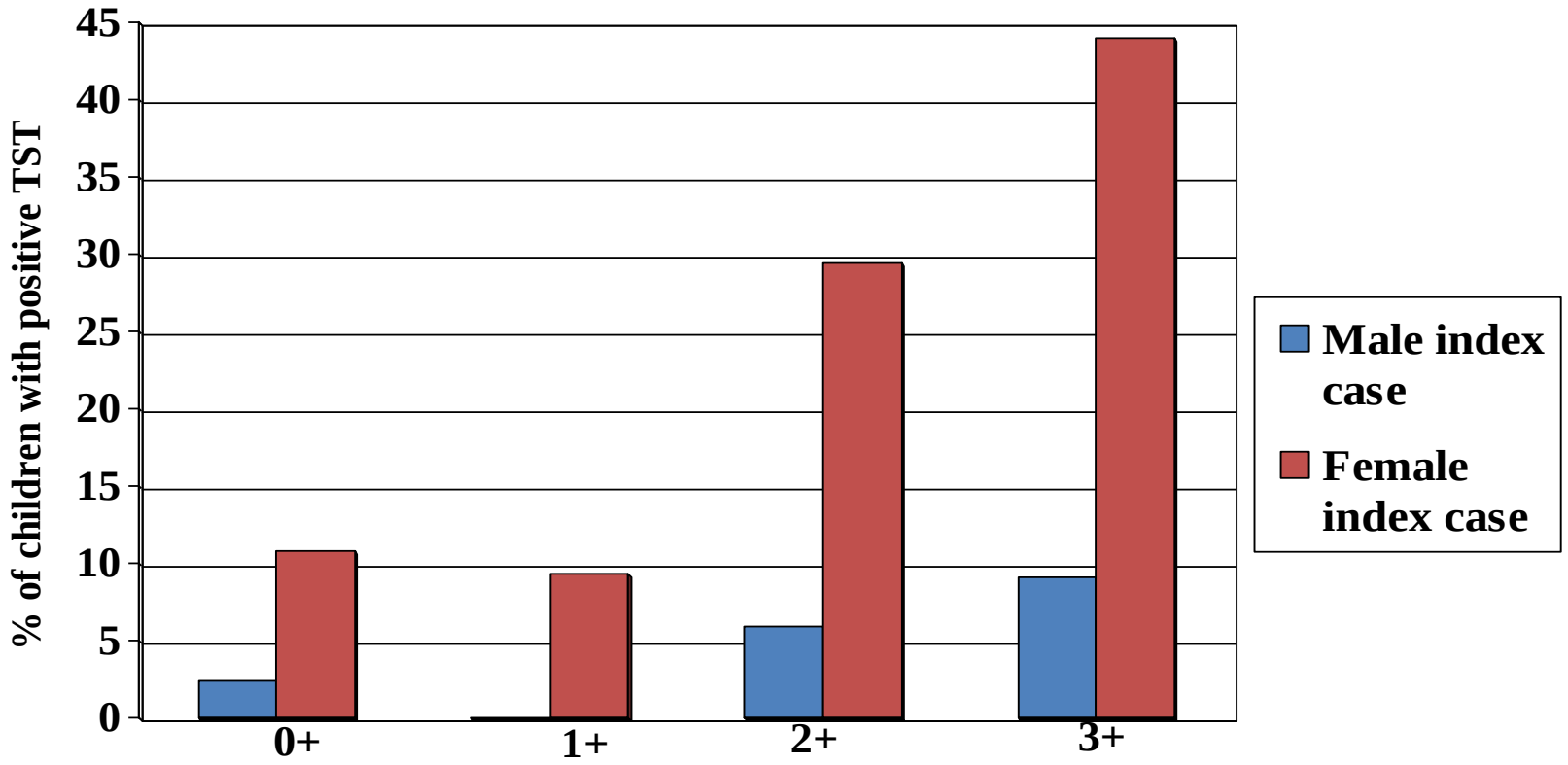
HIV-infected children are at increased risk of exposure to TB

