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ERADICATING TB IN INDIA

Challenges Perspectives Solutions

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Introduction

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Amidst all the talk of India emerging as major centre of tertiary medicare, attracting patients from not just the neighbourhood but across the globe who are keen to avail of the country's relatively high quality, low-cost treatment, India still bears the world's largest burden of tuberculosis (TB), accounting for a quarter of all new infections which claim close to 300,000 lives each year. The associated burden of ill-health morbidity can well be imagined.

Few would have believed that more than a century after the discovery of BCG in 1908, thought to be 'The Vaccine' for TB that was later followed by the widespread use of streptomycin in the 1940s, TB would continue to remain a major health problem. The distressing fact is that though the disease has indeed been eliminated from large parts of the globe, countries like India can claim at best partial success. This very first issue of the Global Policy-Observer Research Foundation Series brings together, in a special issue to be launched on World TB Day this year, a range of articles by leading policymakers, administrators, technical experts and members of civil society working in India's TB landscape to help us understand the nature of challenges posed by TB and what we, both as government and as society, need to do.

It is true that prior to the easy availability of vaccines and antibiotics, TB treatment involved shifting the patient to a more salubrious climate, rest in a sanatorium and a healthy diet. It may thus appear paradoxical that the better availability of medicare, by shifting focus away from the need for better nutrition and pollution-free sanitary environment and clean water—all critical social goods—has possibly contributed to the persistence of the disease. Only now, after decades of epidemiological research, are we beginning to realise that communicable diseases like TB, malaria or kala azar, which are as much social

as personal, require more than drugs. As important as the 'correct' medicine and treatment is the role of public and preventive health measures. It bears repetition that conventional drugs are far less efficacious when administered to patients suffering from chronic undernutrition who are forced to work and live in unhealthy and crowded conditions, vastly enhancing the likelihood of the spread of the disease through infection. Finally, over or incorrect medication leads not only to the development of immunity against drugs but also to the emergence of new varieties of the TB bacillus that require newer and more powerful drugs.

None of the above should be read to imply that containing the spread of and curing TB represents an insurmountable challenge. Most TB is treatable and curable with timely diagnosis and adherence to prescribed course of treatment. The Revised National TB Control Programme (RNTCP) in India has since its inception in 1997 contributed to a significant decrease in mortality figures. With full geographic coverage achieved in 2006, the programme now provides diagnosis to over 1.5 million patients every year. And the Directly Observed Treatment, Short-course (DOTS) strategy, ensures a complete course of treatment with four first-line drugs over a period of six months to an infectious patient. This, it is claimed, has successfully cured over 85% of all identified cases. While undoubtedly creditable, one needs to remember that a significant number of patients still go undetected and that many who begin treatment fail to complete the course, thereby exacerbating the problem and adding to the number of drug-resistant patients.

Clearly the first step in the battle against TB is correct diagnosis. Ineffective and inaccurate diagnosis not only leads to continued patient suffering but, worse, a spread of the infection. Fortunately, the RNTCP has over time scaled up its diagnostic capacity and strengthened its reporting mechanisms, though much more needs to be done. Second, it is crucial that patients be motivated to complete the entire course of the treatment, rarely easy since this involves thrice-a-week visits over six months to a designated centre. Particularly for poor people, the costs of missing out on a daily wage can be daunting. Third is the problem of drug resistance, critical because the unit cost of treating patients who are drug-resistant exponentially goes up. Associated with the problem of drug resistance is the growing incidence of non-pulmonary TB, which too is far more expensive and difficult to diagnose and treat.

All of this demands a major strengthening of the country's public health programme, from funding to personnel. It is insufficiently understood that diseases like TB, malaria or polio have nowhere in the world been handled by the private medicare sector, which finds it unprofitable to lock in its resources to serve poorer patients, be it for diagnostics or treatment. Second, it cannot be stressed enough that without ensuring better nutrition and environmental conditions to the entire populace, mere medication, no matter how good and effectively administered, is unlikely to solve the problem. Finally, we need to understand that bacteria mutate, requiring major investments in new research for diagnostics and treatment. Whether or not our scientists can come up with a magic vaccine, which can prevent the emergence of all varieties of the TB bacillus, the search for newer and more efficacious drugs must continue.

Above all, we—health professionals, public authority and citizens—need to realise that above all else, diseases like TB are not just a problem of the individual patient. They are social diseases which demand a social response, which is best handled by a substantial strengthening of the public health system. Equally, we need to understand that an underfed citizenry forced to live in unsanitary surroundings is unlikely to respond favourably to medicare. Finally, investments in better nutrition and improvement in environmental conditions help manage not just the programme on TB but all similar diseases.

This is why the continued underfunding of public health is so disappointing. It is often not sufficiently stressed that expenditure on health, mainly private, is very high and a major source of indebtedness. A failure to increase public funding on health or to substantially strengthen the National Rural Health Mission and mistakenly place faith in either the private medicare sector or an enhanced medical insurance programme can be fatal for a poor and underfed populace. Equally worrying is the worsening living conditions in our cities, particularly in slums housing well over half of the urban population. Collectively this provides an extremely conducive environment for the continuance and spread of TB.

Fortunately, significant advances have been made (and continue to be made) in responding to the multiple challenges—medical, social and political—thrown up by diseases like TB. There is a lot to learn from, both our own as also the experiences of other countries. Hopefully, this special issue of the GP-ORF series, to be launched on World TB Day this year, will help take the discussion forward. ■

1 The RNTCP: Mission for a TB-free India

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India bears the largest burden of tuberculosis (TB) in the world. The TB prevention and control landscape in India is fraught with challenges at multiple levels, including low risk perception, lack of awareness, social stigma, an unregulated private sector and lack of treatment adherence. The Revised National TB Control Programme (RNTCP) is an initiative aimed at providing countrywide access to TB diagnostics and treatment. Since its introduction in 1997, the RNTCP has been at the forefront of far-reaching transformations at the policy and implementation levels that have changed the face of India's TB prevention and control landscape. It achieved nationwide coverage in 2006 and has contributed to a significant decrease in mortality figures due to TB. Outlining its strategy for the future in the National Strategic Plan (2012-17) for TB prevention and control, the RNTCP is now focusing on increasing the efficacy of its interventions through increased budgetary allocations, proactive private sector engagement and the use of new technology to create a nationwide database and monitor treatment adherence.

In 2006, the RNTCP achieved full geographical coverage within India,[1] providing diagnosis to over 1.5 million TB patients every year.[2] For a programme introduced in 1997, this was no small achievement. A key component of the RNTCP is the Directly Observed Treatment, Short-course (DOTS) strategy, which ensures a complete course of treatment with four first-

line drugs over a period of six months to an infectious patient. The RNTCP has consistently succeeded in detecting more than 70% of the estimated new sputum smear-positive cases of TB since 2008, and has successfully cured over 85% of these cases at over 400,000 DOTS centres spread across India today.[3]

The RNTCP is a programme that is wide-reaching in its scope and comprehensive in its approach. It was necessitated by the magnitude of the threat posed by TB to the people of India. An airborne, infectious disease, TB infects 2.3 million people in India every year,[4] which accounts for over one-fourth of the global incidence. The disease disproportionately affects the poor, especially women and children, with direct and indirect losses amounting to $23.7 billion annually in India.[5]

TB is treatable and curable, with timely diagnosis and adherence to the prescribed course of treatment. The DOTS strategy for treating the disease involves the correct administration of medicine at a designated DOTS clinic in the presence of a doctor, a health worker or a trained volunteer. The patients are required to visit the DOTS centre three times a week. However, it was only when India started developing a programme to tackle TB that the extent of the challenges present became evident.

Low risk perception, lack of awareness and poor adherence to treatment were key challenges in TB prevention and control. This posed a significant risk, as every untreated TB patient is a carrier of the disease and can transmit the TB bacillus in his or her areas of residence and work. The social stigma against TB is another obstacle, as patients avoid getting diagnosed for fear of ostracism from their families and the community.

In the past, TB patients were sent off to sanatoria in the mountains in the hope that the clean mountain air would heal them. Modern medicine, as we see through the examples of sputum tests and DOTS treatment, has provided us with more direct interventions for the diagnosis and treatment of TB. However, it is essential to avoid misdiagnosis of TB and to monitor the patient closely to ensure treatment adherence.

Accurately diagnosing TB is critical for both treatment and control. Not only do ineffective and inaccurate diagnostics lead to patient suffering, they also help spread infection, fuelling India's TB epidemic. To address these challenges, the government has moved against TB on a war footing and has been proactive at both the policy and implementation levels. TB was declared a notified disease in 2012, and all positive cases of TB are required to be registered with the government. The government has also declared blood serology-based tests for TB as illegal. The manufacture, sale, import and distribution of serodiagnostic test kits to diagnose TB were banned in June 2012. The ban was regarded as a very important policy decision and a definitive step towards effective prevention and control of TB in India. It is one of the biggest achievements in TB control in recent times. This is because patients accessing TB care in the private sector were paying large amounts of money for tests that have no scientific basis for detecting TB.

The RNTCP has continued to scale up its diagnostic capacity over the years. It has established a nationwide laboratory network of over 13,000 Designated

Microscopy Centres, which are supervised by the Intermediate Reference Laboratory at the state level, and both the National Reference Laboratory and the Central TB Division (CTD) of the Ministry of Health and Family Welfare at the national level. The RNTCP aims to consolidate its laboratory network and organise a defined hierarchy for conducting sputum microscopy with external quality assessment.[6]

The past five years have also seen increased integration between the RNTCP and the National Rural Health Mission (NRHM). In 2013, the Ministry of Health and Family Welfare ordered the merger of the two bodies in an attempt to improve efficiency by centralising the organisation's administration.[7] The NRHM is a Government of India initiative founded in 2005 with the objective of making quality healthcare accessible and available to the country's rural population. Further integration of the two is planned in the current National Strategic Plan (NSP). The NSP outlines the CTD's vision of universal access to quality diagnosis and treatment over five years for all TB suspects in India. As mentioned in the NSP, one of the proposed activities to engage with the private sector is the development of the Standards for TB Care in India, which will take into account all World Health Organization (WHO) and International Standards for TB Care-endorsed regimens used in the private sector.

Compared to 1990 levels, the programme has contributed to an estimated 43% reduction in mortality due to TB, achieving significant progress towards the Millennium Development Goal of halting and beginning to reverse the spread of the disease. According to the WHO, there were an estimated 8.6 million new cases of TB worldwide in 2012, including 1.1 million cases among people with HIV, and an estimated 1.3 million deaths including 320,000 people with HIV. The WHO's six-point strategy to combat the disease, however, has helped all regions except Africa and Europe to stay on track towards the goal of achieving 50% decline in mortality by 2015.[8]

Another critical challenge in the Indian TB landscape is the issue of drug resistance. Drug-resistant TB is a disease type that shows no response to first-line drugs. It is caused due to either a poorly administered TB drug regimen, or when patients stop taking their drugs before the disease has been fully treated. Resistance to the two most commonly used drugs—isoniazid and rifampicin—is defined as multidrug-resistant TB (MDR-TB). Though MDR-TB can be cured using second-line drugs, the treatment is very complex, expensive and has severe side effects. Second-line treatment options are limited and recommended medicines are not always available. India has taken serious note of MDR-TB, and there is a steady increase in the number of such patients reached by the RNTCP. After complete geographical coverage of the country for programmatic management of drug-resistant TB services, the number of MDR-TB suspects who were offered drug susceptibility testing increased in 2013 with diagnosis of 23,289 MDR-TB cases, of which 20,763 were put on treatment. With early diagnosis of MDR-TB, the outcomes of treatment are expected to improve; however, mortality and default are still around 20% each.[9]

India's fight against drug-resistant TB registered a significant landmark in September 2014, when the country launched the biggest ever anti-TB drug

resistance survey in the world. The survey will provide the RNTCP with a statistically representative estimate of the prevalence of anti-TB drug resistance among new and previously treated patients.

For RNTCP's interventions to increase efficacy, it is vital that the benefits of new technology be harnessed as well. In a world brought closer by the World Wide Web, there is great potential to harness internet-based platforms to fortify our TB control initiatives. In 2012, the RNTCP launched Nikshay, a case-based, web-based portal for tracking and recording TB cases. This portal has provided us with effective data collection and analysis, thereby helping in diagnosis and treatment by identifying various types of TB cases, patterns, degrees in severity and solutions on priority. It has been encouraging that providers have increased information sharing and storage contribution of TB cases in the private sector, which continues to treat over 50% of TB cases in India.[10]

Engagement with the private sector, where over half of all TB patients seek primary care, is another key component of India's fight against TB. India's healthcare system consists of both public and private providers with varying levels of care.[11] Private providers who have poor compliance with RNTCP treatment regimens, including errors in both dosage of drugs and duration of treatment, exacerbate the problem of TB control in India. In many cases, patients are forced to stop their course of treatment due to high costs of medicines in the private sector. It is for this reason that the NSP proposed the development of Standards of TB Care in India, so that appropriate care and treatment is provided by all practitioners, public or private, to all TB patients. The government has set an ambitious goal of providing universal access to quality TB diagnosis and treatment by 2017.[12]

ENGAGEMENT WITH THE PRIVATE SECTOR, WHERE OVER HALF OF ALL TB PATIENTS SEEK PRIMARY CARE, IS ANOTHER KEY COMPONENT OF INDIA'S FIGHT AGAINST TB.

Another important challenge is the regulation of over-the-counter sale of anti-TB drugs. The Government of India's notification, in effect since 1 March 2014, aims to arrest the irrational sale and use of anti-TB drugs and other third and fourth generation antibiotics. The health ministry has notified amendments to the Drugs and Cosmetic Act, 1940, which state that the 46 antibiotics that include anti-TB medicines will only be sold upon presenting a valid prescription from a medical professional.[13]

In India, malnutrition is one of the primary reasons for the high incidence of TB. Malnutrition can lead to secondary immunodeficiency that increases the host's susceptibility to infection. In patients with TB, it leads to loss of appetite, nutrient malabsorption, micronutrient malabsorption and altered metabolism, which leads to wasting. Deficiency in proteins and micronutrients increases the risk of TB. It has been found that malnourished TB patients have delayed recovery and higher mortality rates than well-nourished patients. Therefore, raising the nutritional status of the population can prove to be an effective measure to control TB.[14]

The NSP is backed by the commitment of the Indian government to substantially increase funding for TB control. The NSP proposes a substantial increase in the level of funding, the aim being to reach around $260 million annually by 2016-2017, in line with the growth in the number of TB patients put on treatment (a target of around 1.75 million patients by 2016-2017).[15] In per capita terms, during the 12th Plan, the central government's average annual spending on TB

is proposed to be about $0.18, which is triple the average amount spent, in absolute terms, during the 11th Plan.

While political and administrative authorities focus on the provision of creating policy and the framework within which TB control strategies can be implemented, we must remember that it is the tireless efforts of those working on the ground which really contribute to the RNTCP's success. It is these individuals, working across more than 400,000 DOTS centres in the country, who are the basis of the successful provision of TB diagnosis and treatment to patients. Over and above their role as healthcare providers, they also provide patients with the moral support that is so essential to ensure treatment adherence. Every single one of the thousands of individuals working directly with TB suspects and patients has played a part in powering India's battle against TB.

There are still challenges that remain, however, and we at the CTD are sparing no effort in addressing them. Urban TB control requires focused attention, as crowded, insanitary living conditions provide the TB bacillus with the ideal environment for transmission. There is a need for private sector engagement strategies to evolve and adapt in order to increase their efficacy. Urban pilots in Mumbai, Patna and Mehsana are showing positive results, and the success of these projects will provide us with a blueprint that can be replicated in cities across the country.

We need to understand and accept that while the RNTCP works tirelessly to defeat TB, this is a battle where all of us need to stand together. Greater awareness is instrumental in ensuring that we understand and address TB more promptly and effectively. One of the most heartening moments in recent times was when Amitabh Bachchan agreed to be the voice of TB prevention and control in India. His message of *"TB Harega Desh Jeetega"* (TB will lose and the country will win) has heralded a new phase of greater engagement in TB control from all sections of society. It has affirmed my faith that we are on the right track, and are ultimately destined to conquer this disease. ■

Enhancing the Quality of TB Care in India

2

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India's Revised National TB Control Programme (RNTCP) has made considerable progress in reducing the burden of tuberculosis (TB) in the last decade. However, diagnostic and treatment services by the RNTCP are mostly limited to patients accessing care in the public health system. India's vast, heterogeneous private sector is hardly engaged in TB control. Thus, approximately one million TB patients are either undiagnosed or diagnosed but treated outside the RNTCP. Available evidence suggests that quality of TB care in suboptimal and TB patients (both in the public and private sector) struggle to get rapid, accurate diagnosis and treatment, with an appropriate system to support adherence. This results in delayed diagnosis, ongoing transmission and worsening of the drug-resistant TB situation. Recently, the RNTCP articulated a comprehensive National Strategic Plan (NSP) and formulated the Standards for TB Care in India to provide universal access to quality-assured TB diagnosis and treatment by 2017. Several promising public-private mix models have emerged, and TB advocacy is finally getting traction. Policymakers and political leaders in India now have a unique opportunity to make an impact by making sure the NSP is fully and comprehensively implemented. This will save lives and ensure that the missing million patients get the care they deserve.

Historically, TB has been one of the leading causes of morbidity and mortality among humans. The burden of TB has been reduced substantially in the developed countries in the last century due to improvements in nutritional status, general living conditions, healthcare systems and the introduction of anti-TB drugs. In the mid-1980s and early 90s, TB gained prominence because of the growing number of cases due to HIV infection in Sub-Saharan Africa and an alarming rise in multidrug-resistant cases in the developed countries. This led the World Health Organization (WHO) in 1993 to declare TB a 'global emergency'; since then, a lot of effort has gone into controlling TB.[1] Currently, TB continues to be a major public health problem in many low and middle income countries. In 2013, nine million people developed TB, of which 1.5 million died due to difficulties in accessing appropriate and timely diagnostic and treatment services. Nearly 85% of TB occurs in 22 high burden countries.[2] TB thrives in places where there is poverty, malnutrition, overcrowding, high HIV infection rates and poor health infrastructure.[3]

Tuberculosis in India

India is the highest TB burden country in the world with an estimated annual incidence of 2.1 million cases.[4] There are several reasons why the TB burden is so high; a high baseline infection rate (~40% of the Indian population is estimated to be infected with TB) together with a high prevalence of risk factors such as poverty, malnutrition, overcrowding, smoking and diabetes favours not only the progression of infection to TB disease, but also its transmission.[5,6,7,8,9] Addressing these social determinants will require sustained socio-economic development and reduction in inequities.

DURING 2007-13, RNTCP TREATED 1.3-1.5 MILLION CASES ANNUALLY.

Along with socio-economic development, it is necessary to have health systems in place for early diagnosis and treatment, thereby providing care and support to those who get diseased and reduce the duration for which they are infectious. This will lead to a reduction in morbidity, mortality and transmission, thereby resulting in the reduction of the TB burden. In India, a National Tuberculosis Control Programme was devised in 1962, but was largely ineffective. The slow pace of socio-economic development along with an ineffective public health programme allowed TB to persist in the country for three decades without any changes in the numbers infected.

The early 1990s saw rapid economic development in the country through liberalisation policies that resulted in a GDP growth rate of more than five percent per annum. Towards the end of the last century, the Government of India made amendments to the National Tuberculosis Control Programme and reintroduced it as the RNTCP, incorporating the internationally recommended Directly Observed Treatment, Short-course (DOTS) strategy.

As part of RNTCP, nearly 13,000 sputum smear microscopy centres and more than 500,000 DOTS centres were established to provide decentralised quality-assured diagnostic and uninterrupted treatment services through the public healthcare system. A robust recording and reporting system was put in place that made the public health system accountable for every case diagnosed and treated

under the programme. During the period 2007-13, the RNTCP diagnosed and treated nearly 1.3-1.5 million TB cases annually, achieving an overall treatment success rate of more than 80%. Adoption of the DOTS strategy resulted in standardised diagnosis and treatment of more than 14 million TB patients. It is estimated that more than 2.6 million additional lives were saved between 1997 and 2011 through effective diagnosis and treatment.[10] Modeling has also shown that TB control in India has been highly cost effective.[11]

As a result, the prevalence of TB declined from nearly 430 cases per 100,000 populations in 1990 to 211 cases per 100,000 populations in 2013 and the mortality rate due to tuberculosis declined from 42 per 100,000 populations to 19 per 100,000 populations in 2013.[12] The annual risk of TB infection (a measure of TB transmission in the community) came down from 1.5% in the years 2000-03 to 1.0% in the year 2009-10.[13] However, further progress has been impeded by two major challenges.

First, it is estimated that about a million TB cases annually are being missed by RNTCP,[14] either because TB patients are not diagnosed, or because they are diagnosed but not notified to the programme. This is due to the complex landscape of the Indian healthcare delivery system, which includes many different types of care providers in public and private sectors. RNTCP services are largely limited to patients accessing medical care from public health facilities, with very limited private sector participation. It is estimated that nearly half of the TB patients in the country are diagnosed and treated in the private sector.[15] Even patients who reach public health facilities and are eventually treated by the RNTCP, do so after visiting multiple healthcare providers in the private or informal sectors.[16]

Second, there is a concern about the rising numbers of drug-resistant TB cases in the country.[17] It is estimated that the annual incidence of multidrug-resistant TB (MDR-TB; resistant to two of the most potent anti-TB drugs isoniazid and rifampicin) was 99,000 (range 79,000 to 120,000).[18] More severe forms of drug-resistant TB called extensively drug-resistant TB (XDR-TB; defined as MDR-TB plus resistance to fluoroquinolones and the injectable used in the treatment of MDR-TB) have also been reported; indeed, the situation may be worsening.[19,20] In urban hotspots such as Mumbai, increasing numbers of MDR-TB cases have been identified because of the roll-out of rapid molecular tests. An increasing trend of drug-resistant TB is an indication of mismanagement of tuberculosis,[21] and therefore, it has been argued that there is an urgent need to focus on quality of TB care in the country.[22]

Issues Related to Quality of TB Care in India

TB care rests on three fundamental principles: Early and accurate diagnosis, initiation of the correct drug regimen and patient support to ensure adherence. Healthcare providers play a crucial role in providing TB care. The best practices for diagnosis and treatment have been outlined in the International Standards of Tuberculosis Care (ISTC). India has formulated its own version of these standards, the Standards of TB Care in India, which are largely consistent with the ISTC.

In India, to ensure early diagnosis of TB, it is important to make sure that all persons with productive cough of more than two weeks undergo investigations to rule out pulmonary TB. People usually do not visit health facilities to seek care at an early stage.[23] Even when such patients manage to visit health facilities, nearly one-third of the doctors do not suspect TB,[24] and when they do suspect TB, only a third order sputum tests that can confirm pulmonary TB.

Demonstration of the presence of *Mycobacterium tuberculosis* in sputum is necessary for TB diagnosis. Sputum smear microscopy is widely available at peripheral public health facilities. However, it has its limitations. It fails to detect nearly a third of the pulmonary TB cases, and cannot detect drug resistance. Moreover, India, on average, has one quality-assured sputum smear microscopy centre per 100,000 population and less than one per 10 million population quality-assured diagnostic centre for detection of drug-resistant TB,[25] indicating poor access to these services. In the private sector, sputum tests are rarely used. As a result, there is a delay of nearly two months before a diagnosis of TB is made[26] and about one-third of the TB patients are either missed or are treated empirically without a bacteriologically confirmed diagnosis. The practice of up-front drug susceptibility testing to detect drug resistance is nearly non-existent.

The first-line anti-TB regimens used in the treatment of TB (for six to eight months) in the RNTCP are consistent with ISTC. There are mechanisms to ensure adherence to anti-TB medications in the form of DOTS providers. A recording and reporting system is in place that provides information on how many patients are diagnosed and their treatment outcomes. However, there are two major criticisms of the RNTCP treatment. First, it is an alternate day regimen (anti-TB drugs are consumed by patients thrice a week) rather than a daily regimen. Alternate day regimens are known to have similar treatment outcomes[27] but many providers still consider it an inferior practice. Second, the directly observed treatment system is perhaps not patient friendly. This is evident from the fact that nearly a third of the patients do not consume the drugs regularly and 5-15% of the patients are lost to follow-up before completing their treatment.[28]

On the other hand, the TB drug regimens used in the private sector are quite variable and often not consistent with standards. Nearly one-third of the private practitioners do not seem to know the correct treatment regimen for TB. [29,30] There are no systems to support treatment adherence, and case notifications are not routinely made, even though a governmental order mandates that all TB cases must be notified to the RNTCP. Therefore, long-term outcome of TB patients in the private sector is largely unknown. A formal notification system has been developed by the RNTCP, but is not fully functional to capture information on all TB cases diagnosed and treated in the private sector.

