

Controlling the TB Epidemic in India and Globally: Innovations in New Tools and Delivery Approaches

An Interview with Madhukar Pai

By Sandra Ward
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In 2009, when NBR's Pacific Health Summit focused on tuberculosis (TB), the recent emergence of multidrug-resistant and extensively drug-resistant (MDR- and XDR-TB) forms had raised new challenges for global efforts to eliminate this devastating infectious disease. Since the discovery of anti-TB treatments, decades had passed without new drugs or vaccines on the market. In an interview with NBR published in early 2012, Madhukar Pai (McGill University) spoke about progress in the field of diagnostics since 2009. Now, just one year later, Dr. Pai has promising recent developments to report in the global efforts to eliminate TB. He shares updates on significant breakthroughs in the field of diagnostics, a new FDA-approved TB drug, and renewed government efforts to work with the private sector on controlling TB in India, which struggles with the highest burden of TB in the world.

Q. In 2013, how big a problem is tuberculosis, and what are the prospects for TB elimination?

March 24 is World TB Day and provides a good opportunity to take stock of progress in global TB control. Unfortunately, TB continues to be a major public health threat, causing an estimated 8.7 million new cases each year and an estimated 1.4 million deaths.¹ Early case detection and rapid treatment continue to remain the cornerstone of TB-control strategy. With the incidence of TB declining much more slowly than expected, it is now clear that TB cannot be eliminated by 2050 (i.e., the reduction of annual incidence to less than one case per million population).



Madhukar Pai, M.D., is an Associate Professor of Epidemiology at McGill University in Montreal and a Researcher at the McGill International TB Centre. He also serves as a consultant for the Bill & Melinda Gates Foundation. Dr. Pai has previously served as co-chair of the Stop TB Partnership's Working Group on

New Diagnostics. His research is focused on improving the diagnosis of tuberculosis, with a special emphasis on India, and is supported by grant funding from the Bill & Melinda Gates Foundation, Grand Challenges Canada, and the Canadian Institutes of Health Research. He is a recipient of the Union Scientific Prize from the International Union Against TB and Lung Disease, the Canadian Rising Star in Global Health Award from Grand Challenges Canada, and the Chanchlani Global Health Research Award. Dr. Pai holds a PhD in epidemiology from the University of California–Berkeley and an MD in community medicine from the Christian Medical College in Vellore, India.

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

In February 2013, a high-level meeting was held in Geneva to decide on the post-2015 TB targets.² The meeting participants uniformly shared the aspirational goal of zero TB deaths, zero TB disease, and zero suffering. There was broad agreement on a set of interim targets for 2025 designed to accelerate progress towards this goal. The first is to reduce TB deaths by 75% from 2015 to 2025, which would mean a decrease from a projected 1.2 million TB deaths in 2015 to 300,000 in 2025.

¹ *Global Tuberculosis Report 2012* (Geneva: World Health Organization, 2012), http://www.who.int/tb/publications/global_report/en/index.html.

² "Landmark Meeting on Post-2015 TB Targets Held in Geneva," World Health Organization, February 14, 2013, http://www.who.int/tb/features_archive/post_2015_targets_meeting/en/index.html.

The second interim target is to reduce the TB incidence rate (the number of people who develop TB each year, per 100,000 people) by 40% from 2015 to 2025.

Q. TB control has always been hampered by antiquated technologies and insufficient investments in product development. Is this changing? What do you see as some of the most exciting developments in the diagnosis of TB?

Yes, antiquated tools have historically posed a big challenge for TB control. Achievement of the post-2015 TB targets will require substantially better tools than what we have today. Finally, there is some light at the end of the tunnel. New, accurate diagnostics for TB are finally here and steadily being scaled up. For the first time, a rapid, cartridge-based, automated molecular test—the Xpert MTB/RIF test—is being scaled up for diagnosis of mycobacterium tuberculosis (MTB) and detection of drug-resistance to rifampicin (RIF) in more than 20 countries. The Xpert MTB/RIF technology was developed with the support of the Foundation for Innovative New Diagnostics (FIND) and endorsed by the World Health Organization (WHO) in 2010. There is good evidence supporting its high accuracy. Since then, over 1,900,000 Xpert MTB/RIF cartridges have been procured worldwide in the public sector in 77 of the 145 countries eligible for concessional pricing of \$9.98 per cartridge.³

Inspired by these developments, fast-follower, next-generation molecular TB tests have already emerged on the market, and many companies are now investing in developing TB technologies. In many ways, the Xpert MTB/RIF technology has become the pathfinder for wider use of rapid, accurate molecular tests for TB, as well as for showing that it is possible for healthcare programs to go beyond the century-old, insensitive smear microscopy test. These next-generation molecular tests will help further scale up molecular testing in resource-limited settings and hopefully replace sputum microscopy as the front-line diagnostic tool.

