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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There is a critical need for improved diagnosis of tuberculosis in children, particularly in young children with intrathoracic disease as this represents the most common type of tuberculosis in children and the greatest diagnostic challenge. There is also a need for standardized clinical case definitions for the evaluation of diagnostics in prospective clinical research studies that include children in whom tuberculosis is suspected but not confirmed by culture of *Mycobacterium tuberculosis*. A panel representing a wide range of expertise and child tuberculosis research experience aimed to develop standardized clinical research case definitions for intrathoracic tuberculosis in children to enable harmonized evaluation of new tuberculosis diagnostic technologies in pediatric populations. Draft definitions and statements were proposed and circulated widely for feedback. An expert panel then considered each of the proposed definitions and statements relating to clinical

definitions. Formal group consensus rules were established and consensus was reached for each statement. The definitions presented in this article are intended for use in clinical research to evaluate diagnostic assays and not for individual patient diagnosis or treatment decisions. A complementary article addresses methodological issues to consider for research of diagnostics in children with suspected tuberculosis.

It is widely acknowledged that there is a critical need for improved accuracy of the diagnosis of tuberculosis in children [1–4]. Although acid-fast bacilli smear and sputum culture provide reliable standards in adults, in young children the diagnosis of tuberculosis is usually not confirmed microbiologically, particularly in tuberculosis-endemic settings with limited access to culture facilities. The diagnosis of pulmonary tuberculosis, the most common type of tuberculosis in young children, usually relies on a cluster of epidemiological, clinical, and radiological findings [1, 2]. Sputum is difficult to obtain by expectoration in young children and disease is often paucibacillary; the diagnostic yield even when combining smear and culture is usually <50% [2]. The delay in the identification of *Mycobacterium tuberculosis* using conventional culture methods further decreases the clinical utility of culture in treatment decisions.

The recent surge in the development of new tuberculosis diagnostics for more rapid and accurate diagnosis [5–8] highlights the lack of standardized case definitions for prospective clinical research in children with suspected tuberculosis. Clinical definitions used to date have been inconsistent and have performed variably when evaluated [9]. Although valid for comparisons within studies, these limitations make it impossible to compare diagnostic performance across studies or to provide any data for meta-analyses [3]. It is important that studies of novel diagnostics are conducted in a range of settings and pediatric populations, including young children. There is, therefore, a need for standardized clinical case definitions that can be used for the evaluation of tuberculosis diagnostics in prospective research that includes children in whom tuberculosis is suspected but not confirmed by culture of *M. tuberculosis*.

Expert clinicians, researchers, and other opinion leaders in pediatric tuberculosis were invited to a workshop organized by the National Institutes of Health, "Critical Issues in Pediatric Tuberculosis Diagnostics Research in HIV-Infected and Uninfected Children," that was held 28–30 June 2011. The workshop aims were (1) to obtain consensus on clinical case definitions for intrathoracic tuberculosis diagnosis in children and (2) to standardize methodological approaches for evaluation of new tuberculosis diagnostic tests in children. This article reports on the first of these aims, and an article by Cuevas et al in this issue of the *Journal* [10] reports on the second. The definitions are intended for clinical research use to evaluate diagnostic assays and not for use in making individual patient diagnoses or treatment decisions.

METHODS FOR OBTAINING CONSENSUS

Prior to the workshop, the literature was surveyed and statements were prepared separately for each aim. For the consensus clinical case definitions, the existing literature on tuberculosis in children was reviewed for signs and symptoms, clinical case definitions, existing research case definitions, or existing systematic reviews. Similarly, for the reference standard, the existing literature was reviewed for approaches to an imperfect reference standard when a gold standard is not available. Draft definitions were circulated to experts for review and comment during a series of teleconference calls. Statements were compiled prior to the meeting and constituted the basis for discussion at the workshop.

During the workshop, an expert panel considered each of the statements relating to clinical definitions. These were modified based on expert discussions, following which edited statements underwent a vote. Formal group consensus rules were established and consensus was reached for each statement. A separate expert panel considered statements relating to diagnostic methodological approach [10]. All definitions were further reviewed in a plenary workshop session that included participants from both expert panels.

CONSIDERATIONS ON CHALLENGES FOR DIAGNOSTIC STUDIES

Age Considerations

Although children across the entire age spectrum should be included in tuberculosis diagnostic studies, there is a particular need to ensure the inclusion of children <10 years of age because they represent the greatest diagnostic challenge. Within this group, it is critical that the youngest children (0–2 years) are adequately represented in diagnostic studies. Although studies focusing on young children are the most critical, studies of older children and adolescents are also needed. The 10- to 18-year age group presents a different spectrum of disease manifestations, including adult-type disease, and respiratory samples can be more readily obtained.

