Reference Standard in Pediatric TB Diagnostics Evaluation

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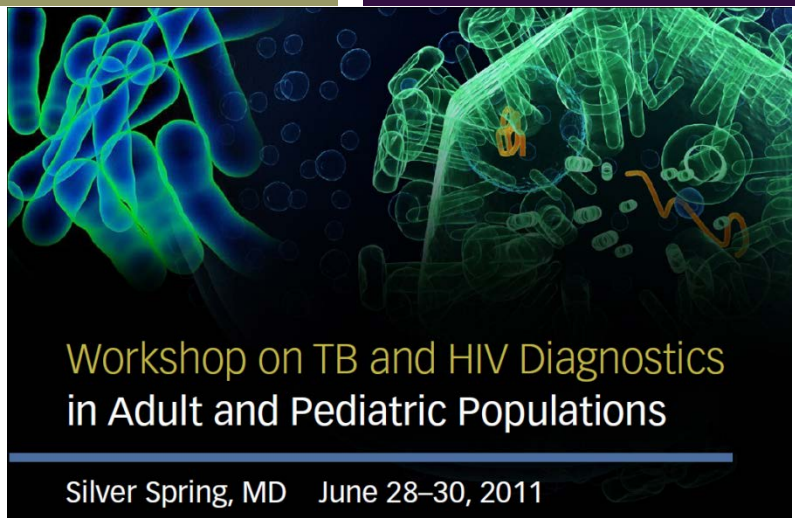

TB in children(1)

- Estimated 10-15% overall TB burden; disproportionate
- Confirming TB Dx in children challenging
  - Most childhood TB smear-negative (paucibacillary)
  - Current diagnostics perform poorly
  - Many cases missed, childhood TB underreported
- Research challenges
  - Lack of a reference standard that performs well
  - Lack of standardized approach for evaluating TB diagnostics in children
  - Studies not comparable, data difficult to interpret
  - Challenges in generating reliable diagnostic accuracy estimates

TB in children(2)

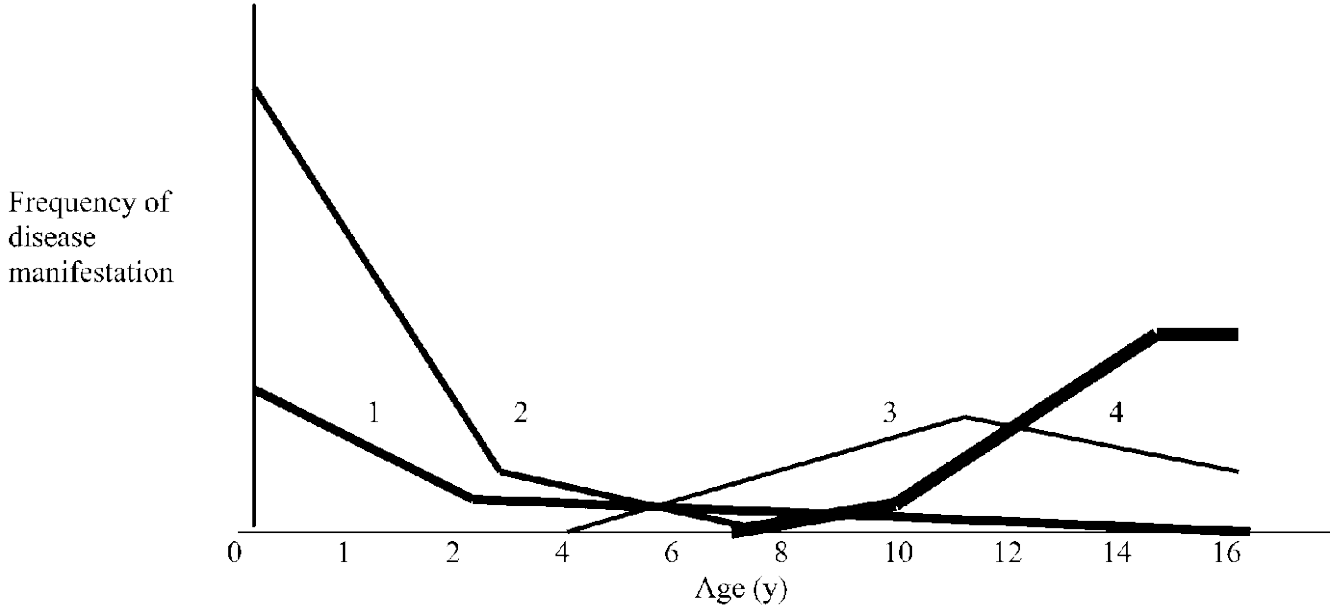

FIG. 2. Age-related manifestations of pulmonary tuberculosis in immune-competent children. 1. Complicated Ghon focus and/or disseminated disease. 2. Complicated lymph node disease. 3. Pleural effusion. 4. Adult-type disease.

