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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.<sup>1</sup> Resistant bacilli are known to emerge more rapidly in the setting of erratic treatment<sup>2</sup> 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.<sup>3</sup> 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.<sup>3</sup> 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.<sup>2,3</sup> 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.<sup>3</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>4</sup> In addition, laboratory techniques, criteria for defining drug resistance and patient interview procedures need to be standardised and strictly adhered to.<sup>4</sup>

As decisions on treatment regimens and control programme management are made by the national tuberculosis control programme (TBCP) in South Africa, 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 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:<sup>4</sup>

- 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 organised by 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 1994. The MRC has also been responsible for drug resistance surveillance in tuberculosis hospitals in South Africa between 1965 and 1995.<sup>5,6</sup> 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 Cape<sup>7</sup> and one in Mpumalanga Province.<sup>8</sup> 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 over the last two years. 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.

This report reflects the final results for Mpumalanga.

## **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.<sup>4</sup>

### 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.<sup>4</sup> The eventual decision in all provinces was to use a cluster design approach, particularly to avoid the risk of missing large diagnostic centers. 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 centers (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 was 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 centers for MDR tuberculosis were excluded to avoid over-estimation of resistance prevalence.

The sample size in each province had to be 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 within 48 hours, 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.<sup>9</sup> 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.<sup>9</sup>

Drug susceptibility tests were done according to the indirect proportion method.<sup>9</sup> Resistance against isoniazid, rifampicin, streptomycin and ethambutol were 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 in the questionnaire was to be assessed by re-interview of a 10% sample of patients in each province, randomly selected from the participating centers;
- 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 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.

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 (UP Department of 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 Virology, 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 only 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 TB 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 in Mpumalanga started in September 2000 and patient intake was completed in April 2002.

### **Response rate**

The sample of diagnostic centres selected in Mpumalanga is presented in Annexure 3 and the response rate by District is provided in Table 1. The provincial target of 762 patients was reached, with 11 Districts contributing or exceeding the required number of patients. Two Districts contributed less than half of the required number of patients, while two Districts contributed less than 30% of the required target.

### **Treatment history (suspects)**

Table 2 indicates the treatment history of persons suspected of having tuberculosis. 67.3% of suspects had no history of previous treatment (range 26.6% to 84.2%) while 20.8% indicated that they had received treatment for tuberculosis for one month or more (range 10.4% to 56.3%). For 11.9% of suspects (range 0.0% to 63.0%) 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. A total of 2 761 specimens were received, from which 2 739 (99.2%) smears and 2 454 (88.9%) cultures were successfully processed.

For the province as a whole, 32.2% of specimens were found to be positive by microscopy (range 10.5% to 75.5%). Positive cultures were obtained from 40.0% of specimens (range 12.5% to 79.7%). High contamination rates (overall 11.1%) were demonstrated, which means that the gain in case finding by culture was difficult to determine accurately.

Assuming that unreadable smears and contaminated cultures followed a similar distribution into either a positive or negative category as those for which results were available, 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 3.11 suspects screened. Case detection by culture was slightly higher, with one culture positive case detected among every 2.50 suspect cases.

## **Demographic profile of culture-confirmed tuberculosis patients**

Table 4 provides the demographic profile of tuberculosis-confirmed patients (n = 877). 65.5% were male and 34.5% were female. Information on age was missing for 1.1% of patients. The mean age of patients was 34.8 yrs (SD 12.2; range 9 - 82 yrs), with 80.7% of patients being younger than 45 yrs. Information on previous treatment was available for 97.9% of patients. 77.9% indicated no history of previous treatment while 20.0% reported that they had been treated for tuberculosis before, a very similar finding to the treatment history recorded among suspects. Among the retreatment patients, 24.6% had previously interrupted treatment, while 49.7% were recurrent cases, having successfully completed treatment before. 57.5% of the recurrent cases had documented proof of previous cure. On the issue of incarceration, information was missing for 3.4% of patients while 11.0% of patients had been or were in prison at the time of sputum collection.

## **Bacteriology results**

Complete bacteriology results for all suspect specimens (n = 2 761) are provided in Table 5. Microscopy results were negative in 67.3% of specimens, positive in 31.9% of specimens and smears were not readable in 0.8%. Cultures were negative in 53.4% of specimens. *M. tuberculosis* was confirmed in 877 (31.8%) specimens, mycobacteria other than tubercle bacilli (MOTT) in 11 (0.4%) specimens and identification of the specific species of *Mycobacterium* was not possible for 93 (3.4%) cultures as a result of the subsequent culture being contaminated or failing to grow. A total of 307 (11.1%) cultures were lost due to contamination. Patients who had 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 = 877). 78.3% of the smears were positive. 90.4% of these were regarded as highly positive, indicated by a grading of 1+ to 3+, with 44.3% having a 3+ result. Similar

results were evident with regard to culture growth, with 78.2% of specimens showing growth of 1+ or more and 69.4% showing 3+ to 4+ growth.

A comparison between microscopy and culture results is provided in Table 7. A high proportion (77.7%) of culture-confirmed specimens were also smear-positive, indicating a gain of 22.3% in additional cases detected by culture.