The situation becomes further complicated when it comes to the diagnosis and treatment of drug-resistant TB. Although RNTCP has formulated guidelines for the programmatic management of MDR-TB, these services were scaled up and made available throughout the country only in 2013, and about 20% of the estimated 100,000 MDR-TB patients in the country were enrolled for treatment that year.[31] It takes about a month and a half for a person with MDR-TB to get

diagnosed and treated, even in urban areas.[32] There is little information on the fate of the remaining patients. All of these issues suggest that a large proportion of TB patients in India do not complete the TB treatment cascade (Figure 1).

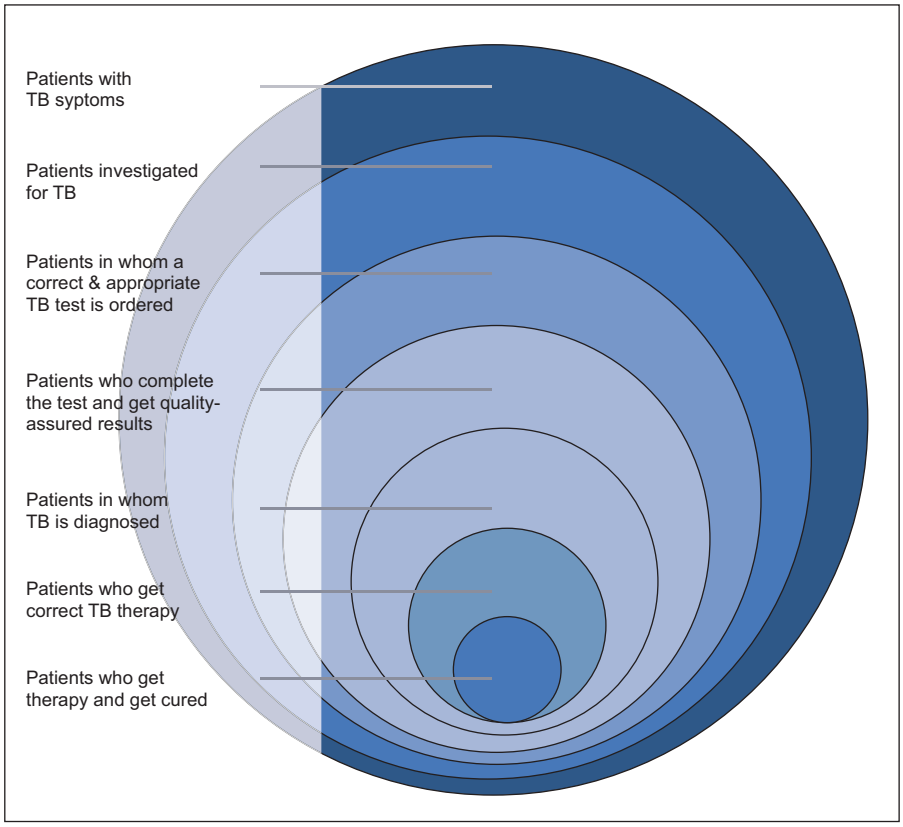

Figure 1: TB Treatment Cascade[33]

Addressing the Challenges

In 2012, the Government of India formulated an ambitious National Strategic Plan (NSP) for universal access to 'quality'-assured TB diagnostic and treatment services to be achieved by the year 2017.[34] While the NSP is comprehensive, a focus on some of the basic issues might help in addressing the challenges faced by TB patients in the country. These include:

- Increasing the number of diagnostic facilities both in the public and private sector that offer quality-assured diagnostic services. Perhaps there is a need to redefine accessibility in terms of availability of such services within a certain distance of all human habitations rather than the current standard of having these based on population norms (e.g., having one diagnostic microscopy centre per 100,000 population, which often results in unequal access to many people).
- Upgrading the existing diagnostic facilities with newer molecular tests (such as Xpert MTB/RIF, a cartridge-based nucleic acid amplification test) that are not only more sensitive and specific in detecting TB, but also diagnose drug-resistant TB in a decentralised manner.
- Increasing the number of treatment centres that offer treatment services for both drug-sensitive and drug-resistant TB and ensuring that they are easily accessible and patient friendly.

- Training and engaging all healthcare providers, both qualified and non-qualified, in the public and private sectors to diagnose and treat TB as per the national and international standards. The local TB control programme managers need to be specifically trained to interact, establish and maintain partnerships will all types of healthcare providers.
- Establishing a quality surveillance system that incorporates methodologies such as exit interviews, prescription audits, mystery clients, and developing indicators that capture information on TB diagnosis and treatment in the private sector beyond the existing notification system.

Recent Developments and Innovative Models

Several recent developments in India are noteworthy, as they illustrate the potential to improve TB care in the country. First is the Mumbai Mission for TB Control,[35] a good example of how a local government can respond to the threat of MDR-TB; in this case, the Municipal Corporation of Greater Mumbai is leading the way in addressing MDR-TB in the city. Their strategy includes: Active case finding in slums; access to rapid diagnostics (Xpert MTB/RIF), including universal drug-susceptibility testing; improving access to effective MDR-TB treatment; extending services and support to providers and patients in private healthcare sector; TB infection control; building empowered communities; and organisational strengthening. Thanks to these initiatives, Mumbai is diagnosing and treating more and more MDR-TB patients, actively engaging the private sector and investing in new technologies, such as those related to information and communication, to enhance notification and follow-up. The Mumbai experience is already becoming a model for other cities in India.

The Initiative for Promoting Affordable and Quality Tests (IPAQT) is a collaboration of non-profit stakeholders and leading private medical diagnostic laboratories in the country to improve the access to WHO-endorsed TB tests. Private laboratories in the network get reagents at significantly reduced prices. In return, they offer the tests at negotiated, ceiling prices to patients, and notify all confirmed cases to the government. In exchange for offering lower prices, test manufacturers and distributors receive greater and more predictable volumes from the previously untapped private market. In short, IPAQT aspires to a "win-win-win" situation where laboratories, suppliers and patients all benefit from a shift from premium pricing to a mass-market (high volume, low margin) model. Within a short period, nearly 90 laboratories have signed up to be a part of this initiative and more than 100,000 WHO-endorsed TB tests have been conducted by member labs.[36]

RNTCP HAS DEVELOPED A FORMAL NOTIFICATION SYSTEM BUT IT IS NOT FULLY FUNCTIONAL.

Many projects are being implemented to improve access and quality TB care in the private sector. The Bill and Melinda Gates Foundation is supporting a Private Provider Interface Agency (PPIA) project in Mumbai and Patna.[37] PPIAs are agencies that aggregate private providers, and educate and incentivise them to provide patient-centric services, including free TB drugs and subsidised diagnostics. Other public-private partnerships include the Global Fund-supported Project Axshya in 374 districts of the country, Operation Asha in Delhi and REACH in Tamil Nadu. These models are attempting to offer TB patients a complete, patient-

centric solution, regardless of where they seek care.[38] Further innovations in this area are clearly needed to ensure small public-private mix projects reach scale.

Recently, advocacy for TB control received a big boost when one of India's most celebrated cinema personalities, Amitabh Bachchan, publicly announced that he was a TB survivor, and became an Ambassador for Mumbai Mission for TB Control (Figure 2). "Satyamev Jayate," one of the country's most popular TV shows on social issues hosted by Aamir Khan, another renowned cinema star, aired an entire episode on the plight of TB patients in the country, bringing much-needed attention to the disease. India's Union Health Minister responded by outlining an ambitious plan to eliminate TB by 2020.[39]

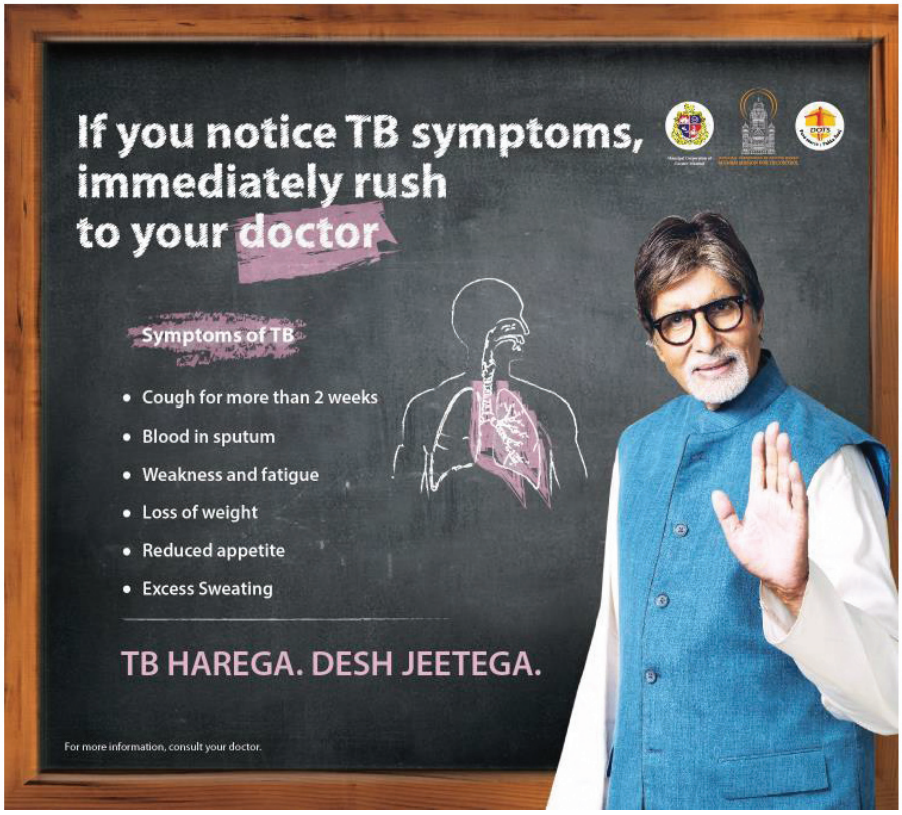

Figure 2: India's Movie Star Amitabh Bachchan's Ad Campaign against Tuberculosis

While eliminating TB is not an impossible task, it must begin by ensuring universal access to quality-assured TB diagnosis and treatment both in the public and private sectors across the country. Unfortunately, despite announcing an ambitious plan to eliminate TB by 2020, India has cut back on its TB control budget, and expenditure on health in general has been reduced.[40] At this critical juncture, policymakers and political leaders in India have a unique opportunity to make an impact by making sure that the NSP is fully and comprehensively implemented. This will save lives and make sure the missing million patients get the quality care they deserve. ■

3 TB Control in India: Mapping the Gaps

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India continues to bear an intolerable burden of disease, mortality and drug resistance related to tuberculosis (TB). The lack of significant decline of TB incidence in India, despite an improved TB treatment programme, is a manifestation of the intrinsic limitations of a germ-centric view of the disease and of a purely treatment-based approach to its control. An alternative and complementary view is an ecological and epidemiological one based on addressing the determinants of the occurrence of the disease and its adverse outcomes, which are currently only partially addressed. A revised map of TB control needs to address these gaps. The burden of TB and its complications in India can be reduced if major drivers of the TB epidemic like widespread undernutrition are addressed; primary healthcare services are improved; the Revised National TB Control Programme adopts a patient-centric and a pro-poor orientation with convenient hours, respectful interactions, nutritional and social support; treatment regimens are revised and aligned with international guidelines; and the government shows the political will to address the state of health and healthcare services in addition to providing the TB control programme with sufficient, stable and sustained funding.

The conventional, germ-centric narrative around TB in India is of a seemingly intractable public health disaster. An annual estimated mortality of 270,000 deaths means that TB claims one life in India every two minutes.[1] In spite of a revised, massive TB control programme offering free diagnosis and treatment, case finding remains static with nearly half of all patients seeking care of uncertain quality from an unregulated private sector, which the programme has been trying to engage with limited success. India has the highest number of patients with multidrug-resistant TB (MDR-TB) globally.[2] In Mumbai, the problem of drug resistance has progressed to a point where up to a quarter of all new patients in public hospitals have multidrug-resistant organisms (resistant to the two key first-line drugs),[3] and patients with resistance to nearly all drugs have also been reported. In this narrative, the apparent solutions include the introduction of improved diagnostic methods, rapid detection of drug resistance, newer drugs and regimes, and an end to the interminable wait for a new and effective vaccine.

This narrative conjures the image of a virulent and rapidly lethal pathogen, causing a disease increasingly difficult to treat and control. A TB expert even called MDR-TB "Ebola with wings."[4] This imagery is at substantial variance with the facts. *Mycobacterium tuberculosis* is a slow growing organism, and the disease may develop months and even years following infection. Active TB after infection with the germ is the exception rather than the rule, developing in only 10% of people with a functioning immune system over a lifetime. Patients with HIV infection have higher risks of progression. *Mycobacterium tuberculosis* is therefore a necessary but not a sufficient cause for the development of TB.

Usually the cell-mediated immune system functions to contain the organism successfully in 90% of those infected, while factors that impair immune response increase the risk of active TB. Once active TB develops, the outcomes can vary from cure in those who receive effective therapy early and adhere to it, to death in patients with advanced disease or with serious coexisting conditions who do not avail of effective therapy. Some patients who receive inappropriate therapy may neither die nor get cured, but remain chronically ill and infectious to others as excretors of drug-resistant bacilli. One of the patients described in the report of totally drug-resistant TB from Mumbai had a history of TB for six years with multiple ineffectual courses of therapy.[5]

The launch of the Directly Observed Treatment, Short-course (DOTS) strategy by the World Health Organization (WHO) was expected to control tuberculosis, i.e., substantially reduce the number of new TB cases by improving case detection and cure rates of patients. This has not been so, even in countries with well-functioning TB programmes, going contrary to the assumption that the cure of TB patients should lead to reduced TB incidence by decreasing transmission of infection. This is not surprising if we consider the epidemiology and pathogenesis of TB in high burden countries like India, where a substantial part of the population (40%), larger than the entire population of the USA, is already infected with *M. tuberculosis*.[6] It is out of this large pool of infected persons that active cases of TB arise through a progression or reactivation of infection. Treatment decreases the transmission of infection to uninfected persons, but diagnostic delays that last for weeks and even months expose a family and the community before the diagnosis of TB. Treatment of active TB

> UNDERNUTRITION IS THE MOST PREVALENT RISK FACTOR FOR THE PROGRESSION OF TB INFECTION IN INDIA: FINDINGS SUGGEST THAT ONE MILLION NEW CASES COULD BE ELIMINATED ANNUALLY IF UNDERNUTRITION IS DONE AWAY WITH IN THE 15-49 AGE GROUP.

also does not address persons with TB infection or the risk factors that put them at risk of developing the disease. BCG vaccine, which offers some protection to children, has been shown to be ineffective in preventing adult infectious TB in India.[7] A recent editorial has commented on a radical approach involving repeated administration of isoniazid preventive treatment on a mass scale.[8] However, administering isoniazid preventive treatment for nine months to 500 million persons every five years is logistically impossible. Moreover, a recent trial of such preventive treatment in South African gold miners showed no lasting effect on TB incidence.[9]

Where does the failure of a treatment-based approach to TB control leave us? Current approaches have largely employed measures based on the germ theory. This theory has undoubtedly given us valuable tools for TB diagnosis and treatment, but it cannot adequately explain the adverse outcomes related to TB infection as they occur in society—why some people suffer from TB while others can coexist with the infection, why some experience adverse outcomes like death and drug resistance while others do not. Opportunities to improve the TB situation have been missed because we have neglected this ecological and epidemiological view of the problem—and failed to address the underlying determinants of TB occurrence, deaths and drug resistance at the population level. If a revised map which addresses these gaps is used to deal with TB effectively as a public health problem, then there is hope. It is an encouraging sign that the new End TB Strategy incorporates some of these perspectives, which this article will highlight in an India-specific context.

Primary Determinants of Health

The primary determinants of health include access to a balanced and nutritious diet, healthy living and working conditions, and safe water and sanitation. The lack of these explains the disproportionate burden of disease suffered by the poor in India. The cell-mediated immune system is of critical importance in protection against TB in infected persons. The TB explosion in Africa since the advent of HIV is a clear illustration that factors which impair cell-mediated immunity can drive TB epidemics. HIV is the most powerful risk factor for progression of TB infection to disease, but accounts for only about 5% of the incident TB cases in India.[10] However, undernutrition, which also impairs immune response to TB, is the most prevalent risk factor for progression of TB infection in India, with nearly 35% of people in the age group of 15-49 years

having a body-mass index (BMI) lower than 18.5 kg/m2.[11] WHO considers that in a country with a healthy population, less than 5% should have a BMI less than 18.5, while a prevalence of 35% would suggest a serious situation of chronic energy deficiency.[12] This translates into more than 250 million people with low BMI, against an estimated 2.5 million with HIV infection. We estimated that 55% (95% CI: 27.4, 75.9) of the TB incidence in India is attributable to undernutrition.[13] These findings suggest that more than one million new cases annually could be eliminated if undernutrition in the age group of 15-49 years were to be eliminated. While much has been written on the impact of HIV on the TB epidemic, the links between TB and widespread undernutrition in India has received far less attention in the policy discourse.

Considerable historical evidence indicates that TB is a disease exquisitely sensitive to living conditions in general and nutrition in particular. While McKeown's deduction of improvements in nutrition as the key factor in the decline of mortality due to TB in England in the period from 1850-1950 has been debated[14,15], Faber's detailed analysis of TB mortality in Denmark during World War I is strongly suggestive of a causal association between food scarcity and TB mortality.[16] Natural experiments in German and French prisoner-of-war camps also showed up to 92% reduction of TB incidence in those soldiers who had access to an additional ration of 1,000 calories and 30 grams protein compared to others who lived under similar conditions of overcrowding and stress but had access only to the prison diet.[17,18] The effect of adequate nutrition and other social interventions was also documented at the Papworth village settlement in UK during the pre-chemotherapy era. Here, TB control was achieved in a single generation, as even young children living in contact with a parent suffering from TB from birth enjoyed protection from TB in spite of being infected by the age of five years.[19,20]

Addressing undernutrition at the population level in India may be one of the most important interventions for reducing TB incidence, as a systematic review has estimated a 13.8% decline in TB incidence per unit increase in BMI.[21] Improvement in nutritional status of the population would also reduce neonatal, infant and under-five mortality, as half of the 500,000 deaths which occur under the age of five years in India are attributable to the effects of undernutrition.[22] The wartime food policy implemented in Britain during the Second World War assured a nutritious diet for everyone irrespective of income, resulting in "rates of infantile, neonatal, maternal mortality and the still birth-rate [that] reached the lowest ever."[23] The goal achieved in wartime Britain is still a distant dream for millions of people living in peacetime India, as they struggle with food inflation and declining calorie and protein intakes.

Primary Healthcare Services

Pulmonary TB can be suspected using simple criteria of cough of more than two weeks duration and can be diagnosed using relatively simple tests like sputum microscopy supplemented with X-rays at the primary level. A persistent problem with India's healthcare system has been the lack of adequately funded, staffed, equipped and functioning primary services in the public sector. The national TB

programme launched in 1962 had envisaged TB diagnosis and treatment as an integral part of the general health services, but it was only at the end of 2005 that the entire country had coverage with one microscopy centre for 100,000 population and assurance of uninterrupted drugs for their treatment. The state of the general health services contributed to the failure of the previous National Tuberculosis Programme.

The poor state of primary healthcare results in people seeking care from the private sector comprising qualified or unqualified practitioners, delays in diagnosis, misdiagnosis and inappropriate therapy. A recent systematic review estimated that patients experienced a median delay of 31 days (IQR 24.5, 35.4) with consultations with an average of 2.7 healthcare providers before the diagnosis was established.[24] A study from Andhra Pradesh reported that 81% of tribal patients had symptoms for eight months or more before treatment was initiated.[25] Audits of private healthcare providers have revealed prescriptions of a multiplicity of inappropriate regimes; 106 practitioners prescribed 63 different regimes in a follow-up of a 1991 study in Mumbai.[26] These factors worsen the disease and promote the development of drug resistance. In south India, where the primary healthcare system is better functioning, the rates of MDR-TB are lower than in north India.[27,28,29,30] While the programme is engaged in increasing case findings through engagement with the private practitioners, there is potential for vast improvements in case finding by strengthening its engagement with the primary healthcare system, including the community-based volunteers.

Pro-patient and Pro-poor Orientation of the Programme

The current WHO strategy rightly emphasises integrated patient-centred care, which in the Indian context has to involve a proactive pro-poor orientation in its programme's philosophy and practices. The poor have up to sevenfold higher risk of disease and death and are severalfold less likely to access and complete treatment.[31] The utilisation of the Revised National TB Control Programme's (RNTCP's) services by patients, including the poor, is influenced not only by the provision of free diagnostic and treatment services (which nevertheless involve substantial indirect costs), but also by the quality of treatment (actual and perceived), quality of interactions with the providers and the organisation of treatment according to patient's convenience. The RNTCP in a recent social action plan acknowledged that "some marginalized groups such as tribal populations, rural poor and urban slum populations are yet to receive the full benefits of the programme."[32] This is worrisome since these are the groups most affected by TB, and measures to make the programme more convenient and to minimise indirect costs still await implementation.

The RNTCP and the WHO earlier emphasised universal Directly Observed Treatment, Short-course (DOTS) therapy done at a health facility or by a community-based volunteer to improve treatment completion rates. However, the conditionality imposed by this form of administration forces urban patients to make thrice-weekly visits to the health facility, which is both inconvenient and costly. A

review showed that treatment success was highest when DOTS was accompanied by provision of social support, enablers and/or incentives.[33] Adherence to TB therapy is a challenge in India for patients, as the treatment is unusually prolonged (lasting months or even years) and is often marked by side effects rendered more frequent by their low body weights. Furthermore, their ability to comply is also compromised by their social instability (many are migrants), loss of earnings, food insecurity, indebtedness, stigmatisation and lack of social support. There have been disturbing reports of suicides in young patients with MDR-TB due to the prolonged nature of treatment and dwindling social support.

Francis Peabody, in the context of patient-centred care, wrote in 1927: "The success of the care of the patient is in caring for the patient."[34] The RNTCP and its providers need to be sensitised to recognise and anticipate social problems in adherence to therapy, e.g., in the case of migrants who may wish to return to their places of origin. Provision of enablers like flexible and convenient timings for patients, family member-based DOT, support for travel, incentives like nutritional and financial support, and behavioural and attitudinal changes on the part of healthcare providers like respectful communication could improve case finding and adherence, which in turn could result in migration of patients to the services of the RNTCP. Nutritional support is particularly relevant in this country, where TB worsens pre-existing undernutrition, rendering it more serious and life threatening. In rural central India, 50% of men and women with pulmonary TB weigh less than 42 kg and 34 kg respectively.[35] Undernutrition in TB patients increases the risk of a number of adverse outcomes—early death, drug toxicity, malabsorption of anti-TB medications, severity of disease and relapse after cure.

PROLONGED TREATMENTS, LOSS OF WAGES, FOOD INSECURITY, INDEBTEDNESS AND STIGMA: A FEW REASONS FOR THE LACK OF ADHERENCE TO TB THERAPY.

Prevention and Management of Drug Resistance

The epidemic of MDR-TB in India is also the result of a delayed response to a problem which was reported in the 1980s, while the first DOTS-PLUS initiative to treat MDR-TB was launched in 2007. It has been estimated that annually around 64,000 cases of MDR-TB arise in India,[36] while there is a larger number of patients with single- and poly-drug resistance. In the year 2013, however, a total of only 20,763 cases were initiated on treatment.[37] This is another outcome of the fact that nearly half of India's TB patients are being treated by the private sector. The infrastructure and utilisation of services for drug-resistant TB are inadequate, while in recent years there have been interruptions in the supply of drugs for MDR-TB patients.[38] Despite the expansion of infrastructure, there is overall currently less than one treatment centre for 10 million population.[39] The only RNTCP-certified laboratory for drug sensitivity testing in Punjab processed less than 500 samples in 2013, while the state registered nearly 5,000 previously treated patients who could have been considered eligible for drug susceptibility testing.[40] Only five laboratories nationwide were certified for testing resistance to second-line drugs as of 2014, and the expansion of this capacity is an urgent need in view of more extensive forms of drug-resistant TB encountered in India.

