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Improving the Diagnostic Ecosystem: A Critical Step in Controlling the TB Epidemic in India and Globally

An Interview with Madhukar Pai

By Erin Schneider
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Despite global efforts to eliminate tuberculosis (TB) through improved prevention, diagnosis, and treatment mechanisms, TB continues to pose a grave threat to health today. In no country is this more true than India, which has the highest burden of TB in the world. However, new breakthroughs in affordable diagnostics do hold promise for effective TB management. As a follow-up to the 2009 Pacific Health Summit on multidrug-resistant tuberculosis (MDR-TB), NBR spoke with Madhukar Pai about progress in the field of diagnostics since 2009 and the current state of MDR-TB in India and globally.

Madhukar Pai, MD, PhD, is an Associate Professor of Epidemiology at McGill University, Montreal. He also holds honorary professorship positions at the University of Cape Town and Stellenbosch University in South Africa and serves as a consultant for the Bill & Melinda Gates Foundation. Dr. Pai previously served as co-chair of the Stop TB Partnership's Working Group on New Diagnostics and on the Coordinating Board of the Stop TB Partnership. His research is mainly focused on improving the diagnosis of TB, with a special emphasis on India. He is a recipient of the Union Scientific Prize from the International Union Against TB and Lung Disease and the Canadian Rising Star in Global Health award from Grand Challenges Canada.

Q. At the 2009 Summit, there was much discussion about the need for rapid, point-of-care (POC) TB diagnostics, which had yet to be developed. Why is there such a need?

In sharp contrast to diseases such as HIV/AIDS and malaria, suboptimal and delayed diagnosis of TB continues to perpetuate the epidemic in many high-burden countries. The need for an instrument-free, laboratory-free, POC test for TB has been articulated by many groups, including patient advocates and civil society. Although the TB diagnostics pipeline is substantially better in 2012 than it was even 5–10 years ago, the absence of a simple, dipstick type of POC test continues to be a gaping hole in the pipeline.[1]

Q. Are there not already several rapid antibody tests for TB on the market? Why are these options not a solution to improving TB diagnosis in India and globally?

Yes, there are several rapid POC tests on the market, based on antibody detection. For decades, researchers and industry pinned their hopes on serological antibody-detection methods for POC test development. Indeed, dozens of serological rapid (lateral flow assays) and ELISA enzyme-linked immunosorbent assay (ELISA) tests got commercialized, even though no international guideline recommended their use. Today, these tests are on the market in at least 17 of the 22 highest TB burden countries, and millions of patients in the private sector undergo serological testing.[2] The situation is particularly bad in India, where we estimate over 1.5 million serological TB tests

1 For more background on POC diagnostics for TB, see N.P. Pai and M. Pai, "Point-of-Care Diagnostics for HIV and Tuberculosis: Landscape, Pipeline, and Unmet Needs," *Discovery Medicine* 13, no. 68 (2012), http://www.discoverymedicine.com/Nitika-Pant-Pai/2012/01/18/point-of-care-diagnostics-for-hiv-and-tuberculosis-landscape-pipeline-and-unmet-needs/.

2 J. Grenier et al., "Widespread Use of Serological Tests for Tuberculosis: Data from 22 High-Burden Countries," *European Respiratory Journal* 39, no. 2 (2012): 502–5.

performed in the private sector. Unfortunately, TB serological tests are neither accurate nor cost-effective,[3] prompting the World Health Organization (WHO) to issue an historic, strong negative recommendation against their use in 2011.[4]

Q. Since 2009, what advances have been made in POC diagnostics for TB and MDR-TB?

The biggest advance is the development and WHO endorsement of Xpert® MTB/RIF (developed by U.S.-based Cepheid Inc.), an automated, cartridge-based nucleic acid amplification test (NAAT) that can detect TB, as well as drug-resistance, within 90 minutes. This technology has greatly stimulated resurgent interest in using molecular tests for rapid diagnosis of active TB and drug resistance and has inspired new players to enter the field of TB diagnostics. While the Xpert MTB/RIF assay is accurate and can potentially be used outside of a laboratory setting by a minimally trained health worker, it falls short of meeting the ideal POC requirements on two important grounds: first, at current prices, it is expensive and unaffordable in many settings; and second, it requires sophisticated equipment that cannot be deployed at the community level.

