EDITORIAL

Tuberculosis Diagnosis — Time for a Game Change

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The effective treatment of tuberculosis is a life-saving intervention. The global scale-up of tuberculosis therapy has averted 6 million deaths over the past 15 years, making it one of the greatest public health interventions of our lifetime.[1] Unfortunately, by the time most patients are treated, they have already infected many others.[2] This failure to interrupt transmission fuels the global epidemic so that every year there are more new cases of tuberculosis than in the previous year.[1]

National tuberculosis programs are particularly challenged by multidrug-resistant tuberculosis. Globally, fewer than 2% of the estimated cases of multidrug-resistant disease are reported to the World Health Organization (WHO) and managed according to international guidelines. The vast majority of the remaining cases are probably never properly diagnosed or treated, further propagating the epidemic of multidrug-resistant tuberculosis. The situation is further worsened by the epidemic of human immunodeficiency virus (HIV), especially in Africa.

For decades there has been little effort to improve techniques for diagnosing tuberculosis.[3,4] Consequently, tuberculosis tests are antiquated and inadequate. The most widely used test (smear microscopy) is 125 years old and routinely misses half of all cases. These inadequacies are particularly problematic since such tests are generally performed in underfunded and dysfunctional health care systems.[4,5] The problem is exacerbated by the widespread use of inaccurate and inappropriate diagnostic tools, such as serologic assays, in many countries.[6]

Fortunately, in the past few years, several improved tuberculosis tests have received WHO endorsement for widespread use.[6,7] In this issue of the *Journal*, Boehme and colleagues[8] describe a new automated nucleic acid–amplification test that may allow a relatively unskilled health care worker to diagnose tuberculosis and detect resistance to a key antibiotic within 90 minutes. This test and others that are likely to follow have the potential to revolutionize the diagnosis of tuberculosis. Thus, in the coming years, rapid diagnosis and targeted treatment will provide the greatest opportunity for stopping the tuberculosis epidemic.

In a large, well-conducted, multicountry study, Boehme et al. evaluated an automated tuberculosis assay (Xpert MTB/RIF) for the presence of *Mycobacterium tuberculosis* (MTB) and resistance to rifampin (RIF). With a single test, this assay identified 98% of patients with smear-positive and culture-positive tuberculosis (including more than 70% of patients with smear-negative and culture-positive disease) and correctly identified 98% of bacteria that were resistant to rifampin.[8]

The assay has several critical advantages over conventional nucleic acid–amplification tests, which have been licensed for nearly 20 years and yet have not had a substantial effect on tuberculosis control. The MTB/RIF assay is simple to perform with minimal training, is not prone to cross-contamination, requires minimal biosafety facilities, and has a high sensitivity in smear-negative tuberculosis (the last factor being particularly relevant in patients with HIV infection).[8]

However promising these findings, issues involving the MTB/RIF assay may limit its global utility. These issues include its high cost, limitations in testing only for rifampin resistance, a platform that detects a relatively small number of mutations, and inability to indicate which patients are “sputum smear–positive” for reporting purposes, infection-control intervention, and treatment monitoring.

On the plus side, the MTB/RIF assay promises to decentralize molecular diagnosis, since it potentially can be used at the point of treatment in a microscopy center or in a tuberculosis or HIV clinic. However, because Boehme et al. used the test at reference laboratories, their study offers only indirect proof of concept for use in such settings. Critical to a rapid scale-up of the test will be the results of additional studies to determine how it performs in such settings and whether its use improves outcomes for patients in a cost-effective manner.

If an improved rapid nucleic acid–amplification test is adopted globally, it could help avert more than 15 million tuberculosis-related deaths by 2050.[9] However, even the most promising diagnostic test will have only limited impact if it does not reach the patients who need it. As with any diagnostic test or intervention, its actual impact will depend on the system in which it is used. Health systems must be strengthened so that patients do not delay in seeking care and have prompt access to appropriate treatment once they receive a diagnosis. Health-system barriers to the use of improved technologies must be anticipated and addressed. Although the burden on health systems will be reduced by a simple dipsticklike, point-of-care assay, such tests are not likely to be available in the short term.[7]

To realize the potential of improved technologies, a diverse set of stakeholders need to support large-scale innovation and delivery. Scientists and industry need to develop radically improved tools, including drugs and vaccines, while offering reasonable pricing that reflects public health needs and economic realities in resource-limited countries. Operational and implementation researchers need to quickly identify and respond to the full spectrum of issues that form the critical path to improving the prevention and control of tuberculosis. Policymakers and regulators must turn scientific evidence into permissive policies and regulations that allow national programs to rapidly incorporate new tools. Funders must increase and reprogram resources to become conduits for innovation and not fund decades-old technologies for years into the future. Programs must maintain focus on the basics of tuberculosis control while quickly modifying delivery systems to take advantage of the benefits of improved tools. Lastly, patient advocates and activists should hold everyone accountable and ensure that communities drive demand for improved systems and tools.

Despite these challenges, it is clear that improvements in diagnostics are driving a virtuous cycle in care: the promise of improved tests drives their uptake, their uptake results in better health outcomes, improved outcomes attract more funding for health care systems, and better-funded systems are an incentive to the development of even better technologies. We are particularly optimistic about the potential role of governments, product developers, and companies in emerging economies with high tuberculosis burdens, such as China, India, Brazil, and South Africa. These countries now have the capacity to develop low-cost generic or novel assays adapted to local contexts and incorporate their scale-up in both national tuberculosis-control programs and private laboratories, supported by successful public–private partnerships. Emerging economies have the potential to become global leaders in innovative product development and delivery. If these countries successfully tackle their own tuberculosis problems, the elimination of tuberculosis by 2050 might become a reality.

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