Determinants of multidrug-resistant tuberculosis in South Africa: results from a national survey

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South Africa (SA) ranks second among the 22 high-burden tuberculosis (TB) countries in terms of TB incidence and seventh in terms of overall TB burden.[1] The TB epidemic is largely a result of historical neglect, health service fragmentation and poor patient management, compounded by one of the fastest growing HIV epidemics ever recorded.[2] In 1996, a revised national TB control programme (TBCP) based on the internationally recommended Directly Observed Treatment, Short-course (DOTS) strategy of the World Health Organization (WHO) was implemented.[3] DOTS uptake has been rapid, with complete coverage achieved in 2002. However, a serious escalation in TB preceded the implementation of the DOTS strategy, complicated by the emergence of multidrug-resistant TB (MDR-TB) in all nine provinces of SA.

MDR-TB, defined as *in vitro* resistance to isoniazid and rifampicin (the two most potent anti-TB drugs), is of global concern. The result of inappropriate use of TB drugs and inadequate TB control, MDR-TB poses an international public health threat due to the difficulties and costs involved in treatment and the adverse implications for effective TB control. The emergence of extensively drug-resistant TB (XDR-TB), defined as MDR plus additional resistance to a fluoroquinolone and one of the injectable anti-TB drugs (kanamycin, amikacin and capreomycin), recently exacerbated public health concerns of a virtually untreatable epidemic.[4]

MDR-TB was first detected in SA in the mid-1980s, with subsequent surveillance data showing low prevalence levels but considerable geographical variation.[5-7] Surveillance was terminated in 1995; however, increasing numbers of MDR-TB patients necessitated a national MDR-TB treatment programme, which was implemented as TBCP policy in 2001.[8] Central to this process was a national survey of anti-TB drug resistance, commissioned by the National Department of Health and conducted over a period of 18 months between 2001 and 2002 by the Medical Research Council (MRC). The main aim of the survey was to quantify the extent of anti-TB drug resistance and to identify associated risk factors. Given the fragmented history of TB control in SA, province-specific surveys were indicated. Survey design allowed for additional data relevant to TB control to be collected. One such component was HIV prevalence, with the survey design providing a unique opportunity to establish the point prevalence of HIV infection in TB patients and to evaluate HIV as a risk factor for TB drug resistance in SA.

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Methods

Study design and sampling strategy

WHO protocols for anti-TB drug resistance surveillance were followed,[9] using a cross-sectional population-based design. Sample size calculation for each province was based on *a priori* assumptions for a minimum expected MDR-TB prevalence of 1%, with a precision of ±1%, within 95% confidence intervals. Multistage stratified cluster sampling with probability proportional to size (PPS) was followed, allowing for a design effect of 2.0. Health districts served as strata while diagnostic centres (primary health care clinics, district and provincial hospitals) served as primary sampling units (PSUs). Provincial sample sizes were proportionally allocated to strata, after which PSUs within strata were ordered alphabetically and then sampled with PPS using the systematic sampling method described by Bennett and co-workers.[10] At least 30 PSUs were selected per province.

The required sample size of 762 culture-confirmed TB patients per province was inflated by 20% to allow for expected losses. Patients with contaminated or nonviable cultures were replaced by consecutive sampling, and intake was terminated when the required sample size was reached. However, given the unavoidable delay in obtaining positive TB cultures, all specimens received were processed and drug susceptibility testing (DST) completed, even if the target patient sample size had been exceeded.

Patient intake

All newly registered patients with culture-confirmed TB at the selected PSUs were eligible for inclusion.The diagnostic algorithm of the TBCP[3] was utilised to identify persons suspected of having TB, and an additional sputum specimen collected before treatment initiation. These were transported to the MRC laboratories in Pretoria for processing.

Data collection and management

Demographic details and detailed TB treatment history were obtained by interviewing TB suspects, using a structured questionnaire based on the standard WHO data collection tools.[9] The main focus of the questionnaire was to obtain adequate information on previous TB treatment (crucial for interpreting anti-TB drug resistance data), and to collect standardised demographic and other TB-related patient information. The number and duration of previous TB treatment episodes were recorded, while clinical and laboratory records were reviewed for outcomes of previous TB treatment.

