



Tuberculosis

Despite sustained progress in control since the formulation of new policy guidelines in 1996, tuberculosis still remains a major public health threat in South Africa. The effects of the rapidly growing concurrent HIV epidemic further compound the prominence of the tuberculosis epidemic and the proportion of TB patients co-infected with HIV is increasing. There is an urgent need to hasten the integrated management of these two epidemics.

The promotion of voluntary counselling and testing (VCT) for HIV in TB treatment centres, provision of materials for advocacy and health education for TB/HIV/AIDS as well as the development of training and management guidelines for dually infected patients will go a long way towards achieving this goal.

The introduction of combination anti-TB drugs during 1999 will assist in improving adherence to treatment as well as reduce the occurrence of drug resistant strains of tuberculosis. However, in order to achieve this, there is need to further the progress already made in delivering directly observed supervised treatment to TB patients, particularly within the context of community-based care.

Improvement within the computerised recording and reporting system to make it simpler and uniform for all the provinces will further assist in more accurate documentation of the tuberculosis burden in the country and lead to targeted interventions where necessary.

The National Tuberculosis Control Programme hopes to achieve its objective of reducing the tuberculosis burden in the country through increased collaboration with other role players at local and regional levels as will be discussed in this report.

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Introduction

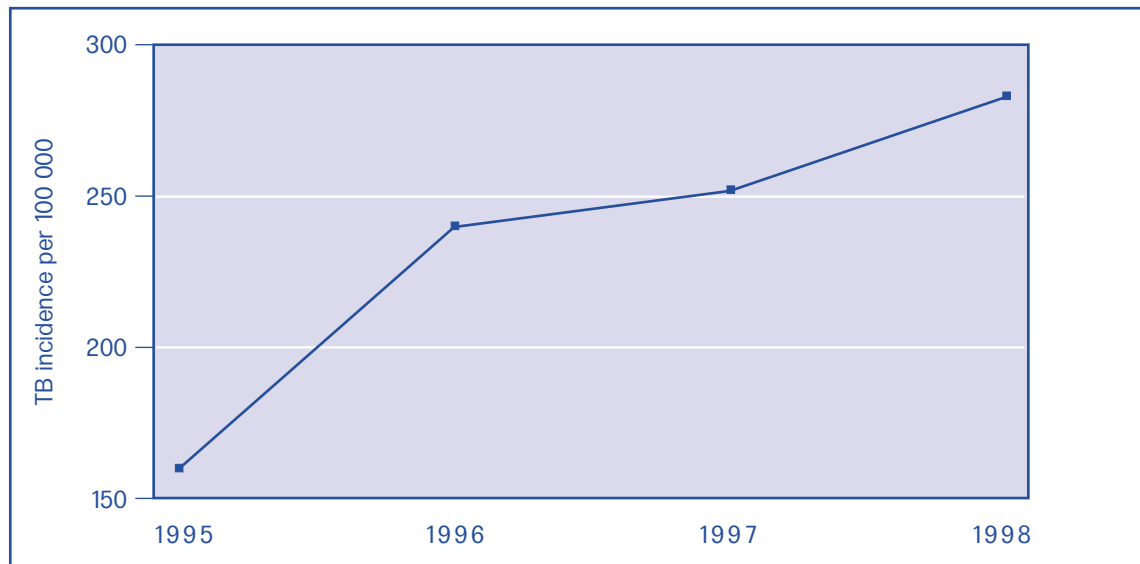
Tuberculosis is still a major global health problem today despite the fact that effective treatment has now been available for over 50 years.¹ The disease accounts for 7% of global deaths annually and more than one in four preventable deaths in developing countries.²

Four of the countries with the highest global tuberculosis incidence rates are in the Southern Africa Development Community (SADC) region, and South Africa is one of them.³ According to the World Health Organisation, South Africa remains one of the 22 countries worst affected by the tuberculosis epidemic.⁴ This year, the country is expected to contribute at least 15% of the total tuberculosis caseload for Africa⁵ yet it accounts for only about 7% of the continent's total population.

Here, as in many other countries in the sub-Saharan Africa region, the epidemic is compounded by the effects of the rapidly growing spread of HIV infection. Currently, it is estimated that South Africa has a TB/HIV co-infection rate of 2 540 per 100 000 and a tuberculosis case fatality rate (death from tuberculosis) of 166 per 100 000, a rate which is not only five times higher than the global TB fatality average of 32 per 100 000, but is second only to Zimbabwe's world wide.⁵

