Consensus Statement on Diagnostic End Points for Infant Tuberculosis Vaccine Trials

Mark Hatherill,1,2 Suzanne Verver,3,4 Hassan Mahomed,1,2 and the Taskforce on Clinical Research Issues, Stop TB Partnership Working Group on TB Vaccines

1South African Tuberculosis Vaccine Initiative (SATVI), 2Institute of Infectious Disease and Molecular Medicine (IIDMM), University of Cape Town, South Africa; 3KNCV Tuberculosis Foundation, The Hague, and 4Center for Infection and Immunity Amsterdam (CINIMA), Academic Medical Centre Amsterdam, The Netherlands

Background. Definition of clinical trial end points for childhood tuberculosis is hindered by lack of a standard case definition. We aimed to identify areas of consensus or debate on potential end points for tuberculosis vaccine trials among human immunodeficiency virus–uninfected children.

Methods. Thirty-eight opinion leaders participated in a Consensus Workshop at the Second Global Forum on TB Vaccines (Estonia, 2010). Outcomes were categorized as unanimity, modified consensus, or lack of consensus. Individual reservations were noted.

Results. Modified consensus was achieved on 3 issues: (1) unsuitability of historical BCG trial end points as sole primary end points for modern infant trials; (2) symptomatic, complicated intrathoracic tuberculosis as an uncommon but clinically relevant disease phenotype; (3) primary complex tuberculosis in younger children as a common, high-risk phenotype, with a high rate of spontaneous resolution. Participants agreed that radiologic diagnosis of intrathoracic tuberculosis would be based primarily on hilar lymphadenopathy. Lack of consensus was noted for (1) significance of isolated culture of *Mycobacterium tuberculosis* and (2) the need for evidence of prior tuberculosis exposure to support a diagnosis of tuberculosis disease. Reservations were expressed regarding use of interferon-γ release assays and the clinical relevance, and potential for misclassification, of primary complex tuberculosis.

Conclusions. The Workshop did not achieve consensus on a single primary end-point definition. Tuberculosis disease phenotypes with optimal diagnostic certainty will be uncommon in the study population. Criteria for composite or multiple end points were identified, and we propose a hierarchy of end-point criteria, based on rate of occurrence, clinical relevance, and diagnostic certainty.

Large proof-of-concept efficacy trials of new tuberculosis vaccines have begun in infants, but immunological correlates of vaccine protection against tuberculosis have not yet been identified [1]. Discovery and validation of such correlates will first require identification of children who are protected, or not protected, against a clinical tuberculosis disease end point by an efficacious vaccine [1]. It follows that definition of clinical, radiologic, and microbiologic end points remains crucial for efficacy trials of new tuberculosis vaccines. Unfortunately, despite a number of published scoring systems and algorithms, and given the lack of sensitivity of mycobacterial culture as a diagnostic gold standard, there is no validated standard case definition for childhood tuberculosis [2, 3]. Ideally, infant tuberculosis vaccine efficacy trials need a single primary end point, characterized by high sensitivity and specificity, direct clinical and public health relevance, and high incidence in the study population. End-point sensitivity is important to detect all cases of tuberculosis and optimize statistical power. However, because misclassification of other illnesses as false-positive tuberculosis cases will dilute observed vaccine efficacy, specificity is vital [4]. The process of end-point definition must also consider the age-specific risk of severe morbidity and mortality for any given
tuberculosis phenotype and the expected rate of occurrence of different tuberculosis phenotypes in a modern vaccine trial study population [5–7].

Efficacy trial end points are traditionally defined with respect to clinically significant morbidity and mortality because advanced disease outcomes have greater public health significance [8]. However, it has been recognized that diseases with a long clinical course, including tuberculosis, may require more pragmatic, proximal end points [8, 9]. Childhood tuberculosis manifests as different phenotypes along a continuum from local pulmonary infection, uncomplicated intrathoracic disease, and complicated intrathoracic disease, to extrapulmonary or disseminated disease and death [6]. Complicated intrathoracic tuberculosis is more common in children ≥3 years of age, and it is in this age group that classical, unremitting respiratory symptoms provide a diagnostic opportunity [5, 6]. However, severe tuberculosis morbidity and mortality might be prevented by a vaccine that interrupts this continuum at any prior time point, including that of recent infection and primary tuberculosis complex. The peak risk for development of tuberculosis disease following primary infection, and progression to disseminated miliary or meningitic tuberculosis, occurs during the first 2 years of life [5, 6]. It could be argued that even asymptomatic primary complex tuberculosis has clinical relevance in younger children, due to the high age-specific risk of disease progression [5, 6]. On the other hand, the majority of primary complex tuberculosis will resolve spontaneously and might remain undetected without active contact tracing in a clinical trial setting [5, 6].

