

# Pediatric Tuberculosis: Reference Standards

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# Diagnosis of Pediatric Tuberculosis

- Diagnosis of TB in children is a major challenge
  - Paucibacillary disease
  - Difficulty in obtaining specimen
  - Variable radiological diagnosis
- Clinical case definitions have traditionally varied
  - Suspect, probable, confirmed
  - Possible, probable, confirmed

# Standardized Terminology

- Diagnostic classifications and reference standards vary across studies
  - Limits interpretation of findings
  - Hinders development of an evidence base
- Standardized research approaches and definitions needed to strengthen the evaluation of new diagnostics for detection and confirmation of TB in children

# Evaluation of Tuberculosis Diagnostics in Children: 1. Proposed Clinical Case Definitions for Classification of Intrathoracic Tuberculosis Disease. Consensus From an Expert Panel

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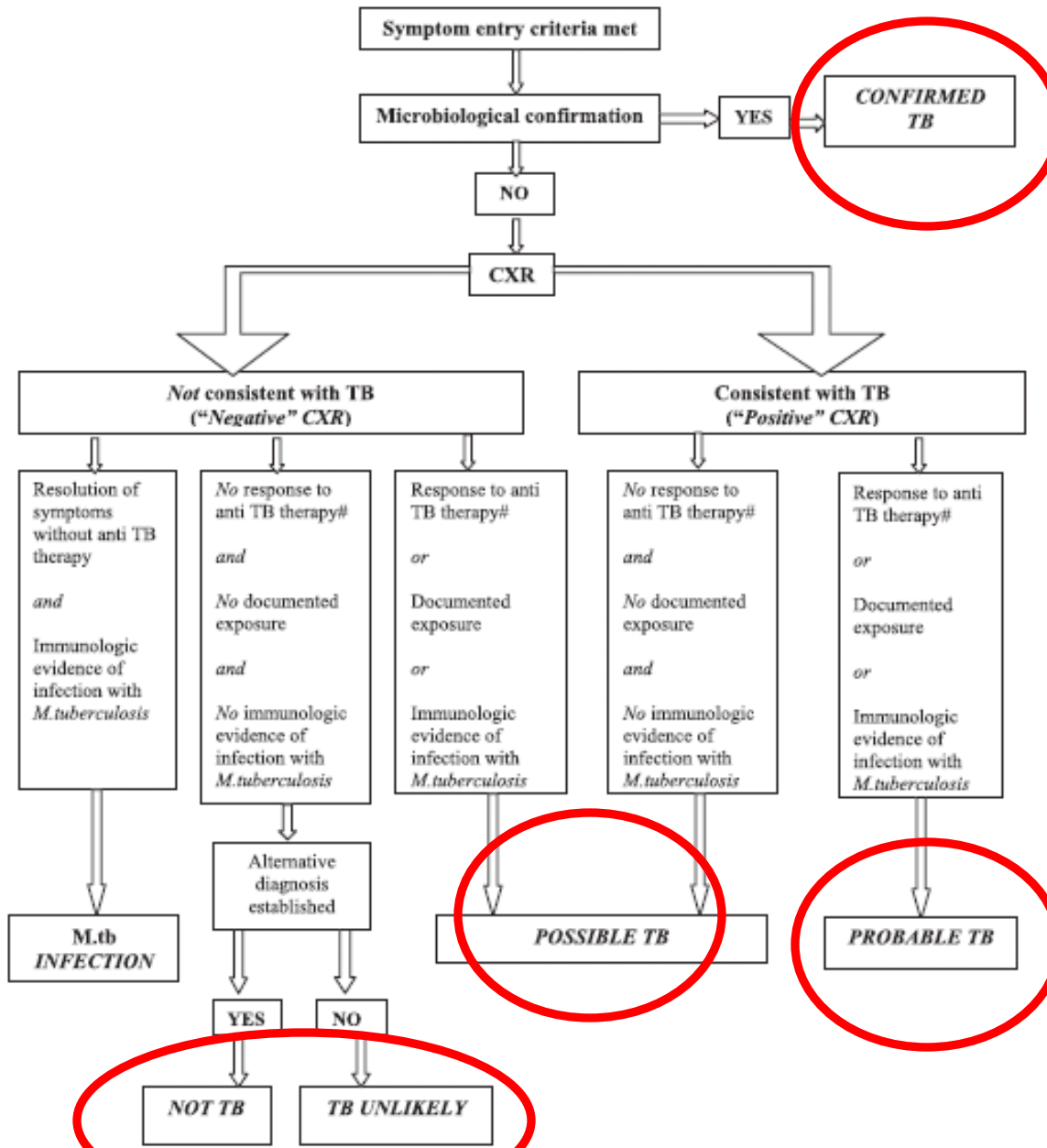
- 2011 NIH Workshop
  - “Critical Issues in Pediatric Tuberculosis Diagnostics Research in HIV-Infected and Uninfected Children”
- Consensus clinical case definitions for intrathoracic tuberculosis diagnosis
  - Intended for use in clinical research to evaluate diagnostic assays and not for clinical decisions

