Obstacles facing an effective national tuberculosis treatment program: a case study of India.

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ABSTRACT

Tuberculosis (TB) is a disease of major significance, being one of the top ten causes of death globally. India bears a disproportionately large burden, accounting for more than a quarter of the world's cases. Over the last 25 years, the Indian Government has scaled-up a national diagnostics and treatment program to cover the entire country. However, there is accumulating evidence that the total TB incidence and that of multi-drug resistance cases has not changed and may even be increasing. In this article, we discuss possible obstacles facing the Indian TB control programme. These include a largely unregulated private sector, underfunding of the Indian health budget, inadequate local knowledge about the disease in TB medication providers, gaps in the current cascade of care (from diagnosis to treatment), prevailing social stigma for TB and a high prevalence of other important comorbidities, such as poverty, diabetes, HIV and smoking. To achieve universal, high quality diagnostics and treatment coverage, effective collaboration with the private sector is key. Furthermore, efficient, evidence-based innovative mobile technologies plus the use of local community healthcare workers can benefit the most socially-marginalized upon whom these obstacles most impact in Indian society.

INTRODUCTION

Tuberculosis (TB) is a disease of major global significance, with an estimated 10.4 million new cases of active disease and 1.8 million deaths in 2015(1). A small number of countries: India, Indonesia, China, Nigeria, Pakistan and South Africa contribute to 60% of total global TB burden. People living with HIV account for 1.2 million (11%) of all new TB cases(1). In addition, there is an estimated 480,000 new cases of multidrug – resistant TB (MDR- TB) [defined as resistance to at least isoniazid and rifampicin] and 100,000 people living with non-MDR rifampicin-resistant TB(1). India, China and the Russian Federation accounts for 45% of the combined total of 580,000 cases rifampicin-resistant TB(1). The number of people with isoniazid-resistant TB is unknown globally, but likely to be several times more than this(2).

Effective TB control requires convenient, early and rapid access to healthcare services. All patients with suspected TB should have a comprehensive medical assessment, diagnostics to confirm disease and rapid anti-mycobacterial drug sensitivity testing. TB treatment requires careful monitoring to avoid side effects and adherence to a long-term drug regimen for a minimum of six months. MDR-TB is more complex: presentation is severely delayed and complicated regimens with multiple side effects are required. Furthermore, the prognosis of MDR-TB is worse and stringent infection control measures are needed in order to minimize transmission within the community(3). This makes MDR-TB an extremely expensive condition to treat properly.

Although governments in countries of high TB burden seek to provide large scale diagnostics and treatment, this has historically been difficult(4). India has a disproportionately large proportion of global TB cases(1). The country currently needs to overcome a number of obstacles before TB control can be achieved. In this article we discuss the challenges faced by India. Our findings are relevant to all countries implementing an effective national TB control programme.

TUBERCULOSIS IN INDIA

Before the late twentieth century, there are limited epidemiological data on TB in India (5). A national review of TB in India in 1992 found that less than half of patients with TB received an accurate diagnosis(5). And of these, under 50% were effectively treated. In response, the Indian government, together with the World Health Organization (WHO) and Swedish International Development Agency (SIDA) created the Revised National Tuberculosis Control Program (RNTCP). The RNTCP was officially launched in 1997(5). The strategy adopted Directly-Observed Therapy - Short Course (DOTS regimen) recommended by WHO at the time for drug-sensitive TB treatment(5).

There are five main components to the RNTCP: (1) strong political will and administrative commitment, (2) diagnosis by quality assured sputum smear microscopy, (3) uninterrupted supply of quality assured Short Course chemotherapy drugs, (4) Directly Observed Treatment and (5) systematic monitoring and accountability(6). The RNTCP is currently the second largest national TB treatment programme in the world, having treated over 19 million TB patients to date(7).

By March 2006 the RNTCP covered the whole of India(8). However the incidence of TB since implementation of the programme has not fallen. In October 2016 the WHO released the 2016 Global Tuberculosis Report. India was estimated to account for more than a quarter of global TB incidence (27%) , 16% of the estimated 480,000 new cases of MDR-TB and more than a third of global TB deaths(1). The report revealed that the TB burden in India for the period 2000 – 2015 had actually increased compared to previous estimates. This was based on a number of published and non-published non-governmental studies, and suggested that the private sector had been managing considerably more cases than previously thought (Table 1, see later). The 2015 estimate of new cases of TB in India of 2.8 million compared to 2.2 million in 2014(9). The 2015 Global Burden of Disease estimates TB as the 6th leading cause of death in India, a ranking that is unchanged since 2005(9). More than 480,000 deaths from TB occurred in 2015, a figure double that of the 2014 estimate of 220, 000(9). Successive reviews of the

