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Review of multidrug-resistant and extensively drug-resistant TB: global perspectives with a focus on sub-Saharan Africa

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Summary Tuberculosis (TB) remains a global emergency and is responsible for 1.7 million deaths annually. Widespread global misuse of isoniazid and rifampicin over three decades has resulted in emergence of the ominous spread of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) globally. These difficult to treat resistant forms of TB are increasingly seen in Asia, Eastern Europe, South America and sub-Saharan Africa, disrupting TB and HIV control programmes. We review the latest available global epidemiological and clinical evidence on drug-resistant TB in HIV-infected and uninfected populations, with focus on Africa where data are scanty because of poor diagnostic and reporting facilities. The difficult management and infection control problems posed by drug-resistant TB in HIV-infected patients are discussed. Given the increasing current global trends in MDR-TB, aggressive preventive and management strategies are urgently required to avoid disruption of global TB control efforts. The data suggest that existing interventions, public health systems and TB and HIV programmes must be strengthened significantly. Political and funder commitment is essential to curb the spread of drug-resistant TB.

keywords tuberculosis, drugs, MDR-TB, XDR-TB, epidemiology, microbiology, treatment

Introduction

Efforts to control the global tuberculosis (TB) epidemic have now been complicated by the emergence of strains of *Mycobacterium tuberculosis,* which are resistant to one or more anti-TB drugs. Multidrug-resistance originates from misuse of anti-TB drugs by physicians, patients and producers (Matteelli *et al.* 2007; Migliori *et al.* 2009) (Figure 1). The identification and spread of multidrug-resistant TB (MDR-TB) (Pablos-Méndez *et al.* 1998; Espinal *et al.* 2001; Shah *et al.* 2005; WHO and IUATLD, 2008; Wright *et al.* 2009), and more recently, of extensively drug-resistant TB (XDR-TB) globally (Holtz *et al.* 2005; Shah *et al.* 2005; Centers for Disease Control and Prevention, 2006; WHO, 2010) is increasingly becoming a major threat to achieving the projected goal of TB control and elimination by the year 2050 as advocated by the Millennium Development Goals (MDGs) and Stop TB Partnership. This review discusses the clinical epidemiology, microbiology, diagnosis, treatment and prevention aspects of drug-resistant TB in HIV-infected and uninfected adults globally, with special focus on MDR-/XDR-TB in resource-limited settings, with an emphasis on sub-Saharan Africa because emerging clinical experience data shows that drug-resistant TB is now more widespread than previously thought.

Methods

A systematic review of all relevant publications on drug-resistant TB was performed via a Medline search using the key words 'Tuberculosis', 'drug resistance' 'MDR-TB' and 'XDR-TB', with the words 'epidemiology, diagnosis, treatment, drug resistance genes, TB control, epidemiology, management, TB control programmes, Africa and prevention' covering the period 31st March 2000 to 1st

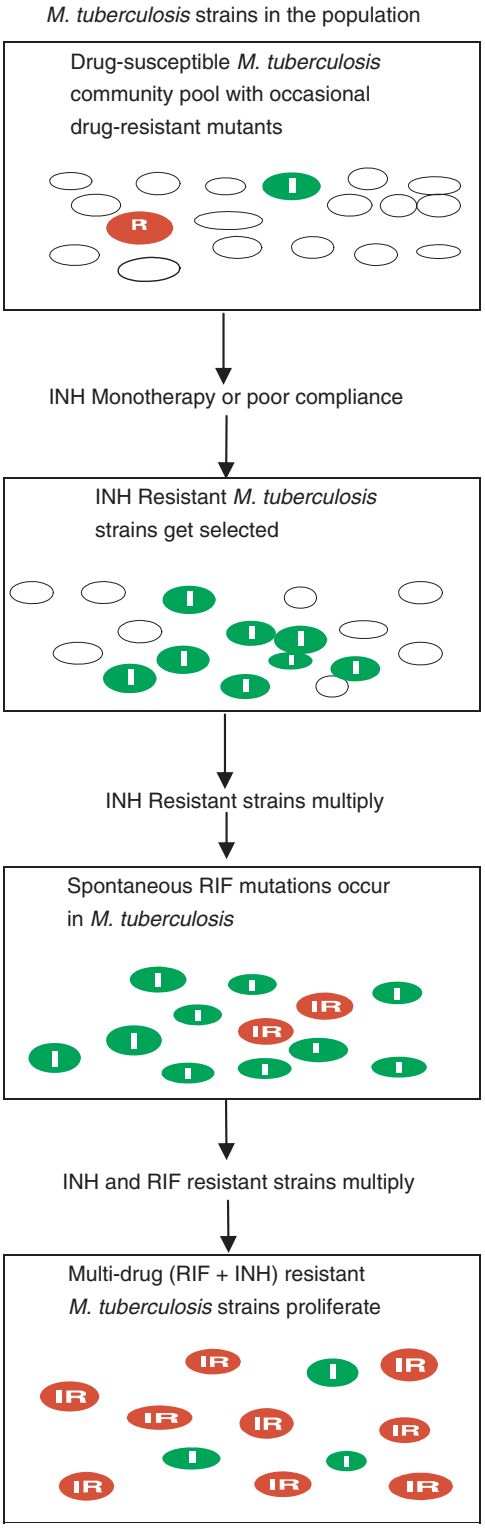


Figure 1 Evolution of multidrug resistance.

April 2010, and all relevant literature from English language medical journals were reviewed. In addition, the US Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report (MMWR) was searched for reports on MDR-TB and XDR-TB published from 2000 to the present and quoted in the review based on priority criteria. Further sources of information were data emerging from current studies and databases on MDR-/XDR-TB in South Africa, WHO publications on TB and drug-resistant TB published over the past 15 years (Schaaf & Zumla 2009) and relevant chapters from two recently published textbooks on TB (Schaaf & Zumla 2009; Zumla & Schaaf 2009).

