

Drug-resistant tuberculosis in South Africa: history, progress and opportunities for achieving universal access to diagnosis and effective treatment

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Drug-resistant tuberculosis (DR-TB) is a significant threat to efforts to end TB in South Africa. Responding to this epidemic requires access to drug-sensitivity testing among all TB patients and effective second-line anti-tuberculosis treatment for all diagnosed patients. South Africa currently treats the third-highest number of DR-TB patients globally, after India and Russia. The 12 527 cases (10% of the global cohort) reported to be enrolled on treatment in 2015 is close to four times the figure reported for 2007, yet represents only 64% of the diagnosed cases in 2015. Treatment outcomes are poor, with a success rate of approximately 50% nationally and globally.

In this chapter we review the emergence of DR-TB in South Africa and progress towards universal access to diagnosis and effective treatment; we also discuss key policy initiatives that have contributed to treatment access and patient outcomes, and highlight opportunities and challenges moving forward.

While DR-TB was first identified in the 1980s, systematic, standardised treatment was only rolled out across South Africa in 2001. Prior to this time, DR-TB treatment was only available in a small number of specialised TB hospitals. Following the publication of the 2008 updated World Health Organization guidelines, the standardised treatment used in South Africa was strengthened with the inclusion of more drugs. Implementation of new diagnostic tests, including the Xpert test from 2011 have significantly increased the number of diagnosed DR-TB cases. A policy supporting decentralised and deinstitutionalised DR-TB treatment provision at lower levels of the health system was introduced in 2011 but to date, implementation has varied. More recently, South Africa has expanded access to the newly available TB drugs.

Defining and piloting models of DR-TB care across different settings and supporting patients throughout treatment are important challenges moving forward. Incorporating new drugs into shorter, more effective treatments that can be delivered through primary care provides an opportunity to improve treatment outcomes and reduce mortality.

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Introduction

In 1996, the South African government declared tuberculosis (TB) a national emergency and the DOTS (Directly Observed Therapy Short-course) strategy was rolled out across the country.¹ At that time, TB incidence was estimated to be high, with emerging epidemics of both HIV-related and multidrug-resistant (MDR) TB.^{2,3} Over the past two decades, the TB epidemic in South Africa has remained among the worst globally, although the annual number of TB patients has declined in recent years.⁴

Currently, South Africa has a large burden of rifampicin-resistant TB (RR-TB), including MDR-TB (Box 1). In 2015, close to 20 000 individuals were reported to have been diagnosed with RR-TB.⁴ While South Africa provides second-line TB treatment for the third-largest number of RR-TB patients globally, a significant gap remains between the number of cases reported as diagnosed and those started on second-line treatment; delays to start treatment are also common.^{4,5} Overall, treatment is successful for approximately half the patients starting treatment, similar to the global treatment success rate.⁴

South Africa was one of the first high-burden MDR-TB countries to roll out second-line treatment for MDR-TB nationally in 2001, and the country has since implemented innovative strategies to improve case detection and patient outcomes. Traditionally, TB programmes have relied on outdated and poorly efficacious tools for diagnosis and treatment; however, there are now improved diagnostics for TB (and TB drug-resistance), and with several new drugs becoming available, improved prospects for better treatment outcomes. In this chapter we describe the emergence of drug-resistant tuberculosis (DR-TB) in South Africa, historical policy approaches, and new developments with the potential to improve patient outcomes and reduce the burden of DR-TB.

Emergence of TB drug resistance in South Africa

Prior to the first democratic election in 1994, the provision of TB treatment in South Africa relied on erratic and unstandardised treatment regimens.^{2,6} At that time, there were 14 different health services providing TB treatment, with no national co-ordination, and reliance on expensive hospitalisation to ensure compliance.³ Drug supplies were reported to be poor and treatment interruptions were common.² Treatment success rates were largely unknown and unreported, but were found to be as low as 18% in one study.⁷ Under such conditions, the emergence of TB drug resistance was unsurprising.

While resistance to key TB drugs is commonly reported to have emerged in the 1980s,^{8,9} there are reports of widespread resistance prior to that time.¹⁰ Before 1994 the majority of TB resistance data came from surveillance conducted by the South African Medical Research Council (SAMRC). A retrospective analysis of surveillance data from hospitals in four provinces suggests that between 1965 and 1970, 29% of patients tested had TB with resistance to isoniazid, 34% had resistance to streptomycin, and 6% had resistance to rifampicin.¹⁰ Resistance to rifampicin is surprising at that point in time, given reported use of the drug from only 1973 in some provinces,^{11,12} and more widespread use from 1980,^{13,a} which may indicate laboratory problems. Nonetheless, MDR-TB incidence was reported to be less than 2% among *Mycobacterium tuberculosis* isolates in the period 1980–1988.¹⁰ The same study reported dramatic declines in resistance over the three time periods tested; isoniazid resistance fell from 29% in 1965–1970 to 14% in 1980–1988. These data were interpreted to suggest that continuing efforts to provide adequate first-line treatment would result in declining TB drug resistance.