Disease Considerations

The diagnosis of intrathoracic tuberculosis is the focus of this discussion; improved diagnosis is vital to better define and manage tuberculosis-related morbidity and mortality in children. The case definitions are, therefore, aimed at studies

Table 1. Clinical Case Definition Categories for Intrathoracic Tuberculosis in Children

Clinical Diagnostic Groups	Definition of Case Categories
Confirmed tuberculosis	Patients with suspected TB should be classified as ''confirmed TB'' when they present with:
	1. At least 1 of the signs and symptoms suggestive of tuberculosis[a]
	and
	2. Microbiological confirmation is obtained[a]
Probable tuberculosis	Patients suspected of tuberculosis should be classified as ''probable tuberculosis'' cases when they present with:
	1. At least 1 of the signs and symptoms suggestive of tuberculosis[a]
	and
	2. Chest radiography is consistent with intrathoracic disease due to *Mycobacterium tuberculosis*[a]
	and
	3. There is at least 1 of the following:
	(a) A positive clinical response to anti-tuberculosis treatment[a]
	(b) Documented exposure to *M. tuberculosis*[a]
	(c) Immunological evidence of *M. tuberculosis* infection[a]
Possible tuberculosis	Patients suspected of tuberculosis should be classified as ''possible tuberculosis'' when they present with at least 1 of the signs and symptoms suggestive of tuberculosis[a]
	and either
	(1) One of the following:
	(a) A positive clinical response to anti-tuberculosis treatment[a]
	(b) Documented exposure to *M. tuberculosis*[a]
	(c) Immunological evidence of *M. tuberculosis* infection[a]
	or
	(2) Chest radiography is consistent with intrathoracic tuberculosis disease[a]
	NB: if at least 1 of (1) and (2) are both present, then this case should be
	classified as ''probable tuberculosis.''
Tuberculosis unlikely	Symptomatic but not fitting the above definitions and no alternative diagnosis established
Not tuberculosis	Fitting the diagnosis for tuberculosis unlikely but with an established alternative diagnosis.

[a] Defined in Table 2.

of symptomatic children with suspected intrathoracic disease due to *M. tuberculosis*. They are not intended for use in studies of diagnostic approaches for infection with *M. tuberculosis* and therefore may not be appropriate for studies that incorporate the active investigation of possible tuberculosis in children who may not have typical or well-defined symptoms, for example, household case-finding studies or infant tuberculosis vaccine trials.

There are 2 main reasons why children with intrathoracic disease are the focus of the clinical case definitions: (1) Intrathoracic tuberculosis represents the largest burden of disease (>75%) [11, 12] and biological sampling methods are the most challenging in this group, especially in young children [2]; and (2) Forms of extrathoracic tuberculosis present with a variety of clinical features depending on the site of involvement (eg, lymph nodes or vertebrae); therefore, diagnosis involves examination of nonrespiratory samples or other investigations. Separate clinical definitions, such as those that have been proposed for lymphadenitis or meningitis caused by *M. tuberculosis*, are therefore required for research purposes [13, 14].

Consideration of Comorbidities

Children with potentially confounding comorbidities (ie, factors that may alter the clinical presentation, disease spectrum, or diagnostic yield) should be included, especially as they often present the greatest diagnostic challenge and highest tuberculosis-associated mortality. These include human immunodeficiency virus (HIV) infection and malnutrition.

CLINICAL CASE DEFINITIONS

In developing case definitions, the panel considered several principles to be important: (1) categorical, simplified approaches should be used to minimize subjectivity and standardize data collection; (2) case definition requirements should not render diagnostic studies unfeasible in low-resource settings; and (3) the paucity of evidence for certain case definition components should not be considered a barrier to constructing a pragmatic framework, as revisions can and will be made as new evidence comes to light. The consensus clinical case definition categories and related definition statements are summarized in Tables 1 and 2.

Children enrolled in diagnostic studies should be evaluated at baseline and followed regardless of initial disease classification or treatment decision. Recommended follow-up should be 2 months after treatment initiation or 2 months after baseline if untreated. Additional suggested data collection time points include 2 weeks after treatment initiation/baseline and 6 months after treatment initiation/baseline (or at completion of therapy).