Definitions for drug-resistant TB

The definitions of drug-susceptible and drug-resistant TB are given in Table 1. 'Pan-susceptible TB' is defined as TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) strains that are susceptible to all first-line anti-TB drugs. MDR-TB is defined as resistance to the two key first-line anti-TB drugs, isoniazid (INH) and rifampicin (RMP/RIF) (Pablos-Méndez *et al.* 1998; Espinal *et al.* 2001; WHO and IUATLD, 2008; Wright *et al.* 2009; WHO, 2010). The term XDR-TB appeared in the literature for the first time in March 2006, in a report jointly published by WHO and CDC, to describe a very aggressive form of disease characterised by high mortality rates (Centers for Disease Control and Prevention, 2006). It is presently defined as TB caused by strains of *M. tuberculosis,* which are the following: (a) resistant to at least INH and RMP (i.e. MDR-TB), (b) *plus* any fluoroquinolone, *and* (c) to at least

Table 1 Definitions of Drug-susceptible and drug-resistant tuberculosis (TB)

Pan (Totally)-susceptible TB	Tuberculosis caused by *Mycobacterium tuberculosis* strains susceptible to all first-line anti-TB drugs.
INH Monoresistant TB	Tuberculosis caused by *M. tuberculosis* strains resistant only to INH
Multidrug-resistant tuberculosis (MDR-TB)	Tuberculosis caused by *M. tuberculosis* strains resistant to at least two first-line anti-TB drugs INH and rifampicin (RMP)
Extensively drug-resistant tuberculosis (XDR-TB)	Tuberculosis caused by *M. tuberculosis* resistant to RMP and INH *plus* any fluoroquinolone, and at least *one* of the three following injectable drugs: capreomycin, kanamycin or amikacin
Pan (Totally)-resistant TB	Tuberculosis caused by *M. tuberculosis* resistant to all first and second-line anti-TB drugs

INH, isoniazid.

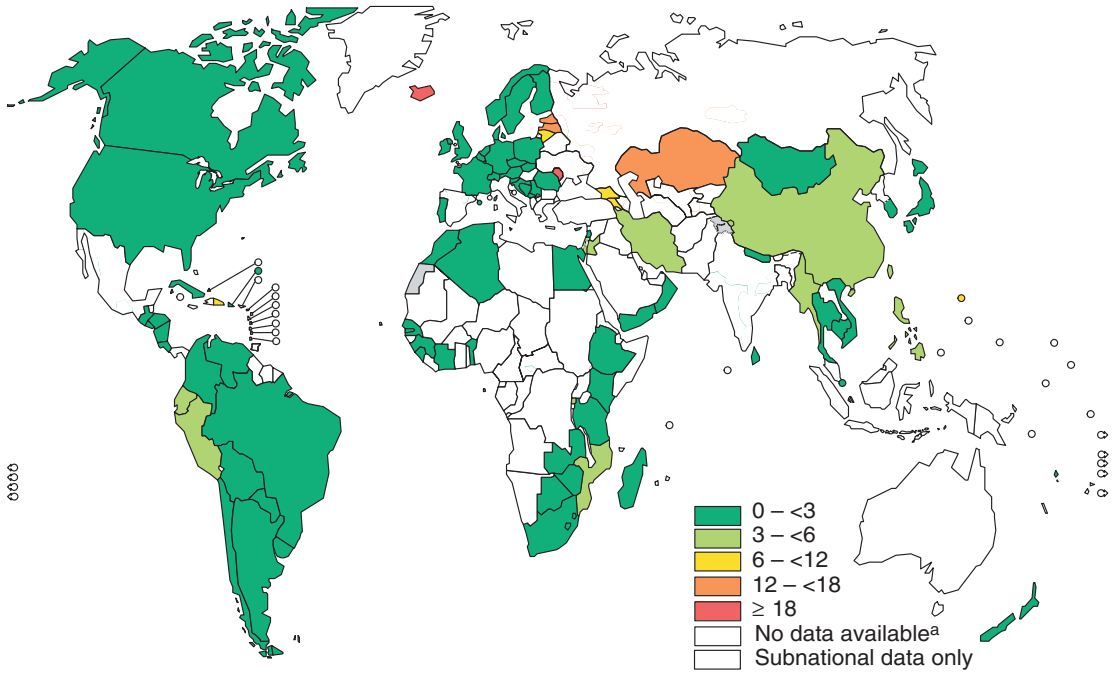
one of three injectable drugs used in anti-TB treatment, capreomycin, kanamycin or amikacin (Holtz & Cegielski 2007; Migliori *et al.* 2007).

Epidemiology of MDR-TB and XDR-TB

The latest data on the extent of drug-resistant TB are summarised in the 2010 WHO MDR-/XDR-TB Global report on surveillance and response (WHO, 2010). The proportions of MDR-TB among all new TB cases is shown in Figure 2. MDR-TB caused an estimated 150 000 deaths in 2008. The 2010 WHO report estimates that 440 000 MDR-TB cases occurred in 2008 (3.6% of the estimated total incident TB episodes). Of these, 360 000 were among new TB cases, and 94 000 were among individuals previously treated. Data on drug-resistant TB from Africa are very scarce. India and China constitute approximately 50% of the global burden of MDR-TB, followed by the Russian Federation (9%). Eastern Europe and Central Asia have reported very high proportions of MDR-TB among new cases (Balabanova *et al.* 2005; Migliori *et al.* 2010). The Russian Federation's surveillance data from 12 of its oblasts and republics reported proportions of 23.8–28.3% MDR-TB among new TB cases in three of its oblasts in the north-western part of the country.

Role of HIV in fuelling the drug-resistant TB epidemic

About 8% of all infections with *M. tuberculosis* occur in people with HIV, making it the most important opportunistic infection worldwide. Over the past two decades, the HIV pandemic has been the most important factor for increased numbers of TB cases being reported in sub-Saharan Africa (Elliott *et al.* 1993; Habeenzu *et al.* 2007; Kehinde *et al.* 2007; Umubyeyi *et al.* 2007; Meskel *et al.* 2008). The spread of the TB epidemic is closely related to the high HIV infection rates in the general population. Recently, co-infection of the two pathogens, *M. tuberculosis* and HIV, has become more noticeable in Eastern Europe and in Asia (Kingkaew *et al.* 2009). Sub-Saharan Africa bears the burden of both very high TB incidence and the highest human immunodeficiency virus (HIV) prevalence rates in the world, and now represents 14% of the global burden of new MDR-TB cases (Amor *et al.* 2008; WHO, 2010).



Australia, Democratic Republic of the Congo, Fiji, Guam, New Caledonia, Solomon Islands and Qatar reported data on combined new and previously treated cases.

Figure 2 Global proportions of MDR-TB among new TB cases. [Reproduced with permission from WHO, (2010)]. MDR-TB, multidrug-resistant tuberculosis.