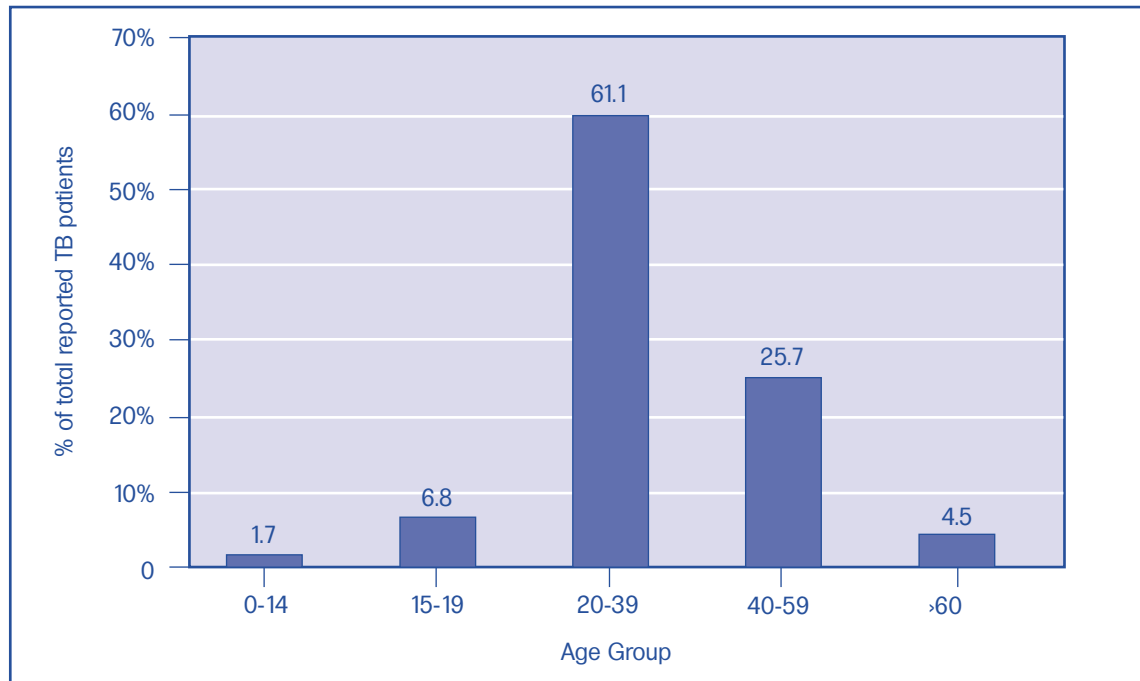
The incidence of tuberculosis, based on figures from national TB quarterly reports, has been rising over the last five years as is illustrated in Figure 1.

Figure 1: Reported incidence of tuberculosis in South Africa 1995 – 1998



Source: Department of Health, Health Systems Research Co-ordination and Epidemiology Directorate, June 2000

Tuberculosis in South Africa mainly affects the economically active age group as is graphically represented in Figure 2, where 86.6% of the TB patients reported in 1999 are in the age group of 20-59 years. This distribution could have ominous economic implications since HIV infection, the most important factor responsible for the progression of latent tuberculosis to active disease, also affects this broad age group most heavily.

Figure 2: Age distribution of TB patients reported in South Africa in 1999

Source: Department of Health, Health Systems Research Co-ordination and Epidemiology Directorate, June 2000

Considerable progress has been made in tuberculosis control efforts in South Africa in the past twelve months. This chapter seeks to highlight trends in tuberculosis control in the country over the past five years with particular emphasis on progress that has been achieved in the past year. Constraints still facing tuberculosis control are discussed and finally recommendations for further action are made.

Focus on progress

Tuberculosis control in the country has undergone major progress during the last year notably in the following areas:

- ◆ Increased case finding
- ◆ Improved bacteriological coverage
- ◆ Further integration of TB/HIV management
- ◆ Expansion in DOTS coverage
- ◆ Further introduction of combination anti-TB drugs
- ◆ Strengthening of partnerships and collaboration both nationally and internationally

Progress is discussed for the above mentioned areas and constraints to progress cited whenever possible. The data presented in the sections below are collated mainly from annual statistics on the tuberculosis epidemic collected by the Department of Health Communicable Disease Control Directorate as well as from projections by the Medical Research Council National Tuberculosis Research Programme.

The National Tuberculosis Control Programme (NTCP) is responsible for co-ordinating the fight against the tuberculosis epidemic in the country. Highlighted below are the short and long term objectives contained in the NTCP strategic plan.⁶

Objectives of the National Tuberculosis Control Programme

- ❖ To achieve sputum smear conversion rates of at least 85% among new sputum smear positive patients and 80% among re-treatment cases at the end of the intensive phase of treatment
- ❖ To cure at least 85% of new smear positive cases with short course chemotherapy anti-TB drugs
- ❖ To ensure accurate measurement and evaluation of programme performance
- ❖ To prevent the development of drug resistance to tuberculosis
- ❖ To reduce mortality and morbidity attributable to tuberculosis in South Africa.

Progress in tuberculosis control discussed in the sections below is evaluated with the above objectives in mind.

Case finding and reporting

Reporting rates continue to be a major impediment to accurate estimation of the tuberculosis epidemic in the country. Consistent under-reporting to the NTCP as evidenced in the trends for 1995-2000 given in Table 1 below results in an under estimation of the national tuberculosis burden.

