MANAGING MULTIDRUG-RESISTANT TUBERCULOSIS IN HOSPITALIZED PATIENTS AT SIZWE TROPICAL DISEASES HOSPITAL: A FIVE YEAR REVIEW OF TREATMENT OUTCOMES

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A research report submitted to the School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment for the degree of Master of Public Health.

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DECLARATION

I, Peter Joseph Njaramba declare that this research report is my own work. It is being submitted for the degree of Master of Public Health at the School of Public Health, University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signed: _____

_____day of_____2005

DEDICATIONS

To my beloved wife Wanjiru, treasured daughters Wamaitha and Nungari, and cherished sons Mugo and Ngaruiya for their endurance during my absence, and for their never-ending trust and confidence that they unreservedly bestowed in me.

ABTSRACT

Management of multidrug-resistant tuberculosis (MDR-TB) is more expensive, lengthy and is associated with less favourable outcomes and more adverse reactions than management of susceptible tuberculosis. The aim of this study was to review the management and treatment outcomes of registered MDR-TB patients hospitalized at Sizwe hospital during a five-year period.

A cross-sectional study with both descriptive and analytic features was done on 237 MDR-TB patients hospitalized from the beginning of June 1998 to the end of May 2003. Data were analysed using SPSS version 12 Software. Main outcome measures were interim treatment outcomes at the end of hospitalization period. These outcomes comprised culture conversion rates, time to culture conversion, transfer out, interruption, and death rates. Multiple logistic regression analysis was performed to determine risk factors for poor treatment outcomes. These poor outcomes were defined as treatment interruption, failure and mortality rates.

The burden of institutional care for MDR-TB patients in this setting was found to involve high numbers of MDR-TB patients for whom the allocated hospital beds were insufficient. Patients with primary MDR-TB, who had no history of non-adherence to treatment, were paradoxically more likely to be hospitalized shortly after diagnosis. Acquired MDR-TB patients were mostly managed as outpatients immediately after diagnosis only to be hospitalized later due to persistent non-adherence or disease severity. Overall, acquired MDR-TB patients were hospitalized in larger numbers than those with primary disease. This reflects the higher prevalence of acquired MDR-TB compared to primary MDR-TB.

Culture turnaround time was on average 19 days. The overall culture conversion rate of the hospitalized patients was low at 41.9 percent. This low culture conversion rate resulted in protracted hospitalization periods and high interim mortality rates. The mean duration of hospitalization, 3.52 months, correlated favourably with the time interval to the first culture conversion of 2.96 months. Hospitalization did not guarantee the expected adherence to treatment. Surgical interventions were done belatedly with resultant high mortality outcomes.

The main reasons given by patients for refusing hospital treatment were visiting traditional healers, solving socioeconomic problems and attending to family matters. A large percentage of hospitalized patients were co-infected with HIV. HIV care and support was incomplete as antiretroviral drugs were not available at the hospital. Among the main findings of the study was the powerful influence HIV status had on poor hospitalization outcomes.

Recommendations arising from the study include the need to provide ARVs at the Sizwe hospital. Admission and discharge guidelines aimed at ensuring adequate beds are reserved for deserving patients should be formulated. Continuing education for service providers must be encouraged and rewarded. Infection control procedures at both community and health institution level ought to be vigorously promoted. Patients known to be hopelessly non-adherent should at least be partially hospitalized in the interest of public health.

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ABBREVIATIONS AND ACRONYMS

ADR	Adverse Drug Reactions
AFB	Acid Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
ARVs	Anti-Retroviral drugs
DOTS	Directly Observed Treatment Short Course
DRS	Drug Resistance Surveillance
DST	Drug Susceptibility Testing
GLC	Green Light Committee
HIV	Human Immunodeficiency Virus
ICD	Intercostal Drainage
IUATLD	International Union Against Tuberculosis and Lung Disease.
MDR-TB	Multidrug-Resistant Tuberculosis.
MOTT	Mycobacteria Other than Tuberculosis
NHLS	National Health Laboratory Service
NTCP	National Tuberculosis Control Programme
PCP	Pneumocystis Carinii Pneumonia
RHT	Refuse Hospital Treatment
SCC	Short Course Chemotherapy
TB	Tuberculosis
WHO	World Health Organization

DEFINITIONS

Primary resistance	Bacterial resistance that occurs in patients with no history of treatment with antituberculosis drugs
Acquired resistance	Bacterial resistance in patients with a record of previous treatment.
Initial resistance	Bacterial resistance in new tuberculosis patients whose previous history of treatment cannot be verified. It is a mixture of primary resistance and undisclosed acquired resistance
First line drugs	Standard essential drugs used in treatment of susceptible TB.
Second line drugs	Drugs reserved for treatment of MDR-TB.
Standardized regimen	Fixed regimen offered to all patients only substituting ethambutol for cycloserine according to drug resistance profiles.
Individualized regimen	Treatment tailored according to the susceptibility patterns of the TB strains infecting an individual.
DOTS-Plus	An integrated strategy for managing MDR-TB using second line drugs within the DOTS strategy. It cures MDR-TB.
Interim treatment outcomes	Treatment outcomes at the end of a designated treatment period. They are early indicators of favourable or poor final outcomes.
Culture conversion rates	Proportion of culture positive cases who have two consecutive negative cultures after intensive therapy taken a month apart.
Transfer out rate	Percentage of patients referred to clinics after culture conversion to continue with treatment under DOTS Plus.
Interruption rate	Percentage of patients who stop treatment for two or more months.
Failure rate	Percentage of patients who are sputum culture positive at the end of the recommended treatment period.
Death rate	Percentage of patients who die during treatment irrespective of cause.
Time interval to conversion	Period between start of treatment and the first of two negative cultures
Drug Interaction	Modulation of the activity of one drug by the prior or concomitant administration of another drug

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CHAPTER 1: TUBERCULOSIS AND HOSPITALIZATION

Tuberculosis is a Curable Disease. Hermann Brehmer, 1854[1]

