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Tuberculosis drug resistance in the Western Cape

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Objectives. Drug resistance is a serious problem in the treatment of tuberculosis and a threat to successful tuberculosis control programmes. Local health workers have expressed concern that the increasing tuberculosis epidemic in the Western Cape is partly attributable to drug resistance. The aim of this study was to determine the prevalence of tuberculosis drug resistance (including multidrug resistance) and to investigate possible relationships between drug resistance and patient demographic characteristics.

Design, setting, subjects, outcome measures. During a defined period, all adult (⩾ 15 years) patients with pulmonary tuberculosis (confirmed by culture) from all tuberculosis clinics in the Western Cape were included. Previous tuberculosis treatment history was obtained by interviews, utilising a standardised questionnaire. Acquired drug resistance was determined on cultures from patients with a prior history of tuberculosis treatment, while initial resistance was determined from tuberculosis cases with no history of previous treatment.

Results. Data from 7 266 patients were analysed. After adjusting for missing information by way of a random sample validation study, 32% of patients were found to have a history of previous treatment, 63% indicated no previous treatment, and in 5% the treatment history was unknown. Rates for initial resistance were found to be low at 3,9% for isoniazid, 1,1% for rifampicin and 0,2% for ethambutol. Combined resistance to isoniazid and rifampicin (multidrug resistance) was found to be 1,1% in patients not treated before. Acquired resistance rates were higher at 10,8% for isoniazid, 4,2% for rifampicin, 0,3% for ethambutol and 4,0% for multidrug resistance.

Logistic regression analysis of the data indicated that drug resistance was not influenced by population group, gender or age. Patients with a history of tuberculosis treatment were found to be at an increased risk of developing drug resistance (relative risk 2,6). Some regions in the Western Cape had higher proportions of previously treated patients with consequent higher acquired resistance rates.

Conclusions. Results from this study indicated that drug resistance is currently not a major problem in the Western Cape, rates comparing favourably with those reported from developed countries and being much lower than those for developing countries. Every effort should therefore be made to maintain the status quo and to prevent the emergence of further resistance. The priority for tuberculosis control in the Western Cape should remain to limit transmission of the disease by reducing the infectious pool through improved cure of (especially) smear-positive cases.

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Tuberculosis accounts for more than 80% of all communicable diseases notified in South Africa and is regarded as one of the most serious health problems affecting the country. The disease is of special concern in the Western Cape, where reported incidence rates are up to three times higher than those for other regions. The coloured population in the Western Cape seems to be at highest risk, with incidence rates in excess of 700 per 100 000 currently being reported.[1]

The standard treatment regimen for new tuberculosis patients in the Western Cape is Rifater, a triple combination agent containing isoniazid, rifampicin and pyrazinamide. Ethambutol is generally only used for retreatment cases and patients who cannot tolerate one of the other first-line drugs. Routine sputum culture and susceptibility testing for isoniazid, rifampicin and ethambutol is done in adult pulmonary tuberculosis patients before treatment is started and after 90 doses of chemotherapy.

Although chemotherapy has been the single most effective tool in the management and control of tuberculosis worldwide, drug resistance reflects a serious failure of this intervention. An increase in the number of cases of drug-resistant tuberculosis (and in particular multidrug-resistant cases) has been observed both locally and internationally, mainly owing to ineffective treatment and, in some instances, to the spread of HIV infection. The latter may indirectly influence drug resistance by increasing the tuberculosis caseload beyond the capacity of existing health services, resulting in lower cure rates and increased acquired drug resistance.[2]

The extent of tuberculosis drug resistance worldwide is difficult to assess with accuracy, since recent data are scarce and bacteriological services are largely absent, especially in developing countries. Internationally there has been a call for the implementation of systematic drug resistance surveillance using standard methods in order to assess this problem more accurately. Surveillance of drug resistance is essential to national tuberculosis control programmes, since trends in so-called 'primary' or 'initial' drug resistance (i.e. drug resistance in cultures from patients who had never been treated for tuberculosis before) provide an indication of the effectiveness of treatment regimens,

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while drug resistance rates in patients with a history of previous treatment (so-called 'acquired' resistance) can point out failures in the management of the disease.[3,4]