Kenyon TA et al, Int J Tuberc Lung Dis 2002; Sinfield R, et al Ann Trop Paediatr 2006;

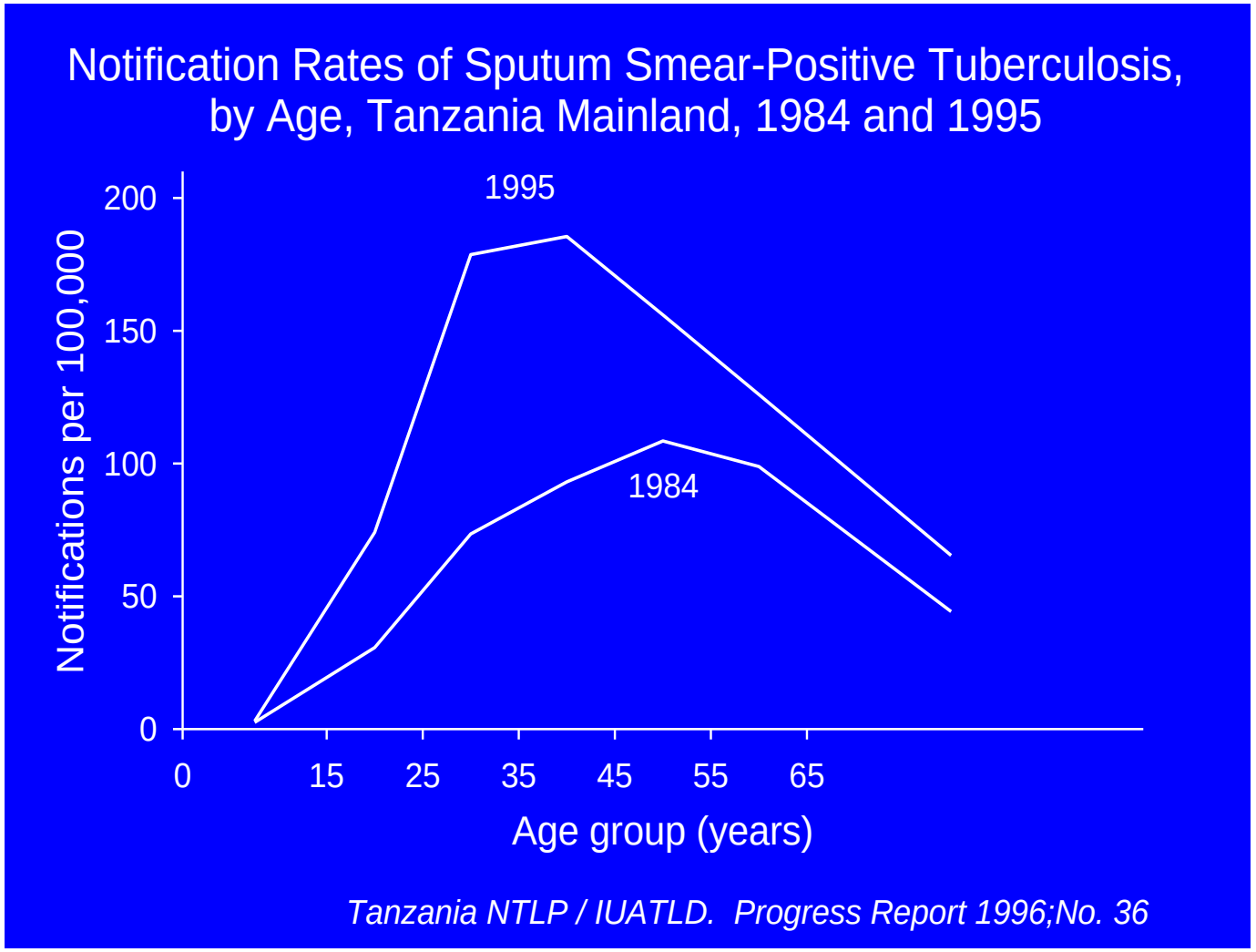
Jackson-Sillah D, et al Trans R Soc Trop Med Hyg 2007; Morrison J, et al Lancet Infect Dis 2008

