

Diagnosis of drug-resistant TB and provision of second-line TB treatment in India: some ethical considerations

JEROME AMIR SINGH^{1,2,3}, ANANT BHAN¹, ROSS UPSHUR^{4,5}

¹ESC Program for Global Health, Sandra Rotman Centre, University Health Network, Toronto, Ontario CANADA, ²Centre for the AIDS Programme of Research in South Africa, Durban SOUTH AFRICA ³Joint Centre for Bioethics and Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario CANADA ⁴Department of Family and Community Medicine and Public Health Sciences, University of Toronto, Toronto, Ontario, CANADA ⁵Sunnybrook Health Sciences Centre Primary Care Research Unit, Toronto, Ontario, CANADA Author for correspondence: Jerome Amir Singh e-mail: singhj9@ukzn.ac.za

Abstract

Background: The GeneXpert® MTB/RIF (hereinafter Xpert) test has demonstrated sensitive detection of tuberculosis (TB) and Rifampicin resistance directly from untreated sputum in less than two hours. India is currently drafting the third phase of its Revised National Tuberculosis Control Programme (RNTCP). This process provides the country's health authorities with an ideal opportunity to revolutionise TB management in the country. The RNTCP is currently conducting a multi-site demonstration study to gather operational evidence to scale up the Xpert test under Indian programme conditions.

Discussion: With the impending publication of RNTCP's third phase, we consider the obligations of India's RNTCP in the light of the World Health Organization's Guidance on ethics of tuberculosis prevention, care and control, published in November 2010.

Summary: India is ethically obliged to phase-in the nationwide deployment of Xpert, a generic equivalent, or a quality lower-cost molecular diagnostic alternative, preferably made in India, as soon as reasonably possible. Further, India is ethically obliged to provide those diagnosed with first-line drug resistance universal access to second-line TB drugs. Doing so will reduce India's morbidity and mortality associated with diagnostic delay, dropout, and mistreatment of TB, and help stem the country's growing TB crisis.

Background

The GeneXpert® MTB/RIF (hereinafter Xpert) test has demonstrated sensitive detection of tuberculosis (TB) and Rifampicin resistance directly from untreated sputum in less than two hours (1). It holds the promise of impacting on TB management by yielding rapid, reliable, and accurate TB diagnosis, and has received World Health Organization (WHO) endorsement as a new molecular diagnostic (2). The WHO Expert Group and the WHO Strategic and Advisory Group for TB have, in addition, also strongly recommended that Xpert should be used as the initial diagnostic test in individuals suspected of multi-drug-resistant (MDR)-TB or HIV-associated TB (3). Xpert has demonstrated very high sensitivity and specificity under controlled conditions, and has been found to be operationally feasible, accurate, and effective in several settings, including India (4).

India is currently drafting the third phase of its Revised National Tuberculosis Control Programme (RNTCP). This process provides the country's health authorities with an ideal opportunity to

realise universal access to quality diagnosis and treatment for the entire population.

Because the Xpert implementation study sites in India (4) were limited in number and not representative of the vast majority of diagnostic centres involved in RNTCP's activities, the RNTCP is conducting a demonstration study at sites that are more representative of typical diagnostic centres in India, where diagnostic technologies such as Xpert are likely to be deployed (5).

Given the impending publication of RNTCP's third phase, we considered India's RNTCP in the light of the WHO's *Guidance on ethics of tuberculosis prevention, care and control* (6), published in November 2010. We conclude that India is ethically obliged to phase-in the nationwide deployment of Xpert, a generic equivalent, or a quality lower-cost molecular diagnostic alternative, preferably made in India, as soon as reasonably possible, and to provide those diagnosed with first-line drug resistance, universal access to second-line TB drugs, and, for those diagnosed with extensively drug-resistant TB, psychosocial and financial support. Doing so will reduce India's morbidity and mortality associated with diagnostic delay, dropout, and mistreatment, and help stem the country's growing TB crisis.