The historical trials that demonstrated efficacy of infant BCG vaccination against childhood pulmonary tuberculosis were conducted in the prechemotherapy era [10, 11]. Disease outcomes were determined over months or years of observation and included specific radiologic features of advanced tuberculosis, such as calcification, cavitation, and miliary disease, and postmortem features of disseminated tuberculosis or tuberculosis meningitis [10, 11]. However, modern tuberculosis vaccine trials will include active surveillance (systematic collection of exposure and symptom data to identify suspected tuberculosis cases for investigation), household contact tracing, isoniazid preventive therapy (IPT), and effective treatment of suspected tuberculosis disease [12]. The disease phenotype in a modern vaccine trial study population is likely to be mild, with a higher proportion of primary complex tuberculosis compared with complicated intrathoracic tuberculosis, and almost no disseminated disease [12]. Early tuberculosis disease phenotypes are likely to be associated with greater diagnostic uncertainty and risk of misclassification [2]. However, these challenges are not unique to tuberculosis vaccines. Clinical trials of malaria and human immunodeficiency virus (HIV) interventions have used coprimary “upstream” end points (reflecting early/mild disease) and “downstream” end points (reflecting advanced/severe disease), as well as composite end points and surrogate end points [8, 9, 13]. Although primary complex tuberculosis fulfills many of the criteria for a valid surrogate measure of severe tuberculosis morbidity and mortality, including causality, it remains to be seen whether any current candidate tuberculosis vaccine will protect against tuberculosis infection or mild disease.

Definition of diagnostic end points for infant tuberculosis vaccine trials is further hampered by the lack of recent evidence from this study population, given the half century since the last randomized controlled efficacy trials of infant BCG vaccination [11, 12, 14]. End-point decisions must be made largely on the basis of inference from epidemiological studies and other clinical or research settings [15]. The lack of direct evidence from this study population does not facilitate a systematic review of diagnostic tools or assessment of evidence within a structured framework [16]. A preliminary needs assessment is urgently required to guide future research efforts and critical analysis of additional relevant evidence.

A Consensus Workshop convened to determine areas of consensus opinion among experts and key stakeholders to lay the foundation for definition of infant tuberculosis vaccine trial efficacy end points that will be feasible, affordable, scientifically valid, and acceptable to licensing authorities. Although the aim of the Workshop was to identify primary end points for infant tuberculosis vaccine trials, the secondary aim was to identify diagnostic criteria for which there is a clear lack of consensus, or important reservations, as priority areas for further research and analysis. The scope of this Consensus Workshop was limited to phase II and III clinical trials of new infant tuberculosis vaccines among HIV-uninfected children, with a focus on those <2 years of age.

METHODS

The Taskforce on Clinical Research Issues of the Stop TB Partnership Working Group on TB Vaccines invited 65 key opinion leaders to attend a Consensus Workshop on Diagnostic Endpoints for Infant TB Vaccine Trials, held at the Second Global Forum on TB Vaccine Trials (Talinn, Estonia, September 2010). Invitees were selected by the Taskforce cochairs (S. V. and H. M.) on the basis of expertise in childhood tuberculosis and tuberculosis vaccine development. A position paper outlining 14 draft statements on diagnostic end points for childhood tuberculosis was prepared by the South African Tuberculosis Vaccine Initiative and circulated prior to the Second Global Forum to structure the discussion (M. H.).

The participatory consensus process aimed to secure the agreement of the majority of participants for or against each of the 14 draft statements, while resolving minority objections by clarification and open discussion. Following a short background introduction (Table 1), each draft statement was presented.
Table 1. Key Background Points

**Clinical features:**

1. In clinical practice among children <2 years of age: (a) Persistent, unrelenting cough for >2 weeks, (b) objective failure to thrive, and (c) positive tuberculin skin testing (TST) or recent tuberculosis exposure are associated with culture-positive or chest radiographic–positive tuberculosis disease [15]. Presence of symptoms is usually the sentinel feature for suspected tuberculosis, but symptom duration may be reduced in very young and immunocompromised children.

2. In a vaccine trial study population among children <2 years of age: (a) Persistent wheeze for >2 weeks and (b) positive TST are associated with culture-positive tuberculosis disease. Symptoms of prolonged cough or failure to thrive may not be associated with culture-positive tuberculosis disease in this study population [17; Luabeya et al, in press, PIDJ].

**Chest radiography:**

1. Radiologic diagnosis of pulmonary tuberculosis disease is complicated by inter- and intraobserver variation in detection of thoracic lymphadenopathy, in the absence of classical features of calcification, cavitation, and miliary pattern [23, 24].

2. Chest radiography compatible with tuberculosis, on the basis of majority opinion of 2–3 expert reviewers blinded to the clinical data, is associated with culture-positive tuberculosis disease in an infant vaccine trial study population [17].