RNTCP suggest that current implementation at the state level is weak, with several staff positions involving program oversight remaining unfulfilled in many states. Furthermore, allocated funds do not always arrive at their intended destinations resulting in many local health centers becoming ill-equipped and doctors employed by the government moving to private practice(10). The end result of this is that if the RNTCP were unchanged in India for the next 20 years, it is estimated that there would be gradual transformation from an epidemic of drug sensitive TB to drug resistant disease (11).

Why is there such a difference between expected and real outcomes? Apart from problems within the RNTCP itself, other issues need to be overcome (Figure 1). This includes longstanding underfunding of an ambitious system, a large and persistent variation in knowledge in those who see patients with TB, multiple complexities associated with TB diagnoses and treatment and most importantly, poor communication and collaboration with a giant private sector(12).

UNCONTROLLED PRIVATE SECTOR

The newly revised WHO TB estimates in India likely reflect regression to the true burden of community TB cases rather than increasing TB incidence. India currently only reports TB incidence based on public sector data(1) (13). Most cases treated inadequately in the private sector are never reported to public health authorities(14). Arinamipathy and colleagues assessed the burden of TB in India treated in the private sector using a large nationally representative commercial analysis of anti-TB products(13). Their findings suggest that 2.2 million TB cases might be treated in the private sector; a number that is twice that of the public sector and three times as much as previously estimated(13). Furthermore, since TB treatment in the private sector is typically paid for by out-of-pocket expenditure, an estimated US $59 million or more has been spent on first-line TB drugs alone in India's private sector(13).

Almost half of Indian patients choose to first seek healthcare from the private sector despite free treatment offered from the public health service(15). There are many

reasons for this. Firstly, access to private providers is often logistically more convenient for the majority of patients. Public RNTCP centers were set up without taking into account which locations had the highest TB burden(16). Consequently, many centers have been located too far for the majority of patients to realistically access on a regular basis.

Secondly, it is commonly perceived that higher quality healthcare can be provided by India's private sector despite evidence to the contrary (see later). A huge number of patients present to Indian hospitals every year, far more than the private system(17). Private healthcare practitioners have always been thought to be less overworked and more adept at medical treatment than public healthcare providers, despite the fact that in reality most work in both sectors (10)(17). Furthermore in 2010, WHO recommended the use of a daily regimen for all patients with TB as an intermittent regimen was associated with drug resistance. During this time, the private sector offered daily regimens to those able to pay for it. Whereas, it has taken almost six years for the RNTCP to implement the recommendation of using a daily regimen(18). This is likely to have negatively influenced public perceptions of the reliability of the RNTCP in achieving best practice.

UNDERFUNDING

The Indian government expenditure on health is one of the lowest in the world, at a gross domestic product of only 1.4%(19). Not only does this limited budget result in chronic underfunding of the current RNTCP, it hinders development of crucially more effective diagnostics in the form of rapid molecular testing as well as their large scale implementation. For example, in addition to inadequate treatment, the RNTCP continues to rely heavily on the relatively insensitive direct smear microscopy technology as a diagnostic. In the public sector, India performs about 72 smears for every rapid molecular TB diagnostic (Xpert MTB/RIF) test. In contrast, the public sector in South Africa (where the government has mandated the use of molecular tests as a

first line diagnostic) performs about two smears for every Xpert MTB/RIF test performed(20).

INADEQUATE ON-THE-GROUND KNOWLEDGE

The symptoms of TB, even when at their most obvious, may be mistaken for routine illnesses. Das and colleagues had simulated patients in good health from the local community to present with carefully standardized symptoms consistent with TB to randomly allocated healthcare providers in Delhi(21). The quality of medical care was measured by adherence to a case-specific checklist of essential and recommended care as well as the likelihood of correct diagnosis and appropriateness of treatment. They found that as few as 21% of TB patients seen by private healthcare providers in low and middle-income Delhi districts were correctly managed, with multiple areas of incompetence in both TB diagnosis and treatment follow-up. Studies also indicate that healthcare workers in the public RNTCP domain have unsatisfactory levels of clinical knowledge about TB (22). A systematic review of 47 studies published from 2000 to 2014 on provider knowledge and practices suggested that less than half of providers in the RNTCP had correct knowledge; less than a quarter order sputum smears for patients with chest symptoms and less than one third of providers knew the standard drug regimen for drug-susceptible TB(22).