MDR-TB and XDR-TB in sub-Saharan Africa

There are scanty data about MDR-TB trends in Africa. According to the 2010 Global WHO Report (WHO, 2010), only 22 of 46 countries of the African Region have provided data on drug-resistant TB (12 having conducted a nationwide survey since 2000 and 10 a sub-national level survey). South Africa is the only country that collects routine surveillance data. Thirty-four countries have reported MDR-TB cases and eight XDR-TB cases. Only three countries (Rwanda, the United Republic of Tanzania and South Africa) have information on the proportion of XDR-TB among MDR-TB cases. The reason why the proportion of MDR-TB among patients with TB is generally low in the African region (with a frequency ranging from 0.5% to 3.9% among new TB cases and 0.0% to 16.7% among previously treated ones) is probably related to poor laboratory facilities for drug susceptibility testing (DST), poor surveillance mechanisms and reporting procedures, outdated databases and sub-optimal coverage of the infrequent surveys. Given the high incidence of TB per population, the rates of MDR-TB cases arising per 100 000 population in some southern African countries are predicted to be 5–6 times higher than those reported in China and India. The latest WHO estimate of the number of MDR-TB cases emerging in 2008 in Africa, most likely an underestimate, is 69 000 cases (WHO, 2010).

Nine African countries rate among the 27 high-burden MDR-TB countries with South Africa estimated to have approximately 20 000 MDR-TB cases annually. Amor and co-investigators based on data from 39/46 countries in Africa estimate that MDR-TB is likely to be more prevalent than previously recognised (Amor *et al.* 2008). Indeed, more recent data indicate higher rates of MDR-TB in several prevalence surveys. Recent surveys from Ethiopia (retreatment cases) (Meskel *et al.* 2008), Nigeria (tertiary hospital) (Kehinde *et al.* 2007), Zambia (prison) (Habeenzu *et al.* 2007) and Rwanda (retreatment cases) (Umubyeyi *et al.* 2007) indicate MDR-TB prevalence rates of 26%, 54%, 9.5% and 9.4%, respectively. Alarming data from Botswana suggest that notification rates of all cases of TB and also of MDR-TB are increasing (Chirenda *et al.* 2009). If this reflects the situation in other high HIV-prevalence countries where TB control programmes have been destabilised, then the situation might be worse than previously thought (Habeenzu *et al.* 2007; Kehinde *et al.* 2007; Umubyeyi *et al.* 2007; Amor *et al.* 2008; Meskel *et al.* 2008; Chirenda *et al.* 2009; Kingkaew *et al.* 2009).

The lack of information on drug resistance in Africa will impede planning of surveillance and activities of the national TB and HIV programmes. Current estimates of MDR-TB cases in many African countries are thus based on mathematical modelling rather than actual studies. Laboratory surveillance for MDR-TB and XDR-TB should be strengthened and expanded across the region, particularly where studies have never been carried out or data are now older than 5 years. Three groups have recently published their studies on the outcome of XDR-TB treatment from South Africa (Gandhi *et al.* 2006; O'Donnell *et al.* 2009; Wright *et al.* 2009; Dheda *et al.* 2010; Gandhi *et al.* 2010a,b). These studies, which are limited by their restricted study design and not representative of the general population, reveal that the drug resistance problem in South Africa is more widespread than previously thought and needs proper definition. It is evident that urgent initiation and implementation of regular comprehensive and methodologically sound surveillance studies from African countries are now needed to gauge the true extent of the TB drug-resistant problem.

Microbiology of MDR-TB and XDR-TB

Drug-resistant TB is a microbiological diagnosis based on susceptibility patterns of the *M. tuberculosis* strains isolated from any patient clinical sample (Table 1). Multidrug-resistant *M. tuberculosis* strains are defined as those that are resistant to INH and RMP. The frequency of resistance to multiple drugs varies geographically, and acquired (secondary) resistance is more common than primary resistance. Drug resistance in *M. tuberculosis* is because of the acquisition of mutations in chromosomally encoded genes (Johnson *et al.* 2009).

The generation of multidrug-resistance in *M. tuberculosis* is a consequence of accumulation of mutations primarily because of inadequate or intermittent therapy or non-compliance (Figure 1). Resistance to INH is because of mutations in the *katG* gene, and about half of all isolates with *katG* mutations have an amino acid replacement at codon 315. The *rpoB* gene, which encodes the β-subunit of RNA polymerase, harbours a mutation in an 81 -bp region in about 95% of RMP-resistant *M. tuberculosis* strains recovered globally. Mutations in the *pncA* gene can cause pyrazinamide (PZA) resistance in approximately 70% of clinical isolates. Approximately 65% of clinical isolates resistant to ethambutol (EMB) have a mutation in the *embB* gene. Clinical and genotypic characteristics of XDR-TB and MDR-TB are now being studied. The following drug resistance genes have been identified in second-line agents: *gyrA* in flouroquinolones, *rrs* for aminoglycosides Kanamycin and Amikacin, *inhS*, *othA* and *ethR* for ethionamide, *alr* and *ddl* for D-cycloserine and *rrs* for Capreomycin. The genotypic characteristics of *M. tuberculosis* isolates from non-HIV-infected patients having MDR-TB and XDR-TB evaluated by spoligotyping and the 24-locus mycobacterial

interspersed repetitive units-variable number of tandem repeats scheme showed that the Beijing genotype was the most common genotype. The clinical features of patients infected with the Beijing genotype and the drug resistance profile of the Beijing genotype isolates were similar to those for the non-Beijing family genotype.

The genotypic analysis of MDR-TB isolates shows that commonly found mutations in drug-resistant isolates are seen from different regions of the world. Transmission chains can be defined by isolates having identical IS*6110* DNA fingerprints, spoligotypes and mutations conferring resistance. Molecular studies on mycobacterial strains can give clues to nosocomial transmission of drug-resistant *M. tuberculosis* strains. A study at King George V (KGV) Hospital, in KwaZulu-Natal (KZN) (Pillay & Sturm 2010) determined the role of nosocomial transmission of drug-resistant TB in 26 patients infected with a new strain of *M. tuberculosis* during treatment. DNA fingerprints 14 of 26 patients with differing isolates matched those of other patients. Four acquired a F15/LAM4/KZN genotype, two acquired fully susceptible Beijing strains. Three of the four F15/LAM4/KZN strains were multidrug-resistant with identical fingerprint patterns, while the fourth was fully susceptible. One of these was acquired during hospitalisation and three after discharge. Both HIV-infected and non-infected patients are at risk of infection with the F15/LAM4/KZN strain in health care facilities and within the community. There is a need for new diagnostic tests (Wallis *et al.* 2010), which can rapidly identify drug-resistant strains of *M. tuberculosis* from clinical samples so patients can be appropriately isolated to prevent nosocomial transmission.