**Microbiological confirmation:**

1. In clinical practice, 5%–25% of children suspected to have tuberculosis are positive by the current gold standard (culture of *Mycobacterium tuberculosis*). Positive culture may occur in children without classical symptoms or radiologic features of pulmonary tuberculosis disease [15, 18–20].

2. In an infant vaccine trial study population, culture confirmation of pulmonary tuberculosis is possible by liquid culture in up to 12% of children suspected to have tuberculosis but may not be associated with symptoms or radiologic features of pulmonary tuberculosis disease [15, 17].

3. It may be difficult to differentiate laboratory *M. tuberculosis* culture contamination from incipient culture-positive tuberculosis disease in children with minimal symptoms.

4. New automated molecular tests for the *M. tuberculosis* genome, such as the GeneXpert MTB/RIF test, have lower sensitivity than mycobacterial culture in paucibacillary tuberculosis patients and are not expected to increase diagnostic yield of childhood tuberculosis disease [21].

Abbreviations: MTB, *Mycobacterium tuberculosis*; RIF, resistance to rifampin.

All comments were recorded, including written submissions, whether in favor, neutral, or against. The Workshop minutes and individual notes of Taskforce chairs were collated to ensure that the outcome of the consensus process and individual views were correctly reflected.

Workshop data were analyzed in terms of 3 possible outcomes: unanimity, modified consensus, or lack of consensus. Unanimity was noted if all participants were in agreement, either in favor of or against each statement. Modified majority consensus was determined on the basis of at least four-fifths agreement. Minority dissenting opinions expressed by less than one-fifth of participants, which were not resolved by clarification or discussion, were classified as specific reservations. Reservations expressed by more than one-fifth of participants were treated as a lack of consensus. Individual participant comments were paraphrased as necessary. The draft manuscript was circulated to all participants for approval of the final report of the Consensus Workshop findings.

**RESULTS**

Thirty-three invitees attended the workshop, and written submissions from 5 absentee stakeholders were considered in the discussion. The 38 workshop contributors, representing 11 countries, included experts with a background in tuberculosis epidemiology, pediatric tuberculosis, tuberculosis vaccine trials, basic science, and tuberculosis vaccine development and manufacture.

The 14 draft statements are listed in Table 2, with the outcome for each statement (unanimity; modified consensus; or lack of consensus), detail of specific reservations, and relevant comments by individual participants.

**DISCUSSION**

Workshop participants achieved broad consensus—and highlighted specific important reservations—on 3 important issues: (1) the unsuitability of historical BCG trial end points (advanced intrathoracic and disseminated or meningitic tuberculosis disease) as the only primary end points for modern infant tuberculosis vaccine trials; (2) the importance of classical, symptomatic, complicated intrathoracic tuberculosis as a clinically relevant but uncommon disease phenotype; and (3) the relevance of primary tuberculosis complex in younger children as a common high-risk phenotype, although with a high rate of spontaneous resolution. Lack of consensus was notable on 2 issues: (1) the significance of isolated culture of *Mycobacterium tuberculosis* in the absence of additional clinical or radiologic evidence of disease and (2) although there was consensus on which criteria constituted evidence of prior exposure to *M. tuberculosis*, there was no consensus as to which of these exposure criteria should be linked to clinical and radiologic evidence to support a diagnosis of tuberculosis.

The Workshop findings do not endorse any single primary end-point definition. The tuberculosis disease phenotypes with greatest diagnostic certainty and direct clinical relevance—that is, advanced, classical intrathoracic disease; disseminated miliary or meningitic disease; and the triad of clinical and radiologic evidence of intrathoracic disease with culture or molecular confirmation of *M. tuberculosis*—are expected to be very uncommon in this study population [7, 12]. However, the consensus on a range of more common, pragmatic end-point criteria may yet allow evaluation of vaccine efficacy using a composite end point, or by...
Table 2. Consensus Outcomes and Specific Comments by Individual Participants

