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The Role of Xpert MTB/RIF Ultra in Diagnosing Pulmonary Tuberculosis in Children

Bacteriological confirmation of pulmonary tuberculosis in young children (<5 yr) can be challenging because of the difficulty of obtaining suitable specimens and the paucibacillary nature of the disease. Mycobacterial culture remains the reference standard for confirming tuberculosis in children. However, cultures are positive in only a minority of cases, with highly variable yields depending on the specific disease phenotype (1). Molecular epidemiology studies raised awareness that drug-resistant strains of *Mycobacterium tuberculosis* are readily transmitted within affected communities, as well as to children, with estimates that the vast majority of drug-resistant tuberculosis cases result from person-to-person transmission rather than acquisition (2). This demonstrates the dire need for not only improved bacteriological confirmation but also routine drug susceptibility testing in young children with tuberculosis.

In this issue of the *Journal*, Zar and colleagues (pp. 1531–1538) present data on the value of the new Xpert MTB/RIF Ultra (Ultra) in hospitalized children suspected of having pulmonary tuberculosis (3). Ultra on one induced sputum (IS) and one or two nasopharyngeal aspirates (NPAs) were compared with mycobacterial culture from a single IS specimen. Compared with culture, Ultra yield from a single IS specimen (74.3%) was much better than from two NPA specimens (54.2%), but multiple specimens provided the best sensitivity: 87% for single IS plus two NPAs. The authors stress the fact that Ultra yield may have been compromised by storage of the original specimens before testing, but DNA is robust, and the expected detrimental effect of freezing at −80°C is minimal. Even if there were some detrimental effects, the results presented represent an underestimation, rather than an overestimation, of the true diagnostic performance using fresh specimens.

These findings represent an exciting advance for tuberculosis diagnostics in children, although two major caveats limit translation. The first is the fact that tuberculosis confirmation was achieved in only a small percentage of children admitted to hospital with possible tuberculosis. Among children treated for tuberculosis (confirmed or unconfirmed tuberculosis), only 40 (27.8%) of 144 tested positive on culture, which demonstrates its suboptimal yield and limitations as a reference standard. "Unconfirmed tuberculosis" is a heterogeneous group in whom the probability of tuberculosis disease is uncertain; however, previous attempts to identify a subgroup with highly "probable tuberculosis" on clinical grounds have been abandoned, and clinical relevance is indicated by the fact that these children received tuberculosis treatment (4).

Ultra was positive in a few of these children with "unconfirmed tuberculosis," which introduces the dilemma of how best to assess the diagnostic performance of a test if the accepted reference standard has poor sensitivity. Given the excellent specificity of Ultra, it would be highly informative to consider Ultra's diagnostic

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accuracy, using a revised reference standard that includes both culture and Ultra. This is usually discouraged to prevent an unrealistic positive assessment resulting from "inclusion bias." However, in situations in which the reference standard has poor sensitivity and the test evaluated has excellent specificity (especially when more than one probe was amplified), this may provide a more accurate assessment of "true diagnostic accuracy." A critical evaluation of discrepant culture and Ultra results would have been useful. It is notable that most culture-negative but Ultra-positive specimens were "trace positive, rifampicin drug susceptibility unsuccessful," which leaves the clinician with the problem of not knowing whether there is susceptibility to rifampicin. Even in those with culture-confirmed disease, in nearly a quarter (7/30; 23%), the Ultra rifampicin susceptibility test was unsuccessful, which implies that culture or line probe assay results had to be awaited for ultimate treatment guidance.

The second major caveat, apart from poor yield, is cost. Even at the highly attractive price of ~10 U.S. dollars per test, Ultra cartridges are expensive compared with overall health expenditure in most tuberculosis endemic settings. This results in huge reluctance to perform multiple tests in children with relatively low yield. However, the reality is that no viable alternative exists in these resource-limited settings, as mycobacterial culture is more expensive and unlikely to be available, and even if available, because of specimen quality, suboptimal specimen transport, and delays in processing, mycobacterial cultures may be negative or overgrown with rapid-growing bacteria. This demonstrates the difficult clinical dilemma in resource-limited settings, and we would argue that access to even a single Ultra test would be a great step forward to assist clinicians in their clinical judgment and management. It also indicates the importance of identifying the method with the highest yield/cost ratio and the need to consider approaches such as pooled specimen testing that may increase the diagnostic yield from a single test or allow multiple respiratory specimens to be tested with one Ultra cartridge (5, 6).

Various respiratory specimen types can be collected, such as gastric aspirates (GA), IS and NPAs, and each have their own advantages and disadvantages. NPA may be easier to obtain, but culture and genotypic yields are lower compared with IS or GA (3, 6). IS and GA are more invasive, but diagnostic yields are higher (3, 6), and in considering the optimal combination of specimens, clinicians need to consider cultural or other barriers to obtain specimens in addition to their combined diagnostic yield (7). We need data on Ultra's performance using GA specimens, as it has demonstrated a better bacteriological yield than IS in one study (6), and single or pooled GA and IS specimens may provide the best yield. Expectorated sputum sampling is possible in older children (>5–6 yr of age), which also requires further evaluation.

Finally, the order in which same-day specimen collections are performed may influence the yield. NPA before IS makes sense if the aim is to limit potential contamination of the NPA from IS (as in the study by Zar and colleagues) (3); however, if the aim is to maximize the yield from two separate specimens, then the best time to perform the NPA is likely directly after the IS. The same would apply to GA collection, where the yield may be optimized if it is performed after IS. This may be worth consideration in future studies.

In conclusion, although Ultra offers an improvement on the previous Xpert MTB/RIF test, this study confirms that the challenges remain similar, with diagnostic yield and cost considerations likely to limit countries' ability to respond to calls for routine testing of multiple specimens. ■

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