Drug-resistant tuberculosis

G L Calligaro, BSc (Hons), MB BCh, FCP (SA), MMed, Cert Pulm (SA);
K Dheda, MB BCh, FCP (SA), FCCP, FRCP (Lond), PhD

Lung Infection and Immunity Unit, Division of Pulmonology and UCT Lung Institute (Pty) Ltd, University of Cape Town and Groote Schuur Hospital, South Africa

Corresponding author: *G L Calligaro (greg.calligaro@uct.ac.za)*

The epidemic of drug-resistant tuberculosis (DR-TB) is a public health emergency that threatens to destabilise global TB control. Although TB incidence and mortality are decreasing in several parts of the world, the overall prevalence of multidrug-resistant tuberculosis (MDR-TB) is increasing in many high-burden countries, particularly in Africa.[1] World Health Organization (WHO) statistics show that almost half a million new cases of MDR-TB develop every year,[2] of which approximately 40 000 (in more than 80 countries) are thought to be extensively drug-resistant tuberculosis (XDR-TB) (Fig. 1). Limited laboratory capacity and lack of widespread drug susceptibility in resource-poor settings mean that only a fraction of that number are correctly diagnosed and started on treatment.[2] This reservoir of undiagnosed and/or untreated DR-TB is largely responsible for driving ongoing person-to-person transmission. Treatment defaulters, delays in initiating treatment, inadequate bed capacity, and poor infection control in healthcare facilities are also important contributors. In South Africa, where high transmission rates and HIV co-infection have combined to produce one of the highest incidence rates of TB in the world, the statistics are equally alarming. South Africa has the fifth highest burden of DR-TB globally, with an incidence of ~2% of new patients and ~7% of retreatment cases;[3] of these, 5 - 10% have XDR-TB.[4] Definitions for DR-TB are shown in Table 1.

Outcomes, challenges and cost of DR-TB treatment

Appropriately identifying and dealing with the threat of DR-TB is critical. Firstly, DR-TB has poorer treatment outcomes when compared with drug-sensitive TB. Of the estimated half a million MDR-TB patients started globally on treatment in 2009, only 48% were treated successfully.[2] Outcomes for XDR-TB are even worse; although the overall success rate for XDR-TB in a recent meta-analysis was reported as 44%, a retrospective study from South Africa showed that fewer than 20% of patients with XDR-TB culture converted within 6 months of initiation of treatment, and that this poor outcome was independent of HIV status.[5] Secondly, DR-TB involves a longer duration of treatment with less potent but more toxic medications (groups 2 - 5 in Table 2), and higher relapse rates occur.[6] Lastly, DR-TB treatment is considerably more expensive than standard TB treatment. Despite only comprising 2.2% of the case burden of TB in South Africa, DR-TB consumes a third of the total estimated national TB budget for the country.[7]

Diagnosis of DR-TB

The laboratory diagnosis of DR-TB has traditionally relied on the demonstration of *Mycobacterium tuberculosis* growth in the presence of specific antituberculous drugs – so-called conventional drug-susceptibility testing (DST). A major disadvantage of this method is the long delay (usually several weeks) in

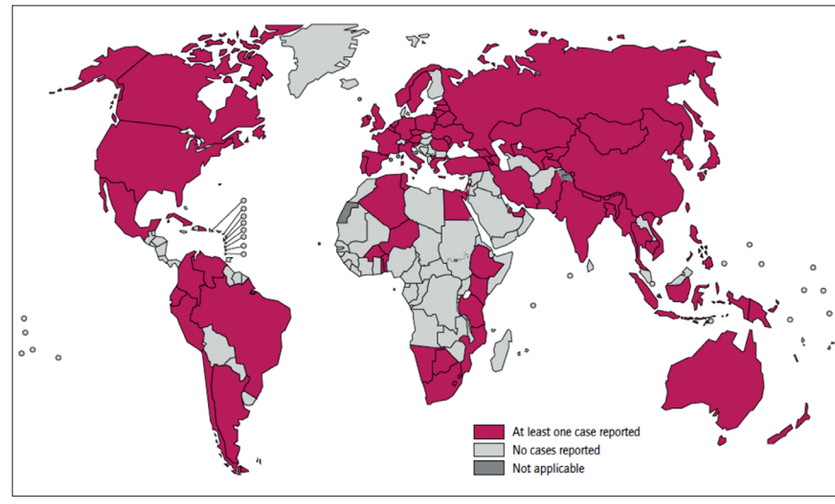

Fig. 1. Countries that had notified an XDR-TB case by the end of 2011.[3]