Under-reporting is mainly due to the following reasons:

- ❖ Delays in the development of functional health districts for the whole country
- ❖ Delays in collecting and collating data from primary health care units where treatment of patients normally takes place, through to the district, provincial and finally national levels often results in fewer reports being sent to the NTCP than the expected 1 628 from all the provinces for each national quarterly report
- ❖ Poor communication between provincial and local authorities in some provinces
- ❖ Differences in the computerised information collecting systems at provincial level result in some data not being easily interpretable and comparable at national level^a
- ❖ TB registers at primary health care level are not always up-to-date in terms of actual numbers of patients on treatment. This is often a result of an excessive number of patients seen at some facilities compounded by relative understaffing experienced in the TB care delivery sections at many of these facilities. Furthermore, at some facilities there is a failure of clinic staff to realise that proper and timely completion of all sections of the TB register is a very important management tool rather than simply another administrative burden.

The figures provided in Table 1 below should therefore be interpreted with the above constraints in mind.

^a H Chabalala, Health Systems Research Co-ordination and Epidemiology Directorate, Personal Communication

Table 1: Reporting completeness for South Africa (1995-2000)

Year	% Reporting facilities	Actual cases of TB reported	Expected cases (assuming 100% reporting rate)
1995	45.3	73 917	164 260
1996	68.0	109 328	160 776
1997	62.7	118 741	188 478
1998	71.6	135 904	188 756
1999	37.0 ^b	87 566	236 665
2000	N/A	N/A	273 635 ^c

N/A = not available

Source: Department of Health, Health Systems Research Co-ordination and Epidemiology Directorate, June 2000

Reporting completeness to the Department of Health has improved considerably over the past five years (see Table 1 above). However, the low reporting rate for 1999 illustrates some of the problems facing reporting to the NTCP as discussed above. Only 37% of reports had been received at the NTCP at the time of writing, ostensibly due to some of the problems noted above.

The high number of projected cases for the year 2000 (273 635) further indicates that the tuberculosis burden for South Africa is actually higher than that calculated using TB register data available to the Department of Health, from provincial quarterly reports.

A further indication of the impact of under-reporting on the estimate of the tuberculosis incidence rate in South Africa is given in the Global Burden of Tuberculosis Report.³

This report calculated an incidence rate of 392 cases per 100 000 for 1997 in South Africa compared to that of 252 cases per 100 000 calculated for the same year from registered cases reported to the NTCP. This discrepancy results from the fact that the Global Burden of Tuberculosis report took into account under-reporting and employed statistical procedures to correct this.

In the same vein, the projected tuberculosis case load for the year 2000 results in an estimated incidence rate in excess of 600 cases per 100 000,⁵ which is well beyond that of 254 cases per 100 000 based on actual registration data for the period 1996-98.⁷

This figure may well be an over estimate but is probably nearer to the true incidence rate for South Africa if under-reporting is taken into account.

In order to counter this problem, the NTCP is currently piloting a new TB electronic register system developed through the Botswana-USA collaboration programme (BOTUSA) in four provinces in the country.

^b Reporting completeness from figures available from the NTCP as of 30/6/00

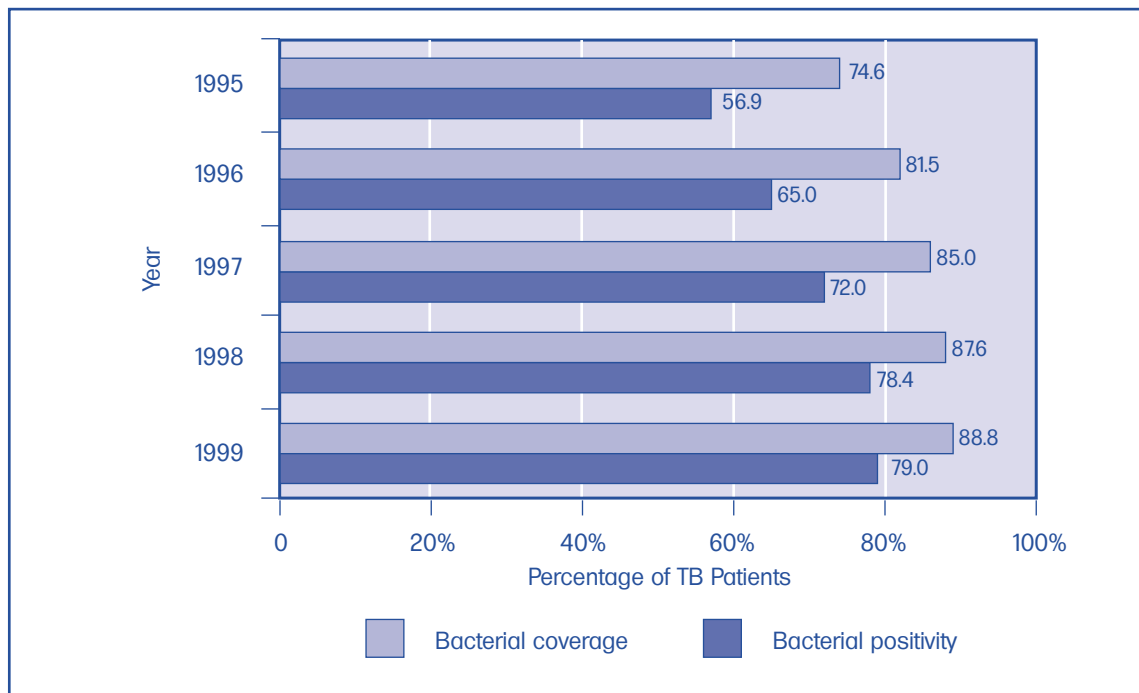
^c Estimated caseload assuming a 100% reporting rate (TB Research Programme, MRC Pretoria)

