INVESTIGATION OF THE COMPARATIVE COST-EFFECTIVENESS OF DIFFERENT STRATEGIES FOR THE MANAGEMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS.

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ABSTRACT

The tuberculosis epidemic is escalating in South Africa as well as globally. This escalation is exacerbated by the increasing prevalence of multidrug-resistant tuberculosis (MDRTB), which is defined by the World Health Organisation (WHO) as resistance of Mycobacteria to at least isoniazid and rifampicin. Multi-drug resistant tuberculosis is estimated to occur in 1-2% of newly diagnosed tuberculosis (TB) patients and in 4-8% of previously treated patients. MDRTB is both difficult and expensive to treat, costing up to 126 times that of drug-sensitive TB. Resource constrained countries such as South Africa often lack both the money and the infrastructure to treat this disease.

The aim of this project was to determine whether the performance of a systematic review with subsequent economic modelling could influence the decision making process for policy makers. Data was gathered and an economic evaluation of MDRTB treatment was performed from the perspective of the South African Department of Health. Three treatment alternatives were identified: a protocol regimen of second line anti-tuberculosis agents, as recommended in the South African guidelines for MDRTB, an appropriate regimen designed for each patient according to the results of culture and drug susceptibility tests, and non-drug management.

A decision-analysis model using DATA 3.0 by Treeage® was developed to estimate the costs of each alternative. Outcomes were measured in terms of cost alone as well as the 'number of cases cured' and the number of 'years of life saved' for patients dying, being cured or failing treatment. Drug, hospital and laboratory costs incurred using each alternative were included in the analysis. A sensitivity analysis was performed on all variables in order to identify threshold values that would change the outcome of the evaluation.

Results of the decision analysis indicate that the individualised regimen was both the cheaper and more cost-effective regimen of the two active treatment options, and was estimated to cost R50 661 per case cured and R2 070 per year of life saved. The

protocol regimen was estimated to cost R73 609 per case cured and R2 741 per year of life saved.

The outcome of the decision analysis was sensitive to changes in some of the variables used to model the disease, particularly the daily cost of drugs, the length of time spent in hospital and the length of treatment received by those patients dying or failing treatment. This modelling exercise highlighted significant deficiencies in the quality of evidence on MDRTB management available to policy makers. Pragmatic choices based on operational and other logistic concerns may need to be reviewed when further information becomes available. A case can be made for the establishment of a national database of costing and efficacy information to guide future policy revisions of the South African MDRTB treatment programme, which is resource intensive and of only moderate efficacy.

However, due to the widely disparate range of studies on which this evaluation was based, the outcome of the study may not be credible. In this case, the use of a systematic review with subsequent economic modelling could not validly influence policy-makers to change the decision that they made on the basis of drug availability.

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CHAPTER 1

1 INTRODUCTION

1.1 Introduction

Multidrug-resistant tuberculosis (MDRTB) is a serious health problem that can be managed by either a tailored drug regimen based on individual drug susceptibility testing (individualised approach), a standard drug regimen for all MDRTB patients (protocol approach), or by a third default strategy of refraining from giving treatment at all. The South African public health service made a policy decision to offer the protocol regimen to all MDRTB patients based on the availability of drugs. This study explores the usefulness of performing a cost-effectiveness evaluation, based on the published literature in aiding such a policy decision by attempting to compare both costs and consequences using evidence-based principles, of each treatment alternative from the perspective of the South African public health service.

1.2 Tuberculosis

Tuberculosis is a disease that has ravaged the continent for centuries.[1,2,3] Despite tremendous efforts to control the disease, it is stated that TB is "humanity's greatest killer".[4,5] The World Health Organisation (WHO) declared TB a "global emergency" in 1993 because this disease kills more adults each year than any other infectious disease.[6,7]

1.2.1 Aetiology

Tuberculosis (TB) is a chronic, recurrent infection caused by the bacillus *Mycobacterium tuberculosis.* Infection is most common in the lungs, but any organ may be affected. TB is an airborne infectious disease with infection occurring by inhalation of organisms dispersed as droplet nuclei from a person who has sputum smear-positive TB. These droplets containing the organisms may remain suspended in the air for several hours and may be inhaled by those that come into contact with

them.[4] Most individuals develop cell-mediated immunity to the infection within two to six weeks. Lesions of *M. Tuberculosis* are infiltrated by lymphocytes and macrophages. These white blood cells kill most of the organisms and 'wall off' the remaining ones, rendering them dormant.[4,8] These dormant bacilli that persist in the alveolar tissues can later start to multiply causing reactivation of the TB infection. It is estimated that approximately five to 15%[4,9,10] of the individuals infected with the organism will develop active TB. In more than half of these cases, activation will occur within the first two years after infection.[4] Any process causing impaired immunity, such as malnutrition, old age, autoimmune diseases, drugs or HIV infection can precipitate reactivation.[11,12,13]

1.2.2 Clinical manifestations of tuberculosis

The onset of TB is insidious and the illness progresses over weeks and months. Effects of the disease may be pulmonary, systematic or physical. Pulmonary effects include cough, wheezing, dyspnoea and possible haemoptysis. Physical findings in pulmonary tuberculosis include crackles in the area of involvement as well as bronchial breath sounds if there is lung consolidation. Systematic effects include fever, night sweats, lethargy and loss of weight and/or appetite.[4,13,14,15]

1.2.3 Epidemiology

Approximately one third of the world's population is infected with the *M. tuberculosis* bacillus.[16,17] Over eight million people become sick[9] and almost two million people die of TB each year[18,19] despite the availability of effective treatment. The WHO have estimated that if control is not further strengthened, nearly one billion people will be newly infected, 200 million people will get sick and 35 million will die from TB between the year 2000 and 2020.[9] Of the eight million new cases, 95% occur in developing countries, with 1.5 million of these occurring in sub-Saharan Africa. In South Africa, approximately 349.4 people in every 100 000 of the population develop active TB each year and 5.8% of these die from the disease.[9] In a population of 43 586 097[20] this means that almost 152 000 people develop active TB each year.

1.2.4 The history of TB treatment

TB is an ancient disease and evidence of TB has been found in Egyptian mummies over 4 000 years old.[1,8,21,22] Each generation afflicted by the disease had different notions of how to cure it - "Bleeding, purging, bed rest, horseback riding, the mountains, the seashore, cod-liver oil, castor oil, phrenic nerve interruption, thoracoplasty, pneumothorax, lucite ball or paraffin plombage, air in the chest, air in the abdomen… the list of attempted remedies from the Greeks to the moderns seems nearly infinite. The length of the roster is a powerful testimony to the lack of efficacy of any of these measures." [3]

Robert Koch identified *M. tuberculosis* as the cause of TB in 1882.[1,11] In the following years, other advances were made in staining methods, the BCG (Bacillus Calmette & Guerin) vaccine and PPD (purified protein derivative) skin tests that introduced a means of detecting infection.[8,23] It was in 1944 that antituberculous agents were first discovered. Streptomycin was the first, followed by isoniazid and para-amino salicylic acid between 1946 and 1952 and rifampicin in 1966.[3,24] Despite these advances, this ancient, debilitating disease has not been brought under control, and prevalence is, in fact, rising.[25]

1.2.5 Current treatment strategies: Directly observed therapy, short course

The WHO has set goals that need to be achieved in order to bring the TB epidemic under control. They aim to achieve a 70% case detection rate and an 85% cure rate.[26] The WHO recommends that these high cure rates be best achieved through an effective directly observed therapy, short course (DOTS) programme.[27]

1.2.5.1 DOTS

A successful DOTS programme consists of five key elements:[23,28]

i. Fully supervised treatment with a standardised short course drug regimen.
ii. Active case detection, with special attention to the use of sputum microscopy.
iii. Reliable drug provision.

iv. Effective monitoring of TB control programs and
v. Government commitment to TB control.

1.2.5.2 The importance of DOTS programmes

Poor compliance and low treatment completion rates result in cure rates of 40% or less.[26] At the end of 1999, 127 out of 211 countries were implementing DOTS.[26] It is the responsibility of the health system and the community as well as the patient, to ensure that treatment is taken regularly and that treatment is completed.[26] With this strategy, cure rates in excess of 85% have been achieved.[29] By ensuring that patients take their medication, new infections are prevented as well as the emergence of drug resistance.[25]

1.2.5.3 Standardised treatment

One of the key elements of a DOTS strategy is the availability of standardised treatment regimens for both new cases and re-treatment cases. A re-treatment case may be a patient who has failed to respond to first-line therapy and still has a positive sputum smear after two months of therapy, or a patient returning after premature interruption of treatment.

New cases

In the South African public sector, standard treatment for new cases consists of two months of a combination drug containing isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) followed by four months of isoniazid and rifampicin. This regimen is abbreviated as 2HRZE/4HR.[30]

Re-treatment cases

The re-treatment regimen consists of three drugs throughout (isoniazid, ethambutol and rifampicin) supplemented by pyrazinamide during the first three months and streptomycin (S) during the first two months. The conventional abbreviation for this regimen is 2SHRZE/1HRZE/5HRE.[28]

1.2.6 Factors contributing to the growing TB epidemic

Despite some of the high cure rates achieved by DOTS programmes, various factors are still preventing the control of the epidemic.

1.2.6.1 The HIV/AIDS epidemic

The worldwide HIV/AIDS crisis has had a significant impact on the growing TB epidemic.[9,31,32] The WHO and UNAIDS have recognised a linear relationship between the prevalence of HIV infection and the incidence of TB in adults in 19 African countries. A linear regression model suggests that as the prevalence of HIV rises from zero to 30%, the incidence of TB will increase from approximately 250/100 000 of the population to over 600/100 000 of the population.[26] A patient infected with AIDS or HIV (at any stage of the infection), has a 7 – 15% probability of developing active TB per year, compared to a probability of 5 – 15% per lifetime in a non HIV-infected person.[4,10,16]

Infection with HIV, with or without AIDS, results in a rapid decline in cell-mediated immunity and an increase in the incidence of many respiratory diseases. The decreased level of immunity may result in endogenous reactivation of a latent tuberculosis infection.[12,33,34] Alternatively, primary infection could progress more rapidly into active TB in HIV-infected persons.[12,33] Infection with *M. tuberculosis* also activates production of latent HIV in white blood cells and thus further accelerates the collapse of the immune system.[35]

At the end of 2001, UNAIDS estimated that there were 40 million people in the world living with HIV.[36] As can be seen in Table 1.1, 28.1 million of these sufferers are situated in sub-Saharan Africa. The UNAIDS estimated that there were approximately three million AIDS-related deaths in the world and 2.3 million AIDS related deaths in Sub-Saharan Africa in 2001[36], 30% of which could be directly attributed to TB.[37]

Table 1.1 UNAIDs estimations of adults and children living with HIV/AIDS at the end of 2001.[36]

	Adults and children living with HIV/AIDS	Adults and children newly infected with HIV	Adult prevalence rate	Estimated adult and child deaths
Sub-Saharan Africa	28 100 000	3 400 000	8.40%	2 300 000
North Africa & Middle East	440 000	80 000	0.20%	30 000
South and South-East Asia	6 100 000	800 000	0.60%	400 000
East Asia & Pacific	1 000 000	270 000	0.10%	35 000
Latin America	1 400 000	130 000	0.50%	80 000
Caribbean	420 000	60 000	2.20%	30 000
Eastern Europe & Central Asia	1 000 000	250 000	0.50%	23 000
Western Europe	560 000	30 000	0.30%	6 800
North America	940 000	45 000	0.60%	20 000
Australia & New Zealand	15 000	500	0.10%	120
TOTAL	40 000 000	5 000 000	1.20%	3 000 000

1.2.6.2 Migration of people

The extensive movement of people due to global trade and air travel is causing TB to spread to areas where it would not normally be problematic. The increasing number of refugees as well as homeless or displaced people, and their crowded, unsanitary living conditions are also a contributing factor. Finally, the difficulties of treating these mobile populations for the required six months have resulted in people remaining infectious for longer periods of time.[38,39]

1.2.6.3 The increase in the world population

The increase in the world's population and the fact that people have a longer life expectancy means that there are more people who can become infected and which contributes to the higher prevalence of TB. This population increase has also contributed to rising unemployment, poverty, overcrowding and malnutrition, leading to an increase in TB prevalence.[40]

1.2.6.4 Poorly managed TB control programmes

Inconsistent or partial treatment of TB results in drug resistant strains of TB. The major problem is encountered when the bacillus is no longer sensitive to the two most potent anti-tuberculosis agents available – isoniazid and rifampicin. This type of TB

has been labelled multidrug-resistant tuberculosis (MDRTB). It has been recognised as a major contributor to morbidity and death in TB patients because of the inability of standard short course chemotherapy to cure it.[41,42,43]

1.3 Multidrug-resistant tuberculosis

Various definitions exist that classify the states of drug resistance. In the past, no standard definition for MDRTB existed, and researchers used different criteria when classifying their patients as having MDRTB. These could range from resistance of the bacilli to more than one standard anti-tuberculosis agent, resistance to at least streptomycin and isoniazid or resistance to at least rifampicin and isoniazid. The differences are quite significant because isoniazid and rifampicin are the two most potent antimicrobials and outcomes of the disease are far less favourable once the bacilli are resistant to them, than with other forms of resistance.[28]

1.3.1 Definitions

Drug resistant tuberculosis

Drug resistant TB is defined as disease caused by *Mycobacterium tuberculosis* resistant to one or more anti-tuberculosis drugs.[44]

Multidrug resistant tuberculosis

The WHO has defined MDRTB as TB caused by *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin.[28]

1.3.2 Classification of MDRTB

Drug resistant TB can be further classified into 'drug resistance among new cases' and 'drug resistance among previously treated cases'.

Drug resistance among new cases

This class was formerly classified as 'primary drug resistance'. It has been defined as the presence of resistant strains in patients where no evidence of treatment for more than one month exists.[38]

Drug resistance among previously treated cases

This class, previously labelled as 'acquired drug resistance', is the term used to indicate resistance in TB cases who have received at least one month of antituberculous therapy.[38]

1.3.3 Mechanisms of tuberculosis drug resistance

Resistance to antituberculous drugs is due to a combination of both natural and man-made causes. Natural resistance can occur due to spontaneous chromosomal mutations in different genes of the bacteria.[45,46] With the *M. tuberculosis* bacillus, resistance does not appear to be conferred through horizontal gene transfer via plasmids or transposons.[3] The rates of mutation vary according to the drugs; the highest proportions of drug resistant mutants that will occur in a population that has never been exposed to antituberculous agents are listed in Table 1.2.

The proportions of resistant bacilli are small, but the majority of cavitatory lesions in tuberculosis infections contain more than 10^7 to 10^9 organisms.[3,46,48] Thus, several naturally occurring mutants resistant to a single agent would be expected in the majority of patients with TB. The probability of a randomly occurring mutant being resistant to more than one drug is equal to the product of the probabilities of resistance for each individual drug. Therefore, the probability of MDRTB occurring without human influence will be the product of the probability of resistance to isoniazid and rifampicin, i.e. $((1 \times 10^{-6}) \times (1 \times 10^{-9}))$, or 1 in every 10^{15} cell divisions.[44,48] The number of bacilli in a single cavitatory lesion does not approach this large figure and thus, spontaneous MDRTB is not common.[47]

Table 1.2 Rates of mutation per cell division at the gene(s) responsible for drug resistance for the main anti-tuberculosis drugs.[3,44,46,48]

	Year of introduction	Genes involved with resistance	Mutation rate*
First-line drugs			
Isoniazid (INH)	1952	Catalase-peroxidase enzyme	10^{-8} to 10^{-6}
Rifampicin (RMP)	1965	RNA polymerase	10^{-10} to 10^{-9}
Pyrazinamide (PZA)	1970	pncA	10^{-5} to 10^{-3}
Streptomycin (SM)	1944	Ribosomal S12 protein 16S r RNA	10^{-8} to 10^{-6}
Ethambutol (EMB)	1968	Mycolic acid synthesis	10^{-7} to 10^{-4}
Second-line drugs			
Ethionamide	1966	?	10^{-3}
Kanamycin / Amikacin	1957	?	10^{-6}
Cycloserine	1955	?	10^{-10}
Capreomycin	1967	?	10^{-3}
Thioacetazone	1950	?	10^{-3}
P-amino salicylic acid (PAS)	1946	?	10^{-8}
Ofloxacin	1987	DNA gyrase A & B	10^{-8}

* Range of values due to different sources of information.

MDRTB is a man-made phenomenon that usually occurs as a result of human error. If a patient harbours a mutant naturally resistant to isoniazid, and is treated only with isoniazid and rifampicin, further spontaneous mutation can result in rifampicin resistance in some of the bacilli. The other organisms will be killed but these will continue to multiply and the patient will develop MDRTB.[3,49] This phenomenon is known as the 'amplifier effect'[7] and can result in strains resistant to as many as five drugs when inappropriate treatment is given to patients.

1.3.4 Human causes of MDRTB

Four main groups of errors have been identified to be the cause of selection of resistant strains of TB:[28,44,50,51]

i. Prescription of chemotherapy.
ii. Management of drug supply.
iii. Patient management.
iv. Patient compliance.

1.3.4.1 Prescription error

The WHO claims that prescription errors are the most common cause leading to the selection of resistant bacilli.[28] These include providing only two or three drugs during the initial phase of treatment in a new patient that happens to be resistant to isoniazid or adding one extra drug to a failing regimen, providing what amounts to monotherapy.

1.3.4.2 Possible drug supply and management errors

The inability of a patient to obtain medication due to lack of financial resources or medical insurance, shortages of anti-tuberculosis agents in health facilities due to poor management or financial constraints in developing countries, and the use of drugs, or combinations of drugs of unproven bioavailablity are examples of drug supply and management errors that could lead to the emergence of MDRTB.

1.3.4.3 Patient management errors

Poor record keeping and a high staff turn-around contribute to a lack of continuity of patient care. Some health care workers do not build good relationships with their patients and fail to provide their patients with knowledge about their condition. Poor staff morale, neglect in obtaining feedback from the patient and failure to provide directly observed therapy are also patient management errors that are contributing to the poor success of first line treatment and thus the development of MDRTB.

1.3.4.4 Patient compliance

Patient co-operation is often a problem in patients who work or live in an unstable environment or are homeless. Patients with a history of alcohol or drug abuse and patients who know someone who was previously treated unsuccessfully usually also adhere poorly to therapy.

The combination of all these factors, both natural and man-made, result in the emergence of MDRTB strains in an entire community as depicted in Figure 1.1.

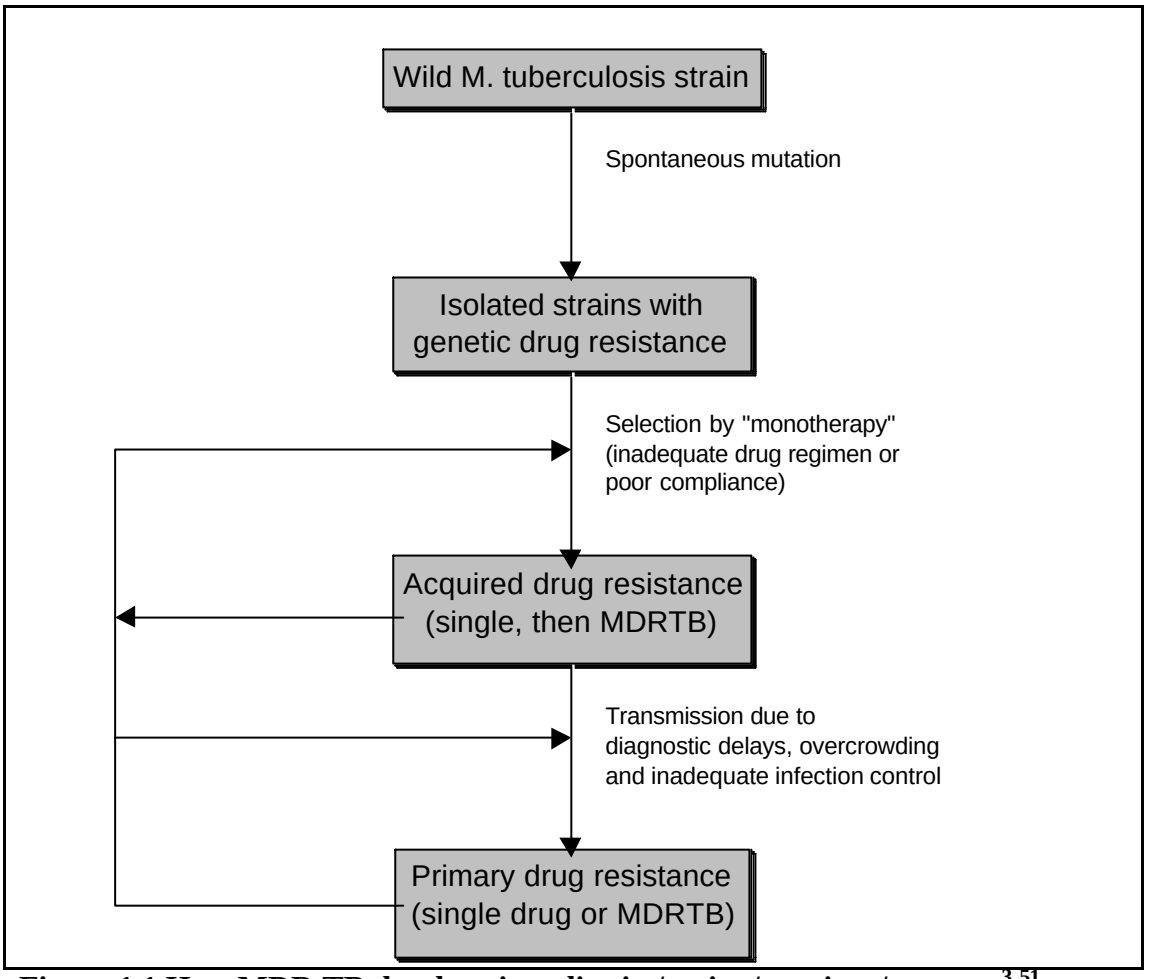

Figure 1.1 How MDR TB develops in a district/region/province/country.[3,51]

1.3.5 Risk factors predisposing people to MDRTB

MDRTB is fast becoming an epidemic in its own right. There are numerous reports of outbreaks in health care facilities[52,53] Researchers are now determining the risk factors that predispose patients to the development or contraction of MDRTB.

Conflicting results have been reported as to whether HIV is a risk factor for MDRTB or not. Some authors report that although the incidence of TB has increased due to HIV infection, prevalence of MDRTB has remained stable.[54,55,56]

Other researchers claim that MDRTB is more likely to occur in patients with HIV infection.[33,57] These conclusions are based on reports from several outbreaks of

MDRTB around the globe, but it has been noted that the epidemiology of MDRTB in an outbreak situation cannot be compared with the epidemiological characteristics of the disease in a non-outbreak setting.[58]

Outbreaks of MDRTB are more common in hospitalised HIV-positive patients than in the community. This is due to the large numbers of HIV-positive patients who have dysfunctional immune systems and are in hospital for the treatment of a variety of opportunistic infections. Nosocomial spread from one or two patients with unidentified drug-resistant TB can be extensive because of the lowered cellular immunity in these patients.[33,53] These outbreaks are characterised by rapid progression and poor outcomes.[52,57]

Two mechanisms have been proposed for a possible interaction between HIV infection and the development of MDRTB:

i. *Higher infection rates and more rapid progression of resistant organisms in the immunocompromised host* – some researchers propose that the drug-resistant strains are less virulent than normal TB strains and it is only in the presence of decreased immunity that infection and subsequent disease will occur.[3] Patients could also be exogenously re-infected with a drug-resistant strain of TB because of the failure of the patient to acquire protective immunity to the bacteria during a previous infection because of an impaired immune system.[10,33,34,35,59]
ii. *Co-infection with HIV and TB can result in acquired resistance* – this is possibly due to the host's inability to inactivate strains that have developed single-drug resistance due to spontaneous mutation. These will continue to propagate and possibly mutate again, resulting in MDRTB.[58]

Researchers do, however, agree that even with appropriate treatment, the outcome of the disease is less favourable in HIV-positive than HIV-negative patients.[35,53,60,61] In the light of available evidence, HIV infection does not appear to influence the incidence of MDRTB in a normal, community setting.[54,55,56] Mycobacterial drug resistance and host immunodeficiency may however, interact synergistically to potentiate the transmission of MDRTB among patients with HIV infection in

hospital.[34] Persons with HIV infection who have TB are often hospitalised in settings with other immunocompromised patients with TB. Patients with unrecognised MDRTB may remain infectious for extensive periods of time due to inadequate treatment, thereby perpetuating the spread of the disease.[34] This conclusion may be premature and current trends must be observed in order to confirm these findings.

Health care workers and family members who are in close contact with an MDRTB patient are also at high risk for developing MDRTB themselves. It is recommended that effective isolation techniques should be in place to protect such individuals and appropriate therapy should be started promptly in order to reduce infectiousness.[49]

Three other groups of patients are at risk of developing MDRTB; TB patients receiving inadequate first-line therapy,[16,48] patients with sputum smears or cultures that are still positive after two months of TB therapy[49] and those with cavitatory pulmonary TB. The latter group of patients are more likely to develop MDRTB due to the larger number of organisms harboured by these patients.[48]

1.3.6 Epidemiological characteristics of MDRTB

Since the introduction of antimicrobial agents in 1944, streptomycin being the first, it became apparent that the use of individual agents, along with other human errors led to resistance. In an attempt to determine the extent of the MDRTB threat, the WHO and the International Union against tubercular lung disease (IUATLD) implemented an anti-tuberculosis drug resistance surveillance project. This project measures the prevalence of resistance to anti-tuberculosis drugs in countries throughout the world with the aid of standardised techniques used by a network of reference laboratories.[3]

1.3.6.1 Global trends of MDRTB

Findings from the two WHO/IUATLD surveys completed in 1996 and 1999 respectively are reported in Appendix 1. The second survey (1996 to 1999) reported a median prevalence of MDRTB in new patients of 1%, with eight of the 54 geographical settings surveyed showing no traces of MDRTB.[38] Comparing the results from the first survey (1994 to 1996) with the second (1996 to 1999), showed

that the only country with a significant increase in MDRTB prevalence in new patients was Estonia, with a prevalence that increased from 10.2% in 1994 to 14.1% in 1998 (probability value = 0.02). France (0.5% vs. 0%) and the United States (1.6% vs. 1.2%) reported statistically downward trends.

Amongst previously treated cases, MDRTB prevalence ranged from 0% in four geographical settings, to 48.2% in the Islamic Republic of Iran. The median prevalence among previously treated patients was 9.3%. Decreases in MDRTB were seen in the Republic of Korea while an increase was observed in Estonia from 19.2% in 1994 to 37.8% in 1998 (probability value = 0.04).[38]

Combined MDRTB cases (new and previously treated) ranged from 0% in Finland and New Caledonia to 18.1% in Estonia with a median of 1.8% across all settings surveyed. Twelve 'hot spots' were identified as having a prevalence of MDRTB of over 5%. In general it was found that where TB control was good, low levels of resistance were present. Thus levels of MDRTB in a community could be used as an indicator of TB control.[38,62]

1.3.6.2 MDRTB in South Africa

There were no reliable figures depicting the incidence of MDRTB in South Africa. The latest estimates published by the Tuberculosis Research Programme, Medical Research Council, were based on field studies performed in the Western Cape, Gauteng and Mpumalanga in 1995 to 1997. These estimates indicated the proportions of patients with newly diagnosed MDRTB cases to be between 1% and 2% of all TB cases. Amongst previously treated patients, this proportion was estimated to be between 4% and 8%.[63]

1.3.7 Significance of MDRTB

The MDRTB epidemic is affecting both patients and health-care systems alike. MDRTB is unable to be cured with short course chemotherapy (SCC).[7] The majority of MDRTB patients treated with SCC remain infectious and transmit the disease to others in their community. The second-line agents that are reasonably effective in

treating MDRTB are expensive; the medication alone can cost up to 100 times that of the SCC. The developing countries that are worst affected by the disease are least able to afford these costs when there are many other health care priorities to deal with on a limited budget. In addition, even with adequate resources, treatment outcomes for MDRTB are poor and inconsistent. Studies have reported cure rates using second line agents of between 56% and 96%.[64,65]

Population characteristics, extent of the disease and differences in the treatment settings could play a vital role in these outcomes, but little research has been done in this area. The second-line agents could cause many debilitating side effects, further increasing the cost of the treatment, decreasing patient compliance and possibly necessitating the removal of the offending agent resulting in an inappropriate drug regimen. The lengthy treatment and hospitalisation causes both patient and family to spend large amounts of time away from work.

1.3.8 Modifications to DOTS required for MDRTB treatment

Because of the inability of DOTS to cure this form of the disease[7], the WHO targets are unlikely to be achieved.[66] With the aim of controlling the impact of MDRTB on the increasing TB epidemic, DOTS-plus, an adaptation of DOTS has been introduced in order to address the new issues. Bastian et al[66] have identified some of the possible changes that need to take place when implementing DOTS-plus. These are summarised in Table 1.3.

Table 1.3 Unresolved issues surrounding DOTS-plus programmes

Current DOTS strategy	Possible Modifications required for DOTS-plus
Standardised treatment throughout therapy.	Individualised treatment regimens when DST* results available.
Diagnosis by microscopy.	Local facilities for culture and DSTs*. Availability of DSTs* for second-line drugs.
Reliable supply of a limited number of first-line drugs.	Provision of an extensive range of highly expensive second-line drugs. Supply of laboratory consumables. Prevention of uncontrolled use of second-line drugs.
Continuous evaluation of patient notifications, smear results and outcomes.	Three-monthly culture and DST* results, and more extensive programmatic reviews may be necessary.
Local government commitment.	Additional support from external governments and agencies.

* Drug susceptibility tests.

The WHO has published guidelines for the management of drug-resistant tuberculosis.[28] Currently, the central debate focuses on the extent to which drug susceptibility testing should be performed, with individualised treatment regimens being based on these results, or whether patients should receive a standardised regimen with limited drug susceptibility testing (DST).[66,67,68]

Developed countries have resources available that are lacking in developing countries, including South Africa. Patients in developed countries have easy access to tertiary or referral care centres where they can be isolated and treated appropriately. In developing countries, such facilities are often not available or are inaccessible to the public. Developing countries also lack the financial and structural resources that are available in developed countries, which allow them to perform reliable, extensive drug susceptibility tests for both first and second-line agents. Many expensive second-line agents recommended for treating MDRTB are unaffordable or are not registered for use and the staffing requirements needed for the extensive patient monitoring and follow-up are often unable to be met in the developing world.

In recognition of these limited resources, many of the developing countries suggest the use of a standardised regimen to be given to all MDRTB patients regardless of their drug susceptibility pattern.[68] The South African public health service has chosen to offer a protocol regimen to their patients in order to reduce costs and error. It is also thought that because of the limited availability of alternative drugs, the protocol

and individual approaches would result in very similar drug regimens.[44] In South Africa, patients are receiving protocol drug regimens despite the fact that they are being treated at tertiary facilities that have access to laboratories. These patients may either be receiving drugs to which the bacilli are not sensitive resulting in significant expenditure on ineffective drug regimens.[67] Other patients may receive more than the necessary number of second-line drugs, thus, increasing costs, increasing the risk of adverse drug reactions and increasing the risk of non-compliance.

1.3.9 Guidelines for the management of MDRTB

Both WHO and South Africa have developed guidelines for the implementation of DOTS-plus programmes.[28,44] The South African guidelines draw on the guidelines from WHO, IUATLD and the Centres for Disease Control and Prevention.

