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**SURVEY OF TUBERCULOSIS DRUG
RESISTANCE IN SOUTH AFRICA
2001 - 2002**



Final Report

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INTRODUCTION

At no time in recent history has tuberculosis been as great a concern as it is today. Despite highly effective drugs, morbidity and mortality due to *Mycobacterium tuberculosis* are increasing and are being fuelled by the HIV epidemic. A most serious aspect of the problem has been the emergence of drug-resistant (particularly multidrug-resistant) tuberculosis, which poses a threat both to individual patients (prolonged and toxic treatment with poor cure rates) as well as to communities (being infectious in many instances).

Although chemotherapy has been the single most effective tool in the management and control of tuberculosis, drug resistance reflects a serious failure of this intervention. Potential causes of drug resistance include inadequate treatment regimens prescribed by health staff, poor case holding of tuberculosis patients, poor drug supply, poor drug quality or use of expired drugs, patient error in following prescribed regimens and misuse of tuberculosis drugs.¹ Resistant bacilli are known to emerge more rapidly in the setting of erratic treatment² and the most important cause of development of drug resistance may well be the error by health professionals in providing adequate treatment regimens and ensuring that patients complete a full course of chemotherapy.

Resistance of *M. tuberculosis* to anti-tuberculosis drugs is a man-made amplification of a natural phenomenon.³ During bacterial multiplication, resistance develops through spontaneous mutation at a defined rate. For example, mutations resulting in resistance to isoniazid occur at an average rate of 10^{-8} per cell division, resulting in naturally occurring resistant organisms in 1 in 10^6 bacilli; the average rate for rifampicin is 10^{-10} , leading to an estimated resistance prevalence of 1 in 10^8 bacilli in drug-free environments.³ Multidrug resistance due to spontaneously occurring mutations is virtually impossible, since there is no single gene involved in such a process and mutations resulting in resistance to the different drugs are not genetically linked.^{2,3} The likelihood of spontaneous mutations resulting in resistance to both isoniazid and rifampicin is the product of the individual probabilities, ie. 1 in 10^{14} . Bacillary populations greater than 10^7 are common in lung cavities of tuberculosis patients.³ Thus, resistant organisms (or mutants) evolve in the absence of drug exposure, but they are diluted within the vast majority of drug-susceptible bacilli. The presence of anti-tuberculosis drugs (particularly when applied erratically) provides selective pressure that favours the resistant mutants which then multiplies to become predominant, especially in patients with a large load of bacilli, eg. those with sputum smear-positive disease.

Erratic exposure to anti-tuberculosis drugs - due to irregular drug supply, poor drug quality, inappropriate prescription and/or poor adherence to treatment - suppresses the growth of susceptible bacilli but permits the multiplication of drug-resistant organisms. This phenomenon is called 'acquired resistance' and is found in patients who have been treated (inadequately) for tuberculosis. Subsequent transmission of these bacilli to other persons may lead to tuberculosis that is resistant from the outset, a phenomenon known as 'primary resistance'.

A critical factor in the emergence of drug resistance is the lack of properly organised systems to ensure prompt diagnosis and effective treatment.³ The level of anti-tuberculosis drug resistance is therefore an indicator of the effectiveness of tuberculosis control efforts and surveillance of drug resistance becomes essential to national tuberculosis control programmes. Trends in drug resistance in cultures from patients who had not been treated for tuberculosis before provide an indication of the effectiveness of treatment regimens, while drug resistance rates in patients with a history of previous treatment point out failures in the management of the disease.⁴ The best way to obtain comparable and reliable estimates on the prevalence and trend of tuberculosis drug resistance is to perform periodic surveys in newly-registered tuberculosis patients. To achieve this, stringent statistical requirements have to be met for selection of adequate and representative patient samples to be examined.⁴ In addition, laboratory techniques, criteria for defining drug resistance and patient interview procedures need to be standardised and strictly adhered to.⁴

As decisions on treatment regimens and control programme management are made by the National Tuberculosis Control Programme (TBCP) in South Africa, trends of drug resistance should be monitored at this level. New tuberculosis treatment regimens have been implemented in South Africa during 1996. Prior to the national survey (reported in this document) the true extent of tuberculosis drug resistance in most provinces was not known although multidrug-resistant (MDR) tuberculosis has emerged in all. MDR tubercle isolates comprise between 5% and 10% of specimens investigated in the major tuberculosis laboratories in the country. This figure cannot, however, be used as an indicator of the extent of MDR tuberculosis, since submission of specimens to laboratories reflects a considerable degree of selection and may over-sample patients with severe morbidity (eg. those with treatment failure, relapsed or drug-resistant disease). Also, laboratories do not receive adequate patient information (eg. on previous treatment). This leads to another serious limitation of laboratory-based surveillance, since serial testing of different specimens from the same patient often takes place, rendering it impossible to obtain accurate denominator information.