Confirmed tuberculosis cases will be children with at least 1 sign or symptom suggestive of tuberculosis and microbiologically confirmed tuberculosis, defined as at least 1 positive culture with *M. tuberculosis* speciation from a specimen representative of intrathoracic disease (Table 2). Children with at least 1 sign or symptom suggestive of tuberculosis, but without microbiologic confirmation, will be classified as either *probable*, *possible*, *unlikely*, or *not* tuberculosis, using an algorithm (Figure 1).

Table 2. Details and Definitions for Research Evaluation and Reporting Purposes

1. Microbial confirmation

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

2. Clinical signs/symptoms suggestive of tuberculosis

(a) Persistent cough

Definition: persistent (>2 weeks), nonremitting cough.

(b) Weight loss/failure to thrive:

Definition: unexplained weight loss: >5% reduction in weight compared with the highest weight recorded in last 3 months.

or

Definition: failure to thrive.

1. Clear deviation from a previous growth trajectory and/or

2. Documented crossing of percentile lines in the preceding 3 months and/or

3. Weight for age z score of ≤ -2 in the absence of information on previous/recent growth trajectory and/or

4. Weight for height z score of ≤ -2 in the absence of information on previous/recent growth trajectory

and

Not responding to nutritional rehabilitation (or antiretroviral therapy if HIV infected)

Persistent unexplained fever

Definition: persistent (>1 week) and unexplained fever (>38°C) reported by a guardian or objectively recorded at least once.

Persistent, unexplained lethargy or reduced playfulness

Definition: persistent, unexplained lethargy or decrease in playfulness/activity reported by the parent/caregiver.

Infants 0–60 days (or neonate)

Additional[a] signs and symptoms suggestive of tuberculosis include

(a) Neonatal pneumonia[b] or

(b) Unexplained hepatosplenomegaly[b] or

(c) Sepsislike illness[b]

3. Interpretation of CXR

CXR reading procedure:

–CXR (2 views) will be read by a minimum of 2 independent and blinded readers who are experienced in reviewing CXRs in children.

–The overall quality of the CXR will be indicated.

–In the case of discordant reading, a third expert reader will be used and a final consensus achieved.

CXR reporting procedure:

–Standardized forms with predetermined terminology to describe CXR abnormalities.

–Essential radiological features with tick boxes (example in Figure 2) will be used by experienced readers.

–Predetermined yes/no options for the CXR reader.

Definition: 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.

4. Tuberculosis exposure

Definition: history of exposure to *M. tuberculosis*.

Reported exposure to a case of tuberculosis (household/close contact) within the preceding 24 months:

–Documented (smear positive and/or culture positive, or tuberculosis treatment).

Table 2 continued.

or

–Not documented but verbal report (smear positive and/or culture positive, or tuberculosis treatment).

Definition: immunological evidence of *M. tuberculosis* infection.

–A positive tuberculin skin test (using 5TU PPD or 2TU RT23) defined as

≥ 10 mm if HIV uninfected.

≥ 5 mm if HIV infected or severely malnourished.

or

A positive IGRA test

5. Response to anti-tuberculosis treatment

Follow-up: All patients enrolled in these studies should be followed after initial evaluation, regardless of the initial disease classification or decision to treat for tuberculosis. Treatment other than anti-tuberculosis treatment (eg, antibiotics for community-acquired pneumonia) and response to such treatment should be recorded.

All patients should undergo clinical assessment and data collection 2 months after baseline or after treatment initiation for those treated with anti-tuberculosis treatment. Note that not all children with symptoms will receive anti-tuberculosis treatment, and follow-up at 2 months would be a useful time (in addition to earlier assessments) to assess resolution of symptoms without anti-tuberculosis treatment and/or clinical response to alternative therapy (if any).

Additional suggested data collection time points:

–2 weeks after baseline or after treatment initiation for those treated with anti-tuberculosis treatment.

–6 months after treatment initiation for those treated with anti-tuberculosis treatment (or at end of anti-tuberculosis treatment).

Appropriate anti-tuberculosis treatment for presumed drug-susceptible tuberculosis should meet the following criteria:

(a) Treatment with standard regimens in accordance with local or international tuberculosis treatment guidelines (define in protocol).

(b) Satisfactory adherence proposed as 80% adherence by pill count or self-reported

Definition: Response to anti-tuberculosis treatment should be evaluated at 2 months after anti-tuberculosis treatment has commenced using standardized forms with tick-box options for recording (eg, improvement or not of each clinical feature suggestive of tuberculosis disease indicated as yes/no option).

