

## Xpert TB diagnostic highlights gap in point-of-care pipeline

For more on the **tuberculosis diagnostics pipeline** see <http://www.finddiagnostics.org/programs/tb/pipeline.html>

For more on **evidence-based tuberculosis diagnosis** see <http://www.tbevidence.org/news.htm>

For more on **TB REACH** see <http://www.stoptb.org/global/awards/tbreach/>

For more on **prizes for tuberculosis diagnostics** see <http://healthresearchpolicy.org/>

Recent unprecedented efforts have led to an expanded tuberculosis diagnostic pipeline, and, in September, publication of the performance of Xpert MTB/RIF in a large multicentre trial was heralded as representing a new era in tuberculosis diagnostics. Xpert is the first automated molecular tuberculosis test developed for point-of-treatment use. But will Xpert and other tests in the pipeline help the patients most in need?

Martina Casenghi (MSF, Geneva, Switzerland) told *TLID* that “the pipeline has delivered new technologies that are certainly promising and interesting advances, such as Xpert, but a point-of-care [POC] test that can be used at the bedside in most rural settings is far away”, she notes. “What is encouraging”, she says, “is that this weakness of the pipeline is being more and more recognised in the scientific and research and development communities, but more focused research efforts are now needed.”

In 2009, MSF and partners reported a survey of field clinicians and laboratory experts, and their requirement was a simple-to-use, relatively non-invasive POC test that would diagnose active pulmonary tuberculosis and allow a decision on treatment initiation, with same-day turnaround, at primary-care level. The

ideal test is non-sputum based—to detect tuberculosis in children and in smear-negative cases.

In findings published in *NEJM* (2010; **363**: 1005–15), a single Xpert MTB/RIF nucleic-acid amplification test, identified 98% of culture-confirmed tuberculosis cases, including 72% of those with smear-negative disease, with specificity of 99%. Rifampicin sensitivity results agreed with phenotypic drug-susceptibility testing in more than 97% of patients. Performance for case detection and discrimination of rifampicin resistance was similar across diverse sites in many countries.

“Xpert is a step in the right direction because it is a point-of-treatment technology that is user friendly and yields rapid results—within 2 h. However, up to now the technology has been sited mainly in reference laboratories and district hospitals”, Keertan Dheda (University of Cape Town, South Africa) told *TLID*. “The real question”, he asks, “is whether Xpert can replace smear microscopy within a clinic or microscopy centre?”

The *NEJM* study assessed the value of Xpert only at reference laboratories, and although it has the potential to be implemented in peripheral settings (eg, district laboratories), this has yet to be shown. According to Camilla Rodrigues (Hinduja Hospital, Mumbai, India), large-scale projects are now underway to examine the value of Xpert as a point-of-treatment assay at such levels. India is one country where Xpert might be used effectively. “We found it worked well and if you take cost out of the equation, the test was rapid, and could be performed with minimal training. Additionally, the assay was not prone to cross-contamination, required minimal biosafety facilities, and showed good sensitivity in smear-negative, culture-positive tuberculosis.”

Madhukar Pai (McGill University, Montreal, Canada) told *TLID* that the

greatest difficulty with implementation of Xpert “is that it is expensive and requires fancy equipment”. Reduced costs of Xpert for low-income countries’ public sectors have been negotiated by the Foundation for Innovative New Diagnostics (FIND), the product-development partnership that did the Xpert study. However, in India, the Revised National Tuberculosis Control Programme now has established quality assured, optimised smear microscopy so Xpert, if found useful in large-scale studies, would still have to be appropriately priced, Rodrigues explains. Pai continues that costs might fall further “with higher volumes and also by developing generic or low-tech versions in countries like China and India”.

In more rural areas, factors such as power supply and yearly calibration restrict the use of Xpert and related technologies. A manual nucleic-acid amplification test is FIND’s next step in the diagnostic pipeline. One such proposed test is the loop-mediated isothermal amplification technology platform (LAMP), which does not require sophisticated equipment but rather indicates a positive test with a visual change. Although LAMP still requires the setting of a peripheral laboratory, it “is another promising technology that could potentially advance case detection in South Africa”, says Dheda.