Clinical features of MDR-TB and XDR-TB

Clinical presentation, symptoms and signs

The clinical presentation, symptoms and signs of patients with drug-resistant tuberculosis in the majority of cases do not substantially differ from that of patients with TB because of pan-susceptible *M. tuberculosis* strains (Gandhi *et al.* 2006; O'Donnell *et al.* 2009; Schaaf & Dheda 2009). Co-infection with HIV further complicates the clinical picture because of other concomitant opportunistic infections (Dubrovina *et al.* 2008; Schaaf & Dheda 2009; Gandhi *et al.* 2010; Grobusch 2010). In the early stages of HIV infection, the clinical features of TB are similar to those of HIV-uninfected patients. Clinical presentation becomes more atypical with progressive immunosuppression. Drug-resistant TB should be suspected in patients who fail to respond to the intensive phase of standard short-course anti-TB therapy, or those who have: had TB previously; a history of poor compliance and substance abuse; been in contact with patients with drug-resistant TB. At least half of the patients with drug-resistant TB have none of these risk factors thus clinical awareness and a high degree of suspicion are required.

Establishing a diagnosis of drug-resistant TB

Accurate and rapid diagnosis of drug-resistant TB is of paramount importance for instituting appropriate clinical management and appropriate infection control measures (Schaaf & Dheda 2009; Wallis *et al.* 2010). The diagnosis is usually suspected on clinical and radiological grounds, and all health practitioners in high TB and HIV endemic areas must have a high index of suspicion of drug-resistant TB. The diagnosis of drug-resistant TB can only be confirmed by molecular microbiological studies as described earlier. When pulmonary TB is suspected clinically in high TB and HIV/AIDS endemic areas, other pulmonary infections should be excluded. These include *Pneumococcus* spp., *Chlamydiae pneumoniae*, *Mycoplasma* spp., *Legionelle* spp., non-tuberculous mycobacteria (e.g. *Mycobacterium avium* complex), *Cryptococcus* spp., *Histoplasma* spp., cytomegalovirus, *Aspergillus* spp., *Candida* spp., and *Pneumocystis jeroveci*. Other non-infectious complications also need to be considered such as sarcoidosis, Kaposi's sarcoma, lymphoproliferative diseases and throe malignancies. The diagnostic steps in the management of HIV-infected and HIV-uninfected patients with drug-resistant TB are similar to those of drug sensitive TB using conventional diagnostic algorithms. All *M. tuberculosis* isolates should be subject to DST (Moore *et al.* 2006; Pai *et al.* 2006; Hoek *et al.* 2008; Martin *et al.* 2008; Pietzka *et al.* 2009). This usually involves direct or indirect DST in selective media using liquid or solid culture, and this may take several weeks before results are available. Furthermore, the costs of these tests are prohibitive, and laboratory capacity and TB programme budgets in African countries are severely limited. Recent advances in molecular technology for DST have improved our ability to rapidly diagnose MDR-TB and XDR-TB (Pai *et al.* 2006; Wallis *et al.* 2010). Appropriate budgetary investments into expansion of laboratory capacity to rapidly diagnose drug-resistant TB and instituting treatment quickly are now required.

Drug treatment of drug-resistant TB

When a diagnosis of MDR-TB is made, it gives the attending physician another chance to cure the patient, thus it is imperative that the best and most comprehensive possible treatment regimen be used to successfully treat the

patient. Failure to effectively treat the patient will lead to further amplification of drug resistance leading to the development of XDR-TB (Espinal *et al.* 2000; Espinal 2003; Quy *et al.* 2003; Chan *et al.* 2004; Saravia *et al.* 2005; Gandhi *et al.* 2010; Grobusch 2010). Patients with MDR TB on treatment should be nursed in isolation until sputum smear microscopy and cultures turn negative. Close monitoring of the patient with DOTS and follow-up is required after patient is discharged from the treatment facility. Table 2 shows drug groups and treatment regimens that are recommended for MDR and XDR in adults. Table 3 shows the serious adverse events associated with these drugs. Available first-line drugs comprise RMP, INH, EMB, PZA and streptomycin (SM). INH and RMP are the most potent of these drugs. Second-line drugs are amikacin, capreomycin, cycloserine, linezolid, prothionamide, rifabutin and any of the flouroquinolones, e.g. moxifloxacin, levofloxacin, ofloxacin, gatifloxacin. The treatment of patients with MDR-TB and XDR-TB relies on drugs that are less potent, need to be administered for a much longer time and are substantially more toxic than those used to treat TB caused by drug-susceptible strains. The cost of a second-line drug regimen is much higher: up to thousands of dollars compared to the cost of about US$ 20 per patient for the standard 6-month short-course, first-line chemotherapy regimen (WHO Category 1). The optimal duration

Table 2 Drug groups for multidrug-resistant (MDR) and extensively drug-resistant (XDR-TB) tuberculosis treatment regimens for adults [adapted from Schaaf and Dheda (2009)]

		Daily dosage in mg for adults (<33 kg – dose in mg/kg)			
Drug group	Drug name	< 33 kg dose in mg/kg	33–50 kg	51–70 kg	>70 kg (also maximum dose)
*Group 1: Oral first-line drugs to which the organism shows *in vitro* susceptibility by DST	Ethambutol	25	800–1200	1200–1600	1600–2000
	Pyrazinamide	30–40	1000–1750	1750–2000	2000–2500
†Group 2: Second-line injectable agents (streptomycin is first-line drug – not for use in MDR/XDR-TB)	Amikacin	15–20	500–750	750–1000	1000
	Kanamycin	15–20	500–750	750–1000	1000
	Capreomycin	15–20	500–750	750–1000	1000
†Group 3: Fluoroquinolones	Ofloxacin	15–20	800	800	800–1000
	Levofloxacin	7.5–10	750	750	750–1000
	Moxifloxacin	7.5–10	400	400	400
‡Group 4: Second-line oral bacteriostatic agents	Ethionamide (or prothionamide)	15–20	500	750	750–1000
		15–20	500	750	750–1000
	Cycloserine (or terizidone)	15–20	500	750	750–1000
		10–20	600	600	900
	Para-aminosalisylic acid (PAS)	150	8 g	8 g	8–12 g
§Group 5: Drugs of unclear use in drug-resistant TB treatment	High-dose isoniazid	16–20			
	Linezolid	600 mg twice daily, but recent data suggest 300 mg twice daily or 600 mg or 300 mg may be effective (see text – New drugs)			
	Amoxicillin/clavulanate	Dosage for DR-TB not well defined. Normal adult dose 875/125 mg twice daily or 500/125 mg three times daily. Higher dose limited by adverse effects			
	Clarithromycin	500 mg twice daily			
	Thioacetazone	150 mg daily (Contraindicated in HIV-infected patients)			
	Imipenem/cilastatin	Usual adult dose 500–1000 mg IV 6-hourly			

DST, drug susceptibility testing.
*Cannot rely on DST – use as additional drug if DST result susceptible or not performed.
†Choose one drug in each of these groups; amikacin preferred to kanamycin in children.
‡Choose one or more of these drugs to make up total of four new drugs.
§Consider use of these drugs if insufficient drugs to build an acceptable regimen with previous groups. Linezolid dosage for TB is still uncertain. Thioacetazone should not be used in HIV-infected patients.