Box 1: Useful definitions for drug-resistant TB

Disease	Definitions	Treatment
TB	Tuberculosis	First-line treatment (6 months) <ul style="list-style-type: none"> ◆ Most effective drugs: isoniazid and rifampicin ◆ Additional drugs: ethambutol and pyrazinamide
DR-TB	Drug-resistant TB (resistance to any TB drug)	
RMR-TB	Rifampicin mono-resistant TB (resistance to rifampicin and susceptibility to isoniazid)	Second-line treatment plus isoniazid
MDR-TB	Multi-drug resistant TB (TB resistant to isoniazid and rifampicin)	Second-line treatment (18–24 months)
RR-TB	Rifampicin-resistant TB (TB resistant to rifampicin, regardless of resistance to other drugs)	<ul style="list-style-type: none"> ◆ Fluoroquinolones: ofloxacin, moxifloxacin, levofloxacin ◆ Second-line injectable drugs: amikacin, kanamycin, capreomycin
PreXDR-TB	MDR-TB with resistance to either a fluoroquinolone OR a second-line injectable drug	<ul style="list-style-type: none"> ◆ Other available drugs: ethionamide, terizidone ◆ Repurposed drugs: linezolid, clofazimine
XDR-TB	Extensively drug-resistant TB (MDR-TB with resistance to both a fluoroquinolone AND a second-line injectable drug)	<ul style="list-style-type: none"> ◆ New drugs recently available: bedaquiline, delamanid

a Personal Communication: Mary Edington, 8 December 2016.

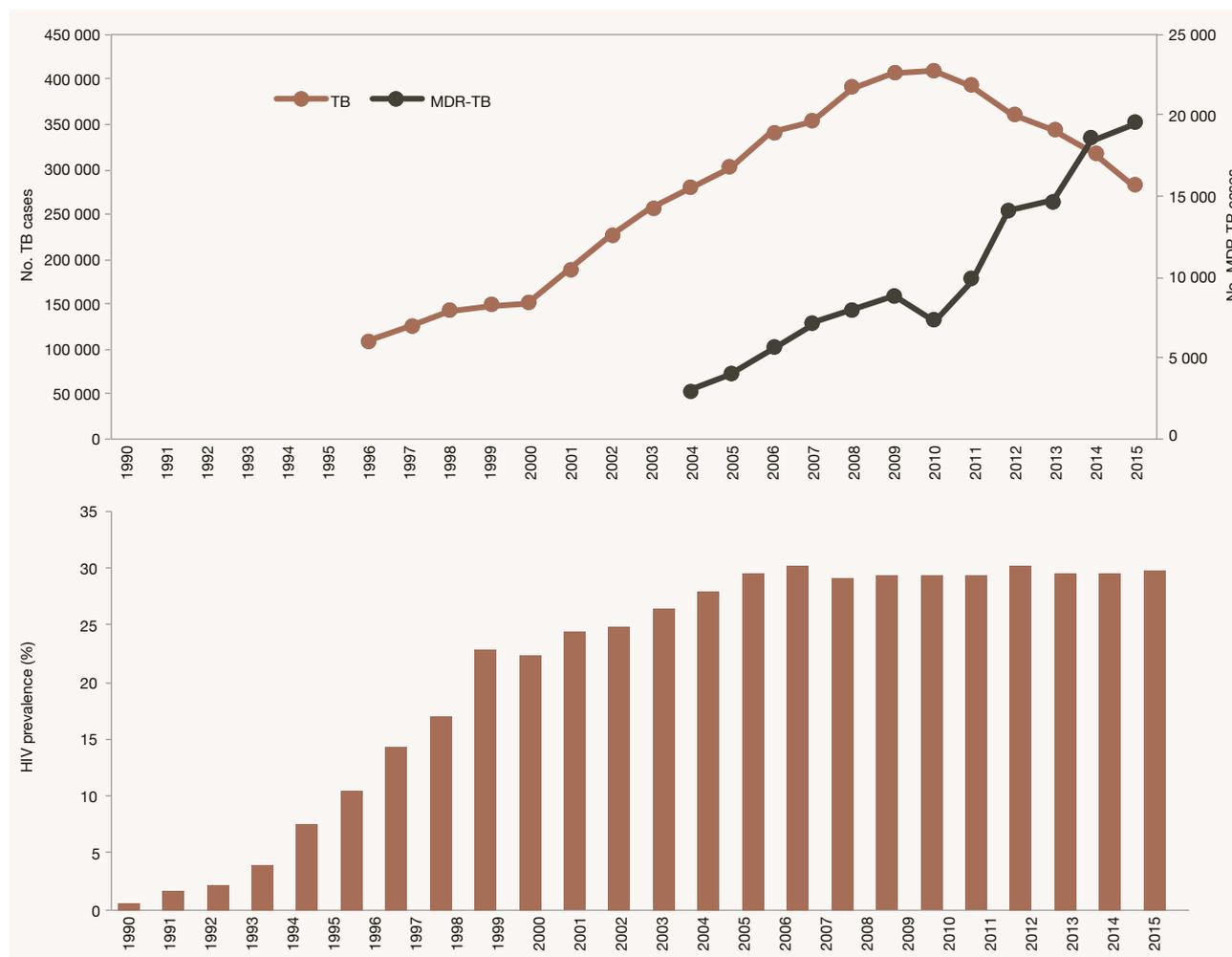
Separate studies suggest that MDR-TB was present across all South African provinces by the early- to mid-1990s.^{13,18} With increasing HIV prevalence there was a dramatic increase in the number of TB patients reported and widespread MDR-TB emergence.^{2,19} Unfortunately, the SAMRC's TB drug-resistance surveillance programme was closed in 1995 due to budgetary constraints, just at the point when the World Health Organization (WHO) warned of the potential spread of MDR-TB in settings like South Africa.²⁰ While the percentage of TB patients with MDR-TB may have appeared relatively low at approximately 2%, since TB rates were high and increasing, this translated into large numbers of patients. Overall, South Africa was recording close to 2 000 MDR-TB cases each year in the mid-1990s.²¹