Table 1. Definitions of types of drug-resistant tuberculosis (DR-TB)

Type	Definition
Multidrug-resistant TB (MDR-TB)	Resistance to isoniazid and rifampicin[21]
Extensively drug-resistant TB (XDR-TB)	MDR-TB plus resistance to any fluoroquinolone and any second-line injectable (either kanamycin, amikacin or capreomycin)[21]
Pre-extensively drug-resistant TB (pre-XDR-TB)	MDR-TB resistant to either a second-line injectable drug or a fluoroquinolone
Extremely drug-resistant TB (XXDR-TB) or Totally drug-resistant TB (TDR-TB)	These terms have been used by various authors to describe strains with more extensive patterns of resistance (to all first-line and second-line drugs).[22,23] However, due to problems with the reliability and reproducibility of *in vitro* drug susceptibility testing for second-line drugs, no international consensus has been reached about the definition of more extensive resistance patterns, and the term 'resistance beyond XDR' is preferred

obtaining DST results. During this interval, patients may be treated with ineffectual regimens that encourage the development of further drug resistance and allow the disease to spread. Rapid growth- and microscopy-based DST, such as the microscopy-observed drug susceptibility (MODS) method and thin-layer agar (TLA) technique, has shortened the delay to less than 2 weeks, but is limited by the need for laboratory infrastructure and intensive labour.[8]

New nucleic acid amplification tests (NAATs) promise to reduce the interval between sample acquisition and the DST result from weeks to hours. They provide rapid DST results at the time of TB diagnosis, potentially increasing the number of cases that are diagnosed with DR-TB and started immediately on the correct treatment, and impacting on transmission rates.[9] Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) is an automated, cartridge-based polymerase chain reaction (PCR) assay that can be performed in decentralised locations, outside of reference laboratories and potentially at a point-of-care by staff with minimal laboratory training. It can deliver simultaneous diagnosis of TB and rifampicin resistance in less than 2 hours. The sensitivity and specificity of the assay for the detection of rifampicin resistance in sputum are 94.1% and 97.0%, respectively.[10] It has been strongly endorsed by the WHO as the first investigation in all patients with suspected DR-TB and/or co-infection with HIV.[11] Another NAAT, the MTBDRplus assay (Hain Lifesciences, Nehren, Germany), offers similar advantages as Xpert® MTB/RIF for MDR-TB detection.[12,13] Unlike Xpert® MTB/RIF, however, it requires formal laboratory infrastructure, but has the advantage of testing for both rifampicin and isoniazid resistance. More recently, the MTBDRsl (second-line) assay was introduced, which tests for drug resistance to second-line injectable drugs, the fluoroquinolones and ethambutol,[14] for use on smear-positive or culture-positive specimens.[15]

Table 2. First- and second-line drugs based on the WHO classification[20]

Group	Drug
Group 1: First-line oral TB drugs	Isoniazid (INH) Pyrazinamide (Z or PZA) Ethambutol (E or EMB) Rifampicin/rifampin (R or RIF) Rifabutin (RFB)
Group 2: Second-line injectable TB drugs	Kanamycin (KAN) Amikacin (AMK) Capreomycin (CAP) Streptomycin (STR)
Group 3: Fluoroquinolones	Levofloxacin (LFX) Moxifloxacin (MFX) Ofloxacin (OFX) Gatifloxacin (GFX)
Group 4: Oral bacteriostatic second-line TB drugs	Para-aminosalicylic acid (PAS) Cycloserine (DCS) Terizidone (TRD) Ethionamide (ETH) Prothionamide (PTO)
Group 5: TB drugs with unclear efficacy or unclear role in treating drug-resistant TB	Clofazimine (CFZ) Linezolid (LZD) Amoxicillin/clavulanate (AMX/CLV) Thiacetazone (THZ) Clarithromycin (CLR) Imipenem/cilastatin (IPM/CLN) High-dose isoniazid (high-dose INH)

Treatment of DR-TB: Novel drugs and adjuvant surgical management

The principles of MDR-TB and XDR-TB treatment are shown in Table 3. Considering the poor treatment outcomes discussed above, the currently available drugs and regimens are clearly inadequate. A number of novel

