

Commentary

Extensively drug-resistant *Mycobacterium tuberculosis*: What are these bugs up to in India?

After the widespread use of rifampicin for more than two decades, multidrug-resistant tuberculosis (MDR-TB; resistance to rifampicin and isoniazid) was recognized as a clinical problem in the early 1990s^{1,2}. Two decades later, MDR-TB is now prevalent over 80 countries worldwide³. Thus, the WHO estimates that of about 10 million total episodes of tuberculosis in 2007, approximately 5 per cent had MDR-TB³ and of these, 40 000 (6.6%) are estimated to have had extensively drug-resistant (XDR-TB, defined as *Mycobacterium tuberculosis* resistant to isoniazid, rifampicin, any fluoroquinolone and at least one of three injectable second-line drugs)⁴. In resource-poor settings XDR-TB^{5,6}, like MDR-TB⁷, is associated with poor outcomes and diverts much needed resources from existing control programmes, as it is exceedingly expensive to treat. There is a paucity of data about the incidence and prevalence trends of XDR-TB in resource-poor settings like Africa, India and China, which harbour the highest burden of the disease. Indeed, Asia contains over 50 per cent of the burden of drug-resistant tuberculosis, and China and India account for over 200,000 MDR-TB cases annually³. Moreover, there are specific areas within India and China with a higher than average reported prevalence^{8,9}. Recent studies have reported alarmingly high levels of MDR-TB in several wards of Mumbai (24% in previously untreated cases)¹⁰ and in 20 per cent of isolates from a study performed in Lucknow¹¹. Jain and colleagues from Mumbai reported a 11 per cent prevalence of XDR-TB in 326 patients with MDR-TB¹⁹. Other studies from India reported an XDR-TB prevalence of between 1.5 and 7.4 per cent^{12,13} with Singh *et al*¹⁴ reporting that 4 out of 12 HIV-MDR co-infected patients had XDR-TB. Thus, there are limited data about the prevalence of XDR-TB in a country, which has one of the highest burdens of TB globally.

The study by Sharma and colleagues¹⁵ is therefore timely. They found that approximately 2.4 per cent of MDR-TB cases had XDR-TB. Is this a cause for concern? It is likely that the true prevalence of XDR-TB in this study has been underestimated for several reasons. Due the small sample size the estimates are relatively imprecise and the confidence intervals wide. It is possible that many severely ill patients with XDR-TB may not have accessed health care, and the lack of routine culture and susceptibility testing within the programme means that many patients with XDR-TB also likely to have been missed. Moreover, there is a significant pre-treatment mortality in patients with XDR-TB. In South Africa, almost 25 per cent of XDR-TB-related deaths in a population with a low prevalence of HIV, occurred before treatment initiation¹⁶. It is noteworthy that this study¹⁵, in contrast to unselected TB suspects, only evaluated patients treated for MDR-TB. Thus, the observation that 2.4 per cent of MDR-TB isolates were in fact XDR-TB and is likely to have been an under estimate, is of concern. Further studies are now required in unselected cohorts of TB suspects and in community surveys to determine the true prevalence of XDR-TB in different parts of the country.

The findings of Sharma *et al*¹⁵ underscore the need to aggressively manage Indian patients with both drug sensitive and MDR-TB. This can be undertaken through better case finding strategies, improved access to new rapid diagnostic tools such as the GenoType® MTBDR^{plus} assay (Hain Lifescience)¹⁷, and access to better drug treatment regimens for MDR-TB, including moxifloxacin. Serious consideration should also be given to improving diagnostic algorithms such as testing all smear positive cases for potential drug resistance. The cost-effectiveness of such an approach is supported by mathematical models¹⁸. Several aspects of treatment deserve mention. A single drug should never be added

to a failing regimen and thus substituting regimen 2 for regimen 1 in patients failing treatment is counter-intuitive. Given the high rates of isoniazid resistance in many parts of India^{19,20} ethambutol should likely be prescribed in the continuation phase to minimize the risk of rifampicin resistance especially when there are significant rates of default or non compliance. As previously outlined²¹ also preventing further cases of drug resistance through improved DOTS coverage, and strengthening of the control programme and laboratory infrastructure, is also imperative.

