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EDITORIAL

Xpert® MTB/RIF for extra-pulmonary tuberculosis: time to look beyond accuracy

EXTRA-PULMONARY TUBERCULOSIS (TB) accounts for ~20% of all TB cases, but its diagnosis is challenging.[1] The World Health Organization (WHO) endorsed the Xpert® MTB/RIF assay for use in pulmonary TB in 2010, and the endorsement was extended for certain types of extra-pulmonary TB in 2013.[2] In this issue of the *Journal*, Kim et al. present data from 1429 patients suspected to have extra-pulmonary TB and whose non-respiratory samples underwent testing with Xpert between 2011 and 2013 in a tertiary care hospital in South Korea.[3] Consistent with the systematic review and meta-analysis[4] that informed the WHO policy recommendation,[2] Kim et al. found widely varying sensitivity across sample types, with acceptable sensitivity in lymph node tissue and cerebrospinal fluid.[3]

The evaluation of new tests for extra-pulmonary TB poses special challenges due to 1) the imperfect sensitivity of culture and the imperfect specificity of composite reference standards; 2) the variety of sample types in extra-pulmonary TB; and 3) varying protocols for sample processing. Due to these challenges, it is important that authors clearly report the definition of their reference standards, present estimates of accuracy with the index test compared to both culture and a composite reference standard, stratify the results by sample type, and report on the sample processing steps used.

The report by Kim et al. covers the above issues, and thus helps increase our confidence in the evidence that informed the WHO recommendation. It may also help extend our knowledge on accuracy in sample types for which data are scarce. However, further research on accuracy should also focus on optimizing sample processing procedures for different sample types to maximize the utility of Xpert in non-respiratory samples.[5]

More importantly, the time has come to look beyond the assessment of accuracy of Xpert alone, and instead evaluate whether its use actually leads to changes in clinical decision-making and improvements in patient-important outcomes.[6,7] Studies should assess whether Xpert indeed reduces time to diagnosis and initiation of appropriate therapy and thus leads to reduced morbidity and mortality. While such research is becoming increasingly available for pulmonary TB, it is virtually nonexistent for extra-pulmonary TB.

As with the case of human immunodeficiency virus associated and pediatric TB, clinical diagnosis (without microbiological confirmation) and empirical therapy are also common in extra-pulmonary TB. The true base case scenario—which any new test has to improve upon to have a clinical impact—thus includes not only conventional tests but also clinical diagnosis.[8] Therefore, neither the improved sensitivity compared to smear microscopy nor the more rapid diagnosis than using culture can simply be assumed to translate into improvements in patient outcomes. It is especially in those circumstances that direct evidence on the impact of new diagnostics on patient outcomes is needed the most, to assess whether new tools can do better than empirical management, which is widespread.

We hope the TB research community will go beyond accuracy studies of Xpert and novel diagnostics, and measure outcomes such as clinical impact, cost-effectiveness, and programmatic impact. This will help not only to advance the field of TB diagnostics, but also to identify the best implementation strategy for new tools.

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