1.3.9.1 Principles of MDRTB management

In their guidelines for the management of drug-resistant tuberculosis, the WHO has devised eight basic principles for the management of the disease.[28]

i. Specialised unit

Treatment of MDRTB involves the use of second-line agents or reserve drugs; these are more expensive, less effective and have many more side effects than standard drugs. These drugs should be available only in specialised units where they can be controlled and used appropriately, and should not be available on the free market.

ii. Designing an appropriate regimen

Time, experience and skill are required when designing an appropriate second-line treatment regimen. The physician or health care worker must also have the time to determine past treatment regimens, compliance patterns and the bacteriological status of the patient by sputum smears, cultures and susceptibility tests.

iii. Reliable susceptibility testing

The specialised unit must have access to laboratory services able to carry out culture and reliable drug susceptibility tests for the essential agents as well as some second-line agents. Quality control measures should be in place, where samples are routinely sent to a second laboratory to confirm that results are accurate.

iv. Reliable drug supplies

As with the first-line agents, the unit must be able to guarantee a reliable supply of the second-line medications in order to ensure that treatment undertaken for an individual can be successfully completed.

v. Priority is prevention

Multidrug resistance should not occur when national TB treatment programmes are effective, which is when standard treatment is meticulously prescribed and administered. MDRTB should always be regarded as a result of failure of effective implementation of the national programme, and top priority and resources should be given to preventing such failure.

vi. Using WHO standard regimens for new cases and re-treatment

Patients with treatment failure after the standard national regimen, relapsed patients and patients returning after premature interruption of treatment should be given the WHO re-treatment regimen which consists of streptomycin, isoniazid, rifampicin, pyrazinamide, and ethambutol for two months, followed by one month of isoniazid, pyrazinamide, ethambutol and rifampicin and finally five months of isoniazid, rifampicin and ethambutol. The WHO guidelines[28] suggest that most patients will be cured with this regimen, with failures due to the use of incorrect regimens and/or failure to ensure that the regimen is directly observed. Very rarely, failure will be due to resistance to three or more of the five drugs in the re-treatment regimen, and these patients are then candidates for second-line therapy. There is some evidence however, that, in re-treatment TB cases with pan-susceptible strains, the cure rate is only 62%.[69] In re-treatment patients with resistance to one or more drugs, this decreases to 52%.[69]

vii. MDRTB as a consequence of poor treatment

As a result of poor treatment either inside or outside (private practitioners) the national TB programme, many patients may have received a wide variety of drug regimens, resulting in multidrug-resistance. The nature of all previous regimens should be precisely determined and this should be taken into account when designing a second-line regimen.

viii. Long-term involvement of staff and financial resources

Once a country has decided to invest resources into developing specialised units for the treatment of MDRTB, skilled and experienced specialists with an ongoing, long-term responsibility should run them. The unit should also be in close contact with a reliable reference laboratory. Inadequately resourced units can do more harm than good, and may even perpetuate and spread MDRTB.

1.3.9.2 Diagnosing MDRTB

MDRTB should be suspected in patients who fail to respond both to first-line and re-treatment regimens despite good documented compliance, as well as those persons who are in close contact with a MDRTB patient. The diagnosis of MDRTB must be made by a laboratory and not on clinical suspicion. Culture and susceptibility tests for isoniazid, rifampicin and ethambutol should be performed on a sputum sample from the patient, and only once it is confirmed that the bacilli are resistant to isoniazid and rifampicin can the patients be classified as having MDRTB. There are various methods for identifying and testing the susceptibility of the TB strain and the WHO/IUATLD group have made a concerted effort to standardise the methods used by different countries and laboratories.

1.3.9.2.1 Methods for diagnosing drug resistance

In general the methods used to diagnose drug susceptibility are widely used and well standardised throughout the world.

i. *The absolute concentration method*

Media containing several sequential two-fold dilutions of each drug are used and resistance is indicated by the lowest concentration of the drug, which, will inhibit growth i.e. less than 20 colonies at the end of 4 weeks.[3]

ii. *The resistance ratio method*

This test is a variant of the absolute concentration method. The resistance ratio is defined as the minimum inhibitory concentration (MIC) of the test strain divided by the MIC of the standard, susceptible strain H37Rv in the same set of tests. A resistance ratio of two or less defines drug susceptibility, while eight or more is considered evidence of drug resistance; strains with intermediate resistance are rare.[3]

iii. *The proportion method and its variants*

This is possibly one of the most widely used methods of diagnosing MDRTB. The ratio between the number of colonies growing on drug-containing medium and the number of colonies growing on drug-free medium indicates the proportion of drug-resistant bacilli present in the bacterial population. High and low dilutions of the inocula are planted on the media so that isolated, countable colonies can be obtained with at least one of the dilutions. The proportion of mutants resistant to the drug concentration tested can be determined and expressed as a percentage of the total number of viable colony forming units in the population. Below a certain fraction, called the 'critical proportion', a strain is classified as susceptible, and above that as resistant. The significant resistance proportion levels for the different anti-tuberculosis drugs are the levels above which the drugs are estimated not to be clinically useful.[3]

iv. *The BACTEC 460® radiometric method*

This is a computerised system that utilises liquid medium instead of the solid media used in the other methods. This method is a variation of the proportion method in which production of ^{14}C-labelled CO_2 (evidence of bacterial growth) in a standard *M. tuberculosis* inoculum in the presence of antimicrobials is compared to the labelled CO_2, produced by a 1/100 dilution of the original inoculum in the absence of antimicrobials. Results can be obtained within one week following inoculation but it

is extremely expensive and laboratories need the appropriate infrastructure, which will include an ability to dispose of radioactive waste.[3]

1.3.9.2.2 Methodology for culture and drug susceptibility testing

Laboratories in South Africa generally use the proportion method for diagnosing drug resistance. Depending on the facilities available, the conventional or the radiometric methods may be used. With the conventional methods, there are a variety of different growth media available for use. These include the Löwenstein Jensen, Middlebrook 7H10 and Ogawa media.[70] There are slight differences between them, the main one being the cost of the ingredients. All media are suitable to use as long as the methodology has been standardised according to guidelines. With the proportion method, the inoculum's size need not be standardised but concentrations of each drug are critical when testing for resistance.[3] The South African MDRTB guidelines suggest some critical concentrations to use on the different media (see Table 1.4). Internationally accepted standardisation has not yet been achieved. Further guidelines for the identification, culture and DST of *M. tuberculosis* are available in the publication by Reider et al.[70]

Table 1.4 Critical drug concentrations (mg/ml) for routine susceptibility testing.[4,44,70]

Drug	Radiometric	Conventional	
	Bactec 12B	Middelbrook 7H10	Löwnestein-Jensen
Isoniazid	0.1	0.2	0.2
Rifampicin	2	1	40
Ethambutol	2.5	5	2
Streptomycin	2	2	4

1.3.9.3 Treatment approaches in South Africa

The South African public health service MDRTB management guidelines make recommendations for the treatment of patients with varying degrees of resistance. They also provide choices for decision-makers in different health-care settings depending on the availability of facilities and resources.

1.3.9.3.1 Management of patients with tuberculosis resistant to a single drug

Standard regimens should still be used in patients with bacilli singly resistant to isoniazid and/or streptomycin. Rifampicin-only resistance is not very common. If the patient does not respond, or is clinically deteriorating, it is recommended that MDRTB should be suspected and culture and sensitivity tests should be repeated.[44]

1.3.9.3.2 Management of patients with MDRTB

Due to the limited efficacy of the standard regimens in patients with MDRTB, second-line, reserve drugs are used. These are more expensive, less effective and have more severe side effects than standard anti-tuberculosis drugs.

Approach one: Standard treatment regimen

The standard treatment regimen for MDRTB patients consists of a four month intensive phase with five drugs (kanamycin, ethionamide, pyrazinamide, ofloxacin and cycloserine or ethambutol), followed by a 12 to 18 month continuation phase with three drugs (ethionamide, ofloxacin, and cycloserine or ethambutol) as indicated in Table 1.5. Cycloserine should only be used if the bacilli are resistant to ethambutol. Drugs should be administered five times per week in clinics and seven times per week in hospitals. The continuation phase may be shortened, provided that 12 months of treatment has been given after sputum conversion as demonstrated by negative cultures in three consecutive months.[44]

Table 1.5 Approach one for the treatment of MDRTB.

	Daily dosage	
Drug	**Average (mg/kg)**	**Maximum (mg)**
Intensive phase: 4 months		
Kanamycin	15	1 000
Ethionamide	10 to 20	1 000
Pyrazinamide	20 to 30	1 600
Ofloxacin or	7.5 to 15	800
Ciprofloxacin	7.5 to 15	1 500
Ethambutol or	15 to 25	1 200
Cycloserine	10 to 20	1 000
Continuation phase: 12 to 18 months		
Ethionamide	10 to 20	1 000
Ofloxacin or	7.5 to 15	800
Ciprofloxacin	7.5 to 15	1 500
Ethambutol or	15 to 25	1 200
Cycloserine	10 to 20	1 000

Approach two: Individualised treatment regimen

With this approach, treatment regimens are based on the results of drug susceptibility tests. This implies that treatment be delayed until susceptibility results are available, or that patients are started on the standardised regimen if the sputum smear is still positive after the re-treatment course while awaiting drug susceptibility test results.

Progress should initially be monitored by monthly smears and cultures until at least three consecutive cultures are negative, and then every three months until treatment is completed. Susceptibilities should only be requested at month three or six if the culture is still positive. Chest X-rays (CXR) can be done every three months until treatment is complete.

Ideally patients should be followed up for two years following completion of treatment with six monthly sputum culture and CXRs. The usual duration of treatment is 18 months, with the minimum duration of treatment with either regimen being 12 months after the first negative sputum culture. An aminoglycoside should be given daily for a minimum of four months. Once culture is negative, it is possible to reduce the dose to three times per week until six months of treatment is completed.

It is necessary to summarise previous treatment(s), drug susceptibility results, compliance history, clinical course and adverse reactions to drugs used previously. Because of the skill and experience required for designing an appropriate regimen, the

guidelines recommend that *Approach two* be followed only in those provinces where the necessary referral mechanisms, specialised centres and medical, laboratory, and administrative expertise exist.

Drugs for the treatment of MDRTB patients are classified according to the bacteriological activity, toxicity and patient tolerance. The main criteria are based on biological data, which determine three groups of drugs available according to their activity and cross-resistance. The rankings and classification of the drugs for the treatment of MDRTB are presented in Table 1.6. Drugs should be selected from the higher-ranking categories if possible (i.e. if the bacteria are susceptible).

Table 1.6 Ranking of anti-tuberculosis drugs for treatment of MDRTB.

Rank	Drugs	Average daily dosage (mg/kg)	Type of activity (category)	Peak serum level: MIC
1	Aminoglycosides		Bactericidal (actively multiplying organisms)	
	Streptomycin	15		20 to 30
	Kanamycin	15		5 to 7.5
	Amikacin	15		10 to 15
2	Ethionamide	5 to 10	Bactericidal	4 to 8
3	Pyrazinamide	20 to 30	Bactericidal (acid pH)	7.5 to 10
4	Fluoroquinolones		Weakly bactericidal	
	Ofloxacin	7.5 to 15		2.5 to 5
	Ciprofloxacin	7.5 to 15		
5	Ethambutol	15 to 20	Bacteriostatic	2 to 3
	Cycloserine	5 to 10	Bacteriostatic	2 to 4

The initial treatment regimen should consist of at least four drugs to which the bacilli have been shown to be susceptible. At least three of these should not have been administered to the patient previously (i.e. for three months or more). Not more than one drug should be chosen from each of the categories and all patients should receive an aminoglycoside during the intensive phase of treatment.

Approach two requires considerable time and expertise, access to drug susceptibility testing (also of the second-line drugs) and close monitoring of the individual patients, with changes in treatment as indicated by susceptibility results. The approach in inexperienced hands can result in too frequent changes of medication, especially if laboratory results are treated rather than patients. *Approach one* requires less access to routine culture facilities, and monitoring of patients is mainly for side effects and culture conversion. The margin of error in *Approach one* is minimised and this

approach is therefore strongly recommended.[44] A second reason that the first approach is recommended in the South African context is that many of the second-line drugs are not available for use and the individualised regimen that results is very similar to the protocol regimen. Second-line drugs not available on the South Africa public health tender, include capreomycin, clofazimine, prothionamide and Para-amino salicylic acid (PAS).[28]

1.3.9.4 Hospitalisation

Once MDRTB has been diagnosed, patients should be referred to a specialised centre for treatment. Ideally they should remain in hospital until sputum cultures become negative and the patient is no longer infectious. Some patients may, however, be successfully managed with ambulatory treatment provided directly observed therapy is ensured, therefore reducing costs, freeing up scarce beds and enabling patients to remain in employment.[44] Patients need to be educated on effective infection control measures. Patients requiring hospitalisation are those in a poor clinical condition, previous treatment interrupters, those with complications, patients experiencing adverse drug reactions and patients with poor social circumstances.[44]

1.3.9.5 Surgery

While chemotherapy alone is sufficient to cure most patients, the South African[44] and WHO[28] MDRTB management guidelines, and Sung et al[71] do acknowledge various indications for surgery in MDRTB patients. At least six months of drug therapy should be given before surgery is attempted in order to lower the bacterial count, and after surgery, the same regimen should be continued for at least 18 months.[28,44]

i. Definite indications for surgery

- Persistence of positive sputum cultures and lack of radiographic and clinical improvement after 6 months of adequate therapy and patient compliance.
- Relapse in the same site after a previous adequate course of chemotherapy in a patient who has been compliant.

ii. Lesser Indications

- In a patient who has undergone sputum conversion but the original profile of drug resistance is so great (4 or more drugs) that if relapse did occur, it may be difficult to re-establish sputum culture conversion.
- In a patient who had undergone sputum conversion but there is residual cavitation or gross lobe or lung destruction and hence the potential for relapse.

1.3.10 Implementation of MDRTB management guidelines

There are many unanswered questions around the appropriate management of MDRTB. No conclusive evidence has been offered to decision-makers in order to guide therapeutic decisions. MDRTB treatment outcomes have only been documented in the form of poor-quality case-series, rather than randomised controlled trials.

In the light of the uncertainty regarding the treatment method of choice, the South African public health service developed MDRTB management guidelines. Initially, the Western Cape was the only province in the country to follow the individualised approach because of the limitations in available resources and alternative second-line drugs. Subsequently, the Western Cape has also chosen to follow the protocol approach. The lack of evidence prevented both the drug regimen and the clinical decision from being made in accordance with evidence-based standards.

The National Drug Policy of South Africa[72] states that the Department of Health aims to "promote the rational choice of drugs and associated items to be used in South Africa, in accordance with the essential drugs concept." Selecting drugs, only where "sufficient proven scientific data is available regarding the effectiveness of any such product", can do this. Ideally, objective evaluations or pilot studies should have been performed in order to justify this choice of treatment method as well as the specific protocol drug regimen that is provided to MDRTB patients. The process of objectively estimating benefits and costs of the treatment of MDRTB was hampered by the paucity of both local and international clinical research in this field.

This study attempted to gather objective estimates of both therapeutic outcomes and costs involved in the management of MDRTB, using three alternative strategies.

1.4 Research Question

In the face of weak comparative efficacy and costing data on the management of MDRTB, can the performance of a systematic review with subsequent economic modelling influence the decision process for policy makers?

1.5 Research objectives

1.5.1 General Objective

The general objective was to perform a pharmacoeconomic evaluation based on a systematic review of the literature and to determine whether the use of these tools could provide additional information that would influence the policy decision to offer standardised treatment to all MDRTB patients. The economic evaluation compared a standardised treatment regimen with an individualised regimen based on results of drug susceptibility testing. These alternatives were compared with the base-case state of withholding drug therapy.

1.5.2 Specific objectives

i. To perform a literature review of the clinical epidemiology and management of MDRTB.
ii. To determine the current MDRTB treatment programmes followed locally in South Africa as well as globally.
iii. To create a practical and comprehensive model of possible MDRTB treatment options and appropriate, measurable therapeutic outcomes.
iv. To incorporate this model into a decision analysis model using DATA (DATA 3.0 by Treeage®).
v. To create a list of all variables that are required to model the disease.

vi. To perform a systematic review of all observational studies published regarding the treatment and outcomes of MDRTB in order to determine:
    a. The literature-derived expected outcomes in terms of mortality, persistent infection, and cure, for the three management options of individualised therapy, protocol regimens and no-treatment of MDRTB patients in the public sector in South Africa.
    b. How these outcomes are influenced by HIV status.

vii. To source and collect or estimate costs required for the decision analysis from a South African perspective.

viii. To analyse the costs of MDRTB treatment in terms of a cost-minimisation analysis as well as a cost-effectiveness analysis measuring the outcomes in terms of the 'number of cases cured' and the 'years of life saved'.

ix. To perform a sensitivity analysis on the outcomes of the pharmacoeconomic evaluation.

x. To assess the integrity and general usefulness of such an evaluation in aiding policy decision, given the limitations of data availability and quality.

The decision to offer the protocol regimen to all MDRTB patients was made on the basis of drug availability in the country. This research aimed to evaluate the added benefit of a cost-effectiveness evaluation of MDRTB treatment alternatives to the decision-making process. Such a study should make the decision-making process more objective and transparent by systematically evaluating both costs and consequences of the alternatives using the best available evidence.

CHAPTER 2

2 PHARMACOECONOMICS

2.1 Introduction

The rise in health care costs is both a global and a local phenomenon.[73] In the United States of America, health care costs are expected to rise by 7.3% per annum until 2011.[74] In the UK, health care costs usually rise by 3% per annum, but by 2004 the annual rise in health care costs is expected to reach 6%.[75] Canada spent 10.6% more on prescription drugs in 2001 than it did the previous year[76], and in the USA, prescription drug costs rose by 17.3% in 2000.[77] This increase in health care expenditure can largely be attributed to rising drug costs' associated with the new breakthroughs in medicine, an increased volume in the use of medicines, changes in demographics and health status of the population, as well as the irrational use of the drugs.[73,76,78,79]

Global statistics show that total health spending generally varies from around 2–3% of gross domestic product (GDP) in low-income countries (<US$ 1 000 per capita) to typically 8-9% in high-income countries (>US$ 7 000).[80] Health expenditure as a percentage of total expenditure also rises as income rises; from 5-6% to 10%[80], but it can account for up to 40% of total expenditure. Drug costs are usually second, only to personnel costs.[81]

Table 2.1 summarises the health expenditures and pharmaceutical expenditures of some regions as a percentage of GDP as they stood in 1990. According to the South African Health Review[82], 4.1% of GDP is spent on health in South Africa, and the percentage of total expenditure that has been spent on health has risen from 23.4% to 24% and 24.2% in 1996, 1997 and 1998 respectively. No figures are available that depict the percentage of GDP that is spent on pharmaceuticals, but it is estimated that 36.6% of private health expenditure and 11.7% of public health expenditure was spent on medicine in 1998.[82]

Table 2.1 Health and pharmaceutical expenditures by region, 1990.[81]

	Health expenditures			Total pharmaceutical expenditures	
Region	Total per Capita (US$)	Public expenditures per capita (US$)	As % of GDP	Per Capita (US$)	As % of GDP
Africa (sub-Saharan)	22	10	4.2	8	0.86
Asia	25	10	4.6	12	0.59
Middle East	97	56	3.5	31	0.74
Latin America and Caribbean	103	62	4	26	0.87
Transitional economies	144	103	3.6	19	NA
Established market economies	1 958	1 196	9.3	137	0.65

Because both private and public health-care funders are unable to keep up with these increasing demands due to budget constraints, a concerted effort is being made to reduce the cost of health care. In the South African National Drug Policy document of 1996, the Department of Health states that it aims to ensure the availability and accessibility of essential drugs (that are safe, effective and of good quality) to all citizens, while lowering the cost of drugs in both the private and public sectors. It also aims to promote the cost-effective and rational use of drugs and to optimise the use of scarce resources.[72]

Various approaches have been used to reduce the cost of health care. Some of these include cost sharing, prescription limits, rebates and cost limits.[83,84,85] The use of prescription limits in the form of a formulary or essential drug list (EDL) is one of the most widely used methods.[86] This method of cost containment has been introduced in South Africa.

2.2 Evidence-based medicine (EBM)

Essential drug lists are lists of drugs that are required to treat the majority of conditions that are prevalent in a country in a cost-effective and efficient manner. During the drug-selection process, effectiveness, safety, quality and cost are the four main criteria taken into account. In order to ensure that an EDL provides the most beneficial treatment to a population, it should be evidence-based.

EBM is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.[87] The process involves turning clinical problems into questions, followed by a systematic literature search, analyses, and use of current research findings to make clinical decisions. The process requires the integration of clinical expertise and judgement with the best available evidence on a patient-by-patient basis.[88]

Evidence is usually sourced from the vast and rapidly expanding mass of medical literature. However, not all of the presenting evidence is considered to be valid or accurate. In order to assess the quality of the evidence, the methodological quality of the research must also be assessed.

2.2.1 Hierarchy of evidence

The randomised controlled trial (RCT) is considered to be the 'gold standard' for providing information on therapeutic effectiveness. However, the question being asked will always dictate the source of the information. Evidence could be sought from studies with alternate designs, however these results are more likely to be misleading.[87] Different study designs are ranked according to traditional usefulness in providing accurate results. This ranking is referred to as the hierarchy of evidence, (Figure. 2.1). Brief descriptions of each type of study design are listed in Table 2.2.

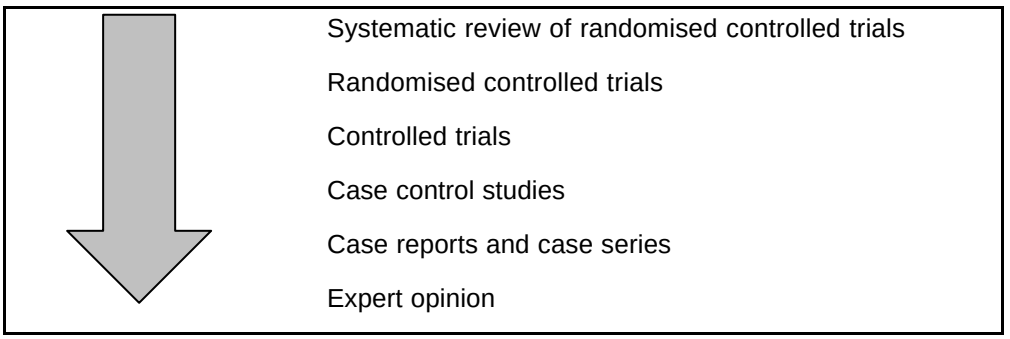

Figure 2.1 The hierarchy of evidence provided by different sources of literature.[89,90]

Table 2.2 Description of selected study designs:[90,91,92,93]

Experimental study designs:	
A study in which a manoeuvre is performed on an animal or a volunteer under artificial and controlled surroundings.	
Randomised controlled trial:	Follow-up of participants randomly allocated to intervention or control groups, with a comparison of outcome rates during the time covered. Randomisation (with concealment of allocation sequence) avoids bias because known and unknown determinants of outcome are on average evenly distributed between intervention and control groups.
Quasi-experimental:	The investigator controls the allocation of participants to different intervention groups but the method falls short of genuine randomisation and allocation concealment.
Observational study designs:	
A study in which natural variation in interventions, or exposure among study participants is investigated to explore the effect of the interventions or exposure on health outcomes.	
Cohort study:	Comparison of outcomes between participants who have been exposed to a risk factor or received an intervention, and a group that has not. The two groups are then followed up prospectively. Alternatively, patients may be identified at some time in the past and followed up to the present.
Case-control study:	Patients with a particular disease or condition are identified and "matched" with controls. Data is then collected on past exposure for possible causal agents or events that make the study group different to the control group.
Cross-sectional study:	Data is collected from a defined population at more or less the same time in order to examine the relationship between other variables of interest. Past experiences may be referred to retrospectively.
Case series:	Description of a number of cases of an intervention and outcome (without comparison or with a control group).

2.2.2 Systematic reviews of the literature

Due to the inability of single studies to detect or exclude, with certainty, differences in the effects of two treatments, reviews of more than one study are becoming very popular sources of evidence for clinical decision-making. Review articles summarise a number of different primary studies and may draw conclusions about the effectiveness of a particular intervention; reviews may or may not be systematic.[90] A systematic review however, is a review of the evidence on a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant primary research, and to extract and analyse data from the studies that are included in the review.[94,95,96,97,98,99,100]

The most well renowned systematic reviews are those undertaken by the Cochrane Collaboration. These types of reviews have various advantages over non-systematic reviews as well as other study designs:[100]

i. Explicit methods limit bias in identifying and rejecting studies.
ii. Conclusions from systematic reviews are more reliable and accurate than those from non-systematic reviews because of methodology used.
iii. Large amounts of information can be assimilated quickly by health-care providers, researchers and policy makers.
iv. Delay between research discoveries and implementation of effective diagnostic and therapeutic strategies may be reduced.
v. Results of different studies can be formally compared to establish generalisability of findings and consistency (lack of heterogeneity) of results.
vi. Reasons for heterogeneity (inconsistency in results across studies) can be identified and new hypotheses generated about particular sub-groups.
vii. Quantitative systematic reviews (meta-analyses) increase the precision of the overall result.

When the results of relevant studies of a systematic review are statistically combined, the review is known as a meta-analysis.[100] A meta-analysis provides a quantitative method of pooling the results of two or more studies that answer the same therapeutic question. This is a cheaper alternative to large, expensive and logistically problematic study designs. Data from several smaller but comparable studies can be pooled in order to reach the necessary number of patients with which relatively small effects can be detected or excluded with confidence.[94] Meta-analyses can also improve the generalisability of study results, especially if many trials exist in different groups of patients. [94]

2.2.2.1 Searching the literature

Electronic databases are the most convenient method of literature searching. The databases are, however, not complete records of all papers that have been published. Only one third of the 10 million medical articles are indexed in Medline®. There is only an estimated overlap of 34% between EMBASE®, a second electronic database of abstracts and Medline®. The degree of overlap in terms of the volume of records ranges from 10% to 75%, depending on the topic of the review. [101,102] Since there is no single electronic database that is comprehensive enough in either subject or

publication coverage to record all publications from all medical journals, it is generally recommended that more than one database be used for a systematic review.

The use of electronic databases may further influence the results of reviews due to publication bias, language bias and location bias.[97] Publication bias occurs because negative results are less likely to be published.[103,104] Basing meta-analyses on trials published only in English could also introduce bias[105], as can the databases that are used to identify relevant literature. Research that is published in developing countries such as India, is often not indexed in the major databases, Medline® and Embase®.[106] Bias can also be introduced by supplementing computerised searches with manual searching of reference lists, again because supportive results are more likely to be cited than unsupportive results.[107] A final source of bias may be introduced by multiple publications of single studies.[108]

2.2.2.2 Critical appraisal

Unfortunately, even study designs promising valid evidence have potentially serious methodological flaws.[91] In order to determine the accuracy, validity, quality, value and relevance of the evidence in a scientific paper, the methodological process needs to be assessed and criticised for purposes of optimal understanding and appreciation.[109]

In a systematic review, both internal and external validity of the studies should be assessed during quality assessment, because the interpretation of the findings of a study depends on design, conduct and analysis (internal validity), as well as on populations, interventions and outcome measures (external validity).[90] This information gained on the quality of a study is usually crucial in determining the strength of the findings. There are various reasons for assessing the quality of studies before inclusion into a systematic review:[90]

i. To determine a minimum quality threshold for the selection of primary studies.
ii. To explore quality differences as an explanation for heterogeneity in study results.
iii. To weight the study results in proportion to quality in meta-analysis.

iv. To guide the interpretation of findings to aid in determining the strength of inferences.
v. To guide recommendations for future research.

When performing a meta-analysis, results are sometimes weighted according to a quality score. Stroup et al[110] feel that these scoring methods often lack demonstrated validity and that results are often not associated with quality. They therefore recommend that methods of quality scoring either be extremely transparent or that sub-group analysis of good and poor-quality studies be performed instead of score-weighting primary research.

Just as each type of clinical question can be answered by a different study design, when critically appraising each study, different questions need to be asked in order to assess some of the key issues in the methodological quality of each study design. Methods of critical appraisal (the assessment of methodological quality) have been covered in detail in various textbooks and papers in order to aid readers and decision makers through the process.[91,93,100,111,112,113,114,115,116,117,118,119]

2.3 Pharmacoeconomics

Drug selection committees have traditionally looked at medication costs purely in terms of acquisition cost. Acquisition cost alone can be misleading, and is usually not a very good indicator of the total cost of treatment. Cheap drugs are not necessarily effective drugs and, consequently, the use of these drugs may result in additional costs due to re-treatment or hospitalisation when patients are not cured. Adverse reactions will increase the total cost of treatment, as will the diagnostic and monitoring procedures required by certain treatments.

Pharmacoeconomics has been described as an integrated tool that systematically aids drug-selection decisions.[120] It takes into account both the effectiveness of a therapeutic modality and its cost. A pharmacoeconomic evaluation can be defined as the comparative analysis of alternative courses of action in terms of both their costs

and consequences.[121] Some of the possible uses of pharmacoeconomic evaluations in clinical decision-making include:[122]

i. Quantifying the differences between two or more effective services or drugs for the same condition.
ii. Illustrating the impact of delivering a given intervention at different intervals, different ages, or to different risk groups.
iii. Evaluating the potential role of new technologies or therapeutic agents.
iv. Identifying key conditions that must be met to achieve the intended benefit of an intervention.
v. Incorporating preferences for intervention services.
vi. Developing and ranking services in order of their costs and expected benefits.

2.3.1 Methods for pharmacoeconomic evaluations

Pharmacoeconomic evaluations ask whether an intervention is worth doing, given other possible uses for the resources. This can only be done where more than one alternative is compared in terms of both the outcome and the cost.[121] Four methods of analysis are used, each using a different outcome measure, viz, cost-minimisation analysis, cost-benefit analysis, cost-effectiveness analysis and cost-utility analysis.[120]

2.3.1.1 Cost-minimisation analysis (CMA)

In CMA, costs are analysed and compared where two or more interventions have been demonstrated to be equivalent in outcomes.[123] Since both of the alternatives accomplish the outcome of interest to the same degree, the least costly alternative would be chosen. A full economic evaluation using the CMA technique requires some evidence proving that the outcome differences between the alternatives are non-existent or unimportant.[121] Because of the strict requirements of therapeutic equality, CMA is not commonly used to assess drug therapies, programmes or services. It can however be useful in assessing cost differences among dosage forms or generically equivalent drugs.[124]

2.3.1.2 Cost-benefit analysis (CBA)

In CBA, all costs and consequences of the alternatives are measured in monetary terms. The outcomes may be expressed as a ratio (benefit to cost) or in terms of a net cost or benefit (benefit minus cost).[125] This method is useful when outcomes are not equivalent and one is unable to reduce them to a single effect common to both alternatives.[121] A disadvantage of CBA is the difficulty of converting some of the non-monetary units, such as the number of medication errors avoided or 'years of life saved', into dollar values. Because of this CBA is not commonly used.[124]

2.3.1.3 Cost-effectiveness analysis (CEA)

CEA is also used to evaluate health care interventions that have unequal outcomes. This type of analysis measures outcomes in natural rather than monetary units. The outcomes for each alternative should be measured in units common to both of the interventions.[124,126] Commonly used measures are 'years of life saved', cases treated or cases diagnosed. This type of analysis determines which programme or treatment option accomplishes a given objective at the least cost.[123] The results of a CEA are usually expressed in terms of an incremental cost-effectiveness ratio (ICER).[121]

The ICER examines the additional cost that one service or programme imposes over another, compared with the additional effects, benefits or utilities it delivers.[121,127] This calculation does not measure the simple ratio of costs to outcomes for the alternative treatment options. Rather it measures incremental costs over incremental outcomes. The formula for this ratio is as follows (Equation 2.1):

$$\text{ICER} = \frac{C_2 - C_1}{O_2 - O_1} \qquad \text{(Equation 2.1)}$$

Where: C_2 = cost of alternative two

C_1 = cost of alternative one

O_2 = outcomes of alternative two

O_1 = outcomes of alternative one

2.3.1.4 Cost-utility analysis (CUA)

A CUA is similar to a CEA, in that it compares alternatives with unequal outcomes in non-monetary units.[121] CUA accounts for effectiveness while integrating patient preferences and satisfaction.[124] In this type of evaluation, consequences are measured using the utility approach, and utility could be measured in quality-adjusted life years (QALYs).[123,128] Utility refers to the value or worth of a specific level of health status or improvement in health status, and quality-adjusted outcomes attempt to quantify the utility derived from changes in health status.[121] The major difficulty in designing and using cost-utility indices is that there is no agreement on a scale for measuring utility.[123] Utility values are either measured on a scale of one (normal health) to zero (dead), with a health state considered worse than death being given a negative utility value.[124,128] Alternatively, the consumer is required to rank choices of health status.[123] QALYs are the number of years at full health that would be valued equivalently to the number of years of life as experienced. If some years were experienced in less than full health, the number of QALYs would be less than the number of life years.[123]

2.3.2 Perspective of pharmacoeconomic evaluations

The viewpoint of a pharmacoeconomic analysis may be that of a specific provider or providing institution, the patient or groups of patients, a third-party payer (public or private), or society i.e. it measures all costs and consequences to whomsoever they accrue.[121]

The perspective chosen is often determined by the nature of the query. For example, it may be desirable to determine the cost of a health-care intervention to society as a result of an inquiry into a potential reduction in gross national product. Alternatively, institutions need cost evaluations of health-care interventions as a method of formulary development. Finally, individuals may want to know the cost of a health-care intervention to determine the change in their quality of life; the cost of medications and other health-care interventions may mean not having enough left over for other activities. Just as each of these perspectives asks a different question, each answer requires the evaluation of a different set of costs.[129]

Obviously, analysts cannot always consider every cost and consequence of a health-care intervention to all members of society. Sometimes the effects are far-reaching and consideration of some items has to be excluded for practical reasons.[121] It is also important to realise that considering only the institution's perspective is very restrictive and it sometimes happens that an intervention is beneficial from a societal perspective but not from an institutional one.[121]

2.3.3 Variables used in pharmacoeconomic analyses

The basic tasks of performing any such evaluation would be to identify, measure, value and compare the costs and consequences of the alternatives being considered. Determining which costs and consequences of each alternative to include in the analysis depends on the viewpoint or perspective from which the study is performed, as well as the specific intervention being addressed.[121] Some of the costs that may be relevant to economic evaluations are listed in Table 2.3.