Table 3 Important adverse effects of second-line anti-tuberculosis drugs

Second-line drug	Adverse clinical effect*	Tests to monitor routinely
Amikacin Kanamycin Capreomycin	Ototoxicity (cumulative dose important) Nephrotoxicity	Audiology (hearing test) – monthly if possible Serum creatinine and potassium levels – monthly, high-risk patients more often
Fluoroquinolones	Gastrointestinal disturbance Insomnia Arthralgia	Clinical observation Serum uric acid if used with pyrazinamide
Ethionamide (or protionamide)	Gastrointestinal disturbance Hepatotoxicity Hypothyroidism	Clinical observation. Prevent by initially splitting dose or increasing dose (drug ramping) Jaundice – serum alanine transferase and bilirubin Thyroid-stimulating hormone levels (free T4) – at least 6-monthly
Cycloserine (or terizidone)	Psychosis, seizures, paresthesia, depression	Clinical observation – all patients to receive preventive pyridoxine
Para-aminosalisylic acid (PAS)	Gastrointestinal disturbance Hypothyroidism	Clinical observation Thyroid-stimulating hormone levels (free T4) – at least 6-monthly
Linezolid	Myelosuppression or thrombocytopenia Lactic acidosis Peripheral neuropathy Pancreatitis (Abdominal pain) Optic neuritis Drug interaction with MAOIs	Full blood count and platelets – weekly at first then monthly Serum lactate level Symptoms of tingling and numbness Clinical and serum amylase as indicated Vision testing Exclude use of monoamine oxidase inhibitors

*Adverse effects of first-line dugs and antiretroviral drugs in HIV-infected patients often have overlapping adverse effects.

of any given combination of anti-tuberculosis drugs for the treatment of MDR-TB and XDR-TB has not been defined yet (WHO, 2009). The effectiveness of third-line anti-TB drugs (amoxicillin-clavulanate, clarithromycin, clofazimine and linezolid, called Group 5 drugs in the WHO guidelines) remains undefined.

Failure of therapy and re-treatment regimens

Failure of therapy is associated with drug resistance, poor drug compliance or insufficient treatment duration (Sonnenberg *et al.* 2001; Korenromp *et al.* 2003; Migliori *et al.* 2002; Caminero 2008). Data from a large retrospective cohort (>5550 cases) have provided evidence that standard short-course chemotherapy, based on first-line drugs, was inadequate to treat patients with MDR-TB (Espinal *et al.* 2000). A 6-year follow-up study from Taiwan found that patients treated with quinolone-containing second-line regimens were significantly less likely to relapse than those treated with first-line drugs (Chiang *et al.* 2006). The Category II re-treatment (regimen 2: INH-EMB-RMP-PZA-SM)/1(INH-EMB-RMP-PZA)/5(INH-EMB-RMP) recommended by WHO is inadequate for settings with a high proportion of MDR-TB patients among those failing a Category I regimens (Sonnenberg *et al.* 2001; Migliori *et al.* 2002; Espinal 2003; Korenromp *et al.* 2003;

Key messages on multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) tuberculosis

- WHO estimates that 440 000 MDR-TB cases occurred globally in 2008 and the spread of MDR-TB now threatens gains made in TB control
- Recent data from South Africa show MDR-TB and XDR-TB are important causes of death in both HIV-infected and HIV-non-infected individuals
- Drug-resistant TB should be suspected in patients who fail to respond to the intensive phase of standard short-course therapy, have had TB previously, have a history of poor compliance, are known contacts of patients with drug-resistant TB.
- WHO infection control guidelines must be carefully followed to prevent community and nosocomial transmission of drug-resistant TB.
- Drug-resistant TB requires serious attention from health personnel, governments, policy makers and funders to bring it under control

Quy *et al.* 2003; Saravia *et al.* 2005; Caminero 2008). Treating MDR-TB patients using Category II regimens also runs the risk of further amplification of drug resistance (Caminero 2008). Hence, the common practice in high-burden settings, in the absence of susceptibility data, to replace standard first-line treatment (regimen 1) with an extended treatment regimen containing SM (regimen 2) in patients failing first-line treatment, translates into adding a single drug to a failing regimen. To prevent the amplification of drug resistance, all re-treatment cases, and those failing a first-line regimen, should have their mycobacterial isolates screened by DST for RMP and INH resistance.

A number of basic rules for the management of these patients have been agreed upon recently (Ghandi *et al.* 2010b). The recommended regimen involves combination of a minimum of four drugs to which the *M. tuberculosis* isolate is likely to be susceptible (more than four could be necessary if four susceptible drugs are not available or if it is necessary to use some drugs belonging to group 5), the choice being based on a stepwise adoption through the five groups of anti-TB drugs categorised by order of efficacy, safety and costs (Table 2). The duration of the intensive phase, when an injectable agent is administered, should be at least 6 months (4 months after culture conversion). The continuation phase (without the injectable drug) should be prolonged until 18 months after culture conversion (Sotgiu *et al.* 2009). Recent data from South Africa suggest that XDR-TB patients with ofloxacin-resistant isolates fared better when treated with moxifloxacin, compared to XDR-TB patients who did not receive moxifloxacin (Dheda *et al.* 2010). Although the optimal duration of treatment for MDR and XDR-TB is not known, a minimum of 18 months after the first negative culture (or 24 months for XDR-TB) is usually recommended (Schaaf & Dheda 2009). MDR/XDR-TB patients are often hospitalised during the intensive phase of treatment or, in the case of XDR-TB, until they become culture-negative. Latest data from South Africa show that XDR-TB is not associated only with HIV-infected individuals (Dheda *et al.* 2010). Treating HIV-infected XDR-TB patients with appropriate anti-TB regimens and with Highly Active Antiretroviral Therapy (HAART) has lower mortality compared to untreated patients, and survival in HIV-infected patients is better than that previously reported. Because current management outcomes of XDR-TB patients in South Africa are poor, prevention of XDR-TB and early detection and management of MDR-TB and XDR-TB through programmatic and laboratory capacity strengthening remain an important priority for high TB and HIV/AIDS endemic areas.

