Reply to Holm et al

To the Editor—We welcome the feedback provided by Holm et al [1] relating to the application of recently published proposed clinical case definitions for reporting of research findings when evaluating diagnostic tests in young children with suspected intrathoracic tuberculosis. The definitions are intended for research use to evaluate diagnostic assays and strategies under controlled circumstances and not for making individual patient clinical diagnoses for treatment decisions under field conditions. These research case definitions were developed to address the need to standardize reporting for diagnostic studies of tuberculosis in children so that consistency in definitions and methods could allow for more valid comparisons between populations and settings [2]. The need to improve the quantity and quality of diagnostic research in children with suspected tuberculosis is universally recognized, and the opportunity provided by the emergence of novel approaches has made this need stronger. The aim is to strengthen diagnostic research in children, and we hope that these definitions can be revised and improved in the future, informed by data and experience obtained by applying and validating them in real-life studies.

We recognize that these definitions have limitations. Although we arrived at these definitions by using formal group consensus rules following careful consideration, not surprisingly agreement was not unanimous for all definitions. There is often a tension between conducting research in locations where there are many eligible children but limited resources and locations with excellent research infrastructure but few eligible children. Similarly, clinical and public health perspectives often apportion different emphasis to the contribution of factors and the level of detail required to make a diagnosis, and there is a lack of data to inform specific definitions. Holm et al [1] highlight some of these limitations, the definition of immunological evidence of infection with Mycobacterium tuberculosis and the definition of treatment response. Another challenge for the panel was to agree on the methodological approach to reading and reporting radiological findings. Chest radiographic findings were considered a critical aspect of the case definition, and the panel applied particular rigor to ensure standard interpreting and reporting of these findings. However, we were aware that the feasibility of this approach might be constrained in the very resource-limited settings where the results of this research need to be applicable. We emphasize the need for rigorous clinical research for pediatric diagnostic studies, while recognizing the tensions of variable levels of resources and pragmatic constraints.

Holm et al [1] indicate that a follow-up period of 2 months might be too short to define treatment response, especially because many children may not have started or may have only recently started anti-tuberculosis therapy at this point. This might be a misunderstanding, as the proposed definitions indicate the follow-up assessment should occur 2 months after initiation of therapy, not from the time of initial assessment or enrollment for suspected disease, which may be considerably earlier. Nonetheless, we accept the inherent potential bias in the classification of children who die or are lost to follow-up before that time, whether receiving anti-tuberculosis therapy or not. These children represent an important high-risk group that should be reported on separately.
We certainly do not consider the tuberculin skin test or the interferon gamma release assay to be diagnostic tests for active tuberculosis, as inferred by Holm et al. Rather, positive results of these tests are markers of infection in a symptomatic child with suspected tuberculosis that add weight to the likelihood of the child having active disease, as does the alternative of a “documented exposure to tuberculosis” [2, 3]. The proposed definitions were aimed to apply in the context of diagnostic research in which it would be presumed that an immunodiagnostic test would be part of the assessment. We agree with the statements relating to the widely recognized limitations of both tests. However, until a better immunodiagnostic test is available in terms of accuracy and application, it would be difficult to suggest a definition for cases that are not confirmed that excludes current markers of infection with M. tuberculosis.

We also agree that reporting of the findings should include all relevant data, such as early death, loss to follow-up, and full test results [4]. The clinical classification proposed for reporting purposes did not intend to exclude such critical data, but rather tried to assess the likelihood of tuberculosis in individuals without a confirmed diagnosis, to have a platform for consistent evaluation of diagnostic tests. The imperfections of these definitions are recognized, and from the onset the panels envisioned the need for revisions based on emerging evidence. We hope these definitions will be widely applied and evaluated by the research community, as further feedback will be essential for validation and improvement. It is further hoped that these definitions will contribute to the emergence of adequately evaluated pediatric diagnostic tests that, in turn, render such definitions unnecessary.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Stephen M. Graham,1 Martina Casenghi,2 Patrick Jean-Philippe,3 Mark Hatherill,4 Anneke C. Hesseling,5 Sharon Nachman,4 Jeffrey R. Starke,5 Soumya Swaminathan,6 and Luis E. Cuevas7

1Centre for International Child Health, University of Melbourne Department of Paediatrics and Murdoch Childrens Research Institute, Royal Children’s Hospital, Melbourne, Australia; 2Medecins sans Frontieres, Geneva, Switzerland; 3Henry Jackson Foundation–Maternal Adolescent Pediatric Research Branch, Division of AIDS National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; 4State University of New York School of Medicine at Stony Brook, New York; 5Department of Pediatrics, Baylor College of Medicine, Houston, Texas; 6South African Tuberculosis Vaccine Initiative, School of Child and Adolescent Health, University of Cape Town, and 7Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa; 8National Institute for Research in Tuberculosis, Chennai, India; and 9School of Tropical Medicine, University of Liverpool, Liverpool, United Kingdom

References


Received and accepted 30 October 2012; electronically published 13 December 2012.

Correspondence: Stephen M. Graham, FRACP, PhD, Centre for International Child Health, University of Melbourne Department of Paediatrics, Royal Children’s Hospital, Flemington Rd, Parkville, Victoria 3052, Australia (steve.graham@rch.org.au).

The Journal of Infectious Diseases 2013;207:871–2
© The Author 2012. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com
DOI: 10.1093/infdis/jis769