Q. Is rapid, POC diagnostic technology affordable and accessible in developing countries such as India? Has this technology been readily and appropriately adopted by clinicians?

Rapid molecular tests such as Xpert MTB/RIF are yet to be scaled up in India. Cost is a big barrier for the public sector, although a field demonstration project on Xpert has been launched by the Revised National TB Control Programme (RNTCP) in India. The RNTCP is currently underfunded and will need substantially higher resources to scale up new technologies.

The private sector is often an early adopter of new technologies in India. However, the pricing of Xpert MTB/RIF assay in the private sector in India and other developing countries is substantially higher than the pricing for the public sector, imposing additional barriers for scale-up. Unless something is done to make the technology more affordable and financially viable via creative public-private partnerships or business models, I cannot see it succeeding in the Indian context. We must keep in mind that TB disproportionately affects poor people in India, and even the poorest of patients seek care in the private sector, which manages over half of all TB cases in India. Poor patients in the private sector deserve better TB diagnosis and treatment. Their care simply cannot be left to market forces.

Q. The apparent popularity of the inaccurate antibody tests raises some interesting questions. What are the market dynamics that allow unreliable tests to succeed in the market, while effective technologies sometimes struggle to get scaled up?

My research collaborators and I have done a root cause analysis on why TB serological tests are so popular in the Indian private sector.[5] In terms of technical and medical causes, the RNTCP's currently low budget does not allow for the scale-up of the newer, WHO-endorsed technologies. Thus, under the RNTCP, most patients have access to only smear microscopy—a test that is insensitive and underused in the private sector because there is no accurate, validated, point-of-care test for TB, serological tests meet a *perceived* need among doctors and patients.

Looking at economic causes, imported molecular or liquid culture tests are too expensive, leaving serological tests as the main alternative. Although serological tests are inaccurate, various players along the value chain profit from their use, and this sustains a market for these tests. Finally, if you look at the role of regulation, TB tests are poorly regulated in India, and this allows a large number of serological kits are on the market. Private healthcare in general is also poorly regulated; doctors in the private sector are outside the scope of the RNTCP and do not necessarily follow standard guidelines.

So, a big challenge for India is to wean doctors and laboratories away from inaccurate TB tests and replace them with validated, WHO-endorsed products. This will require market-based business models that will actually work within the private sector in India. The lessons learned from the serology story can be applied to other validated technologies that need to be scaled up. Increased funding for TB control, the

3 David W. Dowdy et al., "Serological Testing Versus Other Strategies for Diagnosis of Active Tuberculosis in India: A Cost-Effectiveness Analysis," *Public Library of Science Medicine* 8, no. 8 (2011); and K.R. Steingart et al., "Commercial Serological Tests for the Diagnosis of Active Pulmonary and Extrapulmonary Tuberculosis: An Updated Systematic Review and Meta-Analysis," Public Library of Science Medicine 8, no. 8 (2011), available at http://tbevidence.org/2011/11/reviews-on-serological-tests-for-tb/.

4 Rebecca Kennedy and Karuna Luthra, "Diagnosing Inaccuracy: New WHO Policy Shift to End Ineffective TB Practices—An Interview with Dr. Mario Raviglione," The National Bureau of Asian Research, July 26, 2011, http://www.nbr.org/research/activity.aspx?id=161.