Q. What about new TB drugs and vaccines? Is there positive news on that front?

The lack of new drugs and vaccines has been a huge problem for TB control. In 2013, we are still using TB drug regimens that date back to the 1960s and the BCG vaccine that was developed in the 1920s.

At long last, we are seeing progress with new drugs.

On December 28, 2012, the U.S. Food and Drug Administration approved a drug called Bedaquiline as part of combination therapy to treat adults with multidrug-resistant TB (MDR-TB) when other alternatives are not available. This is the first new TB drug approved in over 40 years. Other new TB drugs or combinations are expected within the next 2–3 years, including a moxifloxacin-containing regimen and a novel drug combination treatment (called PaMZ) containing PA-824, moxifloxacin, and pyrazinamide. Shortening TB treatment to 2 or even 4 months should greatly increase cure rates, improve patient adherence, and reduce the likelihood of drug resistance. TB Alliance, a nonprofit, product-development partnership, has spearheaded much of this progress.

In contrast to diagnostics and drugs, progress has been slow with new TB vaccine development, although major investments have been made in this area, especially by the Bill & Melinda Gates Foundation and Aeras (a product development partnership). A new efficacious vaccine can potentially change the trajectory of the epidemic by preventing infection or disease.

Among the various candidate vaccines being evaluated, results from the trial of the MVA85A vaccine were published in February 2013.⁴ The trial showed that the candidate vaccine was safe and well tolerated but did not confer efficacy in the prevention of TB disease when administered as a boost to BCG in young children. Although disappointing, this first TB vaccine efficacy study in nearly a century has provided valuable scientific insights that will be helpful in evaluating other candidates in the pipeline.

Q. You are actively engaged in TB-control efforts in India, which has the highest TB burden in the world. What progress has been made?

Yes, sadly, India continues to have the world's highest burden of TB. TB kills 1 person every two minutes in India and 750 people every day. Global TB control is unattainable without enhanced control of the disease in India. India has been in the news lately because of the international attention around the emergence of totally drug-resistant TB in Mumbai and the growing concern that routine TB control—i.e. the directly observed treatment, short-course (DOTS) strategy—may be insufficient for reducing TB incidence in the country.⁵ By the time TB cases are identified and treatment is initiated, disease transmission has already occurred.

India's Revised National TB Control Programme (RNTCP) has made great progress in the last decade, and free, quality-

³ "WHO Monitoring of Xpert MTB/RIF Roll-out," World Health Organization, <http://www.who.int/tb/laboratory/mtbrifrollout/en/index.html>.

⁴ Michele D. Tameris et al, "Safety and Efficacy of MVA85A, a New Tuberculosis Vaccine, in Infants Previously Vaccinated with BCG: A Randomised, Placebo-controlled Phase 2b Trial," *Lancet* (2013), [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(13\)60177-4/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)60177-4/abstract).

⁵ "Global TB Fight Hits a Wall," *Wall Street Journal*, February 16, 2013.

assured TB diagnosis and treatment is available to all patients who seek care in the public sector. Over the past year, the country's laudable political and administrative commitment has been demonstrated by major increases in the RNTCP budget; a ban of inaccurate, antibody-based serological tests for TB; a national order for mandatory notification of all TB cases; and initiation of a national web-based case notification and tracking system.

The Indian government just approved the National Strategic Plan for 2012–17, which sets an ambitious goal of universal access to quality TB diagnosis and treatment for all patients in India. This goal of universal access will mean increasing the capacity to manage and treat all forms of TB, including drug-resistant TB, as well as substantially greater engagement of the private sector in India, which manages nearly half of all TB cases.

India is currently considering a simple national standard mechanism for guaranteeing universal access to quality-assured free anti-TB drugs to all TB patients in the country, including those being treated in the private sector. Furthermore, the RNTCP has also shown enthusiasm for scaling up newer, WHO-endorsed molecular tests to enhance capacity for rapidly detecting drug-resistance.

Q. This seems like great progress in a short time. Does this mean that the Indian government is willing to invest more domestic resources into TB control?