1.1. The Sanatorium Era

Tuberculosis (TB) is an ancient, highly infectious airborne disease caused by *Mycobacterium tuberculosis*. Hospitalization for pulmonary tuberculosis patients was started in the early nineteenth century. Patient management then was primarily based on the combination of isolation, fresh air, nutritious diet and bed rest. For patients with cavities in the lungs, air was introduced into the pleural spaces to collapse the diseased lungs.[2] Collapse therapy not only rested the diseased lungs but also depleted oxygen necessary for the sustenance of mycobacteria in the cavities. On some occasions, destroyed parts of the lungs were removed surgically. Surgical resection was unpopular due to postoperative complications as there were no antibiotics at the time.[2-3]

Institutional care was believed to be the only way to manage TB with protracted hospitalization periods that ranged from two to as much as ten years.[3] The x-ray machine was invented in 1895 and was immediately used for diagnosis of tuberculosis. This had an effect of increasing the numbers of confirmed tuberculosis patients, creating high demand for hospital beds.[4] Building new sanatoriums and increasing bed capacity to accommodate everyone needing treatment was the most important public health effort in tuberculosis control at the time.[5]

1.2. Discovery of Cause and Cure of TB

On the day of 24th March 1882, Robert Koch described the cause of tuberculosis. The discovery of the tuberculosis bacillus and the methods for its cultivation sparked off an earnest search for the therapy of tuberculosis. Experiments with cultures of *Mycobacterium tuberculosis* represented the basis for detection of new anti-tuberculosis drugs.[3] The discovery of streptomycin in 1944 heralded the era of modern chemotherapy. However, because of the slow growth rate of mycobacteria and their intracellular location, long periods of drug administration were necessary to cure patients. Furthermore, patients treated with single drugs often relapsed due to development of resistance. The problem of resistance was ingeniously overcome by use of combination therapy. The costs of initial combination therapies were expensive as patients were hospitalized for extended periods of time.[2]

1.3. Decline in Hospitalization Trends

The first combination therapy was that of streptomycin and para-aminosalicylic acid which cured tuberculosis in 24 months. The introduction of isoniazid in 1952 shortened the duration of therapy to 18 months. Later, the introduction of rifampicin in the tuberculosis regimens led to development of short course chemotherapy (SCC), standardized regimens that include rifampicin, isoniazid, pyrazinamide, ethambutol, and/or streptomycin. This SCC shortened the course of treatment to 6-8 months and significantly reduced the need for hospital beds. It was realised that drug treatment, which could be given at home, could eliminate the need for hospitalization except for those patients who were seriously ill with tuberculosis.[6]

The study on "Home vs. Sanatorium Treatment" done at Tuberculosis Chemotherapy Centre, Madras in 1959 conclusively showed that hospitalization of tuberculosis patients neither improved the final outcome of chemotherapy nor reduced infection rate among household contacts of admitted patients as patients infected close contacts by the time diagnosis of tuberculosis was made.[7] The current strategy of management of tuberculosis places more emphasis on community based, patient centred approach, with therapy being tailored to suit the individual patient clinical and social circumstances.[2]

1.4. Reasons for Hospitalizing MDR-TB Patients

Unfortunately, treatment of tuberculosis is long term with an inherent risk of patients failing to adhere to treatment especially if the administration of the drugs is not supervised. Treatment of drug susceptible tuberculosis takes as long as six to nine months to ensure cure while using high quality combination therapy. Insufficient infrastructure to effectively treat and control the spread of TB, especially in resource poor countries, has resulted in multi-drug resistant tuberculosis (MDR-TB) that is resistant to both isoniazid and rifampicin two of the most powerful TB drugs available.[8]

The emergence of multi-drug resistant tuberculosis is reversing the gains made in the management of tuberculosis with MDR-TB patients being hospitalized for long duration of time, as the two most effective drugs are technically unavailable to these patients. Instead only expensive drugs that are toxic to the patient and less active against tuberculosis bacilli are used.[9]

Hospitalization of suspected MDR-TB patients ensures confirmatory tests are done, the patients are treated and rendered non infectious, and the risk of disability and death due to the disease and drug toxicity minimized. Patient centred approach

to the management of MDR-TB patients dictates that the hospitalization is kept as short as possible according to patients' response to therapy.

The initial treatment phase of MDR-TB is usually aggressive. Initiation of treatment with inadequate regimens is associated with mortality or protracted shedding of large numbers of bacilli. This shedding of bacilli is associated with high risk of transmission of multi-drug resistant bacilli to contacts.[10] Moreover, there is always a risk of the MDR-TB bacilli developing additional resistance to other drugs. Specialised physicians working at recognised hospitals are needed to institute this aggressive MDR-TB treatment.

Thus, because of the serious personal and public health concerns associated with MDR-TB, hospitalization remains an important component of MDR-TB management particularly in patients who are non-adherent to therapy or have incapacitating social or medical complications.[11]

This research report will describe the hospitalization trends of MDR-TB patients at Sizwe Tropical Diseases Hospital within a five-year study period. Detailed management practices performed on these hospitalized patients will be discussed. The study will subsequently identify predictors of poor outcomes among hospitalized patients. The findings of the study will be valuable in assessing past performance and informing operational planning at the hospital.

CHAPTER 2: THE MANAGEMENT OF MDR-TB

"*We are frightened by the development of multidrug-resistant TB, reaching 10% of all our TB cases in the province of KwaZulu Natal, South Africa"* Dr Zweli Mkhize, MEC for Health, KZN, South Africa, 2000[12]

2.1. *Definition of MDR-TB*

Multi-drug resistant tuberculosis (MDR-TB) is a specific form of mostly pulmonary tuberculosis, due to a bacillus resistant to both isoniazid and rifampicin. These two drugs are the most powerful anti-TB drugs available.[13] The most frequent cause of emergence of drug resistance is previous incorrect or insufficient treatment of patients suffering from susceptible TB.[14] Inadequate treatment selectively kills drug susceptible bacilli and allows drug resistant organisms to multiply leading to acquired drug resistance.