Data entry was done at the MRC, Pretoria, using the standardised software of the WHO/IUATLD Global Anti-Tuberculosis Drug Resistance Surveillance Project (SDR-TB, Version 3.0). Provincial intake was monitored monthly by tabulating patient enrolment per PSU and checking the quality and completeness of clinical and laboratory information. Drug resistance results were used primarily for study purposes and not for individual patient management; however, whenever a case of MDR-TB was diagnosed, the relevant health authorities were notified immediately in order to initiate appropriate treatment.

Laboratory procedures

Conventional methodology for TB microscopy, culture and DST was followed.[9,11,12] Briefly, sputum specimens were digested by the modified Petroff method using 4% sodium hydroxide. Ziehl-Neelsen microscopy was done on the concentrated sediment, after which two slopes of Löwenstein-Jensen (LJ) culture medium were inoculated. Cultures were incubated for 8 weeks at 37°C and examined weekly. *Mycobacterium tuberculosis* isolates were characterised by conventional biological and biochemical tests.[12] DST was done using the indirect proportion method on LJ medium.[9] Resistance was defined as 1% or more growth against critical drug concentrations, i.e. 0.2 µg/ml for isoniazid, 40 µg/ml for rifampicin, 5 µg/ml for streptomycin and 2 µg/ml for ethambutol.[9]

Unlinked HIV testing was done on sputum specimens from culture-confirmed TB patients using the GACELISA test (Wellcozyme*HIV1+2). Where volumes permitted, aliquots of sputum specimens were frozen at –20°C until the culture results became available. For positive cultures, the corresponding aliquots were numerically coded and submitted to the Department of Virology, University of Pretoria. Patient identifiers were removed from the database once the bacteriology reports had been issued and the HIV results added after all other tests had been completed. HIV results linked to individual patients were therefore not known, but estimates of HIV prevalence among TB patients were available by province. This approach obviated the need for individual patient counselling.

Quality assurance

Continuous quality assurance covered sampling, patient enrolment, clinical information and laboratory procedures, according to predefined performance criteria. Weekly questionnaire audits were done to validate information. A random sample (10%) of enrolled patients per province was re-interviewed to validate questionnaire information.

Ethics approval

The study protocol was approved by the MRC Ethics Committee, National Department of Health, and Provincial Research and Ethics Committees. Persons suspected of having TB signed an informed consent form, authorising the bacteriological investigations and use of their data.

Definitions

Drug resistance was defined according to DST results (susceptible or resistant) and patients were classified according to previous TB treatment history. The following conventional definitions applied:[9]

- Drug resistance among new patients: Drug resistance in *M. tuberculosis* cultures from patients who had never been treated for TB or who had been treated for less than 1 month.
- Drug resistance among previously treated patients: Drug resistance in *M. tuberculosis* cultures from patients who had been previously treated for TB for 1 month or more. These included patients identified as recurrent (relapse or re-infection), return after default from treatment, and return after treatment failure.

Statistical analysis

Initial descriptive data analysis was done using SDRTB Version 3 (WHO, 2001). Subsequent analyses were carried out using Stata Release 7 (StataCorp. 2001), accounting for the complex multistage sampling strategy and clustering of patients within PSUs. National drug resistance prevalence estimates were weighted by the number of registered TB cases in each province. Standard chi-square and Fischer's exact two-tailed tests were used to compare differences between demographic variables and resistance to one or more drugs. Associations between exploratory variables (demographics, TB treatment history, hospitalisation, previous TB treatment outcome, HIV infection, imprisonment) and drug resistance were investigated using the Rao-Scott correction to the Pearson chi-square test statistic.[13,14] Multiple logistic regression models, accounting for cluster design and differential sample weights, were then fitted using pseudo-maximum-likelihood estimation methods[15] in order to explore the contribution of independent variables to drug resistance (any and MDR) as binary response variables.