In establishing surveillance of drug resistance at country/provincial level, the following principles have to be strictly adhered to:⁴

- The sample of specimens should be representative of the patients from the country/province under study and sample size should permit standard epidemiological analyses;
- Patient's treatment history should be carefully obtained and available medical records reviewed to clearly determine whether or not the patient had previously received anti-tuberculosis drugs;
- The laboratory methods for susceptibility testing of anti-tuberculosis drugs should be selected from among those that are internationally recommended.

The Tuberculosis Research Lead Programme of the Medical Research Council (MRC) forms part of the Global Network of Supranational Reference Laboratories for Drug Resistance

Surveillance of the World Health Organisation (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD). The MRC Tuberculosis Reference Laboratory was appointed as the Supranational Reference Laboratory for Africa in 1994 and has provided epidemiological advice and laboratory quality assurance for several drug resistance surveys performed in Africa since. The MRC has also been responsible for drug resistance surveillance in tuberculosis hospitals in South Africa between 1965 and 1995.^{5,6} This programme was subsequently suspended due to MRC budget constraints and a Department of Health policy shift to ambulatory treatment for tuberculosis patients in South Africa. Two population-based surveys were subsequently done by the MRC, one in the Western Cape⁷ and one in Mpumalanga Province.⁸ Results indicated low levels of drug resistance in both provinces, but considerable variation in drug resistance prevalence between the two provinces. Prior to the national survey no reliable information on tuberculosis drug resistance was available for the other provinces.

In order to obtain accurate information on the burden and trend of tuberculosis drug resistance in the nine provinces of South Africa, a national survey was conducted by the MRC in 2001 - 2002. Since provinces were at different stages of implementation of the revised tuberculosis control strategy and had historically had varying levels of success in tuberculosis control, province-specific surveys of drug resistance were required.

HIV has never been indicated as a risk factor for drug resistance developing in individual patients; however, outbreaks of MDR tuberculosis in prisons and health care settings have almost invariably been linked to increased susceptibility of contacts due to HIV infection. The prevalence of HIV infection in tuberculosis patients in South Africa is not known, although the HIV epidemic is regarded as one of the most rapidly unfolding epidemics in the world. The survey of drug resistance provided a unique opportunity to reliably establish the point prevalence of HIV infection among tuberculosis patients, since all necessary epidemiological and statistical requirements were met by the study design.

GOAL AND OBJECTIVES

The major goal of the national survey of tuberculosis drug resistance was to evaluate the effectiveness of tuberculosis control in South Africa in the light of drug resistance trends. Specific objectives included the following:

- to accurately quantify the extent of drug resistance in new and retreatment tuberculosis patients;
- to compare the burden and trend of drug resistance in the nine provinces;
- to evaluate the quality of tuberculosis chemotherapy as reflected by drug resistance levels in the nine provinces;
- to estimate the number of MDR tuberculosis patients in each province in order to allow for rational budget and management planning.

MATERIALS AND METHODS

Definitions

Resistance to tuberculosis drugs was defined according to the results of laboratory testing (susceptible or resistant) and patients were classified according to their previous treatment history. The following standardised definitions applied:

Drug resistance among new patients

Drug resistance in *M. tuberculosis* cultures from patients who had not been treated for tuberculosis before or who had been treated for less than one month.

Drug resistance among previously treated patients

Drug resistance in *M. tuberculosis* cultures from patients who had been treated for tuberculosis for one month or more. These patients included cases identified as recurrent (relapse or re-infection), return after interruption, return after failure and failure after retreatment.

Multidrug resistance

In vitro resistance to both isoniazid and rifampicin, with or without resistance to other tuberculosis drugs.

Study design

A population-based, cross-sectional study design was followed, according to the international WHO protocol for drug resistance surveillance.⁴

Sample sizes and sampling strategies

Province-specific calculations of appropriate sample sizes were based on the following:

- Expected prevalence of resistance to the drug with the lowest known or estimated level from previous data (assumed 1% for MDR tuberculosis in South Africa);
- As accurate precision as possible (precision of $\pm 1\%$) but with calculations done to ensure samples that were logistically feasible to obtain;
- A level of confidence around the provincial estimates of 95%.