### **Drug resistance results**

Table 8 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 9.4% (66/702) cultures from new patients and in 23.4% cultures (41/175) from retreatment patients, confirming the association between previous treatment for tuberculosis and drug resistance ( $p < 0.0001$ ). 39 (5.6%) cultures from new patients had strains resistant to one drug only and two (0.3%) patients had four-drug resistant strains. In retreatment cases 12 (6.9%) patients had single drug resistant strains and 12 (6.9%) patients had four-drug resistant strains.

Specific drug resistance profiles are provided in Table 9. Strains with resistance to isoniazid was detected in 7.0 % of new patients and in 18.9% of patients with a previous history of tuberculosis treatment, with mono-resistance present in 3.1% (new) and 2.3% (retreatment) patients respectively. Rifampicin resistance was found in 3.1% of new and 16.0% of retreatment patient cultures, with mono-resistance detected in 0.6% (new) and 2.3% (retreatment) of strains respectively. Ethambutol resistance was low at 1.0% in new patients and high at 9.1% in previously-treated patients, with no mono-resistance found. Strains with resistance to streptomycin were detected in 4.1% of new and 14.3% of retreatment patients, and 1.9% of new patients and 2.3% of retreatment patients had mono-resistance. MDR tuberculosis levels were high at 2.6% in new patients and 13.7% in patients with a prior history of tuberculosis treatment. Of the 18 MDR tuberculosis strains found in new patients, six was resistant to isoniazid and rifampicin only, four strains had associated ethambutol resistance, six strains were also resistant to streptomycin and two strains were resistant to all four drugs. Of the 24 MDR tuberculosis patients with a previous history of tuberculosis treatment, six had strains with resistance to isoniazid and rifampicin, two had associated ethambutol resistance, four were also resistant to streptomycin, and 12 strains were resistant to all four drugs.

Table 10 indicates drug resistance (any and MDR) detected among the different categories of retreatment patients. In general, patients with a previously unfavourable outcome (failed or interrupted) are at increased risk for development of drug resistance when compared to patients with a previously favourable outcome (cure and treatment completed). In this study, drug resistance (any) was detected in 29.4% of patients with unfavourable previous outcome (failure or interruption), compared to 21.8% of patients with a favourable previous outcome (cured or treatment completed). This difference was not statistically significant ( $p = 0.328$ ), probably due to low numbers. MDR showed a similar distribution: 17.7% of patients with an unfavourable outcome had MDR strains, compared to 11.5% of patients with a favourable outcome ( $p = 0.308$ ). High drug resistance levels were detected among patients who had

previously interrupted treatment: 32.6% of these cases had (any) drug resistance and 18.6% had MDR tuberculosis.

Table 11 provides estimates of the total burden of MDR tuberculosis cases in Mpumalanga in 2001. This was derived from MRC estimates on the total provincial tuberculosis caseload for 2001 and the MDR tuberculosis prevalence estimates from this survey. Applying the assumptions from the MRC model of HIV-associated tuberculosis in South Africa<sup>10</sup> to Mpumalanga 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 MDR tuberculosis caseload for Mpumalanga in 2001 was subsequently estimated to be between 484 and 906 cases, consisting of 209 - 391 new patients and 275 - 515 retreatment patients.

#### **HIV status of culture-confirmed tuberculosis patients**

HIV results were available for 74.7% of culture-confirmed tuberculosis patients. Table 12 provides the HIV status of these patients by gender, previous tuberculosis treatment and drug resistance. In Mpumalanga, 67.2% of tuberculosis patients were also infected with HIV. Female patients had slightly higher rates of HIV infection when compared to males (70.7% vs 65.3%), but this difference was not statistically significant ( $p = 0.169$ ). HIV prevalence was similar between new and retreatment patients at 68.3% and 66.3% respectively ( $p = 0.680$ ). Prevalence of HIV infection also did not differ between patients with fully susceptible strains and those with drug resistance, including MDR ( $p = 0.494$ ).

## **DISCUSSION**

Aside from the drug resistance prevalence estimates, results of this survey provided interesting insights into tuberculosis control in Mpumalanga and highlighted areas for further operational research. Also, for the first time, representative information regarding HIV and tuberculosis became available for the province.

Two-thirds of tuberculosis patients detected during the survey were male, while more than 50% of patients were younger than 35 years, indicating the impact of HIV on tuberculosis incidence in the province. One in five patients reported previous treatment for tuberculosis and one in ten patients had a history of having been in prison, known risk factors for drug resistance. History of previous tuberculosis determines the choice of appropriate treatment regimens (Category I for new cases and Category II for retreatment cases). In several Districts this information was not recorded for persons suspected of having tuberculosis, which means that incorrect regimens could have been administered. Districts where this was a notable problem include Shongwe (63.0%), Eerstehoek (19.9%) and Bethal (14.7%), a situation which needs immediate corrective action.

Case detection rates were very high. More than a third of suspect cases were smear and/or-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.<sup>11</sup> In this survey culture examination added about 22%. On average, only two to three 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. Ermelo District needs particular attention, as 80% of specimens from suspects were positive on culture and 76% were positive on microscopy. These figures are highly suspect and probably indicate selective screening for tuberculosis of persons presenting to the health service.

