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Tuberculosis diagnostics: innovating to make an impact

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International Symposium on TB Diagnostics: Innovating to Make an Impact

16–17 December 2010, New Delhi, India

The 'International Symposium on TB Diagnostics: Innovating to Make an Impact' was organized by the International Centre for Genetic Engineering & Biotechnology, New Delhi, India, on December 16–17, 2010, with sponsorship support from the Bill & Melinda Gates Foundation, Foundation for Innovative New Diagnostics and AERAS Global TB Vaccine Foundation. This highly successful symposium attracted more than 300 participants from India and several other countries and covered several aspects of TB diagnostics, including recent scientific advances in TB diagnostics, progress made in expanding the TB diagnostics pipeline including a portfolio of WHO-endorsed, validated new tools and improved technologies, the successful development of newer molecular assays that have the potential to be used at the point of treatment and the growing contributions of emerging economies such as India. In addition to highlighting the positive aspects of TB diagnostics, the symposium speakers also highlighted the need to focus on worrisome aspects of TB diagnosis, including widespread abuse of inappropriate tests that can prevent the use of good diagnostics, lack of quality assurance in laboratories, lack of adequate regulation of diagnostics and how these can pose a major challenge for roll-out and implementation of new tools. The symposium ended with a very stimulating discussion on how India can become a global leader in TB innovations.

Although the global expansion of DOTS, the Stop TB Strategy, has been successful, TB incidence is not falling as expected in many countries, in part because TB patients are not diagnosed and treated immediately. Undiagnosed TB and mismanaged TB continue to fuel the global TB epidemic. Divakar's story illustrates this nicely.

Divakar is a camera person for a very prominent national television news channel in India, and as he bustles around energetically setting up his camera before beginning to shoot, it is difficult to imagine that he has emerged unscathed from what proved to be an almost fatal attack of TB. This is not because the disease is incurable, but because none of the doctors he went to could diagnose it in time and treat him correctly.

He recalls his experiences with a visible shudder: "On developing a cough, which refused to go away with routine household remedies, I visited a general physician who merely heard out my symptoms and prescribed broad-spectrum antibiotics. When I did not get better despite completing the course, he just advised a cough syrup and sent me away." Divakar sought a second opinion at

the All India Institute of Medical Sciences, New Delhi, India, where a chest x-ray ruled out any major illness. More cough syrup prescriptions followed while Divakar continued to get worse. "On some days I was barely able to stand," he recalls, "I would cough violently, bringing up huge amounts of sputum. This tired me out. I was also visibly losing weight." His problem continued unabated and then came a day when he coughed up blood. In total, 6 months had passed by then; he had lost almost 10 kg and he knew there was something very wrong.

His story worsens. He sought help at one of the most prominent chest hospitals in Chennai, India. The doctors there dismissed the x-ray as useless and declared that he needed a series of complicated and expensive diagnostic tests, including a CT scan and two biopsies without telling him what they were suspecting. "I was furious and exhausted by then; I demanded answers and was told that I needed these tests to rule out cancer. I walked out then and went to a government hospital in Chennai."

The doctor at the government hospital looked at Divakar's chest x-ray, performed a clinical examination and other tests. He then diagnosed his

condition as TB and put him on a 6-month course of treatment. Divakar smiles happily as he recounts with relief that he is now healthy and has put the entire episode behind him. He is also indignant as he says, "The doctor at the government hospital remarked that it was evident to even a first year medical college student that my condition was TB. Then why was I made to run around and waste 6 months of my life? Is it because the doctors suspected I had money to waste on expensive diagnostic tests which I did not need?"

Why indeed? Divakar's question and probably questions of hundreds of others like him beg answers. Even more alarming is the story of an elderly gentleman who went to a doctor with a slight cough and a pain in the lower right region of his chest. An ultrasound scan was conducted and surgery scheduled for the very next day to remove his gallbladder as the doctor suspected stones. A second opinion proved it had to do with a patch in the lung and even then there were conflicting opinions between doctors whether the patch was TB or pneumonia. After treatment he went on to live a healthy life for more than 15 years. Now, 15 years later, nothing much has changed. Why is there so much confusion with TB diagnosis? Why is it that there is no conclusive test that can diagnose TB, like there is, for instance, for diabetes?

Mycobacterium tuberculosis was discovered by Robert Koch in 1882 and more than 125 years later TB still continues to infect one third of the global population, causing nearly 9 million new cases of TB and the death of nearly 1.8 million people every year [1]. For decades there has been little effort to improve techniques for diagnosing TB. Consequently, TB tests are antiquated and inadequate [2]. 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 healthcare systems. As highlighted by Michael Specter in a recent article entitled 'A Deadly Misdiagnosis' published in the *New Yorker*, the problem is exacerbated by the widespread use of inaccurate and inappropriate diagnostic tools, such as serological (antibody) assays in many countries [3].