The RNTCP needs to incorporate changes in the schedule of administration of drugs and the content of the treatment regimens as suggested in the 2010

guidelines of the WHO.[41] The programme is still administering drugs thrice weekly and following the regimes for new and previously treated patients suggested in the 1997 version of the WHO guidelines, even though concerns have been raised about the outcomes in new as well as previously treated cases[42].

Political Will

The WHO has set the goal of reduction of TB incidence to 100 per million by 2035 and an ultimate goal of TB elimination by 2050, which translates into one patient per million population.[43] The current annual TB incidence in India is 1,700 per million, which shows the enormous distance we have to cover. The programme will only be able to contain the problem if it has access to sufficient, stable and sustained funding. India's health budget is still 1% of the GDP, of which India's TB control programme historically had the lowest funding among its communicable disease programmes. In the RNTCP, funding improved, but there has been a recent funding cut of 20% in the health as well as TB budget, at a time when the programme was considering intensification of TB control activities in line with the End TB Strategy. The annual estimated incidence of TB in India is 3,300 times that of New York City (which reported 656 cases in 2013), and yet receives an annual funding of only seven times the funding of the Bureau of TB Control of New York City ($16 million).[44] To control TB in India, we need political will to meet the basic needs of our citizens, essential for maintenance of health and protection from disease, and provision of accessible and acceptable basic healthcare services.

In conclusion, the major gaps which need to be addressed are: The primary determinants of health; the state of primary healthcare services; a patient-centred care approach which provides nutritional, psychosocial and financial support; and adaption of the programmatic practices around the patient's needs. There is an urgent imperative for the programme to address the issue of drug-resistant TB with enhanced budgetary allocation, newer diagnostics and better regimes. The TB programme is trying to cover lost ground and needs the wholehearted support of all those who wish to see a change in the dismal scenario of TB in India. The programme will need to flag, to the highest levels of decision-makers, those issues which are not under its direct control (e.g., widespread undernutrition in adults) as well as the state of primary health services which have a critical impact on occurrence and case finding of patients with TB. On its own, it would achieve far more if its diagnosis and treatment practices are quality assured and aligned with the current evidence, and if its engagement with patients is friendly, responsive, flexible and supportive. ■

MDR-TB in India: Past the Tipping Point Now?

4

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"The rise of MDR-TB in the global era is a call to return to the basis of our practice as healers: our mission is to treat the sick, not just the sick who can pay. Our mission is to treat TB, regardless of resistance patterns."

– Paul E. Farmer and colleagues from Partners in Health, 1998

Introduction

Tuberculosis (TB) exists on an epic scale in India and stubbornly remains India's most pressing public health problem. About 300 million Indians are infected, with an estimated annual incidence of more than two million with active disease.[1] Every third TB patient and fifth smear-positive patient in the world resides in India. Despite the much vaunted successes of Directly Observed Treatment, Short-course (DOTS) strategy in India, TB continues to kill 300,000 Indians annually (two deaths every three minutes), a grim statistic that has not changed over the decades. India also houses the largest multidrug-resistant TB population in the world and in what could be called the perfect storm, the combination of poverty, extreme overcrowding, malnutrition, diabetes, indoor pollution, smoking and HIV have conspired to create a cauldron where TB, especially its drug-resistant forms, can thrive and spread.

Definitions

Multidrug-resistant TB (MDR-TB) is defined as high grade resistance to the two main first-line drugs isoniazid and rifampicin.

Extreme drug-resistant TB (XDR-TB) is defined as MDR-TB plus resistance to any one second-line injectable aminoglycoside.

Total drug-resistant TB (TDR-TB) is defined as resistance to all available drugs or all tested drugs.

Epidemiology

MDR-TB:

The most current data on the global and India-specific multidrug resistance (MDR) situation come from the 18th Global Report on TB published by the World Health Organization (WHO) in 2014.[2] The report estimates that a total of 62,000 new cases of MDR-TB emerged annually from the notified cases in India. There was a 2.2% prevalence of MDR in new cases and a 15% prevalence in retreatment cases. The report goes on to note that India, China and the Russian Federation contributed around 60% of the global burden of MDR-TB. It is important to point out here that these "official" figures are probably considerable underestimates of ground reality. They are after all based on subnational surveys of small sample size and come from sentinel centres where programme performance may exceed that in routine locations. The data emerging from hyper endemic cities like Mumbai finds much higher rates of MDR: 24% in newly diagnosed cases (primary MDR) and 41% in first-line treatment failures (secondary MDR).[3] As will be discussed below, the majority of TB and MDR-TB patients first seek treatment in the private sector and till 2012, TB cases were not even notified, with large numbers slipping under the radar. Until India undertakes a truly representative national survey, the true extent of the MDR problem this country faces will be obfuscated by the kind of "statistico-tuberculosis" described above.[4]

XDR-TB:

XDR-TB has in all probability existed for years in India because of the cavalier manner in which second-line drugs, especially fluoroquinolones, are abused. The first XDR series from the country was reported from the Mumbai-based Hinduja Hospital (a large private hospital, armed with a state of the art mycobacterial lab), where a retrospective analysis of all samples sent for sputum culture in 2006 revealed that 11% met the Centers for Disease Control and Prevention definition of XDR laid out just a few months earlier.[5] Since this initial report there have been several other reports from across the country.

TDR-TB:

Higher grades of resistance are also encountered. In the latter half of 2012, four patients with a more extreme form of drug-resistant TB were encountered in Hinduja Hospital's TB clinic. These patients had a drug susceptibility testing (DST) pattern that made them virtually untreatable, with resistance to all the 12 drugs that the mycobacterial lab was performing DST on.[6] The term "TDR," with its accompanying connotation of untreatable TB, stirred up an unprecedented

storm of attention in the lay and medical press, locally and internationally, but eventually served to put drug-resistant TB back on the radar, drawing much needed attention to the large numbers of Indian patients who were languishing from these extreme forms of resistant TB.

Reasons for the Spread of MDR-TB in India

At this stage it would not be out of place to reflect on how MDR-TB succeeded in establishing itself in India.

A failing public programme: The MDR situation in this country has been aggravated by what I would call "public policy paralysis."[7] The Revised National TB Control Programme (RNTCP) for several decades sat by, paralysed, failing to appreciate the scale and severity of the unfolding MDR-TB crisis. So seduced were they by the successes of DOTS in treating sensitive TB that they presumed this would prevent drug-resistant TB as well. There are limits to short-course chemotherapy, and even expertly supervised treatment will not help the patient with drug-resistant TB if he is given drugs to which he is resistant.[8] Yet for years this was precisely what happened: Patients who failed standard treatment and had a high probability of MDR-TB were given a sub-standard regimen of inferior drugs (Category 2) for eight months. Category 2 treatment adds a single new first-line drug, streptomycin, to the four standard drugs. It was a feeble, unscientific and to my mind unconscionable regimen to be giving patients who had failed standard treatment. It only served to further amplify resistance, resulting in what I would call "programmatic selection of MDR and XDR TB." India's large population of MDR-TB patients cannot be wished away, but sadly, that is just what the programme attempted to do over several decades. Indeed, as Engels eloquently argues, the DOTS strategy may have directly contributed to MDR-TB due to its continuing neglect of socio-cultural factors, the authoritative nature of direct supervision and the lack of cooperation with the private sector.[9]

An unregulated private sector: India has a huge and unregulated private health sector. 70% of hospitals are privately run and 76% of doctors engage in private practice. 50% of practicing doctors are of alternative faiths like homeopathy, Ayurveda and Unani, but would not hesitate to take on the initial management of these challenging cases, serving only to amplify resistance with poor prescriptions. A study we conducted in Dharavi, Asia's most densely populated slum in the heart of Mumbai, showed that only 3% of the doctors practicing there were able to provide a correct prescription for a patient with MDR-TB.[10] Without doubt, the poor prescribing practice of Indian private practitioners has fueled the MDR-TB crisis in this country.

Government-related factors: "[O]f all the ills that kill the poor, none is as lethal as bad government."[11] Many of India's health failings have arisen from policy failures, government callousness and bureaucratic myopia with MDR-TB being no exception. Failure of successive governments to grasp the scale and severity of India's MDR problem allowed it to escalate to its present desperate situation. Lack of funding and political will have all contributed.

Patient-related factors: TB in India is shrouded in secrecy, denial, ignorance and ultimately ostracism. "Doctor shopping" is a peculiar Indian trait with the average urban Indian TB patient visiting four doctors before even commencing therapy.[12] Yet as Upshur points out, "the tendency has been to blame the most vulnerable and powerless—the patients who were unable, for a multitude of reasons, to follow treatment through to completion."[13]

Social factors: The harsh truth that TB is a social disease is glaringly brought to light in a country like India that is plagued with seemingly insurmountable social and economic problems. The facts speak for themselves: A population in excess of 1.3 billion, 46% below the poverty line, childhood malnutrition rates of 47% and the highest infant mortality rates (46%) in the world. Despite this, successive Union budgets have allocated no more than 1% of GDP to health in the public sector over the years.

Comorbidities: Some comorbidities like malnutrition and HIV have long been known whilst others like smoking,[14] diabetes,[15] indoor[16] and outdoor[17] pollution have only recently been recognised. All thrive in India, making it the perfect incubator for the creation and spread of MDR-TB.

Indian MDR-TB is caught between the vortices of two competing, sub-optimal systems: An underfunded public programme offering standardised treatment to a small minority, and an unregulated private sector where mismanagement is rife. The unfortunate patient moves across providers and systems in a desperate effort to stay afloat. As Engels eloquently points out, there are different actors involved in TB care in India with each side blaming the others for the current, sorry impasse: "The different actors engaged with TB in India live in different social worlds. These range from the world of the laboratory, to the world of the patients and practitioners, from the world of the Indian NTP to the global health policy world. These worlds have their own focus on what TB is and how it should be controlled… actors in these different worlds often do not really coordinate or cooperate with each other."[18]

Problems in Diagnosis

Too few laboratories: MDR, XDR and TDR-TB remain essentially laboratory-based diagnoses. Despite its population of 1.3 billion, India has only 45 laboratories capable of performing DST. This works out to an abysmally low ratio of 0.2 labs per million population. China in contrast, with its comparable population, has 249 DST capable laboratories.[19] Without more labs capable of performing quality-assured DST, the extent of India's MDR problem will remain submerged from view.

Reliance on inappropriate tests: Large amounts of money are wasted on inappropriate and misleading diagnostics like serological tests.[20] It is estimated that around 1.5 million TB serological tests are performed annually in India at an estimated cost of $15 million a year. Treatment in the private sector is often started or withheld inappropriately based on these tests, with potentially disastrous consequences for the patient. The recent decision by the Indian

government to pass a directive banning these tests was hailed as a step in the right decision but it remains to be seen if they have a strategy in place to rigorously enforce and implement this.

IN 2011, 60 MILLION INDIANS WERE FORCED INTO POVERTY BECAUSE THEY COULD NOT MEET THEIR HEALTHCARE COSTS.

Slow to embrace new technologies: Newer tests like the Xpert MTB/RIF (GeneXpert) need to be rolled out across the country. This test, which diagnoses rifampicin resistance with near 98% accuracy, is likely to have a huge impact if implemented throughout the country. Instead of scaling up this new technology, there are just 54 RNTCP sites across the country offering this test as of 2013. China in contrast has 160 and South Africa, which has embraced this new technology with great enthusiasm, has 207 GeneXpert sites. Evidence to date indicates that implementation of this test could treble the number of Indian patients diagnosed to have MDR-TB, but this will amount to nothing unless systems are in place to treat these additional patients.[21]

Optimal Treatment of MDR-TB in the Indian Context

While DOTS is one of the most cost-effective innovations for treating the patient with sensitive TB, the same cannot be said of MDR-TB. The Indian MDR patient has the option of taking treatment in the private or the public sectors.

Treating MDR-TB in the private sector: The poor knowledge, lack of training and dismal prescribing practice of the average private practitioner has already been alluded to. At the Hinduja Hospital, we have been treating large cohorts of MDR and XDR-TB patients over the last decade on an ambulatory basis, with respectable success rates of 64%.[22] However, there are very few such private centres of excellence with the skill, dedication and determination to shoulder the care of these challenging patients. In our hands, the average cost of treatment for a single MDR case is $3,600. This figure, while less than the costs encountered in treating MDR-TB in most other parts of the world, is still far beyond the reach of the average Indian with an average annual GDP of $900. A recent Union survey from across 30 regions in India, which looked at the demographics of 4,562 Indian TB patients, noted that only 5% had a household income greater than INR 10,000 ($200) a month.[23] A recent report noted that in 2011, 60 million Indians were forced into poverty because they could not meet their healthcare costs.[24] Sadly, most patients with MDR-TB lack the financial capacity needed to fight this disease over the two years of treatment. The majority run out of funds and even intelligent and committed patients are compelled to interrupt treatment, pause whilst they recoup finances and then restart again. These frequent interruptions are one of the factors behind the relentless amplification of drug resistance encountered in India.

Treating MDR-TB in the public programme: Programmatic management of drug-resistant TB is the phrase preferred to DOTS-Plus for treating MDR-TB within the confines of the programme. All patients receive a standardised six-drug regimen called Category 4 for a period of 24 months.[25] There is a real worry in the mind of experts that just as the earlier effete Category 2 was proven to be worthless and eventually scrapped, the new Category 4, by attempting the

Procrustean crime of giving a standard set of drugs to all MDR-TB patients irrespective of their resistance pattern, may end up further amplifying resistance. At least 60% of MDR patients in Mumbai are fluoroquinolone resistant; giving an older fluoroquinolone-like levofloxacin as a pivotal Category 4 drug may not be ideal practice.[26] As Helen Bynum reminds us in her book *Spitting Blood*: "MDR-TB poignantly illustrates an elementary principle in disease control: only very rarely does a one-size program fit all."[27]

As of 2013, only around 20,000 cases have been initiated on MDR-TB treatment across the country. This is a start, but it only represents a small drop in the sea of MDR-TB in the country. Currently, it is estimated that only a small minority of India's huge MDR-TB population is receiving appropriate treatment. The sum of MDR-TB cases lost to follow-up or not evaluated exceeded 40% in India in 2012.[28] The programme needs to recognise the urgency of getting more patients on appropriate treatment at the earliest. It goes without saying that it makes clinical, economic, epidemiological and moral sense to treat these patients now rather than allow the situation to spiral. As Paul Farmer cogently says, "It is failure to treat not treatment failure that is responsible for the vast majority of MDR-TB deaths."[29]

Ten Suggestions for the Future

1. Urgently build laboratory capacity so more cases can be identified, treatment commenced and transmission reduced. It remains one of those sad TB paradoxes that despite India bearing the lion's share of the world's TB burden, it has only one of the 26 supranational reference labs while the EU and US have 14 between them, despite only 1% of the nine million new TB cases occurring in these regions in 2007.[30]

2. Offer DST early to all patients who are failing DOTS instead of subjecting them to Category 2 treatment.

3. Conduct a nationwide survey to accurately determine the extent of India's MDR problem. Ensure that such a survey picks not just the data from the well-functioning districts but also takes into account the alarming numbers of MDR patients encountered in India's mega cities with populations more than 10 million, as these are the epicentres of MDR-TB in this country.

4. Scale up the number of GeneXpert machines across the country and consider using this test upfront as a replacement for sputum smear testing. This would need an infusion of additional funds. Even at the preferential Foundation for Innovative New Diagnostics rate of $20 per disposable cartridge, providing

> AS OF 2013, ONLY ABOUT 20,000 CASES HAVE BEEN PUT ON MDR-TB TREATMENT: THIS IS BUT A DROP IN THE SEA.

this test to just 15% of the TB suspects in the country would consume the entire annual RNTCP budget ($65 million).[31]

5. Move DOTS-Plus beyond the pilot stage to more widespread implementation. Factor in local resistance patterns and DST if known, so these patients are on appropriate individualised second-line drugs. There is no one "standardised" set of drugs that will work on all patients. India's huge MDR populated has waited too long for this basic injustice to be redressed.

6. Make private-public mix (PPM), too long a convenient WHO catchword, a reality. The deeply dysfunctional relationship between the private and the public sectors is one of the major hurdles to integrated TB control in India. Innovative market-based PPMs have been successful in neighboring Pakistan and need local application.[32]

7. Introduce new drugs for the Indian patient who is therapeutically destitute. After a wait of half a century, two new drugs, bedaqualine and delamanid, are finally available in the West. They have been used as salvage therapy in highly drug-resistant Indian patients and have been show to save lives.[33] Despite this, the Indian government has not yet determined how to introduce these novel agents into the chaotic Indian market and what safeguards need to be taken to prevent their abuse. As Farmer says, "the fact that big Pharma focuses on the most lucrative products rather than the most needed is particularly damning for the global poor, whose diseases will never be profitable enough to attract industry but which none the less verge on biblical in scope and horror."[34]

8. Provide additional funding. About 500 drug-sensitive patients can be treated for what it costs to treat a single MDR case. Thus, treating these large numbers of patients will involve additional funds. Scale-up should not divert funds from more cost-effective interventions like quality sputum microscopy and DOTS. Additional funds for diagnosis, manpower and second-line drugs will need to be allocated. Whilst the solution is undoubtedly expensive, the costs will only multiply the longer we procrastinate.

9. Improve infection control facilities in our crowded hospitals and clinics. At present they are almost non-existent and innumerable doctors and nurse have contracted highly-resistant TB from their patients, with several sadly even succumbing to it.[35]

10. Finally, pass legislation to ensure that only designated specialists prescribe and treat MDR-TB in the private sector. This is the only way to ensure that inappropriate prescriptions do not hasten the slide into the hopeless inferno of extreme drug resistance in India. ■

5 India as TB's Innovation Hub

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In spite of far-reaching policy interventions and a national programme that achieved full geographical coverage nearly a year ago, tuberculosis (TB) continues to be one of India's biggest public health challenges. While we continue to evolve newer strategies to ensure more effective TB prevention and control, at the level of care delivery and adherence to treatment regimes, it is important to recognise the need for innovation in TB diagnostics and treatment. Immunisation against TB uses a vaccine that belongs to the last century. With the world taking many strides forward on preventive and treatment interventions for a multitude of diseases, it is time that similar innovations for TB prevention and control are ideated on a priority basis.

TB in India

The scale of the problem TB poses to India is understood by the numbers themselves. With over one-fourth of all new infections worldwide and two deaths occurring every three minutes from TB,[2] the disease poses an alarming threat to India's public health. These numbers persist in spite of the government's Revised National TB Control Programme (RNTCP), which was launched in 1997 and achieved full geographical coverage in 2006.[3] They persist in spite of far-reaching policy interventions in India's TB landscape, namely a nationwide ban on blood

serology tests for TB diagnosis in 2012 and the declaration of TB as a notified disease in the same year.

> *"One of the historic ironies of tuberculosis research is that it has always been assumed that the current interventions would eliminate this disease as a major public health problem. BCG, an attenuated bovine tuberculosis strain, was discovered in 1908, and was thought to be the vaccine for tuberculosis. Streptomycin in the 1940s was hailed as the wonder drug for tuberculosis. Yet even with better antibiotics, tuberculosis remains a major global health problem. Concomitant with these historically shortsighted miscalculations were reductions in support for research on new tools and strategies, based on the assumption that with existing interventions the disease would disappear. It has not."*
>
> - Barry Bloom, MD, Harvard University Distinguished Service Professor[1]

The high incidence of this airborne, infectious disease in India is fuelled by diverse factors, such as undernutrition, lack of awareness and low risk perception. The problem is compounded by the increasing incidence of drug-resistant TB strains, which occur in the first place due to incorrect diagnosis, improper prescriptions and lack of treatment adherence. The regular strain of TB is treated by the RNTCP using the Directly Observed Treatment, Short-course (DOTS) strategy, which involves medication administered to the patient over a minimum duration of six months. Drug-resistant TB strains such as multidrug-resistant TB (MDR-TB) require a minimum duration of 18-24 months to treat, which involves exponentially expensive medication with a lower rate of survival. Untreated MDR-TB patients become carriers of the disease, further complicating an already complex public health challenge.

While the campaign against TB in India has grown considerably in recent years, expanding the reach of critical interventions to a large section of the population, it has been lacking in terms of innovation. There is a clear need to revolutionise TB care in India, not only at the level of delivery of existing interventions and services, but also in terms of research, development and introduction of new anti-TB drugs and diagnostics.

India's Medical Innovation Potential

India has risen to worldwide recognition as a hub of path-breaking, cost-effective innovation. Our space programme is the flag-bearer of Indian innovation throughout the world, most recently sending a spacecraft to Mars on a budget equivalent to a Hollywood science fiction movie. This strength of competitively-priced, cutting-edge technology is by no means restricted to the space programme. India's successes in areas such as information technology and mobile telephony are well documented. The country has also made large contributions in the area of generic drugs and vaccines, being the largest producer of both of these commodities in the world. We do not, therefore,

lack either the resources or the technical expertise to successfully overcome an infectious disease such as TB.

India has the dual advantage of a strong, growing economy and a large talent pool. This provides great potential for India to contribute to what is called as the 'more (value) for less (cost) for more (people)' or MLM innovation, especially in the area of healthcare technologies and delivery innovations.

Possessing the advantages that we do, we have an ideal opportunity to encourage new ways of looking at TB-causing microbes, utilising the talent we have to develop all-new vaccines and diagnostics that can revolutionise the way we diagnose and treat TB. As the bearer of the world's largest TB burden, it falls on India to participate most actively in research and development. A more supportive environment to conduct trials in India will also be extremely helpful in expediting the development of newer, more effective methods to combat the disease.

Tuberculosis in India – Focus Areas for Innovation

As mentioned before, the RNTCP provides free treatment to notified TB patients through the DOTS strategy, using four first-line drugs over a six month regime. Even though the programme has successfully cured over 85% of the cases detected by it,[4] it is clear that much more needs to be done. The RNTCP has provided the infrastructure through which the latest innovations in TB prevention and control, once developed, can be dispensed to all patients.

In order to successfully implement its vision of providing universal access to quality diagnosis and treatment for all TB suspects in India, the RNTCP has developed an innovative strategy termed the National Strategic Plan (NSP) (2012-2017). The NSP outlines the framework through which the RNTCP can take India closer to the long-term goal of TB eradication over a period of five years. The NSP also takes cognizance of the importance of innovations in the Indian TB control landscape. Some areas for innovation include:

Operations research: This aspect of the NSP focuses on specific, targeted research to evaluate the efficacy of prevalent diagnostic and treatment strategies, and to evaluate the steps necessary for their improvement. This includes the development of diagnostic tests that are faster, more accurate and simultaneously capable of detecting drug resistance. It also includes targeted research to determine the comparative efficacy of daily and intermittent treatment regimes.

Innovative financing: Here, the NSP talks about the need to provide financial assistance to patients and suspects in the form of insurance, pre-paid treatment and diagnostic schemes and other market-based initiatives. It also talks about the need to engage with public-private interface agencies in a results-oriented system of reimbursement.

Information and communication technology: The RNTCP took a step forward in modernising its adherence monitoring and case notification procedure by

launching the portal Nikshay in 2012. Further steps to expand the reach of Nikshay can include the development of more user-friendly interfaces through mobile applications, and the encouragement of doctors across the private sector to notify detected cases of TB.

