TB Diagnostic Test validation in childhood TB

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Global TB burden in 2013 – WHO report 2014

	Cases	Range
Total Incident TB cases	9 million (126 cases / lakh)	8.6 – 9.4 million
Children (<15yrs)	550,000 (6%)	470,000 – 640,000
Total TB Deaths	1.5 million	
TB deaths in HIV – ve children	80,000	64,000 – 97,000

WHO/HTM/TB/2014.08

Global TB Report 2014: Burden in Children

- **Incidence: 550,000 (470-640,000) – 6% of 9 million incident TB cases**
- Limitations – assumption that CDR is 66% same as adults, misdiagnosis and age disaggregated data not available from some countries
- **Deaths: 80,000 (64-97,000) among HIV neg children (7% of 1.1 million deaths)**
- Limitations: Many TB deaths could be misclassified as due to malnutrition, pneumonia, HIV-related etc
- TB deaths in HIV+ children not known

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

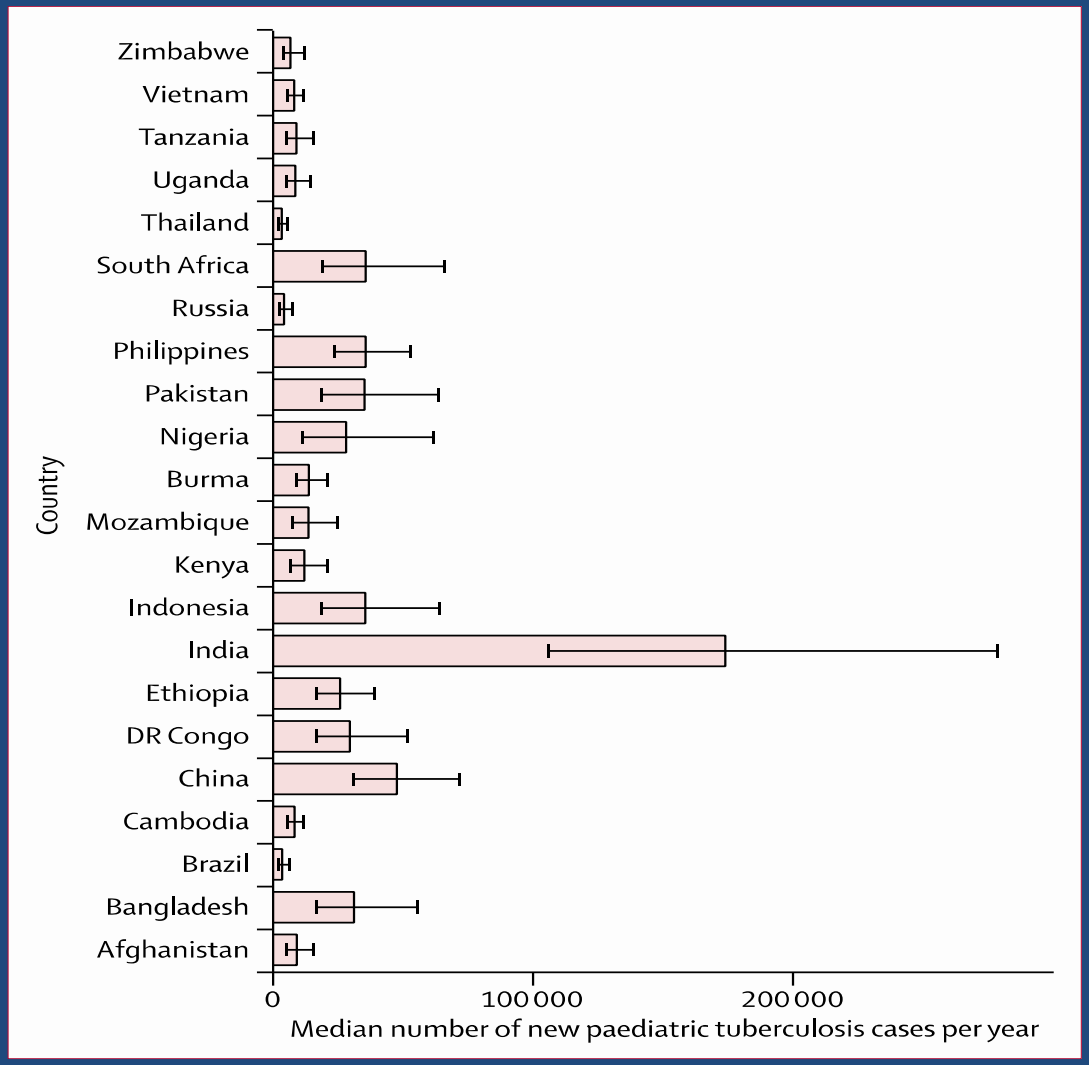
Burden of Pediatric TB in 22 HBC – a mathematical modelling study

