Reference Standards: Paediatric Tuberculosis

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Issues in children

- Range of ages
  - highest burden, most severe illness in infants and children under 2 years of age
  - resurgence in adolescence
- Reliability of reported symptoms – caregiver
- Ability to produce specimens; quantity and quality of specimen
- Development of immunity & passive immunity
- Extra pulmonary disease

Existing methods in children

- Clinical
- Radiological
- Immune diagnosis
  - Skin testing, IGRAs
- Culture confirmation
  - Smear and culture

Reference standards for clinical diagnosis

Clinical diagnosis

- clinical symptoms and signs
- tuberculin skin test
- chest Xray findings

- Sensitivity and specificity problematic – *especially in HIV-infected children, malnourished, young, severe disease*

Clinical diagnosis PTB in children in high burden area

- Symptom based approach
  - Persistent, continuous cough > 2 weeks
  - Weight loss over preceding 3 months
  - Fatigue
- Reasonable performance in HIV-uninfected, older than 3 yrs

Marais et al Pediatr 2006

Symptom based diagnosis of PTB

Combined Variables at Presentation[a]	Value		
	Sensitivity	Specificity	PPV
Low-risk children			
≥3 years and HIV uninfected	82.3	90.2	82.3
High-risk children			
<3 years and HIV uninfected	51.8	92.5	90.1
HIV infected (irrespective of age)	56.2	61.8	61.9

•persistent, non-remitting cough x 2 weeks; wt loss preceding 3 months; fatigue

Marais Pediatr 2006:118

Clinical symptoms

- chronic symptoms – cough x 2 weeks, failure to thrive, weight loss
- ACUTE pneumonia is common in culture confirmed TB
  - 8% children hospitalized with acute pneumonia, *Zar 2000, Graham 2000, Madhi 2002*
  - 53/ 358 (15%) children severe pneumonia, *McNally 2007*
  - 77% culture confirmed – acute symptoms *Moore 2010*

Paediatric TB and chronic cough

- Post hoc analysis of 40 000 children in PCV9 vs placebo study in South Africa
- follow-up 5.3 yrs
- culture confirmed TB lower in PCV9 vs placebo (33 vs 57 cases, 42% reduction)
- HIV-infected (22 vs 39, 44% reduction)
- 77% had cough < 10 days; median cough duration 4 days

Moore et al PIDJ 2010

Clinical scoring systems

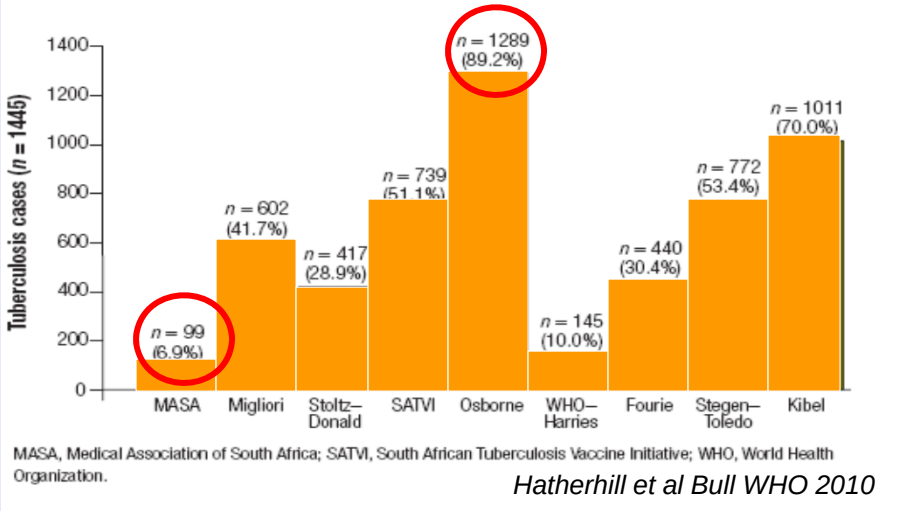
- 16 published scoring systems
  - chronic cough, growth, contact, tuberculin skin test, CXR
  - 5 of 16 adapted for HIV, 1 designed for use in HIV, *Hesseling 2002*
- poorly studied, inadequately validated especially in HIV

Clinical algorithms in children

- wide variability in sensitivity and specificity
- analysis of 9 scoring systems for PTB
- applied to 1445 cases of suspected TB in 11 680 children in BCG study in W Cape (HIV prevalence 2%)
- 7% to 43% diagnosed with definite or probable TB
- 7% to 90% with possible TB/ probable/ definite TB

Hatherhill et al 2010

Proportion of children diagnosed with TB using 9 different scoring systems



MASA, Medical Association of South Africa; SATVI, South African Tuberculosis Vaccine Initiative; WHO, World Health Organization.