As MDR-TB is spread through the air just like susceptible TB, patients with acquired MDR-TB can transmit the resistant bacilli to another person after close and prolonged contact leading to transmitted resistance. The term primary resistance is used to denote MDR-TB infection in patients who have no previous history of TB treatment.[5] For patients whose prior drug use history cannot be verified, the expression 'initial drug resistance' is used. Initial drug resistance is a mixture of primary resistance and undisclosed acquired drug resistance.

MDR-TB should be suspected in patients with persistent positive sputum despite treatment, and in patients who are known contacts of MDR-TB patients. TB culture and drug susceptibility testing (DST) must be done to confirm MDR-TB diagnosis. It is important to note that diseases caused by mycobacteria other than tuberculosis (MOTT) also demonstrate resistance to both isoniazid and rifampicin

and should be distinguished from MDR-TB through culture and isolation of the multi-drug resistant *Mycobacteria tuberculosis.*[15]

2.2. *Public Health Importance of MDR-TB*

Globally, two out of the six billion people are infected with latent tuberculosis with 10 per cent of those infected expected to develop active tuberculosis in their lifetime.[16] The incidence of tuberculosis is currently at 10 million new cases of active tuberculosis per year. Suitable management of drug-susceptible tuberculosis leads to high cure rates. However, the outcomes of MDR-TB management are drastically poor. A prolonged and expensive treatment of MDR-TB achieves a cure rate of about 50 percent or less.[4]

The complete magnitude of the global MDR-TB problem is imprecise since half of the countries with highest levels of TB are resource-constrained, ultimately unable to screen all TB cases for drug resistance.[17] Leading infectious disease experts approximate there are about 300,000 new cases per year of MDR-TB worldwide.[18] There is also new evidence proving drug resistant strains are becoming more resistant, and unresponsive to current treatments. Seventy-nine per cent (79%) of MDR-TB cases are now "super strains", resistant to at least three of the four main drugs used to cure TB.[18] MDR-TB is highly prevalent in many resource-poor countries. These countries also have a huge HIV/AIDS burden.

Human immunodeficiency virus (HIV), through the systematic weakening of the immune system, accelerates the development of latent MDR-TB infection to active disease increasing MDR-TB incidence and caseloads.[19] HIV increases the risk of developing active TB from 10% in a lifetime for HIV negative patients to 10% in a year for those who are HIV positive.[3] Management of drug resistant tuberculosis

in the presence of HIV demands meticulous infection control procedures further straining the financial and technical resources of these resource-poor nations.[20-21]

South Africa's current TB incidence rate is 558 per 100 000 people. A national survey of drug resistance conducted in the year 2001 to 2002 found that about 1.6 % of new TB cases and about 6.7% of previously treated cases were MDR-TB.[22] The World Health Organization (WHO) Report on Tuberculosis states that as of October 2003, there were about 4000 MDR-TB patients in South Africa on treatment with drugs costing an average of USD 3400 per patient.[23] MDR-TB cases are expected to rise due to the spread of HIV/AIDS.

2.3. *Policy Guidelines*

Alarmed by the resurgence of tuberculosis and the poor adherence to treatment, the WHO developed Directly Observed Treatment Short Course (DOTS) strategy in 1991.[24] The strategy is based on five tenets of:

- Commitment by governments to eradication of TB;
- Sputum smear microscopy as the basis of TB diagnosis;
- Direct observation of 6-8 months Short Course Chemotherapy;
- Regular supply of drugs; and
- Standardized screening and reporting systems.

Consistent application of DOTS was found to achieve high cure rates of nearly 95% in areas where there were no MDR-TB.[25] Delayed or poor implementation of the DOTS strategy in some countries results in low cure rates and high prevalence of multi-drug resistance.

The International Union against Tuberculosis and Lung Disease (IUATLD) and WHO released the Global Drug Resistance Surveillance (DRS) Report in 1997. The Report confirmed the serious threat of MDR-TB. In an effort to avoid creation and spread of human made MDR-TB strains that are also resistant to second line dugs, the WHO/IUATLD advocated for the preparation of protocols for the management of MDR-TB.[26] These protocols, prepared in 1998, formed the basis of DOTS-Plus.

DOTS-Plus is modeled using the DOT strategy and is designed to manage MDR-TB using second-line drugs. The two underlying principles of DOTS-Plus are: firstly, DOTS for drug susceptible TB should be the first step in fighting MDR-TB as new MDR-TB cases will be prevented, and secondly, DOTS-Plus should be applied only in areas with effective DOTS-based TB control programmes to minimize the risk of drug resistance to second line drugs.[26]

Consultation with experienced specialists, both locally and internationally, should be considered when a country is initiating MDR-TB management programmes. A committee, the Green Light Committee (GLC) was set up to evaluate proposed country-specific programmes to manage MDR-TB.[27] The GLC process not only ensures the proper use of second line drugs but also endeavours to provide them at favourable prices.

2.4. *Specialized TB Centres.*

The guiding principles in the management of MDR-TB entail provision of effective treatment to render the patient noninfectious, prevent drug resistance, curtail the risk of disability and death, and avoid relapse. Safety, tolerability, and adverse effects of second line TB drugs call for expert monitoring of therapy.

MDR-TB should therefore be managed in an organized, comprehensive, and closely supervised approach in a specialized centre.[28]

The components of specialized centers for the management of MDR-TB include expert tuberculosis/chest physicians, adequate infrastructure, and necessary infection control procedures. The centre should also have reliable laboratory support and drug supply. Establishment of linkages with public health department enables directly observed therapy, contact tracing and systematic follow-up of those managed as outpatients.[29]

In 2000, MDR-TB treatment was implemented as part of the National Tuberculosis Control Programme (NTCP) in South Africa with the starting of one MDR-TB center per province. Specialized management teams at the centers comprise, at least, a respiratory physician or a specially trained medical officer, supported by a dedicated MDR-TB-trained nurse, a social worker and an administrative assistant.[15] The National Health Laboratory Service (NHLS) offers a comprehensive diagnostic laboratory service for these specialized centers.

