Perspective

Transforming TB Diagnosis: Can Patients and Control Programs Afford to Wait?

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For every new public health intervention tool, whether it be antiretroviral drugs for human immunodeficiency virus, bed nets for malaria, or vaccines for rotavirus, there is, and should be, a public debate about whether the benefits of the tool are worth the cost and disruption that will accompany its implementation. The World Health Organization (WHO), as the United Nations agency with primary responsibility for international health policy, norms, and standards, is often criticized for moving too slowly or, rarely, too quickly in providing recommendations about new tools. With regard to Xpert MTB/RIF, the new, rapid, molecular test for tuberculosis and rifampin resistance, we think WHO has got it just about right, moving quickly with an evidence-based policy decision allowing the test's rapid uptake.

THE CONTEXT

Sputum smear microscopy, still the only tuberculosis (TB) diagnostic that is widely available, has notoriously poor sensitivity that leaves at least half of TB cases undetected, gives no information about drug resistance, and is difficult to implement and sustain with controlled quality. The limitations of microscopy are particularly significant when it comes to patients who are human immunodeficiency virus (HIV)-infected or who have multidrug-resistant TB (MDR-TB)—two groups that present unique challenges for TB control and have fuelled a resurgence of the epidemic.

In 2007, following guidance from WHO, which included specific measures to address the needs for proper care for HIV-associated and MDR-TB, the World Health Assembly called for universal access to culture and drug susceptibility testing (DST), marking a seismic shift in diagnostic strategy for disease-endemic countries. The updated Global Plan to Stop TB (2011–2015) responded with a call for significant investment in laboratory services and a dramatic increase in testing of smear-negative and potentially drug-resistant cases with molecular- and culture-based methods.¹ However, the cost of meeting these targets using existing culture and DST tools, which necessitate the construction and maintenance of sophisticated laboratories with containment facilities and practices, could easily overwhelm TB control budgets. Moreover, the actual clinical impact of such testing is limited because systems for the rapid transportation of specimens to these centralized laboratories and the rapid report of testing results are largely unavailable in disease-endemic areas. Reporting delays associated with culture and DST, even using rapid liquid media, has been shown to result in significant diagnostic dropout, decreasing the effectiveness

of culture by 20–30% because culture-positive patients do not get their results.²

HOW A NEW TOOL FITS IN

Into this vacuum stepped a new molecular test, Xpert MTB/RIF. The Xpert MTB/RIF assay, developed through a partnership between the Foundation for Innovative New Diagnostics (FIND), the University of Medicine and Dentistry in New Jersey and Cepheid, Inc., CA, addressed many of the technical hurdles blocking effective case management through culture and DST. By using a bactericidal reagent to liquefy sputum in the first and only manual step in the assay, it eliminated the need for complex biosafety equipment. By using a real-time molecular amplification platform targeting the *rpoB* gene, it delivered case detection and MDR screening in 100 minutes, making it possible to inform patients before they are lost to follow-up. Finally, by automating specimen processing, amplification and detection in a cartridge pre-loaded with all necessary reagents, it essentially eliminated the need for containment infrastructure and molecular training. The cartridge employs a filter for bacterial concentration, which both enhances sensitivity and makes the assay immune to amplicon contamination events that frequently undermine molecular testing. Published evaluations of Xpert MTB/RIF have shown consistent excellent performance, with case detection sensitivity similar to conventional culture,³ but with significant increases in the number of patients started on therapy because of the much faster time to result.^{2,4,5} Accuracy data for the detection of TB in children^{6,7} and for the detection of extrapulmonary TB^{8–11} also show great promise.

The technology has its limitations. It is a sophisticated device that requires annual calibration, maintenance, and stable electricity, and is therefore not suitable for many peripheral diagnostic settings in disease-endemic countries. This is also why research and development efforts must continue to focus on developing tests more suitable for such settings. The technological advantages of Xpert MTB/RIF also come at a cost—Xpert MTB/RIF testing is currently similar to the operational cost of culture, which it is intended to replace or augment, but is more expensive than microscopy. National governments and donors supporting TB control efforts need to know if broad implementation of Xpert testing is cost-effective and if it is affordable.

Published data already exist to help countries know whether Xpert is worth the cost of implementation. Vassall and colleagues¹² modeled the cost-effectiveness of Xpert testing as a replacement for or as an addition to microscopy in India, South Africa, and Uganda. They report that, even when not factoring in the impact of early TB detection and treatment on disease transmission, Xpert MTB/RIF testing was cost-effective, with incremental cost-effectiveness ratios per disability-adjusted life-year averted below the WHO willingness-to-pay threshold. Other studies have found that Xpert

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MTB/RIF testing was cost-effective for reducing premature mortality in patients with advanced HIV infection, both at the time of presentation with TB symptoms,¹³ and before initiation of antiretroviral therapy.¹⁴ Regarding affordability, WHO has estimated that Xpert testing for all symptomatic individuals at risk for HIV-associated TB or MDR-TB would consume < 3% of current global TB control spending.¹⁵

IMPERATIVE TO TEST

The WHO policy guidance on Xpert MTB/RIF recognizes its transformational potential and has provided the information and support necessary to enable countries to make the most appropriate decisions on if, how, and where within their diagnostic algorithms they use Xpert MTB/RIF.^{16–18} This guidance can and should be refined during the Xpert MTB/RIF implementation process; donor monies should fund ongoing research to delineate the most cost-effective approaches for its use. Current WHO guidance explicitly highlights the resource implications of rolling out the technology. These costs must also be balanced against the costs of inaction. For too long, the field of TB diagnostics had been stagnant. That stagnation had dire impact on patients who remain ill and infectious while waiting for a diagnosis, or who are mistreated through syndromic management. The Xpert MTB/RIF assay has a number of limitations, and will not meet the need for point-of-care diagnosis in many low-income countries, but offers an undeniable improvement over other available approaches. National TB control programs recognize this, and more than 47 developing countries have already implemented Xpert MTB/RIF testing in selected services. Early implementation can drive a virtuous cycle in the transformation of TB diagnosis and care: evidence of improved health outcomes in implementing countries will drive accelerated uptake of the test in other settings. This growing diagnostic market can, in turn, spur other groups to develop even better technologies. Furthermore, the process of adapting TB control programs and algorithms to include Xpert MTB/RIF will mean that emerging alternative technologies can be more effectively implemented because the ground will already have been prepared.

It is time to give full value to the promise of early and effective TB and MDR-TB diagnosis, and support countries to improve TB care and control through the implementation of innovations such as Xpert MTB/RIF. The WHO has put in place online mechanisms to rapidly and transparently share field experiences and operational research findings on Xpert MTB/RIF (<https://extranet.who.int/xpertmtbrif>). Other groups are also sharing information about the early implementation of Xpert MTB/RIF, including TB REACH (<http://www.stoptb.org/global/awards/tbreach/interactive/pages/interventions10.html>) and The Union/Treat TB's Xpert Research Mapping Project (<http://xrmt.treattb.org/>). To support the ongoing dissemination of information, we urge all those interested in the rational roll-out of Xpert MTB/RIF to contribute to these initiatives, growing this global knowledge base. Balanced against the cost of inaction, patients and countries cannot afford to wait.

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