<table>
<thead>
<tr>
<th>Statement 1: A clinical trial of a novel tuberculosis vaccine will not successfully demonstrate efficacy unless the following 3 elements are concordant: the phenotype of true tuberculosis disease occurring in the study population; the phenotype of observed tuberculosis disease defined by the trial end point; and the phenotype of tuberculosis disease prevented by the vaccine.</th>
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<tbody>
<tr>
<td>Outcome: Modified consensus</td>
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<tr>
<td>Reservations: (1) A vaccine might demonstrate different levels of efficacy against different tuberculosis disease phenotypes that might be captured by multiple end points.</td>
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<tr>
<td>Comments: (1) Sample size, operational factors, and efficiency of tuberculosis disease surveillance will also impact on whether a clinical trial will demonstrate efficacy.</td>
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<tr>
<th>Statement 2: Historical BCG trial end points alone are not suitable as primary end points for novel tuberculosis vaccine trials in the modern era of effective chemotherapy for tuberculosis, in which the natural history of disease is interrupted.</th>
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<tr>
<td>Outcome: Modified consensus</td>
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<tr>
<td>Reservations: (1) Historical BCG trial end points are precisely what are used to diagnose tuberculosis in clinical practice. Using end-point criteria that bear little resemblance to clinical practice will lead to registration of a product for an indication no clinician recognizes; (2) How else to demonstrate real-life clinical efficacy?</td>
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<tr>
<td>Comments: (1) Historical BCG trial end points are not incorrect, but additional end points are necessary in modern tuberculosis vaccine trials; (2) South African infant cohort studies showed low rates of bacteriologic confirmation in association with a mild disease phenotype; (3) Solid case definitions are needed for infant tuberculosis vaccine trials, which might be composites of bacteriologic, clinical, and radiologic criteria; (4) It is common for modern clinical trials to use end points that are not clinically relevant, but interpretation may be complicated and it would be advantageous to include an end point that clinicians can recognize; (5) It is important that postlicensure studies use severe morbidity outcomes to measure public health impact; (6) Nontuberculosis mortality data should also be collected in large infant trials (possible nonspecific survival benefit).</td>
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<th>Statement 3: Classical, symptomatic, complicated intrathoracic tuberculosis disease is a clinically relevant form of disease but is likely to be uncommon in a modern vaccine trial in which the study population is &lt;2 years of age.</th>
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<tr>
<td>Outcome: Modified consensus</td>
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<tr>
<td>Reservations: (1) The exception would be a minimal intervention trial design using passive disease surveillance methods, which presents clear ethical challenges.</td>
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<tr>
<td>Comments: (1) Disseminated tuberculosis was also uncommon in South African infant cohort studies, probably due to active contact tracing and early therapeutic intervention; (2) Passive disease surveillance methods would not be acceptable on the basis of participant safety (consensus).</td>
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<tr>
<th>Statement 4: Primary tuberculosis disease complex (Ghon complex with regional lymphadenopathy) is an epidemiologically relevant (high-risk) form of tuberculosis disease that is likely to be most common in a modern vaccine trial in which the study population is &lt;2 years of age.</th>
</tr>
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<tr>
<td>Outcome: Modified consensus</td>
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<tr>
<td>Reservations: (1) A vaccine may not prevent primary complex tuberculosis; (2) A vaccine that generates robust protective immune responses may paradoxically increase the rate of detection of primary complex tuberculosis (with adequate containment); (3) In the prechemotherapy era, approximately 60% of children contained and resolved primary complex tuberculosis.</td>
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<td>Comments: (1) Subclinical primary tuberculosis complex is associated with a high risk of progression to severe disease in young children but is a common phenomenon following recent primary infection; (2) The issue of greatest relevance is accurate identification of the protected phenotype. These children will experience reduced risk of disease progression to severe morbidity and mortality, compared with the unvaccinated.</td>
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<th>Statement 5: Clinical trials of novel tuberculosis vaccines should include a classical, symptomatic, complicated intrathoracic tuberculosis disease end point for children &lt;5 years of age.</th>
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<tr>
<td>Outcome: Modified consensus</td>
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<tr>
<td>Reservations: (1) Unless sample size is very large, there may be insufficient numbers of these cases to show a statistically significant difference between vaccines and controls.</td>
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<tr>
<td>Comments: (1) The end point should not be restricted to symptomatic or complicated intrathoracic disease; (2) This end point would not be common, given the proposed disease surveillance methods and use of preventive and curative tuberculosis therapy, but it is highly relevant.</td>
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<th>Statement 6: Clinical trials of novel tuberculosis vaccines should include an asymptomatic primary tuberculosis complex end point for children &lt;2 years of age.</th>
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<td>Outcome: Modified consensus</td>
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<td>Reservations: (1) It may be difficult to define this end point with sufficient specificity, and misclassification will bias vaccine efficacy toward zero; (2) It is highly problematic to distinguish primary tuberculosis complex with adequate containment (static or resolving) from primary tuberculosis complex with inadequate containment (progressive).</td>
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<td>Comments: (1) Such an end point is important, given the risk of progression to severe disease; (2) Clinical significance may be misinterpreted if this phenotype is not well defined; (3) Primary tuberculosis complex should not be the primary end point but might form part of a hierarchy of multiple end points; (4) Tuberculosis vaccine trials should be powered to detect a range of tuberculosis disease phenotypes, including primary tuberculosis complex, but these should be specified a priori and clearly reflected in the study findings.</td>
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Statement 7: *Tuberculosis case definitions that incorporate categories of low-moderate diagnostic certainty (possible or suspected tuberculosis) are not suitable primary end points, on the basis of low specificity and high risk of misclassification.*

**Outcome:** Modified consensus

**Reservations:** (1) Diagnostic features with low to moderate specificity should never be the primary end point but might be used as part of a composite end point, in sensitivity analyses, or as exploratory end points, to adapt and refine end-point definitions in future trials.