Response to anti-tuberculosis treatment is defined as

1. Response to anti-tuberculosis therapy: clinical features suggestive of tuberculosis disease that were present at baseline have improved, and there is no new clinical feature suggestive of tuberculosis.

or

2. No response to anti-tuberculosis therapy: clinical features suggestive of tuberculosis disease that were present at baseline have not improved.

Abbreviations: CXR, chest radiograph; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; PPD, purified protein derivative.

[a] Previous symptoms are all relevant.

[b] If other causes are excluded or not responding to appropriate treatment thereof.

Probable tuberculosis cases will include children with at least 1 sign or symptom suggestive of tuberculosis and a chest radiograph (CXR) consistent with intrathoracic tuberculosis disease and at least 1 of the following: (1) positive clinical response to anti-tuberculosis therapy, (2) documented
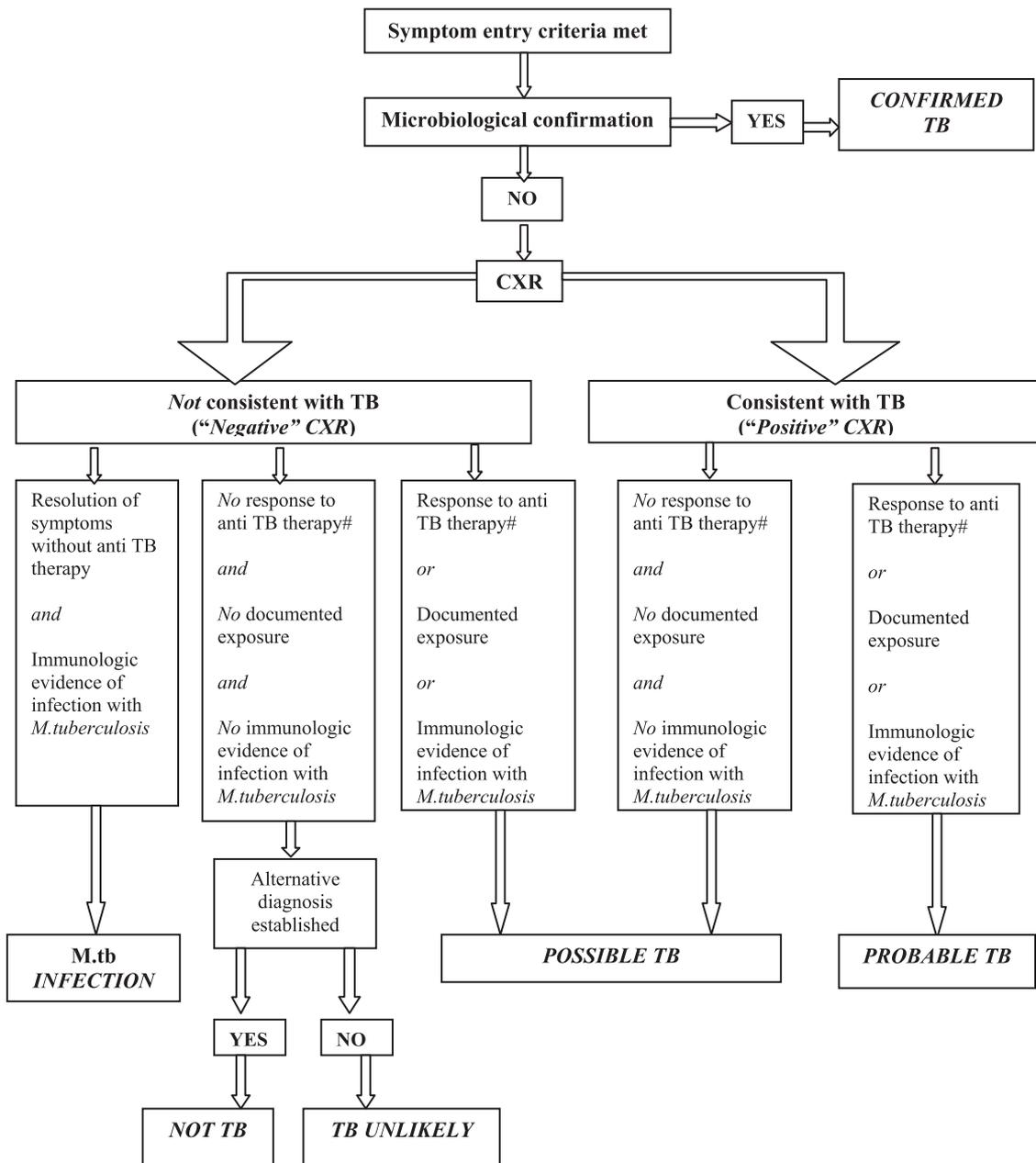
Figure 1. Algorithm for classification of case definitions for research reporting. #Response or no response to anti-tuberculosis therapy is only relevant if anti-tuberculosis therapy was given as determined by clinical indications. A trial of treatment should NOT be used as a diagnostic tool.