Hatherhill et al Bull WHO 2010

Clinical diagnosis

- Standardised case definitions needed for evaluation of novel diagnostics
- NIH workshop June 2011 - *Critical issues in Pediatric diagnostic research*
  - consensus clinical case definitions
  - standardise methodological approaches to new diagnostics in children

Graham in press JID 2012

Clinical case definitions

- Confirmed TB
  - 1 sign/ symptom AND culture confirmation
- Probable TB
  - 1 sign/ symptom AND CXR consistent AND exposure/ response to therapy/ immune evidence of infxn
- Possible TB
- 1 sign/ symptom AND CXR consistent/ exposure/ response to therapy/ immune evidence of infxn
- TB unlikely – symptomatic but no criteria
- NOT TB – alternative Dx

Graham in press JID 2012

Clinical signs/ symptoms

- Persistent (x 2 weeks) cough
- Weight loss / FTT
- Persistent (1 week) unexplained fever
- Persistent, unexplained lethargy
- History of exposure – household/ close contact within 24 months
- Response to treatment – 2 month f/up (also 2 weeks and 6 months) – assess clinical features

Graham in press JID 2012

Clinical diagnostic features

- 1445 children < 2 yrs with suspected PTB in intradermal vs percutaneous BCG study (n=11 680) followed for 2 yrs
- 172 (12%) culture positive; 25(1.7%) HIV pos
- *Assoc with culture pos*: wheeze, lower chest retractions, PPD pos, CXR suggestive
- *NOT assoc* – fever, persistent cough, wt loss/FTT

Luabeya PIDJ 2012

Radiological diagnosis

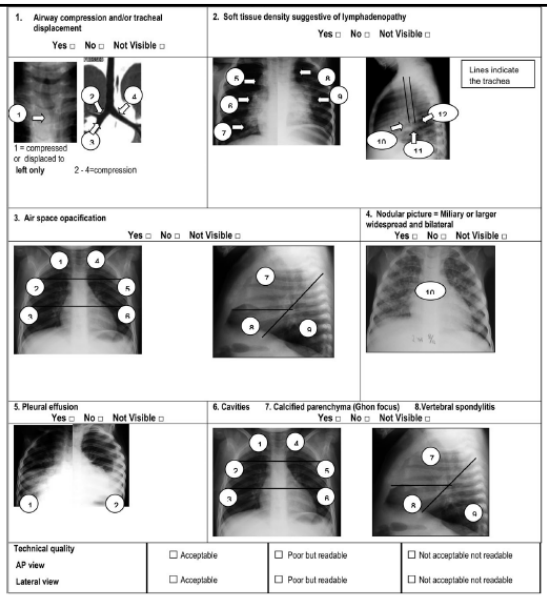
Radiological diagnosis

- Non-specific
- Hilar adenopathy – wide inter and intra-observer variation – *Swingler Arch Dis Child 2005*
  - 100 children suspected PTB – CXRs & CT (ref)
  - 3 paediatricians, 3 primary care Drs
  - Inter-observer agreement – 30%
  - accuracy not improved with lateral CXR
- High prevalence of HIV associated chronic lung disease – 1/3 by age 3-4yrs, *Norton 2001*

Radiological signs

- At least 2 expert readers, 3rd reader for discordant results
- AP and lateral CXRs
- Independent, blind review
- Digital images
- Standardised forms with YES/ NO options

Graham in press JID 2012



Acknowledgements: CXR Review Tool developed by S. Andronikou and The South African Tuberculosis Vaccine Initiative (SATVI).

Figure 2. Example of a chest radiograph (CXR) review template (Courtesy of Mark Hatherill, University of Cape Town). Note: CXR is classified as "consistent with tuberculosis" if there is a positive response for any 1 of the radiographic features at the same location by at least 2 expert reviewers.