Results

New and retreatment TB patients did not differ on independent variables, e.g. gender, age, history of imprisonment, and HIV status (data not shown). Results were therefore combined where indicated. Table I presents the demographics of study patients. Age and gender distributions were similar to those reported routinely by the TBCP.[16] A significantly higher proportion of survey patients reported previous TB treatment (27%) compared with TBCP registration data (14%),[16] a consistent finding across provinces. Sixty-three per cent of retreatment patients had recurrent TB after successful treatment completion, while 27% were retreated after default (23%) or failure (4%). Thirty-five per cent of retreatment patients had been previously hospitalised for TB. A history of imprisonment was recorded in 14% of patients. HIV results were available for 78% of patients (sputum volumes being insufficient to permit aliquoting for the rest); of these, 55.3% were found to be HIV-positive (95% confidence interval (CI) 50.5 - 60.1%).

Table I. Patient demographics

Variable	*N*	Weighted proportion (%)*
Gender		
Male	3 746	63.6
Female	2 115	36.3
Unknown	5	0.1
Age group (yrs)		
0 - 14	44	0.8
15 - 24	978	18.0
25 - 34	1 885	32.5
35 - 44	1 641	27.3
45 - 54	837	13.1
55 - 64	293	5.1
65+	139	2.6
Unknown	49	0.7
Weighted mean (SE)	35.5 (0.65)	
Previous TB treatment		
No	4 206	70.3
Yes	1 508	27.1
Unknown	152	2.6
Previous treatment outcome		
Favourable	941	62.2
Cure	531	32.0
Treatment completion	410	30.6
Unfavourable	386	26.3
Treatment failure	53	3.7
Treatment default	333	22.5
Unknown	181	11.3
Previous hospitalisation (TB)		
No	770	54.2
Yes	532	34.9
Unknown	148	10.9
History of imprisonment		
No	4 899	83.5
Yes	825	14.4
Unknown	142	2.1
HIV status		
Negative	1 939	34.8
Positive	2 700	43.0
Unknown	1 227	22.2

*Proportions weighted by province.

The prevalence of anti-tuberculosis drug resistance in SA is reflected in Table II. Rates were consistently higher in retreatment patients. Resistance to isoniazid was most common, having been detected in 5.7% new and 11.8% retreatment patients. Overall MDR prevalence was low at 2.9%, arising from 1.6% in new and 6.6% in previously treated cases. Twenty-five per cent of MDR strains were resistant to the four first-line TB drugs tested. Thirty-six per cent of MDR strains had associated ethambutol resistance, and 55% had associated streptomycin resistance. Rifampicin mono-resistance was detected in 31 strains. Provincial differences in drug resistance prevalence were confirmed in both new (range 1.0 - 2.7%) and retreatment cases (range 4.0 - 13.9%).

HIV co-infection rates per province varied from 28% to 72% (data not shown). Table III reflects univariate findings of HIV prevalence in the study population: Females had significantly higher HIV infection rates ($p<0.001$). HIV prevalence was highest in patients aged 25 - 44 years, consistent with annual antenatal HIV surveillance data.[17] HIV prevalence was similar in new (56.7%) and retreatment (51.2%) patients ($p=0.134$). No differences in HIV prevalence were found between patients with drug-susceptible TB and those with drug resistance, although MDR-TB patients tended to have slightly higher rates of HIV infection (60.0% v. 55.1%; $p=0.575$).

Determinants of drug-resistant TB originating from multiple logistic regression models are given in Table IV (all patients) and Tables V and VI (retreatment patients only). For new and retreatment patients combined (Table IV), drug resistance was not associated with gender, age, history of previous imprisonment or HIV status, but was significantly associated with previous TB treatment. Retreatment patients had a significantly increased risk for any resistance (OR 2.3; 95% CI 1.72 - 2.98; $p<0.0001$) as well as for MDR (OR 4.4; 95% CI 2.84 - 6.85; $p<0.0001$). HIV-positive patients tended to have a higher risk for MDR (OR 1.3; 95% CI 1.00 - 1.70; $p=0.050$).