**Comments:** (1) Beware of using multiple end-point definitions; (2) Exclusion of other differential diagnoses (eg, asthma; pertussis) may be useful; (3) Response to tuberculosis therapy may be useful to confirm the diagnosis.

Statement 8: *The end point of clinical trials of novel tuberculosis vaccines must include evidence of clinical or radiologic tuberculosis disease. Therefore, infection with Mycobacterium tuberculosis alone, in the absence of any clinical or radiologic evidence of disease, does not meet the case definition for tuberculosis disease.*

**Outcome:** Lack of consensus

**Reservations:** (1) Asymptomatic culture-positive (incipient) disease is well recognized in adults infected with human immunodeficiency virus (HIV); (2) An isolated positive culture in very young children, even if asymptomatic, indicates a risk of progression to disseminated tuberculosis disease; (3) A positive culture meets the case criteria for national tuberculosis control programs, although clinical significance cannot be assessed, because we cannot observe these children without treating them.

**Comments:** (1) Children who are investigated solely on the basis of a household tuberculosis contact might be well and asymptomatic. A positive culture in such a child has a lower pretest probability of tuberculosis disease than in children who have sought medical care; (2) Additional clinical or radiological criteria are needed in combination with positive culture, due to the risk of laboratory error (culture contamination); (3) Culture of *M. tuberculosis* confirms tuberculosis exposure and infection but does not confirm the presence or severity of tuberculosis disease; (4) The relevance of an isolated positive culture depends on whether a vaccine is expected to prevent infection or complicated tuberculosis disease.

Statement 9: *The end point of clinical trials of novel tuberculosis vaccines must link evidence of clinical or radiologic tuberculosis disease with evidence of exposure to *M. tuberculosis* as the possible etiologic agent.*

**Outcome:** Lack of consensus

**Reservations:** (1) Unknown community exposure, outside of the household, is common in high tuberculosis endemic settings; (2) Documentation of additional tuberculosis exposure is not needed if *M. tuberculosis* culture or molecular test is positive.

**Comments:** (1) Ideally, evidence of clinical or radiological tuberculosis disease with evidence of exposure to *M. tuberculosis* should be the primary end point.

Statement 10: *Evidence of current or recent exposure to *M. tuberculosis* includes:*

(a) *Culture of M. tuberculosis*

**Outcome:** Unanimity

**Reservations:** None

**Comments:** (1) Beware of false-positive laboratory culture contamination.

(b) *Molecular test for M. tuberculosis DNA (eg, GeneXpert)*

**Outcome:** Unanimity

**Reservations:** None

**Comments:** (1) Specify the molecular test a priori.

(c) *Interferon-γ release assay (IGRA)*

**Outcome:** Modified consensus

**Reservations:** (1) Insufficient experience with IGRA in infants and young children; (2) No objective evidence to support the use of IGRA for diagnosis of tuberculosis disease; (3) IGRA provides evidence of exposure to *M. tuberculosis* but does not indicate the presence of tuberculosis disease.

**Comments:** (1) New tuberculosis-specific immunologic assays that confirm *M. tuberculosis* disease are needed urgently for tuberculosis vaccine trials, even if these assays are expensive, because the relative cost of developing such assays might be acceptable when compared against the cost of phase III trials; (2) Serial measurements using new immunologic assays may be useful.

(d) *Tuberculin skin test (TST)*

**Outcome:** Modified consensus AGAINST statement

**Reservations:** (1) IGRA should be used in place of TST due to greater specificity; (2) TST provides evidence of exposure to *M. tuberculosis* but does not indicate the presence of tuberculosis disease; (3) Interpretation of TST results in children may be confounded by prior BCG vaccination for up to 2 years.
Table 2 continued.

Comments: (1) There is more experience in young children with the use of TST than with the use of IGRA.
(e) Household exposure to an adult with pulmonary tuberculosis (regardless of smear/culture status)

Outcome: Modified consensus
Reservation: (1) A documented household tuberculosis contact provides evidence of exposure to M. tuberculosis but does not indicate the presence of tuberculosis disease; (2) Unknown community exposure may occur outside the household in high tuberculosis endemic areas but is less likely in very young children.

Comments: (1) The quality of documentation of the type, duration, and proximity of household exposure is important to assess relevance; (2) Maternal exposure is especially relevant; (3) Household exposure is relevant regardless of whether the adult tuberculosis contact is smear or culture positive.

Statement 11: Clinical evidence of tuberculosis in a vaccine trial study population <2 years of age includes persistent, unremitting cough or wheeze for >2 weeks, or objective evidence of failure to thrive.

Outcome: Modified consensus
Reservations: (1) These clinical criteria may not be sensitive in very young children; (2) These clinical criteria are nonspecific; (3) Other differential diagnoses should be excluded.