Proportion of children with TB infection (positive TST) by degree of smear positivity of the source case

Kenyon TA et al, Int J Tuberc Lung Dis 2002



Increased risk of TB exposure among young children in HIV-endemic countries



From: Reider HL. Interventions for TB control and elimination. IUATLD publication 2002

Why is contact screening important?

1. Opportunity to prevent TB-related morbidity and mortality in children and HIV-infected individuals

2. Opportunity to increase case-finding and earlier treatment of undiagnosed active TB cases

Why is child contact screening important? Prevent child morbidity and mortality

- The prevalence of TB infection is high among child contacts

- Child household TB contacts had significant increase risk of all-cause mortality compared to children living in non-TB households in same community
  - If mother had TB, 8-fold increase: MRR 7.82 (95% CI 2.1-30)

AF Gomes et al, Thorax 2011

- Missed opportunities for IPT were common (71%) in at-risk children that later presented with confirmed TB disease
  - 81% were <3 years of age, 25% had disseminated TB and 5% died
  - TB source case was the mother or father in 74/156 (47.4%) children

K Du Preez et al, Ann Trop Paediatr 2011

Why is contact screening important? Increased case-finding

- The prevalence of TB infection and disease is high among contacts

  J Morrison, et al. Lancet Infect Dis 2008

  - All TB cases 4.5% (95% CI 4.3-4.8)
  - Confirmed cases 2.3% (95% CI 2.1-2.5)
  - Latent TB infection 51.4% (95% CI 50.6-52.2)

- TB prevalence significantly higher by active case finding in household contacts (1735/100,000) than with passive case finding (191/100,000)

  R Zachariah et al, Int J Tuberc Lung Dis 2003

- Incidence of TB disease among contacts was 603 per 100,000 (95% CI 370-830)