Given the variation of infrastructure, resources and logistical capacity in the nine provinces, various approaches to selection of patients were discussed with provincial authorities. These included 100% sampling of diagnostic centres within a limited intake-period, simple random sampling, random cluster sampling and population proportionate cluster sampling.⁴ The eventual decision in all provinces was to use a cluster design approach, particularly to avoid the risk of missing large diagnostic centres. Multistage stratified cluster sampling with population proportional to size (PPS) was subsequently done as follows: A cumulative list of tuberculosis cases registered in the preceding year was compiled according to health district

(or region in some provinces) and diagnostic centre (clinics and tuberculosis hospitals). Districts (or regions where appropriate) served as strata and the number of patients required per district was determined proportionally from the total study sample required per province. Second stage sampling followed the same approach to select at least 30 diagnostic centres (clusters) per province. The total number of patients registered in the preceding year was divided by the number of clusters to obtain the sampling interval. A random number was then selected between one and the sampling interval to determine the first diagnostic centre on the cumulative list. The sampling interval was sequentially added to the random number to select the remaining clusters. Consecutive patients were included until the numbers required for each province were reached. In order to facilitate logistics and survey stock control each district was proportionally assigned a specific number of patients to register. This was determined from the proportional contribution of each district to the overall provincial tuberculosis burden in the preceding year.

Special consideration had to be given to the inclusion of tuberculosis hospitals as clusters. In provinces where patients were still routinely hospitalised, these hospitals were included in the sampling frame. Referral centres for MDR tuberculosis were excluded to avoid over-estimation of resistance prevalence.

The sample size in each province was doubled to accommodate the study design and sample sizes were further increased by 20% to account for expected losses such as empty containers, contamination, loss of culture viability, incomplete records etc.

Based on an assumption of 1% MDR resistance in new patients, a precision of $\pm 1\%$ around this estimate and 95% confidence limits, 381 patients had to be registered per province. This number was doubled to 762 to accommodate the cluster design effect and then inflated by 20% to accommodate loss, resulting in a final sample size of 920 confirmed tuberculosis patients per province. However, patients with contaminated or non-viable cultures were replaced by consecutive sampling and intake was terminated when the required sample size of 762 culture-confirmed patients was reached. For ethical reasons all specimens were processed and complete bacteriology (including drug susceptibility testing) done, even if the target sample size was exceeded.

Patient intake

All newly registered patients with culture-confirmed tuberculosis at the selected diagnostic centres were eligible for inclusion. In addition to the initial two sputum specimens required by the TBCP for routine microscopy, a third specimen was collected from all tuberculosis suspects before treatment was started. These specimens were sent to the MRC laboratories in Pretoria, either through the existing networks of the National Health Laboratory Services (NHLS) or by dedicated courier services contracted specifically for this purpose.

Specimens from all persons suspected of having tuberculosis were investigated, ie. not only those from patients with positive sputum smears. This was done to estimate the total burden of tuberculosis in each province. As tuberculosis diagnosis in South Africa is primarily based on smear microscopy, there is a paucity of reliable information on the prevalence of smear-negative culture-positive tuberculosis (expected to be increasing due to HIV co-infection).

During the planning phase of the survey it was estimated by provincial health authorities that approximately 10 tuberculosis suspects would have to be screened to discover one culture-confirmed case. This meant that approximately 9 000 suspects were expected to be screened per province to identify the required number of culture-confirmed patients.

Patient information was collected on a structured colour-coded questionnaire (Annexure 1) after careful interviewing by trained health staff in the selected diagnostic centres. The questionnaire forms part of the standard data collection tools for the WHO/IUATLD Global Working Group on Anti-Tuberculosis Drug Resistance Surveillance but was adapted to accommodate South African needs. The main purpose of the questionnaire was to obtain reliable information on previous tuberculosis treatment and to collect demographic information in a standardised way.

Laboratory procedures

Microscopy, culture and drug susceptibility testing was performed according to international methodology.⁹ Sputum specimens were decontaminated by the modified Petroff method using 4% sodium hydroxide. Ziehl-Neelsen microscopy was done on the concentrated sediment, after which it was cultured on two slopes of Löwenstein-Jensen medium, one slope being enriched with 5% sodium pyruvate. Cultures were incubated for eight weeks at 37°C. They were inspected after 48 hours to detect contamination and thereafter were examined weekly to observe growth. Isolates of *Mycobacterium tuberculosis* were identified by growth rate, colony morphology, niacin production and nitrate reduction tests.⁹

Drug susceptibility tests were done according to the indirect proportion method.⁹ Resistance against isoniazid, rifampicin, streptomycin and ethambutol was determined. Resistance was expressed as the percentage of growth against critical drug concentrations, ie. 0.2µg/ml for isoniazid, 40µg/ml for rifampicin, 4µg/ml for streptomycin and 2µg/ml for ethambutol. Interpretation of resistance was according to conventional criteria, ie. 1% or more growth.

Standardised laboratory reports (Annexure 2) were issued for each specimen received and were sent to the health facilities concerned. These consisted of a preliminary report whenever a positive culture was identified and a final report providing the drug susceptibility test results and species identification. In order not to jeopardise routine tuberculosis control programme activities, microscopy results were issued only once the culture results were available.