Dodd et al. Lancet Global Health 2014;2:453

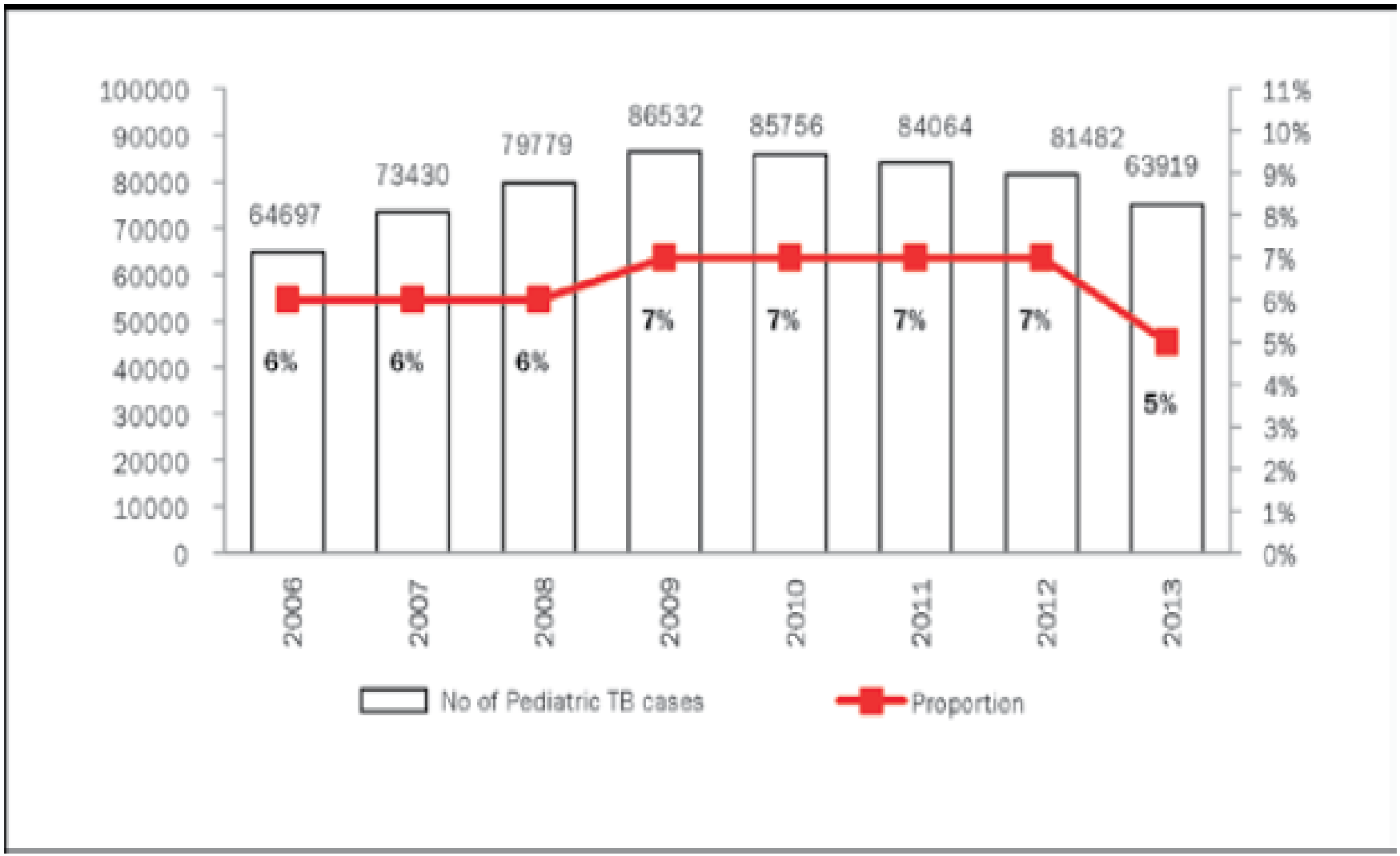
- Using TB prevalence in adults, household exposure and natural history of disease in children, authors modelled that:
  - 15 million children are exposed to TB
  - In 2010, ~7.5 million were infected with *M.tuberculosis* and ~ 650,000 had disease
  - 35% of children with TB were detected
  - India accounts for ~27% of TB burden
  - Proportion of TB burden in children correlated with incidence and varied from 4-21%

Incidence of TB higher than predicted and enormous opportunity for household interventions