  PC Hill et al, PLoS ONE 2008

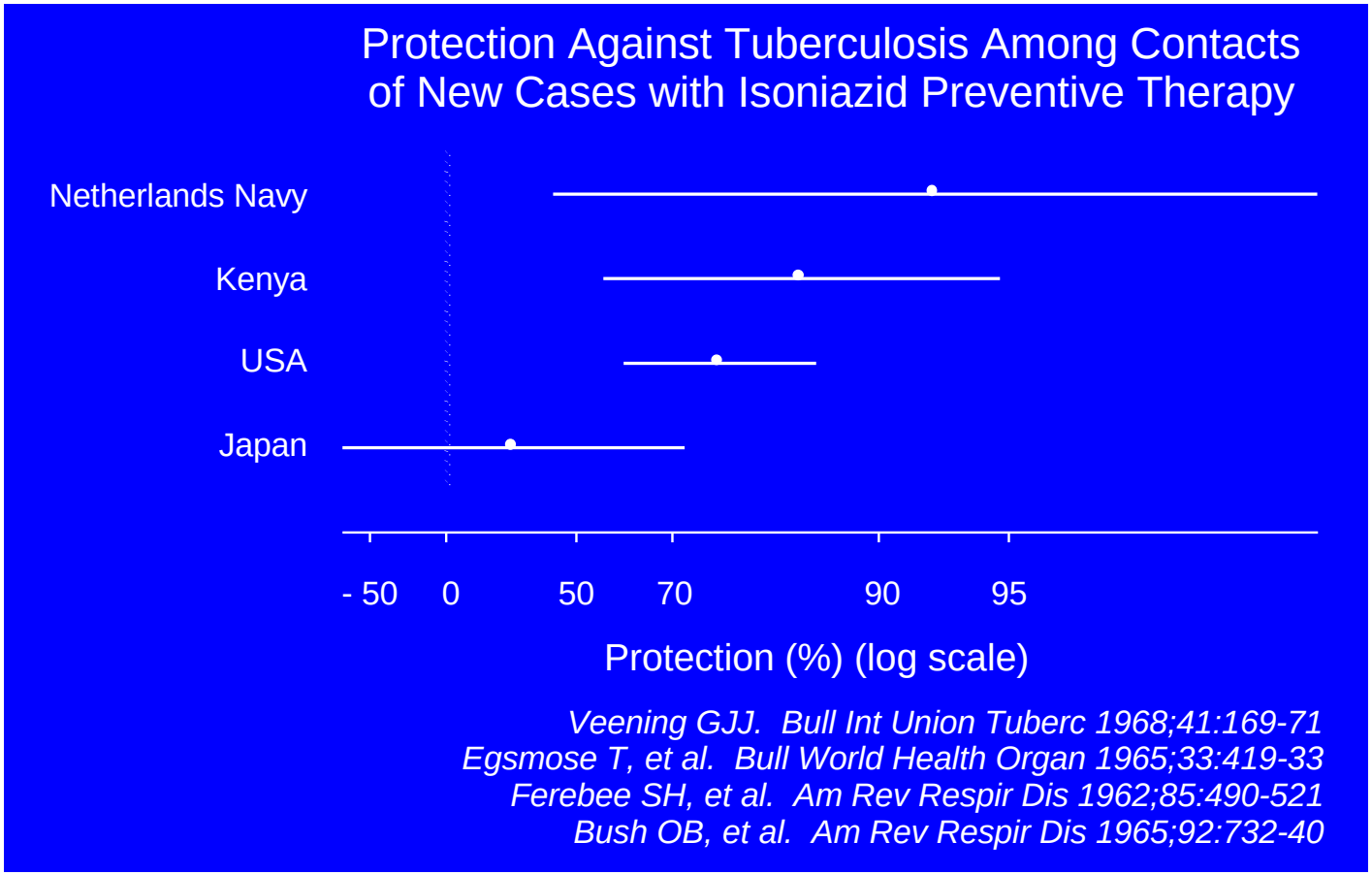
  and in same community, prevalence of TB cases was 1518 per 100,000 among 2174 contacts of 317 adults with smear-positive PTB

  D Jackson-Sillah et al, Trans R Soc Trop Med Hyg 2007

Most studies of IPT efficacy have been done in adults such as below.