Keertan Dheda

Lung Infection & Immunity Unit

Division of Pulmonology & Clinical Immunology

Department of Medicine

University of Cape Town, South Africa &

Centre for Infectious Diseases & International Health

UCL, London, UK

Present address:

H floor, Old Main Bldg. Groote Schuur Hospital

Observatory, Cape Town, South Africa 7925

keertan.dheda@uct.ac.za

keertandheda@yahoo.co.uk

References

- Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh CR, Jr. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med* 1993; 328 : 527-32.
- Pablos-Méndez A, Raviglione MC, Laszlo A, Binkin N, Rieder HL, Bustreo F, *et al.* Global surveillance for antituberculosis-drug resistance, 1994-1997. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *N Engl J Med* 1998; 338 : 1641-9.
- Wright A, Zignol M, Van Deun A, Falzon D, Gerdes SR, Feldman K, *et al.* Epidemiology of antituberculosis drug resistance 2002-07: an updated analysis of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. *Lancet* 2009; 373 : 1861-73.
- WHO. *Report of the meeting of the WHO Global Task Force on XDR-TB*. Geneva: World Health Organization; 2006.
- Dheda K, Shean K, Badri M. Extensively drug-resistant tuberculosis. *N Engl J Med* 2008; 359 : 2390.
- O'Donnell MR, Padayatchi N, Master I, Osburn G, Horsburgh CR. Improved early results for patients with extensively drug-resistant tuberculosis and HIV in South Africa. *Int J Tuberc Lung Dis* 2009; 13 : 855-61.
- Shean KP, Willcox PA, Siwendu SN, Laserson KF, Gross L, Kammeres S, *et al.* Treatment outcome and follow-up of multidrug-resistant tuberculosis patients, West Coast/Winelands, South Africa, 1992-2002. *Int J Tuberc Lung Dis* 2008; 12 : 1182-9.
- World Health Organization. *Anti-tuberculosis drug resistance in the world: the WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance*. Geneva: WHO; 2008.
- Jain S, Rodrigues C, Mehta A, Uwadia ZF. High Prevalence of XDR-TB from a tertiary care hospital in India. In: Proceedings of the American Thoracic Society International Conference; May 2007; San Francisco, USA; p. A510.
- D'Souza DT, Mistry NF, Vira TS, Dholakia Y, Hoffner S, Pasvol G, *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* 2009; 9 : 211.
- Jain A, Mondal R, Prasad R, Singh K, Ahuja RC. Prevalence of multidrug resistant *Mycobacterium tuberculosis* in Lucknow, Uttar Pradesh. *Indian J Med Res* 2008; 128 : 300-6.
- Mondal R, Jain A. Extensively drug-resistant *Mycobacterium tuberculosis*, India. *Emerg Infect Dis* 2007; 13 : 1429-31.
- Thomas A, Ramachandran R, Rehman F, Jaggarajamma K, Santha T, Selvakumar N, *et al.* Management of multi drug resistance tuberculosis in the field: Tuberculosis Research Centre experience. *Indian J Tuberc* 2007; 54 : 117-24.
- Singh S, Sankar MM, Gopinath K. High rate of extensively drug-resistant tuberculosis in Indian AIDS patients. *AIDS* 2007; 21 : 2345-7.
- Sharma SK, George N, Kadiravan T, Saha PK, Mishra MK, Hanif M. Prevalence of extensively drug-resistant tuberculosis among patients with multidrug-resistant tuberculosis: a retrospective hospital-based study. *Indian J Med Res* 2009; 130 : 392-5.
- Dheda K, Shean K, Zumla A, vander Walt M, Streicher E, Govindsamy D, *et al.* Early Treatment Outcomes of Extensively Drug-Resistant Tuberculosis in South Africa are poor regardless of HIV status In: *European Respiratory Society Meeting; 2009*; Vienna: European Respiratory Society; 2009.
- Pai M, Kalantri S, Dheda K. New tools and emerging technologies for the diagnosis of tuberculosis: part II. Active tuberculosis and drug resistance. *Expert Rev Mol Diagn* 2006; 6 : 423-32.
- Dowdy DW, Chaisson RE, Maartens G, Corbett EL, Dorman SE. Impact of enhanced tuberculosis diagnosis in South Africa: a mathematical model of expanded culture and drug susceptibility testing. *Proc Natl Acad Sci USA* 2008; 105 : 11293-8.
- Joseph BV, Soman S, Radhakrishnan I, Madhavalatha GK, Paul LK, Mundayoor S, *et al.* Drug resistance in *Mycobacterium tuberculosis* isolates from tuberculosis patients in Kerala, India. *Int J Tuberc Lung Dis* 2009; 13 : 494-9.
- Hanif M, Malik S, Dhingra VK. Acquired drug resistance pattern in tuberculosis cases at the State Tuberculosis Centre, Delhi, India. *Int J Tuberc Lung Dis* 2009; 13 : 74-8.
- Udwadia ZF. XDR-TB in India : when will we heed the alarm? *J Assoc Physicians India* 2008; 56 : 409-10.