The first national, representative TB resistance survey was conducted by the SAMRC in 2001–2002.⁹ Multidrug-resistant TB was detected among 2.9% of the 5 866 TB patients tested across all provinces; a further 0.4% were found to have rifampicin mono-resistant TB (RMR-TB). These figures were then used as the basis for estimation of the MDR-TB burden; close to 3 300 cases were estimated to have emerged in 2000.²² However, from 2000 to 2010, the number of MDR-TB patients diagnosed nationally increased dramatically, to approximately 8 000 per year in the latter part of the decade (Figure 1).

While the prevailing view in South Africa, and indeed internationally, was that resistance was primarily due to acquired resistance emerging during poor first-line TB treatment, through poor patient adherence, inadequate treatment regimens or lower drug quality,^{14,27,28} several studies suggest that there was significant community transmission of DR-TB strains in South African settings from the mid-1990s.^{17,29,30}

While MDR-TB has been prevalent in South Africa since the 1980s, it was only identified as a major threat to TB control in 2006, with publication of data describing an outbreak of extensively drug-resistant TB (XDR-TB) at a rural hospital at Tugela Ferry, KwaZulu-Natal, where 39% of TB patients had MDR-TB and 6% had XDR-TB.³¹ Fifty-five per cent of XDR-TB patients had never received prior TB treatment, illustrating direct transmission. Many of these patients had recently been admitted to hospital, suggesting nosocomial transmission. Between 2004 and 2007, 210 XDR-TB cases were found among 10 000 MDR-TB cases across South Africa.³² Retrospective analyses have now determined that XDR-TB was present as early as 1992 in the Western Cape,¹⁵ and the XDR-TB strain causing the Tugela Ferry outbreak was present in 2001 in KwaZulu-Natal.²⁹

Figure 1: Reported cases of TB and laboratory-diagnosed cases of MDR-TB (top panel, note different axes), and national antenatal care HIV prevalence rate (lower panel) between 1990 and 2015



Source: WHO 2016;⁴ NDoH 2011;²³ WHO 2015;²⁴ NDoH 2007;²⁵ Ndjeka 2014.²⁶

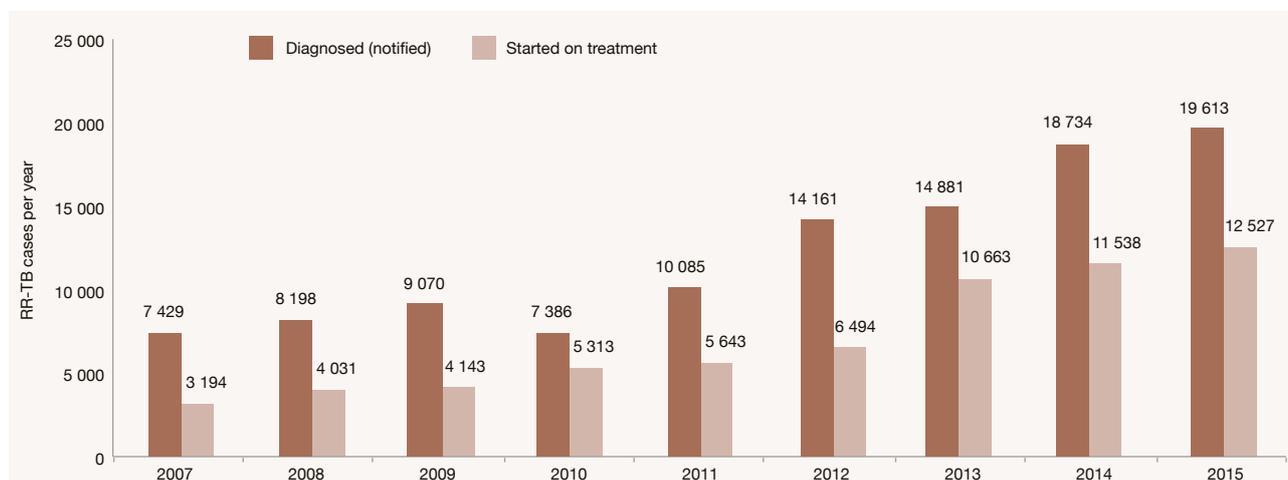
Current epidemiology of drug-resistant TB