GAPS IN THE CASCADE OF CARE

In addition to being missed at diagnosis, a significant number of patients are also lost after being referred following a medical evaluation and once treatment has started(15). On average in India a patient with TB is diagnosed nearly 2 months from presentation; and following consultation with an average of three healthcare professionals(15). This delay (which is generally longer in the private sector) makes it almost impossible to try to find, test and treat others who may have been infected by the index patient(23).

Inevitably the situation is worse in patients with HIV/TB co-infection, where joined up care requires much more co-ordination between services, with as little as 55% of TB patients in the Indian public sector being actually tested for HIV in the first place(24).

SOCIAL STIGMA AND FAILURE OF QUALITY ASSURANCE

Significant social stigma associated with TB continues to prevail in India.(25) This is particularly prominent in those most vulnerable to infection, resulting in fewer patients wanting to seek help. The failure of effective quality assurance of services across the whole RNTCP has meant that there are often severe procurement delays with new diagnostics and drug stock-outs(25). Furthermore, there is still much to do in order to ensure all patients are screened for drug resistance, and that adequate therapy is provided for MDR-TB and extensively drug-resistant TB. In both the 2015 and 2016 WHO Global Tuberculosis reports, India continues to be the country with the largest discrepancy between notification of new cases/relapses and best estimates of incidence, for both TB and MDR-TB(26)(1).

POVERTY, MALNUTRITION, SMOKING AND COMORBIDITIES

India must also tackle a plethora of other public health issues which impact on acheving TB control. Over 65 million people are affected by diabetes in India, a well-known risk factor for TB disease, and which will increase as life expectancy rises(27). Poverty(28), malnutrition(29) and tobacco smoking(30), have been clearly linked with TB and its mortality. An estimated 300 million Indian nationals still live in extreme poverty(28). The poor and socially marginalized communities may initially have greater priorities than accessing healthcare (such as needing food, money and shelter). When these groups eventually do seek help, not only are they often therefore sicker, but they may use cheaper, informal providers who have relatively poor clinical knowledge(15). India has one of the largest populations of malnourished TB patients, with half of all

their TB cases fitting this definition(29).This is greater in younger (15-19) age groups, rural areas, specific caste/tribes and those of low socioeconomic status; all key populations on whom in which diagnostics and treatment should be focused.

India accounts for 10% of the global HIV-TB burden(31). 130,000 new cases are diagnosed annually; and the HIV/TB prevalence is estimated to be around 6%. In a large HIV testing programme in the state of Kamataka, Southern India, 40% of HIV positive cases were previously unknown diagnoses(24). The outcome for HIV/TB coinfected patients is likely to be poor. As only two-thirds of RNTCP centres have a co-located HIV testing facility (and these are concentrated in only six states(31) with 55% of HIV/TB co-infected patients actually being tested at these centres(24)), there is clearly room for improvement within the RNTCP.

FOCUSING ON THE MOST VULNERABLE

In recognition of the scale of the problem, the Indian government has recently announced several policies and plans. These include improving regulation, with a ban on inaccurate serological TB tests (discouraging the misuse of interferon-gamma release assays for active TB), mandatory notification of all TB cases regardless of private or public sector(whether this will actually be effective remains yet to be seen), publication of the standards of TB care in India and an ambitious development of the National Strategic Plan to eliminate TB in India by 2025(32).

Ideally, in any country, a comprehensive monitoring system to which all new cases of TB are reported and a vital registration system that collects all causes of death from TB should be implemented. This would allow for evaluation of the incidence of new infections and levels of TB-related mortality(5). India is finally preparing to roll out its first national prevalence survey in 50 years. This has been key in halving the overall prevalence of TB in China, a country which has been undertaking regular surveys for the last 20 years(33).

Increased awareness of disease burden will hopefully result in increased political commitment and funding allocation to assist the RNTCP. Free and easily accessible accurate diagnostics, followed by free treatment which an affected family can obtain throughout the course of their whole treatment is key. As all obstacles facing effective TB control have the greatest impact on the worst off (Figure 1), the focus should be on the millions of people with TB who are underserved and are at the base of the socioeconomic pyramid. Using self-reported individual level data on 198,754 people, the 2006 Demographic Health Survey suggested that members of the poorest quintile in India are 5.5 times more likely to have TB than those in the wealthiest quintile(28).

