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Perspectives in Implementing Standardized Case Definitions for Tuberculosis Research Involving Children in a Low-Income, High-Burden Setting

TO THE EDITOR—In May 2012, Graham et al proposed clinical case definitions for standardizing the classification of intrathoracic tuberculosis in children, for research evaluating new diagnostic tests in children in whom tuberculosis is suspected but rarely confirmed [1]. The detailed clinical case definitions, which have been developed by an expert panel by consensus agreement, mark a major landmark in tuberculosis research involving children. We recently reported the results of a study evaluating the performance of QuantiFERON-TB Gold In-Tube (QFT-IT) for diagnosing active childhood tuberculosis in Tanzania, a low-income country with a high tuberculosis burden [2].

We classified 211 children with suspected tuberculosis, using a set of diagnostic case definitions derived from previous research studies and adapted to our field setting. As an experiment, we retrospectively applied this new definition to our material and came across a number of issues that warrant consideration by researchers in the process of designing childhood tuberculosis diagnostic studies. Here, we comment on the challenges of follow-up to ensure correct classification and on the use of immunodiagnostic tests in the case definitions.

Follow-up assessment of all children to document their response to anti-tuberculosis treatment or spontaneous recovery is essential for correct classification. We suggest that the proposed follow-up period of 2 months may be too short. Children who do not initially receive tuberculosis treatment may still be ill after 2 months of follow-up and cannot be classified according to the currently proposed case definitions. A longer follow-up period would allow for reevaluation at 2 months and for possible initiation of anti-tuberculosis treatment and evaluation of clinical response.

Another challenge is the high mortality burden among children with suspected tuberculosis in a low-income, high-burden setting. The mortality rate in our study population was 18%, and 77% of subjects who died had not received anti-tuberculosis treatment. If death is perceived as no response to anti-tuberculosis treatment, the classification of deceased children as nonresponders will skew findings toward low disease certainty, creating an unintended bias. If the children who had not received anti-tuberculosis treatment actually died from tuberculosis, the true cause of death would not be registered, leading to classification bias. Future studies should carefully consider how to report data on subjects who die, and verbal autopsies may be useful in the follow-up strategy [3].

Finally, 39% of children in our study did not return for a scheduled 2-month follow-up visit, and only by active tracing in the villages were we able to obtain follow-up data on them [4]. Missing data due to a high rate of loss to follow-up may significantly bias the overall results, and we propose that a strategy for active tracing of children lost to follow-up, among both treated and untreated subjects, be included in the initial study design.

A positive interferon gamma release assay (IGRA) or tuberculin skin test (TST) has been included as a part of the case definitions for classifying tuberculosis, despite several statements against the use of these tests for diagnosing active tuberculosis [5, 6]. In a population with a high proportion of children aged <2 years, children who are infected with human immunodeficiency virus and malnourished, which, for many research studies, is the target population for studies of tuberculosis diagnostic testing, these tests will yield a high number of false-negative and indeterminate results, which will seriously bias the classification results.

We evaluated the performance of the QFT-IT and TST in hospitalized children with signs and symptoms of tuberculosis and found a very high rate of indeterminate results by QFT-IT (27%). In addition, only a few had positive QFT-IT results of (19%; 5 of 27, excluding indeterminate results) or TST (6%; 2 of 31) in the group of children who we considered to have confirmed or highly probable tuberculosis. In very young and severely ill children, the possible benefit of increasing case-detection sensitivity may, therefore, not outweigh the potential poor performance of any immunodiagnostic test. Also, IGFRAs are expensive tests and require advanced technology, whilst the TST requires a return visit, and both tests require skilled staff, which may prevent many study sites from implementing the proposed guidelines in full.

We encourage an evaluation of the actual benefit of including immunodiagnostic tests as part of the clinical case definitions for active tuberculosis in children in regions of high tuberculosis endemicity and hope that the working group may suggest an alternative algorithm for study sites where immunodiagnostic tests are unavailable. The
proposed consensus case definitions will prove invaluable for diagnostic research of childhood tuberculosis, and we hope our comments can help overcome potential challenges in the implementation of future research studies, especially in low-income settings where the tuberculosis burden is high.

Notes

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Potential conflicts of interest. P. R. has been on the speakers’ bureau for Cellestis, has received QFT-IT kits at a reduced price for non-profit research, and is a registered coinventor of technology on the use of IP-10 as a marker for infection with Mycobacterium tuberculosis, for which Hvidovre Hospital has filed patents. All other authors report no potential conflicts.

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