exposure to a household or close contact with a tuberculosis case, or (3) immunologic evidence of *M. tuberculosis* infection by a positive tuberculin skin test (TST) or tuberculosis interferon-γ release assay (IGRA).

Possible tuberculosis cases will include children with at least 1 sign or symptom suggestive of tuberculosis and who have either: (1) a CXR that is not consistent with intrathoracic

M. tuberculosis disease and at least 1 of the following: positive clinical response to anti-tuberculosis therapy, documented exposure to a household or close contact with a tuberculosis case, or immunologic evidence of *M. tuberculosis* infection (TST or IGRA positivity) or (2) a CXR consistent with intrathoracic *M. tuberculosis* disease but none of the other characteristics listed in (1).

Symptomatic children who do not fit into the foregoing categories are either *unlikely tuberculosis* cases (if no alternative diagnosis is established) or *not tuberculosis* cases (if an alternative diagnosis is established, for example, cardiac disease, foreign body aspiration, or asthma). We note that an alternative diagnosis, such as pneumococcal pneumonia or bronchiectasis, does not necessarily exclude tuberculosis because of the possibility of coinfection.

Children who lack clinical symptoms or signs meeting the consensus definition but nevertheless demonstrate a positive culture with *M. tuberculosis*, or CXR consistent with intrathoracic disease due to *M. tuberculosis*, do not fall within the scope of these recommendations. Therefore, these children should not be considered as *confirmed* or *probable* cases in studies of new tuberculosis diagnostics, but they may be appropriate for inclusion in other tuberculosis research. Data on these potential subpopulations should be collected to inform the current evidence base.

DEFINITIONS

The need for standardized terminology to report on exposure to *M. tuberculosis*, clinical signs and symptoms suggestive of tuberculosis, radiological findings, microbial confirmation, and response to treatment is paramount, to harmonize data collection and reporting in pediatric research studies and facilitate comparison across studies. The consensus definitions are listed in Table 2. These definitions are intended for diagnostic studies to enable study comparability. These definitions are not intended to guide clinical decision making or reporting of childhood tuberculosis.

Definition of Confirmation

At least 1 positive culture of *M. tuberculosis* in a sample originating from an intrathoracic site (eg, sputum, gastric aspirate, bronchoalveolar lavage, or intrathoracic biopsy) is sufficient evidence for confirmation. Positive smear microscopy in the absence of a positive culture of *M. tuberculosis* is not sufficient to confirm tuberculosis because false-positive results can be due to specimen contamination with or disease caused by nontuberculous mycobacteria. Multiple respiratory sampling should always be attempted.

Definition of Clinical Symptoms and Signs Suggestive of Tuberculosis

Standardized definitions are proposed for the most common presenting clinical signs and symptoms that prompt clinical evaluation for intrathoracic tuberculosis (Table 2). These definitions are for purposes of reporting of diagnostic evaluation studies of suspected intrathoracic tuberculosis cases and not to define criteria for enrollment in such studies. Importance was placed on chronicity and persistence of unexplained symptoms despite standard treatments for cough, fever, and lethargy, such as antibiotics for community-acquired pneumonia or antimalarial therapy. It is recognized that children with intrathoracic tuberculosis may present with acute symptoms, especially infants, and so might be evaluated for a diagnosis of tuberculosis before the symptoms have become ''persistent.'' It is also recognized that children with intrathoracic tuberculosis may show improvement of symptoms with antibiotics for community-acquired pneumonia as they are also susceptible to bacterial pneumonia. However, in this scenario, symptoms are likely to persist and not fully resolve without anti-tuberculosis treatment.

Agreement was more difficult to reach on whether the nutritional definitions should be broad or restrictive for the proposed terminology for weight loss and failure to thrive. Weight evaluation in settings of high tuberculosis endemicity is often complex because of the high prevalence and impact of comorbidities, such as HIV and malnutrition. Different tools exist to evaluate and report weight loss. Weight loss was defined as an unexplained >5% reduction in weight, compared with the highest weight recorded in last 3 months. The panel felt that either weight loss or failure to thrive could be used, but that using a percentage of median and standard deviation from the median such as z scores might be too technical to apply as a field tool. Therefore, failure to thrive might be defined by any 1 of 4 criteria as listed in Table 2, varying in the level of detail, plus a lack of response to nutritional rehabilitation (or antiretroviral therapy if the child is HIV infected).

