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

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ZARIR F. UDWADIA
MD, FRCP (London), FCCP (USA), Consultant Physician,
Hinduja Hospital & Research Center, Breach Candy Hospital, Mumbai

"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

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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. ■