

Review Article

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Why India should become a global leader in high-quality, affordable TB diagnostics

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The scale up of DOTS in India is one of the greatest public health accomplishments, and yet undiagnosed and poorly managed TB continues to fuel the epidemic such that India continues to have the highest number of TB cases in the world. Recognizing these challenges, the Government of India has set an ambitious goal of providing universal access to quality diagnosis and treatment for all TB patients in the country. Innovative tools and delivery systems in both the public and private sectors are essential for reaching this goal. Fortunately, India has the potential to solve its TB problem with “home-grown” solutions. Just as Indian pharmaceutical companies revolutionized access to high-quality, affordable AIDS drugs through generic production, Indian diagnostic companies could also become the world’s hub for high-quality generic diagnostics. In the long term, India has the potential to lead the world in developing innovative TB diagnostics. For this to happen, Indian industry must move from the import and imitation approach to genuine innovation in both product development as well as delivery. This must be supported by permissive policies and enhanced funding by the Indian government and the private sector. Strict regulation of diagnostics, increased attention to quality assurance in laboratories, and greater engagement of the private health care providers are also needed to effectively deliver innovative products and approaches.

Key words Diagnostics - generics - India - innovation - tuberculosis

Introduction

India has made significant contributions to global tuberculosis (TB) control. India’s public health leadership has conducted innovative projects and translated the best of those into policy through the Revised National Tuberculosis Control Programme (RNTCP) – which became a model for national TB programmes around the world¹. India’s long tradition in public health management has translated these policies into practice so that by 2006, the RNTCP expanded TB services to over 1.1 billion people, met

the WHO objectives for case detection and treatment success, and has India on the path to fulfilling the TB-related Millennium Development Goals². It is no exaggeration to say that India’s scale up of DOTS is one of the greatest public health accomplishments of our generation.

However, this success may also be setting India up for future failure. In the context of such accomplishments it is easy to become complacent – just when it is time to redouble efforts. The facts speak most eloquently to this need for redoubling TB control

efforts. In India, last year there were two million new TB cases, the highest number of cases in any country in the world³; 280,000 deaths from TB, causing the country a staggering US\$23.7 billion² in economic losses; and approximately 100,000 new cases of multi-drug resistant (MDR) and extensively drug-resistant (XDR) TB, only a small fraction of whom is appropriately diagnosed and adequately treated³. All these numbers add up to only one conclusion – simply doing more of what has been done to date will not get India to where it needs to be.

Fortunately, we are at an exciting juncture in TB control with new diagnostic tests endorsed by the WHO, faster acting drug regimens in Phase III trials and four potentially game changing vaccines in Phase II trials. Most importantly, there is global awareness of the need for innovation in the systems that provide TB care⁴. Now is the time for India to again step to the lead in addressing the root causes of its TB epidemic. Simply stated, uninterrupted transmission of TB from undiagnosed and mistreated TB is driving the TB epidemic in India. While India is detecting 70 per cent of TB cases and ensuring that 85 per cent of them are cured - the goals established by the Stop TB Partnership's TB strategy to reduce global cases by one-half between 1999 and 2010 - this is insufficient to interrupt transmission⁵. Delays in diagnosis are all too common and by the time a patient is diagnosed with TB, he or she has already visited multiple doctors, and infected several others⁶.

Several of these delays in diagnosis result from the pathologic relationship between the public and private sector. The private sector plays a dominant role in curative healthcare in India, and yet it is very hard for the government to regulate its quality and availability for the poor. But despite the obvious problems with an unregulated private sector, it is clear that private providers will remain the first point of care for the vast majority of TB cases.

Another major cause of delays in diagnosis is complacency with antiquated and inadequate technology.⁷ In India, the system has become accustomed to inadequate or bad tools. As recently illustrated by Michael Specter in the *New Yorker*, inaccurate TB tests comprise a large market in India⁸. These are primarily serological (antibody) blood tests. We know these tests are inaccurate and inconsistent, yet despite the evidence and strong negative policies from WHO and RNTCP, 1.5 million TB serological tests are done in India every year at a cost of over US\$15 million/₹750

million per year⁹. In poor States like Bihar, people who are struggling to live on less than US\$2/₹100 per day are paying US\$20/₹1000 out of pocket for these tests, which have no clinical utility. Even more shocking is that many of the serological assays used in India are actually made by companies in countries like France and UK, where these tests are not approved for use¹⁰.

There are several reasons why despite - and perhaps because of these challenges - India is poised to become a global leader in high-quality, affordable TB diagnostics¹¹.