Median number of TB Cases by Country, 2010



Trend of Paediatric TB cases out of all New TB cases under RNTCP



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

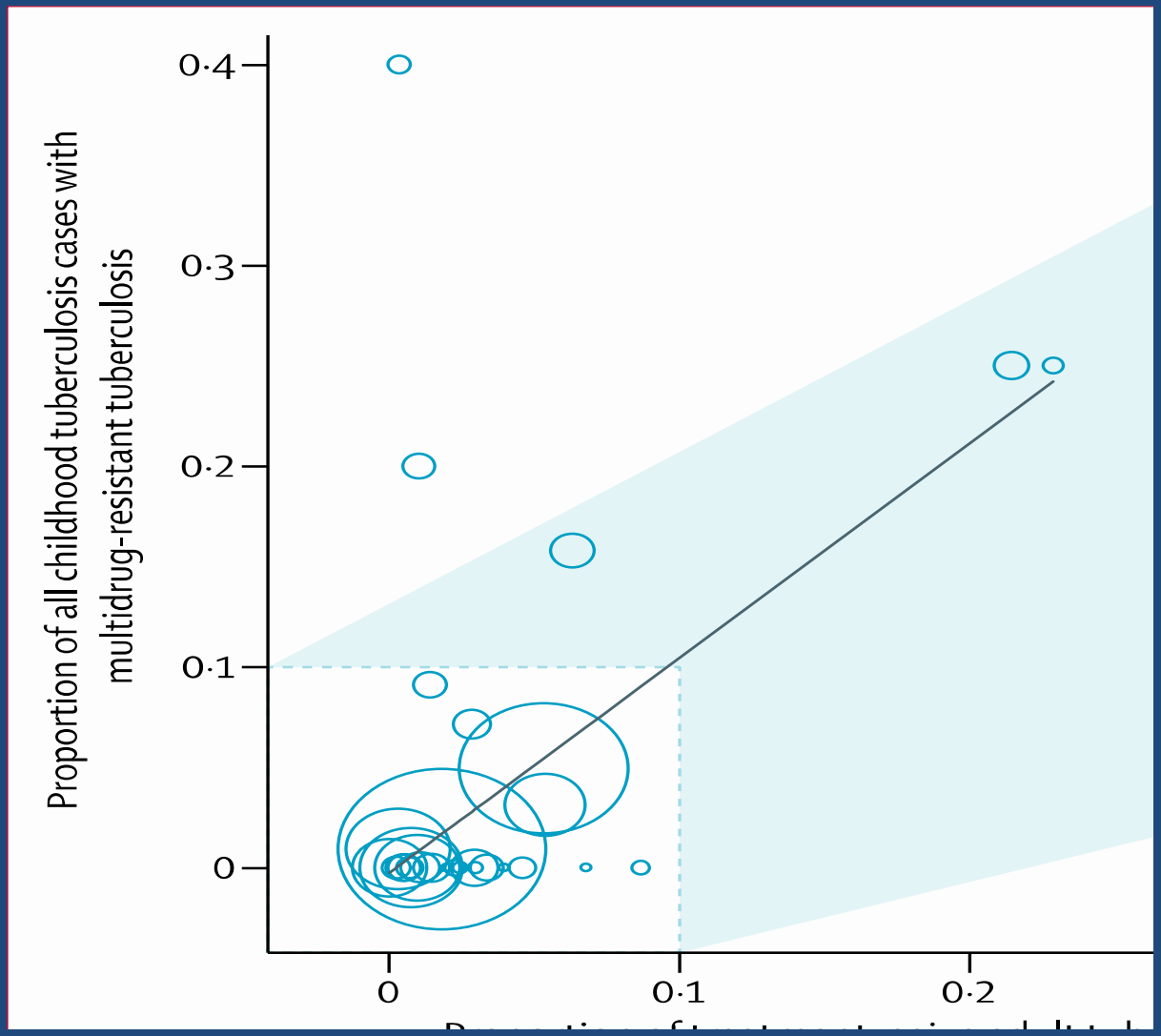
[a] Zignol et al. Multidrug-resistant tuberculosis in children: evidence from global surveillance. *European Respiratory Journal* 2013; 42:701–7.

Incidence of MDRTB in Children: systematic review and global estimates

Jenkins et al Lancet March 24 2014

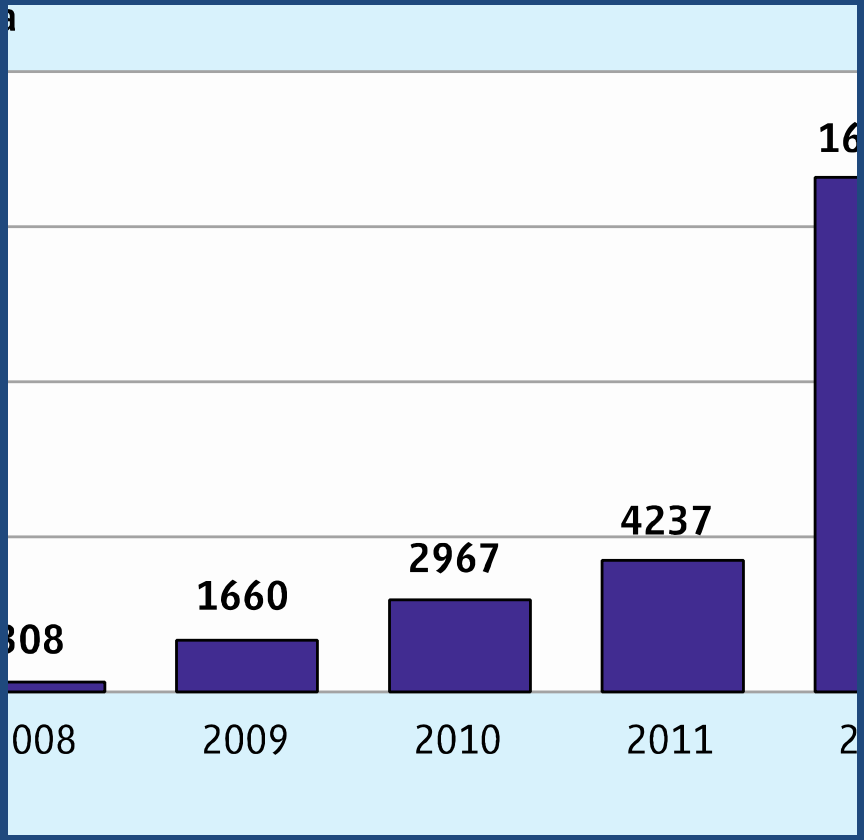
- Reviewed 97 studies of which 33 had data for both adults and children
- Setting specific risk of MDRTB was identical in treatment naïve adults and children
- Estimated ~1,000,000 new TB cases in 2010 of which ~32,000 had MDR disease
- 40% of child TB cases in SE Asia
- 10,000 children with MDRTB (1/3rd global burden) in SE Asia each year

Linear Relationship between the proportion of child and adult MDRTB cases in studies



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, accepted by RNTCP

- 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 .