Innovations under Development

An all-round strategy of innovative interventions for TB prevention and control will be incomplete without the development of newer, more effective drugs and vaccines as well as faster, more accurate diagnostic tests. The following is an outline of the anti-TB vaccine landscape in India at present:

TB vaccines: As of today, there is one vaccine, Bacille Calmette-Guérin (BCG), being used to prevent TB in infants. But while BCG is the most widely used vaccine in the world, it has not successfully eliminated the disease due to its limited efficacy. There is also the fact that BCG is a vaccine developed in the early years of the previous century, and given the pace at which our public health challenges continue to evolve, it is high time that a new vaccine is developed. Research and development for new vaccines would have the biggest impact on the TB epidemic, and remains the cornerstone to reaching global elimination within the coming decades.[5]

Vaccines being developed in India[6]: In India, researchers and academics in collaboration with industries are at work on new TB vaccines, and one hopes to hear of encouraging developments before very long. Two new vaccines that are past their preliminary phases of testing have been enumerated below:

Vaccine	Vaccine Type		Developers	Status
M. indicus pranii	Immunotherapeutic	Whole-cell M. indicus pranii	Department of Biotechnology (Government of India), Cadila Pharmaceuticals	Phase III
VPM1002	Prime	Live recombinant rBCG	Vakzine Projekt Management GmbH, Max Planck Institute for Infection Biology, TuBerculosis Vaccine Initiative (TBVI), Serum Institute of India	Phase IIa

Diagnostics: Currently, smear microscopy and mycobacterial culture are the most widely used diagnostic tests, but microscopy, though relatively fast, is inaccurate—missing over half of cases.[7] While culture is accurate, it is slow, taking from two to eight weeks to produce a definitive result. These tests are simply not accurate and rapid enough for proper diagnosis of TB, particularly in people living with HIV and in children. These diagnostics tests present the risk of causing critical delays in providing timely treatment to TB patients. Early diagnosis of TB is essential to reducing transmission and mortality, which

necessitates the development of diagnostic tools that provide accurate results in a fraction of the current prevalent times taken. We must ensure that newer and more efficacious tests are made affordable and accessible to all suspects and patients, especially those who access the private sector for primary care.[8]

New diagnostic technologies: Several new technologies are available and more are being developed for faster and more accurate TB diagnosis. Many of these are World Health Organization-approved tests and are being used by the government. A test such as Xpert MTB/RIF, for example, is currently being offered by the RNTCP in 18 selected public sector facilities free of charge to all patients accessing these facilities. It is an automated TB detection test that reduces the time of diagnosis from several weeks to just two hours. It can also detect TB in patients co-infected with HIV and detects the presence of MDR-TB. The scaling-up of this test has already been successful in countries like Brazil and South Africa, and has shown to increase the number of TB cases diagnosed and treated. Similarly, another test called the GenoType MTBDRplus version 2 can also diagnose MDR-TB directly from smear-positive sputum samples, providing results in just five hours.[9] This test is also endorsed by the World Health Organizaion and widely used in many high MDR-TB prevalence countries.

However, these tests, developed abroad, remain largely inaccessible to private sector patients because of their high costs both to laboratories and patients. The introduction of innovations for TB prevention and control can only be successful if they are offered at prices affordable not only to patients, but also to private sector diagnostics and treatment providers as well. Again, this points towards the need for indigenous research and development.

Once developed, these indigenous solutions can be demonstrated, adopted and scaled up by the private and public sectors, private organisations, civil society, as well as other donors, all of whom must work together to ensure that these interventions reach and ultimately benefit the end users who need these innovations the most. ■

Stories from the Ground 6

BIJOYETA DAS
Freelance journalist

The tuberculosis epidemic in Mumbai has a number of similarities to the HIV/AIDS epidemic during the 1990s in New York City. There is a lot to learn from the response by the US government in tackling the menace: India could do well to adopt some of the measures.

Mumbai and New York City have endured the same growing pains of swelling populations, harried and crowded lanes, mushrooming high-rises and they are often the destination of migrants.

The two cities have something else in common—invasive diseases. The story of today's tuberculosis (TB) epidemic in Mumbai is uncannily similar to NYC's duel with HIV/AIDS in the 1990s.

The first case of HIV in NYC was reported in 1981. By mid-1990s, at its peak, NYC's HIV/AIDS case rate was more than three times the national average.[1] Fast-forward to today in India, where two people die of TB every three minutes. And it is believed that the prevalence and incidence of drug-resistant TB is higher in Mumbai than in any other part of the country.

HIV epidemic rankled NYC's aplomb. But the city fought back, firmly. Can India emulate NYC's approach as inspiration for its own battle against TB in Mumbai?

TB in India

Six decades of independence and progressive planning may have laid the foundation of a robust economy in India and a mammoth population. But statistics about human resources scream "not enough."

In 1947, the at-birth rate of an Indian was 37 years; it had doubled to 65 by 2011. Infant mortality rates have halved from 146 per 1,000 to 70. Maternal mortality rate was 677 per 100,000 in 1980, which in 2008 reduced to 254.[2]

TB IS NO LONGER A DISEASE AFFLICTING ONLY THE POOR OR EASILY CURABLE.

Despite such galloping strides, these numbers continue to be the highest in the world. India stands abashed at a dismal rank of 135 in UNDP's Human Development Index.

India also holds the dubious tag of having the highest incidence of TB in the world, which remains one of the world's deadliest communicable diseases. In 2013, an estimated nine million people developed TB and 1.5 million died from the disease, 360,000 of whom were HIV-positive.[3] India accounts for a fourth of the global burden of TB and 29% of global mortality due to TB. Two people die of TB every three minutes in India.[4] As many as 3.3 million people are suffering from any one type of TB, and 350,000 lives are lost due to TB every year. Although the number of cases and the incidence have decreased in the last few years, the disease continues to threaten the health and wellbeing of millions of people in India. It is no longer a disease afflicting only the poor. It is no longer a disease that is easily curable with treatment. Emergence of multidrug-resistant TB (MDR-TB) and the newly-detected extensively drug-resistant TB (XDR-TB) poses alarming prospects with devastating consequences. Drug resistance is a man-made problem and a sign of system failure—and India accounts for the greatest number of MDR-TB cases in the world.[5]

Drug resistance arises due to improper use of anti-TB drugs in patients with drug-susceptible TB. This improper use happens because of a number of reasons. Some notable ones are use of improper treatment regimens and failure to ensure that patients complete the whole course of treatment. Essentially, drug resistance arises in areas with weak TB control programmes. What is most important to realise is the fact that a patient who develops active disease with a drug-resistant TB strain can transmit this form of TB to other individuals.

While the government provides free treatment for all TB patients, many still favour the private sector—public health services are apathetic, and facilities unwelcoming. Cramped, grimy conditions, serpentine queues and the lackadaisical attitude of staff further alienate the patient. Government clinics are therefore seldom a first choice. But treatment in the private sector often involves antibiotics being recklessly prescribed, which are in turn erratically swallowed. This bolsters drug resistance. India's private sector currently provides 70 to

80% of outpatient consultations. Mumbai has 50 large private hospitals, 2,000 nursing homes and 8,000 to 10,000 individual private practitioners.

What is more, TB ignites shame and silence. The stigma associated with TB in India drives many to seek the secluded chambers of private practitioners. But this sector is unregulated. Doctors tinker with prescriptions, often suggesting random cocktails of pills.

Moreover, drug-resistant patients who do not respond to standard first-line drugs are referred to private practitioners who are not adept in spotting resistance and instituting compatible treatment.

The Problematic Case of TB in Mumbai

Mumbai, the most populous Indian city, has a disproportionately high prevalence of TB. This megacity is the financial capital, luring migrants from various parts of the state of Maharashtra and elsewhere in the country.

Mushrooming slums epitomise reckless urbanisation. It is home to the largest slum in the world and has a staggering population density of 50,000 people per square kilometre. At the same time, scarcity is written large on the walls: Inadequate water, people jostling for space, waste mismanagement, insufficient toilets, and a soaring indoor and outdoor population.

Mumbai is plagued with the ills so common to any metropolis of the Global South—poverty, overcrowding, malnutrition and a doddering healthcare system—choking the city and abetting the effortless spread of TB.

Mumbai has approximately 12% of Maharashtra's population but accounts for nearly 22% of notified cases of TB and half of drug-resistant TB cases in the state.[6] There is insufficient data, but it is believed that there is a very high rate of drug-resistant TB. A 2012 report from a private hospital about the extent of totally drug-resistant TB alarmed the country and brought to light the magnitude of the TB epidemic in Mumbai and the need for an aggressive public health response.[7]

The risk of developing TB is estimated to be between 26 and 31 times greater in people living with HIV than among those without HIV infection.[8] Mumbai has a relatively high prevalence of HIV/AIDS in India, in certain pockets and few groups. The prevalence appears to be low among the general population but disproportionately high among high-risk groups, such as injecting drug users (14.17%), female sex workers (6.89%), men who have sex with men (9.91%) and STD clinic attendees (11.62%).[9] The city has in the past decade shown an impressive reduction in HIV prevalence. However, it continues to be one of the high-risk areas in the country because of the migration pattern.

These are important factors to be considered and appropriately taken into account in eradication strategies.

HIV Epidemic in NYC

The first cases of HIV in NYC were reported in 1981. It quickly began to ruthlessly affect many, regardless of gender, race or ethnicity. AIDS incidence and mortality peaked in the mid-1990s in the city, and has declined significantly since then. At its peak, the NYC AIDS case rate was more than three times the country average and 40 times the healthy people target set to be achieved by 2010.[10] New York was thrust into infamy as the epicentre of the HIV/AIDS epidemic in the United States.

HIV/AIDS make a person more susceptible to TB: Many with HIV/AIDS ultimately succumb to an infection and TB is a big killer in patients with HIV/AIDS. NYC accordingly witnessed the resurgence of TB in the city. With 3% of the US population, it accounted for 15% of TB cases and 17% of AIDS deaths. The incidence of TB increased from 23 to 50 out of 100,000, with significantly and disproportionately higher incidence in poor areas and low income populations.[11] Inadequate and non-compliance of treatment regimes, homelessness, a diminished public health apparatus in the form of decreased vigilance and the emergence of the HIV/AIDS epidemic were the underlying causes behind the surge and high incidence of TB in NYC. The situation was further complicated by a steadily increasing incidence of drug-resistant forms of the disease. The proportion of cases resistant to at least one drug rose from 19% in 1987 to 28% in 1991, and the multidrug-resistant forms (resistance to the two drugs used in the first-line standard anti-TB regimen) rose from 6% to 14%.[12]

Resonance

Parallels can be drawn between Mumbai's current tussle with TB and the grim spread of HIV in NYC in the 1990s.

The public health authorities of both cities were caught unprepared. It was mistakenly believed that the problems were restricted to a few high-risk groups and in low income populations: NYC's epidemic was initially believed to be a problem restricted only to high-risk groups; Mumbai's epidemic was believed to be only an affliction of the poor.

In both situations the alarm bells started ringing only when it was realised that the epidemic was slowly and steadily spreading into the general population and was not actually restricted to the so-called 'high-risk' groups. Death in NYC's HIV/AIDS epidemic unsettled the US; emergence of drug-resistant TB in Mumbai poses a similar nightmarish scenario for India.

Can Mumbai Emulate NYC?

Feverish urbanisation has bogged down India with homelessness, unemployment and overcrowding. This heightens the vulnerability of the poor migrants.

The large immigrant population living in densely populated areas of Mumbai have added to the quick rise in TB cases. Stigma against the disease has prevented the reporting of what is expected to be a high number of cases.

MUMBAI HAS ABOUT 12% OF MAHARASHTRA'S POPULATION BUT HALF OF THE STATE'S DRUG-RESISTANT TB CASES.

NYC's response to the high rates of TB accentuated by the HIV/AIDS epidemic induced strong collaboration between government and civil society—a valuable lesson for Mumbai.

In 1989, the Centers for Disease Control and Prevention (CDC) announced the goal of eliminating TB from the United States by the year 2010. Initial treatment regimens were broadened, and screening, diagnosis and treatment were provided free of charge. CDC issued guidelines for hospitals to reduce nosocomial spread. Infectious patients were isolated and non-adherent patients were detained to decrease the development and spread of MDR-TB. Individuals infected with TB were tested for drug-resistant strains and treated accordingly.[13] From a peak of over 3,800 cases in 1992, the caseload fell to 1,730 cases in 1997. Rates in children fell substantially, so that in 1997 there were only 56 cases of MDR-TB from a peak of 441 cases in 1992.[14]

Sporadic, inadequate and irregular treatment in the 1970s and 80s led to the development of strains which were resistant to the first-line drugs: TB resistant to two or more of these drugs—usually isoniazid and rifampin—is classified as MDR-TB. By 1989, completion rates of treatment were just 60%, and in some areas, 11%. The different forms of TB spread like wildfire in densely populated areas and hospitals were unprepared. XDR-TB strains also developed. XDR-TB is a rare type of MDR-TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). The situation in Mumbai is similar to the conditions of NYC described above few decades ago.

Lessons to be Learnt

- Inadequate surveillance methods lead to setbacks in detection and delays in response.
- After the New York TB outbreak, new research focused on identifying occurrence of the drug-resistant strains, whether the disease is home-grown or not, whether resistance is primary or acquired, and how much nosocomial spread is occurring.
- Most importantly, adherence to treatment was given paramount importance to stop the emergence of drug-resistant forms. Promotion of the Directly Observed Treatment, Short-course therapy has proved to be the most cost-effective method to control TB and eventually eradicate it.[15] It is also important to identify and treat close contacts that may have become infected from persons with active TB disease.
- Mumbai needs to respond vigorously and effectively to the TB epidemic in the city. It has been proven that TB can be prevented; the need is for political

will and to figure out how much money to spend where in which right way. Improving access, screening and diagnosis of TB, and paying special attention to co-infection TB in those with HIV/AIDS are key to winning the battle against TB in India and in Mumbai. Another critical factor is to rope in all stakeholders, to bolster ties among them to ensure speedy and consistent availability of efficient services for all who need them.

Mumbai's Efforts toward TB Control and Eradication

Clearly, several changes have been introduced in Mumbai to deal with and eventually eradicate TB, which relate to better diagnosing TB, detecting drug-resistant TB, bringing together different sources of healthcare in the city, and implementing an effective strategy to eliminate the suboptimal prescribing practices in the city.

Mumbai, like NYC, is resilient—instead of bowing down, it is plodding its way forward. One zealous effort has been the launch of the Mumbai Mission for TB Control by the Municipal Corporation of Greater Mumbai. Its agenda is clear—to hone in on the problems and to steadfastly weed them out. This objective is epitomised in the campaign *'TB Harega, Desh Jeetega'* (TB will lose, India will win), and is a fine example of increased and sustained interest and effort by stakeholder groups.

This laudable initiative from the Municipal Corporation of Greater Mumbai has improved access, revamped screening and diagnosis of TB, including that of drug-resistant strains. Case detection and treatment has shown steady increase in the last few years.

Mumbai needs to be cheered for launching a special programme to tackle the rising incidence of drug-resistant TB, but this can only be the preface. A more aggressive attack is necessary. An energetic partnership among all sectors, particularly a shared vision, will make the private sector an ally.

A fortified, relentless effort toward better infection control will be paramount in shaking off the grip of TB in the country and Mumbai. ■

The Great Gap

7

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Civil society action can help draw attention to a disease and a public health problem. With its socio-economic implications, tuberculosis (TB) is a disease that requires the successful engagement of all levels of stakeholders in the community. However, civil society urgency in regard to TB seems to be missing. This is a great gap in India's response to TB and leaves the community more vulnerable to the disease.

India has the world's largest burden of TB, with 2.3 million new infections every year out of 8.6 million worldwide.[1] This infectious disease leaves a devastating socio-economic impact, with direct and indirect losses in India amounting to $23.7 billion every year.[2]

India has taken serious note of the public health challenge posed by TB, rolling out the Revised National TB Control Programme (RNTCP) in 1997, which expanded to cover the entire country by 2006.[3] The RNTCP offers free treatment to TB patients through the Directly Observed Treatment, Short-course (DOTS) regime.

A treatable, curable disease, TB can successfully be cured by timely diagnosis of the patient and adherence to the prescribed course of treatment. However, the fact that the disease persists with high incidence in India, in spite of a

comprehensive framework in place to address it, points towards gaps that need urgent redressal.

As a disease which disproportionately affects the poor, renders patients vulnerable to social stigma and which flourishes on account of low risk perception, lack of awareness and inadequate preventive measures, TB poses a social challenge that requires the active participation of stakeholders from outside the existing government programme. Civil society constitutes a significant section of organisations with the human resources and the reach to be able to play a transformative role in the Indian TB landscape. A strong motivation to respond better to urgent health and humanitarian needs posed by infectious diseases such as TB has engendered a debate on how to formalise the significant, at times vital, contribution of civil society organisations in global health governance.

There are significant advantages that may potentially result from the greater engagement of civil society with the RNTCP. Civil society organisations (CSOs) exercise a bidirectional influence on the general public's beliefs, behaviour, as well as on government policies, community structures and government institutions. CSOs that work for on-the-ground implementation of welfare schemes, including health, are armed with the knowledge and understanding of local circumstances to be able to adapt and implement TB care services more effectively.

In the context of TB, CSOs could also play a significant role in resource mobilisation through their influence in the policy environment. They can play a valuable role in implementation support through personnel as well as knowledge of on-the-ground circumstances. As change agents and opinion leaders, CSOs can support advocacy and communication activities to increase awareness about TB, mobilise the community to collectively work against the disease and extend physical and moral support to those suffering from it.

One of the key challenges persisting in the Indian TB landscape, in spite of the RNTCP's scale of operation, is the difficulty faced by those with TB symptoms and patients in accessing diagnosis and treatment due to geographical limitations in difficult-to-reach, remote areas and conflict zones. Many CSOs function in these challenging circumstances, and their engagement offers a unique opportunity for increased early TB case detection and treatment adherence through the generation of demand for services and scaling-up of community-based care.

While the potential benefits of increased CSO engagement in the Indian TB landscape are significant, the response by civil society to public health issues in general and TB in particular is muted and generally non-impactful, if at all it exists. The dialogue on greater civil society inclusion remains on paper. A recent example is the consultations around the Global Fund proposal development—there were hardly any inclusive and representative consultations with the affected communities or the people working close to them. Moreover, the few consultations that did emerge with civil society were more as an initiative from civil society partners working on TB rather than as an invitation from the government.

There is also no collective sense of ownership among civil society representatives apart from the grassroot-level NGOs, who truly know the difficulties faced by

THE CORPORATE SECTOR, MEDIA, THE FILM FRATERNITY, CENTRES OF POLICY AND THINK TANKS HOLD THE POTENTIAL TO CREATE A PLATFORM FOR ISSUES OF TB CONTROL TO COME TO THE FORE.

the patients as well as the realities of the impact of TB on patients' families and communities. Unfortunately, the power to inform and change policy does not lie with grassroot-level NGOs and community structures. NGOs at the grassroots level are required to work closely with the national programme. They hesitate to inform and raise issues experienced at the level of implementation, as they feel the need to co-exist peacefully and are willing to accept status quo. They depend on the support of the local government to allow them to work in the community, and are unwilling to take risks that may impede them in being able to do so.

Since civil society is constituted by a diverse range of individuals and institutions, with influence across different levels of the policy and implementation landscape, we need voices from other non-state actors in order to strengthen civil society dialogue around TB. We need the active support of sections of the community who wield influence and have the power to change opinion. The corporate sector, media, the film fraternity, centres of policy and think tanks hold the potential to prepare the ground and create a platform for issues related to TB control to come to the fore. These groups of civil society members have the authority and expertise as well as the confidence to initiate a dialogue with the national programme.

Another important challenge in the management of TB in India arises from the lack of patient-centric evolution of policies to address the real-world concerns that result in delayed diagnosis and lack of treatment adherence. Patient advocacy is limited and there is no platform for engagement. The recent attempts to create and sustain TB patient forums under Project Axshya of the Global Fund could be the first steps towards creating these platforms. However, these forums need to be nurtured, mentored and championed in order to create a meaningful impact.

Another challenge is the general impression that prevails of there being no patient activism being generated because of the nature of the disease. Popular belief has it that most TB patients are cured after a relatively short course of treatment unlike the HIV community that lives with the disease. However, several factors such as the emergence of drug-resistant strains of TB, the link to poverty and loss of livelihood, which have devastating effects on patients and their families, need to be recognised and brought on board while considering the impact of TB on communities.

There is therefore a need to activate and energise civil society to call on the government to act to stop TB deaths and reach India's missing million.[4]

The prevalence of TB is a threat to the entire community, and brings with it significant economic losses and suffering. The inclusion of all civil society groups in TB control initiatives through an urgent call to action is needed, so as to take ownership of the problem by understanding the issues confronting TB control and its impact on fellow citizens who are affected.

The role of CSOs can be broadly divided into three categories: Firstly, as members of monitoring committees; secondly, as resource groups for capacity building and facilitation; and thirdly, as agencies helping to carry out independent collection of information.[5]

The global experience of CSO engagement for TB control has seen the establishment of initiatives such as the Global Fund and the Stop TB Partnership. The six-point Stop TB Strategy, developed by the World Health Organization in 2006, seeks to builds on the successes of the DOTS regime while also explicitly addressing the key challenges facing TB.[6] On the other hand, the Global Fund to Fight AIDS, TB and Malaria is an international financing organisation that aims to attract and disburse additional resources to prevent and treat HIV and AIDS, tuberculosis and malaria globally.[7] The Global Fund also mentions the role of CSOs as "instrumental"[8] in the furtherance of its initiatives.

As discussed earlier, however, CSO engagement with TB in India has met with very limited success, characterised by a low level of engagement and participation. It was to address this shortcoming that Project Axshya (meaning 'free of TB') was launched in April 2010 as the civil society component of a five-year project funded by the Global Fund.[9] Led by the Union and World Vision India, this project works in 374 districts across 23 Indian states.

There are also other avenues of support that can be drawn upon to augment the implementation of the programme. Leading organisations in the corporate sector can be engaged with to provide support and suggest solutions as part of their corporate social responsibility mandate.

In addition to resource mobilisation, there is a need for greater awareness around TB and the measures necessary for its prevention and control. While there is increasing attention around TB in the media, it is necessary to build its support for TB advocacy. A call to the media to focus on public health and social issues and to showcase nuanced personal testimonials from the community and patients is necessary to raise the profile of TB and sensitise the general public about the disease.

THE RNTCP'S VISION FOR CSO ENGAGEMENT SADLY REMAINS ONLY ON PAPER.

It is a well-established fact that the association of opinion leaders, celebrities from films and sports fraternities plays a critical role in building public support towards issues of social relevance. Reaching out to their legions of supporters, celebrity champions can take the cause of fighting TB and preventing TB deaths to a larger and wider audience.

In addition to the multiple avenues of support, there is a need to constantly evaluate the evolving TB challenge in India, and to develop newer strategies to tackle it. Public health professionals and think tanks must find ways and means to engage the community, support and strengthen community systems to

provide grassroot-level feedback on services and devise a framework to take these issues to the district, state and national levels.

The RNTCP should also critically review its record of engagement with civil society partners for impact and effectiveness. Several "schemes for civil society engagement" have been formulated, revised and reviewed, but have been implemented poorly. The problem is compounded by the fact that the revised set of schemes in the National Strategic Plan for TB control has not been rolled out. The commitment of the programme to civil society engagement exists in policy, as already mentioned, but is not reflected in the budget allocation for private sector and NGO participation, nor are there any attempts to facilitate and simplify the framework for engaging all sectors towards TB control efforts. A strategic framework for engagement needs to be implemented and accelerated.

And finally, but most importantly, we must remember that the end beneficiary of all our strategies, the patient, is the one whose welfare and convenience must be at the core of our efforts. All stakeholders in the Indian TB control scenario need to come together to provide an enabling and inclusive environment to protect patients and strengthen them to be able to voice their concerns and fight for their rights. An inclusive, well-implemented strategy that addresses both the social and the epidemiological aspects of the TB challenge is our best hope towards successfully overcoming the disease in India, and by extension, around the world. ■

8 TB in My Backyard

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India continues to battle infectious diseases like tuberculosis (TB), in spite of a public health system that has grown significantly in recent times and delivered historic successes. The country bears the world's largest burden of TB, losing 300,000 people to the disease every year. In spite of complete geographical coverage achieved by the government's TB control programme, there continue to be gaps that need urgent redressal. In districts like Bolangir in Odisha, where an overwhelming majority of the population lives in remote rural areas, treatment success rates continue to be lower than the national average. Such a situation calls for innovative, efficacious interventions to ensure that the diagnostic and treatment needs of every single TB suspect and patient are met.

India's public health sector has seen significant development in the last few years. As a country, we have been making steady strides forwards on the road to greater, more inclusive development. As we strive to deliver on key governance parameters, public health is a top priority.

India has a history of comprehensive, far-reaching health policies. The effective execution of many of these policies has resulted in historic successes at the level of implementation as well, helping India reach significant public health milestones such as the eradication of smallpox and polio.