Tuberculin skin testing

- Technique dependent
- Variability in measurement
- Standardised application, interpretation
- What constitutes a positive result?
  - Epidemiology MTB, NTM
  - HIV – 5mm
  - BCG
- Poor sensitivity in HIV-infected, malnourished

Causes of false-negative TST	Causes of false-positive TST
Improper placing / interpretation	Improper interpretation
HIV infection	BCG vaccination
Improper storage of tuberculin	non-tuberculous mycobacteria (NTM)
Viral infections	
Live viral vaccines (in 6 weeks)	
Malnutrition, low protein states	
Bacterial infections	
Immunosuppression	
Neonates	
Primary immunodeficiencies	
Severe TB	

WHO guidelines, 2006

Tests for detection of host immune response

Immunological evidence of TB

- Positive tuberculin test (5mm HIV infected or severely malnourished, 10 mm otherwise)

or

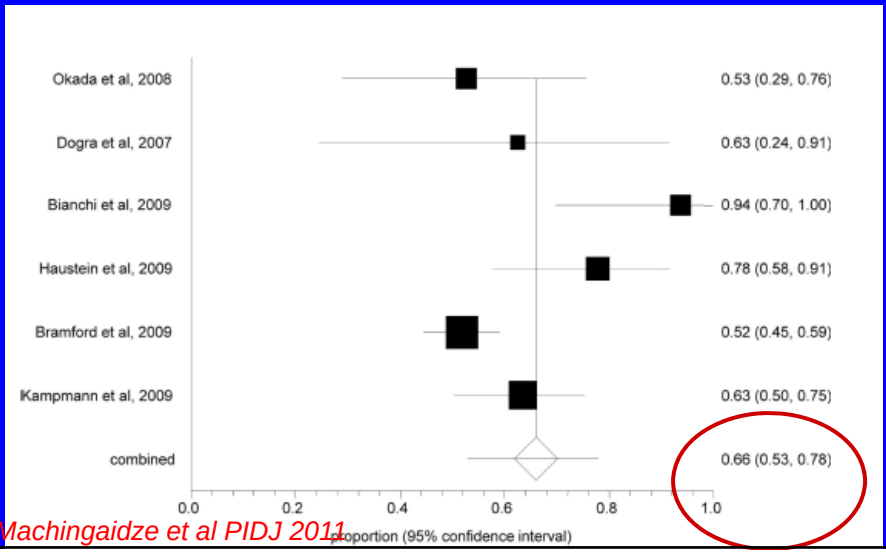
- Positive IGRA

Graham in press JID 2012

IGRA vs TST in children

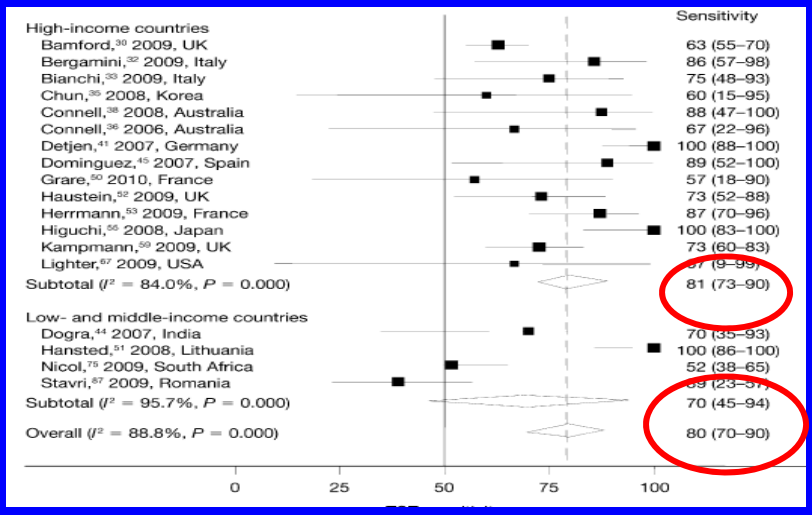
- Meta-analysis 20 studies, *Machingaidze PIDJ 2011*
- IF assays variable sensitivity, higher specificity
- IF assay 55% sensitivity in high burden TB countries vs 70% in low burden
- IF and PPD similar sensitivity for active TB
  - IF and PPD combined increased sensitivity
- Agreement between IF and TST variable – k = 0.17 to 0.86