Comments: (1) The presence of cough or wheeze, fever, reduced playfulness, or failure to thrive may provide a sensitive entry point for further investigation that would reduce the dilemma posed by positive microbiologic or radiologic findings in an asymptomatic child; (2) Clinical criteria should only be used in conjunction with radiologic or microbiologic evidence, as a component of a set of diagnostic findings; (3) Failure to thrive should be rigorously defined.

Statement 12: Radiologic evidence of pulmonary tuberculosis includes calcification, cavitation, and miliary nodular pattern. These features are specific for pulmonary tuberculosis but are likely to be rare in a vaccine trial study population <2 years of age.

Outcome: Unanimity
Reservations: None

Comments: (1) Alternative diagnoses would be considered in HIV-infected children; (2) These features will be uncommon if active case finding and preventive therapy is used; (2) This statement is consistent with findings from South African infant cohort studies; (3) Radiologic evidence should be used in combination with evidence of tuberculosis exposure or symptoms to avoid false-positive misclassification.

Statement 13: Radiologic evidence of pulmonary tuberculosis will be based primarily on detection of paratracheal or hilar lymphadenopathy, with or without airway compression, in this study population.

Outcome: Modified consensus.
Reservations: (1) Very young infants may present with dense lobar opacification, or, less commonly, miliary disease.

Comments: None.

Statement 14: The following radiologic features are not specific for pulmonary tuberculosis in this study population and are not sufficient radiologic evidence alone to meet the tuberculosis case definition.

(a) Pleural effusion
Outcome: Unanimity
Reservations: None
Comments: None

(b) Atelectasis
Outcome: Unanimity
Reservations: None
Comments: None

(c) Air-space opacification/consolidation
Outcome: Unanimity
Reservations: None
Comments: None

* Reworded for clarity after discussion.
stepwise cumulative measurement of multiple end-point criteria, in a descending hierarchy of diagnostic certainty and clinical relevance (or risk of tuberculosis disease progression to severe morbidity and mortality) (Table 3). Although the proposed model is derived from the findings of the Consensus Workshop, it should be noted that this approach is untested and may not provide greater accuracy than other diagnostic approaches [2, 3].

The methodology for end-point classification in historical BCG trials may be inferred from reported case descriptions [10, 11]. It is clear that radiologic features of advanced pulmonary disease, including calcification, cavitation, and a miliary pattern, and postmortem confirmation of disseminated disease and tuberculosis meningitis, were used as final outcome measures in many cases [10, 11]. Provision of IPT and rigorous early case finding lowers the incidence of disseminated tuberculosis disease in research settings, compared with surrounding communities in which national tuberculosis control program (NTCP) resources are limited [12]. Workshop participants agreed that although advanced intrathoracic tuberculosis or disseminated tuberculosis were not appropriate as single primary end points, because these phenotypes would rarely be seen in modern trials, it would be advantageous to include downstream disease outcomes within a composite end point, or hierarchy of multiple end-point criteria. A similar principle applies to inclusion of symptomatic, complicated intrathoracic tuberculosis, which would not be common among children <2 years of age in this study population. There was consensus that this classical symptomatic tuberculosis phenotype would be applicable to all children <5 years. However, it was noted that a clinical trial might be underpowered to demonstrate vaccine efficacy unless the sample size accurately estimated the observed incidence of the symptomatic, complicated intrathoracic tuberculosis phenotype [7].

Meticulous safety surveillance and active tuberculosis case finding is an ethical requirement for a tuberculosis vaccine trial among very young children at risk of severe morbidity and mortality. Consequently, because provision of IPT will truncate further disease progression, investigation of all tuberculosis-exposed and tuberculosis-infected children is necessary, regardless of whether symptoms are present at the time of detection. There was considerable discussion of the clinical and public health relevance of primary complex tuberculosis among Workshop participants. This upstream tuberculosis disease phenotype is expected to be most common in a modern infant vaccine trial and may be relatively asymptomatic, although rapid progression to disseminated or meningeal disease is possible in young children [6, 12]. However, because the outcome of asymptomatic primary complex tuberculosis in the majority of children is containment with resolution, which might not have been detected without active contact tracing, the direct clinical relevance of this high-risk phenotype is uncertain [5, 6]. There was consensus that primary complex tuberculosis in younger children, even if asymptomatic, should be captured within a composite end point or a hierarchy of multiple end points. However, this mild phenotype should not form the primary end point, because it may be problematic to define hilar lymphadenopathy with adequate radiologic specificity, due to interreader variability, and to distinguish resolving from progressive primary tuberculosis complex with inadequate containment [23, 24]. Further, reservations were expressed that an immunogenic vaccine might not reduce, and might paradoxically increase, the incidence of uncomplicated primary complex tuberculosis, independent of protective efficacy against severe tuberculosis morbidity and mortality. Despite these concerns, workshop participants agreed that radiologic diagnosis of intrathoracic tuberculosis would be based primarily on detection of hilar lymphadenopathy. There