In India, ineffective TB diagnostics are a lucrative market. Patients seeking TB care in the private sector are commonly subjected to serological tests, specifically, the antibody-based blood tests including ELISA that are completely ineffective at detecting TB. This is because presence or absence of antibodies in the blood does not correlate well with presence or absence of active TB. Therefore, false-positive and false-negative results are common. If patients who do not have TB are misdiagnosed, they could undergo 6 months of toxic treatment. If patients have active TB and the test misses it, the disease may worsen and they may continue to spread the disease in their community.

According to a preliminary analysis of over 80 laboratories in India, it is estimated that patients undergo more than 1.5 million useless TB antibody tests each year [4]. The absence of regulatory mechanisms results in the import of these inaccurate diagnostics from France, the UK, the USA, Australia or other developed countries, where these tests are not approved for TB diagnosis. These tests generate at least US\$15 million in India alone. In a

country that has >50,000 laboratories, this estimate is probably only a fraction of the total market. It was therefore an opportune time to address issues in TB diagnostics and there is a dire need to devise point-of-care diagnostic methods, which are not only sensitive and specific but also time and cost effective.

With this in mind, the 'International Symposium on TB diagnostics: Innovating to Make an Impact' organized for 16–17 December 2010, by the International Centre for Genetic Engineering and Biotechnology, New Delhi, India, held great relevance. Held over 2 days, it was the fourth of a biannual series entitled 'International Tuberculosis Symposia', under the leadership of Pawan Sharma, the organizer of the symposium.

This symposium held particular relevance for India, given that India is home to the largest number of TB patients in the world and presents challenges as well as opportunities for becoming global leaders in the area of TB diagnostics. As Madhukar Pai, a professor at McGill University (Montreal, Canada) and co-chair of the Stop TB Partnership's New Diagnostics Working Group, pointed out in his presentation on the landscape of TB diagnostics in India, "Against a scenario where the global TB diagnostics pipeline is rapidly expanding and several new tools and strategies are being scaled up, a close look at the TB diagnostics landscape in India is worthwhile."

Having set the rationale for a symposium devoted to TB diagnostics, it provided an opportunity for delegates to take stock of deliverables in the area of TB diagnostics against the back drop of advances made in the basic biology of the disease. Academia, industry and funding agencies came together to discuss and debate the current status of TB diagnostics and find ways to translate research results into reliable point-of-care methods for diagnosis and to develop more robust strategies for epidemiology studies. Scientific and public health leaders from international agencies such as the WHO, TDR, a Special Programme for Research and Training in Tropical Diseases, Bill & Melinda Gates Foundation, Foundation for Innovative New Diagnostics and leading academic institutions participated by making presentations, along with a large number of scientists, industry leaders and researchers from India. A large number of Indian researchers presented their TB research as posters. A total of 30 plenary presentations from leading scientists from across the world and as many as 90 posters of research were featured in the symposium, which was segmented into five categories:

- Pathophysiology of TB and the challenge of diagnosis
- Trailing the bug: TB diagnostics today and tomorrow
- Changing the landscape of TB diagnostics in India
- Diagnostic innovations from India: view from industry and clinic
- Diagnostic innovations in India: enablers and barriers

The sessions followed a logical flow as they first mapped the challenges involved with diagnostics, gave glimpses into what was currently available and looked at ways to fill the gaps. Thereafter, presentations were made on the innovations that held promise and could provide solutions to existing diagnostic problems.

As part of the first theme, Karen Steingart, a physician from the University of Washington (WA, USA), made a presentation that focused on the importance of a simple serological test that could diagnose TB through detection of *M. tuberculosis*-specific antibodies in patient's blood. If associated with a diagnostic accuracy comparable to (or better than) that of sputum smear microscopy, they could potentially replace the latter method. This would simplify first-line TB investigations in peripheral laboratories and potentially extend TB diagnosis and case finding at the point of care. Steingart pointed out that a series of systematic reviews on the performance of the available tests reported the poor performance of these tests [5,6]. These findings were supported by a large laboratory-based evaluation of the commercially available rapid TB serological tests by TDR [7]. The patient and health system costs associated with misdiagnosis were likely to be high. The WHO recently commissioned an update of the systematic review series, which found that published data on commercial serological tests provide inconsistent and imprecise estimates of sensitivity and specificity. None of the tests could replace sputum microscopy. This was clinching evidence that the available diagnostics were neither useful or effective. After reviewing the evidence, a WHO expert group has made a strong negative recommendation against the use of serological antibody tests for TB [101]. The significance of this negative policy was recently covered by the journal *Lancet* in a world report entitled 'WHO recommends against inaccurate tuberculosis tests' [4].