Treatment monitoring for drug-resistant TB

Treatment monitoring is performed to evaluate early predictors of treatment outcome (sputum smear and culture conversion) and to ensure prevention and eventually timely management of adverse events of treatment. In a recent review on XDR-TB (Sotgiu *et al.* 2009), only three (23%) of the 13 studies included in the review evaluated both median time to sputum smear and culture conversion, while four measured the median time to culture conversion. Longer treatment duration and delayed sputum smear conversion were reported in most studies among XDR-TB patients. Median time to sputum smear conversion ranged from 41 to 56 days in MDR-TB patients, while it ranged from 88 to 110 days in XDR-TB cases. The median time to culture conversion ranged from 58 to 99 days in MDR-TB cases; it was substantially different in XDR-TB patients, ranging from 60 to 195 days. In a recent study from South Africa, the culture conversion rate in XDR-TB patients was < 20% and of those who converted, 70% did so within 6 months of initiating treatment (Dheda *et al.* 2010).

Risk factors and treatment outcomes of MDR-TB

There have been several published reports on the treatment outcomes of MDR-TB treated with second-line drugs but methods used to assess outcome varied. Some focused on efficacy of treatment and reported only those who had adequate adherence to treatment and sufficient follow-up data. This approach may have overestimated the proportion of patients with a successful outcome (Goble *et al.* 1993; Park *et al.* 1998; Chan *et al.* 2004). Others reported outcome of the whole cohort of patients without excluding any cases from outcome analysis (Flament-Saillour *et al.* 1999; Kim *et al.* 2001). Laserson *et al.* (2005) proposed standardised definitions for outcome of MDR-TB

treatment, which have enabled international comparison but the definition of treatment has not yet been standardised (Chiang *et al.* 2009). Nevertheless, it is clear that defaulting is one of the major challenges in the treatment of MDR-TB.

Risk factors for adverse treatment outcome in patients with MDR-TB and XDR-TB have been recently reviewed in detail (Dheda *et al.* 2010; Gandhi *et al.* 2010; Grobusch 2010). They include delayed treatment initiation, prior treatment with anti-tuberculosis drugs, use of fewer second-line drugs in a regimen, previously treatment with second-line drugs, prior exposure to fluoroquinolones, resistance to fluoroquinolones or to capreomycin, low BMI, HIV-seropositivity and other immunosuppressive conditions. Treatment outcome of MDR-TB patients from resource-limited settings reported cure rates of 60–75% (O'Donnell *et al.* 2009). The proportion of MDR-TB patients who were successfully treated ranged from 77% among new cases to 69% among previous treated patients. A recent report has confirmed that XDR-TB had higher probability of death, longer hospitalisation, longer treatment duration and delayed microbiological conversion when compared to MDR-TB at TB reference centres in Italy and Germany (Migliori *et al.* 2007). Earlier observations from the Tugela Ferry outbreak in the Republic of South Africa that XDR-TB is untreatable have not been confirmed in other areas of the world where HIV was not a big problem (Gandhi *et al.* 2010). A recent systematic review on MDR-TB and XDR-TB, including studies from North and South America, Europe and Korea (Sotgiu *et al.* 2009), has shown that XDR-TB can be successfully treated in more than 50% of patients. However, treatment duration is significantly longer, and outcomes are in general poorer than for non-XDR-TB patients.

Our latest data from South Africa demonstrated in a large cohort of XDR-TB cases (n = 220, 43% being HIV-seropositive) that the overall mortality was 36%, was similar in HIV-positive and HIV-negative individuals, but significantly lower in HIV-positive patients not treated with antiretroviral therapy compared to those who were (Dheda *et al.* 2010). Thus, overall treatment-related outcomes of XDR-TB were generally poor. This may be related to several factors operating in resource-poor settings, such as the high proportion of patients with prior MDR-TB, malnutrition, re-infection and strain dynamics, among other factors.

Surgical treatment for MDR-TB and XDR-TB

The role of surgery in the management of extensive pulmonary involvement in MDR-/XDR-TB remains controversial (Torun *et al.* 2007; Dravniece *et al.* 2009). Surgical resection of infected lung tissue has been reported to be a useful strategy in the treatment of MDR-TB and XDR-TB. While some studies reported that surgery was associated with a better outcome (Chiang *et al.* 2001; Somocurcio *et al.* 2007), others found no additional benefit of surgery in the treatment of MDR-TB (Torun *et al.* 2007). The contribution of surgical intervention may be useful when medical treatment fails to clear sputum mycobacteria (Chiang *et al.* 2001; Dravniece *et al.* 2009). Surgical intervention is usually indicated for extensive drug resistance with a high probability of failure of medical therapy alone (Iseman *et al.* 1990; Motus *et al.* 2006), but its timing is not yet well defined. Surgical intervention depends on the following two factors: (1) localised lung disease with good chances for complete or nearly complete resection and adequate expected post-operative lung function, and (2) susceptibility of *M. tuberculosis* isolate to anti-TB drugs to ensure post-surgery stump healing (Iseman *et al.* 1990). Effective anti-tuberculosis treatment offered for at least 3 months prior to the surgical intervention to reduce bacillary load is recommended (Iseman *et al.* 1990). Surgical interventions complementing individualised chemotherapy regimens guided by DST have led to treatment success rates in selected MDR-TB patients of >90% in a number of studies, but success rates in patients with XDR-TB are lower. A study from Ekaterinburg (Russian Federation) evaluated the outcomes of 214 culture-confirmed patients with cavitary pulmonary TB (79.9% of them being MDR): 109 underwent artificial pneumothorax, and 105 were treated with chemotherapy only (Motus *et al.* 2006). Among new cases, those who had artificial pneumothorax had a higher proportion of sputum smear conversion than controls (100% *vs.* 70.9%; $P < 0.01$). Similarly, among retreatment cases, the proportion of smear conversion was, respectively, 81% among cases *vs.* 40% among controls ($P < 0.01$). The time to conversion was also faster in group than in control cases (Motus *et al.* 2006). Further studies are necessary to evaluate the role of artificial pneumothorax in treating MDR-/XDR-TB cases.

Public health responses to drug-resistant TB epidemic

Infection control measures and recommendations

WHO policy on TB infection control in health care settings and households has been clearly defined (WHO, 2009). This covers organisational activities (surveillance and assessment at all levels of the health system), administrative controls (triage, cough etiquette, reduction in unnecessary hospital stay, among others), environmental controls (natural ventilation, mechanical ventilation, ultra-violet irradiation and health facility renovation) and personal protection. Personal protection includes both the use of

respirators for health staff and masks for patients on one side and the 'Package of prevention and care for health care workers' on the other side [including HIV prevention, antiretroviral therapy (ART) and INH preventive therapy for HIV-positive health care workers].