Table 2.3 Description of costs that can be included in a pharmacoeconomic evaluation.

Type of cost	Description
Cost	All expenses incurred in the provision of health-care products and services. Examples of costs include fixed costs, variable costs, direct medical costs, direct non-medical costs and indirect costs.
Fixed cost	A cost that does not vary with quantity or volume of output provided in the short run (typically, within 1 year). These costs may vary with time, for example, rent, salaries, insurance and equipment lease payments.
Variable cost	Costs that vary with changes in output volume. These included drugs, devices and supplies.
Direct medical cost	Fixed and variable costs associated directly with a medical condition or health-care intervention. These include costs of services and products used in the care of the patient, and may include expenditures for hospital stays, physician visits, medicine, equipment, supplies and administration costs.
Direct non-medical cost	The cost of providing to the patient all non-medical assistance e.g. food, lodging and emergency transport. These costs may be borne by the patient or the institution.
Indirect cost	The cost of lost or reduced productivity resulting from morbidity or premature mortality due to a medical condition or treatment, as well as informal care-giving costs.

Consequences can also be divided in to three categories, viz. direct, indirect and intangible. Direct benefits will be those directly affecting the patient or the health institution e.g. cost savings or increased leisure time. Indirect benefits will be any savings that are made in lost time at work and intangible benefits will include any changes in the quality of life of both the patient and their families.

2.3.4 Decision analysis

Decision-making involves choosing an action after weighing up the risks and benefits of the alternatives. All clinical decisions are made under conditions of uncertainty, however, the degree of uncertainty decreases when the medical literature includes directly relevant, valid evidence. Decision analysis is the application of explicit, quantitative methods to analyse decisions under conditions of uncertainty and it allows one to compare the expected consequences of pursuing different strategies.[113] The process involves designing a decision tree, which is basically an algorithm of the clinical alternatives and sequences of events that occur during the process of an intervention.[121]

After the decision tree has been designed on paper, it can be modelled on a computer. The clinical algorithm is modelled using probabilities and utilities that are obtained either by direct measurement or literature review. The tree is then evaluated in terms of incremental cost-effectiveness ratios and a thorough sensitivity analysis can be performed.

It is not always necessary to use a decision analysis approach in a pharmacoeconomic evaluation, but it is often employed because of the level of sophistication and the numerous advantages it provides[124,130]:

i. Models can be applied to find threshold values for effectiveness or costs, which, would render the intervention cost-effective.
ii. They can be used to synthesise the best available data on effectiveness and cost.
iii. Simple sensitivity analysis can be done with ease on a variety of variables and utilities that may have been estimated or are liable to change in a different setting.
iv. Models can generalise over the site of care delivery and patient-level characteristics, and the results can therefore by considered more relevant to daily practice.

2.3.5 Sensitivity analysis and discounting

Every economic evaluation contains some degree of uncertainty.[121] This is because costs, consequences and probabilities can never really be one hundred percent correct. Cost could be over or under-estimated, some costs and benefits may have been excluded from the analysis, or the effectiveness of each intervention may have been misjudged. Methodological assumptions and areas of uncertainty need to be critically identified and the analysis should, where possible, be reworked, employing the different assumptions or estimates to test the sensitivity of the results and conclusions to such changes.[121]

If large variations in the assumptions or estimates underlying an analysis do not produce significant alternations in the results, then one would tend to have more confidence in the original results. If the converse occurs, more effort is then required to reduce the uncertainty and/or improve the accuracy of the critical variables.[129]

Estimates that would generally require a sensitivity analysis are those which are subject to debate because no estimates were available and informed guesses were made, those due to known imprecision in the estimation procedure, or those incorporating methodological controversy or the potential for different value judgements.[121]

In a pharmacoeconomic analysis, costs and benefits occurring in future years need to be expressed as 'present values'. This procedure is known as discounting.[121,124,129] Discounting is performed because individuals prefer to receive benefits today rather than in the future and payers would prefer to utilise resources in the future. In this manner, resources can be invested in alternative programmes that could earn a return on investment over time.[129]

Future costs must usually be discounted to reflect their current value, because current and future costs are not valued equally. When a program extends over a period of several years, the present value (PV) of the program may be calculated by multiplying the future costs (FC) by a discount factor (DF). This factor depends on two variables:

the number of years into the future that the expense is incurred (n) and the discount rate (r). Discounting can be expressed by the formula in Equation 2.2:[131]

$$PV = FC \times DF_{(n.r)} \qquad \text{(Equation 2.2)}$$

A discount rate of between 3% and 5% is frequently used, but there is no set rule.[129,133] It is recommended that sensitivity analysis be performed for values between zero and 10% to take any uncertainty into account. Costs are discounted whenever a program extends over multiple years, regardless of inflation.[129] Inflation accounts for the change in price, while discounting accounts for time preference with respect to monetary value.[129]

2.3.6 Limitations of pharmacoeconomic analyses

Throughout the process of performing an economic evaluation, many methodological judgements and assumptions are made. Pharmacoeconomic evaluations are not the solution to all problems, they are merely an aid to decision making. The limitations of such studies must be recognised.[132]

One of the greatest limitations of pharmacoeconomic analyses is the lack of standardisation of the methodology. Many guidelines have consequently been developed in order to improve the quality, reproducibility and comparability of the results.[133,134,135,136] Guidelines include recommendations on which costs and consequences to include according to the perspective of the study, the time frame of the study, discounting, handling of uncertainty and the reporting of results.

2.3.6.1 Study frame and scope

Recommendations on study frame and scope outline the costs and effects to be included in the evaluation. Siegel et al[133] suggest that a societal perspective be taken with all costs and consequences being included in the evaluation. The time frame of the evaluation should reflect the time frame of the outcomes, and where necessary,

outcomes should even be extrapolated into the future in order to measure effects on future generations.[133,137]

Siegel et al[133] also suggest that the evaluation be specific to the population affected by the health care intervention. This does however limit the generalisability across other health care settings with different infrastructures and patient populations.[127,138] It is also vital that the therapeutic intervention being evaluated gets compared with the current best practice.[139,140]

2.3.6.2 Components of the numerator and denominator of cost-effectiveness ratios

Various debates have centred around which costs to include in the numerator of pharmacoeconomic evaluations. Consensus has been reached regarding healthcare services, care-giving costs and other costs associated with illness such as travel expenses.[133] No concrete guidelines are available to guide the inclusion of the cost of time, the cost of 'non-health', both related and unrelated future costs and fixed costs such as administration expenses.[133,138]

Ideally, longevity and quality of life should be taken into account when measuring outcomes, but there is no consensus on the instrumentation required to measure such outcomes.[133,137] In conducting a pharmacoeconomic evaluation, the analyst must investigate the effectiveness of an evaluation – the probability of each outcome occurring and the length of time it lasts.[133] These variables should be derived from the best designed and least biased source relevant to the question and the specific population.

A combination of data should be obtained from both RCTs and observational studies in order to maximise both internal and external validity.[137,138,141,142,143,144] Internal validity refers to the extent to which an instrument measures what it is intended to measure.[143] External validity or 'real world' relevance involves the relevance of the results of economic trials to the specific decision-making context of the policy-maker.[143] By utilising a combination of data sources, researchers can obtain values for variables that are, as far as possible, internally valid but also depict what happens in reality. This data can usually be generalised across populations. Further un-

certainties can be modelled using decision analysis techniques to find threshold values for effectiveness or costs, which would render interventions cost-effective.[143]

2.3.6.3 Handling uncertainty

Univariate and multivariate sensitivity analysis should always be performed on all key values and parameters. Reasonable confidence intervals should be based on statistical methods or simulation.[133]

2.3.6.4 Reporting

Guidelines regarding reporting of results suggest that methodology, data-sources and results be transparent.[127,133,145] Studies should report the physical resources used in an intervention as well as the unit price.[127] This will ensure that decision makers are able to extrapolate the results of the evaluation to their own setting. It is finally recommended that outcomes be reported in the form of incremental cost-effectiveness ratios.[127,133,140]

2.3.7 Ethical issues in the use of pharmacoeconomic evaluations

In some cases, unethical incentives are used as a reason for performing the pharmacoeconomic evaluation. Concerns have been raised about potential biases generated by the conflicts of interest that industry-sponsored research creates. It has been found that the majority of pharmacoeconomic evaluations report positive findings for the sponsor's drug.[146,147] Methodology could be carried out in a certain manner that would favour the sponsored drug, alternatively, Barbieri and Drummond[146] suggest that the drug companies will only sponsor the research if the findings are likely to be positive. Research methodologies and incentives should always remain transparent so that readers can determine for themselves the possibility of bias.

The use of pharmacoeconomics as a tool for aiding drug selection and limiting the availability of drugs, introduces various ethical issues. Pharmacoeconomics can be used to determine the most effective way of utilising available resources. In order to

distribute resources equitably, to treat the most common disease entities in communities or populations, resources need to be diverted from one segment to another.[148,149] During this process, many sacrifices may have to be made in order to ensure that the interests of society as a whole are satisfied. Some effective and useful services may have to be terminated in order to offer others that will provide more benefits to the community as a whole when budgets are only adequate to cover the costs of one of the interventions.

Although 'restrictive' formularies have been shown to reduce the overall cost of health-care, there is an ongoing debate as to whether formularies promote the best possible pharmaceutical care or encourage uneven quality and value. Opponents of the formulary system claim that they create barriers to care and may deny patients much-needed therapies.[150]

Pharmacoeconomics often takes the needs of institutions or society as a whole into account, rather than those of the individual.[148,151] It is possible that an intervention will be cost-effective for an individual but cost-ineffective for a community. The formulary system, unless it is relatively flexible, will prevent the individual from receiving that specific intervention.

Drug selection and restriction will always be surrounded by an aura of controversy. Pharmacoeconomic evaluations, when methodologically sound can, however, provide an objective tool for aiding drug selection in a manner that takes the needs of all people into account. However, when considering the needs of the people, equity has to be taken into account, as well as cost-effectiveness.[152]

CHAPTER 3

3 METHODOLOGY

3.1 Introduction

This pharmacoeconomic evaluation of the management of MDRTB by the South African public health service was preceded by a systematic review of the literature. The literature review focussed on two separate areas, namely MDRTB and pharmacoeconomics. In the first component, the physiology of tuberculosis and MDRTB was investigated along with diagnostic methods, epidemiology and risk factors for the disease. Current treatment regimens as well as potential alternatives were also researched. Secondly, a literature review on pharmacoeconomics was performed. Information was gathered on the methodology, limitations and the ethical considerations of performing research of this type.

3.2 Systematic review of the literature

A systematic review of the literature was performed in an attempt to quantify the effectiveness of second-line combination treatment for MDRTB. Because raw data was unable to be collected, an estimate of efficacy, required for the pharmaco-economic evaluation was obtained from published studies.

No RCTs or completed reviews on the effectiveness of MDRTB treatment were identified. Therefore, effectiveness data was obtained from a systematic review of those observational studies that did discuss the outcomes of MDRTB with individualised treatment. Reviews of observational studies present some challenges due to the inherent biases and differences in the study design as opposed to a RCT design.[110]

3.2.1 Review question

What are the literature-derived expected outcomes in terms of mortality, persistent infection, and cure, for individualised therapy and no-treatment of HIV-positive and HIV-negative MDRTB patients?

3.2.2 Description of study outcomes

The variables and characteristics of the studies collected in the literature review are shown in Appendix 2. Only some of the variables were used to assess the study outcomes. Eight variables collected from the studies were included in the meta-analysis:

i. The mortality rate among MDRTB patients.
ii. The survival rate of MDRTB patients.
iii. The mortality rate among the drug-sensitive group.
iv. The survival rate of patients with drug-sensitive TB.
v. The cure rate of MDRTB.
vi. The persistent infection (non-cure) rate of MDRTB patients.
vii. The cure rate of drug-sensitive patients.
viii. The persistent infection (non-cure) rate of drug-sensitive patients.

Other variables, shown in Table 3.1, were collected in order to gather baseline estimates to include in the decision analysis.

Table 3.1 Variables used in the decision analysis model.

Variable	Definition
pDeath_HIV_pos	The probability of death (due to any cause) in HIV-positive patients.
pDeath_HIV_neg	The probability of death (due to any cause) in HIV-negative patients.
pCure_HIV_pos	Of the patients that did not die, the probability of cure in HIV-positive patients.
pCure_HIV_neg	Of the patients that did not die, the probability of cure in HIV-negative patients.
tTx_ind	The average length of treatment when using the individualised approach.
cDrugs_indiv_dly	The average cost of drug treatment when using the individualised approach.
pDie_noTx	The probability of death in those MDRTB patients not receiving drug treatment.
pCure_noTx	Of patients not dying, the probability of cure in those patients not receiving drug treatment.

3.2.3 Study selection criteria

Certain selection criteria were used when assessing study eligibility.

i. Type of intervention used

Patients had to receive individualised treatment for their MDRTB i.e. the patient's drug regimen was to some extent, based on drug susceptibility testing. The range of drug susceptibility testing could be extensive or narrow; drug susceptibility testing could include only the first-line agents, some or all of the second-line drugs as well. Treatment outcomes using protocol regimens were not collected because these were not identical to the drug regimen followed in South Africa.

ii. Type of Study design

The paucity of high quality RCTs necessitated the inclusion of observational studies with and without comparators.

iii. Study population

Data was only collected for patients that had MDRTB defined as having TB caused by bacilli resistant to at least isoniazid and rifampicin. No restrictions were placed on the geographical location of the patients. Patients could be from developed or developing countries, from primary-care or referral centres. Patients of all HIV status were included and the extent of their tuberculosis, as well as the resistance patterns of the bacilli, could range from mild to extensive. All of these characteristics were recorded during the data-collection stage.

iv. Exclusion criteria

Studies were excluded if only first-line drugs were used to treat the MDRTB; if standard regimens of second-line drugs were used; if outcomes of the treatment were not provided and if no patients satisfied the accepted definition of MDRTB. Some studies were also excluded if the full-text articles were not available in South African libraries.

3.2.4 Search strategy

Two searchers determined which studies to include in the systematic review, principle searcher, Nicole Rockcliffe and Dr A.G. Parrish. Both searchers reviewed the abstracts identified by the search engines and determined which articles to include in the review. Differences were resolved, first by obtaining the full-text article and then by discussion as to its relevancy. Only the principle searcher extracted data from the studies.

EMBASE® and Medline®, both OVID® and Pubmed® versions were used to identify potential articles to include in the analysis. Different search strategies were used for each database that was searched due to the different tools and limited access to some of the databases. Tables 3.2, 3.3 and 3.4 summarise the search strategies used for each database. EMBASE® was accessed via Dialog®[153] by choosing 'medicine', and then 'med research' and 'any topic'. Only the EMBASE® box was ticked and

keywords were entered under the 'main subject' heading. Only English language journals from 'all years' were searched.

Table 3.2 Search strategy used on Medline® (Pubmed®).

Search engine: Pubmed®		
Date of search: 06/12/2001		
Search number	**Query**	**Results**
1	antitubercular	13257
2	mycobacterium	39307
3	opportunistic infection	20852
4	TB	72488
5	isoniazid	9948
6	rifampicin	12005
7	ethambutol	3304
8	pyrazinamide	1977
9	PAS	6456
10	para amino salicylic acid	9
11	amoxycillin	5634
12	ampicillin	22535
13	clavulanic acid	2483
14	kanamycin	12169
15	streptomycin	13107
16	ofloxacin	4028
17	ciprofloxacin	8475
18	aminoglycosides	78529
19	cycloserine	1417
20	"drug resistance"	103608
21	MDR	3808
22	MDRTB	30
23	"multidrug resistant tuberculosis"	1331
24	#1 OR #2 OR #3 OR #4	117904
25	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	134890
26	#20 OR #21 OR #22 OR #23	105311
27	#24 OR #25	240109
28	#26 AND #27	26806
29	efficacy	158863
30	cure	26666
31	"randomised controlled trial"	4174
32	"randomised clinical trial"	11249
33	RCT	852
34	outcome	297622
35	#29 OR #30 OR #31 OR #32 OR #33 OR #34	461492
36	#28 AND #35 AND tuberculosis	393

Table 3.3 Search strategy used on Medline® (OVID®).

Search engine: OVID®; 1966 - Oct 2001 Date of search: 23/01/2002		
Search number	**Query**	**Results**
1	tuberculosis, multidrug-resistant/	1197
2	inh resistance.tw.	44
3	isoniazid resistance.tw.	131
4	rifampicin resistance.tw.	167
5	2 or 3 or 4	318
6	1 or 5	1471
7	case report/	1009891
8	case report.tw.	84092
9	7 or 8	1017351
10	6 not 9	1354
11	prognosis/	174122
12	treatment outcome/	117480
13	treatment failure/	6951
14	disease-free survival/	8638
15	11 or 12 or 13 or 14	293391
16	randomised controlled trials/	20247
17	prospective studies/	136799
18	follow-up studies/	242326
19	longitudinal studies/	29205
20	cohort studies/	32393
21	case-control studies/	38056
22	multicenter studies/	6675
23	meta-analysis/	3956
24	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	461145
25	10 and 24	103
26	10 and 15	108
27	25 or 26	179

Table 3.4 Search strategy used for EMBASE®.

Database: EMBASE® (limited free access via Dialog®) Date of search: 20/03/2002		
Search number	**Query**	**Results**
1	tuberculosis AND((multidrug OR inh OR isoniazid OR rifamp?) AND resistance)	195

Where only preliminary results from studies were available, they were included in the review only if they provided sufficient details as to the outcomes of treatment. Where the e-mail addresses of the authors were available, they were contacted in order to retrieve more information. No hand searching of journals was done but reference lists of relevant articles were searched for additional articles for inclusion into the review. Some papers were unable to be retrieved because they were not accessible through the South African University Library Services.

3.2.5 Study quality assessment

For the purpose of this review, a checklist (see Appendix 2), was used during the data collection stage to guide the quality assessment of the various types of observational studies. They were then classified by the primary reviewer as being of 'good' or 'doubtful' quality.

3.2.6 Data extraction

The primary reviewer extracted data into a database, (Microsoft Access 2000®). The data extraction form can be reviewed in Appendix 2. During the extraction process, various assumptions and modifications were made when handling the data. These are listed below:

i. Specific treatment regimens were classified as 'individualised' if they were not the same as the standard, protocol regimen used in South Africa.
ii. Where non-conventional definitions of MDRTB were used, where possible, outcomes of patients with true MDRTB were recorded. If stratification of the study outcomes for patients with true MDRTB was not possible, the study was excluded.
iii. If HIV status of the patients was not mentioned, they were assumed to be HIV sero-negative. Where patients were of unknown HIV status, they were also assumed to be negative.
iv. When recording the frequency of adverse drug reactions (ADRs), where possible, all types of ADRs were recorded, not only the serious ones that required a change of therapy. Where this was the only figure provided, it was recorded.
v. Patients that were lost or not included in the author's analysis were included for the purpose of this review as 'treatment failures' unless an outcome was provided at a last contact.
vi. If patients were cured before they were lost to follow-up, they were classified as 'cured'.
vii. Where outcomes for some patients were not accounted for, the patients were classified as 'treatment failures'.

viii. Patients dying in the first week of treatment were included in the analysis as 'deaths'. They were not excluded.

ix. In cases where not all deaths could be accounted for according to HIV status, they were assumed to occur in the HIV-positive group as these patients have a greater likelihood of death than HIV-negative patients.

x. Death due to all causes was measured, not only death due to TB.

xi. Length of follow-up was taken from the first day of treatment.

xii. Appropriate follow-up was classified as follow-up until death or at least 6 months after treatment completion.

xiii. Where length of treatment was given as a range, the median was recorded .

xiv. If no mention was made as to whether outpatient treatment was directly observed or not, it was assumed that it was not directly observed.

xv. If a description of the institution was not provided it was assumed to be a primary or secondary care centre; if the study was multi-institutional, it was recorded as a specialised care centre; academic hospitals were also classified as specialised centres.

3.2.7 Data synthesis

Data was synthesised in two sections. Firstly, a meta-analysis was performed using the relative-risk ratios of both the cure and death rates of MDRTB versus drug-susceptible TB patients. The meta-analysis was performed using STATA 7®. No sub-group analysis was done due to the small number of studies able to be included in the analysis.

STATA 7® weighted the studies according to the formula provided in Equation 3.1. The relative risk ratios for the meta-analysis were calculated according to Eauation 3.2 provided below.

$$W_i = \frac{1}{N_i/(E_{cont} \times E'_{exp})} \qquad \text{(Equation 3.1.)}$$

Where: W_i = The weight assigned to each study.

N_i = The number of patients in each study.

E_{cont} = The number of patients with the expected outcome in the control group.

E'_{exp} = The number of patients in the experimental group not experiencing the desired outcome.

$$RR = \frac{E_{exp}/N_{exp}}{E_{cont}/N_{cont}} \qquad \text{(Equation 3.2)}$$

Where: E_{exp} = The number of subjects in the experimental group with the specified end-point.
N_{exp} = The total number of subjects in the experimental group.
E_{cont} = The number of subjects in the control group with the specified end-point
N_{cont} = The total number of subjects in the control group.

The meta-analysis was not used to generate estimates for the economic analysis due to the widely disparate range of studies. A meta-analysis was however performed for the five studies that provided treatment outcomes for both the experimental and control groups in order to determine whether any relationship did exist between MDRTB and drug-susceptible patients.

The small number of trials having control groups that could be included in the meta-analysis prevented the derivation of reliable effect sizes. Estimated cure and death rates in MDRTB patients treated with individualised drug regimens were calculated from the published studies in order to gather some estimate of effect to use in the decision analysis. Cure and death rates were estimated separately for HIV-positive and negative patients. Estimated death and failure rates were also calculated for patients not receiving any drug treatment. Certain characteristics that could possibly have an effect on the outcomes of the studies were recorded and qualitatively analysed. Features that were qualitatively assessed for effect on study outcome include:

i. Study was performed in a developed or developing country.
ii. Study was carried out in a referral centre.

iii. Length of follow-up.
iv. The average number of resistant drugs.
v. Proportion of patients receiving two or more drugs to which the bacilli were susceptible.
vi. Study design.
vii. Patient group was generalisable.
viii. Study quality.
ix. Outpatient treatment was directly observed.

3.3 Pharmacoeconomic analysis

In order to determine which treatment method would be more beneficial in terms of costs and therapeutic outcomes, a complete pharmacoeconomic evaluation was performed. The process of performing this pharmacoeconomic evaluation is discussed below in the step-wise fashion described in the literature.[124]

3.3.1 Defining the problem

From the viewpoint of the South African public health service, is it preferable to offer patients with MDRTB individualised treatment, a standard regimen of second-line drugs, or to withhold drug therapy and offer only palliative care?

3.3.2 Determine the perspective of the study

In South Africa, treatment for TB is free of charge to all members of society. Because the treatment is paid for by the State, this research was undertaken from the perspective of the South African Department of Health. Only costs incurred by the State were included in the evaluation.

3.3.3 Determine appropriate alternatives and outcomes

The alternatives for this evaluation are those given in the South African MDRTB treatment guidelines:

A standard protocol regimen:

Patients not responding to standard, first-line therapy and the WHO re-treatment regimen should have their sputum analysed for resistance against isoniazid, rifampicin and ethambutol. Once the patient has been diagnosed with MDRTB, they should then be sent to a referral centre, if not already there for initiation of drug therapy. All patients will receive the regimen described in Table 1.5. Patients with ethambutol resistance receive cycloserine instead of ethambutol.

Individualised treatment:

Patients failing standard treatment and re-treatment regimens, have a sputum culture performed as well as the full spectrum of drug susceptibility tests. In South Africa, this would include isoniazid, rifampicin, ethambutol, streptomycin, kanamycin, ethionamide, thioacetazone and ofloxacin or ciprofloxacin. In the tertiary referral centres, an individual drug regimen would be designed for each patient according to the results of the drug susceptibility tests. The initial treatment should consist of at least four drugs chosen from nine second-line drugs available in South Africa, to which the bacilli have been shown to be susceptible. The nine drugs available are streptomycin, kanamycin, amikacin, ethionamide, pyrazinamide, ofloxacin, ciprofloxacin, ethambutol and cycloserine. Where possible, at least three of these should not have been administered to the patient previously and all patients should receive an aminoglycoside for at least four months. A patient's progress would then be monitored by monthly smears and cultures until at least three consecutive cultures are negative, and then every three months until treatment is completed. Susceptibilities should be requested at month three and six if cultures are still positive.

Non-drug management:

This alternative was included in order to be able to compare the usefulness of expensive drug treatment. It has been noted that patients with late-stage AIDS have a very poor prognosis in general, and there may be occasions where a patient's condition as a consequence of AIDS is so poor, that it is inappropriate to embark on a course of toxic chemotherapy for MDRTB. Under these conditions it may once again be appropriate to give only palliative treatment.[44] This management strategy could include a limited period of hospital care as well as a limited number of routine laboratory tests at diagnosis.

Three possible outcomes were identified for patients with MDRTB, regardless of the management option received; patients could die, be cured or they could become chronic carriers of TB.

3.3.4 Select the appropriate pharmacoeconomic method

Two economic methods were used to evaluate the alternatives. A CME was performed, based on the assumption that the outcomes of the various alternatives could not be proved unequal. A second analysis was performed for comparative purposes using a cost-effectiveness model that assumed that the outcomes of treatment were indeed unequal. The costs of treatment were measured both in terms of the 'number of cases cured' and the number of 'years of life saved'. The quality of the additional years saved by each of the management options was not taken into account.

3.3.5 Measure and collect variables

Variables were collected from the systematic review that was performed using the published literature reporting outcomes of MDRTB treatment, the results of the DOTS-plus pilot programme in the Northern Province, the South African Department of Health, the PharMIS website[154] and from individuals involved in the treatment of MDRTB at various centres in South Africa. All cost variables included in the decision analysis are listed in Table 3.5.

Table 3.5 Cost variables required for the decision analysis.

Name	Description
Drug Costs:	
cCiprofloxacin	The cost of one 500mg ciprofloxacin tablet
cCycloserine	The cost of one cycloserine 250mg capsule
cEthambutol	The cost of one 400mg ethambutol tablet
cEthionamide	The cost of one 250mg ethionamide tablet
cKanamycin	The cost of one 3ml (1g) vial of kanamycin
cOfloxacin	The cost of one 400mg ofloxacin tablet
cPyrazinamide	The cost of one 500mg pyrazinamide tablet
cStreptomycin	The cost of 5ml of streptomycin from a multi-dose vial
cDrugs_individual	The average cost of drugs per day using individual approach
Other direct medical costs	
cInjec_swabs	The cost of injections, needles and swabs for one administration
cCulture	The cost of performing a sputum culture
cSensitivity	The cost of performing a sensitivity analysis for 1 drug
cHospital	The cost of spending one day in hospital

3.3.6 Resources and schedules

The economic evaluation was based on published data from various sources as no prospective data could be collected for MDRTB treatment outcomes. Resources needed to complete the research were identified. These included access to journal articles, the medical databases and computer software necessary to perform the systematic review of the literature and the decision analysis.

3.3.7 Establish probabilities and outcomes

Death, cure and treatment failure rates using the individualised treatment regimen were derived from the systematic review of the observational studies available. The same information was gathered for the standard, protocol regimen from the results of the DOTS-plus pilot programme in the Northern Cape.[51] Data for patients not receiving any drug treatment was also gathered from published literature, where patients did not receive any treatment for various reasons. The 'years of life saved' for patients with each outcome were estimated from life-expectancy tables for the general population and HIV-positive patients.

3.3.8 Perform a decision analysis

A decision tree model was used so that the effect of assumptions and estimations could be assessed through modelling. The use of a model allows decision makers to pre-emptively identify the variables that contribute significantly to cost and/or consequences of the management program. Data required for monitoring and evaluating purposes can also be identified prior to program implementation. A decision analysis model of the disease was created using DATA 3.0 by Treeage®. This model was used to generate the expected cost of each alternative. These costs were compared alone, as well as in the form of an ICER that compared the cost of the alternatives with respect to the appropriate outcome measures.

3.3.9 Sensitivity analysis and discounting

Univariate and multivariate sensitivity analyses were performed on each variable used in the decision analysis using DATA 3.0. The effects of various assumptions on the outcome of the decision analysis were assessed and threshold values were identified.

Treatment for MDRTB usually lasts between 1 and 2 years depending on the patient's response, and outcome is often apparent within the first year. No discounting was performed in this evaluation because of the short time frame.

3.3.10 Report, discussion and recommendations

In the final step of the pharmacoeconomic evaluation, the results were reported and discussed and recommendations were made, based on the outcomes of the evaluation.

CHAPTER 4

4 RESULTS

4.1 Systematic review of the literature

The literature dealing with the outcomes of MDRTB treatment was limited. Although there were a number of papers investigating the risk factors of the disease, the extent of resistance, epidemiology and outbreak patterns, treatment outcomes were only addressed in approximately 40 publications.

4.1.1 Results of the literature search

Different keyword searches were performed on the search engines. Pubmed® identified the greatest number of articles. This was probably due to the more extensive list of keywords used for the search as compared to the other search engines. Table 4.1 lists the articles that were identified and included in the systematic review as well as the database, which made reference to the article. In total, 29 papers were included.

The primary reviewer, Nicole Rockcliffe, reviewed the abstracts and full-text papers in order to identify relevant articles for inclusion into the review. Only papers reporting the treatment outcomes of patients with MDRTB, defined as TB caused by organisms resistant to at least isoniazid and rifampicin, being treated with individualised treatment regimens were selected for inclusion into the review. No restrictions were placed on the design of the study or the setting in which the study took place. Studies were excluded if they were reviews of other papers, if they did not report the outcomes of the patients, if first-line or standardised regimens were used to treat the patients or if the studies were not available in South African libraries.

As expected, there was only a limited amount of overlapping between the search engines; 51.72% between Pubmed® and EMBASE®; 44.83% between Pubmed® and OVID® and 37.93% between EMBASE® and OVID®. These figures are summarised

in Table 4.2. One cannot compare these figures directly because different search strategies were used for each search engine. On hand searching of the article reference lists, only two additional articles not identified by the search engines were found.[155,156]

Table 4.1 Articles included in the systematic review and the databases from which they were identified.