Discussion

Strides and gaps

While India has made major strides in the fight against TB, particularly in the last decade (7), TB diagnosis in India is still currently characterised by inaccurate diagnosis, especially in the private sector (8-10). The existing diagnostic technologies all have shortcomings: sputum microscopy, the most commonly used is a specific test, but has low sensitivity (11); chest radiography generates a lot of false positives, and serological tests, widely deployed in the private sector, are neither sensitive nor specific, leading to these being banned recently by the Indian health ministry (12). This gap has contributed to India being home to almost 20% of the global TB burden (13, 14) and producing approximately 100,000 annual cases of MDR-TB (15). Almost half of TB patients in India may seek care initially in the private healthcare sector, where ineffective serological testing is widespread (16), and diagnostic, treatment, and reporting practices often do not meet national or international standards for TB (17,18).

Despite its shortfalls and criticism of the existing programme on ethics grounds (19), India's RNTCP deserves praise for its policy reforms, to date. It is currently linking development of MDR-TB diagnostic capacity to the expansion of MDR-TB treatment services under the country's Directly Observed Treatment Short Course (DOTS)-Plus programme -- now rechristened Programmatic Management of Drug Resistant Tuberculosis (PMDT) -- while concurrently rolling out new TB diagnostic technologies, such as molecular line probe assay and liquid culture (7). It has pledged to provide "universal access for quality diagnosis and treatment for all TB patients in the community" (7, 20), including rolling out the PMDT plan nationwide (7). In January 2012, the Indian government pledged to increase health spending from the current one per cent of the country's gross domestic product, to 2.5% during the 12th Five Year Plan period (2012-17) (21). The Planning Commission of India in 2012 raised the allocation for the RNTCP to about Rs710 crore for 2012-13, an 80% increase over the previous fiscal year's budget (22). The Indian government has also recognised that effective TB management will necessitate close engagement with the country's private sector. To this end, the RNTCP has collaborated with India's private sector in TB control activities (23-26). These efforts are commendable as they have improved patient access to TB care (27). It is hoped that the RNTCP scales up such collaborative initiatives in its next phase.

Recognising the problems arising due to the use of serological tests for TB diagnosis, the RNTCP's laboratory committee requested India's Central TB Division to disseminate the WHO's negative recommendation on serology testing to all stakeholders involved in TB control in India. Furthermore, India's Ministry of Health and Family Welfare endorsed the WHO's stance on TB serological testing and encouraged widespread dissemination of the negative recommendation, including to civil society actors, so as to make the change a community movement (28). This was followed by a ban being implemented on the import, sale, manufacture and use of serological tests for TB diagnosis in mid-2012. While these are encouraging measures, the Indian government must go further and ensure that the ban is implemented strictly, and also clarify its stance on the universal provision of second-line treatment regimens.

It is also important for the government to institute an efficient drug resistance surveillance system in the country, covering both public and private providers. Such a system will help keep a tab on existing and emerging drug resistance patterns in both first- and second-line therapy. Availability of such data coupled with widespread availability of drug susceptibility testing can reduce TB morbidity and mortality by helping control the spread of drug resistance. The RNTCP can also examine the feasibility of providing individualised treatment to patients for whom drug resistance patterns are known.

Treatment obligations

Second-line TB therapy is not widely available through India's public health sector; although it is widely available in the unregulated private sector, albeit at prohibitively high costs

for most people. According to WHO's *Stop TB Strategy*, "anti-TB drugs should be available free of charge to all TB patients, both because many patients are poor and may find them difficult to afford, and because treatment has benefits that extend to society as a whole (cure prevents transmission to others)" (29). This position is reinforced in the WHO's guidance document (30).