2.4.1. Criteria for Referral

Referrals to MDR-TB centers are based on either proven MDR-TB following sputum culture and susceptibility tests or clinical suspicion after failure of therapy despite documented good adherence to treatment. It is important to rule out prescription of inappropriate dosages or inadequate number of drugs, patient non-compliance, and malabsorption of drugs before considering mycobacterial resistance.[10] A positive smear after 2-3 months of treatment with first-line drugs should prompt a culture and susceptibility test. If there is a history of close contact with an MDR-TB patient, culture and susceptibilities should be requested on the initial sputum.

2.4.2. Criteria for Hospitalization

Specialized referral centers should ideally have isolation facilities or special wards. However, not all patients who are referred to specialized centers are hospitalized. Patients referred from far may need admission during evaluation and initiation of therapy.[15] Some patients with MDR-TB who are non-adherent to therapy or have complicated medical or social problems pose a threat to public health. They should be hospitalized for at least the first few months until they have produced three consecutive monthly culture-negative sputa.[11] Aggressive treatment of severely ill MDR-TB patients may require monitoring that can only be effected in an institutional setting.[30]

2.4.3. Treatment Regimens

MDR-TB treatment relies heavily on the use of second line drugs. Most drug regimens currently used to treat MDR-TB include residual first-line drugs such as ethambutol, pyrazinamide and streptomycin combined with additional second-line drugs. Second-line antituberculosis drugs include aminoglycosides (such as kanamycin, amikacin, and capreomycin); fluoroquinolones (like ofloxacin and ciprofloxacin); ethionamide; cycloserine and para-aminosalicylic acid. Terizidone is a derivative of cycloserine and shares similar activity profiles. Clofazimine, clarithromycin and amoxicillin-clavulanic acid are also used as new second-line agents.[31]

2.4.3.1. Individualized Treatment Regimens

For individualized treatment regimens, treatment with at least three effective drugs should be continued until the culture becomes negative. Then, a regimen of at least two drugs should be continued for 12 to 24 months depending on response to therapy.[32] Individualized treatment should be based on preceding medication history, results of sensitivity testing and an assessment of the patient's adherence.

Selected drugs should be prioritized based on demonstrated activity against *Mycobacterium tuberculosis* and the clinical evidence of efficacy of the available active compounds.[33] Sputum turnaround time for *Mycobacterium tuberculosis* culture and sensitivity tests take several weeks, so drug regimens are often empirically initiated pending this information.[34] Once drug susceptibilities are available, empiric therapy should be changed to a definitive one with the patient receiving all the drugs to which the *Mycobacterium tuberculosis* is susceptible without reserving some drugs. Adding a single drug to a failing regimen only leads to the development of further resistance.[35]

2.4.3.2. Standardized Treatment Regimens

In resource poor countries drug susceptibility testing may not always be readily available. These countries also bear the brunt of high MDR-TB burden but with limited skills and knowledge in using second line drugs. In such countries, standard treatment protocols are recommended thereby obviating the need for susceptibility testing.[36] Standardized treatment also reduces the expertise needed to select suitable combination of drugs according to susceptibility patterns.

Since 2001 the South Africa National Policy on MDR-TB has recommended a standardized regimen of 4-6 months of kanamycin, pyrazinamide, ethambutol, ofloxacin and ethionamide during the intensive phase. This phase is followed by 12-18 months of ethambutol, ofloxacin and ethionamide in the continuation phase.[15] Cycloserine is used as ethambutol replacement when resistance to ethambutol is detected.

Table 1 illustrates the daily dosages and the most common side effects of residual first and second-line drugs used in treatment of MDR-TB. Second-line drugs are further classified as old (aminoglycosides other than streptomycin; ethionamide,

and cycloserine) or new (macrolides, fluoroquinolones). Fluoroquinolones have increasingly been used in the treatment of MDR-TB after their introduction in the 1980s.[37]

Table 1: Drugs Used in the Treatment of MDR-TB

Drug	Classification	Average daily dose	Adverse effects	Recommended monitoring
Pyrazinamide	Residual first-line drug	15-30mg/kg	Elevated uric acid hepatotoxic.	Measurement Uric acid levels at baseline
Ethambutol	Residual first-line drug	15-25mg/kg	Skin rash and optic neuritis	Visual acuity and red/green colour perception
Streptomycin	Residual first-line drug	15-30 mg/kg	Auditory, vestibular and renal toxicity	Audiometry; serum electrolyte BUN, creatinine levels
Kanamycin	Old Second line drugs	15 mg/kg	Auditory, vestibular and renal toxicity	Audiometry; serum electrolyte BUN, creatinine levels
Amikacyn	Old Second line drugs	20 mg/kg	Auditory, vestibular and renal toxicity	Audiometry; serum electrolyte BUN, creatinine levels
Capreomycin	Old Second line drugs	15-30 mg/kg	Auditory, vestibular and renal toxicity	Audiometry; serum electrolyte BUN, creatinine levels
Ethionamide	Old Second line drugs	250 mg bid initially, increased to 1 g daily	GI complaints (peripheral neuropathy, psychosis), hepatitis, hypoglycemia;	Monitor electrolytes and liver-associated enzyme levels monthly
Cycloserine	Old Second line drugs	250-500 mg PO bid	Psychosis, convulsions, rash	Observe closely for mood and personality changes; consider vitamin B_6 to minimize side effects
PAS	Old Second line drugs	10-12 g/day in 3-4 divided doses	GI intolerance, drug-induced lupus, lymphoid hyperplasia, hepatitis, inhibition of iodine uptake	Monitor liver- associated enzyme levels monthly; test thyroid function with prolonged administration
Thiacetazone	Old Second line drugs	INH: THIAC 300:150 mg	Liver Damage, Skin Rash	Liver function test. Clinical observation
Ofloxacin	New Second line drugs	400-800 mg bid	GI complaints, dizziness, insomnia, headaches;	Clinical Observations and patient self reports
Ciprofloxacin	New Second line drugs	750 mg bid	GI complaints, dizziness, insomnia, headaches;	Clinical Observations and patient self reports
Sparfloxacin	New Second line drugs	200 mg qd	GI complaints, dizziness, insomnia, headaches;	Clinical Observations and patient self reports
Clarithromycin	New Second line drugs	250-500mg bid	GI tract disturbance, Liver damage	Clinical Observations and patient self reports, LFTs
Roxithromycin	New Second line drugs	150-300 mg bid	GI tract disturbance, Liver damage	Clinical Observations and patient self reports, LFTs
Clofazimine	New Second line drugs	2 mg/kg	Skin pigmentation, ichthyosis, GIT symptom, peripheral neuropathy	Clinical Observations and patient self reports
Amoxycillin & Clavulanic acid	New Second line drugs	875mg/125mg bid	GI tract upset, Hypersensitivity	Clinical Observations and patient self reports