	Medline®			
	Pubmed®	**OVID®**	**EMBASE®**	**Ref List**
Total Articles identified by each search engine:	393	177	195	
Hong Kong Chest Service[157]	✓		✓	
Frieden[158]	✓			
Edlin[34]				✓
Lockman[159]			✓	
Fischl[160]	✓			
Pretet[161]	✓		✓	
Mangunnegoro[162]	✓	✓	✓	
Davies[163]	✓			
Turett[164]	✓	✓	✓	
Anastasis[165]	✓			
Telzak[65]	✓	✓	✓	
Geerligs[166]	✓	✓	✓	
Lambregts-van Weezenbeek[167]	✓	✓		
Park SK[168]	✓	✓	✓	
Park MM[169]	✓			
Flament-Saillour[170]	✓	✓		
Franzetti[171]	✓	✓	✓	
Yew[172]	✓	✓	✓	
Salomon[173]	✓	✓	✓	
Telzak[174]	✓		✓	
Maranetra[175]			✓	
Mannheimer[176]	✓	✓		
Schaaf[177]	✓		✓	
Tahaoglu[178]		✓		
Goble[64]			✓	
Zhang[179]		✓	✓	
Hadiarto[180]	✓	✓	✓	
Suo[181]	✓	✓	✓	
Maranetra[182]	✓		✓	
# articles included in review:	23	15	19	1
Total number of articles included in review:		29		
Articles identified by each database as % of all included	79.31%	51.72%	65.52%	

Table 4.2 Extent of overlapping between the medical databases for the articles that were included in the systematic review.

Search engine	Articles identified	% Overlap
Number of articles in EMBASE® and Pubmed®	15	51.72
Number of articles in EMBASE® and OVID®	11	37.93
Number of articles in Pubmed® and OVID®	13	44.83

4.1.2 Studies included in review: descriptive information

The majority of the papers that were identified and included in the review were case series. Some of the papers were case control studies that aimed to determine the risk factors for contracting or developing MDRTB. Studies varied in size, geographical location and quality and in the amount of detail reported. Some of the study characteristics are listed in Table 4.3.

The articles included 21 cases series, seven case-control studies and one cohort study. Quality was 'good' in 12 and 'doubtful' in 17. The quality assessment instrument is in Appendix 2. A single assessor judged quality and was unblinded to the results.

Table 4.3 Descriptions of the studies included in the review.

Author of article	Classification of study	Study quality	Patients included	The proportion of HIV + patients	Date of study	Developed or developing country	Institution description	Generalisable patient group	Ave # resistant drugs	prop pts receiving > 2 susceptible drugs	DOT used
Hong Kong[157]	Cohort study	Doubtful	22	0	June 1986 to Jan 1988	Developed	Specialised	Yes	6.00		No
Frieden[158]	Case series	Doubtful	267	0.86	I Jan 1990 to 1 Aug 1993	Developed	Specialised	No	6.00		No
Edlin[34]	Case control	Doubtful	18	1	Jan 1989 to Apr 1990	Developed	Specialised	No	3.00	0.39	No
Lockman[159]	Case control	Good	46	0	1 Jan 1994 to 31 Dec 1996	Developing	Specialised	No		0.76	No
Fischl[160]	Case control	Doubtful	62	1	1 Jan 1988 to 31 Dec 1990	Developed	Specialised	No	3.21	0.40	No
Pretet[161]	Case control	Doubtful	39	0	1 Jun 1986 to 31 Dec 1988	Developed	Specialised	Yes	5.00	0.95	No
Mangunnegoro[162]	Case series	Doubtful	58	0	Oct-95	Developing	Specialised	No	3.00	1.00	No
Davies[163]	Case series	Doubtful	21	0.38	1 Jan 1996 to 31 Dec 1996	Developing	Primary	No			Yes
Turett[164]	Case series	Good	38	0.89	1 Jan 1991 to 31 Dec 1993	Developed	Primary	Yes	2.91	0.83	No
Anastasis[165]	Case series	Preliminary results	31	0	1 Jan 1991 to April 1994	Developing	Specialised	No	3.00		No
Telzak[65]	Case series	Good	25	0	1 Mar 1991 to 31 Sept 1994	Developed	Specialised	No	4.00	0.92	No
Geerligs[166]	Case series	Good	44	0	1 Jan 1985 to 1 Sep 1998	Developed	Specialised	No	5.00		Yes
Lambregts-van Weezenbeek[167]	Case series	Doubtful	19	0	1993 to 1994	Developed	Specialised	No	2.00		No
Park SK[168]	Case series	Doubtful	99	0	1993 to 1996	Developing	Specialised	No	4.20		Yes
Park MM[169]	Case series	Good	173	0.52	1 Jan 1983 to 31 Dec 1993	Developed	Specialised	Yes	3.00	0.64	No
Flament-Saillour[170]	Case control	Good	51	0.16	1 Jan 1994 to 31 Dec 1994	Developed	Specialised	Yes	3.40	0.71	No
Franzetti[171]	Case series	Good	90	1	1 Jan 1988 to 31 Dec 1996	Developed	Specialised	No	4.00		No
Yew[172]	Case series	Good	63	0	Feb 1990 to June 1997	Developing	Specialised	Yes	3.20		Yes
Salomon[173]	Case series	Doubtful	13	1	1 Jan 1993 to 31 Aug 1993	Developed	Specialised	No	5.50	1.00	Yes
Telzak[174]	Case series	Good	12	1	1993	Developed	Specialised	No	3.80	1.00	Yes
Maranetra[175]	Case series	Doubtful	22	0	Ongoing	Developing	Primary	No	2.00		No
Mannheimer[176]	Case control	Good	13	1	1 Jan 1991 to 31 Dec 1993	Developed	Specialised	Yes	4.00		No
Schaaf[177]	Case control	Doubtful	240	0	1987 to 1993	Developing	Primary	Yes	3.60		No
Tahaoglu[178]	Case series	Good	158	0	March 1992 to Oct 1999	Developing	Specialised	Yes	4.40	1.00	Yes
Goble[64]	Case series	Good	171	0	1 Jan 1973 to 31 Dec 1983	Developed	Specialised	No	6.00	0.60	No
Zhang[179]	Case series	Doubtful	317	0	1992 to 1995	Developing	Primary	No			No
Hadiarto[180]	Case series	Doubtful	37	0	?	Developing	Specialised	No	2.56		No
Suo[181]	Case series	Doubtful	17	0	March 1992 to July 1993	Developing	Primary	No	4.40		No
Maranetra[182]	Case series	Doubtful	81	0	1991 to 1995	Developing	Primary	No			No

i. Patient inclusion and exclusion criteria

In some studies the inclusion and exclusion criteria were explicitly and clearly stated, in others, very few details were provided and the characteristics of the patients were not clear.[34,163,164,174,175,178,179] In the studies that did provide sufficient detail, the patients that were included in each had very different characteristics. Some studies only included patients with culture confirmed MDRTB[161, 162, 163] while others included patients that were only clinically suspected of having MDRTB.[174] One study limited their patient group to those having culture confirmed MDRTB as well as a positive sputum smear.[158]

The definitions of MDRTB also varied between studies. The majority used the standard definition of resistance to isoniazid and rifampicin, but some included patients resistant to isoniazid and streptomycin[34], resistant to any two antituberculous drugs[160] or patients resistant to all three of isoniazid, rifampicin and streptomycin.[157] One study limited their intake to patients resistant to isoniazid, rifampicin, streptomycin and ethambutol.[158]

Exclusion criteria for patients in the various studies included malignancy, pregnancy, hepatic or renal failure.[161,162] In retrospective studies, patients were excluded if files and records were untraceable.[159,169] Exclusion criteria of some of the studies that may introduce confounding and bias, include the exclusion of non-compliant and lost patients,[157,172,173] patients interrupting treatment due to adverse drug reactions[168], patients dying before receiving adequate therapy,[172,64] and patients that had other undefined, serious concomitant diseases.[161] The majority of the studies recorded the HIV-status of the patients but only one study provided information on the proportion of patients concomitantly taking anti-retroviral medication.[176]

ii. Care setting

Of the 29 studies, 22 were set either at specialist care facilities or were national surveys. Seven of the studies were based in an outpatient setting. There was generally sufficient information provided about the facility initiating the treatment, but often details of duration of hospitalisation and post-discharge management were

unclear. Only seven studies mentioned that DOTS was used when patients were not in hospital.[163,166,168,172,173,174,178]

iii. Time of entry into study

The time of entry of patients into the studies was often unclear, possibly because the majority of the studies were retrospective and the information was not available from the records. Of the 29 studies, 18 did not provide any details about the patient's history.[34,158,160,164,165,166,167,168,169,170,171,172,175,176,177,179,181,182] Three studies stated that patients were receiving treatment for the first time[159,163,173] and one study stated that all patients had received both standard and re-treatment regimens before commencing with the second-line drugs.[157] The patients in the remainder of the studies had had TB for periods that ranging from one month to 45 years.[64,161,162,174,178 ,180] Some of the patients were receiving second-line treatment for the second time while for others it was their first treatment episode.

iv. Extent of disease and resistance

Various studies used different methods to describe the extent of the patient's disease. The prevalence of extrapulmonary and cavitatory TB was generally always mentioned.[34,157,158,159,160,161,170,171,172,173] Four studies described the disease as extensive but failed to define 'extensive'.[64,160,172,178]

The studies that were included in the review almost all cited the number of drugs to which the patient was resistant. There was little standardisation between the studies. Some studies tested for resistance only to the first-line drugs,[34,65,159,167,175,176,180] while other studies tested between nine and 16 drugs for resistance.[157,158,161,166,168,171,172,173 174,178] It is therefore impossible to compare the average number of drugs to which the patients in each study were resistant. There was also not sufficient information provided to recalculate the figures taking into account only the first-line drugs to which the bacilli were resistant in order to compare the studies.

v. Laboratory procedures

Fifteen studies made no mention of the laboratory methods used to diagnose resistance and determine drug susceptibility.[34,65,158,155,165,169,170,175,176,179,180,181,182] and 14 provided only scanty details.

vi. Treatment

Despite the fact that the aim of many of the papers was to assess the outcome of MDRTB treatment with second-line drugs, details provided in the papers were insufficient to reproduce the studies elsewhere. The drugs used, dosages used, median number of drugs received by each patient, the median number of susceptible drugs received, the length of time each drug was given for, levels of patient care during treatment and whether DOT was practiced were not mentioned in most papers. Some studies did mention the proportion of patients that received more than two drugs to which the organisms were susceptible.[34,64,65,159,160,161,162,164,170,171,173,174,178] Fourteen studies provided sufficient details to calculate a median daily cost of drug treatment using the individualised approach.

vii. Treatment outcomes

Once again, the lack of information as well as the lack of standardisation amongst the different studies hinders the process of pooling the results. Raw data was often not provided and thus, where treatment outcomes were defined and calculated in different ways, they could not be recalculated in a uniform manner. In the study, by Telzak et al,[174] outcomes were measured in terms of survival and did not differentiate between cures and treatment failures. Studies by Yew[172] and Goble et al[64] excluded patients that died before receiving two and six months of treatment respectively while two other studies measured treatment outcomes in terms of a single sputum culture.[158,180]

In studies that did evaluate outcomes in terms of success, death and failure, definitions were not uniform. Successful treatment was variously defined as requiring between one and three consecutive negative sputum cultures at any stage during treatment,[157, 160,161,162,163] conversion of sputum cultures by the end of treatment,[159,167] or sustained

negative cultures 12 to 24 months after the completion of treatment.[178] Some studies did not define treatment success.[33,65,165,166]

Making the assumption that a six-month follow-up period is the minimum satisfactory follow-up period, only 23 of the 29 studies could be said to have had an appropriate length of follow-up.[64,65,159,160,161,162,163,164,165,166,167,168,171,173,174,175,176,177,178,179,180,181]
Only 21 studies actually mentioned or provided sufficient information to calculate the average or median length of follow-up.[64,65,159,164,166,167,168,169,170,171,173,174,175,176,177,178,179,180,181]

The effect of these factors on treatment outcomes is unknown. It must however be noted that the differences in patient characteristics, definitions, laboratory techniques and the manner in which outcomes were classified and evaluated affect both the internal and external validity of the results and thus prevent the data from being pooled quantitatively.

4.1.3 Meta-analysis

The decision to statistically combine any observational studies is controversial because of uncontrollable confounding and bias.[183,184] However, meta-analysis does provide a way of graphically displaying results in a way that allows readers to see the effect of sample sizes on the weights of each study. It also allows for a formal assessment and explanation of heterogeneity amongst the studies.

A meta-analysis was performed for the five studies that provided treatment outcomes for both the experimental and control groups in order to determine whether a relationship did exist between MDRTB and drug-susceptible patients. Pooled risk ratios of the probability of both death and cure in MDRTB patients as compared to drug-susceptible TB patients were generated. Table 4.4 contains the raw data using death as an outcome.

Table 4.4 The number of deaths occurring in each study in MDRTB as well as drug-susceptible TB patients.

Author	Patients dying (MDRTB)	Patients not dying (MDRTB)	Patients dying (suscep TB)	Patients not dying (suscep TB)
1. Lockman[159]	13	33	5	41
2. Lambregts-van Weezenbeek[167]	0	19	110	1 458
3. Flament-Saillour[170]	19	32	5	46
4. Mannheimer[176]	8	5	8	23
5. Schaaf[177]	115	125	28	75

Table 4.5 contains the calculated risk ratios with confidence intervals as well as the pooled risk ratio that takes into account the weight of each individual study. Sample size was the only factor taken into account when weighting the studies. Figure 4.1 displays these results graphically.

Table 4.5 Risk ratios of the probability of death in the MDRTB and drug-susceptible patient groups.

Study:	RR	95% Conf. Interval		% Weight
Lockman[159]	2.60	1.01	6.70	8.82
Lambregts-van Weezenbeek[167]	0.35	0.02	5.51	4.91
Flament-Saillour[170]	3.80	1.54	9.40	8.82
Mannheimer[176]	2.38	1.14	4.98	8.34
Schaaf[177]	1.76	1.25	2.48	69.12
M-H pooled RR	2.00	1.51	2.65	
Heterogeneity chi-squared = 4.49 (d.f. = 4) p = 0.34				
Test of RR = 1: z = 4.85 p = 0.00				

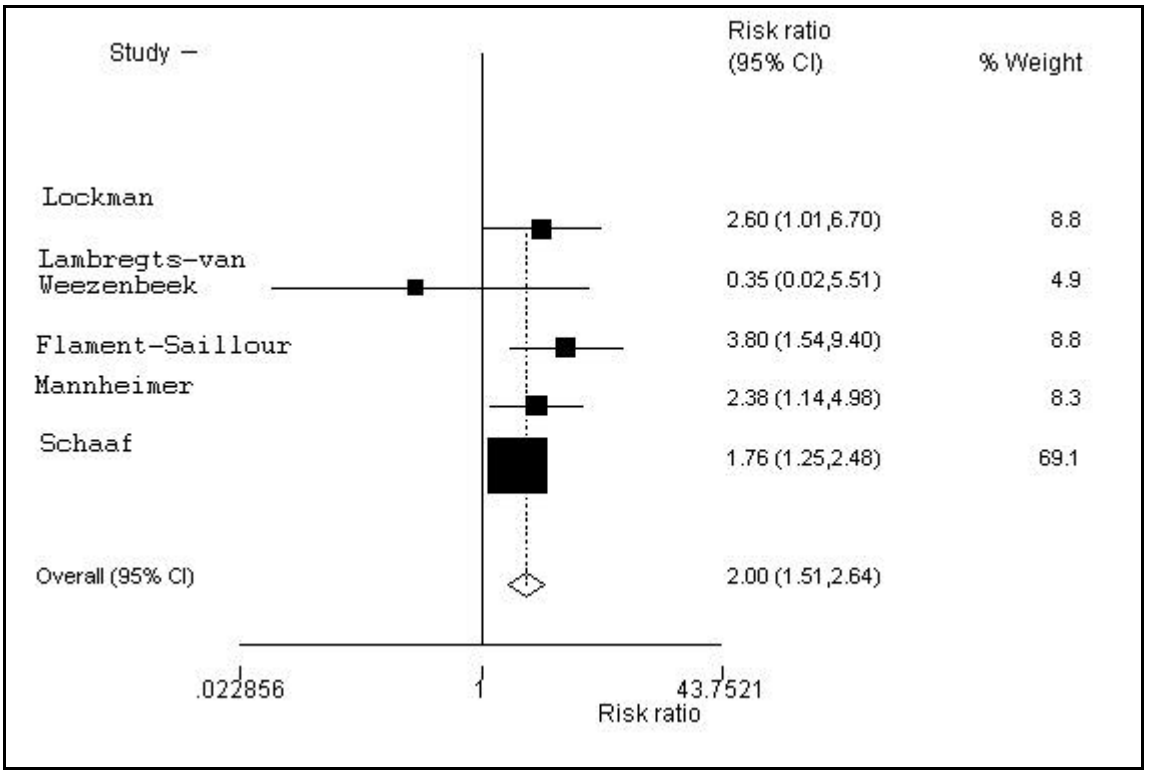

Figure 4.1 Meta-analysis of the likelihood of death in MDRTB versus drug-susceptible TB patients.

The pooled risk ratio of two indicates that MDRTB patients are 100% more likely to die than patients with drug-susceptible TB even with appropriate treatment. The result is largely influenced by Schaaf's[177] study, which contributed most of the weight because its large sample size. The study by Schaaf[177] was a case-control study of HIV-negative patients in a primary care setting that was classified as being of 'doubtful' quality.

The study design and the care setting of each of the other studies varied in most aspects except for the provision of DOTS (see Table 4.3). The different studies were from a combination of developed and developing countries, set in both primary and specialised-care settings and were classified as having variable quality. Study samples had varying proportions of HIV-positive patients. The average number of drugs to which the bacilli were resistant was not known in Lockman's study.[159] Patients in the study by Lambregts-van Weezenbeek[167] were only resistant to an average of two drugs. This could explain the low death rate in this study compared to the others. Although some characteristics of the studies were different, the test for

heterogeneity gives a non-significant probability value of 0.34, which might suggest that any variation in the results is due to sampling variation.[96]

Only four studies provided sufficient information to be included in the meta-analysis using cure as an outcome. Raw data is represented in Table 4.6 and results of the meta-analysis are shown in a tabular form in Table 4.7.

Table 4.6 The number of MDRTB and drug-susceptible patients cured after treatment.

Author	Patients cured (MDRTB)	Patients not cured (MDRTB)	Patients cured (suscep TB)	Patients not cured (suscep TB)
1. Lockman[159]	17	29	28	18
2. Lambregts-van Weezenbeek[167]	9	10	1 286	282
3. Flament-Saillour[170]	17	34	45	6
4. Mannheimer[176]	1	12		
5. Schaaf[177]	65	175	50	53

Table 4.7 Results of meta-analysis assessing the likelihood of cure in MDRTB and drug-susceptible TB patients.

Study:	RR		95% Conf. Interval		% Weight
Lockman[159]	0.61		0.39	0.95	16.11
Lambregts-van Weezenbeek167	0.58		0.36	0.93	17.72
Flament-Saillour170	0.38		0.25	0.56	25.90
Schaaf 177	0.56		0.42	0.74	40.27
	M-H pooled RR	0.52	0.43	0.63	
Heterogeneity chi-squared = 3.33 (d.f. = 3) p = 0.34					
Test of RR = 1: z = 6.72 p = 0.00					

The results of the meta-analysis are represented graphically in Figure 4.2. These results indicate that MDRTB patients are approximately 50% less likely to get cured than drug-susceptible patients. Again the heterogeneity test gives a non-significant probability value of 0.34, indicating a fairly homogenous set of results.

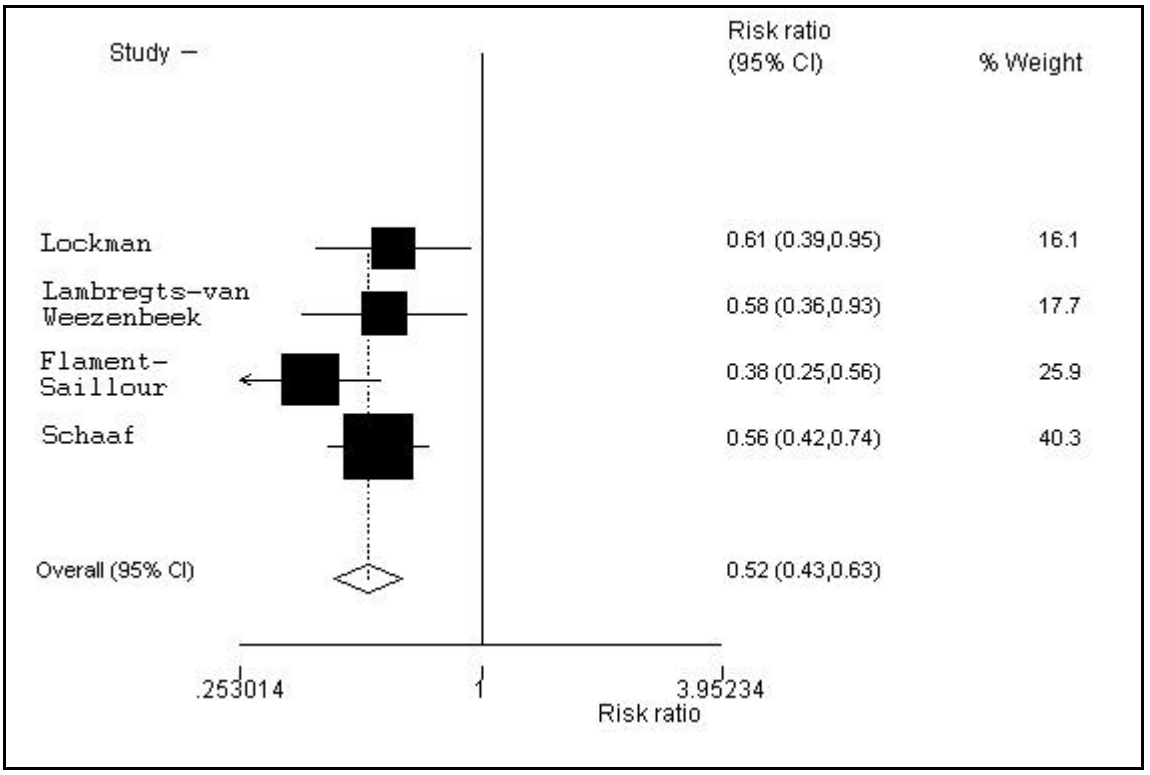

Figure 4.2 Risk ratios of the likelihood of cure in MDRTB versus drug-susceptible TB patients.

Funnel plots (plots of the effect estimates against sample size) are used to detect publication bias in meta-analyses.[185] Funnel plots are based on the fact that precision in estimating the underlying treatment effect will increase as the sample size of component studies increase.[97] In the absence of bias, results should resemble a symmetrical, inverted funnel. Figure 4.3 depicts the funnel plot of the studies used to assess the relationship between deaths in MDRTB versus drug-susceptible TB patients. Figure 4.4 shows the funnel plot of the relative risk ratio of the number of cured patients in each group. On visual inspection, neither of the figures showed any degree of symmetry. The results of this meta-analysis may therefore not be valid due to existence of publication and other biases.[185]

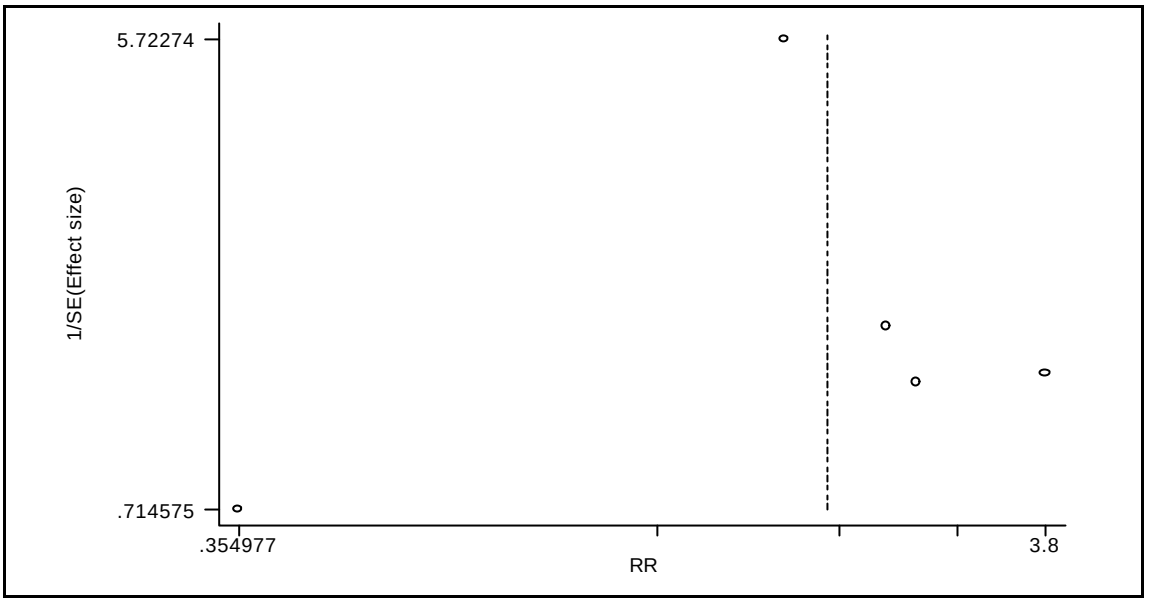

Figure 4.3 Funnel plot of the studies included in the meta-analysis assessing the probability of death in MDRTB vs. drug-susceptible TB patients.

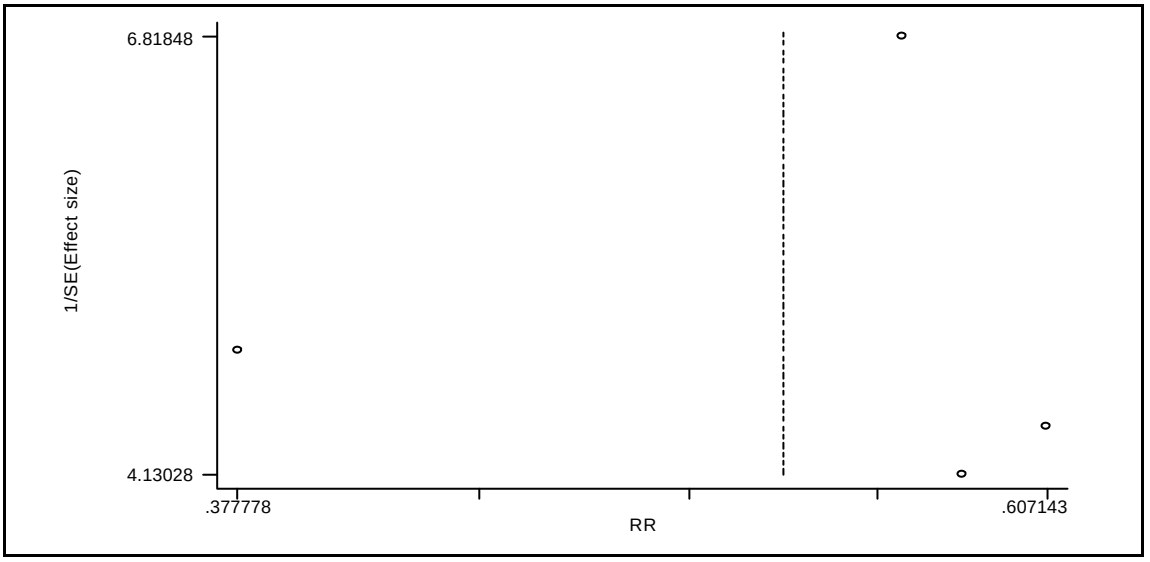

Figure 4.4 Funnel plot of the studies included in the meta-analysis assessing the probability of cure in MDRTB vs. drug-susceptible TB patients.

4.2 Pharmacoeconomic evaluation and decision analysis

A decision analysis model was used in order to determine the costs of treating MDRTB from the South African Department of Health's point of view. The major reason for employing this tool was the poor quality of the data that was available on which to base the analysis. Estimations of the costs were varied in the model in order to assess the impact of the uncertainty. The costs and outcomes of the three

alternative treatment management strategies for the disease, viz. an individualised drug regimen, a protocol regimen and no therapy, were then compared using a cost-effectiveness approach. Death, cure or chronic MDRTB were the three outcomes identified for the disease, and in this evaluation they were measured in terms of the 'number of cases cured' as well as the 'years of life saved' for each end-point.

4.2.1 Variables included in the decision analysis

In order to model MDRTB for the decision analysis, various costs, probabilities and variables had to be collected. Estimations of cost were based on the assumption that the South African MDRTB treatment guidelines[44] were being followed. Baseline estimates for probabilities and the other variables required for the decision analysis model were obtained from the systematic review of the literature, or from the "Guidelines for the implementation of DOTS-Plus in context of the South African TB control programme".[51]

Table 4.8 summarises the costs and variables that were included in this pharmacoeconomic analysis. Direct variable costs include the average daily cost of medication, hospitalisation and laboratory costs for patients treated with either the individualised approach, or the protocol drug regimen approach. Variables pertaining to all three alternatives include the proportions of HIV-positive patients, patients weighing over 50kg and the proportion of MDRTB patients resistant to ethambutol. The time spent in hospital, the length of treatment, the number of laboratory tests and the probabilities of cure and death were determined for each individual alternative.

Table 4.8 Variables and costs included in the decision analysis model of MDRTB treatment.

Costs included in the decision analysis model
Daily cost of medication
Laboratory costs
Daily cost of hospitalisation in a referral centre
Variables
The proportion of HIV-positive patients
The proportion of patients weighing more than 50kg
The proportion of patients resistant to ethambutol
The proportion of treatment time spent in hospital by patients with each of the alternative outcomes
The length of drug treatment
The number of laboratory tests performed for each treatment alternative
The probability of death in both HIV-positive and negative patients for each alternative
The probability of cure in both HIV-positive and negative patients for each alternative

Various costs and related variables were excluded from this pharmacoeconomic analysis. All patients, regardless of the treatment arm, would have initial sputum cultures and drug susceptibility tests performed in order to confirm the diagnosis of MDRTB. Many patients would have this initial diagnosis made at a facility other than a referral centre. These health care facilities may or may not have appropriate laboratory facilities with which to perform the above tests and sputum samples may thus have had to be transported at the expense of the Health Department to an appropriate laboratory. The cost of transporting sputum samples at the initial diagnosis has not been included in this pharmacoeconomic evaluation because it was assumed to be a pre-entry cost.

X-rays, cultures, smears and drug susceptibility tests could be performed at a later stage of the treatment period. For patients being treated with the protocol regimen, it was assumed that subsequent laboratory tests could be performed at local laboratories, thus avoiding additional transport costs. For patients treated with the individualised regimen, it was assumed that they would be managed at a referral centre until an appropriate regimen has been identified. No transport of sputum samples was considered necessary since all referral centres have access to appropriate laboratory facilities.

One expense that was excluded but may well have a significant effect on the outcome of this analysis was the cost of treating adverse drug reactions. The second-line drugs

are known to generate serious adverse effects.[186] Adverse effects include hepatitis, visual disturbances, cutaneous reactions, nausea and vomiting, dizziness, tinnitus and deafness.[157,172,186] Appropriate action for each of these events varies depending on the side effect. Drugs can be withdrawn and possibly reintroduced at a lower dose, or anti-emetics can be provided. Some effects, such as the development of hepatitis may require hospitalisation, intense monitoring and multiple laboratory tests. The expenses incurred by each of these actions ranges from hundreds to thousands of Rands. No valid estimations of the cost of managing adverse reactions were obtained and the decision analysis model is limited in that these costs are not considered.

4.2.2 Estimations of variables and costs included in the analysis

Baseline estimates for the costs and variables were obtained from various sources. This section provides the details of various calculations or the origins of estimates that were used.

4.2.2.1 Per-diem cost per day of hospitalisation in a referral centre.

For the purposes of this economic evaluation, a baseline per diem cost of R161.58 for hospitalisation, excluding drugs was used. This figure was derived using information from the Brooklyn Chest Hospital, the TB referral centre of the Western Cape.[187] The annual budget of the referral centre, excluding drug costs (R18 000 000), was divided by the total number of beds in the facility (305) and the number of days in a year (365.25). The drug budget was excluded from this calculation because MDRTB drugs cost substantially more than normal TB drugs and they need to be calculated separately. It was assumed that all beds in a specialised care centre such as a tuberculosis referral centre cost the same. For the sake of simplicity it was assumed that all patients, if hospitalised, were sent to a TB referral clinic as suggested by the guidelines, and that they were not treated at institutions with inadequate facilities.