Additional help from non-governmental organisations has been useful to connect private and public sectors to slum districts and tribal villages. For example, World Health Partners is a donor-supported social marketing and social franchising model that links local entrepreneurs and medication providers to the specialists and public sector through telemedicine(34). This would enable field workers to have rapid access to expert advice. Operation ASHA is a non-governmental organisation that extends the RNTCP to slum and rural areas throughout India, in an attempt to “reach the unreached”(35). Over the last decade, the availability and use of mobile phones have grown exponentially across the world. Multiple technological innovations now provide promising preliminary evidence of improved retention of TB patients compared with historical cohorts(31). Bigger randomized prospective trials assessing the using of technological innovations are important to strengthen the innovation evidence base prior to national scale-up.

There is accumulating evidence that effective use of community health workers improve important both diagnosis and treatment outcomes(37). A network of medication providers (recruited from the local high risk communities) supported using innovative technology to TB clinicians, dedicated to evaluating new patients, performing re-assessments regularly and managing them if they require admission to hospital, may be the most effective option to target the poorest areas. Heightened focus on education and support of providers, giving them responsibility to monitor and help maintain

patients' adherence to medication would be key. Well-trained pro-active local TB providers could rapidly decrease perceived stigma from local at risk communities, establish trust and a reputation as the central point of care in the area for which they are responsible. This complete and patient-centered strategy would meet the International Standards for Tuberculosis Care(36), recognizing the clinical and psychosocial needs of the most vulnerable

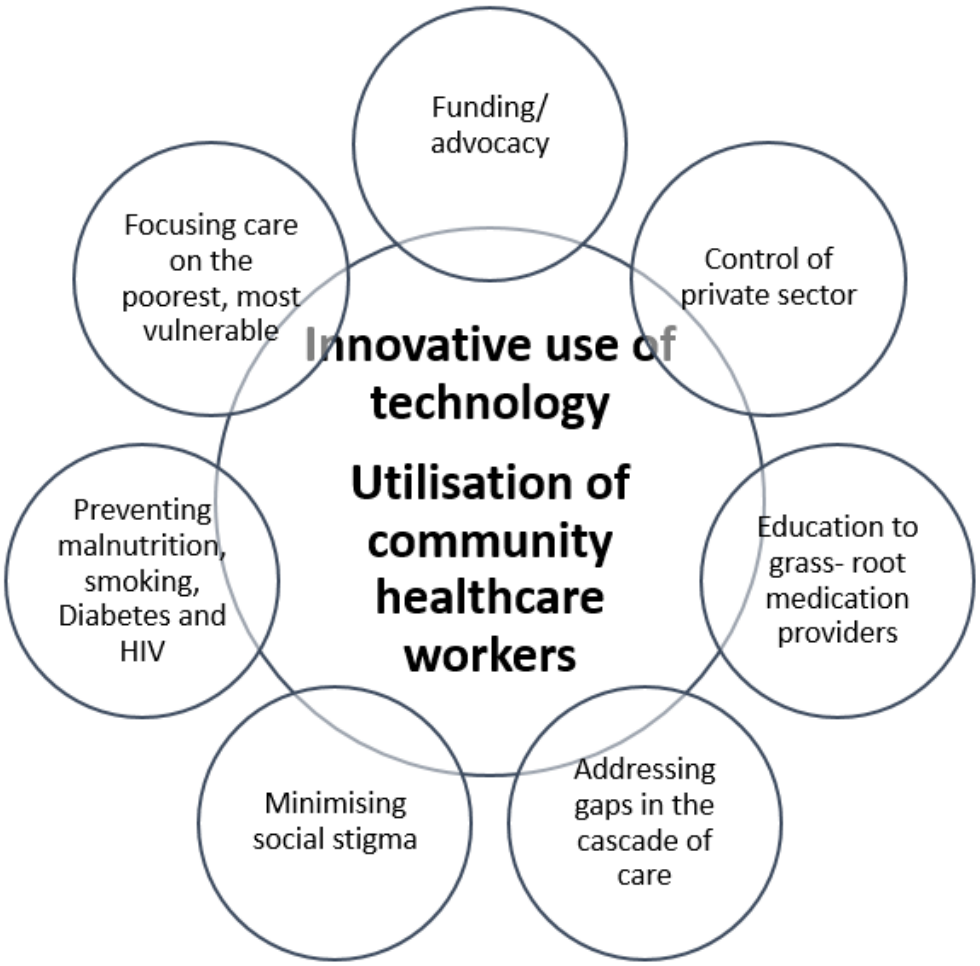
The issues that have confronted India are of global relevance. Their response to these provide important lessons for other high TB burden countries who also need to offer increasingly complex TB control programmes that account for multiple social and physical patient comorbidities yet have limited available resource to tackle them.