It is heartening to note that the Indian government has committed itself to "universal access for quality diagnosis and treatment for all TB patients in the community" and "deploying new rapid diagnostics" (7). It is not clear, though, whether India's pledge entails universal access to second-line TB drugs, given the associated expenses and practical challenges. Second-line TB drugs are of longer duration, more difficult to consume (31), and in India, approximately 100-200 times more expensive than first-line TB drugs (31, 32). It's estimated that treating an MDR-TB patient in India can cost upwards of Rs 1 lakh (33). Given India's split healthcare system, such treatment options are more readily accessible through the country's private sector for patients able and willing to pay. These factors should not deter the Indian government. South Africa provides international precedent for a resource-constrained country with a split healthcare system and high-burden TB, implementing a nationwide rollout of Xpert in the public health sector despite currently having inadequate second-line drugs and related infrastructure for those diagnosed with Rifampicin resistance (34). India may find itself in a similar position, initially, but this should not be a factor against a phased Xpert nationwide deployment as soon as is reasonably possible. According to the WHO guidance document, countries that implement diagnostic testing in the absence of treatment should do so only as a temporary measure, and should establish a timetable for when treatment for multi- and extensively drug-resistant TB will be made available. This holds true even for low-income countries (35). Thus, if a patient in the public health sector is diagnosed with a drug-resistant strain of TB, health authorities would be morally (and, in some settings, potentially legally) obliged to provide that patient, within a reasonable timeframe, with access to efficacious second-line treatment options.

Regardless of whether a rapid, reliable TB diagnostic technology is widely adopted in India's private sector before the state sector, and regardless of whether a patient has been initiated on second-line TB treatment through the private sector, the Indian government is morally obliged to continue providing second-line drugs to these patients, irrespective of their ability to afford the treatment themselves after treatment initiation in the private sector.

India's HIV sector also provides precedent for introducing universal access to expensive second-line drugs. India's National AIDS Control Organization, which falls under the auspices of India's Health and Family Welfare Ministry, recently announced that free second-line therapy for HIV would be made available to all patients who started first-line therapy before 2004 and faced drug resistance, irrespective of whether the first-line therapy was initiated in the public or private sector (36). India's RNTCP should do the same in relation to TB. To this end, it has

laudably committed increased resources to tackling TB, as noted above.

According to the Indian government, aside from the support it received from other donor partners, the World Bank provided it with a credit of US\$ 170 million for the period 2006-2012 for its TB management programme, along with additional financing of US\$ 396 million to support the RNTCP in “meeting its ambitious new Universal Access goals, adequately addressing the challenge of drug-resistant TB, and introducing and scaling-up innovations and new approaches” (7). The government has also approved a health ministry proposal for scaling up services for diagnosis, care and management of drug-resistant TB with funding support from the Global Fund (37).

However, increased spending on second-line TB drugs in India should not come at the expense of basic TB control. Instead, Indian policymakers must skilfully budget for the progressive scale-up of Xpert (or an equivalent test) and the provision of associated second-line drug regimens, whilst simultaneously expanding its universal TB diagnosis and treatment programme. Furthermore, as Xpert’s (or an equivalent test’s) deployment at lower levels of the health system may necessitate confirmatory testing at higher level laboratories for those at low risk of Rifampicin resistance; this will require careful coordination and budgeting. Data from the ongoing Xpert field testing should help inform policy decision making in this regard.

However, should Xpert be adopted nationwide in India, an ethics concern will arise if authorities become aware of drug-resistance prevalence because of Xpert, but nevertheless continue providing patients with sub-optimal treatment, care, and monitoring. Such apathy or inaction on the part of Indian authorities could result in “ethics of inaction” criticisms, a backlash against India’s national TB programme, and jeopardise its future success. Policymakers should realise that the promise of improved tests could drive treatment uptake, resulting in better health outcomes. This could ultimately induce or catalyse the development of even better technologies.

Ethical obligations of the private sector

While the state must practise ethical TB management in India, given the major role that the private sector plays in TB management in India, the private sector also has an ethical obligation to collaborate with the state in managing India’s TB epidemic, and should continue its efforts in this regard (23-26). The private sector must commit to employing only sensitive diagnostic and cost-effective diagnostic technologies, and desist from employing ineffective and banned diagnostic techniques, such as serological testing. Where patients are in need of second-line regimens but unable to afford such treatment, the private sector must refer such patients to appropriate state facilities as soon as they begin offering such treatment.

