

The new face of tuberculosis diagnosis

For more on the Xpert MTB/RIF system see [Newsdesk](#) *Lancet Infect Dis* 2010; **10**: 742–43

For more on the tuberculosis diagnostics conference in India see <http://www.tb-evidence.org/rescentre/presentations/bangalore.htm>

For the 2011 WHO recommendation see http://whqlibdoc.who.int/publications/2011/9789241502054_eng.pdf

For the evidence behind WHO's policy recommendation see <http://blogs.plos.org/speakingofmedicine/2011/08/09/medical-public-health-and-economic-consequences-of-bad-diagnostics-for-tuberculosis/>

For Steingart and colleagues systematic review see *PLoS Med* 2011; **8**: e1001062

For David Dowdy's cost-effectiveness analysis see *PLoS Med* 2011; **8**: e1001074

Developments in technology, new evidence, and fresh policy thinking from WHO and other partners are finally bringing changes to tuberculosis diagnosis. Vital steps are stopping use of inadequate tests and determining niches for newer diagnostics.

Antibody-based serological rapid test kits and ELISA-based assays are widely available in low-income and middle-income countries, especially in India, where about 1.5 million are used annually. A survey of 22 high-burden countries found that these blood tests are used in 17, and results are used as a basis for treatment in at least 11.

On July 20, 2011, WHO recommended that commercial serodiagnostics not be used for diagnosis of active tuberculosis in adults and children, neither as initial tests nor as adjuncts to sputum smears. "There is no evidence that existing commercial serological assays improve patient outcomes, and high proportions of false-positive and false-negative results may have an adverse impact on the health of patients", the statement concludes. WHO stresses that this policy is not intended to stifle research into serological technologies, which might form the basis of much-needed point-of-care tests.

The evidence that formed the basis of WHO's first such negative policy recommendation was published in *PLoS Medicine* on Aug 9. In a systematic review, Karen Steingart (University of Washington, Seattle, USA) and

colleagues noted highly variable and inconsistent performance of available serological tests to diagnose pulmonary and extrapulmonary tuberculosis, although the overall quality of studies was very low.

In a cost-effectiveness analysis, David Dowdy (Johns Hopkins Bloomberg School of Public Health, Baltimore, USA) and colleagues noted that serology, if used as first-line in India, would identify an additional 14 000 cases, but with 121 000 more false-positive diagnoses, 102 000 fewer disability-adjusted life years averted, and 32 000 more secondary tuberculosis cases than with microscopy, at roughly four times the incremental cost to the Revised National Tuberculosis Control Programme (RNTCP). The authors also note that addition of liquid culture to microscopy, which is recommended by WHO, is more effective and less expensive than adjunctive serology.

"Both the scientific community and WHO have spoken—existing serological tests have no role in the diagnosis of active tuberculosis", Dowdy told *TLID*. "The challenge ahead of us is to ensure that the WHO policy is followed as broadly as possible. This will take multidisciplinary engagement of national tuberculosis control programmes, the scientific community, patients, and the private sector. It is no easy task, but our work shows that the negative economic implications of failing to act on this policy are tremendous."

Responses from governments of high-burden countries have been overwhelmingly positive, says Karin Weyer, coordinator of tuberculosis diagnostics and laboratory strengthening at WHO. In an unprecedented step, the Indian Ministry of Health and Family Welfare issued a formal notice stating that serological tests should not be used or paid for, and requested that all stakeholders advocate for a community movement to disseminate this message.

Notably, WHO has had no response from any manufacturers, which, says Weyer, "to me confirms the fact that they knew these tests were ineffective and inaccurate". Now, high-burden countries are being urged to tighten regulation for diagnostics and implement WHO-recommended technologies, including the Xpert MTB/RIF system, liquid culture, and molecular line-probe assays for drug-susceptibility testing.

"We are moving into a new era where there is no 'one size fits all' approach anymore", Weyer comments. "Now, we have a multitude of diagnostic tools and they all have a different place in the laboratory service in any particular country, from national reference laboratory level to peripheral clinics." A dynamic and flexible national approach to diagnosis will be further informed by new data: forthcoming systematic reviews from Steingart and colleagues, including a Cochrane review on Xpert MTB/RIF in resource-limited settings, and cost-effectiveness analyses from Dowdy's group are in the pipeline.

South Africa is taking the lead on changing the face of diagnosis with an ambitious national roll-out that aims to entirely replace sputum smears with peripheral laboratory Xpert MTB/RIF testing within 2 years. An urgent mandate from the minister of health to tackle HIV and tuberculosis co-infection and multidrug-resistant disease has already resulted in a successful pilot covering all provinces. In July, Wendy Stevens of the National Health Laboratory Service told the International AIDS Society conference, Rome, Italy, that Xpert MTB/RIF is generally performing well—in one district in KwaZulu-Natal province, Xpert MTB/RIF achieved 19% positivity compared with 8–9% for microscopy. Also, local epidemic modelling has led to realistic estimates of the increased costs involved for diagnosis and treatment.