India is becoming more ambitious and is setting higher targets

Now that 100 per cent DOTS coverage has been achieved and that the 70 per cent detection/85 per cent cure targets have been met, the Government of India has set an ambitious goal of providing universal access to quality diagnosis and treatment for all TB patients in the country². This is National Strategic Plan (NSP) (2012 - 2017) of the RNTCP. It will be a challenging process, and RNTCP NSP must be carefully planned, fully funded, and effectively managed to ensure its rapid and equitable implementation.

Additionally, throughout this process, increased and careful attention must be paid to measures that will interrupt transmission. In fact, serious consideration must be given to going beyond universal access to care and focusing on the universal interruption of TB transmission. It is not an attractive goal, and it is not even clear how to achieve or measure it, but a focus on interrupting transmission is key to breaking the back of India's TB epidemic⁵. India can lead the world in experimenting with innovative technologies and delivery systems to achieve universal interruption of TB transmission through prompt, accurate diagnosis and appropriate treatment.

India is investing more in TB control

In the economic realities of a developing country, providing US\$14/₹700 worth of first-line drugs to 70 per cent of TB cases is a relatively ambitious and expensive proposition. But India, by digging deeply into its pocket and through aid from international donors, has succeeded in doing this¹². The country currently spends roughly US\$100 million/₹5000 million on TB control each year and in doing so, saves many lives¹². A recent modelling study shows that the scale up of DOTS in India has been cost-effective, with exceptional return on the investment from a societal perspective¹².

In the context of the emerging economic power that India has become, this level of spending is simply inadequate. We know that expanding MDR care and control will cost another US\$100 million/₹5000 million per year. It is likely that achieving universal access to modern diagnostics and private sector engagement will cost yet another US\$100 million/₹5000 million. But not all of these costs need be shouldered by the RNTCP NSP budget. Much of these costs are simply part of the planned improvements in health care systems such as the National Rural Health Mission (NRHM), and there need be contributions from others, including industry, philanthropic foundations, charities, and civil society. If, over the next several years, the proportion of government funds dedicated to health expenditure is increased from 0.9 per cent to between 2- 3 per cent, it is possible that the government TB budget alone could cover all of the planned activities and the scale-up of these new initiatives will be possible.

It is important to frame these investments in the broader context of economic development. The World Bank has estimated that US\$1 spent on TB provides US\$14-25 in economic returns¹³. Increased investment in TB is simply a sound economic investment that will greatly decrease the disease's yearly US \$23.7 billion billion drag on India's growth¹².

India is becoming an early adopter of the world's best new tools

On December 8, 2010, the WHO endorsed GeneXpert MTB/RIF (Cepheid Inc, Sunnyvale, California) - a new cartridge based molecular test for TB, and provided general guidance on how it can be used in countries most affected by the disease¹⁴. Some of the most impressive results of this assessment came from India¹⁵. This test, and more importantly a series of others that will follow, could revolutionize TB control and care by empowering relatively unskilled health care workers to diagnose pulmonary TB with virtual certainty in less than two hours. It will also allow them to determine resistance to rifampicin, a central drug in the treatment of drug-sensitive TB⁴. While much has been made of the ability of this test to diagnose certain types of drug resistance, TB control programmes should think of this first and foremost as a significantly improved way to diagnose drug-sensitive TB. For the first time in history, it provides control programmes the opportunity to rapidly and accurately identify TB and treat all infectious cases, thereby interrupting transmission. It also determines which 95 per cent of infectious cases can be cured with the US\$14 worth

of drugs that are widely available in the existing TB control programmes. This is particularly important in settings with high rates of HIV.

Yet in terms of drug resistance, evidence to date indicates that implementing this test will have the added benefit of tripling the diagnosis of drug-resistant TB. Ironically, it is this benefit that some see as a liability – a common fear is that the number of accurately diagnosed MDR patients may exceed a programme's capacity to treat them. But that fear is rooted in the morally indefensible logic that it is better to ignore many patients with easily treated disease than to work harder for a small number of patients with drug-resistant TB.

Cost and affordability have been key concerns in the process leading up to the WHO endorsement of Xpert MTB/RIF. The Foundation for Innovative New Diagnostics (FIND), co-developer of the test, has negotiated with the test's manufacturer, Cepheid, to achieve a 75 per cent price reduction for the public sector in countries most affected by TB¹⁴. But the real issue in assessing any new diagnostic is not cost, but cost-benefit. When one considers the full spectrum of costs and benefits of quality molecular diagnostics, their cost-effectiveness cannot be denied^{14,16}. But the implementation of new technology is complicated and only India can decide for itself how to balance the urgency of the TB epidemic with the best use of its resources.