Marais BJ, Ann Trop Paed., 2005

Reference Standard in Pediatric TB Diagnostics Evaluation – NIH panel, June 2011

- Aim: propose a standardized approach to evaluating TB diagnostics in children
- Scope:
  - Intrathoracic TB
  - Children ≤ 10 years
- Methods:
  - Literature review focusing on approaches to evaluate diagnostics when reference standards are imperfect
  - Preparation of statements on methods to be used and dissemination to expert panel for review in advance of workshop
  - Consensus obtained at workshop after discussion and vote on each statement. ≥ 75% of panel participants had to agreed to statement and no vetoes.

Reference Standard in Pediatric TB Diagnostics Evaluation – *JID 2012*

SUPPLEMENT ARTICLE

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[a]

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

Cuevas et al, JID 2012;205:S209

SUPPLEMENT ARTICLE

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

Stephen M. Graham,[1,2] Tahmeed Ahmed,[3] Farhana Amanullah,[4] Renee Browning,[5] Vicky Cardenas,[6] Martina Casenghi,[7] Luis E. Cuevas,[8] Marianne Gale,[9] Robert P. Gie,[10] Malgosia Grzemska,[11] Ed Handelsman,[12] Mark Hatherill,[13] Anneke C. Hesseling,[14] Patrick Jean-Philippe,[5] Beate Kampmann,[15,16] Sushil Kumar Kabra,[17] Christian Lienhardt,[11] Jennifer Lighter-Fisher,[18] Shabir Madhi,[19] Mamodikoe Makhene,[20] Ben J. Marais,[21] David F. McNeeley,[22] Heather Menzies,[23] Charles Mitchell,[24] Surbhi Modi,[25] Lynne Mofenson,[26] Philippa Musoke,[27] Sharon Nachman,[28] Clydette Powell,[29] Mona Rigaud,[18] Vanessa Rouzier,[30] Jeffrey R. Starke,[31] Soumya Swaminathan,[32] and Claire Wingfield[33]

Graham et al, JID 2012;205:S199

Reference Standard in Pediatric TB Diagnostics Evaluation - Consensus(1)

- Evaluation should be in two phases: Early and late phases
  - Early phase studies:
    - Culture should be the reference standard
      - High specificity useful to establish index test discriminatory ability

Reference Standard in Pediatric TB Diagnostics Evaluation - Consensus(2)

- Late phase studies:
  - Culture as reference standard
    - Specific but lacks sensitivity
  - Xpert MTB/RIF: insufficient data in children to be considered a reference standard (revisit as data accumulate)
  - A positive sputum smear (without speciation) is inadequate as a definitive reference standard (NTM contamination)
  - Insufficient evidence on performance of current diagnostic tests to develop a laboratory-based reference standard – more studies needed
    - Approach needed to report TB suspect cases with negative culture

Reference Standard in Pediatric TB Diagnostics Evaluation - Consensus(3)

- Proposed approach: evaluate yield of an index test relative to disease certainty (Graham et al.): microbial confirmation, Probable/Possible/Unlikely/Not TB, i.e. proportion of positive and negative tests within each category
- Describe data by diagnostic modality (Chest Xray consistent with TB, TB exposure, immunologic evidence of TB, treatment response) for further elucidation of properties of index test

	Tuberculosis research case definition				
	Confirmed	Probable	Possible	Unlikely	Not TB
Test +	N_1 (%)*	N_3 (%)*	N_5 (%)*	N_7 (%)*	N_9 (%)*
Test -	N_2 (%)*	N_4 (%)*	N_6 (%)*	N_8 (%)*	N_{10} (%)*

Reference Standard in Pediatric TB Diagnostics Evaluation - Consensus(4)

- Statistical methods for evaluation of diagnostics when reference standard inadequate e.g. Latent Class Analysis (LCA) and others, aiming to derive diagnostic accuracy estimates:
  - Methods have many limitations, including that estimated sensitivity and specificity may depend heavily on the model assumptions, which cannot be validated
  - Discordance resolution analysis often statistically flawed and of limited utility
  - More research applying these methods in pediatric TB diagnostics is necessary

Reference Standard in Pediatric TB Diagnostics Evaluation – Consensus(5)

- Approach proposed constitutes a framework for rigorous, systematic, standardized data collection
- May provide additional data to validate definitions or value of individual diagnostic components
- Follow up may provide data to inform clinical validity and impact evaluation
- Panel did not specify a reference standard to obtain diagnostic accuracy estimates.
- Emphasis placed on evaluation stage/diagnostic accuracy (lower quality evidence per GRADE criteria), rather than demonstration stage

Reference Standard in Pediatric TB Diagnostics Evaluation - Acknowledgements

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