# Reference Standards for Intrathoracic TB in Children

Diagnostic Group	Definition of Case Categories
Confirmed TB	<ol style="list-style-type: none"> <li>1. At least 1 of signs/symptoms suggestive of TB and</li> <li>2. Microbiological confirmation</li> </ol>
Probable TB	<ol style="list-style-type: none"> <li>1. At least 1 of signs/symptoms suggestive of TB and</li> <li>2. CXR consistent with intrathoracic TB AND</li> <li>3. Either clinical response to anti-TB treatment or documented exposure or immunological evidence of infection</li> </ol>
Possible TB	<ol style="list-style-type: none"> <li>1. At least 1 of signs/symptoms suggestive of TB and</li> <li>2. Either a positive clinical response to treatment or documented exposure to TB or immunological evidence of MTB infection OR</li> <li>3. CXR consistent with intrathoracic TB</li> </ol>
TB unlikely	Symptomatic but not fitting the above definitions and no alternative diagnosis
Not tuberculosis	Fitting TB unlikely but with alternative diagnosis established

# Consensus Definitions

	Criteria
1. Microbial confirmation	At least 1 positive culture
2. Clinical signs/symptoms	Persistent cough
	Weight loss
	Failure to thrive
	Persistent unexplained fever
	Persistent unexplained lethargy or reduced playfulness
	Neonatal pneumonia or unexplained HSM or sepsis-like illness in infants 0-60 days of age
3. Interpretation of CXR	Reading/reporting
4. TB exposure	History of exposure
	Immunological evidence of MTB infection
5. Response to anti-TB treatment	Follow-up/response

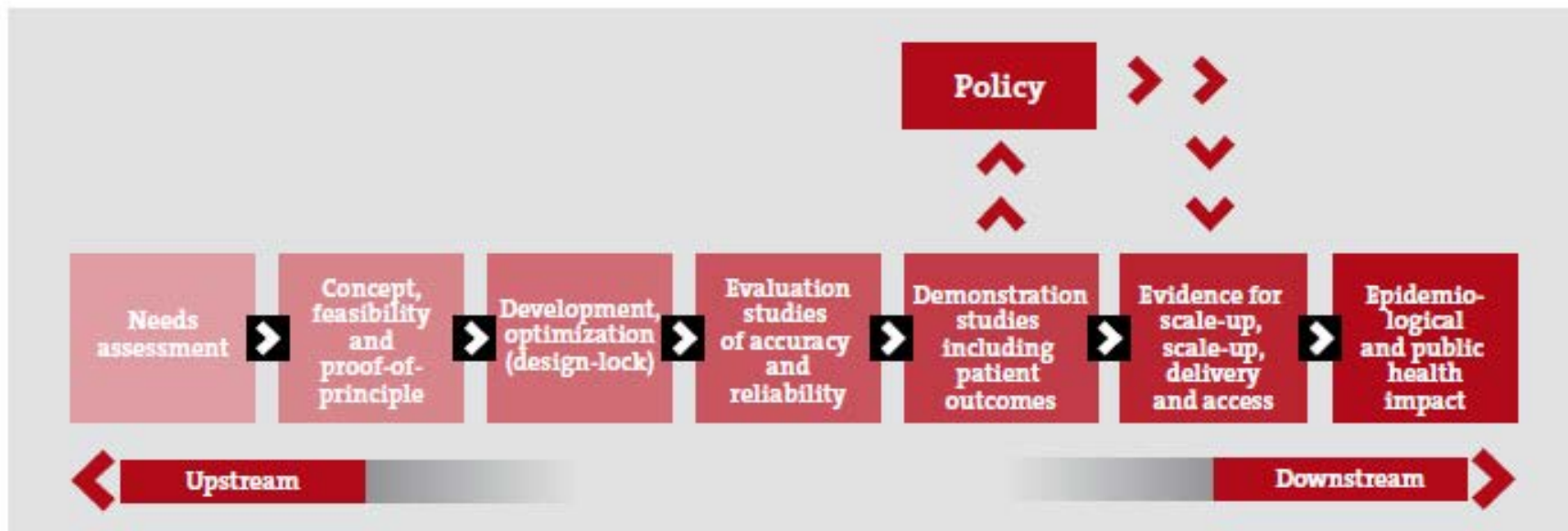


# Evaluation of Tuberculosis Diagnostics in Children: 2. Methodological Issues for Conducting and Reporting Research Evaluations of Tuberculosis Diagnostics for Intrathoracic Tuberculosis in Children. Consensus From an Expert Panel<sup>a</sup>