5 S. Jaroslawski and M. Pai, "Why Are Inaccurate Tuberculosis Serological Tests Widely Used in the Indian Private Healthcare Sector? A Root-Cause Analysis," *Journal of Epidemiology and Global Health*, January 31, 2012, http://www.tbevidence.org/documents/sysrev/serotology/Jaroslawski_Pai_JEGH_2012.pdf.

scale-up of new diagnostics via the RNTCP, stronger regulation of the private healthcare sector (including more stringent regulation of all in-vitro diagnostics), rapid development of R&D within India to bring new diagnostic options to the market, and greater engagement of the private health sector with the RNTCP are critical ingredients for success.

There are some recent promising developments. The Indian government has acted on the WHO policy against serological tests and is on the verge of banning the manufacture and distribution of these tests in India.[6] This is quite remarkable and provides a precedent for other countries to eliminate bad TB diagnostics. Of course, there is still the problem of whether such a ban will be enforced in India, where enforcement of regulation is still quite weak.

Q. Can India innovate in this space and develop new TB diagnostic technologies to replace the suboptimal tests on the market?

Research from India has played a critical role in the development of the global strategy to stop TB. Yet Indian industry and academics have not developed any new tools (diagnostics, drugs, or vaccines) for TB. What does it take to innovate in TB diagnostics in India and to move from importation and imitation to innovation?

India has already made a big contribution in the area of generic drugs and vaccines, and successes in areas such as information technology and mobile telephony have greatly inspired a burgeoning biotechnology industry. With a strong, growing economy, and a large talent pool, there is great potential for India to contribute to what is called the "more (value) for less (cost) for more (people) innovation,"[7] especially in the area of healthcare technologies and delivery innovations.

There are several barriers for innovation in India.[8] For example, we don't have an accurate handle on the size of the TB diagnostics market in the country, and this is often a key requirement for industry investments. The TB community has not put out clearly defined target product profiles that test developers and funders can aim for.

Other concerns raised by industry include: the lack of access to Indian sample repositories for test development and validation; limited funding and R&D facilities for TB; poor regulatory mechanisms to evaluate new tests and assure quality; an unclear prequalification process for TB tests by the WHO; lack of venture capital funding for R&D; lack of celebrity/philanthropic support from within India; lack of awareness about funding opportunities; and weak or nonexistent collaboration between the RNTCP and industry, industry and clinicians, and industry and academia. Companies, especially those not working in TB, want mentorship or technical advice on TB, and it is not clear who they can approach for issues specific to TB. When and how should companies engage with agencies such as WHO (globally) and the RNTCP (within India) for advice, a possible endorsement, or evaluation?

As more TB products are developed, it is not clear which Indian agency or organization can conduct head-to-head validation studies to identify the best products for scale-up. More importantly, which agency or organization should take on an "honest broker" role to bring together key stakeholders that make up the complete value chain for TB innovations in India? Increased industry involvement and investment in TB R&D is an important goal.

Q. Despite efforts by governments and international organizations to control MDR-TB, the disease continues to pose a grave health threat to millions of people around the world. What is the landscape of MDR-TB prevention, diagnosis, and treatment in India? Recently, a hospital in Mumbai reported patients with total drug resistant strains of TB ("TDR-TB"). Is there actually a strain of TB that is completely drug resistant, and if so, what are the implications for global health?

In 2008, the WHO estimated that there were over 99,000 MDR-TB cases in India, which was second only to China. The landscape has not changed much since then, although the RNTCP has made an effort to increase the number of laboratories that can perform culture and drug-susceptibility testing, and has also introduced molecular line probe assays for rapid diagnosis of MDR-TB. Despite this effort, the majority of MDR-TB patients in India do not get adequate diagnosis and treatment for the disease.

There is no accepted definition of TDR-TB, and drug susceptibility testing for second-line drugs[9] remains an

6 "Soon, Ban on Blood Tests to Detect TB," *Times of India*, January 24, 2011, http://articles.timesofindia.indiatimes.com/2012-01-24/india/30658708_1_tb-detection-tb-diagnosis-tb-cases.