Finally, additional clinical syndromes compatible with tuberculosis in infants aged 0–60 days were included to reflect the broad spectrum of nonspecific clinical manifestations in that age range and to encourage inclusion of very young infants in research. Infants with neonatal pneumonia, unexplained hepatosplenomegaly, or sepsislike illness, where other causes are excluded or not responding to appropriate treatment, should be evaluated for tuberculosis when other causes have been excluded or when they are not responding to other appropriate treatment.
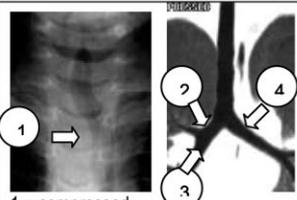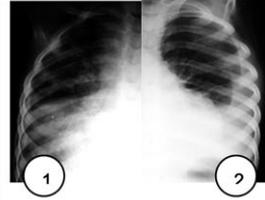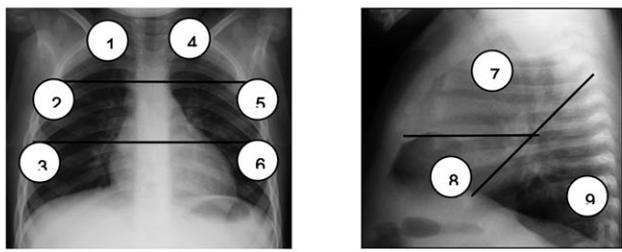
Radiological Definitions: Procedures and Terminology

Discussions on procedures for review, reporting, and classification of CXRs for diagnostic research purposes were contentious, and agreement on the final revised statement was achieved by a narrow margin. The draft statement proposed a rigorous approach, given the pivotal role of CXR in determining tuberculosis diagnoses in young children with smear- and culture-negative disease, and the poor inter- and intraobserver agreement among reviewers for hilar and paratracheal lymphadenopathy, which are the most common diagnostic features expected [15]. This rigorous approach called for an independent review of anterior-posterior and lateral CXR images by 2 expert readers who were blinded to the clinical data, a third reader to resolve discordant opinions, and an

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
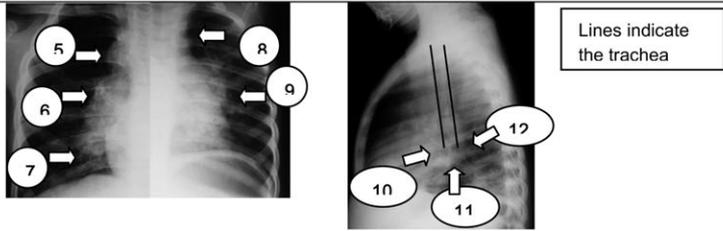
3. Air space opacification

   Yes □   No □   Not Visible □

4. Nodular picture = Miliary or larger widespread and bilateral

   Yes □   No □   Not Visible □
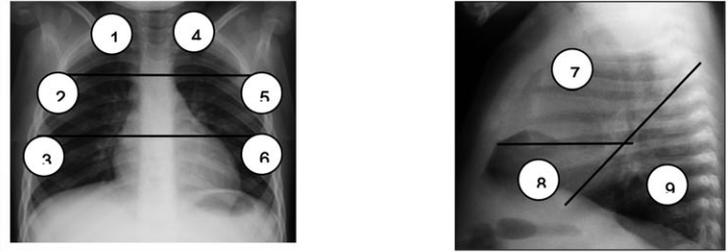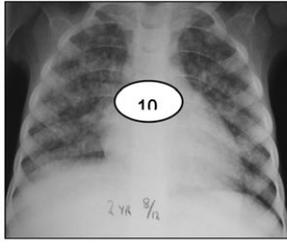
5. Pleural effusion

   Yes □   No □   Not Visible □

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

   Yes □   No □   Not Visible □

Technical quality			
AP view	□ Acceptable	□ Poor but readable	□ Not acceptable not readable
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).

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.

assessment of the technical quality of the image. Independent review, which prevents bias by any individual opinion, and blinding to nonradiographic data, which prevents bias by the clinical scenario, were thought to be key elements.