TB in India Today

TB'S BURDEN ON THE ECONOMY: $3 BILLION IN INDIRECT COSTS AND $300 MILLION IN DIRECT COSTS

However, the irony is that diseases such as TB, which causes two deaths every three minutes in India, continue to glare at us in the face. Today, TB is one of India's greatest public health challenges. India has the highest burden of TB in the world, accounting for one-fourth of all new TB infections worldwide. Every year, about 2.2 million persons develop the disease, of which about 800,000 are infectious, and cause an annual loss of nearly 300,000 Indian lives.[1]

The disease is also a major barrier to social and economic development. An estimated 100 million workdays or three to four months of work time are lost due to illness, affecting potential earning of 20-30% of annual household income. Society and the country incur a huge cost due to TB—nearly $3 billion in indirect costs and $300 million in direct costs.[2]

TB is an airborne infection that spreads in crowded, unhygienic and insanitary environments. A single TB patient has the potential to infect at least 10 people in a year, and thus assumes importance, since the air inhaled by people cannot be controlled and regulated. Every untreated TB patient multiplies the risk of spread of the disease, therefore necessitating the implementation of comprehensive, far-reaching strategies for the prevention and control of the disease.

Multidrug-Resistant Tuberculosis (MDR-TB)

MDR-TB is a far more serious problem that threatens the developments made in TB care and control. MDR-TB refers to a condition of resistance to the two most commonly used active anti-TB drugs. Drug resistance arises due to improper use or administration of antibiotics and/or interrupted, erratic or inadequate TB therapy.

In India, about 3% cases among new TB cases and between 12-17% cases among re-treatment TB cases are being diagnosed as MDR-TB.[3]

Treatment of MDR-TB is found to be extremely tragic for individual patients, expensive, difficult, toxic (often having severe side effects) and often unsuccessful, thereby posing a significant challenge to the country, the government, policymakers and health systems.

The Journey so Far

The Government has made substantial attempts to reduce the prevalence of TB. As per World Health Organization (WHO) estimations, TB prevalence per 100,000 population in India has reduced from 465 in 1990 to 230 in 2012. Further, TB mortality per 100,000 population has reduced from 38 in 1990 to 22 in 2012.

The Indian government has implemented the Revised National TB Control Programme (RNTCP) under the umbrella of the National Health Mission, which, in collaboration with National Informatics Centre, has developed a case-based, web-based reporting system called Nikshay for active reporting of TB cases.

The RNTCP has achieved 100% coverage under the globally acclaimed Direct Observable Treatment, Short-course (DOTS) strategy,[4] with a 70% case detection success rate and 85% treatment success rate.[5]

In the last few years, the entire country has been covered under programmatic management of drug-resistant TB. Establishment and active expansion of second-line drug sensitivity testing facilities have been facilitated, and challenges of HIV-TB and TB co-morbidities are also being addressed.

While banning serological tests for diagnosing TB in 2012, the national government has made provisions for over 13,000 Designated Microscopy Centres and over 10,000 sputum collection centres across the country. For the diagnosis of MDR-TB, 58 Culture & Drug Susceptibility Testing laboratories have been set up. India also launched the world's largest dug-resistance survey in 2014, paving the way for a nationwide programme aimed at diagnosing drug resistance in a timely and accurate manner.

Nikshay facilitates report and record TB cases in a web-based format, so as to enable accurate TB burden estimation, individual case management or monitoring and timely follow-up. It is a user-friendly interface that holds the potential to revolutionise patient monitoring and address obstacles, such as the maintenance of patient records and the continuation of TB treatment on schedule to migrant TB-positive patients. With the implementation of RNTCP and the rolling out of its multiple components, India has taken huge strides in reduction of mortality, morbidity and prevalence due to TB.

From Where I Stand

While we have taken great strides in improving public health levels across the country including those provided for TB, we still have a long way to go before the public health system successfully addresses the needs of diverse rural and urban communities populating all parts of the country. There is a pressing need to prioritise effective prevention and control of TB. Regulating diagnosis and treatment in the private as well as public sector is also essential for controlling the spread of TB.

As a Member of Parliament from Bolangir, a constituency with a sizeable tribal population, I have seen at close hand the gaps in the implementation of the government's health schemes and am aware of the urgent need to address them.

88% of the population of the Bolangir district lives in rural areas,[6] which makes it difficult for them to travel to the district TB office to access diagnosis and treatment. Advanced diagnostic facilities are still out of the reach of my

constituents, with the nearest WHO-approved GeneXpert testing facility nearly 300 km away in Koraput.[7]

Our public health policies, while being comprehensive, face difficulties at the level of implementation. Through a careful process of deliberation and debate, these policies provide the framework within which quality healthcare can be offered to the common people. However, there are challenges at the level of implementation which make all the difference between the success and failure of new, innovative health policies.

This can be understood through the example of TB. Of the 22,180 cases registered under the RNTCP in 2012, Odisha recorded a treatment success rate of 82%.[8] This shows that if we are able to extend the DOTS programme's reach to every TB patient in the state, it would go a long way towards arresting the incidence and subsequent spread of TB.

Bolangir itself has 1,940 TB cases registered under the RNTCP.[9] The treatment success rate for the district stands at 69%, which is indicative of the impact of inadequate infrastructure and a lack of ease of access on the successful implementation of TB control mechanisms.

Challenges

TB is treatable and curable, when diagnosed in time and when the full course of treatment is followed. However, a lack of awareness coupled with low risk perception is an impediment to timely action against the disease. Modern TB drugs are known to cure virtually all patients. This requires prolonged treatment (not being less than six months in any case) for a prescribed duration. Effectiveness of TB drugs leads to improvement in a patient's health in about one to two months, often leading to discontinuation of treatment. Several other problems, such as poverty, unemployment and lack of awareness, also disrupt the course of the treatment.

Despite the availability of services across the country, many cases are being missed. TB control faces unique challenges in tribal, rural and urban poor, the 'hard to reach' populations, due to inadequate infrastructure and the lack of reach and awareness to such people. Availability and access to preventive, curative and informative TB services is affected.

Additionally, there are other problems that hamper the access of ordinary people to healthcare. Private sector treatments are expensive, and are thus out

> 88% OF PEOPLE IN BOLANGIR LIVE IN RURAL AREAS, MAKING TRAVEL TO THE DISTRICT TB OFFICE TO ACCESS DIAGNOSIS AND TREATMENT DIFFICULT.

of the question for a majority of my constituents, who are below the poverty line. They therefore approach the public sector, which poses its own set of problems.

While the national government's RNTCP is a far-reaching initiative that provides DOTS treatment to registered patients free of cost throughout the country, availing these facilities is not always a convenient task.

Firstly, travelling to and from a DOTS centre deprives daily wage labourers of their earnings. When they do reach the DOTS centre, they may encounter a shortage of staff, or unavailability of testing facilities or medication. In a constituency like Bolangir, where less than 12% of the population lives in urban areas, this is a big deterrent.

Further, TB medication requires strict adherence in order for it to be effective and to prevent the disease from mutating into drug-resistant strains. There are many challenges to ensuring adherence. These include default by the patient, lapses in follow-up by health volunteers, reluctance in seeking care due to the social stigma associated with TB, and patients leaving the course midway on account of feeling better after a few weeks of medication.

Another challenge in the TB framework, which is also a cause for higher cases of MDR-TB, is the administration of wrong TB drugs to patients. Cases have been reported wherein patients are being given drugs that they are resistant to or where a patient is in a certain stage of TB but being given drugs meant for another stage. To illustrate, a recent study of eight hospitals and treatment centres across Mumbai, Navi Mumbai and Thane revealed that 57% of patients in the pre-XDR-TB (extensively drug-resistant TB) stage were being given drugs meant for MDR-TB patients.[10]

Availability of adequate diagnostic facilities to differentiate between TB, MDR-TB and XDR-TB is also a serious challenge. This is indicative of the fact that patients are being prescribed drugs without undergoing a proper diagnostic test that would list out drugs they are resistant to.

All these factors in turn contribute to a rising TB epidemic, which is symptomatic of the non-delivery of critical public health interventions to the people.

The Way Forward

TB control requires a comprehensive and multilevel approach.

First and foremost, information about the disease and measures to combat it need to be disseminated up to the most peripheral level to generate awareness and encourage social mobilisation.

Next, timely detection of TB and appropriate intervention in affected persons is necessary.

We need to ensure there are no drug shortages, and that all TB care centres are properly staffed. There also needs to be a provision for flexible timings, so that no one should have to choose between earning their livelihood and seeking medical attention.

The latest in TB diagnostics need to be made available to the people, particularly in the public sector, so that timely diagnosis and initiation of treatment may be done. Patients should undergo drug-sensitivity tests at the earliest, instead of later when their disease progresses. Patients should also be given individualised treatment instead of being fed pre-decided combinations of drugs.

In India, private sector participation is much higher than the public sector. More than half of all TB patients are managed in the private sector, thereby making private sector contribution to TB almost double than that incurred by the government. However, the private sector in India, while large, is unregulated. Misdiagnosis due to inaccurate tests such as serological tests for TB combined with the pervasive availability of over-the-counter drugs aid the development of MDR-TB. An unregulated private sector is also an impediment to the effective implementation of public health policies. India declared TB a notified disease in 2012. This means that all positive TB cases diagnosed must be registered with the government to avail of the free DOTS treatment. The latest RNTCP data[11] shows that Odisha, which has 45,629 registered TB patients, received no case notifications from the private sector. Coupled with the fact that over half of all Indian TB patients seek care in the private sector, this points towards a large number of unregistered patients who require TB care on an urgent basis.

ODISHA HAS A TREATMENT SUCCESS RATE OF 82%, VERY CLOSE TO THE NATIONAL AVERAGE OF 85%.

This can only be made possible through increased private sector engagement. Affordable costs at private sector facilities and adequate regulatory mechanisms are necessary to provide standardised, quality TB care services to those in need of them.

There are positives to be taken away from the current scenario as well. With a treatment success rate of 82%, very close to the national average of 85%, Odisha has the necessary foundation in place to scale up and ensure TB care access to every suspect and patient.

I would like to sum up by saying that India stands at the threshold of achieving great success against TB, having ensured that its state programme now covers the length and breadth of the country. The way forward is to build on the successes of the past through greater commitment and through understanding that conquering TB is not only a win for us in the realm of public health, but in the realm of good governance as well. Innovative strategies to increase the efficacy of our efforts are the need of the hour. As policymakers, we need to study best practices from around the word and study the examples of countries that have been more successful in their battles against TB and other infectious diseases. Only then can we hope to realise the dream of a TB-free India. ■

9 EPTB in Disdain: Indian Public Health Scenario

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Tuberculosis (TB) remains the number one infectious disease and killer in developing countries, particularly in Africa and Asia. Though the pulmonary form of TB is most common, it can affect any part of the body. When the disease is caused outside lungs, it is known as extrapulmonary tuberculosis (EPTB). It can involve one organ or more than two organs, in which case it is known as disseminated form of tuberculosis. In India about one-fifth of all TB cases are EPTB cases. The 2013 World Health Organization (WHO) estimates indicate there are approximately 200,000 new cases every year. On the presumption that the patients with EPTB are not infectious to others unless there is a leaking sinus or direct contact with the lesion, this form of TB is not given its due importance. It is also likely that most national TB control programmes are too preoccupied with open cases in addition to dealing with the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis. Nevertheless, sequel and morbidity due to EPTB could be more serious and debilitating than pulmonary TB, and it could be life-threatening as well. Therefore, no country can afford to ignore EPTB. It is highly desirable that active case detection and comprehensive management of EPTB is instituted in line with pulmonary TB, for which extensive research, funding and political will are needed.

The term 'non-pulmonary' or 'extrapulmonary tuberculosis' is used to describe isolated occurrences of TB at body sites other than the lungs.[1] It is an established fact that, after inhalation of mycobacteria, the bacteria are taken up by unactivated alveolar-macrophages, leading to granuloma formation in the alveoli. However, granuloma formation is not always efficient in controlling the infection, particularly in immunocompromised hosts. Often, these infected macrophages transiently or regularly disseminate in the blood stream of the infected person and help disseminate the infection through haematogenous route to various parts of the body.[2] Highly vascular areas such as lymph nodes, meninges, kidney, spine and growing ends of bones are commonly affected through haematogenous dissemination of these mycobacteria. The other sites are pleura, pericardium, peritoneum, liver, gastro-intestinal tract, genitourinary tract and skin, although mycobacteria can cause disease in any organ where blood is supplied. This article will throw some light on why EPTB remains neglected for national TB control programme managers.

Global Burden of EPTB

There were an estimated 8.8 million incident cases of TB globally in 2010. Most of these cases occurred in Asia (59%) and Africa (26%). India alone accounts for approximately 26% of all TB cases worldwide. Recently it was estimated that in India, 171 new cases of TB occur every 100,000 population (incidence rate) with a country prevalence of 2.6 million.[3] The clinical manifestations of TB could be either pulmonary (PTB) or extrapulmonary, the former being the more common (80%) form, which is also highly infectious. EPTB is not a public health problem, as it is not contagious, but it is a major health problem due to significantly high rate of morbidity and severity of permanent disability in persons residing in both developing and developed countries. In a landmark study done in Netherlands, the overall frequency of EPTB was found to be 38%. However, this frequency varied with nationality: Europeans claimed the lowest (15.1%) and Somalis the highest (58.9%). The frequency was found to be 44% among Asians.[4] In India, EPTB accounts for approximately 15-20% of all types of TB. Most common forms are lymph node TB (35%), followed by pleural (20%), bone (10%) and genitourinary (9%). Cerebrospinal, abdominal, skin etc. account for the remaining 26% of the cases.[1] EPTB is more common in children than adults, presumably due to an immature immune system.[5]

HIV/AIDS and EPTB

TB and HIV infections are globally the deadliest combination of chronic infections. In 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease; this included 320,000 deaths due to HIV co-infection.[3] Severity and manifestations of underlying pathologies depend largely on the level of immunosuppression, but TB can occur at any stage of HIV infection, especially in TB high burden countries. Although each one is highly pathogenic in itself, they have deadly additive pathogenic affect together. Therefore, the HIV-TB co-infection is rightly called the medical "double jeopardy." Coordinated

pathogenesis of HIV and *Mycobacterium tuberculosis* cause a major medical challenge because on the one hand, HIV provides enormous opportunity for *M. tuberculosis* to multiply rapidly within the intracellular milieu and on the other, *M. tuberculosis* provides a favourable environment for HIV to replicate unhindered through TB associated protein malnutrition and increased depletion or non-activation of T lymphocytes.[6] Often, EPTB is likely a marker of underlying immune compromise. HIV infection is associated with an increased risk of EPTB, and the risk increases as the CD4+ lymphocyte count declines.[7]

During early stages of HIV, signs and symptoms are similar to those in HIV-uninfected persons: Lungs are most commonly affected, with cough and fever along with radiographic lesions, and often with cavitation. However, in patients with advanced immunosuppression, extrapulmonary sites are more often involved and the frequency of EPTB is indirectly proportional to the CD4 count (Figure 1). The most frequent extrapulmonary sites of infection are lymph nodes (superficial) and pleura; the less common sites are the brain, pericardium, meninges and abdomen.

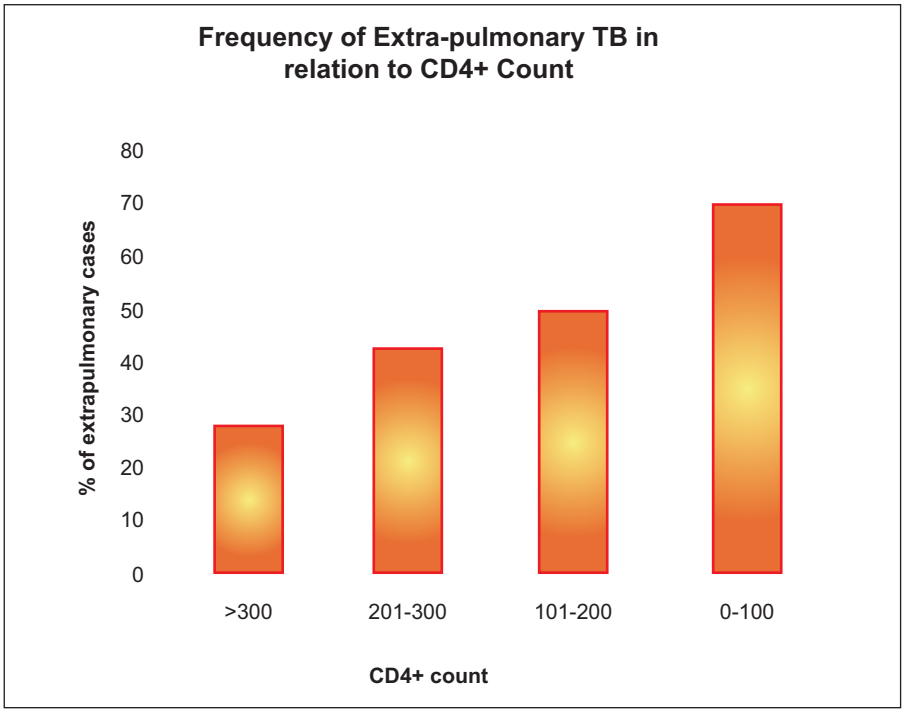

Figure 1: Association of Extrapulmonary Tuberculosis with CD4+ Count in HIV Seropositive Patients

Source: Based on author's research and findings

Diagnosis of EPTB

Patients with EPTB present organ-related symptoms which can develop into serious complications that threaten patients' lives and cause morbidity. Recent reports indicate that the prevalence of EPTB is worsening, and is consequently drawing more public attention. In 2011 19% of new EPTB cases were notified in India.

Diagnosis of EPTB is challenging. Routine methods for TB diagnosis, such as smear for acid-fast bacilli and culture of *Mycobacterium tuberculosis* on solid media, or X-rays, are poorly sensitive worldwide, and nucleic acid amplification tests and liquid culture methods, such as BACTEC MGIT 960, are costly and require sophisticated infrastructure. Moreover, collection of appropriate and site-specific samples is often difficult and cumbersome. Due to these diagnostic limitations and challenges, several kit manufacturers have been arguing in favour of antibody-based immunodiagnostic tests, reasoning that these tests do not require a specimen of the affected organ as is required for microbiological, histological or molecular examinations; furthermore, the antibodies are circulated in the serum. These antibody detection methods have evolved into various formats, such as microtiter well enzyme-linked immunosorbent assays and immunochromatographic assays. However, in 2011 WHO issued strong policy recommendations against the use of these antibody-based commercialised serological tests,[8] subsequent to which the Indian government banned them.

Sankar et al[9] evaluated performance of serological tests (IgG, IgA and IgM) on EPTB patients and the results are presented in Table 1 below. A total of 354 subjects were recruited for the study, of which 61.2% were EPTB patients and 137 (3.7%) were subjects with no suggestive tuberculosis. The tests conducted on persons with no clinical tuberculosis showed 70.8% of such individuals with falsely positive (specificity) IgM antibodies, 77.3% with IgA antibodies and 68.6% with IgG antibodies, thereby putting these many seemingly healthy persons unnecessary on anti-TB medication. Moreover, in truly infected TB patients, less than one-third will be correctly diagnosed to have TB infection while two-thirds will be tested as uninfected, meaning that the latter will not receive treatment if such tests are relied upon and will continue to spread the infection to others. Thus, it was evident that the existing serological tests perform dismally even for EPTB diagnosis. Consequently, if appropriate and site-specific samples can be collected, liquid culture and molecular tests remain the tests of choice in all forms of tuberculosis, including EPTB.[10,11]

Are EPTB-causing Mycobacteria Genotypically Different from PTB-causing Mycobacteria?

Though *M. tuberculosis* complex is the commonest etiological agent in all types of TB, including EPTB in India,[1,2] there is paucity of data on actual incidence and prevalence of various genotypes of *M. tuberculosis* to gauge whether EPTB-causing genotypes are different from PTB-causing genotypes. Genotyping of *M. tuberculosis* helps in tracking the transmission links between individuals, and demonstrates instances in which epidemiologically linked people are infected with unrelated strains. Genotyping can also differentiate between recurrence and re-infection, and can help in understanding if some strains or their genotypes have a special predilection for some body organs.

Mycobacterium tuberculosis is a relatively homogenous group with minimal genetic diversity, yet a high degree of DNA polymorphism—leading to several lineages or families of these mycobacteria—is associated with repetitive DNA

EIA (n=354)		Patient Category		Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LPR (95% CI)
		EPTB cases (n=217)	Non-TB cases (n=137)					
IgM	Positive Negative	63 (29) 154 (71)	40 (29) 97 (71)	29 (23.4-35.4)	70.8 (62.7-77.7)	61.7 (51.1-70)	38.6 (32.8-44.8)	0.9 (0.8-1.2)
IgA	Positive Negative	53 (24.4) 164 (75.6)	31 (22.7) 106 (77.3)	24.4 (19.1-30.5)	77.3 (68.6-83.5)	63.1 (54.4-72.6)	39.2 (33.6-45.2)	1.0 (0.9-1.2)
IgG	Positive Negative	75 (34.6) 142 (65.4)	43 (32) 94 (68.6)	34.5 (28.5-41.1)	68.6 (60.4-75.7)	63.56 (54.5-71.6)	39.8 (33.8-46.1)	1.1 (1.0-1.2)
IgM, IgA	Positive Negative	26 (12) 191 (88)	12 (8.7) 125 (91.2)	11.9 (8.3-16.9)	91.2 (85.3-94.9)	68.4 (52.2-80.9)	39.5 (34.3-45)	1.3 (0.6-2.8)
IgM, IgG	Positive Negative	35 (16.1) 182 (83.8)	22 (16) 115 (84)	16.1 (11.8-21.6)	83.9 (76.8-89.1)	61.4 (48.4-72.9)	38.7 (33.3-44.3)	1 (0.6-1.4)
IgA, IgG	Positive Negative	34 (15.7) 183 (84.3)	15 (11) 122 (89)	15.6 (11.4-21.1)	89 (82.7-93.2)	69.3 (55.4-80.4)	40 (34.6-45.5)	1.4 (0.9-2.2)
IgM, IgA & IgG	Positive Negative	17 (7.8) 200 (92.2)	5 (3.6) 132 (96.3)	7.8 (4.9-12.1)	96.3 (91.7-98.4)	77.2 (56.5-89.8)	39.7 (34.6-45.1)	2.1 (0.3-12.3)
Any EIA*	Positive Negative	113 (52) 104 (48)	70 (51.1) 67 (48.9)	52 (45.4-58.6)	48.9 (40.6-57.1)	61.7 (54.5-68.4)	39.1 (32.1-46.6)	1 (0.9-1)

Table 1: Performance of IgM, IgA and IgG Serology on EPTB Cases

EIA: enzyme-linked immunosorbent assay; Pos: positive; Neg: negative; CI: confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; LRP: Likelihood ratio for positive test.

*Any EIA represents subjects detected positive by at least one of the three (IgM/IgA/IgG) EIA tests.

insertion sequences. Scientists have traditionally used this polymorphism and have fingerprinted these insertion sequences for epidemiological studies. However, the method is cumbersome and requires bulk cultures of *M. tuberculosis*. Recently, spoligotyping and 24 loci mycobacterial interspersed repetitive units (MIRU) were performed to find out genetic profiles of *M. tuberculosis* strains isolated from patients with EPTB in various organs. Drug susceptibility tests were also performed. The study showed that 88% of strains displayed known patterns while 12% isolates had no matching database. The most predominant genotype belonged to the CAS family (57.27%), which is similar to PTB genotypes. Though there was no significant association between specific mycobacterial genetic lineage and site of infection, a significantly high ($p<0.001$) number of Beijing type isolates (28.6%) were isolated from bone and joint samples as compared to cerebrospinal fluid (5%). There was a significant association between Beijing family isolates and multidrug resistance.[11]

Environmental Factors and the Incidence of TB

Mycobacteria originated from the environment and thus the environment still remains highly relevant for the spread and survival of this highly pathogenic bacteria. Epidemiological data indicates that in countries where citizens spit in public spaces and roads and footpaths are swept, the prevalence of TB remains high. Infected patients spit out mycobacteria in areas of common use, the bacteria gets deposited on the ground and becomes airborne with contaminated dust particles when the roads are being swept or when any contaminated soil is handled, and people walking on the roads inhale the bacteria swept up in the air. Evidence indicates that in economically empowered countries, improvement in public hygiene came with education and improved standards in social and public hygiene, such as no spitting in open areas and etiquettes of coughing and sneezing. The emerging economies must therefore equally emphasise social hygiene such as making spitting in open a punishable crime. States too should make appropriate changes and preferably ban cleaning of roads during daytime when public movement is high, and efforts should be made to enhance awareness about civic sense and etiquettes of coughing and sneezing in crowded areas and public places. I strongly feel that these measures will bring down incidence rates of all forms of TB significantly in all high burden countries.