The per diem cost of hospitalisation at José Pearson, the referral TB centre in the Eastern Cape was calculated to be R88 per day[188]. This figure was used as the minimum value for the sensitivity analysis, while R359, the daily inpatient boarder cost at a referral centre for externally funded patients was used as the maximum.[189]

Staffing costs were assumed to be included in the per diem figures. This assumption can be made due to the nature of government institutions and the fact that they employ a set number of staff regardless of daily fluctuations in bed occupancy.

4.2.2.2 Daily cost of medication

The costs of the individual drugs were obtained from the PharMIS website[154] in March 2002. This site was chosen as it provides easy access to up-to-date South African tender prices of pharmaceutical products. PharMIS could not provide the costs of the second-line drugs that were not available on the South African tender. Estimated costs of these drugs were obtained from other sources. Table 4.8 summarises the both local and international unit costs of the antituberculous agents. Exchange rates of $10.47 (US) and $5.73 (Australian) [190] being equivalent to one Rand were used to convert the international costs into South African Rands. As can be seen in table 4.8, there is a fairly good correlation between the South African and International prices of the drugs after conversion into Rand values.

Table 4.8 South African and International estimations of the cost of antituberculous drugs in Rands.

	Source	
Drug	**South Africa (Rands)**	**International (Rands)***
Isoniazid 100mg	0.03	0.037
Rifampicin 450mg	0.58	(150mg tab = R0.33)
Rifampicin 600mg	1.10	
Pyrazinamide 500mg	0.23	0.29
Ethambutol 400mg	0.25	0.21
Streptomycin 1g	1.33	0.69
Kanamycin 1g	6.62	3.98
Amikacin 500mg	7.00	13.62
Ethionamide	1.23	1.91
Ciprofloxacin 250mg	6.11	0.40
Ofloxacin 400mg	10.46	
Cycloserine 250mg	17.79[α]	5.64
Capreomycin 1g		261.94[β]
Clofazimine 100mg	0.77	0.84
Rifabutin 150mg		28.09[χ]
PAS 1g		0.57[δ]
Thioacetazone and isoniazid 50/100		0.05
Thioacetazone and isoniazid 150/300		0.10
Co-amoxiclav 750/375	1.60	
Clarithromycin 500mg	81.19	
Syringes, needles and swabs	0.76	

* Value from International drug price indicator guide except where otherwise indicated[191]
[α]The cost of cycloserine was obtained via the Eastern Cape Department of Health[194]
[β]Estimated cost of capreomycin[192]
[χ]Estimated cost of rifabutin from Australian schedule of pharmaceutical benefits[193]
[δ]Cost of PAS from WHO MDRTB guidelines[28] in 1995. Inflated by 2% p.a[24] for seven years.

4.2.2.2.1 Individualised approach

With the individualised approach, physicians select a number of second-line agents from a list of drugs that are active against *M. tuberculosis*. In South Africa the drugs that are available are similar to those given to patients during the protocol regimen. In other countries a variety of additional second-line agents are available in addition to those registered in South Africa. These include para-amino salicylic acid, Rifabutin and capreomycin. Clofazimine and Thioacetazone are available in South Africa but not on the public health tender.

When DOTS-plus was first introduced in South Africa, Brooklyn Chest Hospital in the Western Cape was the only facility to utilise the individual approach. They have subsequently also opted to follow the protocol approach.[187] There was therefore no local estimate available for the average daily cost of individualised treatment.

Drug usage patterns for the cohorts of patients in the published studies were analysed and used to generate an average daily-drug cost for the study groups using the current South African costs of the drugs. A depot levy of 8% was added to the cost of the drugs.[194] An international estimate was used for those drugs unavailable on South African tender. In the analysis of the daily drug cost of individualised treatment, the effect of excluding the drugs not available in South Africa was examined.

Appendix 3 contains the spreadsheet that was used to analyse the number of patients taking each drug in each of the studies. A minimum dose was calculated for patients weighing less than 50kg as well as a maximum dose for those weighing greater than 50kg. The average daily drug cost for each patient cohort was then calculated by multiplying the number of patients taking each drug by the unit cost per tablet or injection and the number of units required by patients taking either the minimum or maximum dose. The average daily drug costs from the collection of studies were then combined to generate a mean daily cost of individualised drug therapy. Insufficient information was provided to determine the duration of treatment for each of the drugs, therefore, in order to simplify the calculation it was assumed that all patients received all of the drugs on all days. This is not the case with the aminoglycosides, which are stopped after three to four months. The calculated daily cost is therefore over-estimated, but since they only contribute a minimal amount to the total daily cost, this overestimation is only slight. Table 4.9 contains a summary of this information.

Table 4.9 Drug usage and average daily drug costs (in Rands) of individualised regimens used in published studies.

Drug	DDD		Frieden [158]	Hong Kong [157]	Fischl [160]	Pretet [161]	Mangun-negoro [162]	Telzak [65]	Geerligs [166]	Franzetti [71]	Yew [172]	Salomon [73]	Telzak [174]	Maranet-ra [175]	Tahaoglu [178]	Goble [64]
	Patients less than 50kg	Patients over 50kg	Number of patients in each study taking drug													
Isoniazid	200mg	300mg	240	0	29	0	0	0	36	8	63	0	1	0	0	45
Rifampicin	450mg	600mg	237	12	29	0	0	0	5	7	63	0	4	0	0	22
Pyrazinamide	1 500mg	2 000mg	236	4	29	19	50	0	38	6	34	2	5	22	50	101
Ethambutol	800mg	1 200mg	214	14	25	15	50	0	42	8	29	1	9	11	36	62
Streptomycin	750mg	1 000mg	30	0	22	6	1	0	0	3	0	0	3	0	8	16
Kanamycin	750mg	1 000mg	100	7	0	15	20	2	40	0	58	4	2	22	15	70
Amikacin	750mg	1 000mg	0	0	0	0	0	7	0	2	0	0	1	0	120	0
Ethionamide	500mg	750mg	116	12	0	19	0	13	16	0	29	9	11	0	127	126
Ciprofloxacin	500mg	750mg	175	0	14	0	0	13	0	5	0	4	0	0	0	0
Ofloxacin	400mg	800mg	87	10	0	32	50	10	38	0	63	6	12	22	126	0
Cycloserine	500mg	750mg	120	0	0	4	0	11	5	0	46	10	8	0	142	98
Capreomycin	750mg	1 000mg	109	3	0	2	0	8	0	0	0	4	3	0	15	108
Clofazamine	100mg	100mg	53	0	9	2	0	2	0	0	3	0	0	0	11	17
Rifabutin	450mg	600mg	0	13	0	39	0	0	9	3	0	0	0	0	15	0
PAS	10g	12g	48	0	0	2	0	4	0	0	7	0	2	22	124	50
Thiacetazone & Isoniazid	100/200mg	150/300mg	0	0	0	0	0	0	4	0	0	0	0	11	0	0
Co-amoxiclav	750/375mg	1 500/750mg	7	0	0	0	0	0	1	0	4	0	0	0	44	0
Clarithromycin	750mg	1 000mg	0	0	0	0	0	0	2	0	0	0	0	0	27	0
Daily drug cost for cohort; all patients taking minimum dose (Rands)			30 293.30	1 870.66	251.34	4 317.69	683.77	2 329.45	1 748.59	340.15	2 782.32	1 297.23	1 066.63	486.47	14 087.60	25 793.00
Daily drug cost for cohort; all patients taking maximum dose (Rands)			42 169.50	2 574.02	373.28	6 010.84	1 264.57	3 269.17	2 639.16	466.78	4 455.80	1 842.71	1 558.39	786.01	20 509.60	3 4994.20
Number of patients in each cohort			267	18	29	39	50	23	44	8	63	11	12	22	148	171
Daily cost per patient; minimum dose (Rands)			113.46	103.93	8.67	110.71	13.68	101.28	39.74	42.52	44.16	117.93	88.89	22.11	95.19	150.84
Daily cost per patient; maximum dose (Rands)			157.94	143.00	12.87	154.12	25.29	142.14	59.98	58.35	70.73	167.52	129.87	35.73	138.58	204.64

The median, mean and weighted mean values were calculated. The weighted mean was calculated by multiplying the average cost in each study by the number of patients in each study as a proportion of the total number of patients in all of the studies. Each method of pooling the results yielded a slightly different result as can be seen in Table 4.10. When the costs of the drugs not registered in South Africa were included in the calculations, the daily cost of an individualised regimen could range from R8.67[160] to R150.84[64] for patients taking the minimum dose and R12.87[160] to R204.65[64] for patients taking the maximum dose. After excluding the drugs not available in South Africa, the estimated daily costs dropped dramatically. The Fishl study[160] again provided the lowest estimate as no unregistered drugs were used in this cohort of patients. The drugs used by the patients in the Tahaoglu study[178] cost the most after excluding the unregistered drugs; R50.87 and R80.12 for patients taking the minimum and maximum doses respectively.

Table 4.10 Estimated daily drug costs from 14 studies reporting on the treatment outcomes of MDRTB using second-line agents.

		Daily cost of individualised regimen (Rands)		
		Median (Range)	**Mean (95% CI)**	**Weighted mean**
Average daily cost (including drugs not available in SA)	Patients weighing less than 50kg	92.04 (8.67-150.84)	75.22	96.52
	Patients weighing more than 50kg	134.22 (12.87-204.65)	107.20	135.82
Average daily cost (excluding drugs not available in SA)	Patients weighing less than 50kg	22.41 (8.67-50.87)	26.06	30.88
	Patients weighing more than 50kg	35.26 (12.87-80.12)	41.79	48.52

The mean daily costs of R26.06 and R41.79 for patients below and above 50kg respectively, excluding the drugs not registered in South Africa were used as the estimates to be included in the decision analysis. A cost of R0.76 was added to each of these values in lieu of using one syringe (10ml, R0.18), needle (R0.52) and swab (R0.06) per day.[154]

These estimated costs were reduced by 96% for the sensitivity analysis. This figure was chosen because it is the maximum discount obtained for a drug by public health experts, the WHO, Harvard Medical School and Medecins Sans Frontieres (MSF).[195] These discounts were obtained by the negotiation of bulk purchases and the use of generic drugs. The average costs of individualised therapy, including the second-line

drugs not available in South Africa, as found in the Goble study[64] were used for the upper limits of the estimated daily costs for patients weighing above and below 50kg.

4.2.2.2.2 Protocol regimen

Baseline daily drug costs were calculated for the protocol regimen using the guidelines from South Africa. Costs were calculated allowing for differences in doses for patients above and below 50kg, for the substitution of ofloxacin with ciprofloxacin, and the use of cycloserine for patients with bacilli resistant to ethambutol. Table 4.11 provides the cost per dose of each drug that is given to patients as well as the cost of injections and swabs used during drug administration. The additional cost of a syringe (10ml, R0.18), needle (R0.52), and a swab (R0.06), sourced by PharMIS[154] was added to the cost of kanamycin.

Table 4.11 The cost per dose of drugs provided to patients during the protocol regimen

		Daily Dosage					
		Patients weighing under 50kg			Patients weighing over 50kg		
	Cost per dosage unit	Dose:	Number of units/ dose	Cost per dose	Dose:	Number of units/ dose	Cost per dose
Intensive phase: 4 months							
Kanamycin 1g and injection	6.62	750	0.75	5.73	1 000	1	7.38
Ethionamide 250mg	1.23	500	2	2.47	750	3	3.70
Pyrazinamide 500mg	0.23	1 500	3	0.70	2 000	4	0.94
Ofloxacin 400mg or	10.45	400	1	10.45	800	2	20.90
Ciprofloxacin 250mg	6.19	500	2	12.38	750	3	18.57
Ethambutol 400mg or	0.25	800	2	0.51	1 200	3	0.76
Cycloserine 250mg	17.79	500	2	35.58	750	3	53.37
Continuation phase: 12 to 18 months							
Ethionamide 250mg	1.23	500	2	2.47	750	3	3.70
Ofloxacin 400mg or	10.45	400	1	10.45	800	2	20.90
Ciprofloxacin 250mg	6.19	500	2	12.38	750	3	18.57
Ethambutol 400mg or	0.25	800	2	0.51	1 200	3	0.76
Cycloserine 250mg	17.79	500	2	35.58	750	3	53.37

Table 4.12 summarises the total cost of medication for both the intensive and follow-up phases, for patients both under and over 50kg as well as the differences encountered when different fluouroquinolones are used. For patients under 50kg, ofloxacin is the cheaper alternative, while ciprofloxacin is slightly cheaper for patients weighing more than 50 kg. Although a single ofloxacin tablet is more expensive,

patients under 50kg only need take one 400mg tablet of ofloxacin while it is recommended that they take two ciprofloxacin tablets.

Table 4.12 Total costs of drug therapy for both the intensive and follow-up phase of treatment (Protocol regimen).

Cost per day	Below 50kg	Above 50kg
Intensive phase		
Ciprofloxacin and ethambutol	21.78	31.35
Ciprofloxacin and cycloserine	56.86	83.96
Ofloxacin and ethambutol	19.85	33.68
Ofloxacin and cycloserine	54.93	86.29
Follow-up phase		
Ciprofloxacin and ethambutol	15.35	23.03
Ciprofloxacin and cycloserine	50.43	75.64
Ofloxacin and ethambutol	13.42	25.36
Ofloxacin and cycloserine	48.49	77.97

Table 4.13 summarises the costs incurred during the treatment periods that last varying lengths of time. The total costs for the various groups of patients are provided as cost per day as calculated during the first four months of treatment (intensive phase), and then the average cost per day as calculated over 22 months (four months intensive phase plus 18 months follow-up treatment). Patients may then receive treatment for five or seven days a week, depending on whether they are in an in-patient or outpatient setting.

Table 4.13 Total costs of drug treatment for groups of patients with varied treatment times (Protocol regimen).

			Per day	4 months intensive phase		22 months (Including intensive phase)	
				5 days/wk	7 days/wk	5 days/wk	7 days/wk
Below 50kg	Ethambutol resistant	Ciprofloxacin	56.86	4 548.72	6 368.21	22 703.09	31 784.33
		Ofloxacin	54.93	4 394.23	6 151.92	21 853.36	30 594.71
	Ethambutol sensitive	Ciprofloxacin	21.78	1 742.74	2 439.84	7 270.18	10 178.25
		Ofloxacin	19.85	1 588.24	2 223.54	6 420.45	8 988.63
Above 50kg	Ethambutol resistant	Ciprofloxacin	83.96	6 717.09	9 403.92	33 948.64	47 528.10
		Ofloxacin	86.29	6 903.34	9 664.68	34 973.05	48 962.27
	Ethambutol sensitive	Ciprofloxacin	31.35	2 508.11	3 511.36	10 799.27	15 118.98
		Ofloxacin	33.68	2 694.37	3 772.12	11 823.68	16 553.15

To simplify the decision analysis model, the average daily drug cost was used for the cost-effectiveness evaluation. Because the daily drug cost is higher during the

intensive phase, the longer the total treatment time, the lower the average daily cost. For the purposes of the decision analysis, the 22-month period was used to generate a baseline value. The figures used in the decision analysis model are shown in Table 4.14.

Table 4.14 Average daily drug costs for various sub-groups of patients.

Patient wt	Resistance	Fluoroquinolone used	Daily cost of medication
Below 50kg	Ethambutol resistant	Ciprofloxacin	51.60
		Ofloxacin	49.67
	Ethambutol sensitive	Ciprofloxacin	16.52
		Ofloxacin	14.59
Above 50kg	Ethambutol resistant	Ciprofloxacin	77.16
		Ofloxacin	79.48
	Ethambutol sensitive	Ciprofloxacin	24.54
		Ofloxacin	26.87

Decision analysis models used the data pertaining to ciprofloxacin because the efficacy data from the Northern Province was based on the use of this drug, rather than ofloxacin. Sensitivity analysis was performed for this variable because of the extensive variability in the average daily cost due to the use of an alternative fluoroquinolone and the total treatment period. The range that was used for the sensitivity analysis was the baseline cost less 96% with a maximum cost that was double that of the baseline cost. This range covers the differences incurred due to the factors mentioned above.

4.2.2.3 Laboratory costs

Patients having MDRTB require chest X-rays and sputum microscopy, but also additional laboratory procedures to identify and isolate the mycobacterial species. It is also necessary to determine the susceptibilities of the organism to antimycobacterial drugs. These additional services are time-consuming and they employ reagents and special techniques that are not routinely used in either the study of other species or basic tuberculosis services. In general, only laboratories with competent staff and sufficient volumes of work provide these services. There is often only one such laboratory in each province capable of providing these services. Procedures are occasionally performed in private laboratories at additional costs. The protocol

regimen attempts to minimise overall costs by limiting the number of laboratory procedures that are performed.

4.2.2.3.1 Culture and identification

Inoculation of a specimen onto culture medium is necessary for genotypical investigations, precise species identification and drug susceptibility testing.[4] After the Mycobacteria are cultured on one of a variety of media (Löwenstein-Jensen or Middelbrook), the Mycobacterium tuberculosis complex (*M tuberculosis, M bovis or M africanum*) is identified with the Niacin test.[4,70] The costs of these procedures in state-owned laboratories are shown in Table 4.15.

Table 4.15 Prices of laboratory procedures from state-owned and private laboratories (2002).[187,196]

Laboratory procedure	Public hospital laboratory
Culture	R49.35
Niacin identification test	R44.65
Drug susceptibility test (per drug)	R44.65
AFB x 3	R31.43

4.2.2.3.2 Drug susceptibility tests

The total cost of the drug sensitivity tests is calculated according to the number of drugs tested. For the decision analysis model the State prices were used as baseline values while the private-sector figures were included in the range during the sensitivity analysis.

4.2.2.3.3 Chest X-rays and sputum microscopy

According to the 2001 Uniform Patient Fee Schedule, a single chest X-ray costs approximately R28.00.[189] This is in accordance with a report by Dehoney, which stated that in developing countries, chest X-rays cost between $2 and $30.[197] This same report provided estimates for the cost of three sputum smear examinations at $3 or approximately R31.43.

4.2.2.4 HIV status

Even with appropriate treatment, the HIV status of a patient has an influence on the final treatment outcome. The decision analysis had to take into account the different rates of cures and deaths in these two groups. By separating these outcomes, it is also possible to determine the impact of HIV and MDRTB co-infection on the outcomes of the pharmacoeconomic analysis.

In the Northern Cape DOTS-plus report[51], 64% of 129 MDRTB cases were HIV-negative, 7% were HIV-positive and the remainder refused to be tested. It is unknown whether this figure is underestimated or not. It is known that HIV-positive patients are no more likely to become infected with MDRTB than are HIV-negative patients[54,55,56]. The majority of the case-reports collected in the systematic review dealt with a total of 1 699 HIV-negative patients compared to 578 HIV-positive patients. A baseline value of 25% (range seven to 50%) was used for the purposes of the decision analysis model. The baseline estimate was obtained by calculating the proportion of HIV-positive patients in the published studies (578/2 277 patients). The prevalence of HIV in MDRTB patients in the Northern Cape was used as the lower estimate and an upper estimate of 70%[33] was chosen to represent the maximum number of patients having TB with concomitant HIV-infection.

4.2.2.5 Weight of patients

A variable was also created for the proportion of patients that weigh over 50kg. Doses of antituberculous drugs are determined by mass and patients below 50kg receive lower doses of drugs than patients over 50kg. This will obviously have implications on the total cost of drug therapy. There were no published reports on the weight distribution of MDRTB patients, but two studies did report the average weight of the patient group.[162,172] In the study by Yew et al, it was deduced that 14 of the 63 patients (22%) weighed more than 50kg.[172]

Using the estimate calculated above, it was assumed that approximately 22% of patients would have a mass greater than 50kg (95% CI: 14 to 34%). The studies reviewed did not provide an interqaurtile range for weight. However, it is conceivable that most patients would be underweight at this stage of their disease, and the proportion of patients weighing more than 50kg was assumed to range from 14 to 34%

4.2.2.6 The proportion of patients that have bacilli resistant to ethambutol

According to the South African MDRTB guidelines[44], when following the protocol regimen approach, patients resistant to ethambutol should receive cycloserine. The Northern Cape DOTS-plus report states that 53% of cases were resistant to ethambutol. As this figure increases, the total cost of medication used in the protocol regimen will increase because of the cost of cycloserine (R17.79 per tablet). The variable was varied through from 0% to 100% for the sensitivity analysis, as no other sources of data were available with which to estimate the value of this variable.

4.2.2.7 The length of drug treatment

The number of days over which drug treatment is provided is possibly one of the most sensitive factors in this decision analysis. Treatment is usually provided seven days a week on an in-patient basis and five days a week for outpatients. The length of treatment is also determined by the survival period and, with the individualised approach, the doctor's discretion. Patients can die after one day of drug therapy or complete therapy and die years later. Patients failing treatment can have treatment stopped after the fifth month when sputum has failed to covert to negative, or they can continue treatment for up to five years. Even patients that are cured can receive effective treatment for periods ranging from nine to 36 months. In the decision analysis model, variables were created for each treatment scenario and each patient group in that scenario.

4.2.2.7.1 Individualised treatment

Due to the large variability in the lengths of treatment recorded in the various published studies, treatment length was assumed to be the same as that for the protocol regimen i.e. 456 days. For the sensitivity analysis, this was varied from nine months of outpatient treatment alone (180 days) to three years, with treatment being given seven days a week (1 008 days)

For patients failing treatment but not dying, the health-care team could decide to terminate treatment at five months after sputum failed to convert to negative. Alternatively, medication could still be continued for up to 5 years. A treatment duration ranging from 100 to 1 680 days, with an average of 496 days was used in the model. These figures were derived after assuming that patients would receive two-months of in-patient treatment followed by 22 months of outpatient treatment. Upper and lower limits were obtained by assuming that treatment could be provided for a minimum of five months, with treatment given five times per week, to a maximum of five years, with treatment being given seven days per week.

Survival data was reported in eight of the studies that were included in the review.[34,160,164,169,170,171,174,176] The median time of death, as indicated from these studies, was 114 days after the start of treatment. In the study by Turret,[164] the time to death varied from one to 1 027 days after the start of treatment. These figures were used as the upper and lower estimates for this variable.

4.2.2.7.2 Protocol regimen

The time to death was obtained from a cohort of 16 patients that died in the Northern Cape in 1999. The average time to death for new cases was 10.4 months ± 1.8 and 7.9 ± 5.8 months for old cases.[51] The average time to death for all patients was calculated to be 8.8 months or 247 days. The maximum treatment length used for the two groups (death and failure) was only three years, as with this regimen the health care team is advised to stop treatment if the patient is not responding it is therefore unlikely that a patients would receive treatment for five years.[44]

For patients cured, it was assumed that the average patient received four months of intensive-phase therapy followed by eighteen months of follow-up therapy. If two months were spent in hospital and the remainder as an outpatient, the average patient would receive treatment for a period of 456 days. Calculations were based on a 28-day month. The treatment period could range from 280 days to 1 008 days. The lower end of the range assumes that patients receive at least twelve months of therapy after sputum conversion with treatment given five days per week, while the higher value assumes that the patient was cured after a maximum of three years of treatment given seven days per week.

4.2.2.8 The number of days spent in hospital

Apart from the medication, the cost of hospitalisation is the highest expense incurred during the treatment of MDRTB, the total cost obviously depending on the number of days spent in hospital. For purposes of modelling, the variable for the time spent in hospital was included as a proportion of the treatment length for both the individualised and the protocol drug regimens. For non-drug therapy, individual variables were created.

4.2.2.8.1 Individualised treatment and protocol regimen

It is recommended that patients spend the initial treatment period in hospital until they become non-infectious.[44] In general, patients will receive drug treatment for two months after their sputum cultures become negative.[65,168,172,173,178] The average patient receiving protocol treatment could thus be assumed to remain in hospital for two months (56 days) out of the 456 days on which he/she received treatment. This equates to a proportion of 0.12. This figure was used for both the protocol regimen and the individualised treatment option. Upper and lower limits of zero and one were assigned to this variable for the sensitivity analysis because no data is available to calculate a reasonable range in which this value will fall.

Calculating the time spent in hospital as a proportion of the duration of treatment may result in over or underestimations of the actual time spent in hospital. For patients with a short duration of treatment, i.e. those that die early on in the treatment period,

the actual time spent in hospital may be underestimated, whereas time spent in hospital may be overestimated for those with lengthy treatment regimens.

4.2.2.8.2 Non-drug management

Three variables were created for the length of time spent in hospital for patients not receiving drug therapy. It was assumed that all patients would be hospitalised for various lengths of time, despite not receiving drug treatment. In hospital, patients would be able to receive adequate nutrition, be isolated and thus prevent further spread of the disease and their condition could be monitored. The length of time that would be spent in hospital by these patients is dependent on both the condition of the patient, their living conditions at home and the discretion of the medical staff.

Estimations of the time spent in hospital by patients being managed without drugs and the type of facility in which these patients are housed are not available. It was therefore assumed that patients that die would be more ill, would require more care and would spend 20 days in a referral hospital, while surviving patients (cures and treatment failures) would spend 10 days in hospital. Because of the uncertainty in the actual values of these variables, a wide range was used for the sensitivity analysis. All figures were varied from one to 720 days.

4.2.2.9 The number of laboratory tests performed

With each treatment alternative, different numbers of laboratory tests are required. Variables were created for the number of X-rays, sputum smears, cultures (isolation and identification) and drug susceptibility tests that are performed for patients in each treatment branch.

4.2.2.9.1 Individualised approach

When using the individualised treatment approach, one culture should be performed at diagnosis with monthly cultures thereafter until three consecutive negative sputum cultures have been achieved. Cultures should also be performed every three months until the end of treatment, plus every six months for two years after treatment has

been completed. This yields an estimated total of 15 cultures when treatment continues for two years.

Again, no reliable data is available that indicates the actual number of tests that are performed. Therefore, for the decision analysis, a formula based on the length of treatment was used to estimate the number of cultures performed for patients treated with individualised regimens. All patients were assumed to have at least three sputum cultures performed during the first three months of treatment. During the remainder of their treatment, patients not responding to treatment would be monitored closely and were assumed to have sputum cultures performed every month. Those responding favourably to treatment could have the tests performed as seldom as every six months. The average patient was assumed to have sputum cultures performed every three months. Equation 4.1 was used to describe the above:

$$\text{Number cultures}_{indiv} = 3 + [(tTx_{indiv} - 84)/(28 \times iCult_{indiv})] \qquad \text{(Equation 4.1)}$$

Where: tTx_{indiv} = the length of treatment received by patients treated with individualised regimens

$iCult_{indiv}$ = the monthly intervals at which sputum cultures are performed.

Using the individualised approach, the organism has to be tested for drug susceptibility to all drugs including second-line agents. Drugs include rifampicin, isoniazid, ethambutol, streptomycin, ethionamide, kanamycin, ofloxacin and thioacetazone. This means that a minimum of 8 tests have to be performed at least once at the time of diagnosis. The following equation was used to describe the frequency at which these tests are performed (Equation 4.2):

$$\text{Number drug sensitivity tests}_{indiv} = 8 + [(8 \times tTx_{indiv})/(28 \times iSens_{indiv})] \qquad \text{(Equation 4.2)}$$

Where: $iSens_{indiv}$ = the monthly intervals at which drug susceptibility tests are performed.

The majority of patients were assumed to have two more batches of susceptibility tests performed i.e. every eight months in an average 16-month treatment regimen. The testing interval was varied from as rarely as every 16 months to as often as every month because no data was available to generate a more accurate estimate. Patients were also assumed to have one chest X-ray and three sputum smears performed every month for the duration of their treatment.

4.2.2.9.2 Protocol regimen

The MDRTB guidelines suggest that patients being treated with the protocol regimen have one sputum culture performed at the time of diagnosis, one after two months of treatment, one after completion of the intensive phase and then every six months until the end of treatment. The sputum of each patient should also be tested for susceptibility to isoniazid, rifampicin and ethambutol. The actual frequency at which tests are performed is not known. It was therefore assumed that the MDRTB guidelines would be followed implicitly and all patients would have five sputum cultures performed and susceptibility tests for three drugs. Patients receiving the protocol regimen were also assumed to have one chest X-ray and three sputum smears performed monthly.

4.2.2.9.3 Non-drug management

With this treatment alternative, the condition of patients would still be monitored, but to a slightly lesser extent. This would be done in order to assess the patient's progress and whether or not they were still infectious. The average patient was assumed to receive two sputum cultures and have a minimum of two drug susceptibility tests (isoniazid and rifampicin) performed in order to confirm their diagnosis of MDRTB. For the sake of monitoring a patient's progress, they were also assumed to have two chest X-rays and two sets of three sputum smears performed, one set at diagnosis and another in order to determine the final outcome of the patient. There is, however, no data to justify these assumptions.

4.2.2.10 Estimates of outcomes

Probabilities of each outcome were obtained from the collection of case reports from the systematic review. Where possible, information was obtained according to HIV status. Variables for the decision tree were calculated on the basis that patients either died or lived. The patients that lived would then either become cured or develop chronic MDRTB. Cure rates would thus depict the number of patients that were cured as a proportion of patients that did not die.

4.2.2.10.1 Individualised treatment

Median death and cure rates for both HIV-positive and HIV-negative patients were obtained from the literature. The raw data for these groups of patients can be found in Tables 4.16 and 4.17 respectively.

Table 4.16 Treatment outcomes of HIV-negative patients treated with the individualised approach.

Author	Patients included	HIV neg patients	Deaths (HIV neg)	pDeath (HIV neg)	Patients not dying	Cured (HIV neg)	pCure (HIV neg)
Girling[157]	22	22	0	0.00	22	2	0.09
Frieden[158]	267	37	4	0.11	33	4	0.12
Lockman[159]	46	46	13	0.28	33	17	0.52
Pretet[161]	39	39	2	0.05	37	14	0.38
Mangunnegoro[162]	58	58	0	0.00	58	32	0.55
Davies[163]	21	13	5	0.39	8	3	0.38
Turett[164]	38	4	0	0.00	4	4	1.00
Anastasis[165]	31	31	11	0.36	20	14	0.70
Telzak[65]	25	25	1	0.04	24	24	1.00
Geerligs[166]	44	44	6	0.14	38	38	1.00
Lembregts-van Weezenbeek[167]	19	19	0	0.00	19	9	0.47
Park SK[168]	99	99	0	0.00	99	60	0.61
Park MM[169]	173	83	32	0.39	51	33	0.65
Flament-Saillour[170]	51	43	12	0.28	31	17	0.55
Yew[172]	63	63	5	0.08	58	43	0.74
Maranetra[175]	22	22	0	0.00	22	17	0.77
Schaaf[177]	240	240	115	0.48	125	65	0.52
Tahaoglu[178]	158	158	6	0.04	152	77	0.51
Goble[64]	171	171	63	0.37	108	64	0.59
Zhang[179]	317	317	0	0.00	317	244	0.77
Hadiarto[180]	37	37	0	0.00	37	19	0.51
Suo[181]	17	17	6	0.35	11	7	0.64
Maranetra[182]	81	81	0	0.00	81	13	0.16
TOTALS:	2 039	1 669	281		1 388	820	

Table 4.17 Treatment outcomes of HIV-positive patients treated using the individualised approach.