Negotiating, spurring, and supporting ongoing research

Barring negative results from its operational research on Xpert, the Indian government must, in collaboration with funders,

advocacy groups and international agencies, robustly negotiate lower prices with the makers of the Xpert based on economy of scale given the country’s huge TB burden. Simultaneously, it must secure discounted second-line TB drugs with sustained scale-up in mind; India’s strength in generic drug manufacturing should be tapped for this purpose. The Indian government should also spur indigenous innovation by promoting and incentivising the production of viable alternative low-cost, TB rapid diagnostic technologies or generic versions of existing technologies, such as Xpert. Such measures will help drive down the cost of TB diagnostic technologies and, hopefully, ultimately facilitate the elimination of TB in the country. The Indian government should also encourage ongoing operational research that considers various permutations and combinations of new and existing technologies (including smear microscopy but excepting serology) to determine the optimal mix for the Indian context.

Summary

Undetected cases of drug-resistant TB present a significant opportunity cost as drug-resistance incidence and prevalence in India amongst those seeking treatment in the public sector will remain unknown and unmitigated. As a result, valuable public sector resources will be expended on inappropriate treatment regimens, and the prevalence of drug-resistance strains of TB will conceivably grow unchecked. The Indian government’s recent pledge to provide universal access to quality TB diagnostics and care to those who need it, and its deployment of rapid diagnostics technologies such as line probe assay, liquid culture and solid culture in a few centres, is to be applauded. However, Xpert offers the opportunity to get more TB patients diagnosed early, at the point of care, including those with Rifampicin resistance, and placed on therapy to interrupt transmission, than existing technologies employed in India. Accordingly, India’s government is ethically obliged to deploy Xpert, an affordable generic equivalent, or a quality lower cost molecular diagnostic alternative, preferably made in India, at points of care as soon as reasonably possible. Further, the Indian government is ethically obliged to provide second-line TB treatment to those who need it through a comprehensive patient care and management system. Doing so will realise universal access to quality diagnosis and treatment for the entire population. Not only will this have a meaningful impact on India’s TB epidemic, it will allow India to demonstrate inspiring and bold leadership on a major global health threat. This could inspire similar reform elsewhere and eventually lead to meaningful gains against TB globally.

Competing interests

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Appendix 1

Summary of the ethical values particularly important to TB care and control

- Social justice/equity** – A focus on social justice calls attention to the underlying root causes and existence of inequalities in society and requires that we explicitly address them. In some cases, this may mean a redistribution of resources to compensate for existing inequalities and further actions to prevent their perpetuation.
- Solidarity** – Solidarity is primarily about standing together as a group, community or nation.
- Common good** – An infectious disease threatens the health not only of an infected individual, but also of the whole population. The removal or reduction of a threat of infection from a society is therefore something that we can all benefit from. We *all* gain from a society with strong public health facilities to address TB control and treatment.
- Autonomy** – Respect for patient autonomy is generally seen as guaranteeing individuals the right to make decisions about their own lives, including healthcare. Respecting autonomy means that patients generally should have the right to choose among treatment options.
- Reciprocity** – Reciprocity seeks to express the idea that those individuals who put themselves at risk of harm for the sake of others deserve benefits in exchange for running such risks. It might include an obligation to minimise the risks to individual care-givers (by providing protective equipment) as well as positive interventions to treat and compensate individuals when harm occurs as a result of providing care.
- Effectiveness** – The idea of effectiveness includes the duty to avoid doing things that are clearly not working, as well as the positive obligation to implement proven measures that are likely to succeed. Effectiveness is linked to the concept of *efficiency*, which requires that limited resources be used in the most productive manner possible.
- Subsidiarity** – This value promotes the idea that decisions should be made as close to the individual and communities at local level as possible. The idea is that this ought to result in decisions reflecting local interests, concerns and beliefs, and ensure the highest possible involvement by the public.
- Participation** – This principle requires that the public be encouraged to participate in the decision-making process, and that reasons be provided for decisions.
- Transparency and accountability** – This principle requires that decisions be made in an open manner, and that the decision-making process be fair, responsive and evidence-based.

Source: WHO (2010). *Guidance on ethics of tuberculosis prevention, care and control*.

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