This Epi-Info based system is cheap, patient-centred, user friendly and employs a three-level (clinic, district and provincial/national) structure. It requires no prior knowledge of Epi-Info and needs minimal training to learn; furthermore this system can automatically generate case finding and treatment outcome reports for any of the levels noted above. Introducing this data collection system in all provinces will not only ensure uniformity of reporting but also will enable feedback to individual clinics which could have a positive motivational effect on primary health care givers who rarely get access to aggregated National reports.

Bacteriological Coverage^d and Bacteriological Positivity^e of registered TB patients

Trends for these measures are shown in Figure 3 (national trend; 1995-99) and Table 2 (provincial figures; 1998-99).

Figure 3: Bacteriological Coverage and Positivity for new TB patients reported in South Africa 1995 - 1999



Source: Department of Health, Health Systems Research Co-ordination and Epidemiology Directorate, June 2000

^d Bacteriological Coverage measures the percentage of pulmonary tuberculosis patients on whom bacteriological investigation was requested at diagnosis.

^e Bacteriological Positivity refers to the percentage of all registered patients with pulmonary tuberculosis who had a positive smear or culture-positive bacteriological result at diagnosis.

Table 2: Bacteriological Coverage and Positivity per Province 1998 –1999

Province	Bacteriological coverage (%)		Bacteriological positivity (%)	
	1998	1999	1998	1999
Eastern Cape	88.9	N/A	88.2	N/A
Free State	76.9	85.0	68.3	74.0
Gauteng	89.9	93.0	82.4	88.0
KwaZulu-Natal	81.9	81.0	65.2	65.0
Mpumalanga	94.7	97.0	82.3	88.0
Northern Cape	81.8	93.0	69.6	73.0
Northern Province	90.7	90.0	73.8	76.0
North West	81.4	84.0	76.4	78.0
Western Cape	97.2	98.0	91.8	93.0

N/A = not available

Source: Department of Health, Health Systems Research Co-ordination and Epidemiology Directorate, June 2000

Figure 3 and Table 2 above, show that both Bacteriological Coverage and Positivity have increased over the past 5 years, with provinces like Mpumalanga and the Western Cape currently achieving bacteriological coverage rates of 97% and 98% respectively.

This indicates that a higher number of sputum smear positive patients are being identified. This achievement is consistent with the principles of the Directly Observed Treatment – Short course (DOTS) strategy, which aims at proper identification and treatment of sputum smear positive patients who provide the infectious pool from which tuberculosis spreads. Correct identification and cure of these cases using DOTS will eventually lead to a reduction in the tuberculosis burden of South Africa.

It is worth noting however, that Bacteriological Positivity is extremely high in most of the provinces, being higher than the 60-70% expected from a well functioning tuberculosis control programme. In programmes that exceed this expected figure it means that either: many of the TB patients are presenting late to the health services for diagnosis (and hence infecting many of their contacts before they start treatment), or that the tuberculosis screening algorithm for a positive smear result before treatment, as outlined in the NTCP Practical guidelines⁶ is being applied too stringently at clinic level and many of the sputum smear negative patients are being missed.

With the HIV epidemic now well established in South Africa, this could mean that a significant number of dually infected patients are actually not receiving anti-tuberculosis treatment since HIV infection is known to be commonly associated with sputum smear negative tuberculosis.