The choice of the proper denominator is one of the most crucial aspects of epidemiological studies.[5] Since drug susceptibility testing requires a culture of *Mycobacterium tuberculosis,* it follows that all tuberculosis patients with a positive sputum on culture (irrespective of drug susceptibility results) must comprise the denominator for drug resistance surveillance studies.[5,6]

Drug resistance poses a serious threat to tuberculosis control programmes and it has been a concern in the Western Cape that drug resistance may be contributing to the increasing tuberculosis epidemic in the region. The current hospital-based drug resistance surveillance programme of the MRC National Tuberculosis Research Programme[7] has recently been extended to include clinic-based surveillance and a systematic survey was subsequently done in the Western Cape. The aim of this study was to determine the prevalence of tuberculosis drug resistance (including multidrug resistance) in the Western Cape and to investigate possible relationships between drug resistance and patient demographic characteristics such as age, gender, geographical origin and tuberculosis treatment history.

Material and methods

Study region

At the time of the study, the Western Cape region, with an estimated population of 361 736,[8] was divided into seven developmental regions as illustrated in Fig. 1. Notification figures differ widely between these regions, with Breërivier reporting the highest incidence, namely 1 240 cases per 100 000 for 1992. The coloured population accounts for the largest proportion (59%), followed by whites (24%), blacks (16%) and Asians (1%).[8] The area around Cape Town (region 39 or West Cape) is largely metropolitan and much more urbanised than the other development regions. Health service coverage is fairly good in the West Cape but less so in the rural areas.

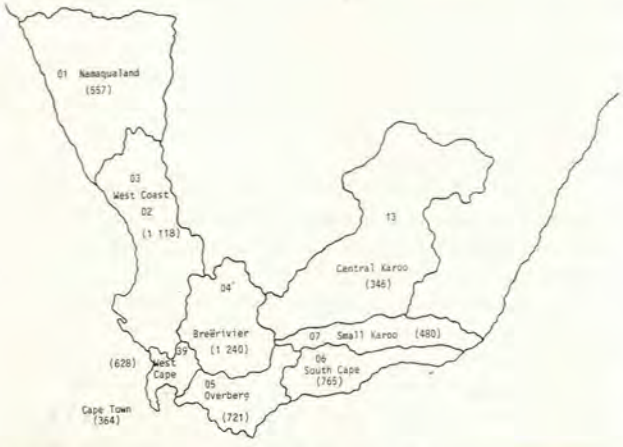

Fig. 1. Tuberculosis incidence in the Western Cape developmental regions (/100 000 population), 1992. Overall incidence 709/100 000.

Study population

The population under study included all adults (≥ 15 years) with confirmed pulmonary tuberculosis by culture from all tuberculosis clinics in the Western Cape between 27 July 1992 and 28 May 1993.

Data collection

A standardised questionnaire was completed for each patient after an interview by clinic nurses who had been trained by the relevant local authorities according to standard guidelines. A sputum specimen was taken from each patient and submitted to the regional laboratory of the South African Institute for Medical Research (SAIMR) in Cape Town together with the questionnaire. Microscopy, culture and drug susceptibility to isoniazid, rifampicin and ethambutol were performed according to standardised procedures.[9-11] The laboratory results and surveillance questionnaires for all specimens yielding a positive culture of *M. tuberculosis* were incorporated into a database developed with Clarion software.

Laboratory procedures

Middlebrook 7H12 (Bactec) culture medium was used for selective primary isolation of mycobacterial strains.[9] *M. tuberculosis* was identified by the niacin production test.[10] Drug susceptibility testing was performed by the economic variant of the indirect proportion method currently in use by the majority of laboratories in South Africa.[11] In essence this method entails the incorporation of the required drug concentrations into Löwenstein Jensen (LJ) egg-based medium before coagulation, while the slants are subsequently inoculated with a standardised inoculum. The following drugs were tested at the indicated concentrations: isoniazid (H) 0,2 µg/ml LJ; rifampicin (R) 30,0 µg/ml LJ; ethambutol (E) 2 µg/ml LJ.

The susceptibility of a strain was judged by determining the proportion of bacilli resistant to a specific drug in comparison with growth on a specific control using international criteria.[10] Resistance was defined as 1% or more bacterial growth.[10]

Definitions

Primary resistance

Resistance indicated in cultures from patients with no history of previous tuberculosis treatment.