Camilla Rodrigues from the P D Hinduja National Hospital and Medical Research Centre, (Mumbai, India), made a strong case for the fact that smear microscopy, the most widely used test worldwide, is inadequate and ineffective in the three groups at greater risk of death, namely HIV-positive people, infants and those with drug-resistant TB. Thus, point-of-care dipstick tests are urgently needed. She made a case for nucleic acid amplification tests, which are able to amplify small amounts of DNA and have been used in four applications, *viz* detection, accurate identification, drug-susceptibility tests and fingerprinting. In particular, the new GeneXpert system, recently endorsed by the WHO, is capable of rapidly detecting TB and drug resistance at the point of care. However, this system remains to be evaluated further for its operation under high temperature environments such as in India where ambient summer temperatures could be as high as 40°C.

Jaya Sivaswami Tyagi (All India Institute of Medical Sciences, New Delhi, India) made a presentation on a multipurpose universal sample processing (USP) methodology for TB diagnosis that involves smear microscopy, culturing and PCR. Combining USP processing with disinfectant treatment enables biosafe handling of infectious samples. The USP technology has been successfully employed for diagnosing TB in smear-negative pulmonary and extrapulmonary samples. In addition to DNA, the detection *M. tuberculosis* antigens are valuable for the efficient diagnosis of TB meningitis.

During the session on 'Changing the landscape of TB diagnostics in India', Kuldeep Singh Sachdeva, Chief Medical Officer of India's Revised National TB Control Programme (RNTCP), made a presentation on the importance of TB diagnostics in the

RNTCP and the new goals for the RNTCP Phase III (2012–2017), which include universal access to TB diagnosis and treatment [102]. Virander Chauhan, Director of International Centre for Genetic Engineering & Biotechnology, India, provided an overview of the challenges faced by Indian academics in developing and commercializing technologies. Peter Small from the Bill & Melinda Gates Foundation gave a talk on why India should become a global leader in high-quality, affordable TB diagnostics [103]. Small emphasized that India has the potential to solve its TB problem with 'home-grown' solutions. India has the ability to become the world's leading supplier of quality diagnostics for TB and is already the world's largest supplier of generic TB drugs. With the world's largest generic drug industry and growing manufacturing capacity, India could eventually export TB diagnostics in the same way, providing more affordable diagnostic options for clinics in low-income settings around the world. In the long term, India has the potential to lead the world in developing innovative TB diagnostics.

India's potential for innovations was beautifully illustrated by Anil Gupta (professor at the Indian Institute of Management, Ahmedabad, Gujarat, India and a coordinator of the Society for Research and Initiatives for Sustainable Technologies and Institutions), who gave an inspiring presentation on grassroots innovations in India, in various fields from agriculture to technology.

This symposium also gave an opportunity for several Indian diagnostic companies to showcase their TB tests. For example, Chandrasekhar Nair (Bigtec Labs, Bangalore, Karnataka, India) presented preliminary results of their microPCR test – a portable, low-cost, handheld PCR test for TB (and other infectious diseases) that may be a cost-effective option for India in the future.

The symposium ended with a panel discussion on TB diagnostic innovations in India, barriers and challenges and how India has the potential to become a global leader in TB innovations. Despite the enormous burden of TB in India, India is yet to produce a new drug, vaccine or diagnostic for TB and the reasons for this lack of innovation were debated during the panel discussion. Several Indian academics are involved in TB research, but lack the ability to convert their scientific work into commercial products. Industry-academia relations are currently weak and need to be strengthened. The Indian healthcare industry, especially pharmaceutical sector, is very good at generics, but weak in research and development. 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 private industry. As emphasized by Small, despite the high burden of TB in India, Indian philanthropic groups and foundations are currently not actively supporting research into TB. Their involvement could greatly help in facilitating innovations using prize models and incentives. Tighter regulation of diagnostics, increased attention to quality assurance in laboratories and greater engagement of the private sector is also needed to effectively deliver innovative products and approaches. With India's strong and growing economy, increased funding

is now available in India for innovations and product development. Various options for funding were described by Shirshendu Mukherjee, Strategic Adviser, R&D Initiative (Wellcome Trust, New Delhi, India), Steven Buchsbaum from the Bill & Melinda Gates Foundation and Bindu Dey from the Department of Biotechnology, Ministry of Science & Technology (New Delhi, India). The challenge would be to convert these resources into useful products that can reach people who need them most.

In conclusion, it is important to point out that the media has a significant role to play in the control of TB and this includes a focus on the importance of accurate and timely diagnosis of this eminently curable disease. The reality, however, is that the media does not see TB as a priority and something needs to be done urgently to change this perception. Some of the ways this could be made possible is through intensive capacity building for journalists on finding interesting ways to report on TB. It also calls for using alternate

spaces available for showcasing TB and the challenges associated with its control. As a first step, a group of journalists in India, as a direct result of the findings presented at the symposium and the inability to find media space for reporting on it, have formed a group known as Journalists against TB and have also started a blog. The blog has attracted considerable attention worldwide, with some very prestigious institutions expressing solidarity [104]. It is a small beginning with immense possibilities.

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