BUN, serum urea nitrogen; CNS, central nervous system; GI, gastrointestinal. INH, isoniazid THIAC, thiacetazone
Adapted from CAPT Angeline Lazarus [38],

2.4.4. Therapeutic Monitoring Practices

Since the drugs used in the treatment of MDR-TB are less active against mycobacteria and more toxic to the patient, the response to treatment and accompanying adverse effects of the prescribed drugs should be monitored closely for optimal drug therapy.

2.4.4.1. Monitoring of Treatment Response

The efficacy of a regimen is determined by the rate of bacteriologic conversion during therapy and the rate of relapse during or after completion of therapy. Bacteriologic and radiographic response should be monitored. Monitoring of response to treatment during hospitalization should include:

- Monthly smear microscopy and culture;
- Monthly weight surveillance; and
- Chest x-ray if sputum smears remain positive after two months of therapy or if new symptoms develop.

Patients should be closely observed during therapy and for the first 12 to 24 months after cure to monitor for relapse.[38]

2.4.4.2. Monitoring for Adverse Reactions

Because second-line drugs can cause serious adverse reactions, patients taking these drugs should be monitored closely throughout the course of treatment.[39] Adverse effects of commonly used anti-tuberculosis drugs and the recommended monitoring practices are shown in Table 1. Patients should undergo baseline measurement of liver-associated enzymes, blood urea nitrogen, platelets, and bilirubin, creatinine, and uric acid levels. These values should be monitored monthly during treatment and whenever symptoms indicative of adverse effects are

reported or observed. By tradition, changes in serum creatinine are used to define and monitor nephrotoxicity while changes in bilirubin are used to monitor hepatotoxicity. An ophthalmologic evaluation for visual acuity and colour vision is recommended at baseline and 3-month intervals in patients receiving ethambutol. If aminoglycosides are used, baseline and monthly audiograms are recommended.[38]

2.4.4.3. Polypharmacy and Drug Interactions

Polypharmacy occurs when prescribed medications duplicate or interact with each other.[40] However, it may also include excessively high dosages. Due to the aggressive approach taken in the treatment of MDR-TB it is not unusual to find patients taking at least six drugs per day usually administered without splitting the doses. Often, co-morbid conditions create need for even more variety of drugs further increasing the chances of adverse effects and drug interactions. Adverse drug reactions are sometimes managed with even more drugs further complicating the situation.

Drug-drug interactions can be defined as the modulation of the activity of one drug by the prior or concomitant administration of another drug. The resultant activity could be beneficial or harmful.[41] Not only do potentially harmful drug interactions present danger to the patient, but also they can greatly increase healthcare costs as they reduce effectiveness of principal drugs. Therapeutic drug monitoring has been recommended in the aggressive therapy of MDR-TB. Drugs to be monitored should exhibit a relationship between serum concentration, efficacy, and/or the incidence of adverse or toxic events.[38] Aminoglycosides theoretically qualify for therapeutic drug monitoring but the expertise and costs required could deter practical implementation of the drug monitoring in many countries.

2.4.4.4. Role of Surgery in MDR-TB

Surgical management of tuberculosis has decreased considerably due to availability of effective drugs. However, patients with MDR-TB may at times show persistence of cavities. Surgery should be considered for such patients with persistent cavities if the disease is well localized and the patient has sufficient respiratory reserve.[42] Minor drainage operations are done for patients suffering from pyopneumothorax. In this condition of pyopneumothorax, air and pus accumulates in the pleural cavities of MDR-TB patients. Management involves drainage using an intercostal drainage (ICD) tube. To avoid wound infection after inserting the tube, daily antiseptic dressings are done.

2.4.4.5. Criteria for Discharge

Hospitalization should ideally be kept short. Patients, who have clinically stable disease, should be discharged after three consecutive culture-negative sputa are obtained on a monthly basis[15] or after six months of intensive phase of therapy. Patients should be discharged on appropriate treatment and must have demonstrated willingness to adhere to medication. Chest Clinic staff should counsel the patient about infection control at home and in the community. To prevent possible spread of MDR-TB, patients should not be discharged to any type of congregate living situation like correctional facilities and nursing homes.[43]

2.4.4.6. Post –Discharge Treatment and Follow up

In order to plan for appropriate outpatient follow-up, providers must, prior to discharge, establish rapport with patients and educate them about MDR-TB. In addition, they should obtain physical addresses, phone numbers, and similar information for the patients' next of kin. Practical arrangements ought to be made with the local clinic that will be responsible for directly observed therapy.[27] At minimum, quarterly visits to the specialized TB centre should be made to ensure

adherence to treatment. After completing treatment, usually 12-16 months after bacteriologic conversion, the patients should be checked periodically for relapse.

CHAPTER 3: REVIEW OF HOSPITALIZATION OUTCOMES

"It may seem a strange principle to enunciate as the very first requirement in a hospital that it should do the sick no harm". Florence Nightingale, 1859 [44]

Past studies on management and outcomes of MDR-TB patients have focused on long-term outcomes of MDR-TB patient management. These studies have entailed follow up of patients with cohort analysis sometimes being conducted 24-36 months after the last patient enrolment. To avoid having to wait for long periods of time to compare treatment success or failure rates of MDR-TB management practices, interim outcome indicators were designed as markers of patients' progress early in the treatment phase.[45] A number of studies have reported on treatment outcomes at the time patients are discharged from hospital. The following brief review is based on hospitalization outcomes of MDR-TB patients.