Retreatment rates among both tuberculosis suspects and confirmed cases were consistently higher than the rate of 11.9% reported by the provincial Tuberculosis Control Programme.<sup>12</sup> On average about 20% of both suspects and tuberculosis cases were found to have received previous treatment, but rates exceeding 28% were noted in four Districts (eg. Barberton, Volksrust, Mmamethlake and Kwamhlanga). Kwamhlanga District was of particular concern, with 56% of suspects providing a history of previous tuberculosis treatment. On the other hand, in Shongwe District the retreatment rate was found to be around 10%. Since decisions on the choice of treatment regimen (Category I or II) are based on the treatment history of tuberculosis patients, these findings have serious implications: A considerable proportion of patients seemed to be misclassified by the routine health services and would consequently receive the wrong treatment regimen. Urgent attention needs therefore to be given to proper interviewing of persons suspected of having tuberculosis at the primary health care services.

Resistance to any tuberculosis drug was detected in strains from one in ten new patients and one in four retreatment patients, with the majority 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%.<sup>3</sup> In countries with poorly functioning control programmes a different picture has been seen, with rates in excess of 20% being reported.<sup>3</sup> In this survey the prevalence of isoniazid was around 7% in new patients and around 20% in retreatment patients. MDR tuberculosis prevalence rates were the highest recorded in the country, with significant increases from the rates recorded in the 1997 survey.<sup>8</sup> Of added concern was the finding that 50% of retreatment MDR tuberculosis patients had strains with four-drug resistance, which would significantly lessen their chance for cure on MDR tuberculosis treatment regimens.

Findings from this survey suggest a very likely scenario for an increase in drug-resistance (including MDR), given late presentation of cases, high interruption rates (>14%)<sup>12</sup> and a high proportion of previously-treated cases. Retreatment cases, including chronics, are the richest

source of drug-resistant bacilli in a community.<sup>13</sup> They are also an important source of infection, since their infectiousness is usually much longer than those of new cases.<sup>14</sup> 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.

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 significantly higher (at least three times) compared to new patients. Of particular concern was the high rates of drug resistance (including MDR) among patients who had previously interrupted treatment, with one in three patients having had any resistance and one in five having had MDR.

An MDR tuberculosis 'hot spot' is defined by WHO as a geographical setting where the prevalence of MDR tuberculosis among new patients exceed 3%.<sup>15</sup> The rate in Mpumalanga is currently approaching this threshold, while the rate among previously-treated patients are the highest ever recorded in South Africa. In addition, given the overall burden of tuberculosis in the province, these prevalence rates translate into a high number (total between 484 – 906) of expected MDR tuberculosis cases per year. The existing burden, together with the scenario for an upsurge of MDR tuberculosis described above, underlines the importance of rapidly expanding and strengthening DOTS implementation throughout the province in order to stop further MDR tuberculosis generation.

Results from this survey confirmed a high prevalence of HIV among tuberculosis patients. More than two thirds of patients were co-infected with HIV, with the rate among female patients being slightly higher. Data from this survey also confirmed international findings<sup>3</sup> that HIV infection is not an independent risk factor for drug resistance nor for MDR-tuberculosis, indicating that HIV-infected tuberculosis patients are not more likely to develop drug resistance than HIV-negative tuberculosis patients. Nevertheless, when tuberculosis patients are not adequately treated, levels of acquired resistance are elevated and co-infection with HIV could be responsible for the rapid spread of primary drug resistant tuberculosis (including MDR).

Lastly, the escalating HIV epidemic in Mpumalanga may worsen the existing problem of MDR tuberculosis rapidly if HIV-associated outbreaks occur as they have in many developed countries. The primary objective should therefore be to contain the current MDR tuberculosis problem and decrease resistance to the lowest possible level. This will require a four-pronged approach, ie. a) achieving and maintaining high cure rates among first-time tuberculosis cases; b) accelerated voluntary counseling and testing programmes for HIV; c) rational and effective treatment of existing MDR tuberculosis cases; and d) continued surveillance of drug resistance.

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.<sup>16</sup> 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.<sup>17,18</sup>

Treatment guidelines for MDR tuberculosis patients in South Africa were implemented as national policy in 2000. Preliminary results from the first cohort of MDR tuberculosis patients treated with a standardised regimen indicated high (78%) culture conversion rates, implying potentially high cure rates.<sup>19</sup> However, treatment interruption 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 interruption rates) is potentially disastrous. Resistance to second-line drugs will emerge rapidly, resulting in an uncontrollable problem with much greater harm than benefit.

Together with rapid DOTS expansion and effective treatment of existing MDR tuberculosis cases, 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. Only through sustained and comprehensive control efforts will the problem of MDR tuberculosis in Mpumalanga as South Africa's first hot spot be addressed in a timely 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 centers, 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 further development of drug resistant tuberculosis, the DOTS strategy should be urgently expanded 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;
- 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 the rapid emergence 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. The next survey should be carried out within two years to rapidly assess the trend in MDR tuberculosis in the province.

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