In 2015, 19 613 patients were reported to have been diagnosed with RR-TB in South Africa.⁴ This figure represents a dramatic increase from 2011 (Figures 1, 2), most likely the result of improved case detection. In 2011, the Xpert MTB/RIF diagnostic test was progressively rolled out nationally, providing access to drug-susceptibility testing (DST) for all individuals being investigated for TB. Xpert simultaneously detects *M. tuberculosis* and rifampicin resistance, theoretically providing results within hours.³³ Prior to this, only patients who reported previous treatment or those considered at high risk of DR-TB (such as individuals with close contact to known MDR-TB patients, healthcare workers and individuals with prison exposure) and those failing first-line therapy, were tested for resistance.

The second and most recent national survey of TB drug resistance was conducted in 2012–2014, with results released in 2016.³⁴ Overall, 4.6% of more than 10 000 pulmonary TB patients were found to have RR-TB, resulting in an estimated RR-TB burden of 20 000/year.⁴ However, national estimates of the incidence and prevalence of RR-TB may mask settings of high prevalence and significant differences across provinces (Figure 3).

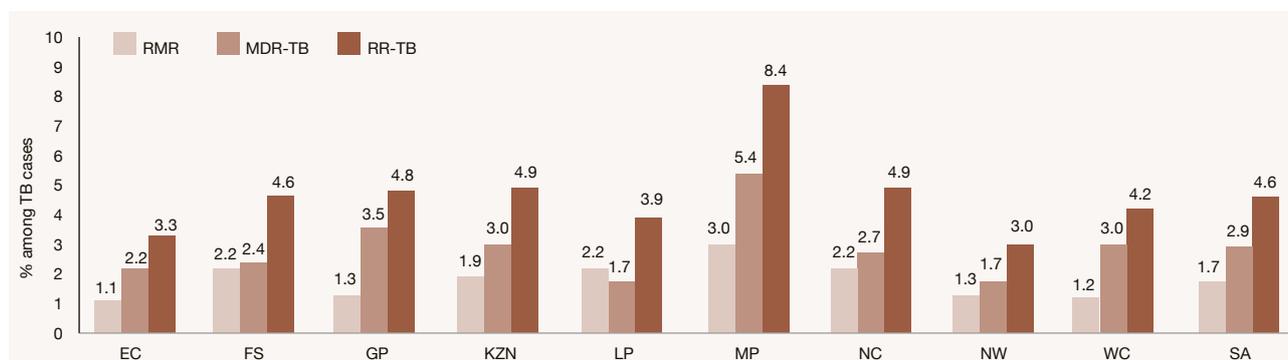
The survey determined that a substantial proportion of RR-TB was due to RMR-TB, but again this varied across provinces, with the prevalence of RMR-TB ranging from 1.1% to 2.2% (Figure 3). While the proportion of MDR-TB was reported to be similar between the 2001–2002 and 2012–2014 national surveys, the level of RMR-TB increased substantially over the decade (Figure 4).

Figure 2: Numbers of RR/MDR-TB patients diagnosed and reported to have started on second-line treatment, by year, in South Africa



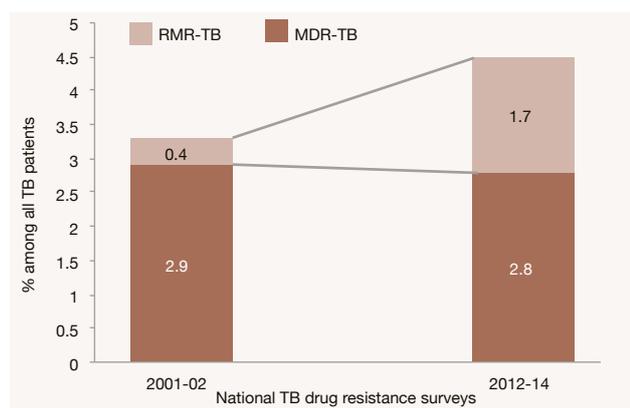
Source: WHO 2016;⁴ NDoH 2011;²³ Ndjeka, 2014.²⁶

Figure 3: Percentage of TB cases found to have RMR-TB, RR-TB, and MDR-TB across provinces in South Africa through the 2012–2014 national survey



Source: National Institute for Communicable Diseases, 2016.³⁴

Figure 4: Change in percentage of RMR-TB and MDR-TB among TB patients between two national surveys