Tuberculosis and the HIV/AIDS epidemic in South Africa

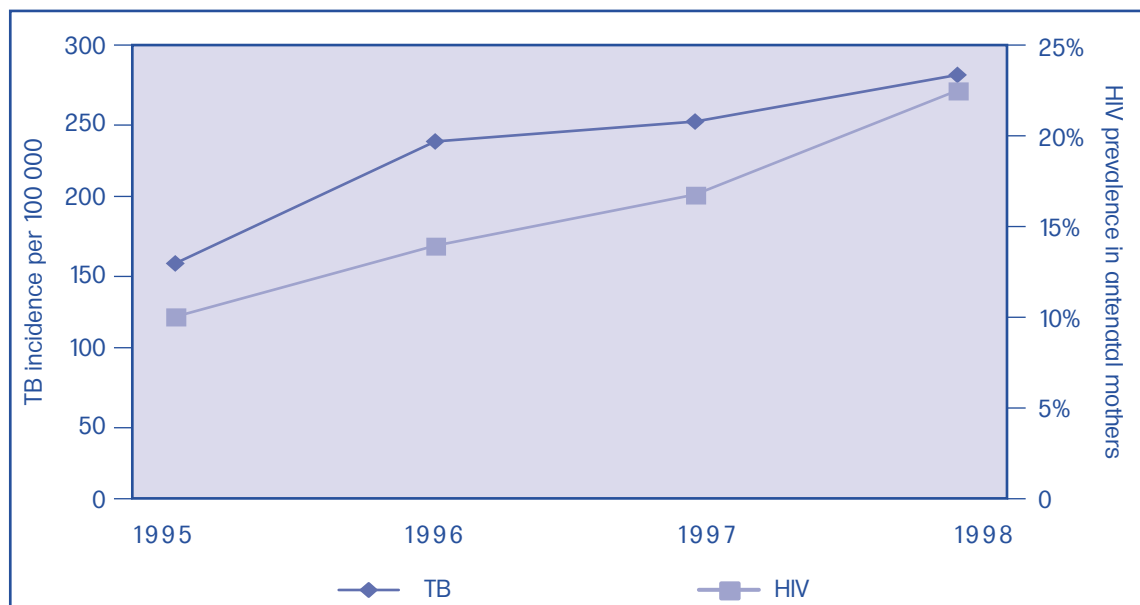
HIV infection, if it remains uncontrolled, has the potential to swamp progress made in tuberculosis control as it is the most important risk factor for the progression from latent to active disease in people infected with the tubercle bacillus.

Tuberculosis reporting rates have significantly increased in the last five years as indicated in Table 1. This increase, though partly attributable to improvements in reporting and case finding over the same period of time, is also a result of the effect of the burgeoning HIV epidemic concurrently ravaging the country.

This synergy between a disease of antiquity and a newer pathogen has resulted in up to 40% of tuberculosis patients in South Africa being co-infected with HIV.⁶ HIV affected individuals have a 30 times higher probability of acquiring tuberculosis than non-HIV infected people. The Medical Research Council estimates that this year, HIV co-infection will lead to an excess 123 616 new cases of tuberculosis which would otherwise not have occurred. This will contribute 42% of the expected caseload for the year.⁵

The increase in HIV prevalence in the country as measured from sentinel surveys of women attending antenatal care, over the period 1995 – 1998 (Figure 4) closely parallels the increase in incidence of tuberculosis.

Figure 4: Tuberculosis incidence vs HIV prevalence in South Africa 1995-98⁸



The prevalence of HIV infection among TB patients varies according to province as indicated in Table 3; which gives the proportion of TB patients who are expected to be HIV co-infected, per province for the year 2000. As shown, KwaZulu-Natal and Mpumalanga provinces are the worst affected. This can directly have an impact on the treatment outcomes for the TB patients as is graphically demonstrated in Figure 5.

Table 3: Estimated tuberculosis caseloads per province and proportion expected to be HIV co-infected in 2000