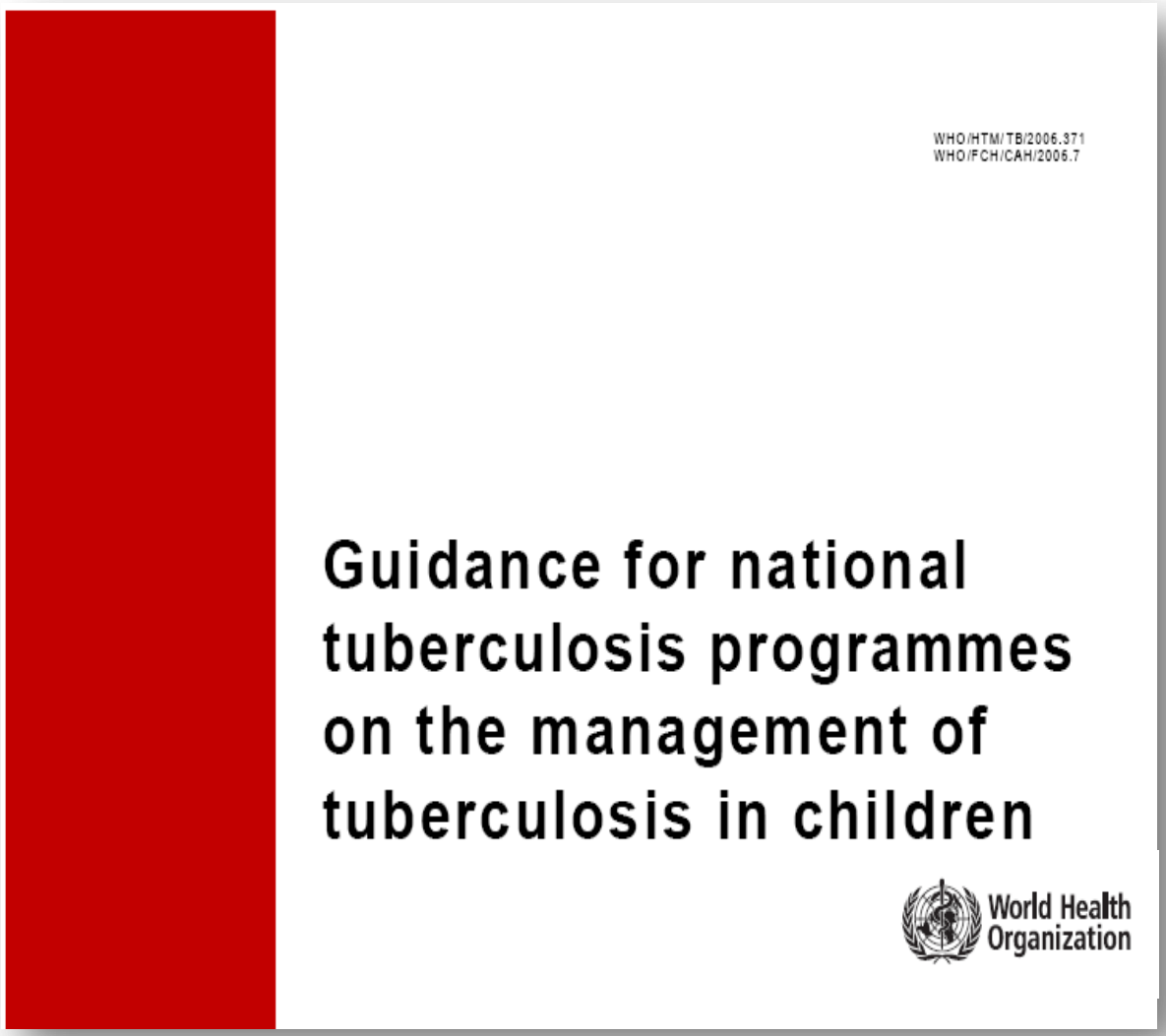
Studies have included children and the efficacy of IPT for preventing disease in children infected with TB and not HIV-infected is over 75%.

IPT needs to be given for at least 6 months duration to be this effective.



