

## Editorial

### **Tuberculosis in India - Can we ensure a test, treatment & cure for all?**

With a quarter of the world's tuberculosis (TB) patients living in India, an estimated 2.3 million new cases and 300,000 deaths each year, the disease is a massive public health challenge for the country<sup>1</sup>. The theme of this year's World TB Day is "Reach the three million: A test, treatment and cure for all" – highlighting the fact that only about two-thirds of the estimated 9 million new TB cases are reported to national TB programmes and subsequently to the World Health Organization every year. In India, while approximately 1.5 million TB patients are notified and treated in the Revised National TB Control Programme (RNTCP), an estimated 1 million are "missing"<sup>2</sup>. A majority of these patients are probably treated in the private sector, while an unknown number are either missed, misdiagnosed or die before a diagnosis can be made. In order to make appropriate national plans and policies to control TB, it is important to understand the true burden of TB in the community, as well as its distribution, risk factors, health seeking behaviour and pathways of care that patients use. This will be possible only when there is full compliance with TB notification through NIKSHAY, an online portal launched by the Government of India in May 2012<sup>3</sup>.

Tuberculosis has been known since ancient times, and its causative agent *Mycobacterium tuberculosis*, is well known for its adaptation to the human host. Biologically, one of the challenges of controlling TB is that the bacterium can survive in a dormant or latent state, and re-activate to produce clinical disease, over a span of an entire lifetime<sup>4</sup>. The reasons for re-activation in a particular individual are still incompletely understood and no biomarker has been developed

that can predict this event. Further, one of the many survival mechanisms of the bacterium is the fact that it resides within macrophages, utilizing many pathways to subvert the host immune system and resist killing<sup>5</sup>. In India, the prevalence of latent TB infection (LTBI) is 50-60 per cent in the adult population and the annual risk of TB infection ranges from 1-1.6 per cent<sup>6</sup>.

The Revised National TB Control Programme was introduced in 1993 (as a pilot programme and later expanded to cover the entire country by 2006) to replace the older National TB Programme. The new Programme included certain key elements that were lacking earlier - standardized diagnosis based on sputum smear microscopy, adequate supply of high quality drugs in patient-wise boxes, directly observed treatment to ensure adherence and a reporting framework that allowed constant monitoring. The fifth component of this so called "DOTS strategy" is political will – strong government support that ensured adequate financing and human resources. The Programme has been consistently achieving the global targets for new smear positive case detection (70%) and treatment success (85%) for the past ten years, and prevalence and mortality rates have been reduced in line with Millennium Development Goals (MDGs)<sup>7</sup>. However, incidence is falling very slowly and the disease is still a huge public health problem, with 300,000 deaths and USD 23.7 billion the direct and indirect costs of TB every year<sup>2</sup>.

The question arises as to why, despite a well functioning programme and all the resources that have been allocated, TB continues to infect and kill hundreds of thousands of Indians each year. The answers can

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be found in multiple domains – biological (in the host and bacterium), social, economic, behavioural, and political. Perhaps, the most important point to consider is that TB is a disease associated with poverty, undernutrition and poor living conditions. The high rates of transmission of drug resistant TB in the slums of Mumbai highlight the importance of well ventilated dwellings and a clean environment<sup>8</sup>. A low BMI is the strongest mediator of the association between poverty and prevalent tuberculosis in India<sup>9</sup>. Recent studies have shown that TB is associated with undernutrition<sup>10</sup> and that death rates are 3-4 fold higher in TB patients with low (<35 kg) body weight<sup>11</sup>, compared to better nourished patients. The solutions for these deep seated social problems must come from many different sectors and cannot be tackled by the health system alone. TB itself is also responsible for massive economic losses incurred by individuals for diagnosis and treatment, leading to further impoverishment and loss of livelihoods.

Pretreatment loss to follow up accounts for 100,000 patients in India each year<sup>3</sup>. A recent meta-analysis found an average pretreatment loss to follow up rate of 18 per cent in African countries and 13 per cent in Asian countries<sup>12</sup>. These patients are at high risk for spreading infection to others and have very high case-fatality rates<sup>13</sup>. In addition, these patients represent an early failure in the overall TB treatment cascade. In India, four studies found rates of pretreatment loss to follow up ranging from 5 to 22 per cent<sup>6,14-16</sup>. Reasons for loss to follow up could be patient-related (*e.g.*, stigma, alcohol abuse, economic factors) or health system-related (*e.g.*, failure to contact patients with positive results, unfriendly staff, long waiting times at health centers). Urgent action needs to be taken to reduce this loss to follow up.