Diagnosis of TB in children

- Diagnosis of PTB in children usually relies on epidemiological, clinical, and radiological findings
- Sputum is difficult to obtain by expectoration in young children
- Disease is often paucibacillary
- Diagnostic yield even when combining smear and culture is usually < 50%
- Lack of standardized case definitions

Paediatr Respir Rev 2011; 12:16–21, JID 2012;205:S199–208

Specimen Collection in Children

- Sputum Induction: outpatient setting, can be performed in young children and infants, no SAE, yield from one IS = 3 GL
- Gastric lavage = bronchoalveolar lavage
- Lymph node aspiration: safe outpatient procedure, yield higher than respiratory specimens, should be done if palpable peripheral LNs
- Combined yield of multiple specimens (sputum, NPA, SI, GA) collected in 1 day similar to yield of specimens collected over consecutive days

Value of bronchoalveolar **lavage** and **gastric lavage** in the diagnosis of pulmonary tuberculosis in children. Somu N, **Swaminathan** et al. Tuber Lung Dis. 1995 Aug;76(4):295-9.

Zar etal Arch Dis Child 2000;82:305, Owens et al Arch Dis Child 2007;92:693, Oberhelman et al Lancet ID 2010; 10:612, Al-Aghbari et al Plos One 2009; 4:e5140, Franchi LM Lancet 1999; 21:1681

Types of Specimens

Specimen	Collection procedure	Age group	Minimum volume	Best collection time	Other comments
Spontaneous sputum	Cough up sputum without prior saline nebulization	>7 years	3 ml	Early morning	If unable to produce enough sputum, consider sputum induction
Induced sputum/ laryngo-pharyngeal aspirate	hypertonic saline nebulization before cough up sputum	Any age	3 ml	Early morning	If child unable to cough, consider laryngo-pharngeal suctioning
Gastric aspirate	Nasogastric aspiration of gastric juice containing swallowed sputum	< 7 years	5 ml	Early morning before out of bed	After waking up and sitting and standing, stomach begins to empty, losing volume of aspirate

Types of Specimens

Specimen	Collection procedure	Age group	Minimum volume	Best collection time	Other comments
Gastric Lavage	Nasogastric instillation of solution to wash off and recover sputum adhered to walls of stomach	<7 years	10 ml	Early morning	Use only if at least 3 ml of gastric aspirate can not be obtained
String Test	Esophagogastro-duodenal nylon yarn that can absorb swallowed sputum	> 4 years	N/A	Unknown, duration probably more important	Consider when good quality or quantity of sputum and aspirate can not be obtained
Naso-pharyngeal aspirate	Nasopharyngeal suctioning to collect secretions from URT, but may also collect from LRT if cough reflex is stimulated	< 6 years	2 ml	Unknown, probably higher yield in morning	Yield tends to be similar to or lower than that of induced sputum or gastric aspirate/lavage