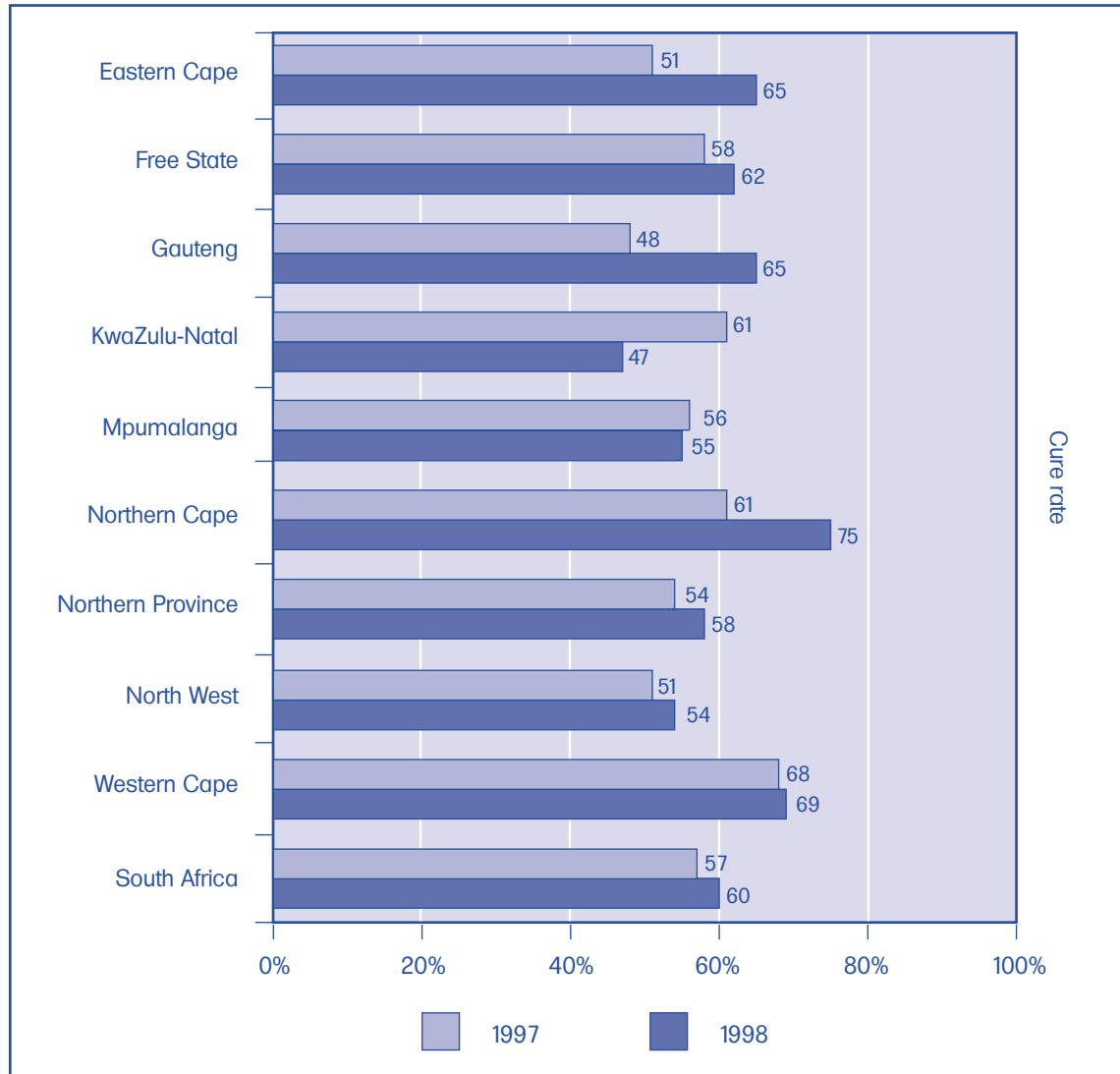
Province	Total TB cases	Proportion HIV positive(%)
Eastern Cape	56 495	40.0
Free State	14 654	51.7
Gauteng	45 598	44.8
KwaZulu-Natal	65 695	64.6
Mpumalanga	15 657	59.1
Northern Cape	4 649	33.2
Northern Province	23 338	36.3
North West	15 549	45.5
Western Cape	34 211	31.6
South Africa	273 365	47.6

Source: Medical Research Council, National Tuberculosis Research Programme

Cure rates

Despite the constraints posed by the HIV epidemic, cure rates for new sputum smear positive TB patients have generally improved (see Figure 5 below). Treatment outcomes for tuberculosis patients registered in any particular year are evaluated one year later, hence the 1997/98 cure rates presented below are the most current complete figures available.

Figure 5: Reported cure rates for new TB patients per province, 1997 and 1998



Source: Department of Health, Health Systems Research Co-ordination and Epidemiology Directorate, June 2000

It is worth noting that those provinces that show a decline in cure rates (Kwazulu-Natal from 61% in 1997 to 47% in 1998 and Mpumalanga from 56% in 1997 to 55% in 1998) also have the highest proportion of HIV infected TB patients (64.4% and 59.1% respectively) as shown by Table 3.

The decline in cure rates as noted above cannot be directly and wholly attributed to the impact of the HIV epidemic. Rather the death rate of TB patients where contributory factors to the cause of death are stated is a more accurate indicator. However, this information is not easily obtainable from registration data as HIV is not routinely tested for in TB patients.

However, one explanation for the decline in cure rates is that more patients are dying from HIV related infections before completion of anti-TB treatment in these provinces. This is an ominous indication that the HIV epidemic has the potential to wipe out progress made in tuberculosis control in provinces like Mpumalanga since 1996.

If the current trends of the impact of HIV on the tuberculosis epidemic in South Africa continue, it is likely that in the next decade an even higher proportion of tuberculosis patients will also be HIV infected. In recognition of this threat, all provincial health departments in the country have agreed to promote the management of TB and HIV as a joint epidemic.

Four TB/HIV integrated management pilot sites were established in the country during 1999. These are sited as follows:

- ◆ Eastern Cape – East London
- ◆ KwaZulu-Natal – Ugu South in Port Shepstone
- ◆ Northern Province – Bushbuck Ridge
- ◆ Western Cape – Langa Central district

These projects seek for best practice in the management of dually infected patients. The goal of the NTCP and the STD/HIV/AIDS Directorate is to increase the availability of voluntary counselling and testing (VCT) services for HIV at tuberculosis treatment points in the country.