Author	Patients included	Number HIV pos	Number deaths HIV pos	pDeath HIV pos	Number not dying	Number cured HIV pos	pCure HIV pos
Frieden[158]	267	230	218	0.95	12	0	0.00
Edlin[34]	18	18	18	1.00	0	0	0.00
Fischl[160]	62	62	60	0.97	2	0	0.00
Davies[163]	21	8	5	0.63	3	2	0.67
Turett[164]	38	34	22	0.65	12	12	1.00
Park MM[169]	173	90	68	0.76	22	8	0.36
Flament-Saillour[170]	51	8	7	0.88	1	0	0.00
Franzetti[171]	90	90	84	0.93	6	3	0.50
Salomon[173]	13	13	2	0.15	11	10	0.91
Telzak[174]	12	12	3	0.25	9	9	1.00
Mannheimer[176]	13	13	8	0.62	5	1	0.20
TOTALS:	758	578	495		83	45	

The individual proportions can be pooled using the following method described by Cochran.[198] The proportion of units falling into a specific class can be estimated by Equation 4.3.

$$p = \frac{\sum_{n} a_i}{\sum_{n} m_i} \qquad \text{(Equation 4.3)}$$

An approximate variance of p can be expressed as follows (Equation 4.4):

$$v(p) = \frac{a_i^2 - 2p(a_i m_i) + p^2(m_i^2)}{n(n-1)(m_i^2)} \qquad \text{(Equation 4.4)}$$

Where: n = the number of studies
m_i = the total number in the *i*th study
a_i = number in the *i*th study with specific outcome
p = as defined in Equation 4.3
$m = (\sum m_i)/n$

The estimated proportions of HIV-positive and negative patients that die and the variance and standard deviations thereof are provided in Table 4.18. This table also contains an estimated probability of cure for patients that survive.

Table 4.18 Estimated proportions of cure and death in HIV-positive and negative patients.

	Estimated proportion	Variance	Standard deviation	Minimum value	Maximum value
Probability of death (HIV-pos)	0.86	0.0027	0.0522	0.15	1.00
Probability of death (HIV-neg)	0.17	0.0042	0.0647	0.00	0.48
Probability of cure* (HIV-pos)	0.54	0.0201	0.1417	0.00	1.00
Probability of cure* (HIV-neg)	0.59	0.0030	0.0550	0.12	1.00

*Probability of cure estimated as a function of surviving patients only.

In each case, the estimated proportions were used as baseline values for the variables in the decision analysis. The minimum and maximum estimates from the published studies were used for the upper and lower limits of the sensitivity analysis.

4.2.2.10.2 Protocol regimen

Treatment outcomes for the protocol regimen were gathered from the data published by Rawlinson et al in their report on the implementation of DOTS-plus in the Northern Cape.[51] Complete information was available for patients that died. Patients that were either HIV-negative or had unknown HIV status had a 0.15 probability of death (95% CI: 0.09 – 0.21), while HIV-positive patients had a 0.56 probability of dying (95% CI: 0.24 – 0.88).

In the above study, data on cures and failures were only included for patients that completed their treatment, which was 60% of 'old cases' and 40% of 'new cases'. It was not possible to estimate the outcomes of the patients that had not completed treatment. Decision analysis estimates for the surviving patients, either cure or treatment failure, were based only on patients that had completed treatment. Of the 63 patients that completed treatment, nine 'old cases' and 14 'new cases' were cured. 16 'old cases' and 10 'new cases', interrupted treatment, failed or were transferred to another facility and were thus classified as failures. Thus, if a patient did not die, there was a 46.94% of becoming cured (95% CI: 0.33 – 0.61). These outcomes are represented in Figure 4.5. The 95% confidence intervals were used as a range for the variables during sensitivity analysis.

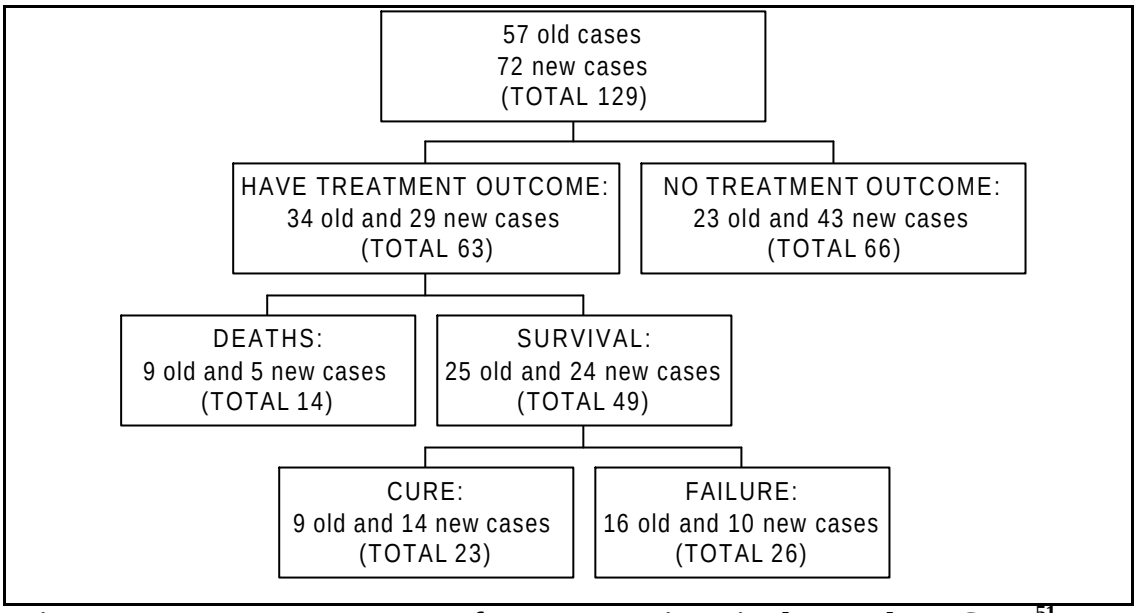

Figure 4.5 Treatment outcomes of MDRTB patients in the Northern Cape.[51]

4.2.2.10.3 Non-drug management

Outcomes of non-drug management were also obtained from the literature. Table 4.19 provides the raw data collected from various articles. Table 4.20 summarises the probability of death and cure for patients not receiving drug treatment as well as the variance, standard deviation and ranges of these proportions. Of the 14 patients not receiving treatment that did not die, two patients were cured spontaneously. Thus, for the decision tree, the estimated proportion of 0.79 was used as the baseline value for the likelihood of death. Fourteen percent of the surviving patients could be expected to be cured spontaneously. All variables were varied from zero to one for the sensitivity analysis, as these were the minimum and maximum values seen in the published studies.

Table 4.19 Treatment outcomes of patients with MDRTB when no treatment is provided.

Author	Number of patients	Number of deaths	pDeath	Number not dying	Number cured	pCure
Davies[171]	6	4	0.67	2	0	0.00
Telzak[65]	2	0	0.00	2	2	1.00
Valway[163]	30	28	0.93	2	0	0.00
Park MM[177]	21	15	0.71	6	0	0.00
Yew[180]	4	2	0.50	2	0	0.00
Telzak[182]	1	1	1.00	0	0	0.00
Pablos-Mendez[164]	1	1	1.00	0	0	0.00

Table 4.20 Median probability of death for MDRTB patients not receiving drug treatment (At end of follow-up period).

	Estimated proportion	Variance	Standard deviation	Minimum value	Maximum value
Probability of death	0.79	0.0072	0.0846	0.00	1.00
Probability of cure	0.14	0.0349	0.1581	0.00	1.00

4.2.3 Decision analysis and cost-minimisation model

DATA 3.0 was used to model the decision trees. The tree was modelled in a step-wise fashion. However, in order to ease the sensitivity analysis, individual values were substituted with variables where assumptions or estimations had to be made as to the actual value of each factor used for modelling the disease.

In the first decision tree, the total drug costs for each alternative were calculated by multiplying the daily drug cost, calculated in the manner described in Section 4.2.2.2.1, with the estimated length of treatment for patients in each outcome category. For calculations of the daily drug cost for the protocol regimen, it was assumed that 22% of the patients had a mass of greater than 50kg, and that 53% of these patients had bacilli resistant to ethambutol and thus received cycloserine. For the individualised treatment regimen, the same weight distributions were used to calculate the average daily drug costs.

Hospital costs for the protocol and individualised approach were calculated by multiplying the length of treatment by 0.12, the figure chosen to represent the proportion of time spent in hospital. These figures were then multiplied by the 'hotel cost' for staying in a tertiary care facility. For the non-drug therapy alternative, the estimated number of days spent in hospital by patients in each outcome category was multiplied by the daily cost of hospitalisation.

Laboratory costs for each alternative were calculated by multiplying the number of laboratory tests by the cost for each test. The drug, hospital and laboratory costs were then added together for each alternative treatment route.

Table 4.21 lists the values of the variables used in the simplified version of the decision tree. Definitions for the abbreviations of the variables used in the trees are available in Appendix 4.

Table 4.21 Variables used to model the decision tree of MDRTB treatment.

Variable	Value
Protocol regimen	
Drug costs:	
Cost of protocol drug regimen for cured patients	R 17 748.52
Cost of protocol drug regimen for patients that die	R 9 652.70
Cost of protocol drug regimen for patients that fail treatment	R 19 305.40
Hospital costs:	
Total cost of hospitalisation for patients cured on protocol regimen	R 8 841.66
Total cost of hospitalisation for patients on protocol regimen that die	R 4 808.62
Total cost of hospitalisation for patients failing with protocol regimen	R 9 617.24
Laboratory costs:	
Laboratory costs for patients cured with protocol regimen	R 1 571.81
Laboratory costs for patients failing treatment with protocol regimen	R 1 130.33
Laboratory costs for patients cured with protocol regimen	R 1 656.71
Total cost:	
Total cost of protocol regimen for cured patients	cDrugs_prot_cure+cHosp_prot_cure+cLab_prot_cure
Total cost of protocol regimen for patients that die	cDrugs_prot_die+cHosp_prot_die+cLab_prot_die
Total cost of protocol regimen for patients that fail treatment	cDrugs_prot_fail+cHosp_prot_fail+cLab_prot_fail
Probabilities of outcomes	
Probability of cure with protocol regimen	0.47
Probability of death with protocol regimen	0.25
Individual regimen	
Drug costs:	
Cost of individualised drug regimen for cured patients	R 13 460.60
Cost of individualised drug regimen for patients that die	R 3 365.15
Cost of individualised drug regimen for patients that fail treatment	R 14 641.36
Hospital costs:	
Total cost of hospitalisation for patients cured on individualised regimen	R 8 841.66
Total cost of hospitalisation for patients dying on individualised regimen	R 2 210.41
Total cost of hospitalisation for patients failing individualised regimen	R 9 617.24
Laboratory costs:	
Laboratory costs for patients cured with individualised regimen	R 2 750.50
Laboratory costs for patients dying with individualised regimen	R 1 096.53
Laboratory costs for patients failing with individualised regimen	R 2 943.95
Total cost:	
Total cost of individualised regimen for cured patients	cDrugs_indiv_cure+cHosp_indiv_cure+cLab_indiv_cure
Total cost of individualised regimen for patients that die	cDrugs_indiv_die+cHosp_indiv_die+cLab_indiv_die
Total cost of individualised regimen for patients that fail treatment	cDrugs_indiv_fail+cHosp_indiv_fail+cLab_indiv_fail
Probabilities of outcomes	
Probability of cure with individualised regimen	0.58
Probability of death with individualised regimen	0.34
Non-drug therapy	
Hospital costs:	
Total cost of hospitalisation for patients that get cured without drugs	R 1 615.80
Total cost of hospitalisation for patients that die without drug therapy	R 3 231.60
Total cost of hospitalisation for patients becoming chronic MDRTB sufferers without drug treatment	R 1 615.90
Laboratory costs:	
Laboratory costs for patients managed without drugs	R 396.16
Total cost:	
Total cost of non-drug management for patients that get cured	cHosp_noTx_cure+cLab_noTx
Total cost of non-drug management for patients that die	cHosp_noTx_die+cLab_noTx
Total cost of non-drug management for patients that become chronic TB sufferers	cHosp_noTx_fail+cLab_noTx
Probabilities of outcomes	
Probability of cure with non-drug management	0.14
Probability of death with non-drug management	0.79

Figure 4.6 depicts the decision tree in its basic format and Figure 4.7 in its rolled-back format. Non-drug management is estimated to cost an average of R3 280, individualised therapy R19 393and protocol treatment, R25 947 for each case treated. If it were assumed that the outcomes of the two treatment alternatives were equal, individualised treatment appears cheaper than the protocol regimen.

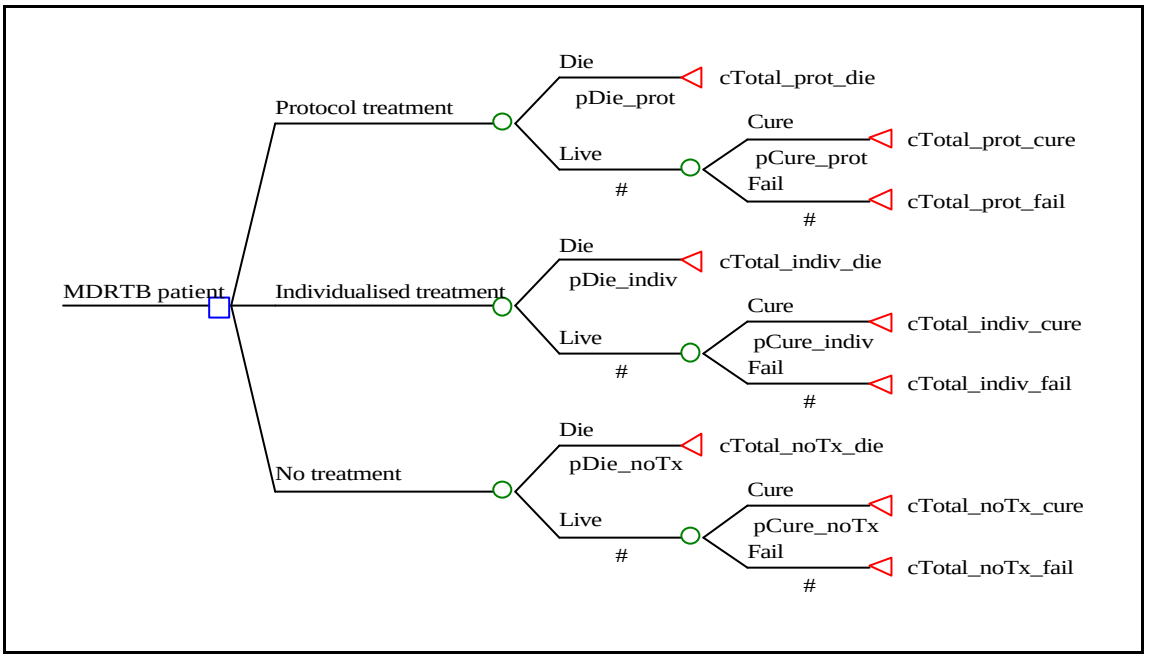

Figure 4.6 The decision tree in its basic format.

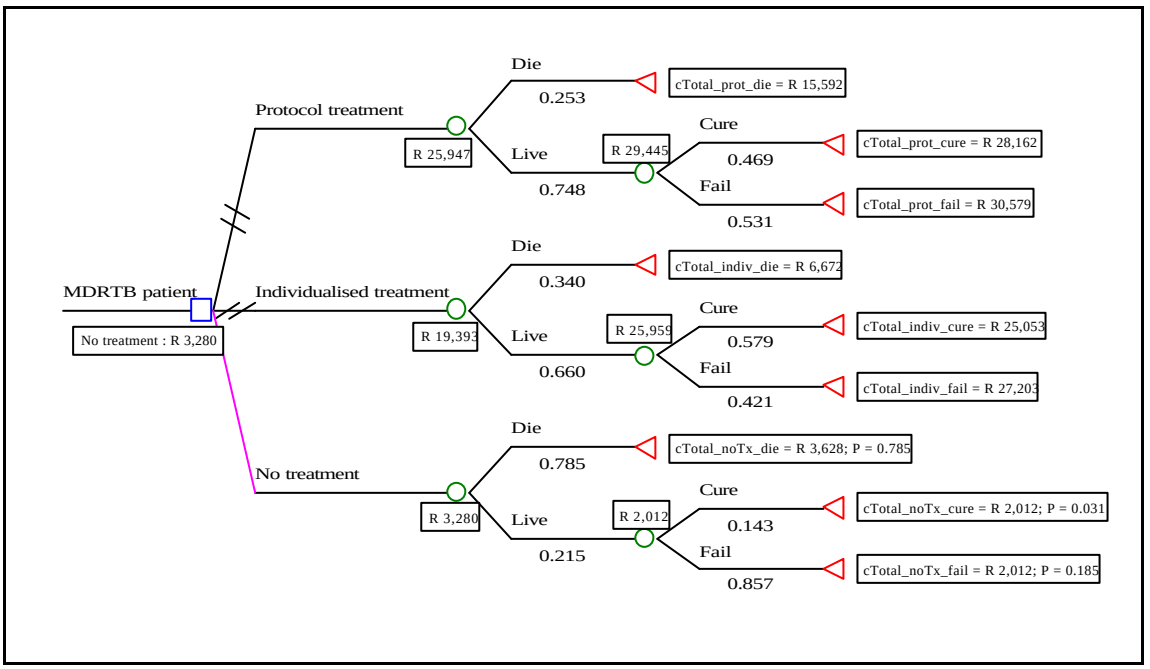

Figure 4.7 Decision tree measuring costs of the alternatives in its rolled-back format.

In order to simplify the process of performing the sensitivity analysis, variables describing the total costs incurred through drugs, hospitalisation and laboratory tests were substituted with variables that described the individual unit costs and consumption. The unit values as well as the formulae that were used to calculate the total costs and probabilities are listed in Appendix 5. The values of each of the variables were derived as discussed in Section 4.2.

Table 4.22 summarises the costs incurred by patients in each treatment arm according to their therapeutic outcomes. Only drug, hospital and laboratory costs were included in this analysis.

Table 4.22 Drug, hospital and laboratory costs incurred by patients receiving each treatment alternative.

Cost	Patient outcome	Protocol Regimen	Individualised regimen	Non-drug management
Drug costs (per patient)	Cure	R 17 748.52	R 13 460.60	R 0.00
	Die	R 9 652.70	R 3 365.15	R 0.00
	Fail	R 19 305.40	R 14 641.36	R 0.00
Hospital costs (per patient)	Cure	R 8 841.66	R 8 841.66	R 1 615.80
	Die	R 4 808.62	R 2 210.41	R 3 231.60
	Fail	R 9 617.24	R 9 617.24	R 1 615.80
Laboratory costs (per patient)	Cure	R 1 571.81	R 2 750.50	R 633.88
	Die	R 1 130.33	R 1 096.53	R 633.88
	Fail	R 1 656.71	R 2 943.95	R 633.88
Total cost (per patient)	Cure	R 28 161.99	R 25 052.76	R 2 249.68
	Die	R 15 591.65	R 6 672.09	R 3 865.48
	Fail	R 30579.35	R 27 202.55	R 2 249.68
'Weighted average' total cost for each alternative		R 25 947	R 19 393	R 3 280

4.2.4 Sensitivity analysis

In order to assess the robustness of the outcomes of the decision analysis model, and the effects of the estimations used to model the disease, a sensitivity analysis was performed on each of the variables used to model the disease. The minimum and maximum values were based on the derivations for each variable discussed earlier in Section 4.2.2.

In this model non-drug management appears to be the "cheapest" alternative. However, this is clearly a clinically unfavourable option as the benefits of preventing new cases of MDRTB and of saving lives through treatment are not apparent from

this model. In South Africa, it is feasible to treat these patients with drug therapy and it is therefore more appropriate to compare the two drug regimens with each other rather than with non-drug management. The majority of the sensitivity analyses were thus performed on a model that allowed comparison of the two drug regimens alone. Since non-drug management always appeared dominant, decision trees were created that were identical to the previous ones, except that the non-drug management branch was excluded.

The variables that caused changes in the results of the decision analysis are listed in Table 4.23 along with the minimum and maximum value assigned to each variable and the relevant section in which each was discussed in the proceeding text.

Table 4.23 Variables for which sensitivity analyses were performed and the ranges of the variables.

Variable	Baseline	Min	Max	Effect on model:	Discus-sed in section
General variables					
Proportion of patients resistant to ethambutol	0.53	0	1	Yes	4.2.4.1
Protocol regimen					
Daily cost of drugs using protocol regimen	R38.92	R1.56	R77.84	Yes	4.2.4.1
The length of treatment received by protocol patients dying	248	1	1008	Yes	4.2.4.2
The length of treatment received by protocol patients failing treatment	496	1	1008	Yes	4.2.4.2
Individualised regimen					
The daily cost of drugs using individualised regimen	R29.52	R1.97	R163.43	Yes	4.2.4.1
Length of treatment for individually treated patients dying	114	1	1027	Yes	4.2.4.2
Length of treatment for individually treated patients failing therapy	496	100	1680	Yes	4.2.4.2
Non-drug therapy					
The number of days spent in hospital by patients not receiving drug treatment that die	20	1	720	Yes	4.2.4.3
The number of days spent in hospital by patients not receiving drug therapy that fail treatment	10	1	720	Yes	4.2.4.3

4.2.4.1 The cost of drug treatment

If the option to manage patients without drugs is excluded, individualised treatment is dominant when the daily costs of the drug regimens are equal. However, as can be seen in Figure 4.8, the cost of individualised treatment regimens have a greater potential to increase significantly. As soon as the daily cost of an individualised regimen becomes greater than approximately R120 per day, the protocol approach is favourable regardless of the cost of the protocol regimen. Substitution of ciprofloxacin with ofloxacin does not appear to have any significant effects on the total cost of protocol treatment. If the proportion of patients with ethambutol resistance remains below 20%, the cost of the protocol regimen becomes less than that of individualised treatment. Reductions in the cost of the second-line drugs would decrease the total costs of both regimens dramatically.

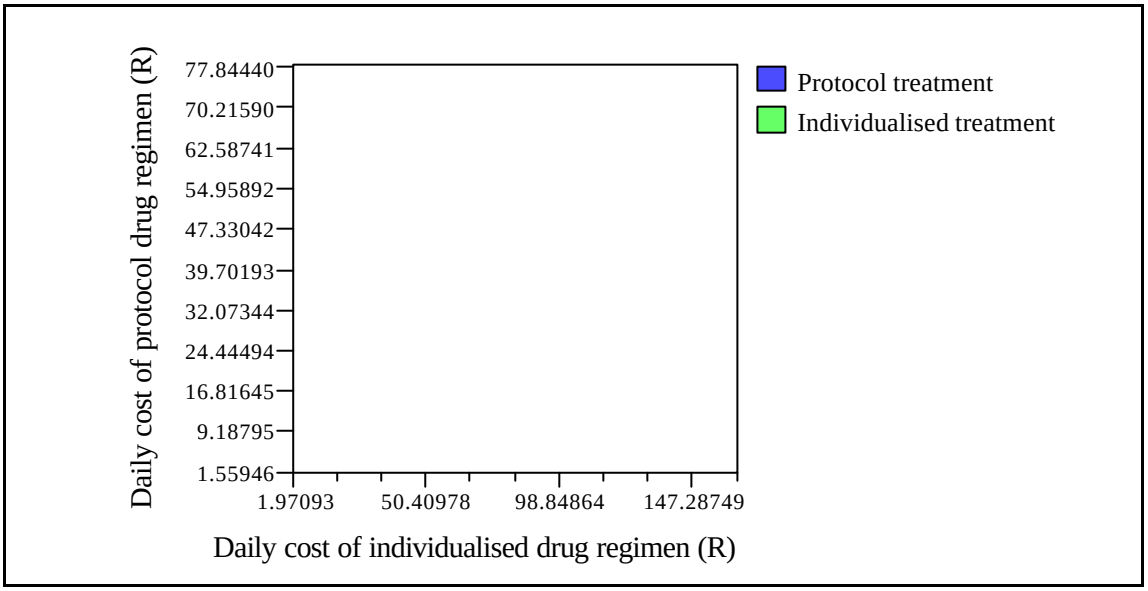

Figure 4.8 Sensitivity analysis of the daily cost of each drug regimen using a model that excluded the non-drug management option.

4.2.4.2 Length of drug treatment

A restriction in the duration of treatment will decrease the costs of drug therapy using either alternative in patients who do not respond favourably (i.e. who die or fail treatment). Figure 4.9 shows the effect of lengthy drug treatment given to patients treated with individualised regimens. It appears to be beneficial to limit the length of treatment received by patients that do not get cured.

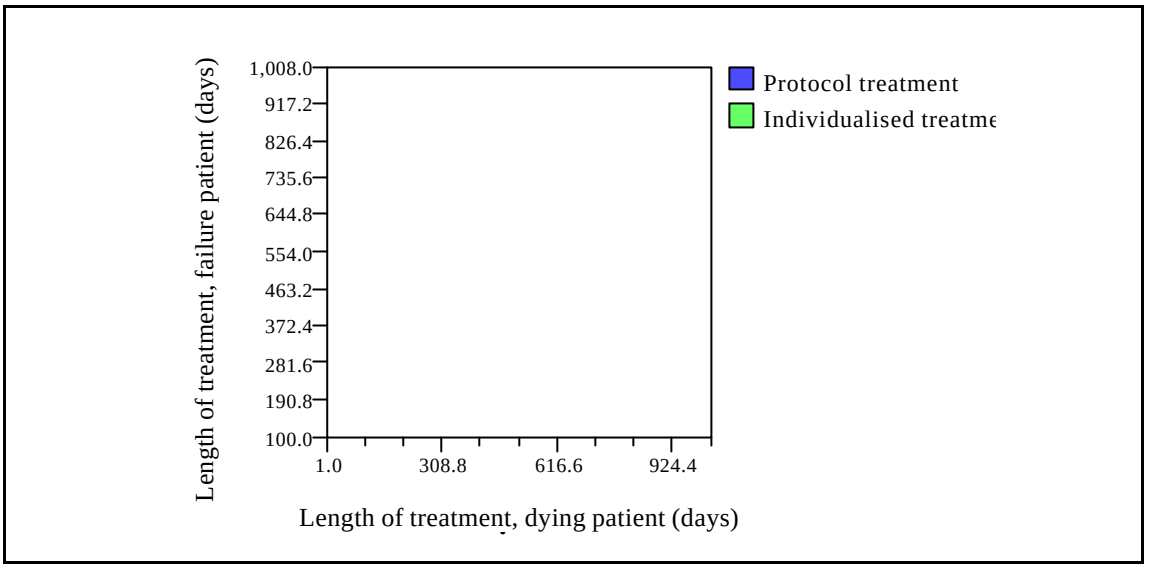

Figure 4.9 Sensitivity analysis of the length of treatment received by individually treated patients that die or fail treatment.

Figure 4.10 shows the effect of treatment length for the patients treated with the protocol regimen. A similar relationship is seen to the one above. If those patients treated with the protocol regimen who do not get cured are given treatment for a limited period of time, protocol therapy can become more cost-efficient than individualised treatment. Using baseline estimates, if the survival time for patients in either treatment category were assumed equal, individualised treatment is still cheaper.

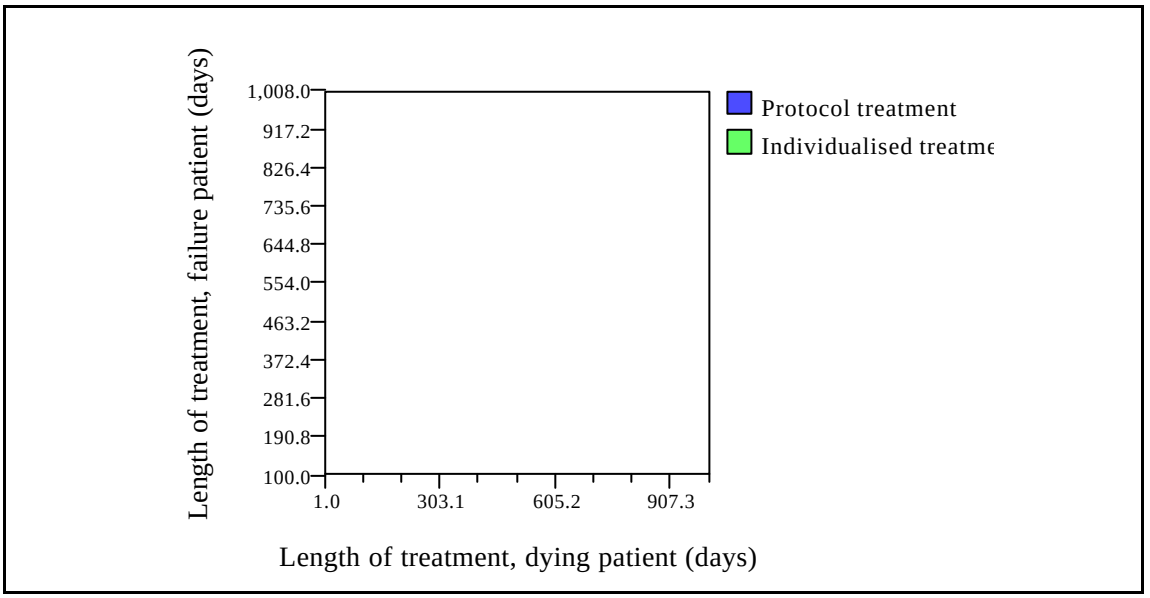

Figure 4.10 Sensitivity analysis of the length of treatment received by patients receiving the protocol regimen that die or fail treatment.

4.2.4.3 Length of hospitalisation, non-drug management

It is not known how long the patients being managed without drug therapy would spend in hospital. Figure 4.11 does indicate that the total cost of the non-drug management branch is significantly increased when patients who do not get cured spend long periods in hospital, to the extent that drug treatment becomes more cost-effective. If patients remain in hospital for lengthy periods of time it would, in terms of cost-effectiveness ratios, be beneficial to treat them. However, if patients are sent out into the community while infectious, many new infections may occur and the total costs may increase.

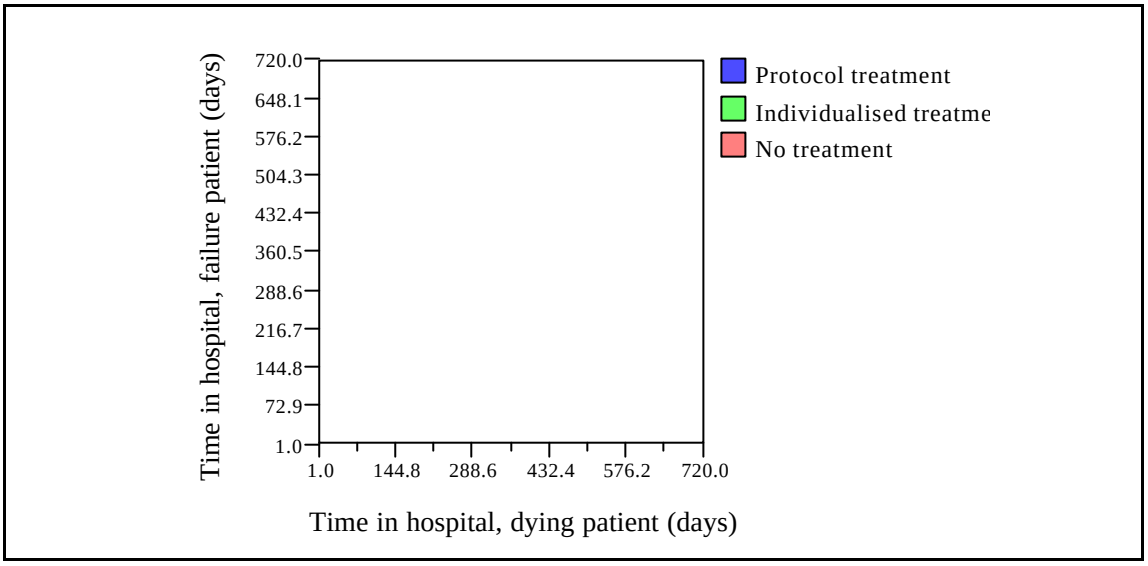

Figure 4.11 Sensitivity analysis of the number of days spent in hospital by patients not receiving drug therapy.

4.2.4.4 Variables not causing changes in the results of the decision analysis.

Some variables had no effect on the outcomes of the cost-minimisation evaluation. These included the prevalence of HIV, the per diem cost of hospitalisation, the outcomes of treatment using either regimen, the length of treatment received by patients being cured, weight distribution of the patients and the frequency with which laboratory tests are performed. A list of these variables can be found in Table 4.24.

Table 4.24 Variables that did not have an effect on the outcomes of the decision analysis model.