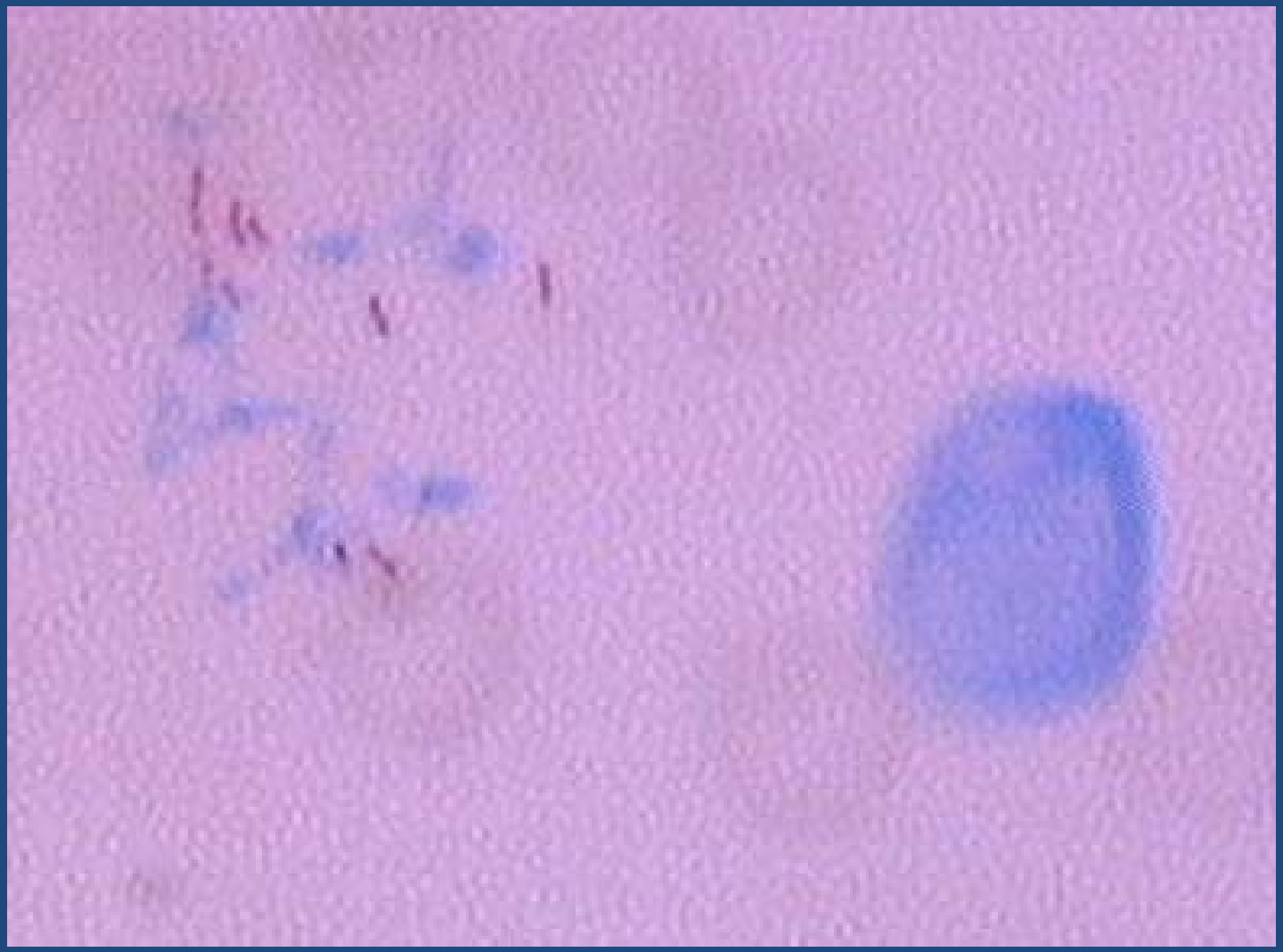
Types of Specimens

Specimen	Collection procedure	Age group	Minimum volume	Best collection time	Other comments
Stool	Uncontaminated by toilet bowl or urine	Any age	1 table-spoon (5 g)	Any time	Bacterialogic yield has been lower than that of sputum and gastric lavage and gastric aspirate
Broncho-alveolar lavage (BAL)	Bronchoscopy	Any age	3 ml	Any time	Bacteriologic yield of one sample is not superior to serial induced sputum or gastric lavage or gastric aspirate
Cerebro-spinal fluid	Lumbar puncture	Any age	2 ml	Any time	Submit 3rd or 4th tube for culture to reduce chance of contamination from skin flora

Types of Specimens

Specimen	Collection procedure	Age group	Minimum volume	Best collection time	Other comments
Serosal (pleura, pericardium, peritoneum, synovium)	Serosal fluid aspirate followed by serosal tissue biopsy	Any age	1 ml	Any time	Bacteriologic yield of tissue is much higher than fluid. Biochemical markers useful in all fluids
Urine	Clean catch, mid-stream urine	Any age	2 ml	1st morning urination	Yield low except in urinary tract TB. Lipoarab-inomannan antigen very sensitive in immuno-compromised HIV positive patients
Blood	Phlebotomy	Any age	5 ml	Any time	Yield very low, use in severely ill HIV infected patients
Fine needle aspiration	Fine needle aspiration and/or biopsy	Any age	Based on type	Any time	Useful because histo-pathological features consistent with TB can be diagnostic

AFB in FNAC of lymph node



Consensus case definition – Intra-thoracic TB

- Harmonize data collection, reporting in pediatric research studies and facilitate comparison across studies
- Prioritises children aged < 10 yrs
- Case definition considers

➢ Exposure to *M.tb*

➢ clinical signs and symptoms suggestive of TB

➢ radiological finding

➢ microbial confirmation

➢ response to treatment

JID 2012;205:S199–208

Clinical signs/symptoms suggestive of TB

- Persistent, non-remitting cough > 2 weeks not responding to a course of antibiotics.
- Weight loss -unexplained >5% reduction compared with highest wt recorded in last 3 months/ Failure to thrive
- Persistent Unexplained fever (> 1 week)
- Persistent, Unexplained Lethargy or Reduced Playfulness
- Additionally in Infants 0–60 days (or neonate)

✓ Neonatal pneumonia or

✓ Unexplained hepatosplenomegaly or

✓ Sepsis like illness

JID 2012;205:S199–208

Exposure to TB and infection

- **Exposure to TB** -Reported exposure to TB contact (household/close contact) with smear positive and/or culture positive, or TB treatment by either documented or verbal within the preceding 24 months
- **Immunological evidence of TB infection:** Positive TB skin test (using 5TU PPD or 2TU RT23)
- ≥10mm HIV-uninfected
  ≥5mm HIV-infected or severely malnourished
- Or A positive IGRA test

JID 2012;205:S199–208

Microbial confirmation

- at least 1 positive culture (with confirmed *M.tb* speciation) from sputum, which could be sampled from
- expectorated sputum
- induced sputum
- nasopharyngeal aspirates
- gastric aspirates
- or string tests (or other relevant intrathoracic samples)

JID 2012;205:S199–208

Chest radiograph

- CXR (2 views) to be read by a minimum of 2 independent, experienced and blinded readers
- Discordant reading - third expert reader opinion for a final consensus
- CXR reporting procedure