Treatment outcomes were subsequently grouped into favourable (cure and treatment completed) and unfavourable (default and treatment failure) to further explore the association between previous treatment and drug resistance (Tables V and VI). Unfavourable outcome was significantly associated with increased risk for any resistance (OR 2.3; 95% CI 1.35 - 3.96; $p=0.003$) and with MDR (OR 3.7; 95% CI 1.55 - 8.74; $p=0.004$). Grouped analysis showed an increased risk for MDR in HIV-positive retreatment patients (OR 1.5; 95% CI 1.04 - 2.07; $p=0.032$).

Expanding previous outcome into the four conventional

Table II. Prevalence of tuberculosis drug resistance in South Africa

	New cases			Previously treated cases			All cases		
	N	Weighted proportion (%)*	95% CI	*N*	Weighted proportion (%)*	95% CI	*N*	Weighted proportion (%)*	95% CI
Total strains tested	4 358	72.9	70.4 - 75.4	1 508	27.1	24.6 - 29.5	5 866	100.0	-
Fully susceptible	4 011	92.3	91.1 - 93.4	1 273	84.5	81.9 - 87.2	5 284	90.2	89.1 - 91.2
Any resistance	347	7.7	6.6 - 8.9	235	15.5	12.8 - 18.1	582	9.8	8.8 - 10.9
H	256	5.7	4.9 - 6.5	176	11.8	9.3 - 14.4	432	7.4	6.5 - 8.3
R	92	1.8	1.3 - 2.3	119	7.5	5.7 - 9.2	211	3.4	2.8 - 3.9
S	183	4.3	3.5 - 5.0	124	8.1	6.6 - 9.6	307	5.3	4.7 - 5.9
E	38	0.8	0.4 - 1.1	41	2.4	1.5 - 3.3	79	1.2	0.8 - 1.6
Mono-resistance	204	4.6	3.7 - 5.5	98	6.5	5.0 - 7.9	302	5.1	4.3 - 5.9
H	113	2.6	2.0 - 3.2	40	2.9	1.9 - 4.0	153	2.7	2.2 - 3.2
R	14	0.2	0.1 - 0.4	17	0.8	0.4 - 1.2	31	0.4	0.2 - 0.5
S	77	1.8	1.3 - 2.3	40	2.6	1.9 - 3.4	117	2.0	1.6 - 2.5
E	0	0	-	1	0.1	0.0 - 0.4†	1	0.03	0.0 - 0.1†
Multidrug resistance	78	1.6	1.1 - 2.1	101	6.6	4.9 - 8.2	179	2.9	2.4 - 3.5
HR	22	0.4	0.2 - 0.6	40	2.7	0.6 - 1.5	62	1.0	0.6 - 1.4
HRS	26	0.6	0.3 - 0.9	27	2.0	1.2- 2.8	53	1.0	0.7 - 1.3
HRE	10	0.1	0.0 - 0.2	9	0.5	0.2 - 0.9	19	0.2	0.1 - 0.3
HRSE	20	0.5	0.2 - 0.7	25	1.4	0.8 - 2.0	45	0.7	0.5 - 1.0
H + other resistance	65	1.5	1.2 - 1.9	35	2.3	1.5 - 3.2	100	1.7	1.4 - 2.1
HS	57	1.3	1.0 - 1.6	30	2.0	1.3 - 2.7	87	1.5	1.2 - 1.8
HE	5	0.1	0.0 - 2.2	3	0.3	0.0 - 0.6	8	0.1	0.0 - 0.3
HSE	3	0.1	0.0 - 0.2*	2	0.1	0.0 - 0.5†	5	0.1	0.0 - 0.2
R + other resistance	0	0.0	-	1	0.1	0.0 - 0.4†	1	0.02	0.0 - 0.1†
RS	0	0.0	-	0	0.0	-	0	0.0	-
RE	0	0.0	-	1	0.1	0.0 - 0.4‡	1	0.02	0.0 - 0.1†
RSE	0	0.0	-	0	0.0	-	0	0.0	-
Resistance to									
One drug	204	4.6	3.7 - 5.5	98	6.5	5.0 - 7.9	302	5.1	4.3 - 5.9
Two drugs	84	1.9	1.4 - 2.3	74	5.0	3.6 - 6.5	158	2.7	2.2 - 3.2
Three drugs	39	0.8	0.5 - 1.1	38	2.6	1.8 - 3.3	77	1.3	1.0 - 1.6
Four drugs	20	0.5	0.2 - 0.7	25	1.4	0.8 - 2.0	45	0.7	0.5 - 1.3