7 R.A. Mashelkar, "Breakthrough Designs for Ultra-Low-Cost Products," TED India 2009, http://www.ted.com/talks/r_a_mashelkar_breakthrough_designs_for_ultra_low_cost_products.html.

8 N. Engel, J. Kenneth, and M. Pai, "TB Diagnostics in India: From Importation and Imitation to Innovation," *Expert Review of Molecular Diagnostics* 12, no. 1 (2012): 21–24, http://www.expert-reviews.com/doi/abs/10.1586/erm.11.80.

9 Second-line drugs are drugs that are used when the first choice drug fails or is not available.

imprecise process. So, it is not quite clear whether the drug-resistant TB reported in Mumbai is totally drug resistant or extensively drug resistant (XDR). It is, however, worrisome and worthy of thought and consideration.

I think a key message is that mismanagement of TB cases is common in India (especially in the private sector), and irrational TB prescriptions, free access to over-the-counter TB drugs, poor adherence of patients to treatments, non-adherence of doctors to international guidelines, and lack of laboratory capacity to diagnose drug resistance are some of the key reasons why MDR-TB has been emerging. Addressing these underlying factors will require multipronged strategies and the engagement of many stakeholders. A big challenge for India is the large, dominant, and mostly unregulated private sector, which is part of the problem and yet also part of the solution. We have yet to come up with innovative business models to engage the Indian private sector on a large scale.

Q. Looking to the future, what are the key issues that must be addressed in order to improve the diagnosis of TB in India?

To improve the landscape of TB diagnosis in India, several efforts are needed in parallel.[10] India must adopt new tools that are accurate, validated, and WHO-endorsed, and replace suboptimal tests with good tests that can impact patient outcomes and reduce TB transmission in the community. Innovative tools and innovative delivery systems that engage both public and private sectors are essential for reaching this goal. The Indian regulatory agency must tighten the regulation of diagnostics in the country and ensure that suboptimal tests are reviewed and removed from clinical use. New TB tests must be subjected to independent validation before approvals are granted. There are positive signs that this may soon become a reality.

In addition to improving diagnosis, we need to get ambitious, and think beyond the Stop TB targets of a 70% case detection rate and an 85% cure rate. India has taken the lead in this area, with its impending launch of the National Strategic Plan (NSP), an ambitious plan for 2012–2017 that aims to provide *universal access* to quality diagnosis and treatment for the entire Indian population.

It is clear that the RNTCP alone cannot meet this goal of universal access. Everyone will need to pitch in, starting with the Indian government, which must fund this groundbreaking TB control plan. The Indian Planning Commission has pledged to increase total health expenditure by the end of the 12th Five-Year Plan (2012–2017) to 2.5% of the GDP, as compared to the current estimate of about 1%. Hopefully, TB control in India will benefit from this increased health spending.

India today is in the middle of a phenomenal growth spurt, and visible progress has been made in many fields. But if India is shining, TB control must not be left behind.[11] While the government must invest more resources in TB control, it alone should not be expected provide all the answers or resources. Indian industry, scientists, celebrities, philanthropists, and high net-worth individuals can and should make a bigger contribution to control a disease that is such a big drain on India's economy. Indian celebrities have championed causes such as HIV/AIDS, polio, and cancer prevention. It would be wonderful if they could step up and do the same for TB. Last, Indian media, civil society, and patient advocates need to synergize their efforts to create demand for better TB care.

The views expressed in this interview are those of Madhukar Pai, and they do not necessarily represent the views of any institution with which he is affiliated.

10 M. Pai, "Tuberculosis Control in India: Time to Get Dangerously Ambitious?" *The National Medical Journal of India* 24, no. 2 (2011): 65–68.

11 India shining: tuberculosis control must not be left in the dark", *Lancet Infectious Diseases* (forthcoming, 2012).