Source: Weyer et al. 2007;⁹ National Institute for Communicable Diseases 2016.³⁴

The 2012–2014 national survey found that 4.9% of MDR-TB patients had XDR-TB.³⁴ However, a further 16.0% were infected with MDR-TB strains with resistance to either a fluoroquinolone or a second-line injectable (pre-XDR-TB), resulting in 21% of MDR-TB patients with significant second-line drug resistance. Similarly, the proportion of XDR-TB among MDR-TB patients varies across provinces. In 2012, the proportion of notified XDR-TB cases ranged from <1% to >20% of MDR-TB cases across provinces.^{35,36} Two recently released South African studies highlight the role of transmission of XDR-TB in communities and health facilities in driving the DR-TB epidemic in South Africa.^{37,38}

While data on the global prevalence of DR-TB among children are scarce, data from routine surveillance across South Africa in 2008 suggest that there is a higher risk of MDR-TB among children aged <15 years than among adults (16.4% of children with TB had MDR-TB).³⁹ In contrast, reports of children being diagnosed routinely with MDR-TB suggest much lower numbers than would be expected given the overall TB burden.^{40,41} Across a 5.5-year period, only 626 children and adolescents with MDR-TB were located through TB hospitals in four South African provinces.⁴¹ These data suggest that

although there is likely to be a substantial burden of DR-TB among children in South Africa, much of this burden remains undiagnosed and therefore untreated.

The drug-resistant TB diagnosis and treatment cascade

In 2015, 12 527 patients were reported to have initiated second-line treatment for RR-TB;⁴ this was only 64% of the number reported to have been diagnosed (Figure 2). The magnitude of this treatment gap was confirmed in a recently published cohort study, where only 63% of RR-TB patients diagnosed in 2013 and followed up retrospectively received second-line treatment within six months.⁵ Factors such as high early mortality, particularly among HIV-positive patients, difficulties in accessing laboratory results, lack of access to second-line treatment provision in primary care, lack of unique patient identifiers, under-reporting, and late updating of records, are likely to have contributed to the treatment gap.

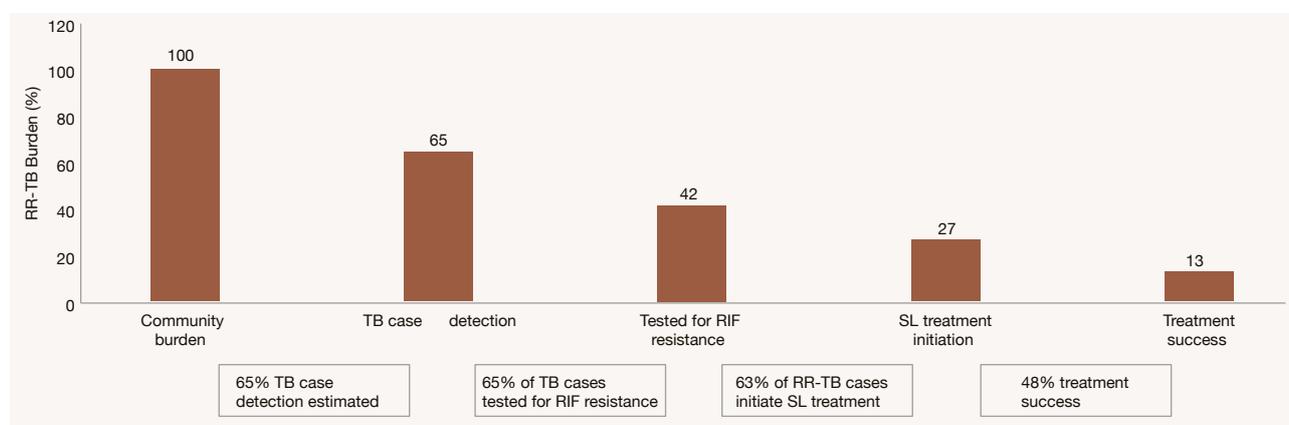
Treatment outcomes are poor among the RR-TB cases reported to have started second-line treatment in South Africa; only 48% of MDR-TB patients and 24% of XDR-TB patients who started treatment in 2013 were reported as being successfully treated, with high rates of mortality, loss from treatment and treatment failure.⁴ Overall, given the likely gap in case detection (based on the estimated case-detection rate for all TB of 63% and bacteriological confirmation <100%⁴) and the significant treatment gap, only 13% of incident RR-TB cases are successfully treated at present (Figure 5).

Policy responses to the epidemic

National guidance for drug-resistant TB treatment

Prior to 2000, only a limited number of specialised hospitals were treating MDR-TB. These included Brooklyn Chest Hospital in the Western Cape, Rietfontein (Sizwe) Hospital in Johannesburg, West End Hospital in Kimberley and King George V (King Dinuzulu) Hospital in Durban.⁴² Treatment outcomes were generally poor; of 343 MDR-TB patients diagnosed from 1987 to 1988 in the then Cape Province, only 33% were reported as cured and alive after five

Figure 5: Simplified RR-TB diagnosis and treatment cascade in South Africa



Source: WHO 2016;⁴ Cox et al. 2017.⁵

years.¹⁸ Similarly poor outcomes were reported from Port Elizabeth, where only 25% of MDR-TB patients treated between 1999 and 2000 were cured.⁴³