*Proportions weighted by province.
†Exact binomial confidence intervals calculated when category numbers <5.
H = isoniazid; R = rifampicin; S = streptomycin; E = ethambutol.

Table III. Univariate analysis of HIV positivity by gender, previous treatment and drug resistance

Variable	*N*	HIV prevalence (%)*	95% CI	Test statistic and *p*-value†
Gender				
Male	2 963	51.5	45.9 - 57.0	F=37.130
Female	1 671	62.2	58.1 - 66.1	$p<0.0001$
Age group (yrs)				
0 - 14	28	14.7	5.8 - 32.7	
15 - 24	780	46.2	42.8 - 49.6	
25 - 34	1 489	66.4	61.2 - 71.2	F=29.260
35 - 44	1 320	59.3	52.1 - 66.2	$p<0.0001$
45 - 54	667	46.9	40.9 - 53.0	
55 - 64	220	36.2	28.3 - 44.9	
65+	98	18.9	11.4 - 29.6	
Previous TB treatment				
No	3 465	56.7	52.6 - 60.7	F=2.280
Yes	1 174	51.6	43.0 - 60.1	$p=0.134$
Drug resistance				
Susceptible	4 166	55.1	50.6 - 59.6	F=0.499
Resistant, MDR	139	60.0	49.5 - 69.6	$p=0.575$
Resistant, not MDR	334	55.8	45.5 - 65.6	

*Prevalence weighted by province, calculated from HIV results known.
†Rao-Scott correction applied to Pearson chi-squared test statistic for heterogeneity.

categories (Tables V and VI), treatment failure was strongly associated with increased risk for any drug resistance (OR 8.4; 95% CI 3.43 - 20.41; $p<0.0001$) and for MDR (OR 13.3; 95% CI 4.94 - 36.02; $p<0.0001$). Patients who had previously defaulted from treatment were also at higher risk, particularly for MDR (OR 3.2; 95% CI 1.28 - 8.09). Drug resistance was twice as high when previous outcome was defined as 'treatment completed' versus bacteriologically proven 'cure' ($p<0.0001$).

Previous hospitalisation was a significant determinant of drug resistance, both for any resistance (OR 2.0; 95% CI 1.32 - 3.10; $p=0.002$) and for MDR (OR 2.8; 95% CI 1.55 - 4.89; $p=0.001$).

Duration of previous treatment was not significantly associated with drug resistance, neither when testing for trend (1-month increase in treatment duration) nor when treatment duration was dichotomised (less than 2 months v. 2 months or longer), although trend analyses suggested a higher risk for any resistance with prolonged treatment duration (OR 1.2; 95% CI 1.0 - 1.49; $p=0.05$).

Discussion

Our data are subject to similar limitations reported for other cross-sectional, population-based studies of TB drug resistance.[18-20] Firstly, misclassification of new and retreatment patients might have occurred, as patients do not always reveal previous TB treatment history. Prevalence of drug resistance in new patients might consequently have been overestimated, although the questionnaire was designed to detect anomalies and medical/laboratory information was scrutinised when available. Reporting errors in duration of TB treatment might similarly have occurred. However, repeat interviews of a 10% random sample of patients in each province did not reveal major discrepancies. Secondly, undetected selection bias may have contributed to inaccurate drug resistance estimates in retreatment patients as calculation of prevalence did not take the actual proportion of previously treated cases per province into account. Thirdly, 22% of patients did not have HIV results because low sputum volumes precluded aliquoting of specimens. These patients were, however, uniformly spread across provinces and did not differ from the rest of the study population in terms of demographic or TB-related data.