Table 3. Principles of management of drug-resistant TB

MDR-TB

- A regimen is based, when possible, on proven or likely susceptibility to at least 4 drugs
- A regimen is generally based on a backbone of a newer-generation fluoroquinolone (moxifloxacin or levofloxacin), and an injectable agent (usually an aminoglycoside, i.e. either amikacin or kanamycin), any first-line drug to which the isolate is susceptible (Table 1), and the addition of category 3 drugs such as cycloserine/terizidone, ethionamide, and others, such that at least 4 drugs, to which the isolate is likely to be susceptible, are being used
- The injectable drugs are used for 6 - 8 months, and longer in certain cases, with the total duration of treatment being suggested to be 24 months
- If the patient has previously been on treatment with a specific drug for ≥3 months, this drug is generally omitted

XDR-TB

- Regimens should be constructed based on prevailing drug-susceptibility testing patterns
- Given the high background rates of TB and MDR-TB in several countries, regimens are often constructed around a backbone of capreomycin and para-aminosalicylic acid
- The intensive phase of treatment with capreomycin should be at least 8 months[8]
- Any drug that the isolate is susceptible to from category 1, and any remaining available drugs from category 3 or 4, are added to the regimen
- Moxifloxacin is usually added despite documented fluoroquinolone resistance, because it has increased antituberculous activity compared with ofloxacin,[24] has been shown to be effective against isolates phenotypically resistant to ofloxacin or ciprofloxacin,[25] and is associated with improved outcomes for patients with XDR-TB[26]
- Low-level resistance to isoniazid (inhA gene mutations) can potentially be overcome with increased doses of the isoniazid ('high-dose INH')[27 - 29]

drugs are undergoing clinical testing, but are unlikely to be available for several years yet.[16] Bedaquiline, the first novel antituberculous drug to emerge in almost half a century,[17] has been cautiously approved by the WHO for patients in whom a regimen containing 4 effective second-line drugs cannot be constructed, or for patients with MDR-TB and documented resistance to a fluoroquinolone (pre-XDR-TB).[18] Linezolid added to the regimen of patients failing standard XDR-TB treatment has been shown to improve culture conversion, but longer-term outcomes are unknown, and cost and toxicity are major concerns.[19] Neither bedaquiline nor linezolid is currently available as part of the National Treatment Programme in South Africa.

Patients with localised disease and adequate pulmonary reserve who have either persistently positive sputum smears and/or cultures despite an adequate trial of appropriate chemotherapy, or those who have relapsed or are thought to be at high risk of relapse, should be considered for surgical resection at specialised centres.

Conclusion

DR-TB has a high mortality, requires complex, lengthy and expensive treatment regimens, and poses a serious threat to TB control in South Africa. NAATs represent important advances in the diagnosis of DR-TB. However, current treatment regimens are far from satisfactory, and more effective, safer, less toxic and cheaper regimens are urgently required.