Luis E. Cuevas,<sup>1</sup> Renee Browning,<sup>2</sup> Patrick Bossuyt,<sup>3</sup> Martina Casenghi,<sup>4</sup> Mark F. Cotton,<sup>5</sup> Andrea T. Cruz,<sup>6</sup> Lori E. Dodd,<sup>7</sup> Francis Drobniowski,<sup>8</sup> Marianne Gale,<sup>9</sup> Stephen M. Graham,<sup>10</sup> Malgosia Grzemska,<sup>11</sup> Norbert Heinrich,<sup>12</sup> Anneke C. Hesselning,<sup>13</sup> Robin Huebner,<sup>14</sup> Patrick Jean-Philippe,<sup>2</sup> Sushil Kumar Kabra,<sup>15</sup> Beate Kampmann,<sup>16,17</sup> Deborah Lewinsohn,<sup>18</sup> Meijuan Li,<sup>19</sup> Christian Lienhardt,<sup>11</sup> Anna M. Mandalakas,<sup>20</sup> Ben J. Marais,<sup>21</sup> Heather J. Menzies,<sup>22</sup> Grace Montepiedra,<sup>23</sup> Charles Mwansambo,<sup>24</sup> Richard Oberhelman,<sup>25,26</sup> Paul Palumbo,<sup>27</sup> Estelle Russek-Cohen,<sup>28</sup> David E. Shapiro,<sup>23</sup> Betsy Smith,<sup>29</sup> Giselle Soto-Castellares,<sup>30</sup> Jeffrey R. Starke,<sup>6</sup> Soumya Swaminathan,<sup>31</sup> Claire Wingfield,<sup>32</sup> and Carol Worrell<sup>33</sup>

- Consensus statements on methodological issues for conducting and reporting research of TB diagnostics in children
  - Focus on intrathoracic TB





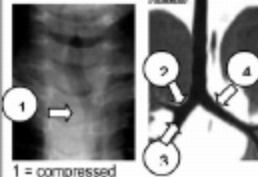
- Enrollment of children using symptom-based criteria
- Stratification by age and HIV status
  - 0 to <2 years
  - 2 to < 5 years
  - 5 to < 10 years
  - $\geq 10$  years
- Development of standard references and standardized approach to procedures, definitions and data reporting

## Template Chest Radiograph Review Tool

**Instructions:**

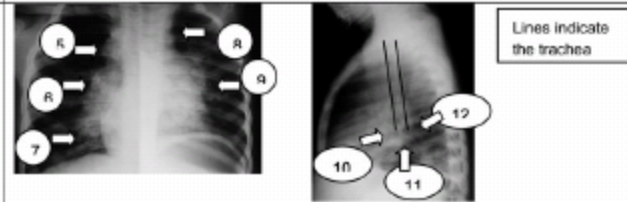
Please indicate any number of locations of abnormality, using an 'X' in the appropriate numbered circle.  
Then tick only one of 'Yes' or 'No' or 'Not Visible' for each category of abnormality identified (numbered 1 – 8).

**1. Airway compression and/or tracheal displacement**  
Yes  No  Not Visible



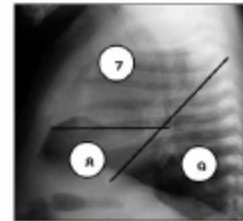
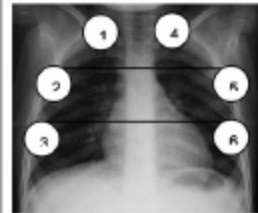
1 = compressed or displaced to left only  
2 - 4 = compression

**2. Soft tissue density suggestive of lymphadenopathy**  
Yes  No  Not Visible

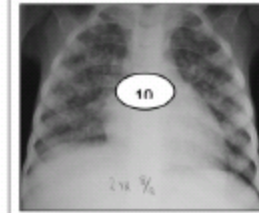


Lines indicate the trachea

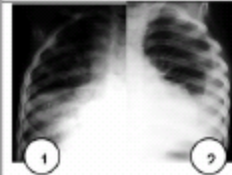
**3. Air space opacification**  
Yes  No  Not Visible



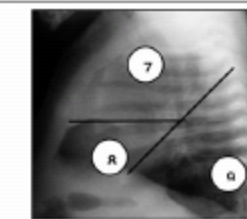
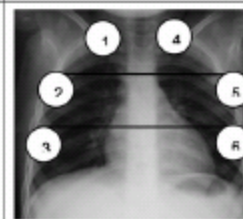
**4. Nodular picture = Miliary or larger widespread and bilateral**  
Yes  No  Not Visible