<table>
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<th>Table 3. Proposed Hierarchy of Infant Tuberculosis Vaccine Trial End-Point Criteria, According to Rate of Occurrence, Diagnostic Certainty, and Clinical Relevance (Risk of Disease Progression) in HIV-Uninfected Children &lt;5 Years of Age</th>
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<tr>
<td><strong>Level 1: Very uncommon; high diagnostic certainty; high clinical relevance</strong></td>
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<tr>
<td>(a) Radiologic evidence of disseminated (miliary) tuberculosis disease^a^</td>
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<tr>
<td>(b) Radiologic evidence of advanced intrathoracic tuberculosis disease (calcification or cavitation)^b^</td>
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<tr>
<td>(c) Clinical evidence of tuberculosis meningitis [22]^c^</td>
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<tr>
<td>(d) Complete triad of clinical and radiologic evidence of intrathoracic tuberculosis disease with culture or molecular confirmation of <em>Mycobacterium tuberculosis</em>^a^</td>
</tr>
<tr>
<td>(e) Extrathoracic disease with histologic, culture, or molecular confirmation of <em>Mycobacterium tuberculosis</em>^a^</td>
</tr>
<tr>
<td><strong>Level 2: Uncommon; moderate diagnostic certainty; moderate clinical relevance</strong></td>
</tr>
<tr>
<td>(a) Clinical and radiologic evidence of intrathoracic tuberculosis disease, with or without evidence of prior tuberculosis exposure^b^</td>
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<tr>
<td>(b) Clinical evidence of intrathoracic tuberculosis disease, with culture or molecular confirmation of <em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>(c) Radiologic evidence of intrathoracic tuberculosis, with culture or molecular confirmation of <em>Mycobacterium tuberculosis</em></td>
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<tr>
<td><strong>Level 3: Common; low diagnostic certainty; clinical relevance uncertain (high-risk phenotype)</strong></td>
</tr>
<tr>
<td>(a) Radiologic evidence of intrathoracic tuberculosis disease (including isolated hilar lymphadenopathy), with or without evidence of prior tuberculosis exposure, in children &lt;2 years of age^b^</td>
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<tr>
<td><strong>Level 4: Uncommon; diagnostic significance uncertain; clinical relevance uncertain</strong></td>
</tr>
<tr>
<td>(a) Culture or molecular confirmation of <em>Mycobacterium tuberculosis</em> only, in the absence of clinical and radiologic evidence of intrathoracic tuberculosis disease^c^</td>
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^a^ Or postmortem confirmation.

^b^ No consensus reached on inclusion of tuberculosis exposure measures.

^c^ No consensus reached on significance of isolated *Mycobacterium tuberculosis* culture or molecular confirmation.
was unanimous agreement that isolated pleural effusion, atelectasis, and airspace opacification or consolidation were non-specific and insufficient radiologic evidence on which to base a tuberculosis diagnosis. Improved imaging techniques and standardized radiologic reporting to reduce the risk of misclassification of intrathoracic lymphadenopathy would be a major advance for infant tuberculosis vaccine trials [23, 24]. The ideal imaging modality should be accurate, with little or no radiation dosage, and crucially, available at vaccine trial sites in developing countries.

The single most contentious issue was the relevance of culture of *M. tuberculosis* in the absence of additional clinical or radiologic evidence of disease. Some participants held the view that *M. tuberculosis* culture was simply confirmation of tuberculosis exposure and infection and should always require supporting evidence of disease. Others felt that culture of *M. tuberculosis* met NTP case criteria and constituted “definite TB,” regardless of whether additional evidence of disease was present [2, 12]. Asymptomatic culture positivity has been documented in the prechemotherapy literature, and most of these children remained well on clinical follow-up [5, 6]. However, culture positivity frequently reflects incipient tuberculosis among HIV-infected adults and might be associated with an increased risk of progression to disseminated disease in young children [25, 26]. Ideally, to distinguish minimally symptomatic tuberculosis disease from laboratory contamination, laboratories that process *M. tuberculosis* isolates for pediatric vaccine trials should have the ability to perform DNA fingerprinting, because children rarely yield more than a single positive culture [18]. The challenges faced in assigning *M. tuberculosis* culture as a primary end point are illustrated by a modern BCG vaccine trial in South Africa. Only 12% of young children investigated as tuberculosis suspects, including asymptomatic contacts, were culture positive for *M. tuberculosis* [7, 12]. This culture-positive rate is comparable to recent community studies elsewhere but is lower than rates reported in earlier studies among hospitalized children [12, 15, 18–20]. Further, although 75% of culture-positive children in this trial were symptomatic, only 28% demonstrated radiologic evidence suggestive of tuberculosis and less than one-quarter of culture-positive children demonstrated both clinical and radiologic evidence of intrathoracic tuberculosis disease [7]. This diagnostic triad would be highly desirable as a primary end point with direct clinical relevance and a high degree of diagnostic certainty, but the low rate of occurrence would require a prohibitively large and expensive clinical trial, given optimal surveillance and early therapeutic intervention.

