

## Research into tuberculosis diagnosis in children



Tuberculosis is an important cause of morbidity and mortality in children worldwide, but estimates of disease burden are inaccurate because most cases are not confirmed.<sup>1</sup> The most common form of childhood tuberculosis is pulmonary disease, and in tuberculosis-endemic communities, most cases present in young children. Collection of respiratory specimens for laboratory diagnosis is difficult in this age group. Most cases are paucibacillary, and therefore mycobacterial culture of specimens is required to optimise diagnostic yield. Studies of tuberculosis diagnosis in children are hampered by the lack of a gold standard for tuberculosis disease and infection, with the limitations of mycobacterial culture and tuberculin skin test well recognised. During the past decade, there has been a surge in development of new diagnostics aiming to provide more accurate and rapid diagnosis. Despite the challenges, new diagnostic techniques need to be studied in children.<sup>2</sup>

In a study by Richard Oberhelman and colleagues<sup>3</sup> in *The Lancet Infectious Diseases* today, multiple specimens were obtained from Peruvian children (median age 3 years) with clinically diagnosed pulmonary tuberculosis for comparison of diagnostic methods. This research group has previous experience with new diagnostic techniques, including nasopharyngeal aspiration for sputum collection and the use of broth culture by microscopic-observation drug-susceptibility (MODS).<sup>4,5</sup> MODS provided a significantly higher and faster yield than did Lowenstein-Jensen culture for confirmation of pulmonary tuberculosis diagnosis. Nasopharyngeal aspiration after cough induction provided a lower yield of culture-positive specimens than did gastric aspiration. The induced sputum technique might have improved the yield because it also includes the use of chest physiotherapy and hypertonic nebulised saline before cough induction. This method was not used in this study but has shown promise compared with gastric aspiration in South African children.<sup>6,7</sup> The lowest diagnostic yield was from stool specimens, including with the use of PCR.

Duplicate PCR was done on all specimens and the results show that the role of PCR in diagnosis of tuberculosis in children is unknown. The potential advantage of PCR over culture would be more rapid

diagnosis with possibly greater sensitivity. In this study, the proportion of samples that were positive by PCR was higher than that for culture in all specimens, especially in those from children with a lower clinical score. This finding might suggest improved sensitivity; however, PCR was negative in 38% of culture-positive children with strong clinical evidence of pulmonary tuberculosis. Furthermore, PCR was positive in a small proportion of controls, raising doubts about specificity of PCR for disease compared with infection.

The low overall yield of culture-confirmed cases in this study of a large number of children, many with strong clinical evidence of pulmonary tuberculosis, emphasises the ongoing diagnostic challenges for research. Patients with a higher diagnostic score were more likely to have tuberculosis confirmed on culture, but this finding does not necessarily mean that those with a higher score were more likely to have tuberculosis. These patients might have pulmonary tuberculosis disease at time of presentation that is more likely to be culture positive than infected patients with a lower score. Without a gold standard, the yield from culture is usually reported in relation to clinical diagnosis, which is affected by selection of patients and definitions used for clinical categorisation.

There are many clinical definitions or scoring systems used for diagnosis of tuberculosis in children, including for diagnostic research purposes that have not been validated and are not comparable.<sup>8,9</sup> Although there is inherent consistency within studies, comparison of a particular diagnostic technique is impossible between studies in different settings that use different clinical definitions for comparison. A distinction needs to be made between a clinical definition for reporting of research findings and an approach to clinical diagnosis that is more individualised, flexible, and usually needs to be made before culture results are available. The recognised difficulties with confirmation of diagnosis have contributed to a common, and perhaps erroneous, perception that the diagnosis of childhood tuberculosis is always difficult. Clinical diagnosis is fairly straightforward in many patients and this unnecessarily negative perception can be a barrier for improving clinical management, supporting child tuberculosis research, and reporting of disease burden.

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A response to the global emergence of drug-resistant tuberculosis is the increasing availability of culture facilities in high tuberculosis-endemic settings. This development provides an important opportunity for child tuberculosis research. In the absence of a gold standard, other analytical approaches also need to be considered and investigated.<sup>10,11</sup> A more consistent approach to diagnostic methods would be very helpful for the purposes of reporting and more meaningful comparison across diagnostic research studies.

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I declare that I have no conflicts of interest. I was a member of a Diagnostic Evaluation Expert Panel on paediatric tuberculosis diagnosis that was hosted by WHO TDR in May, 2010, and attended by clinicians and epidemiologists, where the issues raised in this commentary were discussed, such as improving standardisation of methodology and alternative analytical approaches. I am co-chair of the child tuberculosis subgroup of the New Diagnostics Working Group of the WHO Stop TB Partnership.

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