A process of elimination

When it comes to diagnosing a killer disease, can we do better? Dr Madhukar Pai, of Montreal's McGill University, investigates the implications of TB misdiagnosis…

The internationally recommended tuberculosis (TB) control strategy Directly Observed Treatment – Short course (DOTS), has been a successful public health intervention. Yet TB remains a problem of enormous magnitude that does not receive the attention it deserves. The statistics are compelling – more than nine million new cases and 1.7 million TB deaths in 2009. Although many countries have met the Stop TB Partnership's targets of 70% case detection and 85% cure rate by 2005 (70/85 targets), TB incidence is still not falling or as quickly as expected.

India is a case in point. The country has successfully scaled-up the DOTS strategy to cover 100% of the population, and has already achieved the targets for case detection and cure. Yet, in 2009, India reported over two million TB cases, with 280,000 deaths. Why are these numbers still so high? For one thing, TB is a disease of poverty with several social determinants, requiring broad anti-poverty measures to address it. But another important reason is that TB patients are not diagnosed and cured quickly enough. When this is the case, TB patients may unknowingly spread their infection to their families and communities – further exacerbating the epidemic.

Fortunately, things are rapidly changing. The TB field has acknowledged that existing tools, especially diagnostics, are unlikely to achieve TB elimination and there is now a resurgence of interest and funding in developing new and more effective technologies. Thanks to donors, product development partnerships and researchers, tremendous progress has been made in expanding the TB diagnostics pipeline in particular. In addition, thanks to rapid, evidence-based policy development by the World Health Organization (WHO), several new TB diagnostics and approaches have been endorsed. The WHO is also promising that these policies are now being rapidly translated into programmes to deliver the diagnostics.

Molecular testing

In December 2010, the WHO announced its endorsement of Xpert MTB/RIF (Cepheid Inc, Sunnyvale, USA), a cartridge-based molecular test, which can accurately detect TB and resistance to Rifampin – a commonly used first line TB drug – in less than two hours.[1] This assay is a fully automated system that is simple to perform with minimal training, and that can be done outside a laboratory. For the first time, a molecular TB assay can be placed closer to the patients, opening the possibility of point-of-care diagnosis. The WHO now recommends that Xpert MTB/RIF should be used as the frontline test in individuals suspected of drug-resistant or HIV-associated TB. These recommendations have been backed by efforts to make the test affordable in low and middle income countries.[2]

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Serological tests for TB are widely used in India but are predominantly inaccurate, with no international guidelines supporting their use

Innovative tests such as Xpert MTB/RIF have the potential to save millions of lives. More broadly, improvements in TB diagnostics have the potential to drive a virtuous cycle: the promise of improved tests can drive their acceptance and scale-up, which will lead to better outcomes for patients and more credible health systems able to attract more funding for the development of even better technologies and delivery methods down the road.[3]

In addition to improved diagnostics, TB control programmes are also getting more ambitious in their goals, looking beyond the 70/85 targets. Once again, India provides a good example. It is currently on the verge of launching an ambitious phase of its TB control programme (RNTCP 3 – 2012-2017) that aims to provide universal access to quality diagnosis and treatment for the entire population. As a growing economic power, India is now uniquely placed to support this ambitious control plan and make a success story that can inspire other high TB burden countries and pave the way for a more ambitious global control agenda. India also has the economic and technological capacity to develop low-cost generic or novel diagnostics, and incorporate their scale-up to achieve impact at country level.

While these new diagnostics and ambitious goals are cause for optimism, there are also a number of other gaps in effective TB diagnosis and control that still need to be

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Xpert MTB/RIF is an automated test that can accurately diagnose TB and drug resistance in 2 hours

addressed. These include poor case detection rates and diagnostic delays, mismanagement of TB, lack of adequate regulation of TB diagnostics, lack of laboratory quality assurance, and inadequate funding for TB control.

Even in 2009, the global TB case detection rate was low – only about 63% of all TB cases were picked up. Diagnostic delays are also common, due in part to a reliance on old tools; by the time a patient is diagnosed to have TB, she has already visited multiple care providers, and infected several others. As illustrated in a recent New Yorker story by Michael Specter, mismanagement of TB is a major concern, especially in the private sector in developing countries.[4] There is growing recognition of the widespread use of inaccurate and inappropriate TB diagnostics in many countries.[5,6] Published evidence clearly shows that serological (antibody detection) tests for TB are inaccurate, inconsistent, and have no clinical role in TB diagnosis, with no international guidelines supporting their use. Despite this, an estimated 1.5 million TB serological tests are done in India alone every year at an expenditure conservatively estimated at US$15m per year.[7,8] This cost is substantial, compared to the entire Indian TB control programme budget of $65m.

Tightening regulation

Mismanagement of TB is not only bad for the individual patient; it is also disastrous from a public health perspective. Every mismanaged TB patient serves as a source for new infections in the community. Widespread abuse of inappropriate tests can prevent the use of good diagnostics, and this is a major challenge for implementation of new tools. Recognising this, the WHO recently announced its first negative policy in TB, against the use of TB serological assays.[9] The policy, however, will not preclude research in serological tests, because of the potential for a useful, simple, point-of-care test in future.

While WHO policies provide guidance at the global level, it is up to countries like India to implement them and tighten regulation to prevent abuse of suboptimal diagnostics. Unlike drugs, the regulation of *in vitro* diagnostics is weak in most low and middle income countries, and this allows for bad diagnostics to enter the market despite lack of evidence or policies to support their use. Once on the market, financial gains by various stakeholders (doctors, laboratories, diagnostic companies) keep such products profitable. In addition, there is little laboratory quality assurance in many high TB burden countries. In India, for example, an overwhelming majority of the laboratories have no formal quality certification or accreditation.

Bad diagnostics implemented in bad laboratories make for poor quality of care. Indeed, the New Yorker article and a recent World Report in the Lancet[10] paint a grim picture of the diagnostic and treatment ecosystem in the private sector of resource-limited countries with systemic market failures throughout value chain. These include dumping of useless diagnostics from rich countries into developing countries with weak regulation, private doctors receiving payments/incentives for tests ordered rather than improved patient outcomes, over-reliance on useless tests and under-use of good diagnostics, prescription of incorrect TB treatment regimens, and lack of patient monitoring to ensure adherence to TB treatment.

In conclusion, there are many positive trends in the diagnostic landscape for TB, but technology development will not by itself save lives. Xpert MTB/RIF is an excellent innovation backed by a strong policy, but it is likely to make a big impact only if high-burden countries like India, China, Brazil and South Africa adopt this test, use it to replace inaccurate tests, and address market failures to reduce mismanagement of TB, especially in the private sector. These countries can be global leaders by investing in the scale-up of new diagnostics in both public and private sectors and placing the technology at a level where early diagnosis can be accomplished with prompt initiation of TB treatment for drug-sensitive as well as drug-resistant TB.

If these large, high-burden countries succeed, then global TB elimination will become a realisable goal.

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1 WHO (2010) Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR-TB

2 Ibid

3 Small P M, Pai M (2010) Tuberculosis diagnosis – time for a game change. N Engl J Med, 363:1070-1

4 Specter M (15th November 2010) A Deadly Misdiagnosis. New Yorker 2010

5 Ibid

6 Morris K (2011) WHO recommends against inaccurate tuberculosis tests. Lancet, 377:113-4

7 Specter M (15th November 2010) A Deadly Misdiagnosis. New Yorker 2010

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9 Ibid

10 Ibid

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