

## Drug-resistant tuberculosis

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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.<sup>[1]</sup> World Health Organization (WHO) statistics show that almost half a million new cases of MDR-TB develop every year,<sup>[2]</sup> 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.<sup>[2]</sup> 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;<sup>[3]</sup> of these, 5 - 10% have XDR-TB.<sup>[4]</sup> 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.<sup>[2]</sup> 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.<sup>[5]</sup> 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.<sup>[6]</sup> 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.<sup>[7]</sup>

### 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

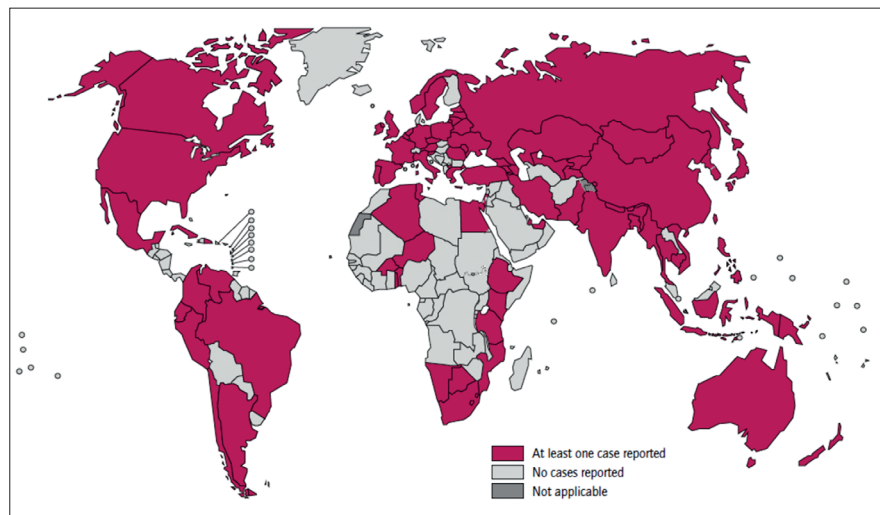


Fig. 1. Countries that had notified an XDR-TB case by the end of 2011.<sup>[3]</sup>

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

Type	Definition
Multidrug-resistant TB (MDR-TB)	Resistance to isoniazid and rifampicin <sup>[21]</sup>
Extensively drug-resistant TB (XDR-TB)	MDR-TB plus resistance to any fluoroquinolone and any second-line injectable (either kanamycin, amikacin or capreomycin) <sup>[21]</sup>
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). <sup>[22,23]</sup> However, due to problems with the reliability and reproducibility of <i>in vitro</i> 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.<sup>[8]</sup>

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.<sup>[9]</sup> 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.<sup>[10]</sup> 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.<sup>[11]</sup> Another NAAT, the MTBDRplus assay (Hain Lifesciences, Nehren, Germany), offers similar advantages as Xpert<sup>®</sup> MTB/RIF for MDR-TB detection.<sup>[12,13]</sup> Unlike Xpert<sup>®</sup> 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,<sup>[14]</sup> for use on smear-positive or culture-positive specimens.<sup>[15]</sup>

### 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 2. First- and second-line drugs based on the WHO classification<sup>[20]</sup>**

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)

**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  $\geq 3$  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<sup>[8]</sup>
- 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,<sup>[24]</sup> has been shown to be effective against isolates phenotypically resistant to ofloxacin or ciprofloxacin,<sup>[25]</sup> and is associated with improved outcomes for patients with XDR-TB<sup>[26]</sup>
- Low-level resistance to isoniazid (inhA gene mutations) can potentially be overcome with increased doses of the isoniazid ('high-dose INH')<sup>[27 - 29]</sup>

drugs are undergoing clinical testing, but are unlikely to be available for several years yet.<sup>[16]</sup> Bedaquiline, the first novel antituberculous drug to emerge in almost half a century,<sup>[17]</sup> 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).<sup>[18]</sup> 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.<sup>[19]</sup> 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.

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