WHO recommends against inaccurate tuberculosis tests

Misleading serology tests for tuberculosis could be worsening the epidemic in some high-burden countries. WHO will be issuing policy advice against their use in early 2011. Kelly Morris reports.

Although no international guideline recommends their use, scores of commercial serology tests for tuberculosis are being sold in high-burden countries. Some are laboratory-based tests, whereas others are rapid dipstick tests, which could fill a vital niche for a point-of-care tuberculosis diagnostic test. "If they worked, the problem of a gap in the pipeline for a point-of-care assay would have been solved decades ago", comments Madhukar Pai, co-chair of the STOP-TB Partnership's new diagnostics working group. "The pity is that they don't work. In fact, they're inaccurate and useless."

WHO is due to release a negative policy recommendation—the first of its kind for the organisation—on current commercial tuberculosis serodiagnostics. Results of several meta-analyses have indicated poor performance of these tests, and in 2008, an assessment of 19 commercial assays by TDR—the UN special programme for research and training in tropical diseases—found that none of the assays were good enough to replace sputum microscopy or as an add-on test to rule out tuberculosis. Manufacturers continue to claim that their tests are effective and fill a diagnostic niche, especially in sputum smear-negative patient groups.

Karin Weyer, WHO coordinator of TB diagnostics and laboratory strengthening, told *The Lancet* that "the negative policy process is a new concept in WHO". But, she says, the process has been identical to that for positive recommendations, such as the endorsement announced on Dec 8 of a fully automated nucleic-acid amplification test (Xpert MTB/RIF, Cepheid) to improve tuberculosis diagnosis.

The available evidence on serodiagnostic kits has now been rigorously assessed, including meta-analyses when appropriate, and reviewed by an independent WHO expert group, says Weyer. "The expert group endorsed the findings from an updated systematic review since the TDR report in 2008 and essentially concluded that we should proceed with negative policy guidance based on the fact that the performance characteristics of these tests were way below what one would want and also because the quality of the data were so weak and so bad that it warranted a recommendation against the use of these tests", she explains.

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"Everyone is aware of the consequences of bad drugs and vaccines, but nobody really thinks about bad diagnostics and what impact they can have", comments Pai. In their report, released at the end of December, the WHO Strategic and Technical Advisory Group for TB acknowledges "the adverse impact of misdiagnosis and wasted resources on patients and health services when using these tests for the diagnosis of active TB", and recommends WHO to proceed with written guidance advising against current serodiagnostic kits. Further targeted research is strongly recommended since potential exists for research to develop accurate serologic assays, which could fill the point-of-care niche. WHO is being careful with preparation of the negative policy so as not to stifle innovation and research investment in tuberculosis diagnostics, says Weyer.

Commercial serodiagnostic kits are widely available, but the problem is probably greatest in India, where Pai estimates that serodiagnostic kits are used on at least 1·5 million people with suspected tuberculosis every year. Such testing is not done through the Revised National TB Control Programme (RNTCP) but through the unregulated private sector, which manages a substantial proportion of tuberculosis cases. Patients pay for serodiagnostic kits, and the market is estimated conservatively at over $US15 million in India alone, compared with $65 million for the entire RNTCP.

Despite country-wide DOTS coverage by the RNTCP, India continues to have more than 2 million new cases of tuberculosis every year. Ongoing transmission will not be reduced without intensified early case detection, which first relies on access to quality diagnosis. Writing in *The New Yorker* on Nov 15, journalist Michael Specter described how, in India, "for most patients, the choices are bleak"—overcrowded public hospitals versus unreliable tests at unregulated private laboratories or clinics.

Everyone in the private-sector chain gets a cut of patient fees—up to $10–30 per serodiagnostic kit—especially the referring doctors and private clinicians, who are often the same individual, Specter reports. Financial incentives perpetuate this system, Pai explains, since: "a private practitioner may not order sputum microscopy because you don't make much money out of a cheap test like sputum smears. The more expensive the test ordered, the more money you get back", he explains.