Quality assurance

Quality assurance of the survey was done to detect operational or systematic errors and to improve compliance with the survey procedures. Quality assurance procedures covered sampling, patient intake, collection of clinical information and laboratory procedures. Pre-determined audit criteria were set whereby quality assurance was achieved. These included the following:

- Questionnaires were to be completed for all patients participating in the study;
- At least 90% of questionnaires were to contain valid information. This was controlled by weekly questionnaire audits to ensure that information was collected correctly;

- The reliability of information collected by the questionnaire was to be assessed by re-interview of a 10% sample of patients in each province, randomly selected from the participating centres;
- Sputum specimens were to be collected from all patients;
- Bacteriological results were to be available for all specimens received, irrespective of the result. All positive cultures were to undergo drug susceptibility testing and identification of *M. tuberculosis*.

HIV testing of sputum specimens

HIV testing of sputum specimens using the GACELISA (Wellcozyme*HIV 1+2, Murex Diagnostics) test kit for saliva specimens has been shown to be highly reliable and reproducible (University of Pretoria, Department of Medical Virology, unpublished information) and was used to establish the HIV status of culture-positive specimens in an unlinked way: Sputum specimens were frozen until the culture results became available. For all positive cultures, the respective sputum specimens were numerically coded and submitted to the Department of Medical Virology at the University of Pretoria, for HIV testing. Patient names were removed from the database once the culture and drug susceptibility reports were issued and HIV results added to the database once all tests were completed. Results linked to individual patients were therefore not known but prevalence estimates of HIV infection among tuberculosis patients in the different provinces were available. This approach obviated the need for individual patient counseling and posed no ethical problems.

Data management

Data were collated weekly using the internationally standardised software of the WHO/IUATLD Global Working Group on Tuberculosis Drug Resistance Surveillance (SDRTB, Version 3.0). Data entry was performed at the MRC using the services of dedicated data clerks. Laboratory reports on microscopy, culture and drug susceptibility tests were issued directly from the database as soon as these results were received from the laboratory. When all tests were completed and the required laboratory reports issued, patient names were removed from the database and the coded HIV results added.

District performance in terms of the number of patients registered was monitored monthly and the Provincial Tuberculosis Managers informed accordingly. Lists outlining problems such as empty containers, leaked specimens and incomplete questionnaires were sent monthly to the provincial TB Managers for follow-up and corrective action.

Data were tabulated quarterly to check on patient enrolment, quality of clinical information and quality of laboratory results. Drug resistance data derived from the survey were to be used primarily for surveillance purposes and not for individual patient management; however, if a case of MDR tuberculosis was diagnosed in the laboratory the relevant clinic was notified immediately for specialised treatment and follow-up. Patients with a positive culture result were notified to the respective clinics for appropriate treatment and follow-up.

Data analysis was done using SDRTB Version 3.0 and Epi Info 6.04.

Ethical approval

The survey protocol was approved by the National Department of Health, Provincial Research and Ethics Committees and by the Ethics Committee of the MRC.

RESULTS

The survey was done in a phased manner in the nine provinces, starting in August 2001 and ending in October 2002. In North West the survey had to be repeated following inadequate or non-response by all except two Districts in the first attempt. In the Northern Cape, serious problems were encountered with noncompliance of health workers with the survey protocol and non-response from the clinics and hospitals selected. Despite several attempts at intervention (also from the National Department of Health) the situation was not rectified. Patient intake after two years was less than 25% of the required total, and serious concerns about selection bias lead to a decision to exclude the Northern Cape from the national survey.

Response rate

The sample of diagnostic centres selected in the various Provinces is presented in Annexure 3 and the response rate by Province is provided in Table 1. All provinces except Limpopo achieved the required target of 762 culture-confirmed tuberculosis patients, although several districts in each of the provinces did not contribute the required number of cases.

Treatment history of suspect cases

Table 2 indicates the treatment history of persons suspected of having tuberculosis in the various provinces, based on weighted proportions per Province. Overall, 66.6% of suspects had no history of previous treatment (range 56.4% in the Eastern Cape to 74.6% in North West) while 30.0% indicated that they had received treatment for tuberculosis for one month or more (range 20.1% in North West to 37.5% in the Eastern Cape). For 3.4% of suspects (range 1.1% in the Free State to 11.9% in Mpumalanga) no information on previous treatment was available.

Case detection by microscopy and culture

The proportion of cases detected by microscopy and culture from sputum specimens of suspects is given in Table 3. Overall, a total of 24 986 specimens were received, from which 24 752 (weighted proportion 99.0%) smears and 22 030 (weighted proportion 87.3%) cultures were successfully processed.