3.1. Duration of Hospitalization

Duration of hospitalization impacts on costs of health care delivery for MDR-TB patients. Additionally, lengthy hospital stays negatively affects the socio-economic status of the hospitalized patients. Duration of hospitalization is therefore an indicator worth reviewing. In Latvia,[46] where second line reserve drugs for TB treatment have been used since June 1997, patients were hospitalized until culture conversion was demonstrated. Average duration of hospitalization was eight months. After conversion, treatment was continued in the ambulatory setting. In another study[47] conducted in the State of Florida USA, 39 of MDR-TB patients admitted to the A. G. Holley State Tuberculosis Hospital had a median duration of hospitalization of 270 days (range, 5 to 1,601 days). Nine of the 39 patients (23%) completed their entire MDR-TB treatment in the hospital, either due to the complexity of their TB, concomitant disease or history of persistent non-

adherence to therapy. Twenty-two patients were discharged from the hospital while receiving treatment for MDR-TB. In another study at the National Jewish Medical and Research Centre for multidrug-resistant tuberculosis, the median length of hospital stay was 93 days.[48]

3.2. HIV and Nosocomial Spread of MDR-TB

People infected with HIV/AIDS are at greater risk of developing MDR-TB. Since 1990 several clusters of multidrug-resistant tuberculosis have been identified among hospitalized patients with the acquired immunodeficiency syndrome (AIDS).[49] Sacks et al reported nosocomial outbreak of MDR-TB in six hospitalized HIV positive women infected while receiving treatment for drug susceptible tuberculosis at the Sizwe Hospital in South Africa.[50] MM Park et al describe the outcome of 173 patients hospitalized at their institution from 1983 to 1994 with multidrug-resistant tuberculosis (MDR-TB). Over half (52%) were known to be HIV-infected. HIV-positive MDR-TB patients had significantly more pulmonary and constitutional symptoms, more extra-pulmonary disease, and fewer cavitary lesions on chest radiographs. Fifty-five percent of the patients in the cohort died; mortality was significantly greater for HIV-positive than HIV-negative patients (72% versus 20%, $p < 0.01$).[51]

3.3. Drug Treatment and Outcomes

In a retrospective analysis of the outcomes in 205 patients treated at the National Jewish Medical and Research Centre for multidrug-resistant tuberculosis, patients received a median of six drugs (minimum = 3, maximum = 10). A total of 196 of 205 patients (96%) received an aminoglycoside or capreomycin. A total of 163 of 205 patients (80%) received a fluoroquinolone. Fluoroquinolone therapy was a significant predictor of initial favourable response.[52] In an Argentinean reference

hospital specialising in infectious diseases one hundred and forty-one adult patients (52.5% female) with resistance to two up to seven drugs were studied. Fifty patients (35.5%) had not been treated previously. The most frequently used second-line drugs were fluoroquinolones, cycloserine and ethionamide.[53]

3.4. Surgical Outcomes

Surgery offers substantial benefit and a notably improved cure rates for patients who have multi-drug resistant TB if the bulk of disease is well localized and can be resected. In carefully selected patients with MDR-TB who had a poor response or an unfavourable prognosis with use of medical therapy alone, surgical therapy had cure rates exceeding 90%. Combining surgery with chemotherapy improved overall cure rate from 29/47(61.7%) to 59/62(95.2%).[5] Improvement of sputum conversion rates decreased the duration of hospital stay. In another study at the A. G. Holley hospital five HIV negative patients underwent a surgical resection of tuberculous cavitary lesions; three of these five patients went on to complete treatment successfully, and two patients died after surgery.[47]

3.5. Adverse Drug Reactions

Monitoring of adverse drug reactions is essential in the management of MDR-TB. The symptoms range from severe nausea, vomiting, and diarrhoea due to mainly ethionamide; thought disorders, seizures and outright psychosis often caused by cycloserine; to otovestibular damage and renal toxicity caused by aminoglycosides. Apart from aminoglycoside toxicity, side effects are most common during the first several weeks of treatment. Wing Wai Yew et al reports on 63 MDR-TB patients treated from February 1990 through June 1997.[54] Twenty-five of the treated patients (39.7%) experienced adverse drug reactions of varying severity. The most common ones were related to the otovestibular and gastrointestinal systems and the

central nervous system. Some patients had multiple adverse reactions. However, modification of drug regimens was needed in only 12 patients.

3.6. Mortality Outcomes

Cure rates during MDR-TB treatment are generally below 50% even in the best circumstances. On average, at least 30% of MDR-TB cases are fatal within two years: the remainder are chronic and continue to be infectious, posing a threat to communities.[17] In a study conducted in the Western Cape, 46% of new cases and 26 % of old cases were cured. Patients with Ethambutol resistance had worse outcomes.[55] In another study at Holley hospital, seven of the 39 patients (18%) died: 5 of the 7 patients died from medical conditions other than TB (3 patients had culture-negative findings and 2 patients had culture-positive findings at the time of death), and 2 of the 7 patients died after surgical resection of their MDR-TB.[47] In a study at the Sizwe Tropical Diseases Hospital, in-hospital fatalities were associated with female sex ($p=.01$), lower haemoglobin ($p<.01$), and weight ($p<.01$), and extensive filtration on chest x-rays. High mortality occurred in the first weeks of admission due to late presentation.[56]

3.7. Problem Statement

Provision of inpatient care for MDR-TB patients is challenging and requires a lot of commitment from both patients and care-givers. The ideal situation would be to hospitalize all deserving cases, quickly render them non-infectious, cause them no harm, and discharge them to community care in order to free hospital beds for other equally deserving cases. Evidence-based admission and discharge planning, rather than availability of beds, should inform hospitalization of MDR-TB patients.