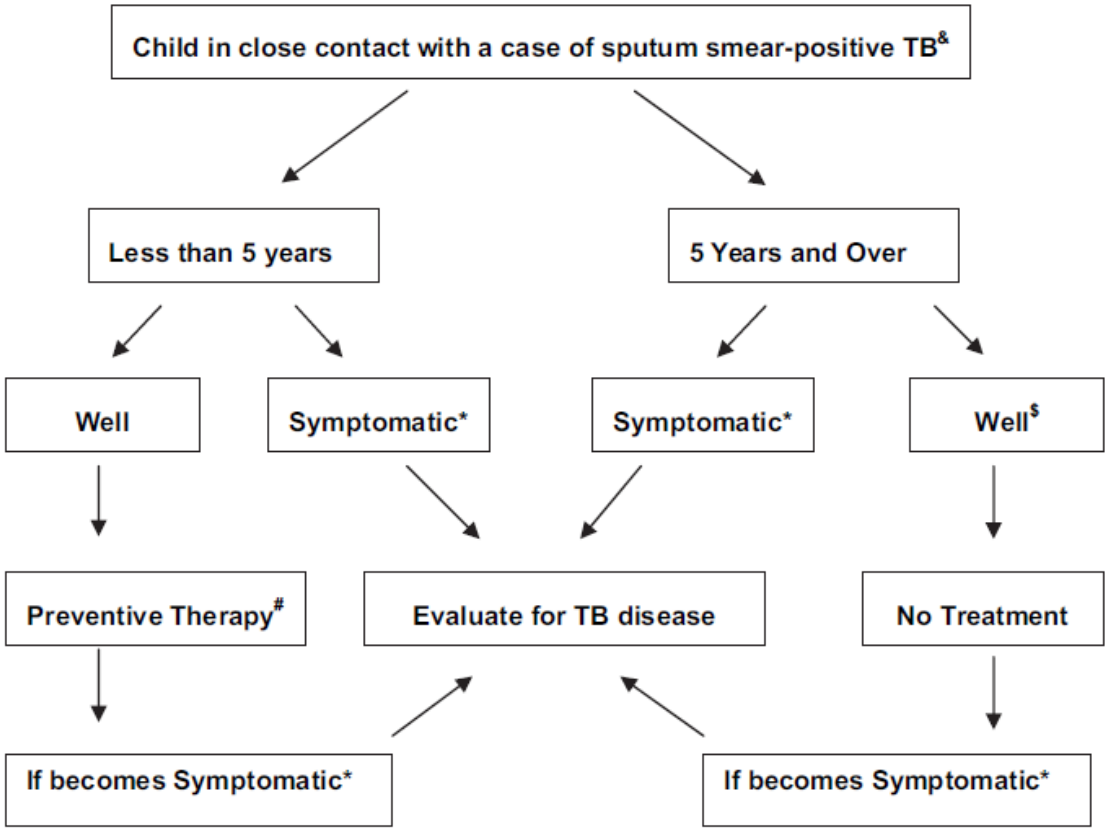
From: Reider HL. Interventions for TB control and elimination. IUATLD publication 2002

Symptom-based screening of child contacts is recommended by WHO



Adapted from the WHO 2006 guidance:

note that HIV-infected children that are contacts with no evidence of active disease should receive IPT irrespective of age.



&Also consider if the mother or primary caregiver has sputum smear-negative pulmonary TB

*Symptomatic: If TB is suspected, refer to local guidelines on diagnosis of childhood TB

Isoniazid 10/mg/kg daily for 6 months

$ Unless the child is HIV-infected (in which case isoniazid 10/mg/kg daily for 6 months is indicated)

Management of child contacts

- **Decentralise**: symptom-based screening provides opportunity to undertake an integrated family-based approach in the community around the source case receiving DOT rather than requiring referral to health facility for all cases

- **Adherence**: to IPT for 6 months is a major challenge

- **Enhanced case-finding**: Note that symptom-based screening also aims to identify symptomatic contacts of any age for investigation for possible TB disease

Management of child contacts

List close contacts

- What is the age of the contact?
- Is the contact HIV-infected?
- Does the contact have any symptoms suggestive of TB?

Checklist of main symptoms

- Persistent cough for more than 2 weeks
- Weight loss or failure to gain weight
- Persistent fever for more than 1 week and/or night sweats
- Fatigue, reduced playfulness, less active

Management of child contacts

Criteria for contacts to receive IPT

- No active TB disease – no symptoms suggestive of TB

  AND

- At high risk of disease following TB exposure
  - < 5 years
  - HIV-infected

Management of contacts	Response	Action
Symptomatic Sputum smear positive	TB treatment	Register
Symptomatic Sputum smear-negative or not available	Refer	Refer
Asymptomatic and high risk	IPT	IPT register
Asymptomatic and not high risk	No treatment	Advise to return if symptoms develop

Sample contact screening register

Name	Age (years)	TB symptoms (Y/N)	Anti-TB treatment (Y/N)	Isoniazid preventive therapy (Y/N)	TB registration number	Treatment outcome	HIV status[a]