There was lack of consensus for whether evidence of clinical and radiological tuberculosis disease was sufficient, or whether additional evidence of exposure to *M. tuberculosis*, should be required to define the end point. There was consensus that a history of a cohabiting adult with pulmonary tuberculosis or a positive interferon-γ release assay (IGRA) was indicative of prior tuberculosis exposure, and that additional evidence of exposure was not required if *M. tuberculosis* culture or a molecular test for the *M. tuberculosis* genome was positive [21, 27]. However, strong reservations were expressed that there was insufficient evidence to support the use of IGRA over tuberculin skin testing (TST) in young children [28].

The Workshop findings are not based on a systematic review of evidence but reflect the output of a participatory consensus process among a representative group of opinion leaders in the field of tuberculosis vaccine development. Published evidence on which to base end-point definitions is scarce, because 50 years has passed since the last randomized controlled efficacy trials of an infant tuberculosis vaccine [11, 12, 14]. However, diagnostic criteria supported by expert consensus opinion should be considered for planned tuberculosis vaccine trials. The Consensus Workshop also identified several contentious issues and knowledge gaps. We caution that the process of defining diagnostic end points for infant tuberculosis vaccine trials is just beginning, and definition of end points for HIV-infected children is likely to be even more challenging. Controversial issues that require ongoing research have been highlighted by this preliminary consensus process, and end-point definitions are likely to be evaluated, adapted, and refined in successive clinical trials.

**CONCLUSIONS**

Workshop participants achieved consensus that historical BCG trial end points, based on advanced intrathoracic and disseminated disease, are unsuitable as the only primary end points for modern infant tuberculosis vaccine trials, owing to the low rate of occurrence of these downstream, severe tuberculosis disease outcomes. There was agreement that symptomatic, complicated intrathoracic tuberculosis, a clinically relevant yet uncommon disease phenotype in this study population, and primary complex tuberculosis among children <2 years of age, a common high-risk phenotype although with a high rate of spontaneous resolution, should form part of a composite end point or hierarchy of multiple end points. No consensus was achieved on whether isolated *M. tuberculosis* culture constitutes an appropriate primary end point per se, in the absence of additional clinical or radiologic evidence of tuberculosis disease. Important reservations were expressed by individual participants regarding the evidence supporting use of IGRA in preference to TST in children; the uncertain clinical relevance and potential for misclassification of primary complex tuberculosis; and the possibility that tuberculosis vaccine candidates may not offer protection against upstream, mild tuberculosis disease phenotypes.

The Workshop on Diagnostic Endpoints for Infant TB Vaccine Trials failed to reach consensus on diagnostic criteria for a single primary end point, because tuberculosis disease phenotypes with
optimal diagnostic certainty and with direct relevance to severe morbidity and mortality, are expected to be very uncommon in this study population. However, acceptable criteria for composite or multiple end points, and controversial areas for high-priority research, were identified. A specific and sensitive diagnostic marker to distinguish incipient or mild tuberculosis disease from latent M. tuberculosis infection and improved imaging techniques for intrathoracic lymphadenopathy in children are needed. Until such diagnostic tools become available, we propose a hierarchy of end-point criteria, based on expected rate of occurrence, clinical relevance, and diagnostic certainty, to guide selection of composite or multiple end points for infant tuberculosis vaccine trials.

Notes
Participants in the Consensus Workshop on Diagnostic Endpoints for Infant TB Vaccine Trials, the Second Global Forum on TB Vaccine Trials, Tallinn, Estonia (September 2010): Lew Barker; [Marcel Behr]; Vicky Cardenas; Bernd Eisele; Macaya Douoguih; Thomas G. Evans; Julhani Esoka; Bernard Fourie; Harleen Grewal; Leander Grode; Mark Hatherill; [Tony Hawkhridge]; Anneke Hesseling; Gregory Hussey; Grace Kiringa; Bernard Landry*; Stephen Lockhart; Hassan Mahomed; [Ben Marais]; Kärstein Ma˚seide; Harriet Mayanja; Bruce McClain; Helen McShane; [Sizulu Moyo]; Opokua Ofori; Shreemanta K. Parida; Robert P. Ryall; Jahit Sacarlal; Jerry Sadoff; Jacqui Mayanja; Bruce McClain; Helen McShane; [Sizulu Moyo]; Opokua Ofori; TB Partnership Working Group on TB Vaccines.

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