Independent, blinded expert panel review requires suitably qualified reviewers who are not part of the immediate study team; this review process is therefore independent of routine case management. These experts might be pediatric radiologists, pediatricians, or physicians, depending on the capacity of the study setting. A reliable and secure system for capture, distribution, and storage of digital CXR images is vital. If digital radiography is not available, hard copy CXR films might be digitalized using a high-quality flatbed scanner. The contrary view was that these high standards might be difficult to achieve at rural field sites, particularly in developing economies with a high tuberculosis burden. It was felt that these stringent requirements would discourage childhood tuberculosis diagnostic research in low-resource settings and that the process might have to be adapted to local conditions.

The draft statement initially proposed that each CXR should be classified by the reviewer as "consistent with tuberculosis," "uncertain," "normal," or "abnormal, but not tuberculosis." This subjective classification was removed and replaced by an approach that requires a "yes" or "no" response to the presence of cardinal radiological features and that indicated the location of abnormal features. This revised approach does not include the option of indicating uncertainty and was unanimously approved. The descriptive terminology for abnormal radiological features should be predetermined and standardized, such as that proposed by Marais et al [16] or as illustrated in Figure 2. Figure 2 is a sample CXR review tool that was developed for use in pediatric tuberculosis vaccine trials. Positive identification by at least 2 expert reviewers of any of these abnormal radiological features, at the same location, classifies a CXR as being "consistent with tuberculosis."

Definitions of Exposure to *M. tuberculosis* and Immunological Evidence of *M. tuberculosis* Infection

A history of exposure to *M. tuberculosis* is defined as a reported close contact to a person with active tuberculosis. The term "close contact" refers to contact within the prior 24 months either within the household or outside the household when there is regular, close contact such as in school or day care. The timing and duration of contact exposure should be recorded when available. As documentation of proof of exposure is often unrealistic in the field, a verbal report of close contact to an index case is acceptable. For research purposes, documentation of an index case can consist of smear and/or culture results and/or response to anti-tuberculosis therapy.

The biological diagnostic hallmark of *M. tuberculosis* infection is primarily based on the cellular immune response of the host, as evidenced by a reactive TST or a positive IGRA. A valid and positive TST or IGRA result is considered immunological evidence of *M. tuberculosis* infection. Despite its recognized limitations, TST has been used for more than a century as an immunological surrogate marker for *M. tuberculosis* infection. In the context of research, albeit arbitrarily, an acceptable definition of a positive TST postintradermal 5TU purified protein derivative or 2TU RT23 (Serum Statens Institut) is a ≥10-mm skin induration in an HIV-uninfected child or a ≥5-mm induration in an HIV-infected or severely malnourished child, regardless of BCG vaccination in the neonatal period. A decade ago, IGRAs emerged as a potential alternative to TST [17]. Studies over the last 10 years in children, mainly in the low tuberculosis endemic setting, have demonstrated the improved specificity of IGRAs compared with TST, but as for TST, the sensitivity of IGRAs is variable [18] and a more sensitive biomarker of *M. tuberculosis* infection is required and is the focus of current research (see McNerney et al in this issue [19]). While the limitations of both tests are acknowledged, the panel has concluded that a positive TST or IGRA result provides evidence of *M. tuberculosis* infection for purposes of research reporting.

Definitions of Response to Antituberculosis Treatment

Response to therapy for intrathoracic tuberculosis requires treatment with a minimum of 3 appropriate anti-tuberculosis medications, and includes an understanding of the complexities of possible exposure and treatment of multidrug-resistant tuberculosis as well as dosing of these therapies across pediatric age ranges. The symptoms of children with tuberculosis usually respond promptly to anti-tuberculosis treatment within 1–2 months of starting therapy, and children tolerate treatment well with a very low risk of toxicity. An appropriate response to therapy includes weight gain (or improvement of failure to thrive), the resolution of symptoms within 2 months, and the improvement of CXR findings in the long term. However, treatment response lacks specificity as an indicator of tuberculosis because other infections causing similar symptoms may resolve while the child is receiving anti-tuberculosis treatment. Furthermore, a lack of response does not exclude tuberculosis as a possible diagnosis. Treatment response to anti-tuberculosis therapy may be poor in children with tuberculosis for a number of reasons: poor treatment adherence, drug-resistant tuberculosis (see Zumla et al in this issue [20]), coinfection with other pathogens, or underlying chronic lung disease. Additionally, HIV-infected children on antiretroviral therapy may present with immune reconstitution inflammatory syndrome as worsening CXR and symptoms but does not represent tuberculosis treatment failure.