“Best Practices in Tuberculosis Control” September 2010, Kigali, Rwanda

Burundi, Kenya, Rwanda, Tanzania, Uganda, Zambia, Zimbabwe

Included emphasis on child TB

Participants devised and agreed on 10 action points for including child TB in NTP activities

Childhood TB and NTPs

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

Child TB training for paediatricians or trainees – clinicians, researchers and/or teachers – held each year in Cape Town since 2007
Ideal for child TB champion within NTP or national child TB steering group

Clinical and training tool

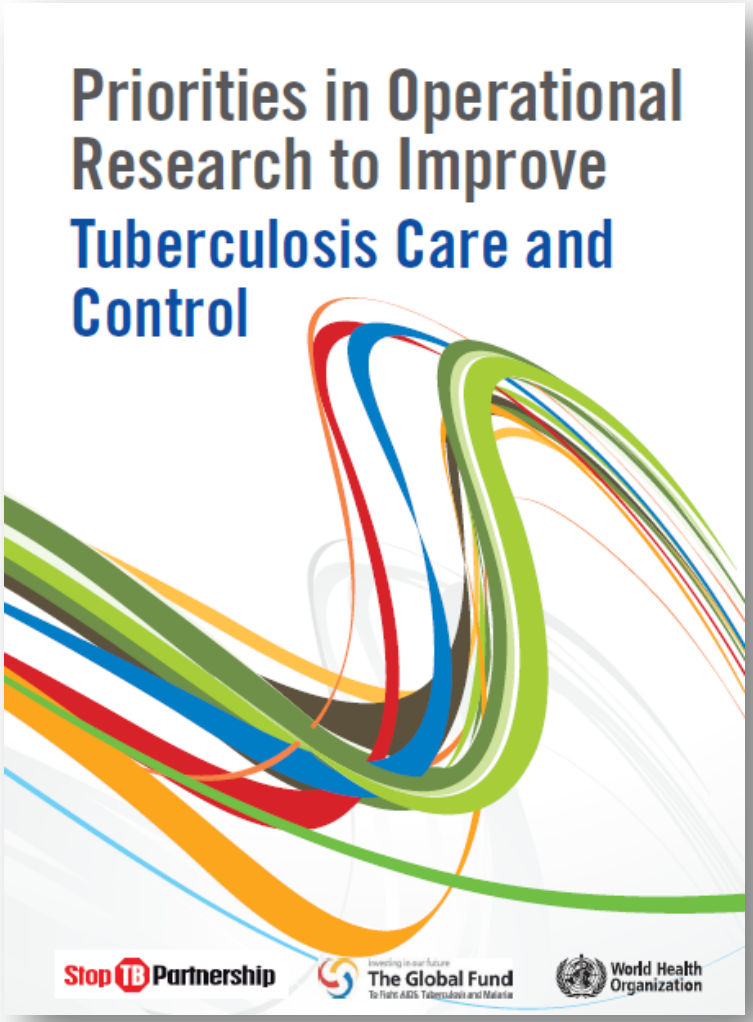
Aimed at peripheral/district health worker