Variable	Baseline	Minimum	Maximum
General variables			
Per diem cost per day in hospital	161.58	88	359
Proportion of HIV-positive patients	0.25	0.07	0.7
Proportion of patients weighing above 50kg	0.22	0.1	0.5
Protocol regimen			
The probability of cure using protocol regimen (of surviving patients)	0.46939	0.3297	0.6091
The probability of death using protocol regimen	0.2525	0.1275	0.3775
The length of treatment received by cured protocol patients	456	280	1008
The number of laboratory tests performed	Varied for each test- see section 4.2.2.9.2		
Individualised regimen			
Monthly interval at which sputum cultures are performed	3	1	6
Monthly interval at which drug susceptibility test are performed	8	1	16
The probability of cure for individually treated patients	0.5787	0.09	1
The probability of death for individually treated patients	0.3404	0.04	0.61
The length of treatment for cured individually treated patients	456	180	1008
Non-drug therapy			
The number of laboratory tests performed	Varied for each test- see section 4.2.2.9.3		
The number of days spent in hospital by patients not receiving drug treatment that get cured	10	1	720

Individualised therapy remained less costly even when it was assumed that patients receiving protocol treatment would be hospitalised in a hospital with a lower per diem cost than a hospital in which individually treated patients would be accommodated. If the per diem bed costs of the hospitals in which patients treated with protocol and individualised regimens were R88 and R161 respectively, the protocol branch was estimated to cost R4 909 per year of life saved. This figure is still greater than the estimated R3 511 per year of life saved for the individualised regimen.

The number of tests performed for patients receiving either protocol treatment, individualised therapy or non-drug management did not have an effect on the estimates of cost. Figure 4.12 shows the effect of changes in the intervals at which sputum cultures are performed for patients treated with the individualised regimens. Even if they are performed every month throughout the treatment period, the cost was only increased very slightly.

The effect of increasing the frequency of performing drug susceptibility tests is shown in Figure 4.13. Again, even if a patient's sputum is tested for susceptibility to all

eight drugs every month throughout the treatment period, costs do not increase sufficiently to change the results of the decision analysis.

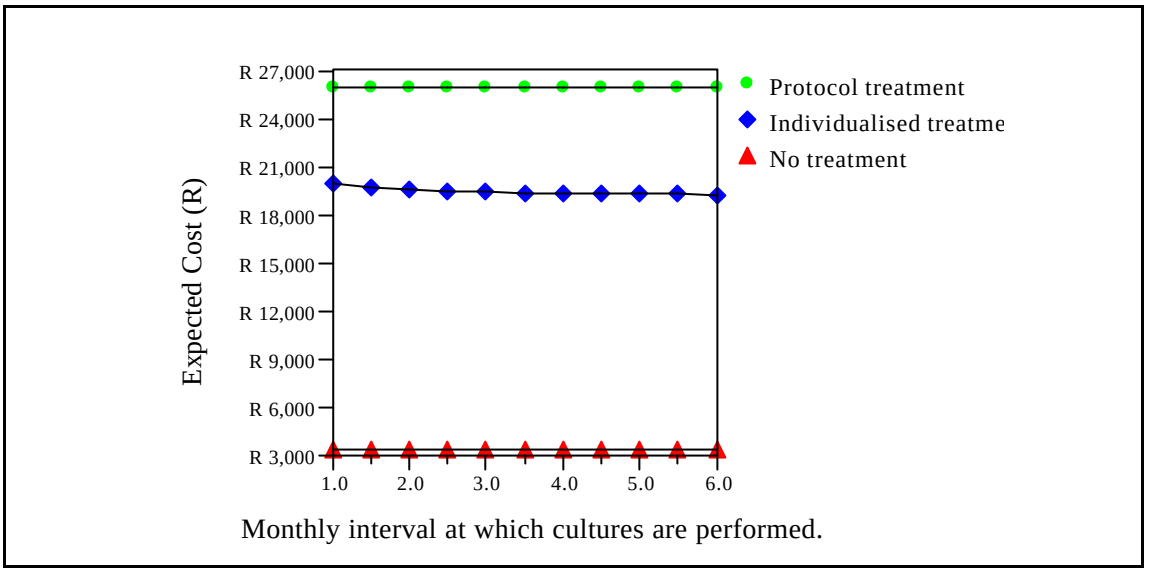

Figure 4.12 Sensitivity analysis of the frequency at which sputum cultures are performed for patients treated with individualised regimens.

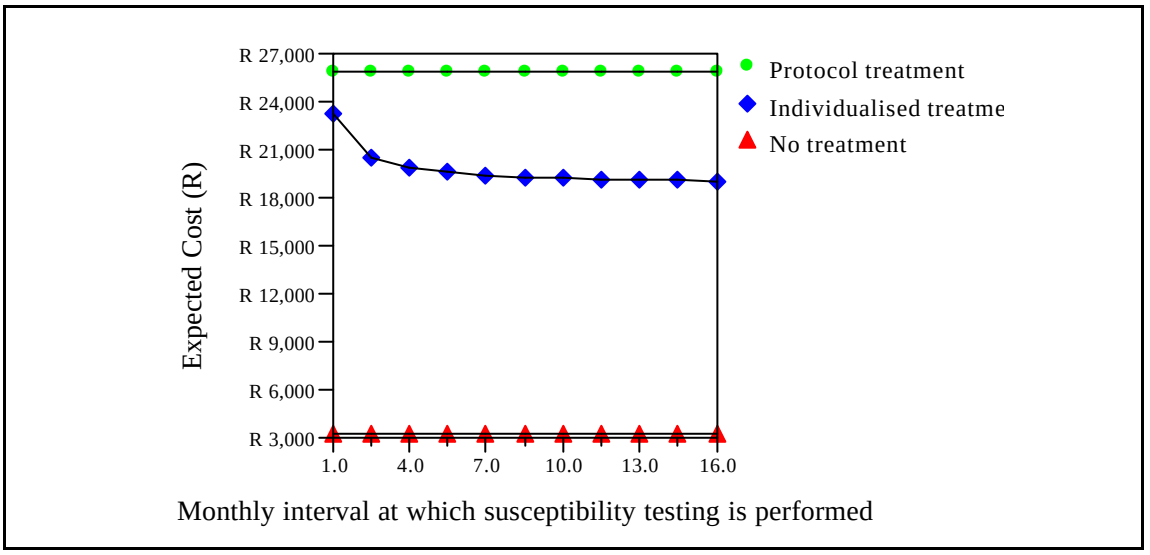

Figure 4.13 Sensitivity analysis of the frequency at which drug susceptibility tests are performed for patients treated with individualised regimens.

Increases in the number of MDRTB patients with concomitant HIV-infection cause the cost per year of life saved to increase for individual and protocol regimens, individualised treatment. However, individualised treatment still remains cheaper (Figure 4.14). A lower HIV prevalence improves the probability of cure, decreases mortality and also increases the number of years of life experienced by both cured patients and those failing treatment.

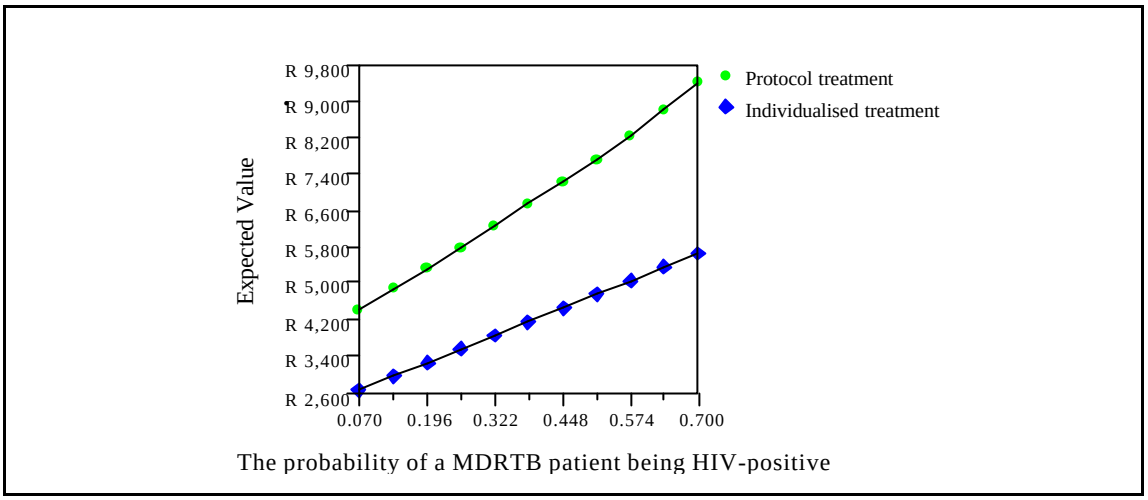

Figure 4.14 Sensitivity analysis of the proportion of patients with HIV co-infection.

The results of the cost-minimisation model are susceptible to changes in some of the variables, particularly the daily cost of drugs, the length of time spent in hospital and the length of treatment received by those patients dying or failing treatment. More accurate estimates of the variables used in the model could have limited the range of results that were generated by the sensitivity analysis.

Figure 4.15 indicates that, when all other variables are held constant, varying the mortality and cure rates for the protocol regimen have no effect on the outcome of the model. The same relationship can be seen with the treatment outcomes of individualised therapy.

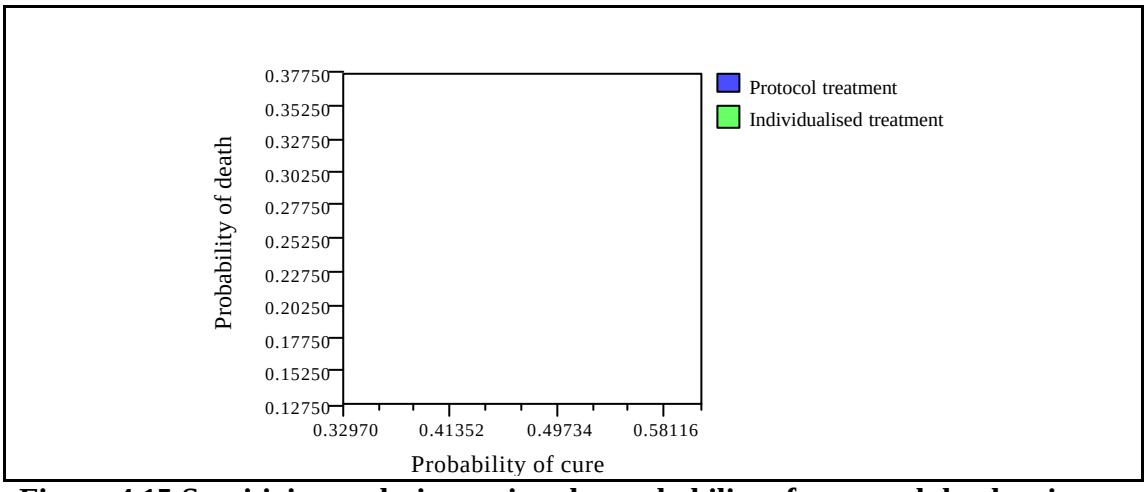

Figure 4.15 Sensitivity analysis varying the probability of cure and death using the protocol regimen.

4.2.5 Cost-effectiveness analysis

The results of the cost-minimisation evaluation are dependent on the assumption that the outcomes of treatment are equal. The results of this model were compared to the results of a cost-effectiveness model that measured the outcomes of treatment in terms of natural units. Two outcome measures were used, namely the 'number of cases cured' and the number of 'years of life saved'. Measuring outcomes in terms of the 'number of cases cured' is very limited. It gives no indication of the additional years of life experienced by patients as a result of drug treatment. Neither of the two measures were able to measure the effect of preventing further transmission of the disease.

4.2.5.1 Costs in terms of the 'number of cases cured'

The decision analysis model in Section 4.2.3 generated an estimated cost for each alternative in question. The cost per case cured can be calculated by dividing the average cost of treating a patient by the probability of cure for each alternative estimated in Section 4.3.2.10. Table 4.25 summarises the expected values for the costs and consequences of the alternatives.

Table 4.25 The average cost per treatment alternative and the estimated cure rate.

	Protocol treatment	Individualised treatment	Non-drug management
Ave cost per treatment	R 25 947	R 19 393	R 3 280
pCure	0.3525	0.3828	0.0294

From this data, the cost per case cured can be estimated at R50 661 for individualised treatment and R73 609 using the protocol regimen. Using Equation 2.1, the public health service is estimated to be spending an additional R216 000 for each case cured by using the protocol regimen rather than individualised treatment. Individualised treatment is suggested to be the dominant alternative because it is both cheaper and more effective in terms of the 'number of cases cured'.

4.2.5.2 Outcomes in terms of 'years of life saved'

The costs of treating MDRTB were also measured in terms of the number of 'years of life saved' by each treatment alternative. Cured patients were assumed to have a normal life expectancy after treatment, while patients failing treatment were assumed to have intermediate life expectancy. Different life expectancies for HIV-positive and negative patients were taken into account.

The life expectancy figures for HIV-negative patients were obtained from the South African Revenue Service (SARS) tables.[199] Estimated life expectancies were calculated according to the demographics of the patients in the studies identified in the systematic review. Both the mean and median age of patients was 38 years and 69% of these patients were male. The calculation described in Equation 4.5 was used to generate an estimated life expectancy (LE) for patients with MDRTB:

$$LE_{38} = \%\ \text{Male patients}\ (LE_{male;38}) + \%\ \text{Female patients}\ (LE_{female;38}) \qquad \text{(Equation 4.5)}$$

$$= (0.69 \times 31.28) + (0.31 \times 37.32)$$

$$= 33 \text{ years}$$

The life expectancies provided were based on population figures that took the increasing number of premature deaths due to HIV/AIDS into account. These figures could therefore be slightly underestimated, but the extent of this underestimation was assumed to be negligible.

Surviving patients that were not cured were assumed to become chronic MDRTB sufferers. These patients were assumed to live for an intermediate period of time. The life expectancy of these patients would be longer than that of dying patients, but they would not survive for the same period of time as cured patients. Although there is no data to support this assumption, it was assumed that these patients survived one third of the time that cured patients lived. The figure was modelled in order to take uncertainty into account and it was varied from one half to one sixth the life expectancy of cured patients. It must be noted that patient's health and quality of life are not taken into account by these figures.

HIV-positive patients with MDRTB were assumed to be in the 'AIDS-related complex' or third stage of the disease. This is the stage in which chronic signs and symptoms of the infection first appear and most cases of active tuberculosis occur.[200] HIV-positive patients at this stage of their disease could be expected to experience an estimated five years of life.[201] This estimate did not allow treatment with anti-retroviral agents.

Using the assumption that 50% of patients with MDRTB were HIV-positive, the average cured patient would live for 19 years, a patient becoming a chronic MDRTB sufferer would live for one third of this value and a patient that died would have their life prolonged by almost 1 year during treatment. Table 4.26 summarises the estimated average life expectancies for patients managed with either alternative.

Table 4.26 Average costs and life expectancies for patients treated with each alternative.

	Protocol treatment	Individualised treatment	Non-drug management
Ave cost per treatment	R 25 947	R 19 393	R 3 280
Ave # of 'years of life saved'	9.465	9.3688	2.4924

The estimated cost per 'year of life saved' is R2 070 for individualised treatment and R2 741 using the protocol regimen. The ICER suggests that the public health service is paying an additional R68 130 for every year of life saved when the protocol regimen is used compared to individualised treatment.

CHAPTER 5

5 DISCUSSION

The magnitude of the benefit from treating MDRTB patients with second-line drugs has not yet been clearly ascertained. Conflicting reports of the effectiveness of treatment can be found in the literature. Systematic reviews of available evidence are usually the best source of information for decision makers.[185]

The systematic review of the literature highlighted the extreme variability in the data that is available, perhaps accounting for the high level of variability in treatment outcomes amongst the studies. Greater standardisation of the methods used when reporting case-series would result in data of a higher quality. The three main areas that require a greater degree of standardisation are patient inclusion criteria, laboratory techniques and the measurement of outcomes.

Additional information on disease severity, resistance patterns and previous treatment history would also improve study reports. Patients with high levels of resistance have fewer second-line drugs available to them with which they can be treated. These patients may have a lower chance of survival or cure. Studies with a high number of patients with extensive resistance may show lower overall cure rates than studies with fewer of these patients.

Patients with more severe TB will be more likely to die than patients with a mild form of the disease. Information therefore needs to be disclosed about the severity of the disease before treatment results from multiple studies can be compared or combined. Authors should also reveal details of previous treatment history of their patients. Long periods of inappropriate treatment may result in more severe disease and more extensive resistance patterns. Some patients who have received various periods of appropriate treatment prior to study entry may have an increased chance of cure.

There are four accepted methods of determining drug susceptibility. The IUATLD has attempted to standardise laboratory techniques in order to facilitate comparison of

results from different laboratories. Authors need to divulge the method, the medium used, the drug concentrations used and the definition they used to define resistance. If there are publisher constraints due to lack of space, this information should, where possible, be made available in a web-based archive.

Although the majority of the researchers did disclose the method they used to determine drug susceptibility, sufficient details regarding the medium used, drug concentrations and definitions used to define resistance were not provided. This lack of information prevents readers from comparing results from various studies or comparing them to patients in their own setting. Patients that may have been classified as having drug resistant TB in one setting may not be classified identically in another setting. This may occur where higher concentrations of drug are used on the testing medium or where sputum was tested using the proportion method and only high levels of resistance were classified as resistant.

The numerous methods of reporting treatment outcomes further prevent the pooling of results from more than one study. This is due to the fact that classification of cured patients differed from study to study. Definitions of cure ranged from one negative sputum culture, type consecutive negative sputum cultures (either at twice-weekly or monthly intervals, depending on researchers) or to a negative sputum culture at the end of the treatment period. A patient thus classified as cured in one setting may not receive the same classification in another. Pooling of results from studies using different definitions is therefore problematic. However, for the purposes of obtaining median estimates of treatment outcome, they were combined regardless of the classification of the study outcome.

Other sources of bias included patients excluded from the analysis, measurement of survival rather than cure and the length of follow up. Intention to treat analysis should be performed in all studies in order to ensure that results closely reflect the real world. Detailed descriptions of any excluded patients were helpful e.g. many of the MDRTB studies excluded patients if they died before receiving at least one month of drug treatment. These patients did, however, need to be included in the outcomes analysis because they did still receive treatment. The effect of their premature death

should rather be taken into account by measuring the average or median length of time that treatment is provided as well as the median time until death.

Relapse of both drug-susceptible and drug-resistant TB is common. Relapses of the disease could occur months or even years after treatment completion and apparent cure. Attempts should be made to standardise an appropriate follow-up period. This would ensure that patient outcomes are handled in the same manner regardless of their location.

Research into MDRTB treatment outcomes poses a number of problems. Prevalence of this form of TB is rising in many countries and is having a significant impact on TB control. However, the number of patients with MDRTB in a single geographical region at any one time is limited. Large-scale trials assessing the effect of various treatment regimens would thus be difficult. Meta-analytic tools can overcome this problem by statistically combining results of individual studies in order to improve statistical power. Unfortunately, many of the countries where MDRTB exists do not monitor their patients and publish the outcomes of treatment. Many of the published results originate from the same institutions and sometimes even report outcomes of the same patients.

The widely disparate range of studies compromises the ability to pool results. Standardising some of the methodological and reporting aspects mentioned above will minimise heterogeneity and facilitate the use of meta-analytic techniques. Many of these suggestions merely promote the basic, good research practice of disclosing details of study methodology and patient handling. If researchers are unwilling to withhold second-line drugs from patients in order to carry out randomised controlled trials, cohort, case-control and case series that are performed should at least be of the highest possible quality in order to ensure validity of the results.

Data on the efficacy of interventions needs to be gathered before it can be translated into effectiveness data. Pharmacoeconomic evaluations are usually based on randomised controlled trials or on data that was gathered from the institution for whom the study is being performed. For the purposes of this evaluation, prospective data was unable to be collected and no randomised controlled trials of the outcomes of

MDRTB treatment appear to have been published. Estimates of effectiveness were therefore gathered from the published cohort, case control and case series.

MDRTB is a potentially chronic or fatal disease. The ideal outcome measure for an economic evaluation would take into account the outcomes of treatment, the effect of treatment on survival as well as the effect of treatment on quality of life. No research appears to have been done on assigning quality of life scores to patients with MDRTB. In this case, the treatment alternatives were assessed using a cost-minimisation approach as well as a cost-effectiveness approach using two measures of outcome; the 'number of cases cured' and the 'years of life saved'. Each measuring tool is limited in its own ability to measure the effects of treatment holistically. However, each tool can be used individually to explore the different effects of treatment.

A cost-minimisation approach to the evaluation suggests that non-drug management is the cheapest alternative. This conclusion is short sighted in that the model does not take into account the cost of treating additional patients that develop MDRTB or economic benefits of improved quality of life through treatment. In South Africa it is not clinically viable to withhold drug treatment unless patients are non-compliant and close to death. The core comparison of this pharmacoeconomic evaluation was thus between individualised and protocol drug treatment. Individualised treatment appeared to be the more cost-effective alternative both in terms of the 'number of cases cured' and the 'years of life saved'.

The results of the cost-minimisation analysis were, however, susceptible to changes in the cost of both drug regimens and the length of treatment received by patients treated with either drug regimen.

The model was not susceptible to changes in the frequency with which laboratory tests are performed, the prevalence of HIV, the per diem cost of hospitalisation, weight distribution of the patients and the estimated survival time for patients failing treatment or becoming cured.

Individualised drug therapy was favoured when the cost of the drug regimen was reduced. This could be achieved by limiting the use of expensive, second-line drugs when the bacilli are susceptible to some of the cheaper alternatives. Drug procurement through world buying groups such as the Green Light Committee has resulted in discounts of up to 96% for some of the second-line drugs.[195]

Significant reductions in the cost of drug therapy could also be achieved if the length of drug treatment is limited in those patients who have not responded favourably after a certain period of time. A case can be made for withdrawing treatment in patients whose sputum cultures have not become negative after receiving treatment for longer than two to three years.

The cost of hospitalisation was also a significant contributor to the total cost of treating MDRTB. Compliance, social circumstances and the clinical condition of patients should be taken into account when hospitalisation is being considered. Patients should not be detained in hospital for lengthy periods of time when it is possible to manage them effectively in an out-patient setting. If, however, they do remain in hospital, these patients should, in order to maximise cost-effectiveness, preferably be treated with drug therapy. Ideally patients should only remain in hospital until their sputum has converted to negative in order to ensure that MDRTB is not spread to the community. It is important to bear in mind that premature discharge may have deleterious effects on compliance and ultimately therapeutic outcome. Decreased hospitalisation costs resulting from patients being hospitalised in non-referral centres is not significant to the overall outcome of the model.

Regardless of the cure and mortality rates of either treatment alternative, this model suggests that individualised treatment is always the favourable option. Even if cure rates are lower in developing countries compared to more developed countries, the costs are still estimated to be lower for individualised treatment.

This model is limited in that it is not based on data specific to South Africa. Estimations of the variables had to be obtained from studies carried out in a variety of settings with different second-line drugs. The comparability of this data with the data used for estimating treatment outcomes for the protocol regimen is also suspect. No

accurate data was available for the daily drug cost of individualised drug treatment and the length of individualised treatment. Variables used to estimate the baseline case of non-drug management were also estimated. The daily cost and length of drug treatment did affect the outcomes of the decision analysis. The evaluation was also based on the assumption that the MDRTB treatment guidelines were being followed. This was specifically the case with estimating the protocol regimen branch. Failure to follow guidelines may alter both costs and outcomes. These variables did not however influence the results of the decision analysis.

This model did not take into account some of the costs incurred in the treatment of MDRTB patients. The cost of DOTS programmes and of managing adverse drug reactions were excluded. It was also assumed that laboratory facilities would be freely available at the referral centres and that no transport costs would be incurred.

The cost of absence from work and loss of productivity to society and the individual were not measured. The length of time that patients remained in hospital would affect these factors. The effect of quality of life and disease-free periods were also not taken into account. A Markov process could also be added to a future model that would take both the cost of relapses and further infections into account. This could be done by estimating the number of new infections caused by patients who are still infectious and adding the cost of treating these patients to the total cost per case cured or year of life saved as was done in a similar study by Suárez et al.[202]

Finally, although the modelling process was advantageous in that it allowed for the holistic evaluation of MDRTB treatment programmes rather than the subjective evaluation of logistic considerations, it was limiting in that the disease process had to be simplified in order to model it in a mathematical manner.

The decision tree models can be credited for their use of unit variables. The models are therefore easy to adapt to other settings. The decision tree was also designed to take HIV-status and associated treatment outcomes into account, which allowed us to assess the impact of the HIV epidemic on the outcomes of MDRTB treatment. Although many of the variables in the model were estimated or assumed, it allowed

for a sensitivity analysis that covered a wide range of feasible values for each variable.

Due to the paucity of data and the widely disparate range of studies and the lack of comparability of the outcomes for each alternative, the results of the study may not be credible. In this case, the use of a systematic review with subsequent economic modelling could not validly influence policy-makers to change the decision that they made on the basis of drug availability.

However, the decision analysis model could be used to highlight some of the areas where dramatic cost-savings can be made and where data needs to be collected for monitoring purposes. The total costs of drug treatment with either regimen can be reduced with the aid of buying groups. Drug treatment should not be continued indefinitely if the patient is not responding favourably to treatment and patients should also not be detained in hospital for longer periods than necessary.

The pharmacoeconomic evaluation did suggest that individualised treatment may be more cost-effective than the use of a protocol regimen. In the light of these results, the pragmatic choice of using the protocol regimen that was based on operational and logistic concerns may need to be reviewed. Individualised therapy appears to have the ability to actually reduce daily drug costs and improve patients' outcomes. The additional costs of laboratory investigations and hospitalisation in a referral centre are outweighed by the benefits they provide.

A second alternative to nationwide implementation of individualised treatment may be the development of a clinically proven regimen with a backbone of protocol drugs. Knowledgeable clinicians could then adapt this regimen, within certain confines, according to the individual sensitivities.

MDRTB treatment is resource intensive and only of moderate efficacy. An ongoing national audit of both the cost and effectiveness of MDRTB treatment needs to be implemented, maintained and made accessible to the public. In this way, policy can be evaluated and reviewed. This information can be used to guide any future policy revisions.

CHAPTER 6

6 CONCLUSIONS

Decision makers are aware of the lack of reliable evidence on the efficacy of second-line treatment for MDRTB patients. Practical and functional guidelines that allow researchers from different geographical and patient-care settings to follow a more standardised methodology when studying MDRTB patients should be created. Particular areas requiring attention are the patient inclusion and exclusion criteria and the presence of control groups, laboratory methods and the measurement of patient outcomes. Standardisation of these variables will enable comparison of these studies and will facilitate the use of meta-analytic techniques that combine the results of multiple studies. This increases the statistical power of the results and the ability to handle variability in outcomes from different studies.

Decision makers are currently focusing on determining the most 'appropriate' treatment for MDRTB. Appropriate treatment may depend on the infrastructure, experience and resources that are available in each individual setting.

Using baseline estimates, the decision analysis model suggested that individual-ised treatment may be more cost-effective than the protocol regimen in terms of cost alone, as well as in terms of the 'number of cases cured' and the number of 'years of life saved'. However, due to the widely disparate range of studies on which this evaluation was based, the outcome of the study may not be credible. In this case, the use of a systematic review with subsequent economic modelling could not validly influence policy-makers to change the decision that they made on the basis of drug availability. The study did highlight the need for an ongoing national audit of both the cost and effectiveness of MDRTB treatment that needs to be implemented and maintained.

APPENDIX 1

Global MDRTB statistics

The prevalence of MDRTB among new TB cases, previously treated cases and the combined prevalence of MDRTB by country or geographical region (1996-1999).[38,203]

Country	Year	Prevalence of MDRTB (%)					
		Patients tested	New TB cases	Patients tested	Previously treated cases	Patients tested	Combined drug resistance
Australia	1996	0	No Data	0	No Data	750	2
Belgium	1997	0	No Data	0	No Data	791	2
Botswana	1998	638	0.5	145	9	?	1.2
Canada	1997	0	No Data	0	No Data	1 593	1.1
Central African Republic (Bangui)	1999	464	1.1	33	18.2	?	2.8
Chile	1997	732	0.4	149	4.7	?	1.1
China (Henan Province)	1996	646	10.8	726	34.4	?	15.1
China (Guangdong Province)	1999	461	2.8	63	17.5	?	4.3
China (Hong Kong SAR*)	1996	4 424	1.4	783	9.6	5 207	2.6
China (Shandong Province)	1997	1 009	2.9	220	19.5	?	6.4
China (Zhejiang Province)	1999	802	4.5	140	35	?	9.4
Columbia	1999	201	0.5	0	No Data	0	No Data
Cuba	1998	284	0	43	7	327	0.9
Czech Republic	1999	311	1.6	52	11.5	?	2
Denmark	1998	412	0.5	32	3.1	444	0.7
England and Wales	1997	3 053	0.8	189	13.2	3 242	1.5
Estonia	1998	377	14.1	82	37.8	?	18.1
Finland	1997	410	0	2	0	412	0
France	1997	787	0	65	3.1	?	0.4
Germany	1998	1 455	0.9	256	6.3	1 711	1.7
Guinea	1998	539	0.6	32	28.1	?	1.5
India (Tamil Nadu State)	1997	384	3.4	16	25	?	7.1
Islamic Republic of Iran	1998	666	5	56	48.2	?	6.7
Israel	?	0	No Data	0	No Data	307	8.1
Italy	1999	683	1.2	127	33.9	?	6.7
Latvia	1998	789	0	224	23.7	?	12
Malaysia	1997	1 001	0.1	16	0	?	0.1
Mexico (Baja California, Oaxoca and Sinaloa)	1997	334	2.4	107	22.4	?	7.3
Morocco (Casablanca)	1998	510	2.2	0	No Data	0	No Data
Mozambique	1999	1 028	3.5	122	3.3	?	3.5
Nepal	1999	104	1	27	7.4	?	1.4
Netherlands	1996	1 042	0.6	172	0.6	1 214	0.6
New Caledonia	1996	93	0	12	0	105	0
New Zealand	1997	179	1.1	21	0	200	1
Nicaragua	1998	564	1.2	0	No Data	0	No Data
Northern Ireland	1997	41	0	0	No Data	0	No Data
Oman	1999	133	0.8	0	No Data	0	No Data
Norway	1996	138	2.2	6	16.7	144	2.8
Peru	1999	1879	3	260	12.3	?	4.3
Poland	1997	2976	0.6	994	7	?	1.3
Puerto Rico	1997	160	2.5	12	16.7	172	3.5
Republic of Korea	1999	2370	2.2	283	7.1	?	2.7

Russian Federation (Tomask Oblast)	1999	417	6.5	232	26.7	649	13.7
Russian Federation (Ivanovo Oblast)	1998	222	9	54	25.9	276	12.3
Scotland	1997	299	0.3	8	12.5	307	0.7
Sierra Leone	1997	117	0.9	13	23.1	?	2.6
Singapore	1996	980	0.3	151	4	1131	0.8
Slovakia	1998	589	0.3	157	8.3	746	2
Slovenia	1997	290	0.7	36	2.8	326	0.9
South Africa (Mpumalanga Province)	1997	661	1.5	100	8	?	2.5
Spain (Barcelona)	1998	315	0.3	69	11.6	?	1.4
Sweden	1997	356	0.6	24	8.3	380	1.1
Switzerland	1997	322	0	40	12.5	362	1.4
Thailand	1997	1137	2.1	0	No Data	0	No Data
Uganda (GLRA supported zones[á])	1997	374	0.5	45	4.4	?	0.8
United States of America	1997	12063	1.2	612	5.6	12675	1.4
Uruguay	1997	484	0	16	6.3	500	0.2
Venezuela	1998	221	0	24	8.3	NA	0.4
Median		**474**	**1**	**64**	**9.3**	**NA**	**1.8**
Minimum		**41**	**0**	**2**	**0**	**NA**	**0**
Maximum		**12 063**	**14.1**	**994**	**48.2**	**NA**	**18.1**
Weighted mean[â]		**1 313.5**	**2.8**	**194.4**	**17.6**	**NA**	**5.1**

* Special Administration Region

[á] German Leprosy Relief Association

[â] Arithmetic mean weighted by number of TB cases in the country/geographic setting

Trends in drug resistance among new and previously treated cases of tuberculosis.38,203

New cases

	Patients with Drug Resistance*																		
	1994			1995			1996			1997			1998			1999			
Country	**No.**	**% DR**	**%MDR**	**No.**	**% DR**	**%MDR**	**No.**	**% DR**	**%MDR**	**No.**	**% DR**	**%MDR**	**No.**	**% DR**	**%MDR**	**No.**	**% DR**	**%MDR**	**P Value for DR**	**P Value for MDR**
Australia[á]				63	9.5	0.7	750	10.5	2											0.03
Belgium[á]				763		1.2	750		1.7	791		2								
Botswana							4	3.7	0.2				638	6.3	0.5					
Canada[á]							1 407	10.4	0.6	1 599	10.2	1.1								
Chile				920	10.8	0				732	9.3	0.4								
Cuba							700	8.3	0.7	241	8.7	0	284	4.6	0					
Czech Republic				393	3.3	0.8										311	3.5	1.6		
Denmark				382	9.9	0.3	383	8.6	0	405	13.8	0.2	412	13.1	0.5				0.04	
England and Wales				2 742	6.9	1.1				3 053	7.2	0.8								
Estonia	266	28.2	10.2							332	29.5	11.1	377	36.9	14.1				0.01	
Finland	405	3.7	0	450	3.5	0	427	3.1	0	410	5.2	0								
France				1 491	8.2	0.5				787	9.3	0								0.03
Germany										1 765	5.9	0.7	1 455	8.9	0.9				0.001	
Latvia										587	29.3	9	789	29.9	9					
Nepal							787	9.8	1.1							104	5.8	1		
Netherlands[á]				1 104	14.1	1.1	1 214	11	0.6										0.02	
New Zealand							418	4.8	0.7	179	11.2	1.1							0.004	
Northern Ireland				59	3.4	1.7				41	4.9	0								
Peru							1 500	15.4	2.5							1 879	18.7	3	0.01	
Puerto Rico				369	10	1.9				160	11.3	2.5								
Republic of Korea	2 486	10.4	1.6										2 370	10.6	2.2					
Russia (Ivanovo Oblast)				33	24.2	6.1	259	26.3	4.6	201	21.4	5	222	32.4	9					
Scotland				290	3.4	0.3				299	3.7	0.3								
Sierra Leone							463	28.1	1.1	117	24.8	0.9								
Spain (Barcelona)							218	9.6	0.5				315	3.5	0.3				<0.001	
Sweden	402	5	0.5	436	8.9	0.2	391	7.2	1.3	356	7.9	0.6								
Switzerland							320	6.6	0.6	322	3.1	0							0.04	
United States							13 511	12.3	1.6	12 063	12	1.2								0.004

Previously treated cases

	Patients with Drug Resistance*																			
	1994			1995			1996			1997			1998			1999			P Value for	P Value for
Country	No.	% DR	%MDR	No.	% DR	%MDR	No.	% DR	%MDR	No.	% DR	%MDR	No.	% DR	%MDR	No.	% DR	%MDR	DR	MDR
Botswana							114	14.9	6.1				145	22.8	9					
Cuba							11	100	9.1	25	36	24	43	32.6	7				<0.001	
Czech Republic				23	17.4	8.7										52	21.2	11.5		
Denmark				29	13.8	3.4	36	11.1	5.6	44	9.1	2.3	32	12.5	3.1					
England and Wales				148	32.4	16.9				189	22.2	13.2							0.03	
Estonia	26	46.2	19.2							48	41.7	25	82	59.8	37.8					0.04
Finland	11	27.3	27.3	7	42.8	14.3	7	42.8	0	2	0	0								
France				195	21.5	4.1				65	20	3.1								
Germany										310	18.1	6.8	256	18.4	6.3					
Latvia										197	33	17.8	224	30.8	23.7					
New Zealand							19	5.3	0	21	19	0								
Peru							458	36	15.7							260	23.5	12.3	<0.001	
Puerto Rico				22	27.3	13.6				12	58.3	16.7								
Republic of Korea	189	52.9	27.5										283	21.9	7.1				<0.001	<0.001
Russia (Ivanovo Oblast)							33	100	27.3	95	38.9	9.5	54	68.5	25.9					
Sierra Leone							172	52.9	12.8	13	61.5	23.1								
Spain (Barcelona)							44	29.5	20.5				69	23.2	11.6					
Sweden	37	8.1	2.7	24	12.5	0	26	11.5	3.8	24	16.7	8.3								
Switzerland							46	23.9	8.7	40	27.5	12.5								
United States							833	23.6	7.1	612	20.9	5.6								

* DR denotes resistance to any drug, and MDR, multidrug resistance. P values were calculated by the standard chi-squared, Fischer's exact test, or the chi-squared test for the trend. P values are shown only for significant differences.

