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Automated Digital Microscopy in New Tuberculosis Diagnostic Algorithms

Can It Boost Case Finding?

The World Health Organization (WHO) has recently launched its innovative End TB Strategy, supporting the vision of a tuberculosis (TB)-free world with zero death, disease, and suffering caused by TB (1, 2), as well as the concept of TB elimination (3, 4).

The new strategy clearly supports universal access to quality TB diagnosis and treatment, on top of a new vaccine. In the last couple of years, the TB diagnostic armamentarium has been substantially strengthened by the introduction of the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA) (5). This test demonstrated high sensitivity (89% in pulmonary TB, being close to 100% in sputum smear-positive and 68% in sputum smear-negative patients) and specificity (99%) for detecting TB compared with culture (5, 6). In addition, the Xpert MTB/RIF assay showed a pooled sensitivity and specificity of 95% and 98%, respectively, for detecting resistance to rifampicin (6), which is presently the core anti-TB drug (7–9). The test, which is easy to perform, provides a result in less than 2 hours, allowing prompt clinical action while waiting for culture and drug susceptibility testing. For the first time, after more than a century, we can replace smear examination as the first diagnostic test for TB diagnosis.

Unfortunately, in spite of the efforts of the international community (6.2 million Xpert MTB/RIF tests were performed between 2011 and 2014) (10), it is unlikely that more than 10% of the patients with presumptive TB have access to this test globally (11). Although the cost of this test has significantly decreased in the last years (to $9.98 per cartridge) (12), it is still considerably higher than that of sputum smear microscopy (11). This is why in several low-income countries, TB diagnosis still relies mostly on sputum microscopy (11).

While the accessibility of the Xpert test is being expanded to all patients with presumptive TB worldwide, efforts also have been made to develop diagnostic algorithms able to reduce the number of tests performed in field conditions and to ensure adequate sensitivity in detecting TB cases.

The algorithm proposed in this issue of the *Journal* by Ismail and colleagues (pp. 1443–1449), from South Africa, is interesting (13). It is based on the automated digital microscopy (TBDx automated system). This promising new technology is able to process digital microscope images to identify alcohol acid-fast bacilli (AFB), whose performance, within a properly designed diagnostic algorithm, have not been formally tested. Ismail and colleagues evaluated the performance of the new diagnostic tool by processing 1,210 samples from a prospective cohort of patients with presumptive TB, in parallel with conventional sputum smear microscopy and liquid culture. The specimens that resulted positive for TB with the new diagnostic underwent Xpert MTB/RIF evaluation. The authors calculated sensitivity and specificity of the two algorithms, using either the new test followed by Xpert for the "low-positive" samples (one to nine putative AFB) only, or the new test alone in comparison with liquid culture. Of the 1,009 samples eligible for evaluation, 109 yielded a positive *Mycobacterium tuberculosis* culture.

The new diagnostic resulted in 70 specimens (68 culture-positive) having $\geqslant$10 putative AFB (high positivity) and 207 specimens (19 culture-positive) having one to nine putative AFB (low positivity). In the algorithm in which "low-positive" results on the new diagnostic were confirmed by Xpert, the sensitivity was 78% (85/109) and the specificity 99.8% (889/900). With the new test followed by Xpert, only 21% of the Xpert tests otherwise needed (207/1009) would be used, with significant savings. Using the new test alone, the new diagnostic yielded 62% sensitivity and 99.7% specificity.

The authors concluded that the new diagnostic used within a diagnostic algorithm including Xpert yielded high specificity coupled with reasonable sensitivity in active TB cases, having the potential to be used as a triage tool; that this approach reduced significantly the number of Xpert test needed, this being probably the most relevant finding of the study; and that, importantly, when used within the "stand-alone" approach, the new diagnostic performed like a highly experienced TB microscopy technician in settings in which trained microscopy technicians are difficult to find for various reasons.

The study, as clearly underlined by the Ismail and colleagues, has several limitations, including the following: it was conducted in a single laboratory that, being a reference center, probably has performances higher than the average available in the country; it is expected that sputum smear microscopy will perform suboptimally in settings with high HIV prevalence; the contaminated cultures have been excluded from the analysis (n = 128/1,210); and traditional fluorescence microscopy was used, rather than the newly recommended light-emitting diode technology, which is expected to increase detection rates (14).

Although the results of this study are very promising (especially to limit the number of Xpert tests to be done), the short-term goal should be to ensure access to Xpert for all patients with presumptive TB in both high- and limited-resource settings.

With this approach, it will be possible to diagnose the maximum number of patients with TB with a minimum delay while cutting the transmission of TB bacilli within the community.

Furthermore, this approach will allow clinicians to prescribe the correct treatment from the beginning for all potential multidrug-resistant TB cases, ensuring higher chances of cure while reducing the possibility of selecting additional drug resistance (7–9).

The consistent use of Xpert in countries with a high TB burden, with South Africa being one of them (15), will be essential to ensure rapid and quality diagnosis of TB and multidrug-resistant TB and to notably increase the detection of these cases (5).

We do hope that all countries globally will be able, very soon, to access Xpert for all patients with presumptive TB. Of course, it should be available at an affordable cost irrespective of income status; intermediate-income countries are presently the most disadvantaged, as they do not meet the requirements for special pricing.

This is one of the preconditions to achieve zero TB-related death, diseases, and suffering (1, 2).

From our perspective, the algorithm presented by Ismail and colleagues (13) will be very useful in the bridging period needed to ensure universal access to Xpert, which will last, we hope, no more than 2–3 years. ■

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