TABLE 1: Evidence base behind WHO's increased estimates for the burden of TB in India, 2000-2015. All sources cited from WHO 2016 Global Tuberculosis Report (1)

Author, Year	Type of study	Study aims	Study population	Findings	Conclusions drawn
Satyanarayana et al 2011	Cross sectional Community Based Survey, 30 districts. Patients identified through door to door survey and interviewed using a semi-structured questionnaire	To estimate the proportion of patients accessing TB treatment outside the Revised National Treatment Program of India (RNTCP) and identify their basic demographic characteristics	30 districts out of 374 global fund project districts selected by stratified cluster sampling technique	73,249 household visited. 761 TB patients identified. 54% took treatment under the RNTCP. Remaining 46% were on treatment from outside sources, and unlikely to be part of the TB notification system. These were more likely to be patients from rural areas (adjusted OR 2.5, 95% CI (1.2-5.2) and where TB was diagnosed in a non-governmental health facility (adjusted OR 14.0, 95% CI 7.9-24.9).	Nearly half of self-reported TB patients were missed by national TB notification system.
State-wide study, 2011	State-wise prevalence study	To estimate the prevalence of TB and report back to WHO. This was the country's first state-wise prevalence study.	Gujarat, India	Prevalence in Gujarat, adjusted for all ages and all forms of TB in 2011 was 390 cases per 100 000 population. Gujarat is a relatively wealthy state in India; given the link between levels of income and TB disease burden, it is unlikely that TB prevalence in Gujarat is higher than the national average.	This is much higher than the national estimate published by WHO in 2015 global TB report of 250 prevalent cases per 100 000 population.
Wells *et al*., 2011	Health data was used to analyse private TB drug consumption in 10 high burden countries after first mapping how well IMS data coverage overlapped with private markets.	To examine the size and characteristics of private sector TB drug sales in high burden TB countries.	10 high TB incident countries – India, China, Indonesia, South Africa, Bangladesh, Pakistan, the Philippines, Russia, Vietnam and Thailand,	India, Indonesia, the Philippines and Pakistan had private first line TB drugs sufficient to treat 65-117% of the estimated new TB cases in those countries in a given year with a full daily 6-8 month regimen. A wide variety of strengths were sold' this variability was highest in India.	Particularly large and stable private sector markets for TB drugs is present in India, Indonesia, the Philippines and Pakistan
Arinaminpathy et al 2016	Mathematical estimation study, using a large nationally representative commercial dataset on sales of 189 anti-tuberculosis products available in India to calculate the amount of anti-tuberculosis treatment in the private sector	To estimate the amount of anti-tuberculosis products sold in the private sector.	India	17.793 million patient months (95% credible interval 16 709 to 19841 million) of anti-TB treatment in the private sector in 2014, twice as many as the public sector. If 40-60% of private sector diagnosis is correct, and if treatment in the private sector lasts on average 2-6 months, 1.19-5.34 million tuberculosis cases were treated in the private sector alone.	India's private sector treats an enormous number of patients for tuberculosis.

District level household and facility survey, 2013	Prevalence study based on interview screening in 2012-2013	To estimate prevalence of TB, although not as per WHO handbook guide	India	Estimated prevalence based on interview screening was 592 cases per 100 000	Estimated TB prevalence is higher than WHO estimations in India
Mandatory TB notification, 2012-2014	National mandatory TB notification	National mandatory TB notification; rolled out on a web based reporting system	India	In 2014, number of notified cases increased by 29% compared with 2013, number of notified cases in 2015 was 34% higher than 2013. Most of the increase was related to more coverage of notifications from the private sector in a small number of districts	TB notification in India is increasing
Institute for Health Metrics and Evaluation, 2015	A large body of cause of death data from international registries and verbal autopsy surveys	To generate estimates of deaths and mortality rates broken down by age, sex, cause year and geography	Worldwide	Estimated number of TB deaths is much higher than previously published WHO estimates	Estimated number of TB deaths is much higher than previously published WHO estimates

FIGURE 1: Innovative use of technology, along with efficient use of community healthcare workers (big central circle), can help address the many issues that face effective national TV control in India (small peripheral circles)



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