The weighted rate of specimens found to be positive by microscopy was 28.3% (range 17.9% in North West to 38.7% in KwaZulu-Natal). Positive cultures were obtained from 34.5% of specimens (range 23.1% in North West to 44.8% in KwaZulu-Natal). High contamination rates (12.7% overall) were demonstrated, which meant that the gain in case finding by culture was difficult to determine accurately.

Assuming that unreadable smears and contaminated cultures followed an unbiased distribution into either a positive or negative category, crude estimates of the ratio of suspects to cases were calculated, as shown in Table 3. On average, one smear-positive case was detected for every 3.5 suspects screened. Case detection by culture was similar, with one culture positive case detected among every 2.9 suspect cases.

Demographic profile of culture-confirmed tuberculosis patients

Table 4 provides the demographic profile of culture-confirmed tuberculosis patients (n = 5 866). 63.6% of patients were male, 36.3% were female and for 0.1% no information on gender was provided. The mean age of patients was 35.5 yrs (SD = 0.65). Information on previous treatment was available for 97.4% of patients. 70.3% indicated no history of previous treatment while 27.1% reported that they had been treated for tuberculosis before, a very similar finding to the treatment history recorded among suspects. Among retreatment patients, 22.4% had previously interrupted treatment while 62.6% were recurrent cases, having successfully completed treatment before. 56.4% of the recurrent cases had documented proof of previous cure. On the issue of incarceration, information was missing for 2.1% of patients while 14.4% of patients had been or were in prison at the time of sputum collection. 34.9% of patients reported previous hospitalisation for TB while for 10.9% of patients information on hospitalisation was not recorded.

Bacteriology results

Complete bacteriology results adjusted for Province are provided in Table 5. Individual provincial results are given in Annexure 4. Microscopy results were positive in 28.0% of specimens, while unreadable smears were reported in 1.0%. Cultures were negative in 57.2% of specimens. *M. tuberculosis* was confirmed in 5 866 (23.9%) specimens. Nontuberculous mycobacteria were identified in 58 (0.2%) of specimens. Identification of mycobacterial species was not possible for 1 181 (6.1%) cultures as a result of nonviable or contaminated subcultures. A total of 2 956 (12.7%) initial cultures were lost due to contamination. Patients who had initially contaminated cultures were systematically replaced and the determination of drug resistance was therefore not affected.

Table 6 indicates the grading of microscopy and culture results for the *M. tuberculosis* strains identified (n = 5 866). Individual provincial results are provided in Annexure 5. Overall, 79.4% of smears were found to be positive. 91.4% of these were regarded as highly positive, indicated by a grading of 1+ to 3+, with 42.6% showing a 3+ result.

Microscopy and culture results are compared in Table 7. A very high proportion (79.9%) of culture-confirmed specimens were also smear-positive, indicating a gain of 20.1% in additional cases detected by culture. Considerable differences in the proportion of smear-negative, culture-positive cases (ie. gain in case detection by culture) were observed among the provinces, ranging from 15.5% in the Western Cape to 28.2% in Gauteng, as indicated in Table 8.

Drug resistance results

Table 9 provides drug resistance results for confirmed tuberculosis patients according to treatment history and the number of drugs against which their strains were found to be resistant. Drug resistance (any) was detected in 7.8% cultures from new patients and in 15.5% cultures from retreatment cases ($p < 0.001$). 4.6% of cultures from new patients had strains resistant to one drug only while 0.5% had four-drug-resistant strains. In retreatment patients, 6.5% had single drug-resistant strains while 1.4% had strains showing resistance to all four drugs tested.

Drug resistance profiles for the country as a whole, weighted by Province, are provided in Table 10. Provincial profiles are given in Annexure 6. Strains with resistance to isoniazid were detected in 5.7 % of new patients and in 11.8% of patients with a previous history of tuberculosis treatment, with mono-resistance present in 2.6% (new) and 2.9% (retreatment) patients respectively. Rifampicin resistance was found in 1.8% of new and 7.5% of retreatment cultures, with mono-resistance detected in 0.2% (new) and 0.8% (retreatment) of strains respectively. Ethambutol resistance was very low at 0.8% in new patients and 2.4% in previously-treated cases, with mono-resistance only detected in 0.1% of retreatment patients. Strains with resistance to streptomycin were found in 4.3% of new and 8.1% of retreatment patients, with mono-resistance reported in 1.8% of new patients and 2.6% of retreatment patients. MDR prevalence was low in new patients at 1.6%, but significantly higher at 6.6% in patients with a prior history of tuberculosis treatment.