[á] Data are for all patients (with no distinction made between new and previously treated cases). In the Netherlands, no distinction was made during the first year of the study.

APPENDIX 2

Data collection form

Variable	Description
Study Characteristics:	
Journal reference	
Author	
Study description	*0=case series, 1=case control and 2=cohort*
Retrospective or prospective design	*0=prospective; 1=retrospective*
City/country of study	
Developed/Developing world	*0=developed; 1=developing*
Date of study	*Commencement to completion*
Commenced before 1990 or after 1990	*0 = trial started before 1990, 1 = trial started after 1990*
Institution	*Name of institution at which study took place*
Description of institution	*0 = primary-care facility or unknown, 1 =specialised or teaching hospital*
Quality appraisal checklist:	
Who wrote the study?	*Qualifications and descriptions of researchers*
Was the aim stated?	*0=no; 1=yes*
Why was the study performed?	*Aim of the study*
Was the aim to determine the efficacy of MDRTB treatment?	*0=Primary aim was not to determine treatment outcomes; 1=Yes*
Was the design appropriate to the aim?	*0=no; 1=yes*
Who has been studied?	*Description of patients*
Inclusion criteria	*Patient inclusion criteria*
Exclusion criteria	*Patients exclusion criteria*
Recruitment	*Description of recruitment process*
Time of entry of patients into study	*Description of the disease stage at which patients entered the study*
Constant time of entry?	*Where all included patients at the same stage of the disease? 0=no; 1=yes*
Generalisable patient group?	*0=no; 1=yes*
Reasons	*Reasons for yes/no generalisable patient group*
Was the population group justified?	*0=no; 1=yes*
Was the sample size justified?	*0=no; 1=yes*
Were patients lost?	*0=no; 1=yes*
Number lost to FU	*The number of patients lost during follow-up*
Was this due to the patient group of different follow-up methods?	*0=no; 1=yes*
Was the diagnosis accurate?	*0=no; 1=yes*
Were measurements valid?	*0=no; 1=yes*
Was measurement accurate?	*0=no; 1=yes*
Was there evidence of surveillance bias?	*0=no; 1=yes*
Were statistical methods described?	*0=no; 1=yes*
No relevant issues were ignored	*0=no; 1=yes*
No untoward events occurred	*0=no; 1=yes*
Proposed follow-up time	*Ideal follow-up time (days)*
Actual follow-up time	*Actual mean/median follow-up time (days)*
Analysis allowed for passage of time?	*0=no; 1=yes*
Numbers add up?	*0=no; 1=yes*
Basic data is adequately described?	*0=no; 1=yes*
Statistical significance was assessed?	*0=no; 1=yes; 2=NA*
What do findings mean?	*Description of study conclusions*
Results are not susceptible to outside influences?	*0=no; 1=yes*
No important events were overlooked?	*0=no; 1=yes*
Null findings are appropriately handled?	*0=no; 1=yes*
Results compare with other reports?	*0=no; 1=yes*
Study is relevant?	*0=no; 1=yes*
Study quality	*0=doubtful; 1=good*

Patient demographics:	
Mean age of patients in group	*Age (years)*
Range (age)	*Range of ages of patients included*
Mean weight of patients in group	*Weight (kg)*
pMale	*The proportion of male patients in study group*
pBlack	*The proportion of black patients in the study group*
pWhite	*The proportion of white patients in the study group*
pOther	*The proportion of patients of other cultural groups*
The number of patients included in the study	*The number of patients the authors included in the study*
The number of patients included in the study (adjusted)	*The number of patients included in the outcomes analysis after including lost patients and those excluded for deaths.*
Medical history:	
pPrimary MDRTB	*The proportion of included patients with primary MDRTB*
Mean duration of TB	*The mean length of time that patients have been suffering from TB (days)*
Range (duration TB)	*The range in the patient group of the duration of TB (days)*
The number of HIV-positive patients	
The number of HIV-negative patients	
pAIDS	*The proportion of patients diagnosed with AIDS*
pExtensive disease	*The proportion of patients with extensive/serious TB*
pBilateral disease with cavity	*The proportion of patients with bilateral, cavitatory TB*
pExtrapulmonary TB	*The proportion of patients with extrapulmonary TB*
Drugs taken previously	*The average number of drugs taken by patients during previous treatment episodes*
Average number of first line drugs resistant	*The average number of first-line drugs to which the patients in the group are resistant*
Average number of drugs resistant	*The average number of drugs to which the patients in the group are resistant to*
Number of drugs tested for susceptibility	*The number of drugs tested for susceptibility for the patients*
Susceptibility testing method used	*Method of susceptibility testing and medium on which tests were performed*
Defn resistance	*The definition of resistance applied to susceptibility tests*
Defn MDRTB	*The definition of MDRTB used in the study*
pTrue MDRTB	*The proportion of included patients with true MDRTB (isoniazid and rifampicin)*
Drug treatment:	
Treatment regimen followed	*0=non-drug therapy; 1=individualised therapy; 2=standardised regimen*
Median # of drugs received	*The median number of drugs received by patients in the group*
Ave # of susceptible drugs used	*The average number of susceptible drugs used by patients in the group*
pPt receiving >2 suscep drugs	*The proportion of patients receiving two or more susceptible drugs*
pPt receiving > 6 drugs	*The proportion of patients receiving more than six drugs*
Was drug treatment described?	*0=no; 1=yes*
tTreatment	*The median length of drug treatment received*
Drug (1,2,3...) name	*The name of each drug provided to patients in the group*
Dose (drug 1,2,3…) for pts <50kg	*The dose of each drug provided to patients with mass less than 50kg*
Dose (drug 1,2,3…) for pts >50kg	*The dose of each drug provided to patients with mass greater than 50kg*
Number of patients receiving drug (1,2,3…)	*The number of patients in each study receiving each drug*
DOT	*Was directly observed therapy practised? 0=no; 1=yes*
pHospital	*The proportion of patients hospitalised at any stage during treatment*
tHospital	*The median length of time spent in hospital*
Range (tHospital)	*The range of times spent in hospital by patients in each group*

Treatment outcomes:	
pADR	*The proportion of patients developing any ADR*
pSurgery	*The proportion of patients undergoing additional surgery*
pSputum conversion	*The proportion of patients whose sputum cultures converted to negative during the FU period*
tSputum conversion	*The mean time to sputum conversion (days)*
Range (sputum conversion time)	*The range of sputum conversion times*
Number failed (HIV pos)	*The number of HIV-positive patients failing treatment (recalculated to include lost patients)*
Number failed (HIV neg)	*The number of HIV-negative patients failing treatment (recalculated to include lost patients)*
Number deaths (HIV pos)	*The number of HIV-positive patients dying (all-cause death)*
Number of deaths (HIV neg)	*The number of HIV-negative patients dying (all-cause death)*
tDeath	*The median time of death (Days)*
Number cured (HIV pos)	*The number of HIV-positive patients cured after FU period*
Number cured (HIV neg)	*The number of HIV-negative patients cured after FU period*
Non-drug management:	
# no Tx	*The number of patients not receiving drug therapy*
pHIV pos (no Tx)	*The proportion of HIV-positive patients not receiving drug therapy*
Number failed (no Tx)	*The number of patients not receiving drug therapy, failing treatment*
Number deaths (no Tx)	*The number of patients not receiving drug therapy, dying*
Number cured (no Tx)	*The number of patients not receiving drug therapy, getting cured*

APPENDIX 3

Estimation of the average daily drug cost for individualised drug regimens

Antituberculous drug usage in published studies and the average daily cost of individualised regimens

		Author		Frieden[158]	Hong Kong[157]	Fischl[160]	Pretet[161]	Mangun-negoro[162]	Telzak[65]	Geerligs[166]	Franzetti[171]	Yew[172]	Salomon[173]	Telzak[174]	Maranetra[175]	Tahaoglu[178]	Goble[64]
	Cost per dosage unit		Total pts in study	267	18	29	39	50	23	44	8	63	11	12	22	148	171
Isoniazid 100mg	0.03	Number of pts		240	0	29	0	0	0	36	8	63	0	1	0	0	45
		Min dose (# tablets)	2	13.58	0	1.64	0	0	0	2.04	0.45	3.57	0	0.06	0	0	2.55
		Max dose (# tablets)	3	20.38	0	2.46	0	0	0	3.06	0.68	5.35	0	0.09	0	0	3.82
Rifampicin 450 or 600mg	0.58	Number of pts		237	12	29	0	0	0	5	7	63	0	4	0	0	22
		Min dose (# tablets)	1	136.94	6.93	16.76	0	0	0	2.89	4.05	36.40	0	2.31	0	0	12.71
	1.10	Max dose (# tablets)	1	260.75	13.20	31.91	0	0	0	5.50	7.70	69.31	0	4.40	0	0	24.20
Pyrazinamide 500mg	0.23	Number of pts		236	4	29	19	50	0	38	6	34	2	5	22	50	101
		Min dose (# tablets)	3	166.03	2.81	20.40	13.37	35.18	0	26.73	4.22	23.92	1.41	3.52	15.48	35.18	71.05
		Max dose (# tablets)	4	221.37	3.75	27.20	17.82	46.90	0	35.64	5.63	31.89	1.88	4.69	20.64	46.90	94.74
Ethambutol 400mg	0.25	Number of pts		214	14	25	15	50	0	42	8	29	1	9	11	36	62
		Min dose (# tablets)	2	108.11	7.07	12.63	7.58	25.26	0	21.22	4.04	14.65	0.51	4.55	5.56	18.19	31.32
		Max dose (# tablets)	3	162.17	10.61	18.95	11.37	37.89	0	31.83	6.06	21.98	0.76	6.82	8.34	27.28	46.98

Streptomycin 1g/5ml	1.33	Number of pts		30	0	22	6	1	0	0	3	0	0	3	0	8	16
		Min dose	0.75	29.92	0	21.94	5.99	0.99	0	0	2.99	0	0	2.99	0	7.98	15.96
		Max dose	1	39.90	0	29.26	7.98	1.33	0	0	3.99	0	0	3.99	0	10.64	21.28
Kanamycin 1g	6.62	Number of pts		100	7	0	15	20	2	40	0	58	4	2	22	15	70
		Min dose	0.75	496.69	34.77	0	74.50	99.34	9.93	198.68	0	288.08	19.87	9.93	109.27	74.50	347.68
		Max dose	1	662.25	46.36	0	99.34	132.45	13.25	264.90	0	384.11	26.49	13.25	145.70	99.34	463.58
Amikacin 1g	6.99	Number of pts		0	0	0	0	0	7	0	2	0	0	1	0	120	0
		Min dose	0.75	0	0	0	0	0	36.73	0	10.50	0	0	5.25	0	629.64	0
		Max dose	1	0	0	0	0	0	48.97	0	13.99	0	0	6.99	0	839.52	0
Ethionamide 250mg	1.23	Number of pts		116	12	0	19	0	13	16	0	29	9	11	0	127	126
		Min dose (# tablets)	2	286.24	29.61	0	46.88	0	32.08	39.48	0	71.56	22.21	27.14	0	313.39	310.92
		Max dose (# tablets)	3	429.36	44.42	0	70.33	0	48.12	59.22	0	107.34	33.31	40.72	0	470.08	466.38
Ciprofloxacin 250mg	6.11	Number of pts		175	0	14	0	0	13	0	5	0	4	0	0	0	0
		Min dose (# tablets)	2	2138.36	0	171.07	0	0	158.85	0	61.106	0	48.88	0	0	0	0
		Max dose (# tablets)	3	3207.54	0	256.60	0	0	238.27	0	91.64	0	73.32	0	0	0	0
Ofloxacin 400mg	10.46	Number of pts		87	10	0	32	50	10	38	0	63	6	12	22	126	0
		Min dose (# tablets)	1	910.02	104.60	0	334.72	523.00	104.60	397.48	0	658.98	62.76	125.52	230.12	1 317.96	0
		Max dose (# tablets)	2	1 820.04	209.20	0	669.44	1 046.00	209.20	794.96	0	1 317.96	125.52	251.04	460.24	2 635.92	0

Cycloserine 250mg	17.79	Number of pts		120	0	0	4	0	11	5	0	46	10	8	0	142	98
		Min dose (# tablets)	2	4 269.60	0	0	142.32	0	391.38	177.90	0	1 636.68	355.80	284.64	0	5 052.36	3 486.84
		Max dose (# tablets)	3	6 404.40	0	0	213.48	0	587.07	266.85	0	2 455.02	533.70	426.96	0	7 578.54	5 230.26
Capreomycin 1g	261.94	Number of pts		109	3	0	2	0	8	0	0	0	4	3	0	15	108
		Min dose	0.75	21 413.20	589.35	0	392.90	0	1 571.61	0	0	0	785.81	589.35	0	2 946.77	21 216.70
		Max dose	1	28 550.90	785.81	0	523.87	0	2 095.48	0	0	0	1 047.74	785.81	0	3 929.03	28 289.00
Clofazamine 100mg	0.77	Number of pts		53	0	9	2	0	2	0	0	3	0	0	0	11	17
		Min dose	1	40.64	0	6.90	1.53	0	1.53	0	0	2.30	0	0	0	8.44	13.04
		Max dose	1	40.64	0	6.901	1.53	0	1.53	0	0	2.30	0	0	0	8.44	13.04
Rifabutin 150mg	28.09	Number of pts		0	13	0	39	0	0	9	3	0	0	0	0	15	0
		Min dose (# tablets)	3	0	1 095.51	0	3 286.53	0	0	758.43	252.81	0	0	0	0	1 264.05	0
		Max dose (# tablets)	4	0	1 460.68	0	4 382.04	0	0	1 011.24	337.08	0	0	0	0	1 685.40	0
PAS (g)	0.57	Number of pts		48	0	0	2	0	4	0	0	7	0	2	22	124	50
		Min dose (g)	10	272.78	0	0	11.37	0	22.73	0	0	39.78	0	11.37	125.03	704.69	284.15
		Max dose (g)	12	327.34	0	0	13.64	0	27.28	0	0	47.74	0	13.64	150.03	845.63	340.98
Thiacetazone & Isoniazid 50/100 or 150/300mg	0.05	Number of pts		0	0	0	0	0	0	4	0	0	0	0	11	0	0
		Min dose (# tablets)	2	0	0	0	0	0	0	0.37	0	0	0	0	1.02	0	0
	0.10	Max dose (# tablets)	1	0	0	0	0	0	0	0.39	0	0	0	0	1.07	0	0

Co-amoxiclav 750/375mg	1.60	Number of pts		7	0	0	0	0	0	1	0	4	0	0	0	44	0
		Min dose (# tablets)	1	11.20	0	0	0	0	0	1.60	0	6.40	0	0	0	70.43	0
		Max dose (# tablets)	2	22.41	0	0	0	0	0	3.20	0	12.81	0	0	0	140.85	0
Clarithromycin 1g	81.19	Number of pts		0	0	0	0	0	0	2	0	0	0	0	0	27	0
		Min dose	0.75	0	0	0	0	0	0	121.78	0	0	0	0	0	1644.00	0
		Max dose	1	0	0	0	0	0	0	162.37	0	0	0	0	0	2192.00	0
Minimum average cost per day to treat one patient				113.46	103.936	8.67	110.71	13.68	101.28	39.74	42.52	44.16	117.93	88.89	22.11	95.19	150.84
Maximum average cost per day to treat one patient				157.94	143.00	12.87	154.12	25.29	142.14	59.98	58.35	70.73	167.52	129.87	35.73	138.58	204.65

APPENDIX 4

Definitions of variables used in the decision analysis models

Variable	Definition
cCulture	The cost of one sputum culture
cDrugs_indiv_cure	The total drug cost for individually treated patients that get cured
cDrugs_indiv_die	Total drug cost for individually treated patients that die
cDrugs_indiv_dly	The average daily drug cost for all patients treated with individualised regimens
cDrugs_indiv_dly_high	Average daily drug cost for individually treated patients weighing greater than 50kg
cDrugs_indiv_dly_low	Average daily drug cost for individually treated patients weighing less than 50kg
cDrugs_indiv_fail	Total drug cost for individually treated patients that fail treatment
cDrugs_prot_cure	Total drug cost for patients getting cured after treatment with the protocol regimen
cDrugs_prot_die	Total drug cost for patients dying after treatment with the protocol regimen
cDrugs_prot_dly	The average daily drug cost for all patients treated with protocol regimen
cDrugs_prot_dly_EMBr_high	The daily cost of the protocol regimen for patients over 50kg that are resistant to ethambutol
cDrugs_prot_dly_EMBr_low	The daily cost of the protocol regimen for patients under 50kg that are resistant to ethambutol
cDrugs_prot_dly_EMBs_high	The daily cost of the protocol regimen for patients over 50kg that are sensitive to ethambutol
cDrugs_prot_dly_EMBs_low	The daily cost of the protocol regimen for patients under 50kg that are sensitive to ethambutol
cDrugs_prot_fail	Total drug cost for patients that fail after treatment with the protocol regimen
cHosp	Per diem cost of hospitalisation in a tertiary care centre
cHosp_indiv_cure	The total cost of hospitalisation for individually treated patients that get cured
cHosp_indiv_die	The total cost of hospitalisation for individually treated patients that die
cHosp_indiv_fail	The total cost of hospitalisation for individually treated patients that fail treatment
cHosp_noTx_cure	The total cost of hospitalisation for patients getting cured without drug therapy
cHosp_noTx_die	The total cost of hospitalisation for patients dying with non-drug management
cHosp_noTx_fail	The total cost of hospitalisation for patients failing with non-drug management
cHosp_prot_cure	The total cost of hospitalisation for patients getting cured with protocol regimen
cHosp_prot_die	The total cost of hospitalisation for patients dying after receiving the protocol regimen
cHosp_prot_fail	The total cost of hospitalisation for patients failing treatment after receiving the protocol regimen
cLab_indiv	Total laboratory costs for individually treated patients
cLab_noTx	Total laboratory costs for patients managed without drugs
cLab_prot	Total laboratory costs for patients treated with the protocol regimen
cSens	The cost a drug susceptibility test for a single drug
cTotal_indiv_cure	The total cost of curing one individually treated patient
cTotal_indiv_die	The total cost of treating one individually treated patient that dies
cTotal_indiv_fail	The total cost of treating one individually treated patient that fails
cTotal_noTx_cure	The total cost of non-drug management for patients that get cured
cTotal_noTx_die	The total cost of non-drug management for patients that die
cTotal_noTx_fail	The total cost of non-drug management for patients that fail
cTotal_prot_cure	Total cost of curing of curing one patient using the protocol regimen
cTotal_prot_die	Total cost of treating one patient that dies with the protocol regimen
cTotal_prot_fail	The total cost of treating one patient that fails with the protocol regimen
cXRayAFB	The estimated cost of one chest X-ray and one set of three AFB sputum smears
iCult_indiv	The monthly intervals at which sputum cultures are performed for individually treated patients
lSens_indiv	The monthly intervals at which drug susceptibility tests are performed for individually treated patients
nCases_cured	The 'number of cases cured' by each treatment alternative in each outcome category
nCultures_indiv	The number of cultures performed for individually treated patients
nCultures_noTx	The number of cultures performed for patients managed without drug therapy
nCultures_prot	The number of cultures performed for patients receiving protocol treatment
nDays_hosp_noTx_cure	The number of days spent in hospital by a patient not receiving drug therapy that gets cured
nDays_hosp_noTx_die	The number of days spent in hospital by a patient not receiving drug therapy that dies
nDays_hosp_noTx_fail	The number of days spent in hospital by a patient not receiving drug therapy that fails
nSens_indiv	The number of drug susceptibility tests performed for individually treated patients

nSens_noTx	The number of drug susceptibility tests performed for patients treated without drug therapy
nSens_prot	The number of drug susceptibility tests performed for patients treated with the protocol regimen
nXRayAFB_indiv	The number of chest X-rays and AFBs (x3) that get performed for individually treated patients
nXRayAFB_prot	The number of chest X-rays and AFBs (x3) that get performed for patients treated with protocol regimen
nXRayAFB_noTx	The number of chest X-rays and AFBs (x3) that get performed for patients managed without drugs
pCure_indiv	The total probability of cure for an individually treated patient
pCure_indiv_HIVneg	The total probability of cure for an HIV-negative individually treated patient
pCure_indiv_HIVpos	The total probability of cure for an HIV-positive individually treated patient
pCure_prot	The probability of cure when using the protocol regimen
pDie_indiv	Total probability of death for individually treated patients
pDie_indiv_HIVneg	Probability of death in an HIV-negative patient treated with individualised regimen
pDie_indiv_HIVpos	Probability of death in an HIV-positive patient treated with individualised regimen
pDie_noTx	Probability of death for patients managed without drug therapy
pDie_prot	Total probability of death for patients receiving protocol regimen
pDie_prot_HIVneg	Probability of death in an HIV-positive patient treated with protocol regimen
pDie_prot_HIVpos	Probability of death in an HIV-negative patient treated with protocol regimen
pEMBr	The probability of a patient being resistant to ethambutol
pFail_noTx	The probability of treatment failure for patients managed without drug therapy
pHIV_pos	The probability of a patient being HIV-positive
propTime_hosp	The proportion of treatment time spent in hospital by patients treated with various drug regimens
p_over50kg	The probability that a patient will weigh greater than 50kg
tTx_indiv_cure	The length of treatment received by individually treated patients that get cured
tTx_indiv_die	The length of treatment received by individually treated patients that die
tTx_indiv_fail	The length of treatment received by individually treated patients that fail
tTx_prot_cure	The length of treatment received by patients treated with the protocol regimen that cure
tTx_prot_die	The length of treatment received by patients treated with the protocol regimen that die
tTx_prot_fail	The length of treatment received by patients treated with the protocol regimen that fail

APPENDIX 5

Variables used to model the decision analysis tree

General variables	Value
cHosp	R 161.69
cCulture	R 94.00
cSens	R 44.65
cXRayAFB	R 59.43
p_Over50kg	0.2
pEMBr	0.53
pHIVpos	0.5
propTime_hosp	0.13
Protocol regimen	
Drug costs:	
cDrugs_prot_cure	cDrugs_prot_dly*tTx_prot_cure
cDrugs_prot_die	cDrugs_prot_dly*tTx_prot_die
cDrugs_prot_fail	cDrugs_prot_dly*tTx_prot_fail
cDrugs_prot_dly	(p_over50kg*((pEMBr*cDrugs_prot_dly_EMBr_high)+((1-pEMBr)*cDrugs_prot_dly_EMBs_high)))+((1-p_over50kg)*((pEMBr*cDrugs_prot_dly_EMBr_low)+((1-pEMBr)*cDrugs_prot_dly_EMBs_low)))
cDrugs_prot_dly_EMBr_high	77.16
cDrugs_prot_dly_EMBr_low	51.6
cDrugs_prot_dly_EMBs_high	24.54
cDrugs_prot_dly_EMBs_low	16.52
Length of treatment:	
tTx_prot_cure	456
tTx_prot_die	248
tTx_prot_fail .	496
Hospital costs:	
cHosp_prot_cure	propTime_hosp*tTx_prot_cure*cHosp
cHosp_prot_die	propTime_hosp*tTx_prot_die*cHosp
cHosp_prot_fail	propTime_hosp*tTx_prot_fail*cHosp
Laboratory costs:	
cLab_prot_cure	(nCultures_prot*cCultures)+(nSens_prot*cSens)+(nXRayAFB_prot_cure*cXRayAFB)
cLab_prot_die	(nCultures_prot*cCultures)+(nSens_prot*cSens)+(nXRayAFB_prot_die*cXRayAFB)
cLab_prot_fail	(nCultures_prot*cCultures)+(nSens_prot*cSens)+(nXRayAFB_prot_fail*cXRayAFB)
nCultures_prot	5
nSens_prot	3
nXRayAFB_cure	tTx_prot_cure/28
nXRayAFB_die	tTx_prot_die/28
nXRayAFB_fail	tTx_prot_fail/28
Probabilities of outcomes:	
pCure_prot	0.47
pDie_prot	(pHIVpos*pDie_prot_HIVpos)+((1-pHIVpos)*pDie_prot_HIVneg)
pDie_prot_HIVneg	0.15
pDie_prot_HIVpos	0.56
Individual regimen	
Drug costs:	
cDrugs_indiv_cure	cDrugs_indiv_dly*tTx_indiv_cure
cDrugs_indiv_die	cDrugs_indiv_dly*tTx_indiv_die
cDrugs_indiv_fail	cDrugs_indiv_dly*tTx_indiv_fail
cDrugs_indiv_dly	(p_over50kg*cDrugs_indiv_dly_high)+((1-p_over50kg)*cDrugs_indiv_dly_low)
cDrugs_indiv_dly_high	41.8
cDrugs_indiv_dly_low	26.06

Length of treatment:	
tTx_indiv_cure	456
tTx_indiv_die	114
tTx_indiv_fail	496
Hospital costs:	
cHosp_indiv_cure	propTime_hosp*tTx_indiv_cure*cHosp
cHosp_indiv_die	propTime_hosp*tTx_indiv_die*cHosp
cHosp_indiv_fail	propTime_hosp*tTx_indiv_fail*cHosp
Laboratory costs:	
cLab_indiv_cure	(nCultures_indiv_cure*cCultures)+(nSens_indiv_cure*cSens)+(nXRayAFB_indiv_cure* cXRayAFB)
cLab_indiv_die	(nCultures_indiv_die*cCultures)+(nSens_indiv_die*cSens)+(nXRayAFB_indiv_die* cXRayAFB)
cLab_indiv_fail	(nCultures_indiv_fail*cCultures)+(nSens_indiv_fail*cSens)+(nXRayAFB_indiv_fail* cXRayAFB)
nCultures_indiv_cure	3+((tTx_indiv_cure-84)/(28*iCult_indiv))
nCultures_indiv_die	3+((tTx_indiv_die-84)/(28*iCult_indiv))
nCultures_indiv_fail	3+((tTx_indiv_fail-84)/(28*iCult_indiv))
nSens_indiv_cure	8+((tTx_indiv_cure*8)/(28*iSens_indiv))
nSens_indiv_die	8+((tTx_indiv_die*8)/(28*iSens_indiv))
nSens_indiv_fail	8+((tTx_indiv_fail*8)/(28*iSens_indiv))
nXRayAFB_cure	tTx_indiv_cure/28
nXRayAFB_die	tTx_indiv_die/28
nXRayAFB_fail	tTx_indiv_fail/28
Treatment outcomes:	
pCure_indiv	(pHIVpos*pCure_indiv_HIVpos)+((1-pHIVpos)*pCure_indiv_HIVneg)
pCure_indiv_HIVneg	0.59
pCure_indiv_HIVpos	0.54
pDie_indiv	(pHIVpos*pDie_indiv_HIVpos)+((1-pHIVpos)*pDie_indiv_HIVneg)
pDie_indiv_HIVneg	0.17
pDie_indiv_HIVpos	0.86
Non-drug management	
Hospital costs:	
cHosp_noTx_cure	nDays_hosp_noTx_cure*cHosp
cHosp_noTx_die	nDays_hosp_noTx_die*cHosp
cHosp_noTx_fail	nDays_hosp_noTx_fail*cHosp
nDays_hosp_noTx_cure	10
nDays_hosp_noTx_die	20
nDays_hosp_noTx_fail	10
Laboratory costs:	
cLab_noTx	(nCultures_noTx*cCultures)+(nSens_noTx*cSens)+(nXRayAFB*cXRayAFB)
nCultures_noTx	2
nSens_noTx	2
nXRayAFB	6
Treatment outcomes	
pCure_noTx	0.14
pDie_noTx	0.79

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