



Xpert MTB/RIF: a game changer for the diagnosis of pulmonary tuberculosis in children?

The diagnosis of pulmonary tuberculosis in young children is challenging because clinical and radiological features are often non-specific.¹ Achieving a definite diagnosis through microbiological confirmation is especially problematic in this population owing to the typically low bacillary burden and the difficulty in obtaining a quality respiratory specimen. For adults, WHO has endorsed a single Xpert MTB/RIF assay for initial diagnosis, especially in people with HIV and in those with suspected drug-resistant tuberculosis.² A consensus has not yet been reached on the value of the Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in young children. Xpert MTB/RIF has been shown to give a rapid diagnosis on induced sputum,^{3,4} nasopharyngeal aspirate,⁵ and gastric aspirate⁶ samples in about 70% of children in hospital with culture-confirmed tuberculosis. Most children with suspected tuberculosis, however, present to primary care clinics with less severe disease.

In this context, in *The Lancet Global Health*, Heather Zar and colleagues report findings from the first study to assess the accuracy of Xpert MTB/RIF in young children presenting to a primary-care facility with symptoms of pulmonary tuberculosis.⁷ Primary analysis was done in 309 children in whom four samples (two induced sputum samples and two nasopharyngeal aspirates) could be collected. On the first induced sputum sample, Xpert MTB/RIF assay detected 12 of 28 culture-confirmed cases, and on the first nasopharyngeal aspirate sample, it detected eight of 28 culture-confirmed cases. Tests on repeat samples improved the sensitivity of Xpert MTB/RIF to 16 of 28 culture-confirmed cases on two induced sputum samples and 11 of 28 culture-confirmed cases on two nasopharyngeal aspirate samples. On the basis of these results, the investigators suggest that Xpert MTB/RIF on two specimens should be recommended in children with suspected tuberculosis. At an estimated cost of US\$26.5 per assay in South Africa (excluding the costs of biospecimen collection),⁸ two Xpert MTB/RIF assay on induced sputum samples would have diagnosed 16 cases of pulmonary tuberculosis at a cost of \$1025 per patient diagnosed. Doing Xpert MTB/RIF on two

nasopharyngeal aspirate samples, which might be more feasible in most resource-poor settings because it does not require access to electricity or oxygen, would have diagnosed 11 cases at a cost of \$1491 per person diagnosed.

Whether repeat sampling (induced sputum, nasopharyngeal aspirate, or both) should become the initial diagnostic for paediatric tuberculosis in low-income countries thus becomes an important question. Zar and colleagues state that studies of cost efficacy of repeated specimens in children are needed. A decision to endorse this strategy should also be guided by the ability of the Xpert MTB/RIF assay to affect the management of patients. The diagnostic thought process usually starts with the generation of a differential diagnosis, followed by estimation of the pre-test probability, performance of a diagnostic test, and estimation of a post-test probability. Health-care workers generally start treatment when the post-test probability exceeds a threshold. When a negative test result decreases the post-test probability low enough to refute the hypothesis, health-care workers rule out the diagnosis and assess the next diagnostic hypothesis.⁹ In Zar and colleagues' study, tuberculosis treatment was started in 180 (47%) of 384 participating children. Of all children started on treatment, almost 90% were Xpert-MTB/RIF-negative, suggesting that the Xpert MTB/RIF results did not substantially change health-care workers' pre-test assessment of the probability of children having tuberculosis. The possibility that the strategy of empirical treatment for paediatric tuberculosis will change in the near future is unlikely in view of the absence of a reference standard against which new diagnostics for paediatric tuberculosis can be reliably assessed.

What reasoning could determine whether one or two induced sputum or nasopharyngeal aspirate samples are obtained for Xpert MTB/RIF in young children in high-burden, low-income countries? Zar and colleagues' included only 31 children with HIV, restricting the ability to assess the value of Xpert MTB/RIF stratified by HIV status. An alternative to Xpert MTB/RIF for the diagnosis of tuberculosis in young children in primary

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care could be the use of the urine lipoarabinomannan assay. Although this assay has been shown to be useful in adults with severe immunosuppression,¹⁰ no data have been published on its performance in children with HIV. The most compelling reason might be the suspicion of drug-resistant tuberculosis. In such cases, rapid knowledge of the presence of rifampicin resistance can inform which children should receive extended treatment with potentially toxic second-line drugs.

Despite the crucial need for rapid, accurate, and affordable diagnostics for pulmonary tuberculosis in young children, it seems unlikely that Xpert MTB/RIF will be the game changer that high-burden countries are desperately waiting for.

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I declare that I have no conflicts of interest.

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