Limited laboratory capacity together with a lack of human and financial resources contributes to a paucity of reliable and representative data on anti-TB drug resistance in Africa. SA is one of the few African countries where comprehensive and representative information on anti-TB drug resistance is available. Results from SA compare favourably with rates of MDR-TB reported globally,[18-20] despite extensive and prolonged local use of rifampicin and a relatively short history of DOTS implementation. However, given the high TB burden, low MDR-TB prevalence levels translate into a high

Table IV. Determinants of drug resistance from multiple logistic regression models all patients

Variable	*N*	Proportion resistant (%)*	OR (95% CI)	*p*-value
		Any drug resistance		
Gender				
Male	2 856	9.7	1.00	0.164
Female	1 602	11.1	0.80 (0.56 - 1.12)	
Age group (yrs)				
15 - 24	769	8.3	1.0	
25 - 34	1 452	10.1	0.99 (0.60 - 1.62)	
35 - 44	1 282	10.9	0.93 (0.52 - 1.67)	0.353
45 - 54	650	10.9	1.21 (0.63 - 2.34)	
55 - 64	213	10.6	1.97 (0.89 - 4.38)	
65+	92	15.2	1.06 (0.25 - 4.44)	
Previous TB treatment				
No	3 328	8.1	1.00	<0.001
Yes	1 130	16.2	2.27 (1.72 - 2.98)	
Previous imprisonment				
No	3 827	10.4	1.00	0.247
Yes	631	9.2	0.82 (0.58 - 1.15)	
HIV status				
Negative	1 856	9.7	1.00	0.264
Positive	2 602	10.6	1.13 (0.91 - 1.42)	
		Multidrug resistance		
Gender				
Male	2 856	3.1	1.00	0.189
Female	1 602	3.3	0.80 (0.56 - 1.12)	
Age group (yrs)				
15 - 24	769	2.6	1.0	
25 - 34	1 452	3.0	0.99 (0.60 - 1.62)	
35 - 44	1 282	3.0	0.93 (0.52 - 1.67)	0.430
45 - 54	650	3.9	1.21 (0.63 - 2.34)	
55 - 64	213	5.2	1.97 (0.89 - 4.38)	
65+	92	3.0	1.06 (0.25 - 4.44)	
Previous TB treatment				
No	3 328	1.8	1.00	<0.001
Yes	1 130	7.0	4.41 (2.83 - 6.85)	
Previous imprisonment				
No	3 827	3.2	1.00	0.382
Yes	631	2.8	0.77 (0.42 - 1.39)	
HIV status				
Negative	1 856	2.9	1.00	0.050
Positive	2 602	3.4	1.30 (1.00 - 1.70)	

*Proportions weighted by province.

case burden. Extrapolating the study findings to TBCP case registration data[16] and to WHO estimates of the TB burden in SA,[1] conservative calculations indicate at least 6 000 MDR-TB cases in SA per year, confirming robust projections made previously[2, 21, 22] and supporting the contention that MDR-TB epidemiology should not be described by prevalence estimates alone, but should include underlying TB incidence and absolute numbers of MDR-TB cases.

MDR-TB is ascribed to several overlapping medical and programmatic failures, including poor patient management, lack of treatment supervision, interrupted drug supply, poor drug quality, and poor TB control, all of which are to some extent relevant in SA. MDR-TB levels are, however, surprisingly low given the extensive use of rifampicin, often under past chaotic treatment conditions. SA is one of only a few countries where fixed-dose combination (FDC) formulations for TB

Table V. Determinants of drug resistance from multiple logistic regression models – retreatment patients