Way Forward

EPTB is a disease which is caused by the same pathogen that causes PTB, yet its public importance is low. This is mainly because TB control programme managers think that PTB is a threat to society given excretion of mycobacteria by index patients, as compared to EPTB, which by-and-large remains confined to the site of infection. However, its potential of severity and morbidity cannot be undermined. Moreover, treatment may be altogether different depending on the site of involvement, as supporting and symptomatic treatment also need to be instituted along with anti-tubercular treatment in these cases. The most important challenge in EPTB is confirmatory diagnosis. Several forms of EPTB (e.g., bone TB, intestinal TB, mediastinal TB) are extremely difficult to diagnose bacteriologically or by molecular means. Nevertheless, imaging technologies have come as a boon for EPTB. Techniques like computerised tomography, ultrasound, magnetic resonance imaging and positron emission tomography are some of the recent diagnostic aids. Scientists are working hard to find out more specific biomarkers to make confirmatory diagnosis of such difficult cases. Extensive research and proportionate funding are needed to understand the overall burden of non-pulmonary TB, the anatomical sites and risk factors, if any. ■

10 Combating TB: A Global Perspective

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Countries in different parts of the world tailor their tuberculosis (TB) control programmes according to their specific requirements. There is an imperative need for sharing the knowledge and best practices of these programmes internationally. Global cooperation is needed to fight such devastating diseases across continents and borders, since such infectious diseases cannot be contained and kept isolated within specific geographical boundaries.

TB continues to threaten the health and wellbeing of millions of people in the world. In 2013, out of an estimated 8.6 million people infected with *Mycobacterium tuberculosis*, nearly 1.3 million people lost their lives, making TB one of the world's deadliest communicable diseases. The sad reality is that a third of the 8.6 million people who contract TB every year do not have access to medical services they need. Many of them live in the world's poorest and most vulnerable communities. In 2013, 5.7 million newly diagnosed cases were notified to national TB programmes. About three million people with TB were "missed," either because they were not diagnosed or because they were diagnosed but not reported.[1] India accounts for 24% of the global burden of TB.[2]

The Millennium Development Goals, the international goals that United Nations member states and the world's leading development institutions agreed to achieve

by the year 2015, had targeted the reversing of TB incidence by 2015. This has been achieved substantially. The incidence of tuberculosis has been falling at an average rate of 1.5% per year between 2000 and 2013. There is also a significant fall in the global prevalence of TB. The Sustainable Development Goals being developed have sought to end the epidemic by 2030 along with AIDS, malaria and other communicable diseases. This will require a concerted effort from all affected countries to come together in sharing knowledge, technology and innovative practices and programmes to combat the menace of TB.

Different countries have faced different hurdles in fighting the scourge of TB. Major overhauls and committed authorities have helped countries reduce the burden of the disease. Over the years the case detection rates and treatment success have improved tremendously. It is estimated that 37 million lives were saved between 2000 and 2013 through effective diagnosis and treatment.[3]

TB in India

TB is one of India's greatest public health challenges. India bears the highest burden of TB in the world, accounting for one-fourth of the global incidence—2.3 million cases annually.[4] According to the World Health Organization (WHO) Global Tuberculosis Report 2014, 300,000 Indians perish because of TB each year. The rise of drug-resistant TB is a major concern and a big threat for the Indian public health system. With an estimated incidence of 64,000 cases,[5] multidrug-resistant TB (MDR-TB) poses enormous strain on the public health system for diagnosis and a great financial strain because of the much higher expenses related to treatment. The treatment of drug-resistant TB spread over two years can cost between INR 200,000 and 500,000. Moreover, the treatment is so complex and toxic that almost a third of MDR patients die during the therapy. The Directly Observed Treatment, Short-course (DOTS) strategy along with the other components of the Stop TB Strategy, implemented under the Revised National Tuberculosis Control Programme (RNTCP) in India, is a comprehensive package for TB control. The RNTCP is the largest TB control programme in the world, with more than 100,000 patients on treatment every month. RNTCP has achieved the global target of 70% case detection and an 85% treatment success rate. The grim situation in India in the 1990s influenced the government to rechristen the existing national programme's name. As a result of the rapid expansion of the programme to cover the entire population by 2006, treatment success rate tripled from 25% to the present 85%. The RNTCP's aim to increase case treatment to 90% by 2017 is a welcome move. But despite these efforts, TB remains one of the leading causes of mortality in India, killing two persons every three minute, which amounts to nearly 1,000 people every day.

TREATMENT OF DRUG-RESISTANT TB CAN COST INR 200,000 TO 500,000 OVER TWO YEARS.

After complete geographical coverage of the country for programmatic management of drug-resistant TB services, the number of MDR-TB suspects who were offered drug susceptibility testing increased in 2013 with diagnosis of 23,289 MDR-TB cases, of which 20,763 were put on treatment. With early diagnosis of MDR-TB, the outcomes of treatment are expected to improve, but mortality and default are still around 20% each.[6]

For better tracking and recording TB cases, the RNTCP launched Nikshay, a case-based, web-based portal. Its contribution has led to effective data collection and analysis, thereby helping in diagnosis and treatment by identifying various types of TB cases, patterns, degrees in severity and solutions on priority. This has led to increased information sharing of cases from the private providers who continue to treat 50% of TB cases in India.

The National Strategic Plan (NSP) (2012-17) that outlines the Central TB Division's vision of universal access to quality diagnosis and treatment over five years for all TB suspects in India is backed by the commitment of the federal government to substantially increase the investment for TB control. The NSP proposes a substantial increase in the level of funding, the aim being to reach around $260 million annually by 2016–2017, in line with the growth in the number of TB patients put on treatment (a target of around 1.75 million patients by 2016–2017).[7]

The National Forum on Tuberculosis was launched in 2013 to raise awareness and promote advocacy. The forum brought together parliamentarians, policymakers and civil society representatives to discuss the challenges for TB prevention and control. The forum has been at the forefront of pushing for national level policy changes. The forum has also had extensive interactions with policymakers, experts and stakeholders from other countries to learn from successful programmes and interventions. Cross-pollination of ideas and strategies from different countries go a long way in fighting the disease in a quicker and more efficient manner.

International Successes in TB Control

Cambodia, China, India and Estonia are laudable examples where governments have tackled the TB burden with a proactive approach.

China: China has more than one million new cases every year, making the TB epidemic in China the second largest in the world. The TB programme was put in place in 1981 but was plagued with poor treatment compliance, a deficient network of diagnostic laboratories, and an inadequate system of reporting and evaluating cases.[8] By 1990, TB was the leading cause of death among adults (360,000 died of TB that year alone). In 1991, the government sprang to action, embarking on a 10-year Infectious and Endemic Disease Control project to curb the TB epidemic. In partnership with the WHO, the Chinese government implemented DOTS in 13 provinces that account for roughly half of the Chinese population.

TB mortality declined sharply between 1990 and 2011 at a rate of 8.6% per year. In 2010, China achieved the TB control targets set by the Millennium Development Goals—five years ahead of the target date set by the UN. Over the past 20 years, China has reduced TB prevalence and mortality rates by half.

Cambodia: A couple of decades ago, in the 1990s, Cambodia had one of the world's highest TB rates and a health system weakened by decades of conflict and economic hardship. The country's health system had completely fallen

through, with less than 50 doctors left out of a former force of 600. The newly elected government in 1993 re-launched its national TB programme. Over the past decade, new approaches that provide universal access to TB care through primary health centres halved the number of new cases and helped the country meet global targets for case detection and treatment.[9]

PERU, ESTONIA AND THE PHILIPPINES ARE INSPRING EXAMPLES OF STRONG POLITICAL WILL TO TACKLE AN EPIDEMIC.

Decentralisation of health services was the result of the reconfiguration of the Cambodian health system, which cut down the number of hospitals and brought universal access to TB to the grassroots level. Experts from WHO and Japan International Cooperation Agency worked closely with the Ministry of Health to adapt the global strategy for TB control to meet local needs and conditions. Pilot studies tested interventions in targeted communities before they were expanded on a national scale.

A National survey in 2011 found TB prevalence had fallen from the 2002 rate of more than 1,500 cases to 820 cases per 100,000 people—a 45% reduction in nine years. This was a result of a clear evidence-based policy and plan, strong technical expertise, government commitment and leadership, as well as sustained support from international donors and partners. Although the Cambodian government has achieved considerable success in reducing the incidence of TB, they still have a long way to go, as 820 TB cases is still an unacceptable high index.

Partnerships and Political Will—Key Components of Success

There is a radical need to build international cooperation and coalitions to fight diseases like TB by sharing knowledge, innovation, technology and best practices of proven interventions. In addition, at the core of every TB strategy must lie the government's political will. This cannot be overemphasised, as it is the lynchpin to all other aspects of TB prevention and control. Peru, Estonia and the Philippians are inspiring examples of how an epidemic can be brought under control with meagre resources but exceptional, strong political will.

Keeping this in mind, an international initiative, the Global TB Caucus, was founded in October 2014 at the inaugural Global TB Summit. The Summit brought together elected representatives from around the world to galvanise the political support needed to tackle TB, and to draw a clear vision for the role of parliamentarians in combating the epidemic. The Barcelona Declaration was launched with an ambitious target of representatives from 100 countries signing the Declaration by December 2015.[10] The Summit has been lauded as a landmark moment in the fight against TB epidemic, as it was the first time when political representatives joined hands to evolve strategies for TB prevention and control. The Declaration also asserted the need for a new model of research and development for introducing new drugs, diagnostics and vaccines. The next Summit will be held in Cape Town, South Africa. This event will also be held in conjunction with the Union World Conference on Lung Health in December 2015. Twenty-two of the highest TB burden countries are scheduled to meet at the next conference.

National policies are central to translating global policies into practice. This requires stronger engagement of national policymakers, researchers and implementers in the global policymaking environment. Formal and informal multistakeholder partnerships and information sharing through networking facilitate transfer of knowledge, best practices and policies across countries. India should continue active participation in all global efforts towards eradication of TB.

The Final Push for TB Control in India

India has been at the forefront of TB control and research since the start of the 20th century. Considering the enormity of the problem, many constraints and competing priorities, the progress India has made in TB control and prevention is indeed a remarkable success story. Though not a victory as yet, the RNTCP and the renewed commitment of the government to tackle TB on a firm footing augur well for TB control in India. On the other hand, there are challenges to face, particularly those related to MDR-TB. There is need for further policy development, planning and additional financing. Success of TB control in India is essential for the world's fight against the disease.

This will also require further strengthening international collaboration and encouraging cross-country learning to correct our course and fine-tune our programme to achieve its targets in the shortest possible timeframe in the most cost-effective manner.

The key is to strengthen the monitoring and evaluation system with indicators of programme performance, quality, logistics, human resources, expenditure and budget, and advocacy, communication and social mobilisation activities. The challenge is now to sustain the existing DOTS-based programme while introducing services to address TB/HIV, treatment for MDR-TB, strengthening laboratory services, and integrating TB services in all health facilities of both public and private healthcare sectors.

India is in a position to achieve Stop TB partnership targets, but this will require partnerships, an increase in funding and human resources. This will also require more active partnership with all healthcare providers, NGOs, academics and the private sector. ■

Building BRICS against Tuberculosis

11

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The creation of the BRICS is consistent with realist international relations theory that would expect rising powers to seek instruments to advance their interests. However, regime theory, developed to explain how international institutions shape cooperation beyond short-term interests, can help in assessing prospects for joint action by the BRICS on specific issues. Tuberculosis (TB) control is a highly technical area of common concern for the BRICS, which account for over 40% of the nine million estimated new TB cases annually and more than half of the estimated drug-resistant TB cases worldwide. Cooperation on TB control is an explicit agenda item for the BRICS, and the recently-created New Development Bank is positioned to provide support. This could take the form of financing for TB control in individual BRICS and other countries, but the small membership of the BRICS also raises the possibility of truly collaborative action on issues such as pharmaceutical procurement, quality standards and research. International relations theory suggests that the BRICS' recent commitment to ambitious TB control targets should be taken seriously, given their investment in promoting the legitimacy of the grouping as an international regime.

*The findings, interpretations and conclusions expressed in this work are entirely those of the authors and should not be attributed in any manner to the World Bank, its Board of Executive Directors, or the governments they represent.

Introduction

The ongoing shift in relative economic power towards rapidly growing economies has been accompanied by changes in global political relationships, including progressive institutionalisation of the BRICS, consisting of Brazil, Russia, India, China and South Africa. The BRICS countries are increasing their policy coordination on a range of issues. A topic of concern to all five member countries is potentially a relatively non-controversial and thus low-hanging fruit to demonstrate the ability of the BRICS to achieve effective coordinated action—control of TB. This article will examine why TB is considered an important potential area for coordination between the BRICS, as well as look at what international relations theory may suggest about the prospects for concrete action.

BRICS meetings since 2006, including six summits between the five countries' leaders by the end of 2014, have provided a forum for coordination on issues such as reform of international financial institutions, and significantly, for the creation of several new institutions like a Contingent Reserve Arrangement and a New Development Bank in 2014.[1] The Contingent Reserve Arrangement, with an initial capital of $100 billion, is to have functions analogous to the International Monetary Fund, designed to provide balance of payments support to its members. Analogous to the World Bank, the New Development Bank, with starting capital of $50 billion, is to fund infrastructure and "sustainable development" projects.

TB IS AN IDEAL EXAMPLE OF A TECHNICAL ISSUE THAT IR THEORY WOULD EXPECT TO BE ADDRESSED THROUGH INTERNATIONAL REGIMES SUCH AS THE BRICS.

The creation of the BRICS and their institutions is entirely consistent with realist international relations theory. This theory would expect these countries to seek instruments to advance their interests in the face of resistance to an increased role in international institutions established after the Second World War. In this view, the BRICS as an entity provides an instrument for coordination towards common interests without unduly constraining its members, while the New Development Bank and other institutions provide alternative options to the organisations dominated by Western countries. With regard to what the BRICS institutions may do in practice, realist theory would suggest that they will directly reflect the economic and political interests of their members, particularly the more powerful. In cases where this does not happen, the institutions will be sidelined.[2]

However, noticing that in many cases international institutions do in fact shape and often constrain the actions of countries, even powerful ones, the regime theory of international relations suggests that countries often accept some limits to their freedom of action. International regimes embody informal and formal norms, rules and procedures of decision-making that facilitate cooperation motivated by more than short-term self-interest.[3] International policy cooperation can become institutionalised, often in response to a crisis. In this case, the BRICS are responding to their increasing conviction that existing organisations such as the United Nations Security Council and the Bretton Woods institutions are unlikely to reallocate voting rights in their favor in the near future. Cooperation can occur even without the coercive power of a global hegemon, when these states view such policies as being in their best interest. Once established, institutions tend to be maintained and lead to

enhanced cooperation because of greater provision of symmetric information, increased costs of reneging on commitments (including to the reputations of members), provision of public goods and enhancement of the global standing of members.[4] Moreover, institutions comprised of or dominated by a small number of countries are more likely to take decisive decisions compared to those with larger membership. Nonetheless, it is recognised that international regimes and institutions are likely to be most active and effective on issues that do not touch on core economic and security concerns.[5]

Based on this theory, we should expect BRICS countries and emerging BRICS institutions to increasingly coordinate on development policy issues, particularly on issues that affect them all and where tangible progress would enhance their legitimacy and stature as global powers. A highly technical issue that has been identified as a common area of concern for the BRICS is TB control. Noticing that all the BRICS count among the list of countries with high TB burdens, and indeed suffer from the same number of new TB cases annually (over 3.7 million) as the other 17 high-burden countries combined, observers as well as the BRICS governments themselves are exploring possibilities for coordination.[6]

The Importance of the BRICS to TB and vice versa

The concept of the BRICS encompasses the notion that the rising wealth of the five countries is analogous to the historical path followed by Western countries, that the BRICS are in the midst of their own Industrial Revolution. The early stages of the original Industrial Revolution involved massive rural-urban migration with accompanying social disruption, poor living and working conditions—and disease. TB in particular is associated in the popular imagination with the urban poverty and crowding of that era. Spread through the air, TB is a bacterial disease that attacks the lungs and can also infect other parts of the body. The disease is often fatal without effective treatment. At the end of the 18th century, a quarter of the deaths recorded in parish registries in England have been attributed to TB.[7]

Today, the populations of the BRICS countries suffer from an estimated 430,000 deaths annually due to TB, 30% of the estimated worldwide total, including an estimated 100,000 deaths involving both HIV and TB. Annual TB mortality rates in the BRICS range from three (Brazil and China) to 169 (South Africa) per 100,000 population, which can compare to, for example, 0.56 in the United Kingdom. It is estimated that there are over 3.7 million new cases of TB annually in the BRICS, over 40 percent of the worldwide total (Table 1). The importance of the BRICS with regard to TB is due largely to the size of their populations (43 percent of the world population), especially India and China. At the same time, while India experiences the greatest number of deaths due to TB in the world, China, Brazil and Russia have the largest TB burdens in their respective regions and South Africa has among the highest rates of new cases in the world.[8]

In each BRICS country, TB is closely associated with HIV/AIDS; this is particularly acute in South Africa, where about half of new TB cases are infected with HIV. Also contributing to the perception of the disease as a priority for the

BRICS is the growing challenge of drug-resistant TB, considered a major threat to the progress made in TB control over the past decades.[9] With interrupted or sub-optimal treatment, the causal agent, *mycobacterium tuberculosis*, can develop resistance to one or more of the antibiotics used to treat the disease. At the same time, a large proportion of drug-resistant TB cases are due to transmission of a resistant strain from person to person. Some cases have been identified that are resistant to all anti-TB drugs tested. It is currently estimated that there are a total of 480,000 new cases and 210,000 deaths from drug-resistant TB worldwide. Together, India, Russia and China account for more than half of estimated drug-resistant TB cases.[10]

Perceptions of the importance of the disease to the BRICS may also be shaped by the historical association of TB with poverty, rapid industrialisation and urbanisation. In fact, after increasing during the first part of the Industrial Revolution, mortality due to TB in Western countries underwent a continuous decline from the latter half of the 19th century into the 20th century, due first to improved living and nutritional conditions and then to the advent of effective antibiotic treatment in the 1950s.[11] However, over the past decades, the estimated numbers of annual new TB cases and deaths in the BRICS have either risen or, in the case of Brazil, only gradually declined (Figure 1), despite the economic growth they have experienced. Even in China, which has had a

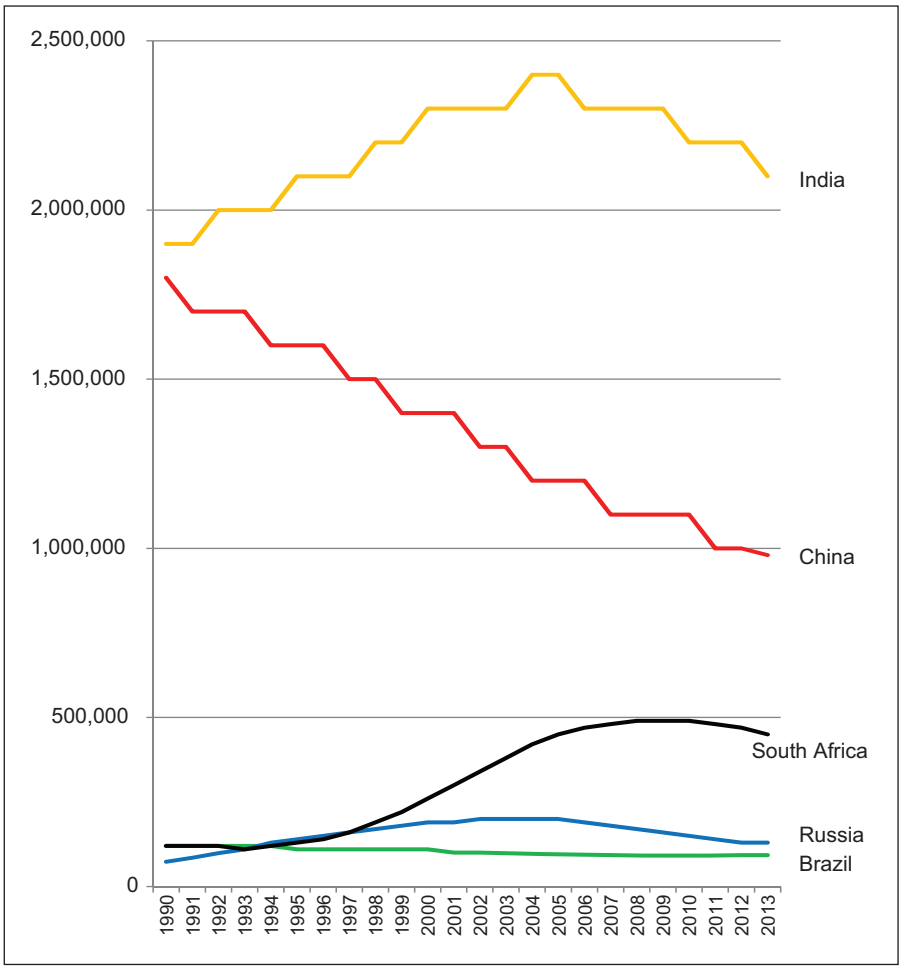

Figure 1: Estimated Number of Annual New TB cases[12]

steady average annual rate of decline in the number of new cases since 1990 (2.5%), the annual number of new cases is still almost one million.[#] Increased TB burdens experienced by Russia, India and South Africa from the early 1990s to the mid-2000s are associated with slow or deteriorating economic growth, population growth and the HIV/AIDS epidemic, while improvement since then is associated with better economic conditions as well as expanded TB services. As the Russian case in particular illustrates, throughout history, during times of social disruption, TB can increase rapidly, but decreases only slowly.

It is the poorest and most marginalised populations that are at the highest risk of TB,[13] and the populations of the BRICS countries include millions of very poor people. Almost 400 million people live on less than $1.25 per day in the BRICS, mostly in India and China, but with some millions also in Brazil and South Africa, while in Russia, 15 million people are under the national poverty line.[14] Recent economic growth has brought many people in the BRICS countries out of poverty. However, with the exception of Brazil, the BRICS countries have also undergone rising inequality, with the better-off 20% of the population in these countries benefitting more than the poorest 20% from economic growth during the decade of the 2000s.[15] The extent of poverty and widening inequality are important reasons why TB remains a problem in the BRICS, despite the growing wealth of these countries as a whole.

TB Control in the BRICS

That TB, including drug-resistant TB and HIV-TB, continues to be a major problem in the BRICS, despite their growing wealth, also reflects the fact that this is a difficult disease for health systems to deal with. Diagnosis of pulmonary and infectious cases can be relatively straightforward, but many other TB cases, including among children, are more difficult to identify. More importantly, there are often long delays between infection and diagnosis, as people suffering from TB symptoms like chronic cough go from provider to provider receiving inadequate care. Treatment of drug-susceptible TB is generally successful for most patients, but involves taking a combination of drugs over a period of six to nine months. With regard to drug-resistant TB, diagnosis and effective treatment require laboratory capacity, while there are commonly long delays before a patient is tested. It is estimated that currently over half of drug-resistant TB cases are not detected. Treatment of drug-resistant TB involves drug combinations to be taken over at least two years, costing $5,000 or more per course. Currently, only about half of drug-resistant cases treated worldwide have successful outcomes.[16] It is evident that control of TB on a large scale requires adequately-funded, well-organised and effective health services.

In addition, these services need to be accessible to the poorest and most marginalised populations who are at the highest risk of TB. In all the BRICS, the urban and rural poor, as well as particular groups such as migrants, homeless,

[#] China has done three TB prevalence surveys and therefore, estimates are fairly robust. However, Russia, India and South Africa have not conducted national prevalence surveys so TB burden estimates depend on models and assumptions.

prisoners and people dependent on drugs and alcohol, face difficulties in accessing effective care for TB, although Brazil has used social safety net programmes, such as conditional cash transfers, to provide support to poor and vulnerable patients.

In all the BRICS countries, public funding is crucial to making progress on TB control. It is notable that funding for TB control programmes in all the BRICS is mostly from domestic sources. Their average of 95% of total funding (with a low of 66% in India and high of 100% in Russia) contrasts with just 28% in the 17 other countries that are classified as having a high TB burden. TB programme funding differs considerably across the BRICS in absolute terms, ranging from $69 million in Brazil to $1.8 billion in Russia.[17] However, aside from Russia, which spends over $14,000 per estimated new annual TB case, funding per case in the other four countries is in the same order of magnitude, under $800. Funding per case in India is lowest ($120) among the BRICS.