➢ overall quality of the CXR

➢ Standardized forms with predetermined terminology to describe CXR abnormalities

CXR ‘‘consistent with tuberculosis’’ - positive response for any 1 of the radiographic features, at the same location, by at least 2 expert reviewers

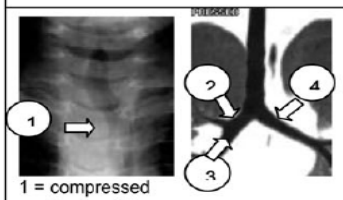
JID 2012;205:S199–208

Template Chest Radiograph Review Tool

Instructions:
Please indicate any number of locations of abnormality, using an 'X' in the appropriate numbered circle.
Then tick only one of 'Yes' or 'No' or 'Not Visible' for each category of abnormality identified (numbered 1 – 8).

1. Airway compression and/or tracheal displacement

Yes □ No □ Not Visible □

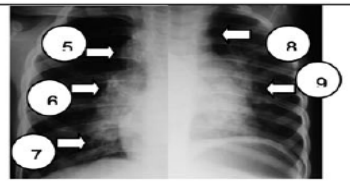


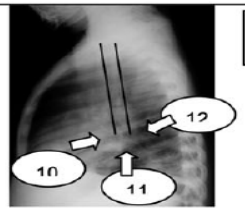
1 = compressed or displaced to **left only**

2 - 4=compression

2. Soft tissue density suggestive of lymphadenopathy

Yes □ No □ Not Visible □

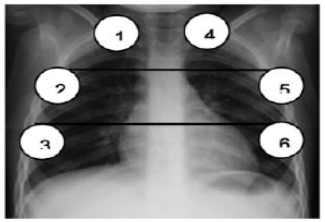


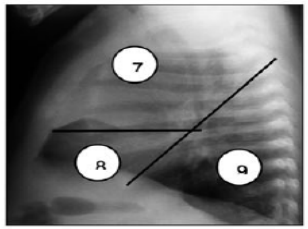


Lines indicate the trachea

3. Air space opacification

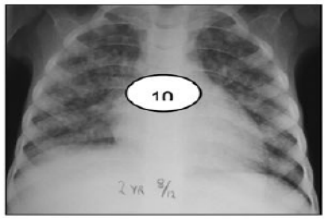
Yes □ No □ Not Visible □





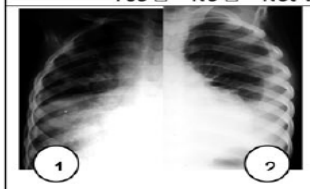
4. Nodular picture = Miliary or larger widespread and bilateral

Yes □ No □ Not Visible □



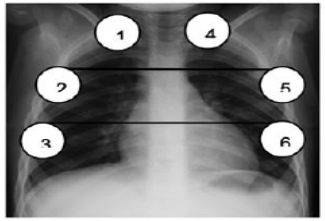
5. Pleural effusion

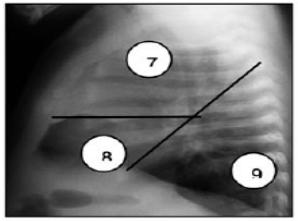
Yes □ No □ Not Visible □



6. Cavities **7. Calcified parenchyma (Ghon focus)** **8.Vertebral spondylitis**

Yes □ No □ Not Visible □





Technical quality	☐ Acceptable	☐ Poor but readable	☐ Not acceptable not readable
AP view			
Lateral view	☐ Acceptable	☐ Poor but readable	☐ Not acceptable not readable