Following the introduction of the DOTS strategy in 1996, the first national guideline for the treatment of MDR-TB (DOTS-Plus) was produced in 1997 and revised in 1999.²⁷ However, there are reports that MDR-TB treatment was not actively promoted initially because it was considered more important to cure new TB cases at first diagnosis, through the effective implementation of the DOTS programme.⁴⁴ This thinking may have been based on the notion that effective first-line treatment would reduce DR-TB prevalence.⁴⁵ However, in 2000 the MDR-TB guidelines were formally endorsed, and from 2001, DOTS-Plus implementation was actively supported.⁴⁶

The 1999 guideline described the provision of either individualised or standardised treatment regimens. The former is the provision of a multidrug treatment regimen based on DST results for each patient, while the latter describes a standard treatment regimen given to all MDR-TB patients in the absence of individual DST. In reality, standardised regimens were chosen across South Africa as second-line DST was not widely available. To receive treatment, all patients were referred to a provincial 'specialist' MDR-TB unit. Most patients were admitted either until conversion of sputum cultures to 'negative' or for the duration of the intensive phase, although the guidance allowed for ambulatory treatment after initial evaluation and treatment initiation.²⁷

From 2000, the standardised regimen consisted of a four-month intensive phase using five drugs: kanamycin, ethionamide, pyrazinamide, ofloxacin and either cycloserine or ethambutol. This was followed by a 12–18-month continuation phase using three drugs (ethionamide, ofloxacin and cycloserine or ethambutol).²⁷ Slight modifications to this regimen were made in different provinces.⁴⁷ Treatment outcomes were consistently poor on this regimen; an analysis of treatment outcomes for patients from eight provinces treated between 2000 and 2004 suggested successful treatment in 46% of patients.⁴⁷

In the absence of routine second-line DST, the use of standardised regimens containing relatively few active second-line drugs is thought to contribute to the emergence of further resistance,⁴⁸ even with good adherence.^{49,50} In response, the standardised treatment regimen for MDR-TB was strengthened with the routine inclusion of terizidone in 2010, and a switch from the use of ofloxacin to moxifloxacin across different provinces in 2011/12.

In 2006, release of the revised WHO DR-TB treatment guidelines⁵¹ coincided with publication of the XDR-TB outbreak in KwaZulu-Natal,³¹ together prompting revision of the national DR-TB guidelines. A revision of the guidelines emphasising standardised treatment as national policy was drafted in 2008. In 2011, after further revision, guidelines were released including strategies for decentralisation and deinstitutionalisation of MDR-TB treatment.²³ This was prompted by insufficient numbers of hospital beds to provide hospitalisation for all MDR-TB patients, the cost of lengthy hospitalisation,⁵² and the consequent long waiting lists at most major provincial specialist TB hospitals.^{53–55} In addition, the guidelines described the provision of community-based treatment for MDR-TB patients who were sputum smear-negative, through a system of satellite MDR-TB units at various health system levels, with oversight at provincial level.

Decentralisation and deinstitutionalisation of drug-resistant TB care

Input for the national decentralisation policy was provided from the implementation of pilot programmes in KwaZulu-Natal and the Western Cape (Box 2). In KwaZulu-Natal, a programme to provide ambulatory second-line treatment was first introduced in uMzinyathi District, the setting of the well-publicised XDR-TB outbreak. Early treatment outcomes and patient adherence were reported to be much improved.^{56,57} In the Western Cape, a decentralised treatment programme was implemented in the densely populated township of Khayelitsha, Cape Town, and was associated with increased proportions of diagnosed patients receiving treatment and reduced delays to treatment initiation, resulting in a greater proportion of the number of diagnosed patients being treated successfully.^{58,59}

Box 2: Pilot DR-TB decentralised programmes in KwaZulu-Natal^{56,57} and the Western Cape^{58,59}

	KwaZulu-Natal pilot	Western Cape pilot
Setting	uMzinyathi district (predominantly rural)	Khayelitsha Sub-district (peri-urban township in Cape Town)
Treatment initiation	Treatment initiated by doctors at a district-level hospital	Treatment initiated by doctors at primary health care clinics
Provision of daily injections	Mobile, nurse-led teams visiting patient homes	Patient attendance at primary care clinics
Role of centralised hospital	Management of children, patients with XDR-TB and medically complex patients	Admission of clinically unwell patients and referral of medically complex patients

Since 2011, progress towards achieving greater treatment decentralisation has been relatively slow. In 2013, 56% of all RR-TB patients were still admitted to a tertiary-level or specialist TB hospital to start treatment, and only 19% were started on treatment in primary care.⁵ By November 2015, all provinces were reported to have decentralised sites, reaching the target of one DR-TB treatment initiation site per district.⁵³ Many districts and several provinces still require mandatory hospital admission to initiate second-line treatment.