3.8. Rationale for this Study

There is need to monitor and evaluate treatment outcomes so as to make comparisons with set targets, other MDR-TB units, and the same MDR-TB unit over time. Identification and tackling of predictors of poor treatment outcomes for hospitalized MDR-TB patients will enable optimal hospitalization practices for MDR-TB patients. This research report will describe the hospitalization trends, management practices, and predictors of poor outcomes of MDR-TB patients at Sizwe hospital within a five-year study period. Such a study targeting hospitalized MDR-TB patients at Sizwe Hospital has not been done since the introduction of standardized MDR-TB treatment regimens. The outcomes of the study will be valuable in assessing past performance and informing situation-specific operational planning at the hospital.

CHAPTER 4: RETROSPECTIVE STUDY OF MDR-TB INPATIENTS

"Evidence based health care promotes the collection, interpretation, and integration of valid, important and applicable patient-reported, clinician-observed, and research-derived evidence." Evidence-Based Medicine Working Group, 1997 [57]

In this chapter, the research methodology utilized in the study of the management practices of hospitalized MDR-TB patients at Sizwe hospital will be discussed.

4.1. Aims and Objectives of the Study

4.1.1. Aims

The aim of this study was to review the admission trends, management practices, and interim treatment outcomes of registered multidrug-resistant patients admitted at Sizwe hospital during a five-year period.

4.1.2. Objectives:

The key objectives of the study were to:

1) Document the total number of culture confirmed MDR-TB patients admitted each year from 1st June 1998 to 31st May 2003.
2) Describe the demographic characteristics of the MDR-TB patients hospitalized during the five-year period.
3) Examine the prescribing patterns and therapeutic monitoring practices for registered MDR-TB patients hospitalized during the five-year period mentioned above.
4) Analyse the interim treatment outcomes of culture-conversion, transfer out, interruption, failure and death rates among admitted MDR-TB patients at the end of the hospitalization period.
5) Identify risk factors associated with poor outcomes of interruption, failure and death in MDR-TB patients hospitalized at Sizwe hospital.

4.2. Research Design

A cross-sectional study with both descriptive and analytic components was done. The study entailed a detailed retrospective review of medical records of patients with culture-confirmed MDR-TB admitted at Sizwe hospital from 1st of June 1998 through to 31st May 2003.

4.3. Study Location

The study was conducted at Sizwe Tropical Diseases Hospital (formerly Rietfontein), a century old, 500-bed, referral hospital for patients with complicated TB, multidrug-resistant TB or HIV/AIDS. Tropical diseases like malaria, typhoid, and Congo fever are also managed at the hospital.[58] The hospital is located in Gauteng Province of South Africa. The hospital had, for the entire period of the study, a 25-bed ward dedicated for MDR-TB patients.

4.4. Study Population

The study population comprised all culture-confirmed MDR-TB patients consecutively admitted at Sizwe hospital between early June 1998 and end of May 2003. Patients confirmed to be suffering from diseases due to MOTT, those with single drug resistance to either rifampicin or isoniazid and those that were clinically managed on first line drugs but belatedly confirmed MDR-TB patients after discharge or death were excluded from the study.

4.5. Study Sample

From the manual TB register the total number of eligible patients was found to be 278 for the five year period. Of this, 237 files accounting for 252 hospitalizations were readily retrieved and studied. If the true culture conversion rate is estimated at 50%, then studying 237 patients was adequate to determine and estimate the conversion rate with a 95% Confidence Interval with a precision of +/- 2.5%

4.6. Data Collection Methods

Measurement, to obtain the values for the variables being studied, was done by reviewing the MDR-TB patients' medical records. MDR-TB cases were identified using the manual TB register and then the files were retrieved for data capturing. Files were obtained from the filing room, MDR-TB wards, surgical wards, and from the archives. The following data were then captured:

- Demographic details, clinical characteristics and previous history of treatment were captured without capturing the patients' personal identifiable variables to protect their privacy and confidentiality.
- All bacteriological tests performed for diagnostic purposes, for monitoring treatment and for defining endpoints of both the initial and continuation phase were recorded.
- Prescribing patterns in both phases of therapy were noted. The drug regimens that were used, the dosage, frequency, and dates of starting and stopping the treatment were also captured.
- Clinical monitoring practices and radiological tests were captured. The number of surgical interventions done and the institution the operations were carried out were also recorded.
- Interim outcomes at discharge were entered into the data capture forms. These outcomes included culture conversion rates, transfer out rates, and refusal of hospital treatment, absconding, failure and death rates.

4.6.1. Reliability and Validity

The data capture form was pre-tested and the preliminary results indicated the need to revise the tool as some of the information was not uniformly recorded in the medical records. See Appendix A for the pre-tested and revised data capture sheet. The content validity of the data being abstracted was regularly checked by comparing data available from the patient's registration form, admission form, transfer form, clinical progress notes, and medication sheets. At the conclusion of each day's data abstraction exercise the completed data forms were manually checked for completeness and correctness. Any necessary clarification of the data was then done the following day.

4.7. Data Capturing and Analysis

The collected data were then coded and captured using Ms Excel 2000 software. Data cleaning was done to check and correct for typing errors, coding errors or obvious range errors. New variables including age of patients on admission, duration of hospitalization and sputum turnaround times were calculated using the MS Excel Software. Determination of drug interactions was done based on the pharmacological activities of the prescribed drugs using Martindale 30th Edition for reference. The cleaned data were then exported to SPSS version 12 Software for analysis according to a prepared analysis plan (See Appendix B). Descriptive statistical analysis obtained group means or proportions for numeric data variables. For ordinal and nominal data variables, frequency and cross-tabulation statistics were obtained. A comparison between variables was made using Student's independent samples t tests for numeric variables and χ^2 tests for categorical variables. Multiple logistic regression analysis was performed to identify the variables that were independently associated with adverse outcomes during hospitalization.

4.8. Ethical Clearance

Clearance was sought from and subsequently granted by the Committee for Research on Human Subjects of the University of the Witwatersrand prior to conducting the study (see Appendix C). The right of entry into the hospital and access to the medical records was obtained from the Chief Executive of the hospital and the Gauteng Department of Health.

4.9. Results

The study results are discussed in the following sections of patients' demographics, clinical characteristics, and hospitalization practices. Further sections describe baselines tests done on admission, prescribed drugs, and monitoring of treatment. The last sections document surgical interventions and hospitalization outcomes at the end of the hospital stay.

