

Xpert MTB/RIF and pulmonary tuberculosis: time to delve deeper?

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I find out what the world needs, then proceed to invent it. Thomas Edison.

If Edison, the world's most prolific inventor, had to get around to creating a new diagnostic test for tuberculosis (TB), he would have considered himself pleased with the Xpert MTB/RIF test. Here is the new diagnostic test for TB that the physician in the developing world has been waiting for. It does two things, and does them both well. It diagnoses TB with a higher sensitivity than a sputum smear examination: a single Xpert MTB/RIF test diagnoses 98% of sputum smear positive cases and around 70% of smear-negative patients.¹ More importantly, for the physician practicing in areas with a high prevalence of multi-drug resistant TB (MDR-TB), it diagnoses rifampicin resistance (a surrogate marker for MDR-TB) with around 98% sensitivity and specificity, thus identifying patients who need second-line drugs.² That it does this with safety, speed and simplicity is what makes this test a 'game changer'.³ A result is obtained within 90 min, lopping off 6–8 weeks from the time that a traditional culture would take to diagnose MDR-TB. Called a 'laboratory in a cartridge', the test comprises of a cartridge-based system using an automated real-time, PCR-based assay with molecular beacon technology. The test, which is easy to learn, can be performed by a technician with 2 days of training. Robust enough to be performed in emergency departments and small laboratories in hospitals across the developing world, it poses substantially less of a biohazard risk and hence obviates the need for bio safety cabinets, which are anyway conspicuous by their absence in these regions.⁴

This test, initially evaluated in sputum samples for pulmonary TB, has been tested with success in a few small studies for diagnosing pulmonary TB from

bronchoalveolar lavage fluid (BALF).^{5–8} When it comes to extra-pulmonary sites, recent studies from Italy,⁹ Germany¹⁰ and India¹¹ demonstrate the impressive yield of the Xpert MTB/RIF from a variety of extra-pulmonary sites. The Italian study, which represented the largest number of non-respiratory samples tested with the Xpert MTB/RIF to date (1476 samples from 1068 patients), found an impressive overall sensitivity of 81.3% and specificity of 99.8%. Biopsies, pus, urine and cerebrospinal fluid (CSF) had sensitivities of >85%, gastric aspirates around 80% and cavitary fluids (pleural, ascitic) around 50%. These figures represent considerable advances on the poor yield from traditional cultures.

Despite being superior in accuracy to smear microscopy, the diagnostic performance of Xpert MTB/RIF is likely to be equally dependent on the quality of the sputum specimen provided. Samples with a predominance of saliva are unlikely to bear mycobacteria, and are consequently reported as being negative for TB when tested with smear microscopy.¹² A recent study from Indonesia reported that of the subjects who submitted sputum smears for examination, only a third could produce at least one good sample.¹³ The inadequacy of good quality sputum specimens could possibly have contributed to the fact that in 2011, 44% of the 4.7 million new cases of pulmonary TB reported to WHO were sputum smear negative.¹⁴ Thus, in the potentially underdiagnosed population of sputum-scarce individuals with possible TB, the successful use of Xpert MTB/RIF on BALF would be a useful addition to a limited armamentarium of available diagnostic tools. The study by Theron *et al*¹⁵ is the first large prospective study that explores the utility of the test in BALF specimens collected from individuals with possible TB in a high-HIV burden setting endemic for TB.

The study, conducted in Cape Town, South Africa, enrolled 154 individuals with suspected pulmonary TB who were referred for bronchoscopy. These individuals had symptoms and radiographic features compatible with TB and either had two consecutive smears that were negative for acid-fast bacilli or were unable to expectorate sputum. In addition to

measuring the diagnostic accuracy of the test, the authors attempted to measure the clinical impact of the test by comparing phase I, in which the test was studied in a research milieu, with phase II, in which the results of the test informed clinical practice. Even in this population, in which a majority (72%) of included individuals were sputum-scarce and likely to have a lower mycobacterial burden, the Xpert MTB/RIF test demonstrated an overall sensitivity of 93% (95% CI 77% to 98%), which was significantly higher than that for smear microscopy (58%, 95% CI 39% to 75%), with comparable specificities. The performance was similar in persons living with HIV, and was not affected by centrifugation of the BALF. Genotype MTBDR_{plus} assay performed on five of the 11 false-positive Xpert MTB/RIF results from the study (with culture as the reference standard) in which samples were available suggested these results to be true positives, possibly indicating inaccuracies in the reference standard. The median time-to-detection for smear-negative individuals with TB was shortened from 29 days (IQR 18,41) to 0 days (IQR 0,0), and the percentage of individuals on empiric TB treatment (those presumptively treated on clinical and radiological grounds without definitive laboratory evidence of disease) decreased from 79% in phase I to 20% in phase II. However, the use of the Xpert MTB/RIF test neither significantly impacted the overall proportion of patients who were initiated on anti-TB treatment nor did it significantly change the time to treatment initiation. This was attributed to a high proportion (79%) of all treated individuals being treated empirically in phase I, only a quarter of whom were later proven to have TB.

The individuals in this large, prospective study were well characterised and thoroughly investigated, and the conduct of the study in two phases allowed for comparisons in the clinical impact of the test. As rightly pointed out by the authors, there is a need for assessing the true clinical impact in a real-world setting before implementing tests based on the assumption that improved accuracy in a research setting translates into a significant positive clinical impact. This is especially true for a test such as a bronchoscopy and the collection of BALF, which is invasive, expensive and likely to be only offered in tertiary care institutes in the developing world. The gain in the lowering of biohazard risks from the use of Xpert MTB/RIF may also be offset by the increased risk to healthcare workers and patients from such

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procedures, which are known to generate infectious aerosols.¹⁶ The cost of the use of Xpert MTB/RIF is also a crucial aspect in the assessment of the feasibility of the use of this technology, especially in the developing world. The steady decline in the cost of each cartridge has been encouraging. The cost per cartridge is currently pegged at \$9.98, half that of its initial cost of \$18.68 when this test was first endorsed by WHO in 2010.¹⁷ The test has been proven to be cost-effective, but this does not necessarily denote affordability. For example, providing the test to just 15% of individuals with possible TB in India would consume the entire annual TB budget of the Indian Revised National TB Control Program.¹⁸ An easier, relatively inexpensive and more accessible procedure such as the use of sputum induction techniques has been reported to consistently improve the performance of smear microscopy,¹⁹ but was not investigated by the authors in the study, and is a potential target for future diagnostic research.

In conclusion, in a high-HIV burden setting endemic for TB, Xpert MTB/RIF, when performed on BALF specimens, significantly outperforms smear microscopy in individuals with possible TB who have scarce sputum. However, whether such an enhancement in performance characteristics of a diagnostic test for pulmonary TB results in better clinical outcomes in a cost-effective and affordable manner and in comparison with alternative strategies such as those employing the use of induced sputum remains unproven, and should be the focus of future research.

Competing interests None.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Pinto LM, Udwadia ZF. *Thorax* 2013;**68**:987–988.

Published Online First 4 July 2013



► <http://dx.doi.org/10.1136/thoraxjnl-2013-203485>

Thorax 2013;**68**:987–988.
doi:10.1136/thoraxjnl-2013-203885

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