Drug-resistant TB diagnostics

Xpert testing was commenced at the same time as the release of the national decentralisation policy. By 2013, the majority of South Africans investigated for TB had access to Xpert. In addition to improved TB diagnosis compared with sputum smear microscopy, the Xpert rollout aimed to improve RR-TB case detection and reduce the often lengthy delays to receive DST results using conventional culture techniques. Xpert implementation partly explains a dramatic increase in the reported number of diagnosed RR-TB patients since 2011 (Figure 1), and has likely contributed to a substantial reduction in the delay to second-line treatment for those found to have RR-TB, despite a number of issues with implementation.⁶⁰ According to a large nationwide retrospective cohort study, the median time between patient submission of a specimen for diagnosis and the initiation of second-line treatment fell from 44 days in 2011 to 22 days in 2013.⁵ While substantial, this reduction in delay is still some way from the national five-day target.⁶¹

Novel drugs for treatment

More recent policy initiatives have included expanded access to the new anti-tuberculosis drug, bedaquiline. Bedaquiline was the first new TB drug to become available since rifampicin in the 1960s and has been shown to improve patient outcomes when added to the standard MDR-TB second-line regimen.⁶² Early outcomes from a clinical access programme have been promising, with 76% of XDR-TB or pre-XDR-TB patients who completed six months of bedaquiline showing sputum culture conversion.⁶³ Based on these data, guidance on the use of bedaquiline was released by the National Department of Health (NDoH) in 2015.⁶⁴

Bedaquiline is currently recommended for the treatment of patients with pre-XDR-TB, XDR-TB and MDR-TB under circumstances where an effective treatment regimen cannot be formulated with other second-line drugs. As of December 2016, a total of 3 846 patients have received bedaquiline in South Africa.⁶⁵ The emergence of TB drug resistance and key policy responses are described in Box 3.

The promise of improved diagnostics, shorter treatment regimens and new drugs

While Xpert implementation has improved RR-TB case detection, the diagnosis of second-line drug resistance and therefore XDR-TB and pre-XDR-TB still relies largely on conventional culture-based methods. Culture-based methods delay the diagnosis of second-line resistance and therefore delay the initiation of appropriate treatment, potentially contributing to the development of further resistance.⁴⁹ In South Africa, only 38% of RR-TB cases diagnosed in 2015 were reported to have received second-line DST.⁴ Correct identification of second-line drug resistance, i.e. resistance to a fluoroquinolone and/or a second-line injectable drug will be required to allocate patients to revised treatment regimens appropriately, based on new policy objectives. These include increased access to new TB drugs such as bedaquiline and the second new TB drug to receive approval globally, delamanid, along with rollout of a new shortened DR-TB treatment regimen.

In 2016, the WHO produced a recommendation on the use of a 9–12-month shortened regimen for MDR-TB treatment that utilises existing second-line TB drugs and drugs not registered for TB treatment but found to be effective against TB (repurposed drugs).⁶⁶ The shortened regimen is based on a regimen first used under operational research conditions in Bangladesh that resulted in significantly improved treatment outcomes,⁶⁷ and more recent evidence from several other countries; however, there are as yet no clinical trial data.⁶⁸

In response, the NDoH in South Africa has started a process of revision of the DR-TB guidelines, including use of the shortened MDR-TB regimen. Discussions have also included the possibility of a bedaquiline-containing nine-month regimen to be implemented at certain sites under operational research conditions.⁶⁹

In line with these initiatives, and in order to improve access to second-line DST, the National Health Laboratory Service is in the process of replacing culture-based DST with the Hain MTBDRsl test, a rapid-line probe assay that detects most of the genetic mutations that confer resistance to the fluoroquinolones and the second-line injectable drugs.⁷⁰ While this test is more rapid, and has high specificity (when resistance is identified it is usually correct), sensitivity is suboptimal, i.e. a significant proportion of MDR-TB patients with second-line resistance may be missed with the test.⁷¹

While the use of a nine-month regimen containing bedaquiline is being contemplated, clinical trials are under way that should provide clearer evidence for effective MDR-TB regimens. Trials under way in South Africa include the STREAM trial testing a nine-month bedaquiline-containing regimen, the NeXT trial, which is trialling 6–9-month all-oral regimens containing bedaquiline (both for MDR-TB only), and the NiX-TB trial testing a three-drug regimen including bedaquiline, pretomanid (a similar drug to delamanid) and linezolid (a repurposed drug) for patients with XDR-TB.⁷² Early results from the NiX-TB trial are promising; of those who completed the six-month treatment, all were cured.⁷³ The new initiatives currently being discussed and the promise of more effective treatment regimens provide hope that greater inroads can be made into the DR-TB epidemic in South Africa.

