Diagnosis of paediatric tuberculosis: the culture conundrum

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Paediatric tuberculosis is probably underdiagnosed, with the 22 countries with the highest burden notifying a lower proportion of cases in children (3·5%) than expected (11·0%).[1] Diagnosis is often made late or at post mortem because of inadequate case detection.[2,3] New rapid diagnostics are, therefore, a priority. In this issue of *The Lancet Infectious Diseases,* Matthew Bates and colleagues[4] add to recent evidence that suggests that a new nucleic amplification test (Xpert MTB/RIF; Cepheid, Sunnyvale, CA, USA) represents an advance. The novelty of the study was that the microbiological diagnosis of tuberculosis was made from a concentrated gastric lavage sample. The sensitivity of the Xpert MTB/RIF assay from gastric lavage was 68·8% (33 of 48 samples; 95% CI 53·6–80·9) and specificity was 99·3% (735 of 740 samples; 98·3–99·8) with respect to culture (table). The assay detected significantly more cases than smear microscopy (sputum 90·0% [nine of ten samples; 95% CI 54·1–99·5] *vs* 30·0% [three of ten samples [8·1–64·6]; gastric lavage 68·8% [33 of 48 samples; 53·6–80·9] *vs* 25·0% [12 of 48 samples; 14·1–40·0]; table). Xpert MTB/RIF seems to be highly specific (98–100%) and clearly more sensitive than smear microscopy in the context of childhood tuberculosis, irrespective of the type of sample. The shorter time to diagnosis than culture-based techniques suggests that Xpert MTB/RIF will probably allow treatment to be started sooner.[8] However, the test should not be used on a single sample to rule out tuberculosis.

Another potential advantage of Xpert MTB/RIF is the incorporation of rapid detection of rifampicin resistance, which potentially enables the start of more appropriate treatment weeks ahead of standard culture-based drug-sensitivity testing. Data on resistance are scarce in children. Bates and colleagues documented three cases diagnosed with Xpert MTB/RIF, one of which was a false positive. It is equally important not to inadvertently deny a child the powerful rifampicin-containing regimen that remains effective in most cases worldwide.

The overall very high specificity of Xpert MTB/RIF when compared with culture might at first seem encouraging. However, this finding relates to a clinical limit of detection of 131 colony forming units per mL.[9] Even with optimum application of these invasive approaches, detection of *Mycobacterium tuberculosis* in gastric aspirates or induced sputum is only achieved in less than 20% of clinically suspected cases of tuberculosis.[10,11] Children are more likely to develop severe and disseminated forms of tuberculosis that are paucibacillary and thus it is much more difficult to obtain microbiological proof. The limited ability of culture to provide evidence of true tuberculosis disease implies that estimates of the sensitivity and negative predictive values of Xpert MTB/RIF are probably overstated. If culture of gastric lavage aspirates misses true disease 70% of the time, the sensitivity of Xpert MTB/RIF might be as low as 21%, corresponding with a negative predictive value of 83%. Although the search for new diagnostic techniques that produce reliable results faster than culture will result in treatment being started earlier, benchmarking against culture will not provide improvements in the true accuracy with respect to active tuberculosis. Indeed, an improved diagnostic technique should have low specificity relative to culture; it must identify disease that culture fails to identify. However, solutions that might provide better estimates are problematic.

Two recent consensus statements are intended to aid standardisation of a clinical case definition and methods to assess diagnostics,[12,13] but the bulk of diagnoses worldwide will continue to rely not on culture or Xpert MTB/RIF, but on clinical algorithms that have not been validated and which show poor concordance.[10] Greater efforts to apply clinical algorithms should be consistently encouraged.

The absence of an operational gold standard to diagnose childhood tuberculosis has encouraged the use of latent class analysis.[14] Latent class analysis assumes a relation between multiple diagnostic tests assessed simultaneously to provide information about the probably true (unobserved) state of disease. However, although this type of analysis has appeal, detailed

	Sample	Smear positive	Xpert MTB/RIF positive
Nicol et al (2011)[5]	Two induced sputa	39% (27/70)	74% (52/70)
Zar et al (2012)[6]	One nasopharyngeal aspirate One induced sputum	24% (21/87) 32% (28/87)	56% (49/87) 74%(64/87)
Rachow et al (2012)[7]	Up to three sputa or induced sputa	25% (7/28)	75% (21/28)
Bates et al (2012)[4]	One sputum One gastric lavage	30% (3/10) 25% (12/48)	90% (9/10) 69% (33/48)

Table: **Diagnostic sensitivity of sputum-smear microscopy and Xpert MTB/RIF when compared with a gold standard of any positive microbiological culture (solid and liquid media)**

assessments of the varied latent class approaches have shown the resulting sensitivity and specificity estimates to be highly dependent on the assumed relations.[15] Furthermore, verification of which of the many possible assumed relations between tests is appropriate is not generally feasible.[15] Hence, latent class analysis is unlikely to provide more confidence about our understanding of the effectiveness of Xpert MTB/RIF in identifying the presence or absence of true tuberculosis disease. Studies including rich collections of clinical and microbiological data should contribute to a better understanding of optimum diagnostic strategies, especially when incorporating reasonable working assumptions specific to tuberculosis. However, the robustness of such an approach needs verification.

In conclusion, Xpert MTB/RIF, an incremental advance, can be applied to gastric lavage aspirates from children to improve the proportion of cases diagnosed early. The definitive test for paediatric tuberculosis remains to be found. The poor performance of culture continues to be a stumbling block for the assessment of new tests. Development of robust methods that overcome this limitation are needed.

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