Up-to-date with current guidelines

Management algorithms

Includes TB in HIV-infected

Child TB, NTP and operational research



Child TB and NTP

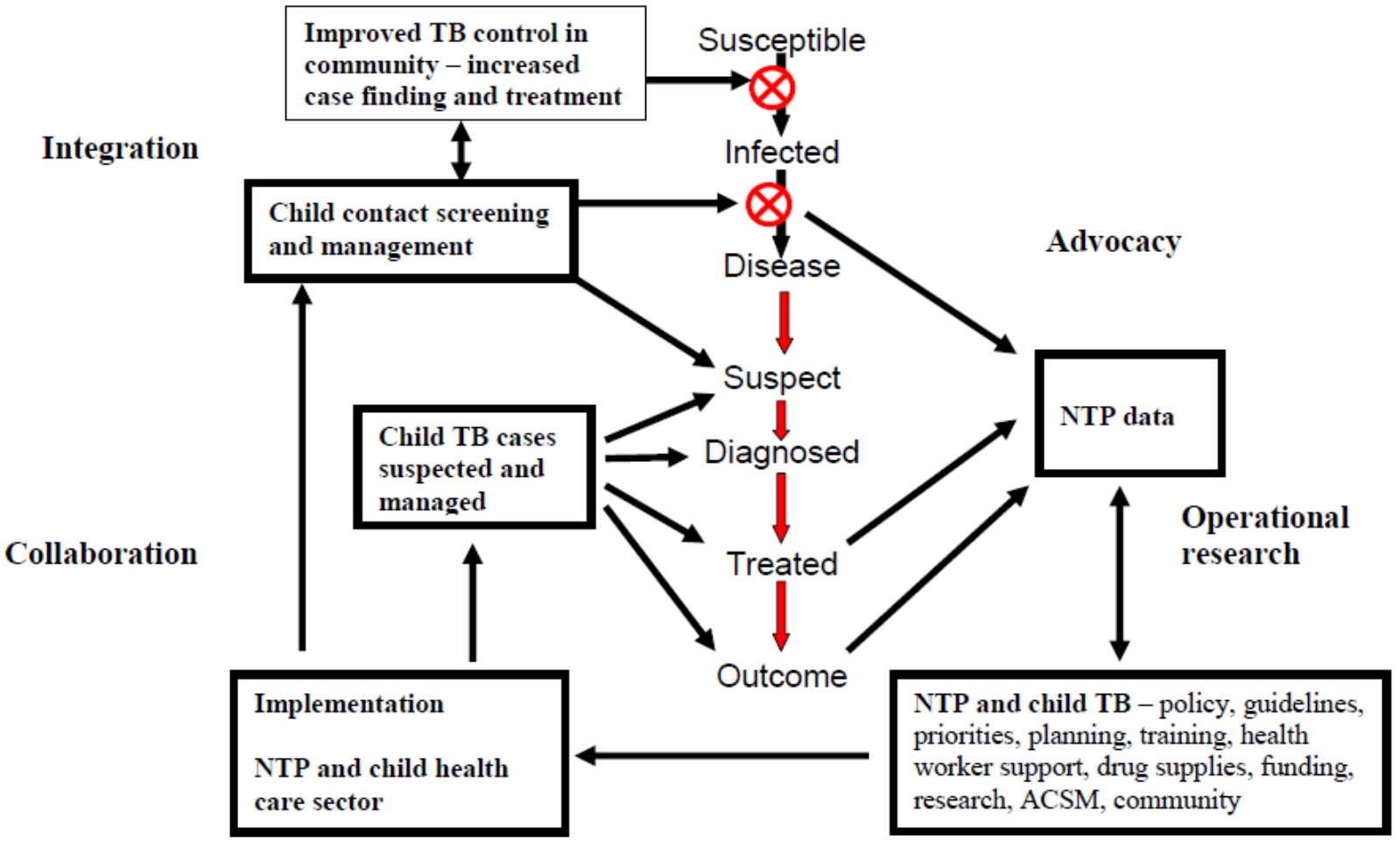
Operational research is a critical tool

- Identify barriers
- Identify main management issues
- Identify OR priorities
- Advocacy
- Implementation
- Monitoring progress

Operational research course for NTP staff held by IUATLD annually

Roadmap for TB in children

Figure. Interventions that target stages of the continuum in children from susceptibility to disease and outcome



" There are many contributions which the pediatrician can make to a TB control program.

First the negativism about tuberculosis so prevalent in pediatrics must be overcome…"

Edith Lincoln, 1961

FIGURE 1. Edith Lincoln at the commencement of her studies

Donald PR. Edith Lincoln, an American Pioneer of Childhood Tuberculosis. *Pediatr Infect Dis J* 2013