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Totally drug-resistant tuberculosis (TDR-TB) in India: every dark cloud has a silver lining

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In the early weeks of January 2012, a report of four cases of tuberculosis from Mumbai, India, stirred up a storm.[1] India bears a giant's share of the world's multidrug-resistant tuberculosis (MDR-TB) burden, but these cases were different even though they came from a centre (Hinduja Hospital and Research Center) which has been reporting on the alarming escalation in drug-resistant TB in Mumbai over the last two decades. The four patients described in this report were resistant to all first-line (isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin) and second-line drugs (kanamycin, amikacin, capreomycin, ofloxacin, moxifloxacin, ethionamide and para-amino salicylic acid) to which they were tested. That the report came from Mumbai's most reputed mycobacterial laboratory, accredited for drug susceptibility testing (DST) by the Revised National TB Control Program (RNTCP), and serving as the de facto reference mycobacterial laboratory for the city added to the veracity of this report. The choice of the term 'Totally Drug-Resistant' for these four cases was found unpalatable by the Indian health authorities, who initially denied the very existence of 'totally drug-resistant tuberculosis (TDR-TB)'. This, despite there being reports of strains with similar extreme patterns of resistance, from Italy and Iran in the past, none, however, having stirred up the hornet's nest of attention among media and health organisations as the Indian report did.[2 3] The government's response of initial denial served only to stir up matters further. WHO, though more measured in its response, at a meeting of experts (TDR-TB: a WHO consultation on the diagnostic definition and treatment options) on March 20-21st, 2012, in Geneva, decided that there was not enough evidence to support the creation of yet another category of resistance (TDR), but admitted that patterns of resistance even more extreme than Extensively Drug-Resistant TB (XDR-TB) were being encountered, and were cause for great concern.

Since the initial report, we have encountered in this single outpatient department, an additional 11 patients with the same resistance pattern. All these patients reflect the way MDR-TB is mismanaged in India. These 15 patients (mean age 30 years, eight men) had seen an average of four doctors (both in the public and private sectors), and received a mean of nine drugs for an average duration of 24 months before being labelled 'TDR-TB' by us. India's RNTCP has, with its Directly Observed Therapy Short-course (DOTS) programme, transformed TB case detection and cure rates in the country, and has, undoubtedly, been one of India's greatest public health success stories. However, the rising number of patients with MDR-TB tends to eclipse these successes. In an ideal world, all patients suspected to have drug-resistant TB need to have access to DST, and then receive second-line drugs, under supervision, within the confines of a government-run MDR-TB programme (DOTS-plus). Sadly, to date, only about 6000 of the vast numbers of MDR patients in India,[4] are actually receiving treatment under the Programmatic Management of Drug Resistant TB (PMDT), the programme within the RNTCP for management of DR-TB. The majority fall prey to unscrupulous private practitioners whose poor prescribing practice only serves to amplify drug resistance. A study from Dharavi, one of Asia's largest slums, located in the heart of Mumbai, audited the prescribing practice of 106 such private physicians, and found that only five could prescribe a correct prescription for a hypothetical case of MDR-TB.[5] The majority of prescriptions were inappropriate, and served only to further amplify resistance, converting MDR to XDR and then to TDR-TB. A recent study by Dalton *et al*[6] showed that indiscriminate use of second-line drugs is a strong and consistent factor contributing to resistance to these drugs and the increased XDR rates encountered globally. In no other country are second-line drugs used as freely and prescribed by such a wide and diverse range of medical practitioners as in India.

The 15 patients described above were all started on a variety of salvage regimens, along with aggressive surgical resections in some of the patients. To date, six seem to be responding clinically and microbiologically to their treatment; however, five have succumbed to their disease.

These cases, and the international attention they received, served to greatly increase the profile of drug-resistant TB in India. Despite TB existing on an epic scale here, with 300 million Indians infected and 300 000 deaths a year, this disease tends to be shrouded in secrecy and stigmatised.[7] Suddenly, TB was in the front pages of every Indian newspaper, and this extra attention for a disease which had been marginalised served to galvanise public attention. Equally commendable, after the initial squabbling about terminology had died down, were the responses of the public officials in the city of Mumbai, State of Maharashtra, and in the central government.