Initial resistance

A term used for drug resistance in new tuberculosis patients and allowing for undisclosed previous treatment, i.e. 'initial resistance' refers to primary plus undisclosed acquired resistance. This rate may be up to twice the rate for true primary resistance[3] and the term is preferred by some authors when dealing with large population-based studies. It has also been the preferred term for this study.

Acquired resistance

Resistance indicated in cultures from patients with one or more previous tuberculosis treatment episodes.

Multidrug resistance

M. tuberculosis resistant to (at least) isoniazid and rifampicin.

Analysis

The data were exported to Epi Info Version 5[12] for descriptive analysis. Because of a relatively high proportion of missing information (19%) on the crucial variable of previous treatment history, a random sample of 300 patient records were reviewed retrospectively and the missing information was collected. The expected results based upon the distribution of missing data found from the validation study were calculated and compared with the study results.

Estimates of initial and acquired drug resistance were made with 95% confidence intervals. Multivariate logistic regression was performed to investigate the association of demographic variables with drug resistance, using SAS.[13]

Results

Study limitations

Because of perceived operational difficulties and the absence of information on tuberculosis drug resistance in the Western Cape at the time, a random sample survey was not acceptable to the local health authorities. It was therefore decided to investigate sputum specimens from all tuberculosis patients during a defined period. This approach resulted in difficulties with validation of data and motivation of clinic staff and could have contributed to the problem experienced with incomplete data. Since it was impossible to monitor every clinic it may also have happened that questionnaires were not completed for all patients. Nevertheless, the sample studied is considered to be representative because of its comprehensiveness, allowing reliable calculations of tuberculosis drug resistance in the Western Cape to be made.

Exclusions

During the study period a total of 8 830 questionnaires and laboratory reports were received for 7 832 patients. Of these 1 564 were excluded for the following reasons: 998 questionnaires and reports originated from requests for repeat investigations, 447 cultures were identified as mycobacteria other than tuberculosis, 69 were from children aged under 15 years, 26 questionnaires contained illogical data, 8 cultures were not identified owing to contamination, and 16 cultures were not identified because the organisms lost viability before differential tests could be performed. Data from the first specimen sent for each of 7 266 (92,7%) adult patients with sputum cultures positive for *M. tuberculosis* were therefore available for analysis.

Demographic data

The demographic characteristics of the study population are summarised and compared with official 1992 notification figures in Table I. The ratio of males to females was 1,7:1,0. The majority of patients (63,9%) were from the coloured population group. The median age was 33 years. Most patients (67,5%) came from the West Cape development region.

History of previous tuberculosis treatment

The treatment history of patients according to development region is presented in Table II. From the unadjusted data, 26% of patients gave a history of prior treatment for tuberculosis, 54% claimed never to have received tuberculosis treatment prior to the current episode, and for

Table I. Demographics of the study population compared with 1992 notification figures, Western Cape tuberculosis drug resistance survey

	Study population		Notification data: Pulmonary TB, 1992		Notification data: All cases, 1992	
Demographic characteristics	No.	%	No.	%	No.	%
Gender						
Male	4 187	57,6	12 728	61,3	15 264	59,5
Female	2 415	33,2	8 032	38,7	10 361	40,4
Unknown	664	9,1	13	0,1	13	0,1
Race						
Asian	4	0,1	2	0,01	3	0,01
Black	1 866	25,7	6 131	29,5	7 879	30,7
Coloured	4 640	63,9	14 362	69,1	17 429	68,0
White	42	0,6	262	1,3	309	1,2
Unknown	714	9,8	16	0,1	18	0,1
Development region						
Namaqualand	76	1,1	338	1,6	341	1,3
West Coast	612	8,4	2 251	8,4	2 371	9,3
West Cape	4 902	67,5	11 752	73,7	15 896	62,0
Breërivier	527	7,3	2 430	14,8	2 511	9,8
Overberg	346	4,8	1 366	5,5	1 421	5,5
South Cape	540	7,4	1 472	8,8	1 890	7,4
Karoo	263	3,6	718	3,1	755	3,0
Total	7 266	100,0	20 773	100,0	25 638	100,0

Source: Department of Health, Directorate Epidemiology.

the remainder this information was unknown (3%) or missing (16%). The expected proportions based on the results of the validation study are as follows: 32% with a prior history of treatment, 63% with no prior history and in 5% prior history unknown.