Expansion in DOTS coverage

The South African Tuberculosis Control Programme aims to reduce the TB burden in the country through the provision of supervised anti-TB treatment to all patients. This objective at provincial level is being achieved through the establishment of Demonstration and Training Districts (DTDs) to assist health workers with the implementation of the DOTS strategy.

The number of (DTDs) in the country increased from 63 at the end of 1998 to 130 as of July 2000 (see Table 4 below). 84% of the districts in the country now have clinics offering tuberculosis treatment to patients based on the principles of the DOTS strategy.

Sputum smear conversion rates in one-third of these DTDs are greater than 80%. This has resulted in more patients being cured, further reducing the infectious pool as well as preventing the development of drug resistant tuberculosis strains.

At this pace of DOTS expansion, (up from 36% in 1998 to 84% by July 2000) the goal of the National Tuberculosis Control Programme to have the whole country covered with DOTS and at least half the districts achieving sputum smear conversion rates of greater than 80% by the end of 2001, is likely to be achieved.

It is of importance to note however, that the most accurate way of assessing DOTS coverage should be in terms of actual patient numbers receiving supervised anti-TB medication and not the number of DTDs. Usage of only DTD coverage data may give a rather skewed picture as many of these training districts have only a very small number of clinics actually practising DOTS and hence small patient numbers. This could result in little or no epidemiological impact on the overall tuberculosis situation for the country. Unfortunately, it is not possible at present to obtain an accurate estimate of the number of patients actually getting directly supervised anti-TB treatment as this information is not routinely recorded in the TB registers at clinic level.

Table 4: Number of Demonstration and Training Districts per province, July 2000

	No. of Districts ^f	No. of DTDs
Eastern Cape	21	19
Free State	14	12
Gauteng	25	19
KwaZulu-Natal	11	6
Mpumalanga	16	12
Northern Cape	5	5
Northern Province	19	14
North West	18	18
Western Cape	25	25
South Africa	154	130

Source: Department of Health, National Tuberculosis Control Programme, July 2000

Introduction of combination drugs

There was a further drive towards the introduction and increased availability of combination drugs for the treatment of tuberculosis during 1999. Combination drugs though more expensive than single drug preparations greatly simplify treatment regimens and reduce the daily number of tablets a patient has to take at clinic level. They also ease ordering and stock control at district level.

Reducing the number of tablets a TB patient has to swallow may have a positive impact on compliance and hence improve cure rates and reduce the need for re-treatment. More importantly, combination drugs also reduce the likelihood of development of multi-drug resistant strains of tuberculosis, which are up to 100 times more expensive to treat than drug sensitive tuberculosis.

In the long term therefore, these drugs will prove more cost-effective than single drug preparations and should be advocated for all TB patients by the National Tuberculosis Control Programme.

Bulk procurement of anti-TB drugs through the Southern Africa Tuberculosis Control Initiative (SATCI) has been proposed. This will result in effective drugs being bought at more affordable prices from international manufacturers hence reducing expenditure as well as leading to a better procurement practise for SADC countries.

The challenge for the NTCP now, is to standardise the drug combinations available so as to avoid having too many different preparations and strengths, which may serve to further confuse health care providers and TB patients.

^f The number of health districts has decreased from 174 in 1998 to 154 currently

TB/HIV collaborative programme – strengthening local and international partnerships

South Africa under the auspices of SATCI has joined efforts initiated by the Africa regional office (AFRO) of the World Health Organisation and the UNAIDS inter-country office in moving towards a regional integrated framework for the recognition and management of tuberculosis and HIV as a joint epidemic. Areas cited for integration in the management of these two epidemics include: advocacy, information dissemination, planning, training, case management, disease surveillance, partnerships and operational research.

SATCI's immediate objectives are as follows:

- ◆ Promotion of voluntary counselling and testing (VCT) for HIV in TB services
- ◆ Providing advocacy and health education materials for TB/HIV/AIDS
- ◆ Development of generic management guidelines for TB/HIV/AIDS patients
- ◆ Development of training modules on the management of TB/HIV/AIDS patients
- ◆ Creating an inventory for TB/HIV research in the region.

In South Africa, the TB/HIV pilot sites already mentioned aim to achieve some of the objectives outlined above. At these sites, strategies are being developed to seek practical ways of linking DOTS, community-based home care and care provided through the general health service, through integration of tuberculosis and HIV control programme activities.

Non-governmental organisations have also been recognised as important partners and have been co-opted in this venture. The TB Alliance DOTS Support Association (TADSA) for example, has been contracted by both the NTCP and the STD/HIV/AIDS Directorate, to develop a manual for training tuberculosis treatment supporters in community-based care for dually infected patients.