The available evidence indicates that current tests lack either the necessary sensitivity or specificity or both to be an effective diagnostic test, and for many of these tests, false results far

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India has more than 2 million new cases of tuberculosis every year

outnumber true results. Low sensitivity means increased false-negative results, which increase morbidity, mortality, and ongoing transmission of tuberculosis. Low specificity means more false-positive results; patients might then be given 6 months of potentially toxic treatment, while their underlying pathology remains uninvestigated and undiagnosed.

Many commercial tuberculosis serology kits are manufactured in China or India, but some are from western countries, such as France, the UK, Canada, and the USA. These manufacturers are selling high volumes of their test kits in countries such as India, although their tests are not licensed or used in the countries that make them.

During WHO's systematic review process, says Weyer, "we quickly discovered that manufacturers of these commercial serodiagnostics simply change the name of the test frequently and re-market and re-sell the same test under a new brand name. So, teasing out which test belonged to which brand name and updating the previous review by TDR proved to be a real challenge, as we wanted to be as solid as we could possibly be on the actual evidence."

The key question is how much will the WHO guidance affect the sale and use of these tests in the private sector? "The ideal is that the public sector would be attractive enough and use state-of-the-art new tests, so that patients don't feel that they need to go to the private sector to get what they think may be a better diagnosis", says Weyer.

However, given the extent of private-sector medicine, the concept of public–private mix (PPM) is being hailed in some quarters as the key to increasing efforts to tackle tuberculosis. The final report of WHO's subgroup on PPM for tuberculosis care and control advised earlier this year that countries need to scale up PPM, and involve provider groups outside national programmes to develop national strategic plans. Recommended approaches also include certification and accreditation of care providers and laboratories, and a system for mandatory notification of tuberculosis.

To achieve PPM recommendations, regulation of private-sector medicine will need to be developed and implemented in high-burden countries. What is absent from the PPM report is recognition that regulatory frameworks for diagnostic tests are also often weak or non-existent. WHO is helping countries establish regulatory systems to review the local relevance of diagnostics, and determine whether such tests should be marketed and sold, says Weyer. But, she foresees "a long-term difficult process", as local expertise and capacity are often limited and regulatory frameworks need to be drawn up and passed through national legal systems country by country.

"Public-private partnership is the way to go", asserts Camilla Rodrigues, a physician at the private Hinduja Hospital, in Mumbai, India, who has trialled the Xpert MTB/RIF system for diagnosis and drug-resistance testing of tuberculosis for more than 3 years. Rodrigues would like to see physician education on the unreliability of serology in endemic regions and laboratory accreditation encouraged. National governments need to provide guidelines for tuberculosis testing with "strict regulation in place for defaulters", she says, adding that laboratories need diagnostic algorithms and strengthened capacity both for gold-standard tests, such as culture, and validated new molecular tests.

Weyer agrees, but notes that: "PPM alone will not overcome barriers presented by the lack of country regulatory frameworks for new diagnostics". Nevertheless, market forces could play a part in developing and implementing better tuberculosis diagnostics. If Xpert MTB/RIF or other technologies are developed to become point-of-care tests, the private sector already has the infrastructure to deliver, and effective diagnostics could successfully replace inaccurate tests, says Pai.

The chief executive of a large private Indian diagnostic laboratory chain, Sanjeev Chaudhry, told *The Lancet* that Super Religare Laboratories strongly concurs in discouraging use of serodiagnostic kits in Indian settings. However, mere policy change might not be effective with the current magnitude of the challenge, he says, so, "instead of change in policy by private lab(s) in isolation or even as a consortium, we seriously feel that collective and dedicated efforts are required equally by the public- and private-sector service providers".

As pathology service providers are expected to offer and satisfy the needs of the market, Chaudry continues that "we need to have an alternative cost-effective option along with appropriate awareness among clinicians and doctors". Rodrigues notes that "the Indian diagnostic market is thriving. There is certainly potential for low-cost, accurate, and newer tests to be produced in India which will lower the cost."

WHO guidance will be very clear, Weyer confirms, "to reflect the current commercial serodiagnostic tests but not to jeopardise future research and new antigen and biomarker discovery programmes that would guide and inform the development of point-of-care tests".

Kelly Morris