Table II. Treatment history according to development region (unadjusted values), Western Cape tuberculosis drug resistance survey

Development region	Treatment history		
	Previous treatment (%)	No previous treatment (%)	Unknown (%)
Namaqualand	22	49	29
West Coast	25	61	14
West Cape	25	54	21
Breërivier	34	46	20
Overberg	23	58	19
South Cape	38	49	13
Karoo	24	58	18
Total	26	54	19

Drug resistance

Drug susceptibility test results were available for all study cases. The results presented here reflect the unadjusted rates. These did not differ significantly from the expected rates based on the random sample validation study.

Initial resistance

Of the 7 266 cases, 3 928 were defined as 'new' patients and resistance in this group was termed 'initial'.

Initial resistance to the three major tuberculosis drugs is presented in Table III. Resistance to isoniazid was relatively low at 3,9% and is in agreement with a previous estimate by Bohmer and others.[14]

Initial resistance to rifampicin was low at 1,1%. Since almost all tubercle strains showing resistance to rifampicin had associated isoniazid resistance, the estimate for multidrug resistance in new patients is also approximately 1%.

Initial resistance to ethambutol was found to be very low at 0,2%.

Table III. Initial and acquired drug resistance, Western Cape tuberculosis drug resistance survey

Drug	Resistance (%)*			
	Initial (*N* = 3 928)	Acquired (*N* = 1 920)	Unknown (*N* = 1 418)	Overall (*N* = 7 266)
Isoniazid	3,9 (3,3 - 4,6)	10,8 (9,4 - 12,3)	9,0 (7,5 - 10,5)	6,8
Rifampicin	1,1 (0,7 - 1,4)	4,2 (3,3 - 5,1)	2,2 (2,7 - 4,7)	2,4
Ethambutol	0,2 (0,04 - 0,3)	0,3 (0,05 - 0,5)	0,2 (0,0 - 0,4)	0,2
MDR†	1,1 (0,7 - 1,4)	4,0 (3,1 - 4,9)	3,4 (2,4 - 4,4)	2,3

* 95% confidence intervals in parenthesis.
† Resistance to isoniazid and rifampicin.

Acquired resistance

A total of 1 920 patients gave a history of tuberculosis treatment and bacterial resistance occurring in this group was termed 'acquired'.

Acquired resistance to the three first-line drugs is presented in Table III. Both isoniazid and rifampicin resistance are almost three times higher than the corresponding initial rates, at 10,8% and 4,2% respectively. Resistance to ethambutol, albeit low at 0,3%, seems to follow a similar trend. Multidrug resistance is also significantly higher at 4,0%.

Multidrug resistance

Data on multidrug-resistant tuberculosis are very scarce at this stage. In New York City, USA, the overall rate has been reported to be around 19%,[7] while the national figure is estimated to be 3,5%.[15] A recent report from India indicated multidrug-resistant tuberculosis in 33,3 - 61,5% of previously treated cases.[16] Against these figures and the extent of drug-susceptible tuberculosis in the Western Cape the multidrug-resistant tuberculosis problem (1% initial, 4% acquired) seems to be relatively small. However, the actual number of cases already presents a significant burden to the regional tuberculosis service, since multidrug-resistant tuberculosis is notoriously difficult and extremely expensive to treat and cure rates are low.

Association between demographic variables and drug resistance

Drug resistance rates did not vary by population group, gender or age. There were, however, significant differences in different geographical regions, as indicated in Table IV. These results were based on small sample sizes and should be interpreted with caution. Nevertheless, both initial and acquired drug resistance rates were lower in the West Cape when compared with the rest of the region. Acquired drug resistance was significantly higher in the Breërivier, Overberg and South Cape regions ($P < 0,001$). Initial drug resistance was significantly higher in Breërivier, Karoo and Weskus plus Namaqualand. Breërivier also had significantly higher initial drug resistance rates than the South Cape.

Table IV. Drug resistance in development regions, Western Cape tuberculosis drug resistance survey

Development region	No.	Resistance (%) (any drug)	
		Initial	Acquired
Namaqualand and West Coast	580	5,6	12,9
West Cape	3 880	3,2	8,6
Breërivier	421	7,9	19,3
Overberg	280	4,5	17,3
South Cape	472	3,8	14,6
Karoo	215	6,5	9,7

Coloured patients had a higher proportion of cases with a history of prior treatment (34%) than blacks (30%). Among black women the proportion giving a history of treatment was the lowest (24%), while among coloured males it was the highest (35%).