WHO and the Stop TB Partnership are engaged in an initiative to expand laboratory capacity in resource-poor settings, while the European and Developing Countries Clinical Trials Partnership invested €8.5 million in 2009 in three consortia, which will also build capacity, including an assessment of ten new diagnostics, including Xpert, in primary care in areas of high HIV prevalence in Africa. However, an estimated 3 million people every year either fail to gain access to accurate tuberculosis diagnosis and effective



Sample analysis at a peripheral setting microscopy centre in Ethiopia

treatment, or are managed with unknown quality of care. For these people, says Casenghi, “what we are pushing for is a POC test that really requires very limited infrastructure to decentralise tuberculosis diagnosis and overcome problems of capacity building in endemic countries, which, despite efforts in recent years, remains a critical gap to be filled”. Laboratory strengthening needs to be done in parallel with decentralising tuberculosis diagnosis and treatment to improve access to care, she urges.

For primary-care and health-post levels, FIND indicates two technologies that might be available in a few years—a dipstick for urinary antigens and a dipstick antibody test. The first urinary antigen under study is lipoarabinomannan (LAM). Dheda says that “the urine LAM strip test is a truly POC assay but is mainly useful in HIV-infected patients with advanced immunosuppression. However, given that high burden of HIV in Africa, this test could potentially be very useful.” *Mycobacterium tuberculosis* is excreted in urine, so “the advantages of using urine as a clinical specimen and the current evaluation of POC dipstick formats make urine diagnostics an exciting frontier of tuberculosis research”, says Dheda.

The August publication of a serological profile of the *M tuberculosis* proteome, provides potential for identification of antibody biomarkers, since the pool of antigens recognised during active tuberculosis is relatively small (PNAS 2010; 107: 14703–08). Such research might eventually lead to tests similar to the immuno-chromatographic tests now used for malaria, Rodrigues hopes, although she admits tuberculosis diagnosis is far more complicated. So far, no effective antibody detection test is on the market, and WHO is planning a negative policy recommendation on available tests. New tests will need to overcome confounding by previous or latent tuberculosis, or environmental mycobacterial exposure.

Many other biomarkers and test platforms are being investigated, but Casenghi is concerned that “the most prominent strategy so far has been to focus on the low-hanging fruit”—eg, adapting technologies developed for high-income countries for use in developing countries, which usually requires substantial laboratory capacity. “A shift in strategy is needed now”, she says, to start research “with an upfront objective of delivering tools suitable for implementation in most peripheral and resource-limited settings”. To switch the focus to the health-care level where most patients are seen, TB REACH, an initiative of the Stop TB Partnership, recently awarded US\$18.5 million to 30 projects from 19 low-income countries. The projects all target populations with restricted access to health care, and will investigate “innovative techniques, interventions, and activities that result in increased tuberculosis case detection, reduced transmission and prevention of the emergence of drug-resistant forms of tuberculosis at the most basic health outpost”. The second wave of TB REACH funding will be launched at the end of this year.

To incentivise innovation further, several groups are exploring the idea of a tuberculosis diagnostic prize fund. The X Prize Foundation has already approved such a prize and is seeking funds while another was recently proposed by various governments and non-governmental organisations, including MSF. The latter prize—\$100 million for a test to be used where no laboratory facilities exist—is now under consideration by WHO, and, says Casenghi, the final award will be contingent on availability and affordability, including a licensing strategy by the developer to promote competition, she explains. Pai told TLID that his group and partners are exploring the option of a TB Prize for India, and are now seeking interest from Indian philanthropic groups and foundations. And recently, the Bill and Melinda Gates Foundation committed



National reference laboratory in Ho Chi Minh City, Vietnam

to funding the Results for Development Institute for several years: one of the first assessments will analyse the potential of prizes to drive investment in needed new health technologies, including tuberculosis diagnostics.

Ultimately, says Dheda, national governments and tuberculosis programmes of high-burden countries will make the decision to use a POC test and will pay for the tests. Pai advocates that middle-income endemic countries, such as India, China, Brazil, and South Africa, “can and must invest more resources in tuberculosis control because tuberculosis is impacting them in a big way, and with strong or growing economies, they can afford to invest more”. Resulting technologies might also benefit low-income countries in a manner akin to that seen with HIV tests and generic antiretrovirals produced in India and Brazil.

The bottom line, says Pai, is that to tackle the global epidemic, “tuberculosis transmission must be interrupted and this will require diagnosing more and more cases and putting them on appropriate therapy”. Thus, Casenghi concludes, “Efforts to develop POC tests and to enhance capacity for treatment have to run in parallel, otherwise the effect of the introduction of an effective tuberculosis test would be diluted by lack of access to treatment.”

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