To be a global leader in high-quality affordable diagnosis, India must also find a way to control the use of inappropriate technology. Recently, a WHO Expert Group reviewed the evidence on TB serological tests and made a strong negative recommendation against the use of these tests for diagnosing active tuberculosis¹⁰. In the coming decade, leadership in improving TB diagnostics will depend as much on a country's capacity to prohibit the use of bad tests as it does on its ability to encourage the use of good tests.

India is developing the capacity to develop and produce its own quality TB diagnostics

India has long been the leading supplier of generic TB drugs. More recently, the Indian drug industry has played a catalytic role in providing access to lifesaving antiretrovirals (ARV) to the world's poor. This has saved millions of lives, while concurrently providing economic value to investors. India is uniquely poised to have the same impact on global TB diagnosis and subsequent treatment. India should work to develop

low-cost generic versions of quality molecular assays that will not only increase access to these tests within the country, but could have significant impact globally¹¹. These domestic products will be critical to meet the country's health care providers' growing addiction to diagnostic certainty, and would benefit poor patients all over the world.

There is growing evidence that India is now contributing to the research and development of innovative new TB drugs, especially in the biotechnology sector. In lock step, India must capitalize on its scientific and engineering excellence to invent and develop the next wave of TB tests. Most critical is the development of innovative point of care (POC) tests. Point of care diagnostics put the power of clarity in the hands of mothers, daughters and patients themselves. These are truly revolutionary. Although this type of test is still some way off for TB, recent biomarker and platform discovery efforts are very encouraging^{17,18}.

The emergence of a vibrant TB diagnostics industry in India has value far beyond its humanitarian impact. There is a significant global market for these tests that can be tapped into if India makes quality assured TB diagnostics¹⁹. The single threat to this vision is quality. It is not easy to monetize quality in diagnostics. Currently, it is not possible to know what kind of quality one gets when ordering PCR tests from private laboratories in India. For India to reach its potential as a global leader in TB diagnostics, or any diagnostics for that matter, there is simply no getting around the need for ensuring quality through a stringent regulatory and enforcement system.

India is experimenting with ways to integrate innovative tools and delivery systems

New tools in themselves have no value. These only have impact in the context of the systems in which these are implemented.⁴ In turn, these systems will have maximal impact only if these are able to evolve and adapt to take advantage of new technologies. The feasibility of engaging the independent private sector in India has been demonstrated in many small-scale pilot projects. In 2006, Dewan and colleagues identified 24 projects that engaged private providers in DOTS and found that they contributed 23 per cent of new smear positive cases in their areas and exceeded the 85 per cent treatment success target²⁰. The cost-effectiveness of this approach has been amply proved. Now is the time for India to get past the research and to move toward implementing and

evaluating these types of programmes on a scale commensurate with the dominant role of the private sector²¹. Small-scale and pilot projects are simply not adequate. The need of the hour is socially-oriented, yet economically viable, innovative business models that combine public and private financing. With the recent WHO endorsement of Xpert MTB/RIF¹⁴, it is particularly urgent that these efforts be a platform for testing and accelerating the roll-out of new diagnostic technologies.

Conclusion

There is great potential for India to become a global leader in the development of high-quality, affordable diagnostics. Indeed, there is already compelling evidence that India is increasing its ambition, increasing its investment in TB control, aggressively adopting the world's best diagnostic technology, developing its own diagnostics tests, and integrating innovative tools and systems. In this context, the importance of RNTCP National Strategic Plan cannot be overemphasized. The RNTCP alone cannot succeed with this ambitious new plan. It demands that all stakeholders play a role in what is essentially a national problem. But India is not alone in crafting the future of TB control. Other emerging economies share the capacity and ingenuity to be global pioneers in the development and roll out of new innovative tools and strategies for TB control.

The world is on the brink of a paradigm shift in global health. The old paradigm, exemplified by HIV and malaria, is one in which the rich world comes up with solutions and pays for their delivery in the poor world. India can lead the new paradigm, in which emerging economies will solve their own problems and in so doing become global leaders for change. India, China, Brazil and South Africa can all play a key role as early adopters of innovation and radically improve TB control by providing models of success. These countries can also work collaboratively on TB innovation and control through, for example, the trilateral IBSA framework between India, Brazil and South Africa. The availability of ARVs tipped HIV control into becoming a global obsession, and interventions such as bed nets and artemisinin-combination therapies tipped malaria control into a well-funded global elimination campaign. Along these lines, the current series of next generation diagnostic technologies coming down the pipeline can tip TB into the prominence it deserves. India could lead that charge.

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