Results from the logistic regression model are presented in Table V. Both previously treated and new patients in the West Cape region showed a significantly lower probability for drug resistance (0,086 and 0,032 respectively) than the mean values predicted for the region as a whole (0,134 and 0,052 respectively). Patients from Breërivier showed the

opposite, with significantly higher values (0,198 and 0,080 respectively). For the other regions, the values observed (acquired resistance 0,134 and initial resistance 0,052) were adequate to fit the expected proportions. From this it can be concluded that patients with a history of previous tuberculosis treatment in general have an almost three times higher risk of presenting with drug resistance (relative risk 2,6).

Table V. Observed and predicted probabilities for drug resistance, Western Cape tuberculosis drug resistance survey

Development region	Sample size	Probability for drug resistance		
		Observed	Predicted	SE
Patients treated before				
Namaqualand and West Coast	168	0,131	0,134	0,010
West Cape	1 124	0,085	0,086	0,007
Breërivier	179	0,196	0,198	0,023
Overberg	80	0,175	0,134	0,010
South Cape	202	0,144	0,134	0,010
Karoo	61	0,098	0,137	0,025
Patients not treated before				
Namaqualand and West Coast	407	0,056	0,052	0,005
West Cape	2 509	0,033	0,032	0,003
Breërivier	238	0,079	0,080	0,011
Overberg	196	0,046	0,052	0,005
South Cape	260	0,038	0,052	0,005
Karoo	153	0,065	0,054	0,011

Discussion

As can be seen from Table I, the male/female ratio, the population group distribution and the age distribution of the study group were similar to those of tuberculosis patients notified in the Western Cape in 1992. The proportions of study cases from the various development regions were similar to the proportions of notified pulmonary tuberculosis cases, except for the West Cape and Breërivier. The reason for the slight differences observed in the latter regions is not clear.

If the monthly average of cases entered into the surveillance study is compared with the monthly average of *notified* pulmonary tuberculosis cases in 1992 a large discrepancy becomes apparent: the number of pulmonary tuberculosis cases notified was more than twice the number of patients entered into the surveillance study. It is known that a large proportion (16%) of pulmonary tuberculosis cases notified from the Western Cape are children under the age of 15 years (R. Eggers — personal communication), who were excluded from our study. Patients notified without bacteriological confirmation of the diagnosis as well as those notified from institutions others than clinics and those diagnosed incorrectly probably account for the rest. This matter is of obvious concern and requires urgent investigation.

Table II indicates that Breërivier and South Cape had higher proportions of patients reporting a previous history of tuberculosis treatment. Although the patient numbers were relatively low, these two regions also showed higher acquired resistance rates. This may reflect the difficulties with provision of supervised treatment which are encountered in the more rural areas and warrants further investigation.

The association between previous tuberculosis treatment and drug resistance has been well documented[15-17] and has again been confirmed by our study. A very high proportion (32%) of patients reported a prior history of tuberculosis treatment. It was not possible to categorise the reasons for retreatment, such as treatment failure, relapse, defaulting or chronic cases. The default rate in the Western Cape health region is reported to be around 17%[1] and would account for some of these retreatments. Further investigation is, however, necessary to elucidate the reasons for retreatment, since the estimated so-called 'cure ratio' reported for the Western Cape was 93% in 1992.[1] In addition, a recent study at four clinics in the West Cape region revealed that only 62% of adult tuberculosis patients took 75% or more of the prescribed treatment doses, implying that 38% were possibly exposed to erratic or inadequate therapy.[18]

Initial resistance to isoniazid is generally accepted as a sensitive indicator of the overall success of a treatment programme in a country, since this drug is widely used in treatment regimens. In most developed countries where eradication of tuberculosis is well advanced, initial isoniazid resistance is below 10%.[3,15] In developing countries, however, a different picture is seen, with rates for initial isoniazid resistance in excess of 20% reported from various countries in Africa (F. Portaels — personal communication) and rates higher than 13% from countries such as Haiti[19] and India.[20] Relative to these figures, the rates for initial resistance observed in the Western Cape seem to indicate that drug resistance is currently not a major problem.