**5. Pleural effusion**  
Yes  No  Not Visible



**6. Cavities**    **7. Calcified parenchyma (Ghon focus)**    **8. Vertebral spondylitis**  
Yes  No  Not Visible



**Technical quality**

AP view

Lateral view

Acceptable

Acceptable

Poor but readable

Poor but readable

Not acceptable not readable

Not acceptable not readable

# Methodological Issues

**Table 2. Layout for Additional Reporting of Index Test Results**

	Tuberculosis Research Case Definition				
	Confirmed	Probable	Possible	Unlikely	Not Tuberculosis
Test +	$N_1$ (%) <sup>a</sup>	$N_3$ (%) <sup>a</sup>	$N_5$ (%) <sup>a</sup>	$N_7$ (%) <sup>a</sup>	$N_9$ (%) <sup>a</sup>
Test -	$N_2$ (%) <sup>a</sup>	$N_4$ (%) <sup>a</sup>	$N_6$ (%) <sup>a</sup>	$N_8$ (%) <sup>a</sup>	$N_{10}$ (%) <sup>a</sup>

- To better assess accuracy of tests, test summaries should be reported with respect to the disease certainly classification

# Research Definitions for Drug-Resistant Tuberculosis in Children

- Sentinel Project on Pediatric Drug-Resistant Tuberculosis (2011)
  - > 200 researchers, healthcare providers and advocates from > 40 countries
- Establishment of standardized definitions for key variables, terms, and outcomes in research
  - Not intended for use by clinicians for management of children with DR-TB infection or disease

# Consensus Definitions

- Epidemiology
  - Exposure
    - DR-TB index, source, and contact case
- Disease classification
  - TB infection, DR-TB infection, TB disease, DR-TB disease
- Type of treatment
  - DR-TB treatment, DT-TB preventive therapy
- Categories of drug resistance
  - Mono-resistant, poly-resistant, MDR, XDR

# Consensus Definitions

Table 2. Classification According to Previous Disease Episodes, Diagnostic Certainty, and Description of Drug-Resistant Tuberculosis Disease in Children

	Recommended Term	Definition
Certainty of diagnosis of TB disease [18]	Confirmed TB disease	At least 1 of the signs and symptoms suggestive of TB disease <sup>a</sup> and microbiological confirmation of <i>M tuberculosis</i>
	Probable TB disease	At least 1 of the signs and symptoms suggestive of TB disease <sup>a</sup> and the CR is consistent with intrathoracic TB disease <sup>b</sup> and presence of 1 of the following: (a) a positive clinical response to TB treatment, (b) documented exposure to a source case with TB disease, or (c) immunological evidence of TB infection
	Possible TB disease	At least 1 of the signs and symptoms suggestive of TB disease <sup>a</sup> and either (a) a clinical response to TB treatment, documented exposure to a source case with TB disease or immunological evidence of TB infection, or (b) CR consistent with intrathoracic TB disease <sup>b</sup>
Certainty of diagnosis of DR-TB disease	Confirmed DR-TB disease	At least 1 of the signs and symptoms suggestive of TB disease <sup>a</sup> and detection of <i>M tuberculosis</i> from the child with demonstration of genotypic or phenotypic resistance
	Probable DR-TB disease	DR-TB contact and diagnosis of probable TB disease
	Possible DR-TB disease	Diagnosis of probable TB disease together with either (a) contact of a source case with TB disease who has risk factors for drug resistance <sup>c</sup> or (b) failure of first-line TB treatment
Previous episodes and treatment	Previous TB disease episode	An episode of TB disease in which treatment was given for at least 1 month, after which there was a reported symptom-free period of ≥6 months before the start of the current DR-TB disease episode
	DR-TB disease episode	If DR-TB disease is subsequently confirmed, a TB disease episode that began when the child is first documented to have presented to the healthcare system, when the specimen was obtained that eventually confirmed DR-TB disease, or when the child commenced any TB treatment, whichever is the first available documented event [27]
	Previously treated with first-line TB drugs	Treatment for 1 month or more with any drug in Drug Group 1 [2]
	Previously treated with second-line TB drugs	Treatment for 1 month or more with any drug in Drug Groups 2-5 [2]
Site of TB and disease severity	ICD-10 code	Code to be recorded [31]
	Severe disease	A clinical syndrome classified as uncontrolled, <sup>d</sup> disseminated, <sup>e</sup> or complicated <sup>f</sup> [29]
	Nonsevere disease	A clinical syndrome classified as controlled (limited), non-disseminated, and uncomplicated [29]

# Conclusions

- Pediatric TB comprises a substantial portion of the global burden of TB
- Currently there is a paucity of informative data on diagnostics of pediatric TB
- Standardization of definitions and terminology will allow improvements in data collection for clinical research and strengthen the evaluation of new diagnostics for confirmation of TB in children