In India, private-sector engagement is a particular issue, where some 45%



Leticia Ferreira/The Lilly MDR-TB Partnership

South Africa's minister of health has encouraged use of Xpert MTB/RIF

of patients are diagnosed and treated privately. One hope is that improvement of the RNTCP will allow it to out-compete ineffective private-sector tests. With an ambitious tuberculosis control goal of universal access in the next 5 years, the Ministry of Health and Family Welfare is planning improvement of sputum smear testing and scale-up of solid and liquid culture and line-probe assays. The precise role of Xpert MTB/RIF is unclear at present, but one option might be to pay the private sector for tests where infrastructure is already established, comments Madhukar Pai (McGill University, Montreal, Canada).

Another proposal is the development of effective generic competition and new diagnostics by emerging economies such as India. What is sorely needed is a simple, cheap, point-of-care diagnostic test and an indigenous, economic, molecular test for drug resistance, Kuldeep Singh Sachdeva, of the Indian government's Central Tuberculosis Division said

at a recent tuberculosis diagnostics conference in Bangalore, India. "The conference brought together for the first time representatives from industry, government, donors, academia, hospitals, civil society, and the media to discuss what it takes to innovate in tuberculosis diagnostics in India", explains Pai, conference co-chair. "This conference has sparked a lot of interest in developing affordable molecular tests", he explains. Efforts are now underway to create an Indian tuberculosis Diagnostics Task Force, to support, fund, and guide test developers, researchers, and industry, to liaise with governmental agencies such as RNTCP and Drug Controller General of India, and to validate and scale up any new promising technologies from India.

Steingart notes other proposals that include mentoring companies that are not working in tuberculosis and encouraging distributors of tests to participate in novel diagnostic

development. "Considerable research is underway on new biomarkers and approaches to the serological diagnosis of tuberculosis", she comments.

"There is a real need for an overhaul of research design and funding for diagnostics. With commercial serodiagnostics, most studies are not well designed and also are designed and heavily supported by industry, which may lead to conflicts of interest and introduce publication bias", Weyer concludes. Because novel tuberculosis diagnostics are often developed in high-income countries with low tuberculosis or HIV incidence and high resource availability, performance characteristics are very different when used in high-incidence settings. WHO is now urging potential manufacturers to engage with them early in the development process, to ensure that product specifications, end-user requirements, and study design are adequately addressed.

Kelly Morris

Infectious disease surveillance update

Dengue in Pakistan

More than 4000 cases of dengue fever have been reported in the Punjab region of east Pakistan over a 2 month period—a substantial increase over previous years. Regional capital, Lahore, is particularly badly affected, with authorities in the city ordering the closure of all state-run and private schools for 12 days in an attempt to control the spread of the virus, transmitted by *Aedes* spp mosquitoes. 438 patients are receiving treatment in hospitals across the region, and at least eight people have died.

Anthrax in Zambia

An outbreak of anthrax in Chama District in northeast Zambia is thought to have originated from infected hippopotamuses in Luangwa River. The number of suspected cases reached 278 by Sept 7, with five deaths attributed to the outbreak. Eastern Province

medical officer, Kennedy Malama, told a local radio station that the country's ministry of health had established that those affected had contracted the disease through consuming or coming into contact with hippopotamus meat and had warned against eating meat from game animals. *Bacillus anthracis* infection is thought to have killed more than 90 hippopotamuses in the district in recent weeks.

Botulism in France

On Sept 5, French health authorities reported eight cases of botulism, with five in the southern district of Vaucluse and three in the Somme district in the north of the country. All eight individuals had consumed either a green olive and almond tapenade or a spreadable tomato paste, produced in the Vaucluse by French food company La Ruche under the brand names "Les Délices de Marie-Claire", "Les Secrets

d'Anais", and "Terre de Mistral". All of the products have been tested and were contaminated with *Clostridium botulinum* neurotoxin. The items have been withdrawn from sale and the company's production facility halted.

Hand, foot, and mouth disease in Vietnam

A large outbreak of hand, foot, and mouth disease in Vietnam has killed 98 people so far this year, with three-quarters of the deaths in children age 3 years or under, according to WHO. By early September more than 42 000 cases of the disease, which can be caused by several viruses of the Picornaviridae family, had been reported across the country, with authorities acknowledging more than 2000 new cases in the first week of September alone.

Neil Bennet

For more on **dengue in Pakistan** see <http://tribune.com.pk/story/251095/epidemic-dengue-steadily-makes-its-way-across-pakistan/>

For more on **anthrax in Zambia** see <http://allafrica.com/stories/201109080846.html>

For more on **botulism in France** see http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1315371899455

For more **HFMD in Vietnam** see http://www.wpro.who.int/vietnam/media_centre/press_releases/hfmd_pr.htm