Sensitivity of Quantiferon for active TB in children



Machingaidze et al PIDJ 2011

Sensitivity of TST for active TB in children



Mandalakas et al Int J T Lung Dis 2011

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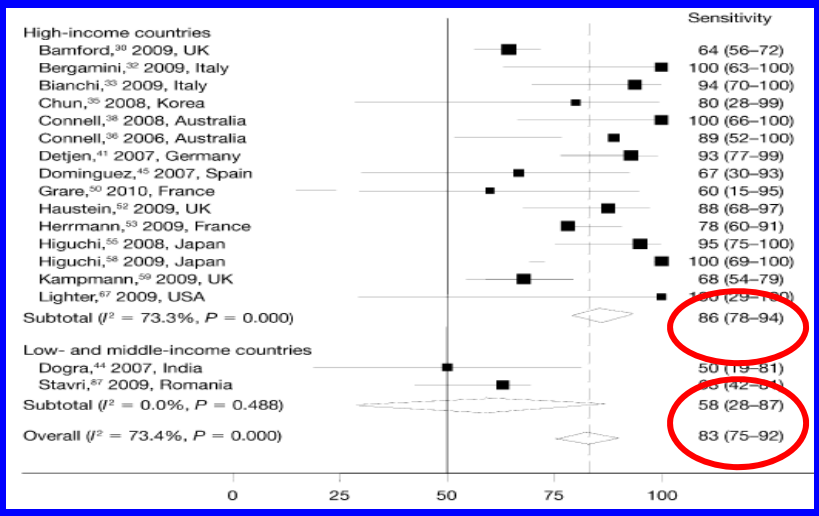

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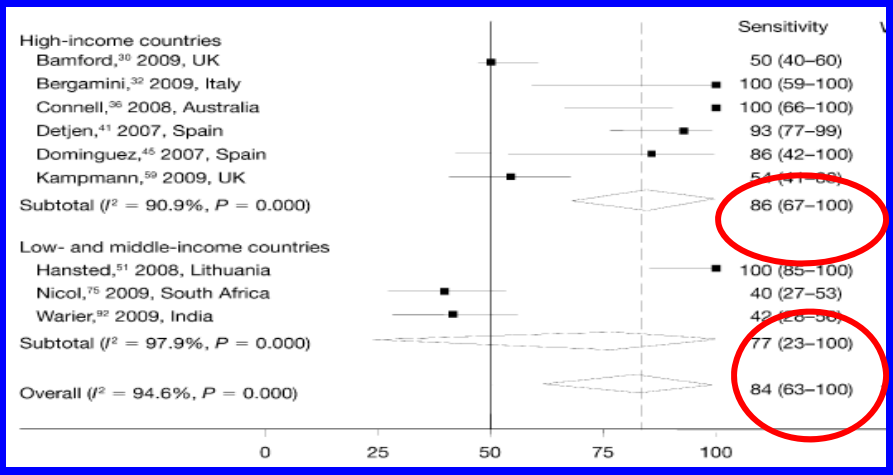
Sensitivity of T-Spot for active TB in children



Mandalakas et al Int J T Lung Dis 2011

Microbiological diagnosis

Microbiological diagnosis

- NOT reference standard for diagnosis in children
- Prevailing perceptions:
  - not feasible / possible / practical
  - not useful - paucibacillary disease
  - not possible in infants or young children
  - no place in primary care settings
- Different diagnostic standard for adults

Microbiological confirmation children

- BUT micro diagnosis is
  - possible
  - feasible in very young
  - confirms diagnosis
  - especially useful for drug resistant TB
- specimens -gastric lavage, induced sputum, NPAs, ear swabs, blood, stool, nasal secretions, fine needle aspiration

Microbiological confirmation children

- BUT even when culture or PCR based diagnosis possible in children
  - most are smear negative, culture negative
  - 25% of culture positive children are Xpert negative
- Many are probable TB - treated based on clinical diagnosis

?? How to evaluate a new diagnostic in the absence of a gold standard