Of the 78 MDR tuberculosis strains found in new patients, 28.2% were resistant to isoniazid and rifampicin alone, 12.8% had associated ethambutol resistance, 33.3% had associated streptomycin resistance and 25.6% strains were resistant to all four drugs (Table 10). Of the 101 MDR tuberculosis strains from patients with a previous history of tuberculosis treatment, 39.6% had resistance to isoniazid and rifampicin only, 8.9% had associated ethambutol resistance, 26.7% had associated streptomycin resistance and 24.8% of strains were resistant to all four drugs (Table 10).

Considerable differences in drug resistance (any) and MDR levels were evident among the provinces, as indicated in Table 11. Any resistance in new patients was lowest in the Western Cape (5.6%) and highest in the Eastern Cape (11.3%). In retreatment patients resistance levels were lowest in the Western Cape (7.9%) and highest in Mpumalanga (23.4%). MDR prevalence in new patients was lowest in the Western Cape (0.9%) and highest in Mpumalanga (2.6%). Similarly, in retreatment patients, MDR prevalence was lowest in the Western Cape (3.9%) and highest in Mpumalanga (13.7%). Ongoing problems with patient classification rendered the distinction between new and retreatment patients very difficult for the Free State.

Table 12 indicates drug resistance (any and MDR) detected among the different categories of retreatment cases. Higher levels of drug resistance (any) was detected among patients with a previous unfavourable outcome (failed or interrupted), compared to patients with a favourable outcome (cure or treatment completed); however these differences were not statistically significant ($p = 0.055$). MDR prevalence in patients with a previous unfavourable outcome was double when compared to patients who had successfully been treated before ($p < 0.001$). 25.5% of treatment failure cases were found to have MDR, while resistance (any) was recorded in 39.9%.

Table 13 provides an estimate of the total burden of MDR tuberculosis cases in South Africa in 2001. This was derived from MRC estimates on the total provincial tuberculosis caseload for 2001 and the MDR tuberculosis prevalence estimates from the survey. Applying the assumptions from the MRC model of HIV-associated tuberculosis¹⁰ and using the survey findings on the proportion of retreatment cases and MDR prevalence rates, two sets of estimates were determined: in the worst case scenario the burden of MDR tuberculosis was

calculated using tuberculosis caseload estimates from Scenario 1 in the MRC model (no control of either the tuberculosis or HIV epidemic). In the best case scenario the MDR tuberculosis burden was calculated using Scenario 4 of the model (optimal control of both tuberculosis and HIV). The total MDR tuberculosis caseload for South Africa in 2001 was subsequently estimated to be between 4 983 and 9 329 cases, consisting of 2 053 to 3 844 new cases and 2 930 to 5 485 retreatment cases.

The estimated burden of MDR tuberculosis per Province is provided in Table 14, showing that KwaZulu-Natal and the Eastern Cape are most severely affected by absolute numbers of MDR tuberculosis cases, given the large overall burden of tuberculosis in these two provinces.

HIV status of culture-confirmed tuberculosis patients

HIV results were available for 77.8% of confirmed tuberculosis patients. Table 15 provides univariate analysis of the HIV status of these patients by gender, previous tuberculosis treatment and drug resistance, adjusted by Province. Provincial results are given in Annexure 7. Overall, 55.3% of tuberculosis patients were also infected with HIV, with provincial rates ranging from 28% in the Western Cape to 72% in the Free State. Female patients had significantly higher rates of HIV infection when compared to males (62.2% vs 51.5%, $p < 0.0001$). HIV prevalence was similar between new and retreatment patients (56.6% vs 51.6%, $p = 0.134$).

No differences in HIV prevalence were found between TB patients with drug susceptible disease and those with drug resistance, including MDR ($p = 0.575$) on simple univariate analysis. However, multiple logistic regression analysis (comparing all the different variables at the same time) revealed that previous tuberculosis treatment was a significant risk factor for subsequent drug resistance (any), with an odds ratio (OR) of 2.3 (95CI 1.7 – 3.0 $p < 0.001$). The association of previous treatment with MDR was even more pronounced (OR 4.4; 95 CI 2.8 – 6.9; $p < 0.001$). HIV-positive patients previously treated for tuberculosis tended to have a higher rate of MDR (OR 1.5; 95 CI 1.0 – 2.1; $p = 0.032$). Exploring the association of previous treatment with drug resistance further, two risk factors for MDR were prominent, ie. if the outcome of previous treatment was unfavourable, defined as failure or default (OR 3.7; 95 CI 1.6 – 8.7; $p = 0.004$) and if previous treatment took place in hospital (OR 2.9; 95 CI 1.6 – 5.1; $p < 0.001$).

DISCUSSION

Aside from the drug resistance prevalence estimates, results from the survey provide interesting insights into tuberculosis control in South Africa and highlighted areas for further operational research. Also, for the first time, representative information regarding HIV and tuberculosis became available for the country.