Yes, there are many signs that the Indian government is willing to make greater investments in TB control, with less reliance on external funding. TB control in India is part of the National Rural Health Mission (NRHM), which has a \$12 billion annual budget. The NRHM leadership has sent a strong message that the TB-control program (i.e., RNTCP) will be bold and innovative in its approach, funding will not be a constraint, and TB control will be fully funded with domestic sources.

On the one hand, this is truly exciting and a sign that India's economic growth in the past decade may be translated into tangible benefits via enhanced TB control. On the other hand, I worry that the current economic slowdown is already causing the government to scale back the planned increase in health expenditure per capita. The Indian Union Budget for 2012-13 allocated 373.3 billion rupees for health and family welfare, an 8% increase over the previous year's budget. This marginal increase, after adjusting for inflation, amounts to a decline in real rupee terms.

Q. What about other emerging economies? Are they starting to take the lead on TB control?

Indeed, there is evidence that the BRICS (Brazil, Russia, India, China, and South Africa) countries are contributing

significant new resources to global health and development and seem to be keen on tackling TB with greater domestic funding and innovative approaches. For example, China has made great progress in TB control, and South Africa is showing leadership as an early adopter of new diagnostic technologies.

In January 2013, health ministers from all the BRICS countries resolved to collaborate on developing capacity and infrastructure to reduce the prevalence and incidence of TB through innovation in new drugs and vaccines, diagnostics and the promotion of consortia of TB researchers to collaborate on clinical trials of drugs and vaccines, strengthening of access to affordable medicines, and delivery of quality care.⁶ This is a laudable proposal and I hope India will make a solid contribution. Right now, India's expenditure on the health sector continues to be the lowest amongst the BRICS countries and this situation must improve.

Q. You began by describing the progress made with new TB diagnostics and drugs. What promise do these new developments hold for addressing India's TB challenges? Will these new technological innovations be sufficient to turn the tide?

TB control in India is at a critical juncture. The routine, basic DOTS program has been scaled up and may have reached its limits because TB incidence is not declining. Therefore, innovative solutions are needed to go beyond current gains and address the challenges of drug-resistant TB by leveraging the potential of the private sector to help achieve the new goal of universal access.

We know that TB case-finding has stalled and many cases remain either undiagnosed or ineffectively treated. Delays in diagnosis or ineffective treatment lead to ongoing transmission, facilitating the spread of the disease. Patients often seek care in the informal and private sectors, and they remain outside the reach of the RNTCP.

Patients in the private sector pay a lot for tests that are inaccurate and for treatment that is unsupervised, unsupported, and frequently falls far short of expected standards. Poor treatment practices drive the development of drug resistance, which endangers patients as well as the healthcare system. Without effective engagement of the private health sector, the new vision of TB control is unlikely to be achieved.

It is thus clear that India will need to invest in new diagnostics and drugs and scale them up to achieve impact. But technologies alone cannot solve the problem. Innovative delivery approaches and business models are needed, especially to engage the dominant Indian private sector. India is experimenting with several new approaches. For example, the Initiative for Promoting Affordable and Quality TB Tests

⁶ "Delhi Communique," Government of India, Press Information Bureau, January 12, 2013, <http://pib.nic.in/newsite/erelease.aspx?relid=91533>.

(I-PAQT; www.ipaqt.org), which was launched in March 2013, is a consortium of more than twenty large, accredited private labs in India that will offer WHO-endorsed tests such as Xpert MTB/RIF at affordable prices, replacing inaccurate tests that are popular in the private sector. Such initiatives are also needed to improve the quality of private-sector TB treatment.

Q. Are you hopeful that this new, ambitious strategy that has been articulated will succeed in India??

The National Strategic Plan, if fully implemented, can have a big impact. Last year, a high-level joint monitoring mission reviewed the Indian TB-control program, and I was part of this mission. The mission endorsed the National Strategic Plan with its vision of universal access. The mission also recommended complete financing and encouraged annual implementation planning of proposed activities. Yet for early detection and appropriate treatment of all TB patients, irrespective of care in public or private sectors, RNTCP will have to strengthen supervision and management systems, extend case-finding to the community level, engage the private sector, and support innovation at all levels.

I am hopeful that India can turn the tide on TB, especially if the government and private sector work together. Many of the key elements for a transformational TB-control strategy for India are already there. It is time to connect the “dots” and make it happen. ~



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1414 NE 42ND STREET, SUITE 300
SEATTLE, WA 98105 • 206-632-7370

1301 PENNSYLVANIA AVENUE NW, SUITE 300
WASHINGTON, D.C. 20004 • 202-347-9767

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