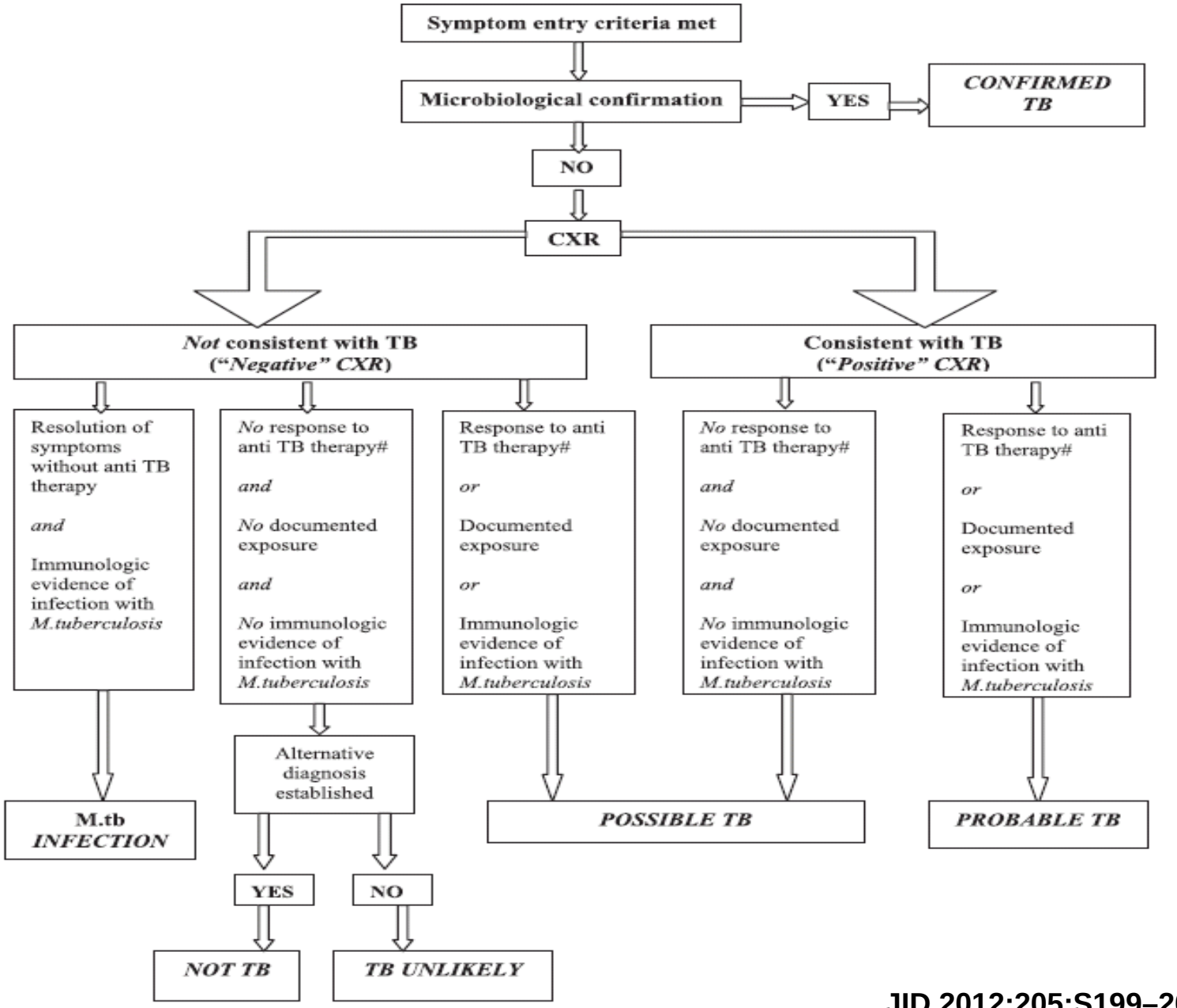
Acknowledgements: CXR Review Tool developed by S. Andronikou and The South African Tuberculosis Vaccine Initiative (SATVI).

Response to anti-TB treatment

- All patients enrolled in these studies should be followed 2 months after initial evaluation, regardless of the initial disease classification or decision to treat for TB
- Treatment other than ATT (eg, antibiotics for community-acquired pneumonia) and response to such treatment to be recorded
- In children who had received 80% treatment as per local treatment guidelines - Response to anti-TB treatment: Clinical features suggestive of TB disease that were present at baseline have improved, and there is no new clinical feature suggestive of TB

JID 2012;205:S199–208

Algorithm for classification by case definition



JID 2012;205:S199–208

Phases in clinical evaluation of new diagnostic test

- Early proof-of-principle evaluation phase - diagnostic test to distinguish symptomatic children (with microbiologically confirmed TB) from healthy controls (with and without *M.tb* infection) with reliable reproducibility
- Case-control or cross-sectional studies or on well characterized banked specimens
- Possibility of spectrum bias

JID 2012;205:S209–15

Phases in clinical evaluation of new diagnostic test

- Late evaluation studies - to measure test accuracy where it is clinically indicated and the test performance in clinical settings is as close as possible to real-life settings
- Enrolls children with the full spectrum of suspected intrathoracic TB, including those in whom a microbiological confirmation was not obtained or when alternative organisms were identified. avoiding the spectrum bias

JID 2012;205:S209–15

Enrollment of children

- Adequate representation of the appropriate age groups
- Conducted in relevant subgroups where the test may perform differently - HIV, malnutrition, or young infants
- Multiple coordinated studies at complementary sites

JID 2012;205:S209–15

Reference standard

- Paucity of data on the performance of culture in children - varies with clinical presentation, disease severity, HIV status, age, and the type of specimen tested
- Impossible to compare across studies in the absence of uniform case definitions and a suitable reference standard to adequately discriminate TB from non-TB
- Culture has high specificity – to be used as the only confirmatory test in symptomatic children in early-stage evaluations

JID 2012;205:S209–15

Standardised approach to procedures and data collection

- Standardised laboratory methodologies - sample collection, processing, transport and storage, specific diagnostic tests
- Procedures for quality assurance
- SOP for uniform collection of all data required in the clinical case definition and for obtaining microbiological confirmation (type of samples to be collected, number of cultures, and choice and sequence of laboratory tests)

JID 2012;205:S209–15

Classification of enrolled children

- Classified objectively into the proposed diagnostic categories via independent systematic review, using all data collected as specified per protocol
- Categorization should be retrospectively reviewed by an independent reviewer(s) unaware of the initial classification
- Tests should receive blinded interpretation with regard to each other