Not all children who present with symptoms suggestive of intrathoracic tuberculosis in the context of a diagnostic evaluation study will be treated for tuberculosis, as alternative diagnoses will be considered and treated accordingly. Other

treatments, such as antibiotics for community-acquired pneumonia, and response to such treatment should be routinely recorded, as the information is important for classifying children in the "not tuberculosis" category (Table 1 and Figure 1).

Formal follow-up assessment for treatment response should be at 2 months after initiation of anti-tuberculosis treatment, and is done on the basis of clinical features. Response to treatment at this time and other follow-up time points, including at the end of treatment, should be recorded on standardized forms with predetermined terminology and tick-box options for recording. Treatment of identified comorbidities and treatment response must be recorded. Additionally, adherence should be recorded and observed therapy may be needed to ensure adherence. Given the lack of an evidence-based definition for response to tuberculosis treatment as a diagnostic criterion, the panel highlighted the need for rigorous future research in this area.

DISCUSSION

A significant proportion of the tuberculosis disease burden, morbidity, and mortality in areas with high tuberculosis prevalence occurs in children [1, 21, 22]. However, tuberculosis diagnosis is usually not microbiologically confirmed [2]. Improved tuberculosis diagnostic tests in children would not only improve individual clinical management but would allow for a more accurate determination of the global burden of tuberculosis in children, improve clinical research for the prevention and treatment of pediatric tuberculosis, and allow greater integration of pediatric tuberculosis into national tuberculosis control programs [23].

Progress in developing better tuberculosis diagnostics has been slow. There is an urgent need for a rapid, reliable, and affordable diagnostic test for tuberculosis [6]. It is critical that new tests be properly validated in children of all ages as well as in adults (Nahid et al, this issue [24]). The consequences of undiagnosed, untreated tuberculosis in young children are substantial and are exacerbated due to the rapid progression to disseminated tuberculosis [25]. Additionally, microbiological confirmation and drug susceptibility testing are essential in the context of the emerging drug-resistant tuberculosis epidemic, affecting children as well as adults [20, 26, 27]. New, improved diagnostics may provide the opportunity to expand on the definition of confirmed tuberculosis in the future [7, 10].

Because of the lack of a microbiological "gold standard," it has been difficult to evaluate the sensitivity and specificity of clinical definitions of tuberculosis in children. Clinical scoring systems have been developed, but they lack standard symptom definition and adequate validation [4, 9, 28]. Various attempts to improve specificity of symptom definition have not performed well in some of the groups at highest risk for severe disease and poor outcomes, including children <3 years of age, HIV-infected children, and malnourished children [29, 30]. There are examples of clinical case definitions in adults with sputum smear–negative pulmonary tuberculosis [31, 32]. However, there are important differences in clinical and radiological findings between adults and children with intrathoracic tuberculosis, as well as important epidemiological variations in high-burden settings that will affect the predictive value of clinical criteria.

The CXR is an important part of the clinical assessment for intrathoracic tuberculosis in children, and is critical to define "probable" tuberculosis cases. Therefore, the panel applied particular rigor to the development of a standardized approach to CXR assessment, including recommendation for evaluation by 2 independent readers experienced in reviewing pediatric CXRs and blinded to clinical categorization, and the use of standardized forms with predetermined terminology to describe radiologic findings.

Similarly, the panel attempted to apply rigor to the definition of response to anti-tuberculosis treatment that is based on 2 essential elements: (1) recording clinical response on standardized forms with clear definition of timeline and (2) ensuring adequacy of treatment with attention to correct dosage, adherence, drug susceptibility of the organism when known, and management of comorbidities. It is acknowledged that the evidence base in this regard needs to be expanded.

Trials using these clinical case definitions should employ robust data collection methods, using standardized and harmonized data definitions and data standards as well as standardized laboratory procedures. This will allow for the discrimination of the factors most predictive of the outcome of interest and for the refinement of elements used in the case definitions, as well as comparison between studies.

It is important to emphasize that the clinical case definitions for intrathoracic tuberculosis are not intended for clinical management but for the standardization of research results of tuberculosis diagnostics. It will be important to develop similar case definitions for extrathoracic tuberculosis in children. Finally, these definitions are not intended to be used for studies of *M. tuberculosis* infection, which will require different methodologies and will likely use TST or IGRA as the reference standard for comparison. Emerging data and high-quality evidence should inform these proposed consensus case definitions.

Notes

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