References

1. Streicher EM, Muller B, Chihota V, et al. Emergence and treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in South Africa. Infection, genetics and evolution. Journal of Molecular Epidemiology and Evolutionary Genetics in Infectious Diseases 2012;12(4):686-694.
2. WHO. Multidrug-resistant Tuberculosis (MDR-TB): 2013 Update. Geneva: WHO, 2013.
3. WHO. Global Tuberculosis Report 2012. Geneva: WHO, 2012.
4. Dheda K, Migliori GB. The global rise of extensively drug-resistant tuberculosis: Is the time to bring back sanatoria now overdue? Lancet 2012;379(9817):773-775. [http://dx.doi.org/10.1016/S0140-6736(11)61062-3]
5. Dheda K, Shean K, Zumla A, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: A retrospective cohort study. Lancet 2010;375(9728):1798-1807.
6. Orenstein E, Basu S, Shah N, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: Systematic review and meta-analysis. Lancet Infect Dis 2009;9(3):153-161. [http://dx.doi.org/10.1016/S1473-3099(09)70041-6]
7. Pooran A, Pieterson E, Davids M, Theron G, Dheda K. What is the cost of diagnosis and management of drug resistant tuberculosis in South Africa? PLoS One 2013;8(1):e54587. [http://dx.doi.org/10.1371/journal.pone.0054587]
8. Dheda K, Theron G, Peter JG, Symons G, Dawson R, Willcox P. TB drug resistance in high-incidence countries. Tuberculosis. 58: European Respiratory Society Journals Ltd, 2012:95-110.
9. Menzies NA, Cohen T, Lin HH, Murray M, Salomon JA. Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: A dynamic simulation and economic evaluation. PLoS Medicine 2012;9(11):e1001347.
10. Chang K, Lu W, Wang J, et al. Rapid and effective diagnosis of tuberculosis and rifampicin resistance with Xpert MTB/RIF assay: A meta-analysis. J Infect 2012;64(6):580-588. [http://dx.doi.org/10.1016/j.jinf.2012.02.012]
11. WHO. Automated Real-Time Nucleic Acid Amplification Technology for Rapid and Simultaneous Detection of Tuberculosis and Rifampicin Resistance: Xpert MTB/RIF System. Geneva: WHO, 2011.
12. Barnard M, Albert H, Coetzee G, O'Brien R, Bosman ME. Rapid molecular screening for multidrug-resistant tuberculosis in a high-volume public health laboratory in South Africa. Am J Respir Crit Care Med 2008;177(7):787-792. [http://dx.doi.org/10.1164/rccm.200709-1436OC]
13. Barnard M, Gey van Pittius NC, van Helden PD, Bosman M, Coetzee G, Warren RM. The diagnostic performance of the GenoType MTBDRplus version 2 line probe assay is equivalent to that of the Xpert MTB/RIF assay. J Clin Microbiol 2012;50(11):3712-3716.
14. Rutledge JA, Crouch JB. The ultimate results in 1654 cases of tuberculosis treated at the modern Woodmen of America sanatorium. Am Rev Tuberc 1919;2:755-763.
15. Hillemann D, Rusch-Gerdes S, Richter E. Feasibility of the GenoType MTBDRsl assay for fluoroquinolone, amikacin-capreomycin, and ethambutol resistance testing of *Mycobacterium tuberculosis* strains and clinical specimens. J Clin Microbiol 2009;47(6):1767-1772.
16. Field SK, Fisher D, Jarand JM, Cowie RL. New treatment options for multidrug-resistant tuberculosis. Therapeutic Advances in Respiratory Disease 2012;(5):255-268. [http://dx.doi.org/10.1177/1753465812452193]
17. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 2009;360(23):2397-2405. (Epub 2009/06/06.eng.)
18. WHO. The Use of Bedaquiline in the Treatment of Multidrug-resistant Tuberculosis: Interim Policy Guideline. Geneva: WHO, 2013.
19. Lee M, Lee J, Carroll MW, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med 2012;367(16):1508-1518. [http://dx.doi.org/10.1056/NEJMoa1201964]
20. WHO. Treatment of Tuberculosis: Guidelines. 4th ed. Geneva: WHO, 2009.
21. WHO. Multidrug and Extensively Drug-resistant TB (M/XDR-TB). Geneva: WHO, 2009.
22. Udwadia ZF, Pinto LM, Uplekar MW. Tuberculosis management by private practitioners in Mumbai, India: Has anything changed in two decades? PLoS One 2010;5(8):e12023. (Epub 2010/08/17.eng.)
23. Velayati A, Masjedi M, 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. (Epub ahead of print.) [http://dx.doi.org/10.1378/chest.08-2427]
24. Cox H, Ford N, Keshavjee S, et al. Rational use of moxifloxacin for tuberculosis treatment. Lancet Infect Dis 2011;11(4):259-260. (Epub 2011/04/02.eng.)
25. Kam KM, Yip CW, Cheung TL, Tang HS, Leung OC, Chan MY. Stepwise decrease in moxifloxacin susceptibility amongst clinical isolates of multidrug-resistant *Mycobacterium tuberculosis*: Correlation with ofloxacin susceptibility. Microbial Drug Resistance 2006;12(1):7-11.
26. Jacobson KR, Tierney DB, Jeon CY, Mitnick CD, Murray MB. Treatment outcomes among patients with extensively drug-resistant tuberculosis: Systematic review and meta-analysis. Clin Infect Dis 2010;51(1):6-14. [http://dx.doi.org/10.1086/653115]
27. Sirgel FA, Donald PR, Odhiambo J, et al. A multicentre study of the early bactericidal activity of anti-tuberculosis drugs. J Antimicrob Chemother 2000;45(6):859-870. (Epub 2000/06/06.eng.)
28. Jayaram R, Shandil RK, Gaonkar S, et al. Isoniazid pharmacokinetics-pharmacodynamics in an aerosol infection model of tuberculosis. Antimicrob Agents Chemother 2004;48(8):2951-2957. (Epub 2004/07/27.eng.)
29. de Steenwinkel JE, de Knegt GJ, ten Kate MT, et al. Time-kill kinetics of anti-tuberculosis drugs, and emergence of resistance, in relation to metabolic activity of *Mycobacterium tuberculosis*. J Antimicrob Chemother 2010;65(12):2582-2589. (Epub 2010/10/16.eng.)