The mean age of patients was 36 years, indicating the impact of HIV on tuberculosis incidence in the country. One in four patients reported previous treatment for tuberculosis, and one in three reported previous hospitalisation for TB, shown to be risk factors for drug resistance.

Case detection rates were very high. On average almost a quarter of suspect cases were smear-positive and more than 30% were found to be culture positive. Over 75% of culture-positive specimens were also found to be positive on microscopy, while grading of the results showed high levels of positivity. Examination of sputum specimens by culture usually identifies between 30% and 50% additional cases.¹¹ In this survey culture examination added about 20%, ranging from 16% in the Western Cape to 28% in Gauteng. On average, only three to four suspects were screened before a case was detected by microscopy or culture. These findings indicate late presentation of tuberculosis cases to the health services (ie. when they are already very ill), too strict screening algorithms being used at clinics and hospitals (ie. too few suspects screened for tuberculosis) or selected screening of suspects taking place (eg. specimens only taken from obviously ill persons). Further studies are necessary to investigate possible reasons for patient delay and to evaluate the application of existing screening algorithms.

Contamination of cultures was a considerable problem and was related to delays between sputum collection and processing in the laboratory. Courier services had to be used during the survey in several rural areas as transport of specimens from the participating centres proved to be a serious problem. The difficulties around specimen transport were particularly widespread in KwaZulu-Natal, Eastern Cape and Limpopo Province and need urgent attention. Also, improved laboratory capacity in almost every province would be essential for future surveys.

Retreatment rates among both tuberculosis suspects and confirmed cases were consistently higher than the rate of 14% reported by the National Tuberculosis Control Programme.¹² On average, a third of survey cases had received previous treatment. Since decisions on the choice of treatment regimen (Category I or II) are based on the treatment history of tuberculosis patients, this finding has serious implications: A considerable proportion of patients seemed to be misclassified by the routine health services and would consequently receive the wrong treatment regimen.

The association between previous tuberculosis treatment and drug resistance has been well documented and was again confirmed by the results from this survey. Drug resistance rates (including MDR) among retreatment patients were double those in new patients. Among retreatment patients those with a previous unfavourable outcome (failed or interrupted) had significantly higher rates of MDR compared to those with a previous favourable outcome

(cured or treatment completed). As previous treatment has been shown to be a risk factor for drug resistance, urgent attention needs to be given to proper interviewing of persons suspected of having tuberculosis at primary health care services. Retreatment cases, including chronics, are the richest source of drug-resistant bacilli in a community.¹³ They are also an important source of infection, since their infectiousness is usually much longer than those of new cases.¹⁴ Thus, settings with a high proportion of retreatment cases are expected to have a higher number of resistant strains circulating in the community and, therefore, higher prevalence of drug resistance among both new and previously treated cases.

Resistance to any tuberculosis drug was detected in strains from one in ten patients, with the majority of patients having single drug (usually isoniazid) resistant strains. Resistance to isoniazid, especially among new tuberculosis patients, is regarded as a sensitive indicator of the overall effectiveness of a treatment programme, as isoniazid has been used for long periods of time in almost all tuberculosis control programmes. In most countries where tuberculosis control is well-advanced, the prevalence of isoniazid resistance among new patients is below 10%.³ In countries with poorly functioning control programmes a different picture has been seen, with rates in excess of 20% being reported.³ In this survey the prevalence of isoniazid was relatively low at around 6% in new patients and 12% in retreatment patients. These observations should, however, not lead to a false sense of security, as the scenario for an increase in drug resistance (including MDR) is already present in every province, given late presentation of cases, high interruption rates¹² and high proportions of previously-treated cases.

An MDR tuberculosis 'hot spot' is defined by WHO as a geographical setting where the prevalence of MDR tuberculosis among new patients exceeds 3%.¹⁵ The national rate in South Africa is currently well below this threshold; however, given the overall burden of tuberculosis in the country, relatively low prevalence rates translate into a high number of at least 6000 MDR tuberculosis cases per year. Mpumalanga Province needs special consideration, showing the highest rates of MDR tuberculosis in the country, an increasing trend following the 1997 survey⁸ and almost reaching the 'hot spot' level of 3% among new patients. In contrast, MDR tuberculosis prevalence rates were the lowest in the Western Cape and showed a stable trend when compared with the 1995 survey,⁷ indicating the benefit of rapidly improving tuberculosis control programme delivery and comprehensive management of MDR tuberculosis patients over many years.