As expected, the drug resistance rates were much higher in patients who had previously received antituberculosis therapy, a finding consistent with studies done elsewhere. Breërivier had the highest acquired resistance rates, while the South Cape and Overberg regions also had higher rates than West Cape. It would appear that treatment management systems in these areas may not be functioning as well as they could and may require further investigation to identify specific problems. However, when compared with figures for acquired resistance reported from other developing countries it is clear that acquired resistance in the Western Cape is also relatively low: acquired resistance to isoniazid has been reported to be as high as 55,8% in India,[20] and 57% in Korea.[21] Extremely high rates of acquired resistance to rifampicin have been reported from countries such as Saudi Arabia (34 - 42%),[22,23] India (37%)[20] and Korea (13%).[21]

Conclusions

Drug resistance rates in the Western Cape compare favourably with resistance rates reported in developed countries and are much lower than those reported in developing countries. Drug-resistant (including multidrug-resistant) tuberculosis is a man-made problem and its further development must be avoided. This will require an intensive effort aimed at improving the success of initial tuberculosis treatment, since the best way to prevent drug resistance occurring is to ensure that initial treatment is successful in more than 85% of new smear-positive cases.[24]

Improvement in the success rate of initial treatment will require attention to caseholding and prevention of defaulting, which will require improved management at clinic level. Experience from successful tuberculosis control programmes assisted by the International Union against Tuberculosis and Lung Disease[25,26] in developing countries suggests that, apart from maintenance of regular drug supplies, an important factor in improving the success of initial short-course chemotherapy is rigorous cohort analysis of treatment outcome at treatment centre level. This is currently not possible from routinely collected control programme data but has been addressed in the model for a national register of all tuberculosis cases, developed by the TBRP and implemented nationally in January 1995.

The Centers for Disease Control and Prevention in the USA recommend the use of a four-drug regimen in areas where initial isoniazid resistance is higher than 4%.[27] The prevalence of initial isoniazid resistance in the Western Cape is currently around 4%. However, in some areas rates of more than 5% have been recorded, albeit on small numbers of patients. The current practice of prescribing a three-drug regimen for new cases in the Western Cape seems therefore to be adequate, but could be strengthened by routinely adding ethambutol during the first 2 months of treatment. The continued use of pyrazinamide for 6 months is questionable, however, since pyrazinamide is a sterilising drug acting in macrophages and in areas of acute inflammation during the onset of treatment, with little effect in later stages.[28] Given the side-effects associated with prolonged administration of pyrazinamide, discontinuation of this drug following satisfactory patient response after 2 months should be considered.

Although internationally recognised recommendations for retreatment regimens based on specific patterns of acquired drug resistance do not exist, the general consensus is that, where acquired isoniazid resistance is high, a fifth drug should be added to retreatment regimens.[27] In the Western Cape, where acquired isoniazid resistance is approximately 11%, the addition of streptomycin to the standard four-drug regimen, at least until drug susceptibility results are obtained, would seem to be appropriate.

Ongoing surveillance of drug resistance is obviously required. However, in view of the relatively low resistance rates among new tuberculosis cases, an alternative, more cost-effective screening policy should be considered. Surveillance could be conducted on a random sample of tuberculosis clinics where more time can be spent on training and motivation of clinic personnel to ensure that all the relevant information is collected. Obviously, comprehensive screening should continue to detect resistance in groups at high risk, such as those who have received previous treatment, or those who are still sputum-positive after 2 months of treatment or who are contacts of drug-resistant cases.

Finally, if sufficient resources are available after adequate allocation to initial treatment efforts, attempts should be made to treat the existing and emerging (multidrug)-resistant cases adequately. However, this requires prolonged treatment with expensive drugs under specialist supervision, ongoing support and monitoring of patients. Care must, therefore, be taken not to direct resources from the treatment of new (especially smear-positive) tuberculosis cases. The priority for tuberculosis control in high prevalence areas such as the Western Cape therefore remains to reduce transmission by reducing the infectious pool of tuberculosis cases. The most effective way of achieving this is to cure smear-positive cases. Improved initial treatment of tuberculosis will also prevent the development of further drug resistance.

The study was a major undertaking that required a much-appreciated input from the local health authorities services. We are particularly indebted to the nursing staff from Western Cape tuberculosis clinics and the regional SAIMR mycobacteriology laboratory staff for their dedicated efforts. Thanks are also due to Mrs R. Julyan and Mrs S. Welken of the TBRP for their assistance in the collection of information and capture of the data.

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