TB was finally made a notifiable disease on 7 May 2012. This was vitally important. The majority of TB patients in India choose to go to private practitioners for treatment, and these patients are completely outside the purview of DOTS and DOTS-plus programmes. All reports of the epidemiology of TB in India must be tempered by the fact that patients with TB in the private sector are rarely if ever notified and, hence, WHO figures of 3% and 17% resistance in new and re-treated cases, respectively, are probably considerable underestimates. With notification made compulsory across all private hospitals and laboratories in India, accurate surveillance, and a more precise idea of the epidemiology, will be forthcoming. The impact of this was immediate. In 2012, as per Mumbai health officials, 6 months after starting intensified efforts to control MDR-TB, 1407 MDR-TB patients were identified from the 6561 TB patients screened, compared with the 181 diagnosed from the 354 screened in 2011.[8]

Laboratory capacity in the public sector was also rapidly increased with the

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rapid scale-up of diagnostic laboratory capacity by sixfold in less than 2 weeks. Molecular tests and the first GeneXpert machines were finally introduced into the public TB programmes in Mumbai and will, hopefully, play a major part in rapid diagnostics here. The Sewri hospital an ancient sanitarium-type relic from the past, with 1000 beds, underwent a face-lift almost overnight, had additional funds allocated for DOTS-plus activities, and thoracic surgeries began to be performed here again after decades of inertia.

Manpower and budgets for TB control were significantly increased as well. An additional 24 RNTCP managers were appointed, one for each of the 24 municipal wards. It is hoped that this will improve programme implementation. Most heartening of all, the annual budget for TB in Mumbai increased sixfold as well.

The changes extended beyond the city of Mumbai with its huge population of 18 million, to the State of Maharashtra (one of the country's most populous states) as well. Plans to rapidly expand the geographic coverage of PMDT, the programme within the RNTCP for management of DR-TB were set in motion through the entire State, including proactive efforts to involve the private sector in TB control. As initial proof of this, the State offered to take over the care of the first 12 of the 15 TDR patients who had been diagnosed and treated in the private Hinduja hospital, offering the same salvage regimens we had originally initiated these patients on.

Changes filtered beyond city and state to the national level as well. The Indian Union health ministry had several high-level administrative and technical meetings culminating in a decision to increase funding for TB control across the country by 70% in the next Union health budget. They also moved to ban the inaccurate but widely used serological tests on which India wastes US$18 million annually.[9]

Thus, the dark cloud of TDR-TB has at least a silver lining. For the 15 patients with the most extreme resistance, it may all have come too late, but changes that may impact on TB control in India have been set in motion. However, we have miles to go and promises to keep. Laboratory capacity needs further strengthening with larger numbers of TB patients screened at an earlier stage. There are no more than a handful of private and public laboratories capable of accurate DST to first-line and second-line drugs. Without strong laboratory infrastructure in place, MDR, XDR and TDR cannot be diagnosed, as these are essentially laboratory-based diagnosis. DOTS-plus must be rolled out across the country at a faster pace. India's huge population of MDR patients (110 000 at last WHO count) have been clamouring for this basic injustice to be righted, so they finally have access to second-line drugs in the public sector.[10] Public Private Mix, for too long a convenient catch-word, must become a reality if TB and MDR-TB are ever to be overcome in a country where 70% of TB patients choose to initially go private. Seamless integration of services across the public and private sectors with these two competing systems reaching out to each other, rather than eyeing each other with hostility, is the need of the hour. Finally, we would make a strong plea that second-line TB drugs are prescribed with restraint, and only by experts who are equipped with the knowledge to prescribe them. Regulation must be brought into play to ensure this to prevent the relentless amplification of resistance that leads to the sad but cautionary tale of TDR-TB in India.

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REFERENCES

1. **Udwadia ZF,** Amale RA, Abjani KK, *et al*. Totally drug resistant tuberculosis in India. *Clin Infect Dis* 2012;**54**:579–581.
2. **Migliori GB,** De Laco G, Besozzi G, *et al*. First tuberculosis cases in Italy resisted to all tested drugs. *Euro Surveillance* 2007;**12**:3194.
3. **Velayati AA,** Masjedi MR, Farnia P, *et al*. Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug resistant strains in Iran. *Chest* 2009;**136**:420–425.
4. http://www.tbcindia.nic.in/ (Last accessed 2 Sept 2012)
5. **Udwadia ZF,** Pinto LM, Uplekar MW. Tuberculosis control by private practitioners in Mumbai, India: has anything changed in two decades? *PLoS One* 2010;**5**:e1203.
6. **Dalton T,** Cegielski P, Akksilp S, *et al*. Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries: a prospective cohort study. *Lancet* 2012. http://dx.doi.org/10.1016/S0140–6736(12)60734-X
7. **Gopi PG,** Subramani R, Santha T, *et al*. Estimation of burden of tuberculosis in India for the year 2000. *Indian J Med Res* 2005;**122**:243–248.
8. http://articles.timesofindia.indiatimes.com/2012–08–22/mumbai/33321694_1_drugresistant-mumbai-tb-control
9. **Bhargava A,** Pinto L, Pai M. Mismanagement of tuberculosis in India: causes, consequences, and the way forward. *Hypothesis* 2011;**9**:e7.
10. **WHO report 2010 Global Tuberculosis Control**. *Epidemiology, strategy and financing*. Geneva: WHO, 2010.