In Brazil, Russia and China, the proportion of estimated annual new TB cases that is identified by the government TB programme is above 80%, while it is about 70% in South Africa and 60% in India. In all the BRICS, once patients have been identified treatment outcomes are successful for more than 70% of non-drug-resistant cases that are diagnosed and put on treatment.[18]

All the BRICS need to make further efforts in order to reach most or all TB cases with effective care—and to reach them closer to the time of infection. Each country faces different challenges in expanding access to healthcare.[19] Brazil has had considerable success in improving government primary healthcare services, including TB services, used by the 75% of the population that is not covered by health insurance, but there are still challenges to reaching poor and

	Population 2013 (million)	Annual new TB cases 2013	Annual TB deaths 2013	GDP per capita 2013 ($ current)	TB programme funding 2014 ($ million)	TB programme funding per new TB case ($)
Brazil	200	93,000	6,500	11,208	69	744
Russia	143	130,000	18,400	14,612	1,827	14,054
India	1,252	2,100,000	278,000	1,499	252	120
China	1,386	980,000	41,700	6,807	282	288
South Africa	53	450,000	89,000	6,618	162	360
Total BRICS	3,034	3,753,000	433,600	5,259	2,592	691
Remaining 17 high TB burden countries	1,451	3,630,000	817,760	2,014	429	118
World	7,125	9,000,000	1,460,000	10,610		

Table 1: BRICS and TB

Note: TB cases and deaths include HIV-infected cases.

Source: World Health Organization, World Bank

isolated groups.[20] The government has put strict controls on the sale of anti-TB drugs in the private sector while providing them free-of-charge through the public system, which has avoided problems with unregulated TB care in the private sector that have been observed in other countries.[21] In Russia, most primary healthcare, including TB care, is provided through government facilities, although informal payments are common and there are challenges to improving care for marginalised populations.[22] In contrast with the TB programmes in the other BRICS, hospital-based care is emphasised, including inpatient stays, while surgery is also commonly used to treat the disease.[23] In India, government primary health services, including TB services, are available free-of-charge to the population, but low funding has led to significant gaps in supply and quality, leading hundreds of thousands of TB patients annually to seek care in the largely unregulated private sector. The government recently took steps to improve regulation and intends to implement strategies for collaboration with private sector providers.[24] In China, TB services are coordinated by the national programme and provided through community-level health services, but many patients go directly to hospitals which have an incentive to raise revenue through fees and drug sales.[25] Many of these costs are paid by government insurance schemes that cover 95% of the population, although only 70% of the cost of care for drug-resistant TB is covered, and there is a need to improve coordination between hospitals and the TB programme.[26] In South Africa, the government health system serves more than 80% of the population that is without private health insurance, although it is under-resourced, leading to gaps in supply and quality. The government is developing a national health insurance programme[27] which should help increase access to TB care.

Potential for Cooperation

Health was not initially an area of focus for the BRICS leaders but was introduced at their third summit in China in 2011, followed by a health ministers' meeting a few months later. The declaration they issued largely focused on their common positions with regard to existing international organisations, notably the World Health Organization.[28] This provides an example of how the BRICS as an institution has been used to facilitate coordination to advance the common interests of the BRICS countries, particularly in relation to the existing international system. This is in line with the realist perception of the BRICS as a grouping that reflects the interests and power of its individual members.

Also consistent with a realist view of the BRICS coordination as simply reflecting the ongoing shift in global economic power is the notion that the BRICS should take on a greater share of the costs of TB control in their own counties, so that existing international funding can focus elsewhere.[29] At the same time, the possibility has been raised of coordinated support by the BRICS for TB control in their own and other countries. As early as 2011, the BRICS health ministers advocated "inclusive global public health cooperation projects,"[30] while in 2014, the New Development Bank was tasked with mobilising resources for both the BRICS and "other emerging economies and developing countries."[31] At their 2014 meeting, the BRICS health ministers

asserted that "sustainable development," part of the New Development Bank's mandate, includes health.[32] In the realist perspective, this prospect of BRICS financing for development in other countries could be considered to advance their interests in terms of enhancing their stature and influence internationally. It has even been suggested that the BRICS step in to support TB control where many traditional international donors do not for political reasons, such as in Iran and North Korea.[33]

However, the possibility of New Development Bank support for TB control in the BRICS and other countries moves us more into the realm of regime theory, where the BRICS as an institution would act towards common objectives in a way that individual countries could not. This could indeed take the form of support to programmes in individual countries, similar to the actions of existing organisations such as the World Health Organization, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the World Bank, all of which have contributed to TB control programmes in the BRICS countries over the past decade. Such international support can bring, along with funding, new ideas and technical knowledge as well as outside impetus for innovation, oversight and accountability. On the other hand, although there is scope for exchanging information about national efforts, the challenges faced by individual BRICS countries—care for marginalised groups in Brazil, drug-resistant TB in Russia, engagement with the private sector in India, economic incentives of hospitals in China, HIV/AIDS in South Africa—involve complex social, economic and organisational issues that are likely most effectively addressed through strong action by the countries themselves.

More interestingly, given the small size of its membership, the BRICS may be in a position to move beyond the traditional model of international development assistance, involving country-specific programmes, towards truly joint activities. Indeed, from the beginning of their discussions on health, the BRICS have focused on policy coordination, initially vis-à-vis existing international organisations and agreements, but now more and more relating to independent initiatives.

The various declarations of the BRICS health ministers from their four meetings since 2011 mention numerous health problems, including TB, and commit themselves to coordination on a broad range of policy issues. In 2013, they adopted a "BRICS Framework for Collaboration on Strategic Projects in Health," involving work on public health, health systems and biomedical research.[34] More specific issues related to TB have also been included in the BRICS discussions and technical work. Knowledge-sharing is advocated, for example, taking advantage of the large datasets potentially available from TB programmes in the BRICS, as well as coordination on technical questions, such as unresolved issues relating to drug-resistant TB treatment and diagnosis and treatment of pediatric TB.[35] Indeed, with each taking the lead on service delivery innovations (for example, India on information technology, China on treatment adherence and South Africa on diagnostic technology), the BRICS are in a position to define modern TB control.

In 2014, the BRICS health ministers adopted a "cooperation plan" on TB.[36] Much of the plan is focused on issues related to pharmaceuticals and diagnostic

IN 2014, BRICS HEALTH MINISTERS ADOPTED A "COOPERATION PLAN" ON TB, MOSTLY FOCUSED ON ISSUES OF PHARMACEUTICALS AND DIAGNOSTIC TECHNOLOGY. THEY ALSO SET THE 90-90-90 TB TARGET, THUS TAKING A LEADING ROLE IN SETTING THE INTERNATIONAL AGENDA FOR TB CONTROL.

technology, the potential importance of which cannot be overstated given the fact that India and China produce most of the anti-TB medicines that are used in poor and middle-income countries. The health ministers' declarations repeatedly mention support for exceptions to international agreements on intellectual property in cases of health emergencies, with the aim of retaining flexibility to produce generic medicines even if they are on patent in Western countries (important to HIV treatment, but also potentially important to TB). Possibilities are also raised for coordination between the BRICS on drug quality standards and pricing, indicating potential for joint procurement following the BRICS own quality standards, which would greatly affect the global market for anti-TB drugs. Repeated endorsement of coordinated support for research on anti-TB medicines and vaccines similarly holds the potential to be transformational given the small scale and slow pace of current research.[37] Effective coordinated action on these issues would require the BRICS to fund and implement truly joint activities, something which is difficult for existing multilateral organisations to do.

Similarly, the limited membership of the BRICS may make it easier to formulate clear decisions and commitments. In 2014, the BRICS health ministers made a commitment "to aspire towards a 90-90-90 TB target (90% of vulnerable groups screened, 90% diagnosed and started on treatment with 90% treatment success),"[38] thus taking a leading role in setting the international agenda for TB control. Regime theory would suggest that this could potentially be important, insofar as the five countries, particularly after committing funds to joint institutions like the New Development Bank, have clearly made a strong commitment to the BRICS as an entity. This suggests that achieving clear objectives such as the 90-90-90 TB target may be considered important by each government to the legitimacy and stature of the BRICS as a regime (and thus to their own stature). In addition, unlike similar global objectives, such as the Millennium Development Goals, credit or responsibility for the attainment of the TB control targets cannot be diffused given the small membership of the BRICS.

The TB problem is an ideal example for the type of complex technical issue that international relations theory would expect to be addressed through international regimes. Recent efforts by the BRICS to coordinate on TB control provides hope that the emerging BRICS institutions will contribute to a sum that is greater than the individual parts of the efforts of each country, with a potential large impact on TB control worldwide. ■

ENDNOTES

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1 "TB India 2007, RNTCP Annual Status Report," Directorate General of Health Services, Ministry of Health and Family Welfare, 2007, http://www.tbcindia.nic.in/Pdfs/TB%20INDIA%202007.pdf.
2 "Joint Monitoring Mission, RNTCP India," World Health Organization, 2013.
3 "Standard Operating Procedures Manual for State Drug Stores," Central TB Division, Ministry of Health and Family Welfare, 2008, http://tbcindia.nic.in/pdfs/SOP%20for%20SDS%20Drug%20Stores.pdf.
4 "TB India 2014, RNTCP Annual Status Report," Central TB Division, Ministry of Health and Family Welfare, http://www.tbcindia.nic.in/Pdfs/TB%20INDIA%202014.pdf.
5 "TB India 2012, RNTCP Annual Status Report," Directorate General of Health Services, Ministry of Health and Family Welfare, http://www.tbcindia.nic.in/Pdfs/TB%20INDIA%202012.pdf.
6 "TB India 2014."
7 J. Singh, "Health ministry merges TB programme with rural health mission," *Down to Earth*, 2013, http://www.downtoearth.org.in/content/health-ministry-merges-tb-programme-rural-health-mission.
8 World Health Organization MDG 6: Combat HIV/AIDS, malaria and other diseases, http://www.who.int/topics/millennium_development_goals/diseases/en/.
9 "TB India 2014."
10 M. Uplekar, V. Pathania and M. Raviglione, "Private practitioners and public health: weak link in tuberculosis control," *Lancet* 358, no. 9285 (September 15, 2001): 912-16.
11 Shah Utkarsh and Mohanty Ragini, "Private sector in Indian Healthcare Delivery: Consumer Perspective and Government Policies to promote private sector," *Information Management and Business Review* 1, no. 2 (2010): 79-87, http://www.ifrnd.org/IMBR%5C1(2)%20Dec%2010%5CPrivate%20Sector_Indian%20Healthcare%20Delivery.pdf.
12 "TB India 2011, RNTCP Annual Status Report," Central TB Division, Ministry of Health and Family Welfare, http://www.tbcindia.org/pdfs/RNTCP%20TB%20India%202011.pdf.
13 R.K. Dwivedi, "Regulating Sale Of Anti-Tuberculosis Drugs Hailed," *Modern Ghana*, March 21, 2014, http://www.modernghana.com/news/530795/1/regulating-sale-of-anti-tuberculosis-drugs-hailed.html.
14 K.B. Gupta and et al, "Tuberculosis and nutrition," *Lung India* 26, no. 1 (2009): 9-16, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2813110/.
15 "Joint Monitoring Mission, RNTCP India."

2

1 M.C. Raviglione and A. Pio, "Evolution of WHO policies for tuberculosis control, 1948-2001," *Lancet* 359, no. 9308 (2002): 775-80.
2 "Global Tuberculosis Report 2014," World Health Organization, 2014, http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf?ua=1.
3 K. Lonnroth et al, "Drivers of tuberculosis epidemics: the role of risk factors and social determinants," *Social Science & Medicine* 68, no. 12 (2009): 2240-6.
4 "Global Tuberculosis Report 2014."
5 Catherine R. Stevenson et al, "Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence," *BMC Public Health* 7 (2007), http://www.biomedcentral.com/1471-2458/7/234/.
6 A. Bhargava et al, "Undernutrition and the incidence of tuberculosis in India: national and subnational estimates of the population-attributable fraction related to undernutrition," *National Medical Journal of India* 27, no. 3 (2014): 128-33.
7 Olivia Oxlade and Megan Murray, "Tuberculosis and poverty: why are the poor at greater risk in India?," *PLoS One*, November 19, 2012, http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0047533.
8 V. Gajalakshmi et al, "Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43 000 adult male deaths and 35 000 controls," *Lancet* 362, no. 9383 (2003): 507-15.
9 V.K. Chadha, "Tuberculosis epidemiology in India: a review," *International Journal of Tuberculosis and Lung Disease* 9, no. 10 (2005): 1072-82.
10 "TB India 2012: RNTCP Annual Report," Central TB Division, Ministry of Health and Family Welfare, Government of India, March 2012, http://tbcindia.nic.in/pdfs/TB%20India%202012-%20Annual%20Report.pdf.
11 M. Goodchild et al, "A cost-benefit analysis of scaling up tuberculosis control in India," *International Journal of Tuberculosis and Lung Disease* 15, no. 3 (2011): 358-62.
12 "Global Tuberculosis Report 2014."
13 V. Chadha et al, "Trends in the annual risk of tuberculosis infection in India," *The International Journal of Tuberculosis and Lung Disease* 17, no. 3 (2013): 312-9.
14 "Global Tuberculosis Report 2014."
15 S. Satyanarayana et al, "From where are tuberculosis patients accessing treatment in India? Results from a cross-sectional community based survey of 30 districts," *PLoS One*, September 2, 2011, http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0024160.

[16] Sunil K. Kapoor et al, "How Did the TB Patients Reach DOTS Services in Delhi? A Study of Patient Treatment Seeking Behavior," *PLoS One*, August 6, 2012, http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0042458.
[17] R. Ramachandran et al, "Surveillance of drug-resistant tuberculosis in the state of Gujarat, India," *International Journal of Tuberculosis and Lung Disease* 13, no. 9 (2009): 1154-60.
[18] "Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 Global Report on Surveillance and Response," World Health Organization, 2010, http://apps.who.int/iris/bitstream/10665/44286/1/9789241599191_eng.pdf?ua=1&ua=1.
[19] Z.F. Udwadia et al, "Totally drug-resistant tuberculosis in India," *Clinical Infectious Diseases* 54, no. 4 (2012): 579-81.
[20] A. Dalal et al, "Resistance patterns among multidrug-resistant tuberculosis patients in greater metropolitan Mumbai: trends over time," *PLoS One* 10, no. 1 (2015).
[21] Anurag Bhargava, Lancelot Pinto and Madhukar Pai, "Mismanagement of tuberculosis in India: Causes, consequences, and the way forward," *Hypothesis Journal* 9, no. 1 (2011), http://www.hypothesisjournal.com/?p=989.
[22] M. Pai and J. Das, "Management of tuberculosis in India: time for a deeper dive into quality," *National Medical Journal of India* 26, no. 2 (2013): 65-8.
[23] S. Satyanarayana et al, "Health-care seeking among people with cough of 2 weeks or more in India. Is passive TB case finding sufficient?," *Public Health Action* 2 (2012): 157-61.
[24] S. Achanta et al, "Tuberculosis Management Practices by Private Practitioners in Andhra Pradesh, India," *PLoS One*, August 13, 2013, http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0071119.
[25] "Global Tuberculosis Report 2014."
[26] C.T. Sreeramareddy et al, "Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review," *International Journal of Tuberculosis and Lung Disease* 18, no. 3 (2014): 255-66.
[27] World Health Organization, *Treatment of Tuberculosis Guidelines* (Geneva: World Health Organization, 2010), http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf?ua=1.
[28] U.M. Jha et al, "Risk factors for treatment default among re-treatment tuberculosis patients in India, 2006," *PLoS One* 5, no. 1 (2010).
[29] Achanta et al, "Tuberculosis management."
[30] S. Bharaswadkar et al, "Tuberculosis management practices of private practitioners in Pune municipal corporation, India," *PLoS One*, June 4, 2014, http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0097993.
[31] "TB India 2014, RNTCP Annual Status Report," Central TB Division, Ministry of Health and Welfare, Government of India, 2014, http://www.tbcindia.nic.in/pdfs/TB%20INDIA%202014.pdf.
[32] N. Singla et al, "Impact of Introducing the Line Probe Assay on Time to Treatment Initiation of MDR-TB in Delhi, India," *PLoS One* 9, no. 7 (2014).
[33] Bhargava, Pinto and Pai, "Mismanagement."
[34] S.K. Sachdeva er al, "New vision for Revised National Tuberculosis Control Programme (RNTCP): Universal access - "Reaching the un-reached"," *Indian Journal of Medical Research* 135, no. 5 (2012): 690-4.
[35] Mumbai Mission for Tuberculosis Control, http://www.stoptb.org/news/stories/2014/ns14_084.asp.
[36] Initiative for Promoting Affordable and Quality Tests, http://www.ipaqt.org/home.php.
[37] Puneet Dewan, "How India is moving the needle on TB," *Bill & Melinda Gates Foundation*, January 8, 2015, http://www.impatientoptimists.org/Posts/2015/01/How-India-is-moving-the-needle-on-TB.
[38] M. Pai, P. Yadav and R. Anupindi, "Tuberculosis control needs a complete and patient-centric solution," *Lancet Glob Health* 2, no. 4 (2014), http://www.thelancet.com/journals/langlo/article/PIIS2214-109X%2814%2970198-6/fulltext?rss=yes.
[39] S. Bagcchi, "Indian government outlines plan to try to eliminate tuberculosis by 2020," *BMJ* 349 (2014).
[40] Kanchan Srivastava, "TB epidemic looms large with Rs 2,000 crore fund cut, erred policy," *DNA India*, January 10, 2015, http://www.dnaindia.com/mumbai/report-tb-epidemic-looms-large-on-rs-2500-crore-funds-cut-poor-management-2051254.

3

[1] "TB India 2014, RNTCP Annual Status Report," Central TB Division, Ministry of Health and Family Welfare, Government of India, http://www.tbcindia.nic.in/Pdfs/TB%20INDIA%202014.pdf.
[2] "Global Tuberculosis Report 2014," World Health Organization, 2014, http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf?ua=1.
[3] D.T. D'Souza et al, "High levels of multidrug resistant tuberculosis in new and treatment-failure patients from the Revised National Tuberculosis Control Programme in an urban metropolis (Mumbai) in Western India," *BMC Public Health*, 9 (2009): 211.
[4] L.B. Reichman, "TIMEBOMB revisited 10 years later: can we sustain progress or are we losing the war?," Sir John Crofton Memorial Lecture, *The International Journal of Tuberculosis and Lung Disease* 17, no. 11 (2013): 1377-82.
[5] G. Anand, "A Woman's Drug-Resistant TB Echoes Around the World," *The Wall Street Journal*, September 8, 2012.
[6] A.K. Chakraborty, "Epidemiology of tuberculosis: current status in India," *Indian Journal of Medical Research* 120, no. 4 (2004): 248-76.
[7] T.P Trial, "Trial of BCG vaccines in South India for tuberculosis prevention," *Indian Journal of Medical Research* 72, Supplementary (1980): 1-74.
[8] A.S. Azman and D.W. Dowdy, "Bold thinking for bold results: modeling the elimination of tuberculosis," *International Journal of Tuberculosis and Lung Disease* 18, no. 8 (2014): 883.
[9] G.J. Churchyard at al, "A trial of mass isoniazid preventive therapy for tuberculosis control," *New England Journal of Medicine* 370, no. 17 (2014): 1662-3.
[10] "Global Tuberculosis Report 2014."

[11] "National Family Health Survey (NFHS-3), 2005-06: India: Volume I," International Institute for Population Sciences (IIPS) and Macro International, 2007, http://www.rchiips.org/nfhs/NFHS-3%20Data/VOL-1/India_volume_I_corrected_17oct08.pdf.
[12] "Physical status: the use and interpretation of anthropometry," World Health Organization Expert Committee Report, http://www.who.int/childgrowth/publications/physical_status/en/.
[13] A. Bhargava et al, "Undernutrition and the incidence of tuberculosis in India: national and subnational estimates of the population-attributable fraction related to undernutrition," *National Medical Journal of India* 27, no. 3 (2014): 128-33.
[14] T. McKeown and R.G. Record, "Reasons for the Decline of Mortality in England and Wales during the Nineteenth Century," *Population Studies* 16, no. 2 (1962): 94-122.
[15] S. Szreter, "Rethinking McKeown: Relationship between Public health and social change," *American Journal of Public Health* 92, no. 5 (2002): 722-5.
[16] K. Faber, "Tuberculosis and Nutrition," *Acta Tuberc Scandinavica* 12, no. 4 (1938): 287-335.
[17] G.B. Leyton, "Effects of Slow starvation," *Lancet* 248, no. 6412 (1946): 73-9.
[18] A.L. Cochrane, "Tuberculosis among Prisoners of War in Germany," *British Medical Journal* 2, no. 4427 (1945): 656-8.
[19] E.M. Brieger, *The Papworth Families: A 25 Years Survey* (London: Heinemann, 1944).
[20] A. Bhargava et al, "Can social interventions prevent tuberculosis?: the Papworth experiment (1918-1943) revisited," *American Journal of Respiratory and Critical Care Medicine* 186, no. 5 (2012): 442-9.
[21] K. Lonnroth et al, "A consistent log-linear relationship between tuberculosis incidence and body mass index," *International Journal of Epidemiology* 39, no. 1 (2010): 149-55.
[22] "The Children-Nutrition," UNICEF India, February 13, 2015, http://www.unicef.org/india/children_2356.htm.
[23] H.E. Magee, "Application Of Nutrition To Public Health: Some Lessons Of The War," *The British Medical Journal* 1, no. 4447 (1946): 475-82.
[24] C.T. Sreeramareddy et al, "Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review," *International Journal of Tuberculosis and Lung Disease* 18, no. 3 (2014): 255-66.
[25] A. Banerjee et al, "Acceptability of traditional healers as directly observed treatment providers in tuberculosis control in a tribal area of Andhra Pradesh, India," *The International Journal of Tuberculosis and Lung Disease* 8, no. 10 (2004): 1260-5.
[26] Z.F. Udwadia, L.M. Pinto, M.W. Uplekar, "Tuberculosis management by private practitioners in Mumbai, India: has anything changed in two decades?," *PLoS One* 5, no. 8 (2010), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2918510/.
[27] M.R. Joseph, "Surveillance of anti-tuberculosis drug resistance in Ernakulam District, Kerala State, South India," *International Journal of Tuberculosis and Lung Disease* 11, no. 4 (2007): 443-9.
[28] S. Swaminathan et al, "Anti-tuberculosis drug resistance in patients with HIV and tuberculosis in South India," *International Journal of Tuberculosis and Lung Disease* 9, no. 8 (2005): 896-900.
[29] A.K. Maurya et al, "Trends of anti-tuberculosis drug resistance pattern in new cases and previously treated cases of extrapulmonary tuberculosis cases in referral hospitals in northern India," *Journal of Postgraduate Medicine* 58, no. 3 (2012): 185-9.
[30] S. Sethi et al, "Prevalence of multidrug resistance in Mycobacterium tuberculosis isolates from HIV seropositive and seronegative patients with pulmonary tuberculosis in north India," *BMC Infectious Diseases* 13 (2013), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3610146/.
[31] "Addressing poverty in TB control: options for National TB Control Programmes," World Health Organization, 2005, http://whqlibdoc.who.int/hq/2005/who_htm_tb_2005.352.pdf.
[32] "Revised National Tuberculosis Control Programme. Social action plan," Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, 2013.
[33] C.P. Chaulk and V. A. Kazandjian, "Directly Observed Therapy for Treatment Completion of Pulmonary Tuberculosis," *Journal of the American Medical Association* 279, no. 12 (1998): 943-8.
[34] F.W. Peabody, "The care of the patient," *Journal of the American Medical Association* 88, no. 12 (1927): 877-82.
[35] A. Bhargava, M. Chatterjee et al, "Nutritional status of adult patients with pulmonary tuberculosis in rural central India and its association with mortality," *PLoS One* 8, no. 10 (2013), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3812022/.
[36] "TB India 2014, RNTCP Annual Status Report," Central TB Division, Ministry of Health and Family Welfare, Government of India, http://www.tbcindia.nic.in/Pdfs/TB%20INDIA%202014.pdf.
[37] "TB India 2014."
[38] "India must address worrying stock out of tuberculosis drugs," *Medecins Sans Frontieres*, June 17, 2013, http://www.msf.org/article/india-must-address-worrying-stock-out-tuberculosis-drugs.
[39] "TB India 2014."
[40] "TB India 2014."
[41] World Health Organization, *Treatment of tuberculosis: Guidelines* (Geneva: World Health Organization, 2010), http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf.
[42] A. Bhargava and Y. Jain, "The Revised National Tuberculosis Control Programme in India: Time for revision of treatment regimens and for rapid upscaling of DOTS-plus initiative," *National Medical Journal of India* 21, no. 4 (2008): 187-91.
[43] "Global strategy and targets for tuberculosis prevention, care and control after 2015," World Health Organization, http://www.who.int/tb/post2015_TBstrategy.pdf.
[44] "Bureau of Tuberculosis Control Annual Summary, 2013," New York City Department of Health and Mental Hygiene http://www.nyc.gov/html/doh/downloads/pdf/tb/tb2013.pdf.