Variable	Any drug resistance			
	N	Proportion resistant (%)*	OR (95% CI)	*p*-value
Gender				
Male	675	16.4	1.00	0.728
Female	244	15.0	1.12 (0.59 - 2.11)	
Age group (yrs)				
15 - 24	103	14.1	1.00	
25 - 34	277	13.0	0.84 (0.48 - 1.45)	
35 - 44	310	19.3	1.30 (0.74 - 2.29)	0.173
45 - 54	161	15.4	1.06 (0.51 - 2.21)	
55 - 64	45	18.8	1.15 (0.38 - 3.49)	
65+	23	17.6	1.17 (0.32 - 4.34)	
Previous treatment outcome				
Favourable	648	14.9	1.00	
Unfavourable	270	18.7	2.31 (1.35 - 3.96)	0.003
Treatment outcome category				
Cure	358	10.8	1.00	
Treatment completion	290	19.0	2.07 (1.27 - 3.37)	
Treatment default	231	14.7	2.00 (1.17 - 3.42)	
Treatment failure	39	42.0	8.37 (3.43 - 20.41)	<0.0001
Previous hospitalisation (TB)				
No	537	12.3	1.00	0.001
Yes	382	21.5	2.08 (1.36 - 3.20)	
Previous treatment duration				
1 - 2 months	96	11.1		
3 - 4 months	122	17.1	1.22 (1.00 - 1.49)†	0.046
5 - 6 months	393	16.3		
>6 months	265	17.7		
Previous imprisonment				
No	730	16.6	1.00	0.414
Yes	189	13.7	0.78 (0.42 - 1.43)	
HIV status				
Negative	418	15.3	1.00	0.444
Positive	501	16.7	1.15 (0.80 - 1.65)	

*Proportion weighted by province.
†Odds ratio for trend, i.e. 1-month increase in treatment duration.

treatment have been used extensively, ever since the late 1970s.[5] SA also became the first country to exclusively implement four-drug FDCs in 2000, resulting in the treatment regimen for new TB cases being fully FDC-based. It is our hypothesis that extensive use of FDCs, particularly during the two decades preceding DOTS implementation, has prevented an escalation in drug resistance and been the primary cause of observed stable trends.

Results from this study showed retreatment rates consistently higher than those reported in the TBCP. Since regimen choice depends on previous TB treatment history, a real risk exists for TB patients to be misclassified and consequently receive inappropriate treatment. The association between previous treatment and drug resistance has been well described and was again confirmed by this study, highlighting the need for accurate history taking by health care workers prior to starting patients on TB treatment. Our findings also confirmed that failure of first-line treatment is the strongest determinant of MDR-TB, underscoring the need for rapid improvement in TB control and for ensuring cure of patients the first time around.

While emergence of anti-TB drug resistance is primarily treatment-related, patient characteristics (including HIV infection) are thought to facilitate transmission of drug-resistant strains. A dual scenario for increasing drug resistance in SA therefore presents itself: Firstly, high default rates from first-line treatment remain a feature of TB control in SA, with barely 50% of patients being classified as cured.[16] DOTS delivery is hampered by competing health priorities, ongoing restructuring

Table VI. Determinants of drug resistance from multiple logistic regression models – retreatment patients

Variable	N	Multidrug resistance: Proportion resistant (%)*	Multidrug resistance: OR (95% CI)	p-value
Gender				
Male	675	6.5	1.00	0.970
Female	244	7.9	0.99 (0.50 - 1.95)	
Age group (yrs)				
15 - 24	103	4.7	1.0	
25 - 34	277	7.4	1.47 (0.75 - 2.96)	
35 - 44	310	7.1	1.43 (0.69 - 2.97)	0.894
45 - 54	161	6.1	1.40 (0.63 - 3.12)	
55 - 64	45	10.2	1.78 (0.38 - 8.20)	
65+	23	5.9	1.28 (0.19 - 8.64)	
Previous treatment outcome				
Favourable	648	5.6	1.00	
Unfavourable	270	9.7	3.67 (1.55 - 8.74)	0.004
Treatment outcome category				
Cure	358	3.4	1.00	
Treatment completion	290	7.9	2.56 (1.22 - 5.37)	
Treatment default	231	6.9	3.21 (1.28 - 8.09)	
Treatment failure	39	25.9	13.34 (4.94 - 36.02)	<0.0001
Previous hospitalisation (TB)				
No	537	4.2	1.00	<0.001
Yes	382	10.7	2.87 (1.63 - 5.05)	
Previous treatment duration				
1 - 2 months	96	4.6		
3 - 4 months	122	6.4	1.31 (0.97 - 1.76)†	0.074
5 - 6 months	393	7.9		
> 6 months	265	6.5		
Previous imprisonment				
No	730	7.9	1.00	0.083
Yes	189	3.0	0.49 (0.15 - 1.13)	
HIV status				
Negative	418	5.7	1.00	0.032
Positive	501	7.9	1.46 (1.04 – 2.07)	