Box 3: Timeline of key events relevant to the emergence and response to DR-TB in South Africa

	Year(s)	
Emergence of INH, Rif and Strep resistance reported	1956–1970	
	1980	Expanded use of Rif for TB treatment
XDR-TB detected retrospectively in the Western Cape	1992	
MDR-TB across South Africa	1994	
TB declared a national emergency	1996	DOTS strategy introduced
	1997	First national guidelines for MDR-TB treatment
	1999	MDR-TB treatment guidelines revised
	2000	Standardised MDR-TB regimen introduced
First national survey of DR-TB	2001	Second-line treatment for all MDR-TB (DOTS Plus strategy introduced)
XDR-TB defined and identified at Tugela Ferry	2006	
	2008	Draft revised guidelines on MDR-TB treatment available
Xpert introduced and rolled out across country	2011	Revised guidelines including decentralised and community management
Second national DR-TB survey	2012	Bedaquiline accessible (compassionate use programme only)
	2014	Bedaquiline expanded clinical access programme
Introduction of second-line LPA	2017	Introduction of new and shortened regimens planned

Ongoing challenges

Challenges remain before universal access to effective, acceptable MDR-TB treatment becomes a reality. Central are issues around delivering a complex treatment regimen, often associated with adverse events, at lower levels of a struggling health system. Varying success with regard to decentralisation of effective MDR-TB services across South African districts can be partly explained by variable funding available for policy directives, insufficient infrastructure, lack of adaptation of models of care to different geographical and epidemiological settings, and poor district management capacity with insufficient provincial support. In the context of a health system buckling under a quadruple burden of disease,⁷⁴ a myriad of human-resource issues impact on DR-TB service delivery, including rapid turnover of staff, inadequate support, low motivation and a reluctance to 'take on' additional workload, and ineffective mechanisms of accountability.⁷⁵

Given the high rate of HIV infection among TB and DR-TB patients, the provision of integrated treatment services remains a priority. Interactions between antiretroviral and TB medications often complicate treatment,⁷⁶ and the management of DR-TB and HIV via two separate programmes is likely to result in additional burdens on patients and staff.^{77,78}

A further challenge is the diagnosis and treatment of DR-TB among children. While it is estimated that 25 000 children globally develop MDR-TB each year, very few are diagnosed and treated.^{39,79} This is largely due to the difficulties in obtaining bacteriological TB confirmation in young children and therefore DST.⁸⁰ As a result, the diagnosis of DR-TB is often inferred based on close contact with a known DR-TB patient. The investigation of all child contacts of each diagnosed DR-TB patient is challenging and insufficiently conducted in most high-burden settings, including South Africa.

Poor treatment adherence is often cited as contributing to the DR-TB epidemic and the development of additional resistance during second-line treatment. As currently used second-line drugs are associated with significant adverse events and are poorly tolerated,⁸¹ low completion rates are unsurprising; patients may stop treatment when the side-effects become intolerable, when they start to feel better, or due to perceived futility when they remain sputum culture-positive months into treatment.⁸² Maintaining adherence, even to a shortened nine-month regimen, requires consistent and sympathetic support from healthcare workers and other significant individuals in patients' lives. Providing such support has been difficult in the face of overburdened clinics and the stigma attached to DR-TB.

Similarly, activities needed to receive a DR-TB diagnosis and continue treatment over a prolonged period are often associated with catastrophic expenditures for patients and their families.^{83,84} Drug-resistant TB patients are eligible for disability grants in South Africa, but these grants are often delayed, and are insufficient to support families where the patient had been the family breadwinner.^{83,85,86}

Conclusions and recommendations

South Africa is uniquely positioned to develop and implement innovative strategies to respond to the DR-TB epidemic, having relatively well-developed healthcare infrastructure, including laboratory services. There is strong government commitment to improve both the diagnosis and treatment of DR-TB, exemplified by recently implemented strategies. These include the staged implementation of the Xpert test for all individuals investigated for TB; decentralisation and deinstitutionalisation policies; scale-up of access to the new drug bedaquiline, and increased financial allocations for DR-TB services.

However, the implementation of DR-TB services is a provincial competency, and success in combating the epidemic will depend on the extent to which implementation challenges within each province are addressed and overcome. Towards the end of 2015, the WHO reviewed the decentralisation of DR-TB services in South Africa, and reported that the extent and quality of services varied across provinces.⁵³ Recommendations arising from the review include strategies to reduce community transmission and improve service delivery.

Recommendations to reduce transmission include early identification of DR-TB patients, screening of household contacts, educating household members about DR-TB transmission, and universal DST for all patients under TB investigation. Within healthcare facilities, infection-control programmes should be supported, outpatient treatment should be provided whenever possible, and in some cases health facilities should be redesigned. In order to improve DR-TB service delivery, the review recommended the following: accelerated decentralisation of DR-TB care; full integration of DR-TB services into district-level services; alignment of the DR-TB programme with other health system aspects; alignment of the DR-TB data-management system with the District Health Information Software, implementation of a unique patient identifier; greater provincial oversight, and functional provincial DR-TB clinical management teams providing clinical expertise, guidance and oversight on patient management.

Implementation of the shortened MDR-TB treatment regimen and further scale-up of bedaquiline and other drugs have the potential to improve individual patient outcomes dramatically and to reduce ongoing community transmission of DR-TB. However, to optimise the window of opportunity afforded by these new strategies, models of service delivery have to take localised health systems and human-resource constraints into account, while striving to be patient-centred.

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