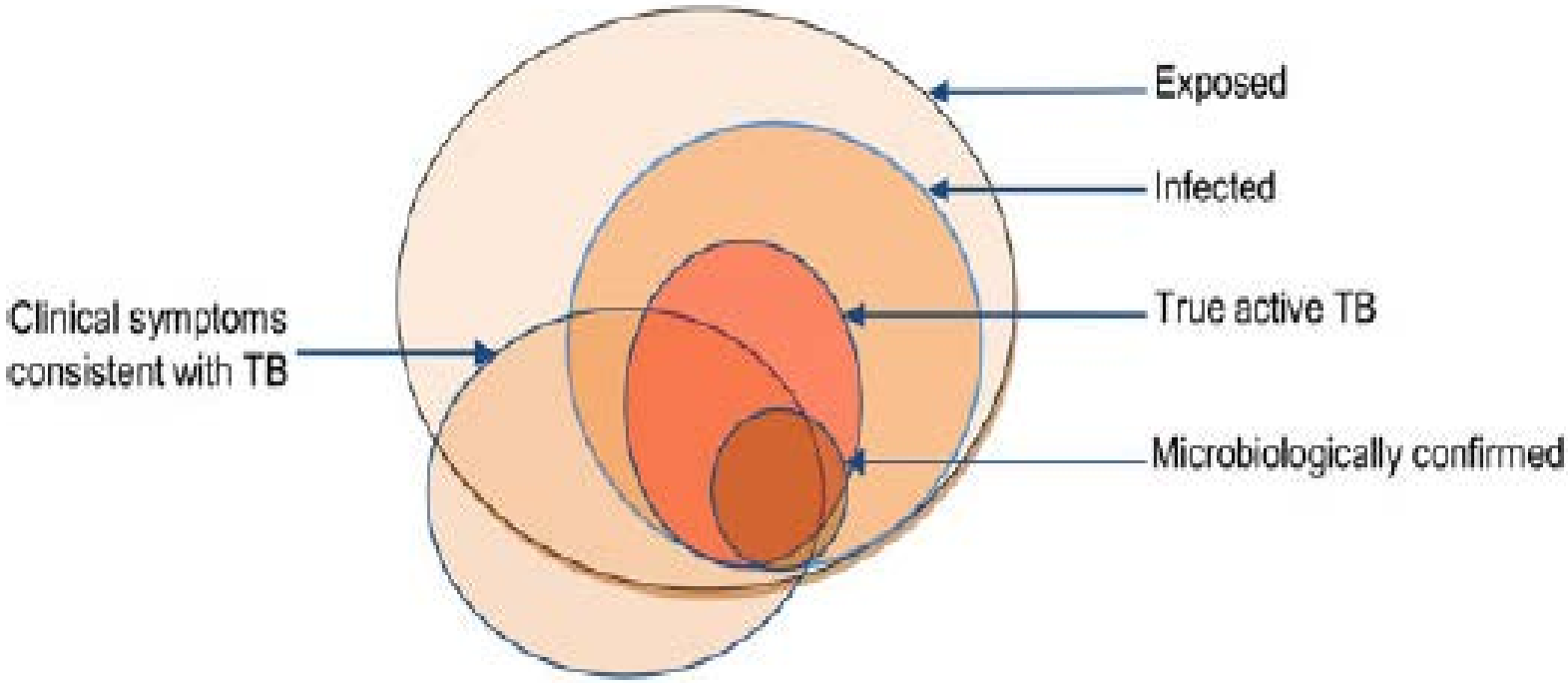
JID 2012;205:S209–15

Reporting of test results

- High proportion of TB cases missed by culture would bias the estimates of sensitivity, specificity of the diagnostic under consideration
- New diagnostic test results to be reported as the proportion of positive tests among culture-positive children and the proportion of negative tests among culture-negative children
- Characterization of the discordant cases important
- Follow STARD guidelines

JID 2012;205:S209–15

Schematic of the disease spectrum within a study population



JID 2012;205:S209–15

Layout for Reporting of Test Results

	Tuberculosis Research Case Definition				
	Confirmed	Probable	Possible	Unlikely	Not Tuberculosis
Test +	N_1 (%)[a]	N_3 (%)[a]	N_5 (%)[a]	N_7 (%)[a]	N_9 (%)[a]
Test −	N_2 (%)[a]	N_4 (%)[a]	N_6 (%)[a]	N_8 (%)[a]	N_{10} (%)[a]

The research case definition is described in Graham et al.

[a] Column percentage.

Reporting should include inconclusive results of all candidate tests performed and, as much as possible, stratification by age, HIV status, and clinical severity.

JID 2012;205:S209–15,JID 2012;205:S199–208

Xpert MTB/RIF for the diagnosis of pulmonary TB and rifampicin resistance in children

- **Xpert MTB/RIF should be used rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having MDR TB or HIV-associated TB** (Strong recommendation, very low quality of evidence)
- **Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial test in all children suspected of having TB** (Conditional recommendation, very low quality of evidence)

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Xpert MTB/RIF for the diagnosis of extra pulmonary TB in children

- **Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (lymph nodes and other tissues) from children suspected of having extrapulmonary TB**
  (Conditional recommendation, very low quality of evidence)
- **Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from children suspected of having TB meningitis**
  (Strong recommendation given the urgency of rapid diagnosis, very low quality of evidence)

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IGRA

- **Interferon-gamma release assays (IGRAs) should not replace the tuberculin skin test (TST) in low- and middle-income countries for the diagnosis of latent TB infection in children or for the diagnostic work-up of children (irrespective of HIV status) suspected of TB disease in these settings** (Strong recommendation, low quality of evidence)

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Serodiagnostics

- **Commercial serodiagnostics should not be used in children suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status** *(Strong recommendation, very low quality of evidence for the use of commercial serodiagnostics)*

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