4

1 V.K. Chadha, "Tuberculosis in India: a review," *International Journal of Tuberculosis and Lung Disease* 9, no. 10 (2005): 1072-82.

2 "Global Tuberculosis Report 2014," World Health Organization, http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf?ua=1.

3 D.T. D'souza et al, "High levels of multidrug resistant tuberculosis in new and treatment failure patients from the Revised National Tuberculosis Control Program in an urban metropolis (Mumbai) in Western India," *BMC Public Health* (2009): 2001-11.

4 I. Harper, "Interconnected and Inter-infected: DOTS and the Stabilization of the Tuberculosis program in Nepal," in *The Aid Effect: Giving and Governing in International Development*, eds. David Mosse and David Lewis (London, Ann Arbor, MI: Pluto Press, 2005): 126-49.

5 S. Jain et al, "High prevalence of XDR-TB from a tertiary hospital in India" (abstract A510 at American Thoracic Society 2007 International Conference, San Francisco, CA, USA, May 18-23, 2007).

6 Z.F. Udwadia et al, "Totally drug-resistant tuberculosis in India," *Clinical Infectious Diseases* 54, no. 4 (2012): 579-81.

7 Z.F. Udwadia, "India's multidrug-resistant TB crisis," *Annals of the New York Academy of Sciences* 953 (2001): 98-105.

8 P. Farmer et al, "The dilemma of MDR-TB in the global era," *International Journal of Tuberculosis and Lung Disease* 2, no. 11 (1998): 869-76.

9 N. Engel, "New diagnostics for multi-drug resistant tuberculosis in India: innovating control and controlling innovation," *BioSocieties* 7 (2012): 50-71.

10 Z.F. Udwadia, L. M. Pinto and M.W. Uplekar, "Tuberculosis control by private practitioners in Mumbai, India: has anything changed in two decades?" *PLoS One*, Auust 9, 2010, http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0012023.

11 "Helping the poorest," *Economist*, August 12, 1999, http://www.economist.com/node/231482.

12 M.W. Uplekar and S. Rangan, "Private doctors and tuberculosis control in India," *Tubercle & Lung Diseases* 74, no. 5 (1993): 332-7.

13 R. Upshur, J. Singh and N. Ford, "Apocalypse or redemption: responding to XDR-TB," *Bull World Health Organ.* 87, no. 6 (2009): 481-3.

14 V. Gajalakshmi et al, "Smoking and mortality from tuberculosis and other diseases in India," *Lancet* 362, no. 9393 (2003): 507-15.

15 L. Pinto and Z.F. Udwadia, "Why "STOP TB" is incomplete without quit smoking," *Indian Journal of Chest Diseases and Allied Sciences* 53, no. 1 (2011): 9-10.

16 P.V. Lakshmi et al, "Biomass fuel and risk of tuberculosis: a case-control study from Northern India," *Journal of Epidemiology and Community Health* 66, no. 5 (2012): 457-61.

7 S.S. Hwang et al, "Impact of outdoor air pollution on the incidence of tuberculosis in the Seoul metropolitan area," *Korean Journal of Internal Medicine* 29, no. 2 (2014): 183-90.

8 N. Engel, "New diagnostics for multi-drug resistant tuberculosis in India: innovating control and controlling innovation," *BioSocieties* 7, no. 1 (2012): 50-71.

9 "Global Tuberculosis Report 2014."

20 A. Bhargava, L. Pinto and M. Pai, "Mismanagement of tuberculosis in India: causes, consequences, and the way forward," *Hypothesis* 9 (2011): 1-13.

21 D.W. Dowdy et al, "Is scale-up worth it? Challenges in economic analysis of diagnostic tests for tuberculosis," *PLoS Med* 8, no. 7 (2011).

22 Z.F Udwadia and G. Moharil, "MDR-TB treatment in the Indian private sector: results from a tertiary private hospital in Mumbai," *Lung India* 31, no. 4 (2014): 336-41.

23 "The Global Fund Round 9 TB Project Activity Report 2010-11," Project Axshya.

24 A. Shepherd-Smith, "Free drugs for India's poor," *Lancet* 380, no. 9845 (2012): 874-5.

25 "TB in India," Central TB Division, Ministry of Health and Family Welfare, Government of India, 2014, http://www.tbcindianic.in/rntcp.html.

26 D. Agrawal et al, "Increasing incidence of fluoroquinolone resistant Mycobacterium tuberculosis in Mumbai, India" *International Journal of Tuberculosis and Lung Disease* 13, no. 1 (2009): 79-83.

27 Helen Bynum, *Spitting Blood: The history of tuberculosis* (Oxford: Oxford University Press, 2012).

28 D. Falzon et al, "MDR-TB around the world: what progress has been made?" *Europe Respiratory Journal* 45, no. 1 (2015): 150-60.

29 P.M. Farmer et al, "The dilemma of MDR-TB in the global era" *International Journal of Tuberculosis and Lung Disease* 2, no. 11 (1998): 869-76.

30 Z.F. Udwadia, "MDR, XDR, TDR tuberculosis: ominous progression," *Thorax* 67, no. 4 (2012): 286-8.

31 C.A. Evans, "GeneXpert – a game-changer for tuberculosis control?" *PLoS Med*, July 26, 2011, http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001064.

32 J.A Khan et al, "Engaging the private sector to increase tuberculosis case detection: an impact evaluation study," *Lancet Infectious Diseases* 12, no. 8 (2012): 608-16.

33 Z.F. Udwadia, R.A. Amale and J.B. Mullerpattan, "Initial experience of bedaqualine use in a series of drug resistant tuberculosis patients from India," *International Journal of Tuberculosis and Lung Disease* 18, no. 11 (2014): 1315-18.

34 P.E. Farmer, "Chronic Infectious Disease and the Future of Health Care Delivery," *New England Journal of Medicine* 369 (2013): 2424-36.

35 M. Pai and D.J. Christopher, "Protecting young healthcare trainees from tuberculosis: can we overcome apathy," *National Medical Journal of India* 24, no. 4 (2012): 198-200.

5

1. "The need for new vaccines," *Aeras*, 2014, http://www.aeras.org//pages/need-for-new-vaccines.
2. "About RNTCP," TBC India, Ministry of Health and Family Welfare, Government of India, http://www.tbcindia.nic.in/rntcp.html.
3. "TB India 2007: RNTCP Annual Status Report," Central TB Division, Ministry of Health and Family Welfare, Government of India, http://www.tbcindia.nic.in/Pdfs/TB%20INDIA%202007.pdf.
4. "Standard Operating Procedures Manual for State Drug Stores," Central TB Division, Ministry of Health and Family Welfare, Government of India, 2008, http://tbcindia.nic.in/pdfs/SOP%20for%20SDS%20Drug%20Stores.pdf.
5. "The need for new vaccines," *Aeras*, 2014, http://www.aeras.org//pages/need-for-new-vaccines.
6. Mike Frick, "The Tuberculosis Vaccines Pipeline," *Pipeline Report*, July 2014, http://www.pipelinereport.org/2013/tb-vaccine.
7. "Global Tuberculosis Report 2012," World Health Organization, p.66, http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf.
8. B.G. Batz, G.S. Cooke and S.D. Reid, "Towards Lab-Free Tuberculosis Diagnosis," Treatment Action Group, Stop TB Partnership, Imperial College London and Médecins Sans Frontières, August 2011, http://www.treatmentactiongroup.org/sites/tagone.drupalgardens.com/files/tbpocdiafull.pdf.
9. "Line Probe Assay," Tuberculosis, FIND, http://www.finddiagnostics.org/programs/tb/find_activities/line_probe_assay_1.html.

6

1. "AIDS in New York City, 1981-2007," New York City Department of Health and Mental Hygiene, 2009, http://www.nyc.gov/html/doh/downloads/pdf/dires/epi-surveillance-aids07.pdf.
2. Poonam Kuruganti, "Healthcare achievements of post-independent India," *The Health Site*, August 17, 2012, http://www.thehealthsite.com/diseases-conditions/healthcare-achievements-of-post-independent-india/.
3. "Global Tuberculosis Report 2014," World Health Organization, http://www.who.int/tb/publications/global_report/gtbr14_executive_summary.pdf.
4. Bijoyeta Das, "In Pictures: India's drug-resistant TB crisis," *Al Jazeera*, February 17, 2014, http://www.aljazeera.com/indepth/inpictures/2014/02/pictures-india-drug-resistant-tb--2014210100656564.html.
5. Nerges Mistry, Monica Tolani and David Osrin, "Drug-resistant tuberculosis in Mumbai India: An agenda for operations research," *Operations Research for Healthcare* 1, no. 2-3 (2012): 45-53.
6. Mistry, Tolani and Osrin, "Drug-resistant tuberculosis in Mumbai."
7. Soumya Swaminathan and Chapal Mehra, "The missing million tuberculosis patients hold the key," *Hindustan Times*, February 12, 2015, http://www.hindustantimes.com/analysis/the-missing-million-tuberculosis-patients-hold-the-key/article1-1316284.aspx.
8. "Tuberculosis and HIV," World Health Organization, 2013, http://www.who.int/hiv/topics/tb/en/.
9. "India HIV & AIDS Statistics," *Avert*, http://www.avert.org/india-hiv-aids-statistics.htm.
10. "AIDS in New York City, 1981-2007."
11. Richard Coker, "Lessons from New York's tuberculosis epidemic," *BMJ* 317, no. 7159 (1998): 616-20.
12. Coker, "Lessons from New York's."
13. Coker, "Lessons from New York's."
14. "Information Summary 1997," Bureau of Tuberculosis Control, New York City Department of Health, http://www.nyc.gov/html/doh/downloads/pdf/tb/tb1997.pdf.
15. Katherine Floyd et al, "Cost and cost-effectiveness of PPM-DOTS for tuberculosis control: evidence from India," *Bulletin of the World Health Organization* 84, no. 6 (2006): 425-504.

7

1. "TB India 2014, RNTCP Annual Status Report," Central TB Division, Ministry of Health and Family Welfare, Government of India, http://www.tbcindia.nic.in/Pdfs/TB%20INDIA%202014.pdf.
2. "TB India 2012, RNTCP Annual Status Report," Central TB Division, Ministry of Health and Family Welfare, Government of India, http://tbcindia.nic.in/pdfs/TB%20India%202012-%20Annual%20Report.pdf.
3. "TB India 2007, RNTCP Annual Status Report," Central TB Division, Ministry of Health and Family Welfare, Government of India, http://tbcindia.nic.in/pdfs/TB%20India%202007.pdf.
4. "World TB Day 2014 Concept Note," Stop TB Partnership, http://www.stoptb.org/assets/documents/news/WORLD%20TB%20DAY%202014%20concept%20note.pdf.
5. "Role of civil society organisations in facilitating community based monitorin," National Health Mission, Ministry of Health and Family Welfare, Government of India, http://nrhm.gov.in/communitisation/community-action/role-of-civil-society-organisations-in-facilitating-community-based-monitoring.html.
6. "The Stop TB Strategy," World Health Organization, http://www.who.int/tb/strategy/en/.
7. The Global Fund, www.theglobalfund.org.
8. "Civil Society," *The Global Fund*, http://www.theglobalfund.org/en/civilsociety/.
9. "Project Axshya," *The Union*, http://www.theunion.org/what-we-do/technical-assistance/tuberculosis-and-mdr-tb/project-axshya.

8

1. "TB India 2014, RNTCP Annual Status Report," Central TB Division, Ministry of Health and Family Welfare, Government of India, http://www.tbcindia.nic.in/Pdfs/TB%20INDIA%202014.pdf.
2. "About RNTCP," TBC India, http://www.tbcindia.nic.in/rntcp.html.
3. "TB India 2012, RNTCP Annual Status Report," Central TB Division, Ministry of Health and Family Welfare, Government of India, http://tbcindia.nic.in/pdfs/TB%20India%202012-%20Annual%20Report.pdf.
4. "TB India 2007, RNTCP Annual Status Report," Central TB Division, Ministry of Health and Family Welfare, Government of India, http://www.tbcindia.nic.in/Pdfs/TB%20INDIA%202007.pdf.
5. "Standard Operating Procedures Manual for State Drug Stores," Central TB Division, Ministry of Health and Family Welfare, Government of India, 2008, http://tbcindia.nic.in/pdfs/SOP%20for%20SDS%20Drug%20Stores.pdf.
6. "Bolangir District: Census 2011 data," Census 2011 India, http://www.census2011.co.in/census/district/417-balangir.html.
7. Answer by Ghulam Nabi Azad, Former Minister of Health and Family Welfare, to a question by Kalikesh Narayan Singh Deo, February 7, 2014, http://164.100.47.132/LssNew/psearch/QResult15.aspx?qref=149575.
8. "TB India 2014."
9. "TB India 2014."
10. Malathy Iyer, "57% of TB patients given wrong drugs," *Times of India*, February 15, 2015, http://timesofindia.indiatimes.com/india/57-of-TB-patients-given-wrong-drugs/articleshow/46248551.cms
11. "TB India 2014."

9

1. S.K. Sharma and A. Mohan, "Extrapulmonary Tuberculosis," *Indian Journal of Medical Research* 120, no. 4 (2004): 316-53.
2. K. Gopinath, S. Kumar and S. Singh, "Prevalence of mycobateremia in Indian HIV-infected patients detected by the MB/Bact automated culture system," *European Journal of Clinical Microbiology and Infectious Diseases* 27, no. 6 (2008): 423-31.
3. "Tuberculosis Profile: India," World Health Organization, 2015, https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=IN&LAN=EN&outtype=html.
4. L.A.M te Beek et al, "Extrapulmonary Tuberculosis by Nationality, the Netherlands, 1993-2001," *Emerging Infectious Diseases* 12, no. 9 (2006): 1375-82.
5. V.K. Arora and S.P. Agarwal, "Paediatric Tuberculosis: An Experience from LRS Institute of Tuberculosis and Respiratory Diseases," in *Tuberculosis Control in India*, eds. S.P. Agarwal and L.S. Chauhan. (New Delhi: Directorate General of Health Services, 2005), http://tbcindia.nic.in/pdfs/Tuberculosis%20Control%20in%20India12.pdf.
6. A. Munawwar and S. Singh, "AIDS associated tuberculosis: a catastrophic collision to evade the host immune system," *Tuberculosis* 92, no. 5 (2012): 384-7.
7. S. Singh, M.M. Sankar and K. Gopinath, "High rate of extensively drug-resistant tuberculosis in Indian AIDS patients," *AIDS* 21, no. 17 (2007): 2345-7.
8. "Commercial Serodiagnostic Tests for Diagnosis of Tuberculosis: Policy Statement," World Health Organization, 2011, http://whqlibdoc.who.int/publications/2011/9792415052054_eng.pdf. 2011.
9. M.M. Sankar et al, "Diagnostic performance of commercially available enzyme-linked immunosorbent assay kit in the diagnosis of extrapulmonary tuberculosis," *Journal of Laboratory Physicians* 5, no. 1 (2013): 11-6.
10. M.M. Sankar et al, "Usefulness of multiplex PCR in the diagnosis of genital tuberculosis in females with infertility," *European Journal of Clinical Microbiology and Infectious Diseases* 32, no. 3 (2012): 399-405.
11. M.M. Sankar et al, 2012. "Molecular characterization of Mycobacterium tuberculosis isolates from North Indian patients with extrapulmonary tuberculosis," *Tuberculosis* 93, no. 1 (2013): 75-83.

10

1. "World TB Day Concept Note," Stop TB Partnership, 2014, http://www.stoptb.org/assets/documents/news/WORLD%20TB%20DAY%202014%20concept%20note.pdf.
2. "Global Tuberculosis Report 2013," World Health Organization, http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf.
3. "Global Tuberculosis Report 2014," World Health Organization, www.who.int/tb/publications/global.../gtbr14_executive_summary.pdf.
4. "TB India 2014, RNTCP Annual Status Report," Central TB Division, Ministry of Health and Family Welfare, Government of India, http://tbcindia.nic.in/pdfs/TB%20India%202014-%20Annual%20Report.pdf.
5. "TB India 2014."
6. "TB India 2014."
7. "Joint Monitoring Mission, Revised National Tuberculosis Control Programme," India Country Office, World Health Organization, 2013.
8. Lindsay Morgan, "Successful Tuberculosis Control Program in China Incorporates Results Based Financing (RBF)," World Bank Feature, http://www.rbfhealth.org/sites/rbf/files/RBF_FEATURE_China_TB.pdf.
9. "Cambodia turns a TB health crisis into an opportunity," World Health Organization, October 2012, http://www.who.int/features/2012/tb_cambodia/en/.
10. "About the Global TB Caucus," *The Global TB Caucus*, http://www.globaltbcaucus.org/#!about/c21pi.

11

[1] "Treaty for The Establishment of a BRICS Contingent Reserve Arrangement" and "Agreement on the New Development Bank," Ministry of External Relations, Government of Brazil, 2014, http://brics6.itamaraty.gov.br/agreements.
[2] L.E. Armijo and C. Roberts, "The Emerging Powers and Global Governance: Why the BRICS matter," in *Handbook of Emerging Economies*, ed. R.E. Looney (Abingdon and New York: Routledge, 2014): 503-24.
[3] S.D. Krasner (1983) "Structural causes and regime consequences: regimes as intervening variables" and R. Jervis, "Security Regimes," in *International Regimes*, ed. S.D. Krasner (Ithaca: Cornell University Press, 1983); R.O. Keohane and J.S. Nye, *Power and Interdependence* (Boston: Little, Brown and Company, 1977).
[4] R. Keohane, *Beyond Hegemony* (Princeton: Princeton University Press, 1984).
[5] R. Keohane (1998) "International institutions: Can interdependence work?," *Foreign Policy*, Spring 1998, 82-96.
[6] J. Creswell et al, "Tuberculosis in BRICS: challenges and opportunities for leadership within the post-2015 agenda," *Bulletin of the World Health Organization* 92(2014):459–460, http://www.who.int/bulletin/volumes/92/6/13-133116/en/.
[7] J.F. Murray, "A Century of Tuberculosis," *American Journal of Respiratory and Critical Care Medicine* 169, no. 11 (2004): 1181–86.
[8] "Global TB Report 2014," World Health Organization, 2014, http://www.who.int/tb/publications/global_report/en/.
[9] N.R. Gandhi et al, "Multidrug-resistant and extensively drug-resistant TB: a threat to global control of TB," *Lancet* 375, no. 9728 (2010): 1830-43.
[10] "Global TB Report 2014."
[11] Murray, "A Century of Tuberculosis."
[12] "Global TB Report 2014."
[13] O. Oxlade and M. Murray, "Tuberculosis and Poverty: Why Are the Poor at Greater Risk in India?," *PloS One* 7, no. 11 (2012), http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0047533.
[14] "World Development Indicators," World Bank, 2014, http://databank.worldbank.org/data/views/variableSelection/selectvariables.aspx?source=world-development-indicators.
[15] "Special Focus: Inequality in Emerging Economies (EEs)," Organization for Economic Co-operation and Development, 2011, http://www.oecd.org/els/soc/49170475.pdf.
[16] "Global TB Report 2014."
[17] "Global TB Report 2014."
[18] "Global TB Report 2014."
[19] R. Marten et al, "An assessment of progress towards universal health coverage in Brazil, Russia, India, China, and South Africa (BRICS)," *Lancet* 384, no. 9960 (2014): 2164–71.
[20] "Brazil's Primary Care Strategy," Universal Health Coverage Study Series, World Bank, 2014, http://www.worldbank.org/en/topic/health/publication/universal-health-coverage-study-series.
[21] Institute of Medicine, *The Global Crisis of Drug-Resistant Tuberculosis and Leadership of China and the BRICS: Challenges and Opportunities* (Washington: National Academic Press, 2014), http://www.iom.edu/Reports/2013/The-Global-Crisis-of-Drug-Resistant-Tuberculosis-and-Leadership-of-China-and-the-BRICS.aspx.
[22] L. Popovichet al, "Russian Federation: Health system review," *Health Systems in Transition* 13, no. 7 (2011), http://www.euro.who.int/__data/assets/pdf_file/0006/157092/HiT-Russia_EN_web-with-links.pdf?ua=1.
[23] Institute of Medicine and Russian Academy of Medical Sciences, *The New Profile of Drug-Resistant Tuberculosis in Russia: A Global and Local Perspective* (Washington: The National Academies Press, 2011), http://www.ncbi.nlm.nih.gov/books/NBK62461/.
[24] K.S. Sachdevaet al, "New Vision for Revised National Tuberculosis Control Programme (RNTCP): Universal access - Reaching the un-reached," *Indian Journal of Medical Research* 135, no. 5 (2012): 690-4, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3401704/.
[25] "The Long March to Universal Coverage: Lessons from China," Universal Health Coverage Studies Series, World Bank, 2013, http://www.worldbank.org/en/topic/health/publication/universal-health-coverage-study-series.
[26] Institute of Medicine, *The Global Crisis*.
[27] C. Keeton, "Bridging the gap in South Africa," *Bulletin of the World Health Organization* 88, no. 11 (2010): 797–876.
[28] "Declaration of the I Meeting of BRICS Health Ministers, Beijing, China, July 11, 2011," Ministry of External Relations, Government of Brazil, 2011, http://brics6.itamaraty.gov.br/category-english/21-documents/167-brics-health-ministers-meeting.
[29] M. Raviglioneet al, "Rebalancing the global battle against tuberculosis," *LancetGlobal Health*2, no. 2 (2014),http://www.thelancet.com/journals/langlo/article/PIIS2214-109X%2813%2970166-9/abstract.
[30] "Declaration of the I Meeting."
[31] "Agreement on the New Development Bank."
[32] "Communiqué of the IV Meeting of BRICS Health Ministers," Ministry of External Relations, Government of Brazil, 2014, http://brics6.itamaraty.gov.br/category-english/21-documents/242-ivhealth.
[33] Molly Anders, "Can the BRICS bank rally global outcasts around TB treatment?," *Devex*, November 6, 2014, https://www.devex.com/news/can-the-brics-bank-rally-global-outcasts-around-tb-treatment-84733.
[34] Creswell et al, "Tuberculosis in BRICS."
[35] Institute of Medicine, *The Global Crisis*.
[36] "Communiqué of the IV Meeting of BRICS."
[37] Médecins Sans Frontières, "BRICS countries must boost investments in research to defeat deadly drug-resistant tuberculosis crisis," press release, Rio de Janeiro, December 5, 2014, http://www.msfaccess.org/about-us/media-room/press-releases/brics-countries-must-boost-investments-research-defeat-deadly.
[38] "Communiqué of the IV Meeting of BRICS."

INDIA BEARS THE WORLD'S LARGEST BURDEN OF TUBERCULOSIS (TB), ACCOUNTING FOR ONE-FOURTH OF ALL NEW INFECTIONS. GIVEN THAT IT KILLS NEARLY 300,000 PEOPLE IN INDIA EVERY YEAR, THE PREVENTION AND CONTROL OF TB IS A CHALLENGE AT MULTIPLE LEVELS, REQUIRING THE UNITED EFFORTS OF A DIVERSE RANGE OF STAKEHOLDERS. WHILE INDIA HAS BEEN PROACTIVE AGAINST TB IN RECENT YEARS, THERE IS STILL A LONG WAY TO GO. THIS SPECIAL ISSUE FEATURES ARTICLES FROM LEADING POLICYMAKERS, ADMINISTRATORS, TECHNICAL EXPERTS, JOURNALISTS AND MEMBERS OF CIVIL SOCIETY WORKING IN INDIA'S TB LANDSCAPE. IT OUTLINES THE MULTIFACETED NATURE OF THE TB EPIDEMIC, ITS IMPACT ON COMMUNITIES, LEARNINGS FROM GLOBAL SUCCESSES AND THE WAY FORWARD TOWARDS TACKLING THE DISEASE SUCCESSFULLY.

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