While treatment issues are primarily responsible for the development of tuberculosis drug resistance, patient characteristics (including HIV infection) are believed to influence the dynamics of transmission of drug resistance strains.¹⁵ Although MDR tuberculosis prevalence levels are still relatively low, the escalating HIV epidemic in South Africa may change the situation rapidly if HIV-associated outbreaks occur as they have in many developed countries. Decreasing the number of previously treated cases through high cure rates and low interruption rates among new patients will prevent the escalation of drug resistance (including MDR). Directly observed treatment (DOT) has been shown to be a key factor in achieving high cure rates and maintaining low prevalence of drug resistance. Evidence from both developed and developing countries has shown that the likelihood of drug resistance can be reduced by ensuring patient adherence through direct supervision of treatment. By using

DOT, Botswana has been able to achieve high cure rates of new cases and maintain a low prevalence of drug resistance, even in the presence of an escalating HIV epidemic.¹⁶ Evidence from New York City showed that rates of drug resistance declined dramatically after the implementation of universal DOT, even in a population with a high proportion of intravenous drug users and homeless persons.^{17,18}

The existing burden of MDR tuberculosis in South Africa, together with the scenario for an upsurge in the epidemic as described above, underlines the need for improved DOTS delivery throughout the country in order to stop the generation of MDR tuberculosis. Of great concern is the risk for MDR tuberculosis posed by treatment in hospitals, as defined in this survey, suggesting noncompliance of tertiary-level health care staff with TB CP policies and/or undetected nosocomial transmission of MDR tuberculosis.

Treatment guidelines for MDR tuberculosis patients in South Africa were implemented as national policy in 2001. Preliminary results from the first cohort of MDR tuberculosis patients treated with a standardised regimen indicated high (75%) culture conversion rates, implying potentially high cure rates.¹⁹ However, treatment default after discharge from MDR treatment centres has been identified as a major problem which needs to be addressed immediately. While the clinical importance of treating individual cases of MDR tuberculosis cannot be denied, the public health implication of treating MDR tuberculosis in settings that are unable to guarantee acceptable cure rates (affected by high default rates) is potentially disastrous. Resistance to second-line drugs will emerge rapidly, resulting in an uncontrollable problem with much greater harm than benefit.

HIV and sustainability of the MDR tuberculosis treatment programme will be major determinants of the future course of the MDR tuberculosis epidemic in South Africa, with DOTS delivery most likely to affect the current epidemic. If MDR tuberculosis can be controlled early through effective therapy and new cases prevented through cure of tuberculosis patients the first time around, an HIV-associated MDR-tuberculosis epidemic could be averted. The primary focus should be on containing the current MDR tuberculosis problem and decreasing the prevalence of drug resistance to the lowest possible levels. This will require a systematic five-pronged approach, ie.

- i) Prevention of development of MDR through improved DOTS delivery. This will require close monitoring and confrontation of poor DOTS performance at the earliest opportunity;
- ii) Rational and effective treatment of existing MDR tuberculosis patients under DOTS-Plus, with the emphasis on improved case-holding;
- iii) Expanded HIV counseling and testing, linked to targeted treatment programmes;
- iv) Systematic implementation of appropriate infection control measures in hospitals; and
- v) Continued surveillance of drug resistance to monitor trends.

Surveillance of drug resistance must become a routine part of tuberculosis control in order to follow trends and take immediate action. Surveys need to be repeated at three to five-year intervals, as at least three surveys will be necessary to properly evaluate trends. (A repeat survey in Mpumalanga is required within the next two years in order to make a rapid assessment of the apparently increasing MDR tuberculosis epidemic). Only through sustained

and comprehensive control efforts will the problem of MDR tuberculosis in South Africa be addressed in a timeous and effective manner.

RECOMMENDATIONS

- Reasons for the high proportion of cases detected among tuberculosis suspects should be determined and addressed without delay. Late presentation of tuberculosis patients at primary health care centres, evaluation of health service practices towards screening and diagnostic algorithms, and laboratory capacity and practices should form part of such an investigation;
- Techniques for interviewing persons suspected of having tuberculosis need to be evaluated immediately, in order to address the discrepancies in previous treatment history detected in this survey;
- In order to prevent the development of drug-resistant tuberculosis, DOTS delivery should be urgently improved to achieve cure rates above 80% and interruption rates below 10%. DOTS delivery should be closely monitored and poor performance confronted at the earliest opportunity;
- Hospital policies and procedures for tuberculosis treatment delivery should be evaluated as a matter of urgency and appropriate measures taken to ensure compliance with TBCP policies. Infection control should be addressed as a priority.
- Treatment for MDR tuberculosis patients should be made available to all cases detected and every attempt made to ensure case-holding. Sound tuberculosis control should underline the implementation of MDR treatment to prevent amplification of resistance to the second-line drugs;
- Surveillance of drug resistance should continue and become part of routine tuberculosis control activities. Longitudinal data on drug resistance will provide valuable information on trends and assist with resource planning and allocation. Surveys should be carried out every three to five years, with the follow-up survey in Mpumalanga to be done within the next two years.

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