Tuberculosis infection control measures in most health care facilities in the developing countries are virtually non-existent because of poor investment by governments into their health systems and TB programmes (Kranzer *et al.* 2010). Implementation of comprehensive infection control measures is not usually feasible, but implementing simple triage systems to separate potentially infectious (coughing) patients, and providing masks to patients and/or staff could be easily carried out. Ideally, patients with drug-resistant TB must be cared for in hospitals equipped with negative pressure isolation facilities, administrative hospital protocols to deal with such patients and appropriate environmental protective measures should be taken. Adequate ventilation (>12 air changes/h) obtained by opening windows and doors is the most important and easily implemented measure other than diagnosing and treating infectious cases early and effectively and separating suspected cases from other susceptible people such as children and HIV-infected individuals. Cough etiquette is also a cost-effective intervention that needs to be implemented at all levels. A recent modelling study on infection control outcomes estimated that half of anticipated XDR-TB cases could be averted by applying a combination of available strategies in developing countries (WHO, 2009). Appropriate safety measures using negative pressure category 3 cabinets, masks and gloves should be implemented by laboratory staff when dealing with biological samples from patients suspected of having drug-resistant TB strains.

Contact tracing of workmates and family members for drug-resistant TB

By the time a patient is diagnosed with drug-resistant TB, most of his/her contacts will have been infected. Both hospital and community-based health care workers are at risk of acquiring drug-resistant TB (Kranzer *et al.* 2010). Contact tracing is one of the most fundamental measures to detect active cases of TB, and these services must be aligned to all health services. Everyone diagnosed with drug-resistant TB must be isolated, and infection control procedures described earlier should be followed.

Importance of proper implementation of TB programme control measures to control drug-resistant TB

There are only a limited number of treatment options for drug-resistant TB because the numbers of safe and effective TB drugs are few. An urgent and comprehensive TB programme response to the drug-resistant TB epidemic is required to tackle a grave situation, which threatens to derail gains made in TB control. The extent of MDR-TB and XDR-TB in areas of high HIV prevalence needs to be defined. Laboratory capacity (trained staff and appropriate equipment) needs to be established to undertake DST to facilitate rapid diagnosis of drug resistance. The HIV/AIDS epidemic continues to generate large numbers of TB cases, and the close association between the two diseases poses major challenges to TB and HIV control programmes of all developing countries (Lalloo & Pillay 2008; Abdool Karim *et al.* 2009). There is an urgent need for government national TB programmes to synergise their activities with HIV/AIDS programmes and ensure that control methods that are known to work are implemented. TB and HIV programmes must be aligned together and their capabilities strengthened to improve diagnostic capabilities, improved treatment rates and monitoring of drug-resistant TB. Priorities for HIV-infected patients with TB are improved case detection rates, HIV screening procedures, initiating antiretroviral therapy and INH prophylactic therapy as appropriate, increasing treatment completion rates, accurately diagnosing drug-resistant cases by introducing the latest available technologies for rapid detection, effectively treating drug-resistant cases, implementing effective contact tracing and infection control measures. TB control programmes are dependent on the health systems they are part of and governments should wake up to the emergency that drug-resistant TB poses. They must ensure that greater emphasis is given to diagnosing and treating patients with TB and TB/HIV/AIDS based on existing principles of TB care.

Global recommendations for prevention and control of drug-resistant TB

In 2007, pressed by the emerging threat represented by MDR-TB and XDR-TB, WHO formulated a policy to address this epidemic at the global level (Shah *et al.* 2005; WHO and IUATLD, 2008; WHO, 2010). The major recommendations formulated by the expert panel were (i) to improve the 'quality' of TB control globally to prevent the selection of MDR-TB and XDR-TB mutants, and (ii) to further improve the organisation of early diagnosis and effective treatment of the existing cases. WHO developed a broader approach, known as the new Stop TB Strategy, built upon the existing well-known DOTS strategy as the element of continuity. The new strategy is composed of six elements: (1) pursue high-quality DOTS expansion and enhancement; (2) address TB/HIV, MDR-TB and other challenges; (3) promote health system strengthening; (4)

engage all care providers; (5) empower people with TB and communities; and (6) enable, promote and fund research.

Recent advances in rapid diagnostics and treatment for drug-resistant TB

New technological advances for rapid diagnostics for MDR-TB

Current DST testing laboratory methods take a few weeks before the results are available; the need for rapid identification of drug-resistant TB is great. Newer molecular-based diagnostic technologies for rapid identification of drug-resistant genes from patient sputum samples, albeit very expensive presently, have been recently introduced (Pillay & Sturm 2010; Wallis *et al.* 2010). These show promise for early diagnosis and rapid institution of effective chemotherapy. This would improve management and cure rates of patients with drug-resistant TB. This will also allow for national TB programmes to improve MDR-TB surveillance, notification and instituting infection control. They include Gene Xpert (Cepheid), the line probe assays (e.g. Hain MDRplus assay and InnoLip assay) and the mycobacteriophage assays. For identification of drug resistance, bacteriophage amplification assays have shown high specificity and sensitivity in culture *M. tuberculosis* isolates, but evidence is lacking for their use on clinical specimens. Gene Xpert is a user-friendly 'closed' system nested real-time PCR assay that enables a rapid confirmation of TB and also simultaneously determines susceptibility to RMP. Formats to detect resistance to other drugs are under development. The line probe assays amplify a resistance-containing gene segment, e.g. the *rpoB* gene 'hotspot', and the PCR products are hybridised to oligonucleotide probes on a nitrocellulose strip (line probe; this is an 'open' system) (Pai *et al.* 2006). A variation, the Hain MDRplus sl version, can rapidly detect resistance to several drugs. There are several studies currently evaluating these technologies at research field sites in high endemic TB areas. If found to be useful, the cost of these machines will drop to affordable levels as sales increase and donor funding is justified.