Multi-drug resistant TB

The actual prevalence of multi-drug resistant TB (MDR TB) in South Africa is not known with any degree of certainty but a survey is currently being conducted by the Tuberculosis Research Programme of the Medical Research Council to accurately estimate the prevalence of MDR tuberculosis in all of the provinces. This will help quantify the MDR problem in the country and assist the development of targeted interventions for identified hot spots.

As part of the DOTS Plus initiative, which is a joint collaborative effort between the Medical Research Council TB Research Programme and the National/Provincial Tuberculosis Control Programmes, specialised centres for the treatment of MDR tuberculosis have been established. These aim to evaluate the effectiveness of treating MDR TB patients using a standardised regimen of second line anti-TB drugs and to monitor the reduction of the burden and spread of multi-drug resistant strains of the tubercle bacillus.

Conclusions

Tuberculosis caseloads have doubled in most provinces over the last five years, reflecting improved reporting rates, but also a real rise in the incidence rate for the country. However, reporting rates continue to be a major impediment to accurate estimation of the incidence

of tuberculosis. Bacteriological Coverage has continued to improve with some provinces now achieving a nearly 100% coverage rate.

The rapid rise of HIV prevalence in South Africa from less than 1% in 1990 to 22.4% in 1999⁹ has definitely played a crucial role in the increase of tuberculosis patient numbers.

There has been a positive expansion in DOTS coverage and the NTCP goal of achieving DOTS in all districts by 2001 looks as if it will be achieved. The challenge is to ensure that all tuberculosis patients in these districts are actually receiving supervised treatment.

The proposed bulk procurement of TB drugs for the region should be put into practice as South Africa not only contributes about 40% of the TB burden in the SATCI countries but accounts for up to 50% of the expenditure on anti-TB drugs bought in southern Africa. Cure rates of new smear positive TB patients have marginally improved but are still well below the 85% target of the NTCP.

Therefore constraints to further progress should be addressed so as to achieve better treatment outcomes and reduce the burden of tuberculosis.

Recommendations

Whilst efforts to contain the tuberculosis epidemic in the country over the last five years have been notable, the following areas still require especially sustained attention in order to achieve the objectives of the Tuberculosis Control Programme:

❖ *Expansion and sustainability of DOTS*

Supervision of anti-tuberculosis therapy is one of the cornerstones of the revised TB control strategy of the NTCP. A further increase in the provision of directly observed treatment (DOT) for TB patients and the development of accurate methods to monitor this should be undertaken. DOT ought to be fully functional at primary health care and community level, and this should be evident from improved cure rates, if integrated management of dually infected (HIV and TB) patients is to be effective.

There is need for sustained commitment by health care providers and other role players, notably NGOs and civic leaders, to educate the public as well as to facilitate and advocate for the expansion of community-based supervision of tuberculosis treatment. Otherwise, there is a danger that the introduction of integrated community-based TB/HIV/AIDS care may be seen as another burden placed on the shoulders of unpaid community volunteers.

❖ *Further progress in the integration of HIV/TB management*

Even on a global scale, tuberculosis does not attract as much attention and socio-political mileage as HIV and other major health problems.¹⁰ Perhaps linking the management of TB and HIV will go a long way towards changing this perspective and result in the channelling of much needed funds to efforts aimed at combating tuberculosis. Regional partnerships should be encouraged in order to strengthen cross-border support in combating the dual epidemic as well as standardisation of control strategies.

Guidelines are being developed for the provision of co-trimoxazole and isoniazid prophylaxis for patients with TB and HIV co-infection. These should be standardised. It is also imperative that the concept of community-based management of TB/HIV patients be further developed into practical programmes. To achieve this objective,

building on capacity already present through voluntary lay health worker programmes for DOTS support at community level is of vital importance.

Tuberculosis treatment services should offer:

- ◆ Voluntary counselling and testing for HIV infection
- ◆ Education on HIV/AIDS
- ◆ Condoms
- ◆ Management of opportunistic infections for HIV patients

HIV services should offer:

- ◆ Education on tuberculosis
- ◆ Diagnostic facilities for tuberculosis
- ◆ TB prophylactic treatment for HIV patients at high risk
- ◆ Directly observed treatment for HIV patients with TB

◆ *Improving the monitoring and reporting system*

Accurate measurement and evaluation of programme performance is one of the key objectives of the South African National Tuberculosis Control Programme. In seeking to achieve this objective, it is important that a uniform, computerised data collection system be established for the whole country, to augment the paper-based system already in place and that the current situation of incompatible systems be overcome. The electronic system currently being piloted in four provinces should eventually cover the whole country.

◆ *Sustained prevention and management of MDR tuberculosis*

Multi-drug resistant tuberculosis spreads just as easily as drug sensitive strains but is prohibitively expensive to treat. It is therefore imperative that the development of this dangerous form of tuberculosis be prevented by ensuring improved compliance to anti-TB medication through effective patient treatment support systems and provision of combination drugs.