TB is also the cause of serious social barriers including a deep-seated stigma leading to abandonment, ostracization and discrimination within the community and at the workplace<sup>17</sup>. A massive community education campaign is required to educate and inform people about the nature of this disease and available prevention and treatment options. Delays in diagnosis and drop-outs from treatment can be reduced only when patients are fully informed and empowered.

Looking forward, there are several areas where a re-thinking of strategies and newer approaches are required. While the public sector is still using sputum smear microscopy as the primary tool to diagnose TB,

it is important to note that the technique is 125 years old and misses half of all TB cases<sup>18</sup>. Newer nucleic acid based technologies like CB-NAAT (Xpert MTB/Rif), Line probe assay (LPA) and other indigenously developed kits (like Molbio's Truenat test) have the potential to revolutionize diagnosis of TB, providing a quick diagnosis from a variety of pulmonary and extra-pulmonary specimens<sup>19</sup>. Cost is an important factor limiting scale-up of these new tools; hence, a locally manufactured diagnostic test would lower costs and facilitate expanded access. The Indian Council of Medical Research, Ministry of Health and Family Welfare and the Department of Biotechnology have jointly established a Task Force to evaluate indigenously developed diagnostics for TB in a time bound manner. The impact of molecular diagnostics will be particularly noticeable in the management of smear negative, paediatric and extra-pulmonary TB<sup>20</sup>.

Although the public sector offers free TB treatment services, critical challenges in treatment adherence remain unaddressed. These include: long commute to the government health facility; long queues; "hidden" costs such as X-rays and hospital stays; loss of income due to travelling; alternate day visit to the public health facility eventually taking a toll on livelihoods. In the private sector, there is a great variability and heterogeneity in the quality of care provided, with irrational treatment regimens, lack of supervision and poor follow up being common. Apart from incurring out-of-pocket expenditure, patients often stop treatment prematurely, thus increasing their chances of developing drug resistance, as well as spreading the infection to others.

The Government of India recently issued the Standards of TB Care in India (STCI); this provides a platform to engage with the private sector for effective TB prevention and control. The Standards take into account World Health Organization and International Standards for TB Care (ISTC) endorsed recommendations and lay down guidelines in the domains of diagnosis, treatment, public health and social inclusion<sup>3</sup>. This document had input from stakeholders across the TB landscape and has the potential to make a profound impact on TB prevention and control in India. Further, if TB drugs can be regulated and their misuse controlled, further expansion of drug resistance can be curtailed. This will be particularly important as new TB drugs (*e.g.*, Bedaquiline and Delamanid), which have recently been approved by the regulatory authorities in the USA and Europe, find their way into Indian markets. While ensuring access to these new and

lifesaving drugs for Indian patients, the government has to ensure rational and controlled use.

Apart from drug treatment, TB patients from the poorer sections of society may need incentives (extra food entitlements, transport vouchers, cash, *etc.*) to help them complete therapy. This is particularly true for those with multi and extensively drug resistant TB, who need to take prolonged courses of treatment and who often cannot return to work for months. While no randomized clinical trial has shown improved bacteriologic outcomes with nutritional supplementation, the design of these studies probably excluded those most likely to benefit and did not examine outcomes like change in lean muscle mass, quality of life, ability to return to work and impact on families<sup>21</sup>. A recent review has reported that food provision is not only a biological, but also a behavioural intervention, and underscored that unresolved food insecurity can be an impediment to treatment adherence and consequently to good treatment outcomes<sup>22</sup>.

In summary, TB control in India requires locally generated tools, solutions and strategies in the areas of diagnostics, treatment, vaccines, awareness generation and community engagement, amongst others. There is a need to invest more in research and development and bring together the public and private sectors for effective translation of academic leads into useable products. Research in TB must encompass not only the domains of basic science, epidemiology and clinical trials, but also include operational and implementation research to test strategies that can reduce the burden of TB in the community. A multi-disciplinary approach will be required to meet the challenge of this age-old infectious disease that continues to haunt us in the 21<sup>st</sup> century.

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