Cheaper alternative technologies for diagnosis of drug-resistant TB

There are other accurate and cheap alternative methods described for use in resource-poor settings, and drug susceptibility results are often available within 2–3 weeks. These include microscopic observation DST (MODS), which relies on identifying the characteristic cording of *M. tuberculosis* in liquid medium using an inverted light microscope (Moore *et al.* 2006). The main drawback is that it is labour intensive. Thin-layer agar microscopically detects early growth of *M. tuberculosis* on a thin layer of agar; the platform can be simplified and standardised to detect resistance on colorimetric grounds. The nitrate reductase assays rely on a *M. tuberculosis* produced nitrite-induced colour change (Griess reaction) to detect growth in selective media (Martin *et al.* 2008). Novel approaches include the high resolution melt assay, which is able to identify clinical isolates harbouring mutations conferring RMP resistance by comparing DNA melt profiles of their RMP resistance determining region to the DNA melt profiles of a wild type standard (Hoek *et al.* 2008; Pietzka *et al.* 2009). The challenge is now to determine how these technologies will perform in high and low-burden MDR-TB settings, what impact they may have on outcomes, and how best to combine them with existing low cost diagnostic tools in high-burden settings. Several studies are ongoing at present evaluating how the Hain MDRplus assay performs when included as early as possible in diagnostic algorithms in high TB incidence, low income countries.

Newer anti-TB drugs pipeline and drug regimens

The Global Alliance for TB drug development has a number of drugs in the pipeline. These will soon be evaluated in good clinical practices (GCP) randomised controlled clinical trials for their to shorten the duration of anti-TB chemotherapy, to test their effectiveness for use in patients with drug-resistant TB (Lienhardt *et al.* 2010; Ma *et al.* 2010). The diarylquinoline Tibotec Medical Compound (TMC)207, which has a unique mode of action inhibiting mycobacterial ATP synthase, showed delayed bactericidal activity in early bactericidal activity studies in new patients with TB, with no serious TMC207 related adverse effects. Other promising bactericidal and potentially sterilising compounds currently evaluated in phase 1 trials and Early Bactericidal Activity (EBA) studies are the two nitroimidazoles, PA-824 (nitroimidazo-oxazine) and OPC-67683 (dihydroimidazo-oxazole), sudoterb (pyrrole LL-3858 and an EMB derivative (diamine SQ109). The process from drug discovery, safety and pharmacokinetic studies to phase I, I, III studies takes nearly 20 years before a product comes into the market. A new initiative called 'Critical Path to TB Regimens' (CPTR) consisting of industrial, funder and NGOs partners aims to drastically reduce the amount of time needed to register novel drug regimens for treatment of all forms of TB (TB Alliance, 2010). It is important that clinicians and public health officers are regularly updated on all new developments in this area.

Potential immunotherapies for drug-resistant TB

The sub-optimal treatment outcomes currently achieved for XDR-TB and MDR-TB cases call for innovative new strategies to increase treatment effectiveness. Adjunct immunotherapy to drug treatment has been discussed for some time now. The aim of immunotherapy is to 'realign' or improve the immune response by either promoting protective (Th1) immunity or blocking harmful immune (Th2) responses. Currently available immunotherapeutic agents can be divided into three categories: immunoregulatory approaches, immunosuppressive therapy and supplement effector cytokines.

Immunoregulatory approaches are seeking to alter the nature of the immune response (Churchyard *et al.* 2009). They can be divided into three sub-groups, those for which (i) good manufacturing practices (GMP) manufacturing capacity exists (High dose IVIg, HE2000-16α-bromoepiandrosterone, multidose heat-killed *Mycobacterium vaccae* or *Mycobacterium w*, anti-IL-4), those for which (ii) GMP manufacturing capacity can be established [DNA vaccine (HSP65)] and (iii) the others (Dzherelo, SCV-07 SciCLone, RUTI).

Immunosuppressive therapy seeks to increase access of antibacterial drugs, or their susceptibility to them. They include thalidomide (lowering TNF levels), etanercept (blocking TNF) and prednisolone (having a broad anti-inflammatory effect). Supplement effector cytokines are aimed at enhancing the anti-microbicidal activity of the existing drugs. They include recombinant human (rh) IFN-gamma and rh-IFN-gamma, rh-IL-2, rh-granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-12. Studies are being planned to evaluate the use of adjunct immunotherapy (e.g. multiple doses of either *M. vaccae*, *M. w* or IVIG) for the treatment of MDR-TB and XDR-TB patients. They will be conducted in parallel involving study cohorts in South Africa and Eastern Europe. As this is a novel area, it will be several more years before efficacy data are available and included (if proven to be effective) in programmatic management of MDR-TB and XDR-TB cases in resource-limited settings.

Global efforts to tackle MDR-TB and XDR-TB

Further key steps in the fight against MDR-TB and XDR-TB are documented by the Global MDR-TB and XDR-TB Response Plan and the outcomes of the governmental conference organised in China in April 2009 to develop the Beijing Call for Action (World Health Organization, 2007). The document committed the 27 high-MDR-TB burden countries to undertake a specific set of actions for MDR-TB and XDR-TB containment and prevention. Recommendations for increased investment by national TB Programmes in HIV/TB endemic areas are as follows:

(1) Preventing XDR-TB through basic strengthening and alignment of TB and HIV programmes by increasing case detection and effective treatment of drug sensitive TB. The new Stop TB strategy and the Global Plan to Stop TB are the key reference documents to guide these priority interventions.
(2) Improving management of individuals suspected to be affected by MDR-TB and XDR-TB through accelerated access to laboratory facilities with rapid DST test for RMP and INH resistance, DST for MDR-TB cases and improved detection of cases suspecting of harbouring MDR strains both in high and in low HIV prevalence settings.
(3) Strengthening management of MDR and XDR-TB and treatment design in both HIV-negative and positive individuals, through adequate use of second-line drugs and patient-centred approaches to ensure support and supervision.
(4) Standardising the definition of MDR-TB and XDR-TB.
(5) Increasing contact tracing and screening.
(6) Health care worker infection control and protection mainly (but not exclusively) in high HIV prevalence settings.
(7) Implementing immediate MDR-TB and XDR-TB surveillance activities.
(8) Initiating advocacy, communication and social mobilisation activities to inform and raise awareness about TB and drug-resistant TB.

Within the framework of these recommendations, USAID in collaboration with WHO and other partners has developed a tool (known as 'MDR/XDR-TB Assessment and Monitoring Tool') to be used for (i) preparing national or sub-national plans for MDR/XDR-TB prevention and control; (ii) providing baseline information and monitoring progress; (iii) providing data and analysis to prepare Green Light Committee (GLC) and Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) applications; (iv) providing information to guide requests for external technical assistance; and (v) providing information to guide donor investment in MDR-/XDR-TB interventions. This suggests that using existing interventions, public health systems and TB and HIV programmes must be strengthened significantly, and political and funder commitment is essential to curb the spread of drug-resistant TB.

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