*Proportions weighted by province.
†Odds ratio for trend, i.e. 1-month increase in treatment duration.

of health services, slow implementation of district-level reforms, and limited management capacity at service delivery level. Results from this study confirmed default from treatment as a risk factor for MDR-TB, indicating the need for systems to rapidly recall patients who are starting to miss treatment, rather than the current passive recording of patients who have met the conventional definition of (2-month) default.

Secondly, a history of sub-optimal TB control together with the rapidly progressing HIV epidemic has created a fertile environment for transmission of drug-resistant TB in SA. At least one in two TB patients was found to be co-infected with HIV in this study, with co-infection rates exceeding 60% in several provinces. Both nosocomial and community transmission of MDR-TB have been confirmed in SA by epidemiological and molecular genetic studies. Nosocomial transmission in particular has been closely associated with HIV infection, and the first documented outbreak of MDR-TB in SA exclusively involved HIV-positive individuals.[23] Of great concern is the increased risk for MDR-TB posed by hospitalisation as identified in this study, suggesting non-compliance with TBCP policies and/or undetected nosocomial transmission of MDR-TB. Crowded, congregate settings and the absence of appropriate infection control strategies in most public health facilities in SA make institutional transmission of MDR-TB (and XDR-TB) a distinct possibility. Moreover, increasing availability of antiretroviral therapy conceivably brings together in health care settings highly susceptible individuals (often with advanced HIV infection) and those

with undiagnosed drug-resistant TB, setting the scene for explosive outbreaks with high mortality, as recently reported in KwaZulu-Natal.[24]

The role of HIV as an independent risk factor for MDR remains inconclusive and controversial. Controlling for a multitude of co-variables, this study indicated an increased risk for MDR in retreatment TB patients with concomitant HIV infection. Host- or drug-related factors may be involved, although the reason(s) remain unclear. Of particular concern were the 31 patients who had rifampicin mono-resistant strains despite having received FDC formulations. Seventeen of these were retreatment patients, 15 of whom were HIV-positive. Poor absorption of anti-TB drugs or inadequate drug intake as a result of HIV-related enteropathology may have contributed to the emergence of MDR-TB in these patients, but more studies are urgently needed.

There is every reason to believe that the full brunt of MDR-TB still has to be felt in SA. Although it is difficult to accurately predict the impact of the HIV epidemic on MDR-TB, weaknesses in TB control stand to be brought into sharp focus should (when?) these two epidemics coincide. This highlights the crucial need for a multi-faceted approach to avert large-scale, HIV-potentiated, drug-resistant TB epidemics in SA. The primary focus should be to contain the MDR-TB problem and to decrease drug resistance to the lowest possible level. This will require a systematic five-point strategy, i.e.:

1. Prevention of MDR-TB through improved TB control, with poor performance being confronted at the earliest opportunity

2. Effective treatment of existing MDR-TB cases to prevent XDR-TB

3. Expanded HIV counseling and testing, linked to targeted TB preventive therapy and antiretroviral treatment programmes

4. Urgent implementation of appropriate infection control measures in congregate settings

5. Continued surveillance of drug resistance trends, with surveys incorporating an HIV component repeated every 3 - 5 years.

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