4.9.1. Description of MDR-TB Patients

To describe the characteristics of the MDR-TB patients a total of five variables were analysed. Three variables; Gender, Race and Occupation were measured at the nominal scale. Age, a ratio scale, was recoded into Agegroup5, an ordinal type of variable.

4.9.1.1. Gender and Race

Overall, a total of 237 MDR-TB patients were admitted within the five year study period. There were more males than females with a total of 155 (65.4%) males and 82 (34.6%) females ($\chi^2 = 22.485$, $P<0.05$). An overwhelming majority (94.1%) of the patients were of African descent (147 males, 76 females). Another 3.4% of the patients were coloureds (3 males, 5 females). Three white males and a female (1.7%) and one Indian male (0.4%) were also hospitalized within this period.

4.9.1.2. Age

The age of admitted patients ranged from 6 to 70 years with a mean of 34.5yrs. Males tended to be older than females (t=3.591, P<0.05) with the average age of males being 36.3yrs (95% C.I. 34.59 - 37.96) compared to 31.2 (95% C.I. 29.06 - 33.35) of the females. This is represented by the following stem and leaf plot.

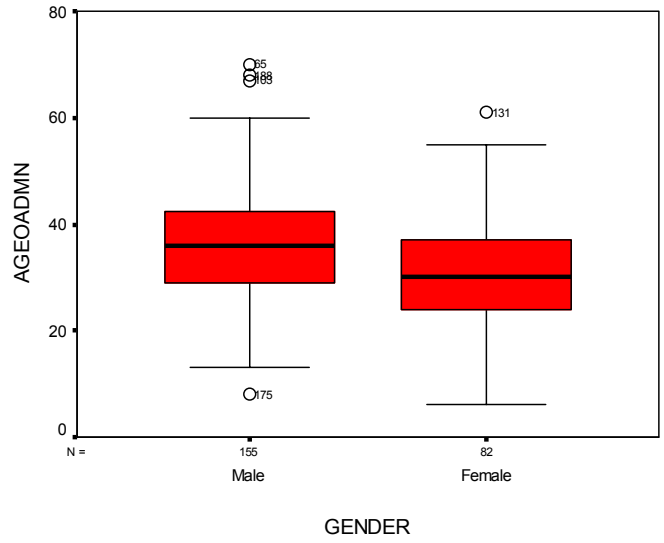

Figure 1: Plot of Age on Admission by Gender

Over the years, the average age of the hospitalized patients remained fairly constant as shown in Table 2 below.

Table 2 : Annual Mean Age on Admission

YEAR	Mean	N	Std. Deviation
1998	33.05	19	8.84
1999	35.85	34	12.23
2000	34.17	52	11.42
2001	34.14	44	10.7
2002	35.52	62	10.44
2003	32.85	26	8.24
Total	34.52	237	10.6

Figure 2 shows patients aged 31-35 years were hospitalized most while patients aged below 15 and those over 55 years were admitted least of the times.

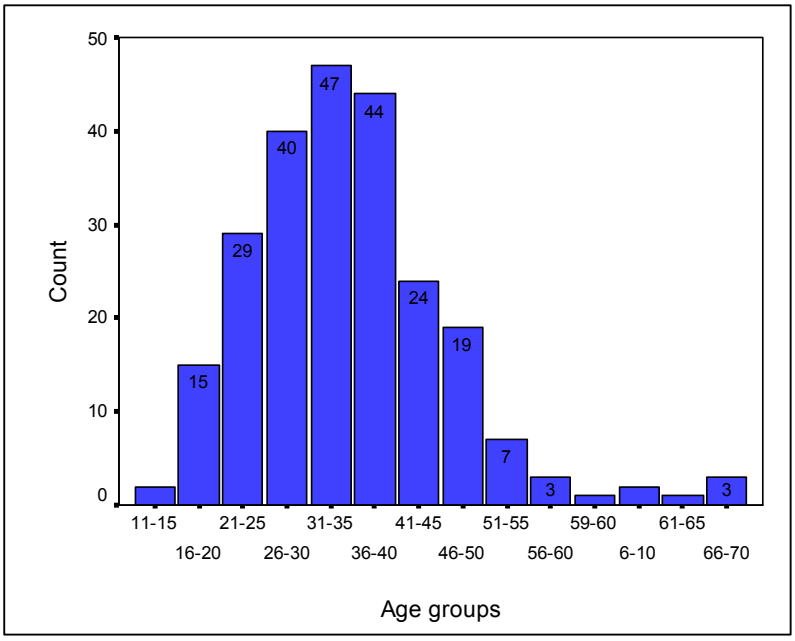

Figure 2: Age Groups of Admitted Patients

4.9.1.3. Occupation

Only 25.3% (n=60) of the patients reported being employed. Specific jobs and careers for those employed were not routinely recorded. A large percentage of the patients (62.4%, n=148) were unemployed. The rest of the patients were prisoners (7.2%, n=17), students (2.5%, n=6), pensioners (1.7%, n=4), and children (0.8%, n=2).

4.9.2. Clinical Characteristics

A total of five variables measured at nominal scale and another variable measured at ratio scale were analysed to illustrate clinical characteristics of the hospitalized patients. The nominal variables comprised: History of contact with TB patients, Previous TB treatment, Current HIV status, Type of MDR-TB diagnosed, and Concomitant diseases. Duration of previous TB treatment was measured at ratio scale.

4.9.2.1. Type of MDR-TB

This variable had three categories of MDR-TB: Acquired, Primary and Nosocomial MDR-TB. Nosocomial infections are technically primary MDR-TB but were studied separately to indicate the level of infection control at the hospital as nosocomial infections are picked up in a hospital setting. All the patients included in the study had pulmonary MDR-TB. The largest percentage of the patients had acquired MDR-TB (63.7%, n=151). Nearly a third of the patients (30.4%, n=72) had primary MDR-TB. Fourteen patients (5.9%) acquired the MDR-TB in the hospital.

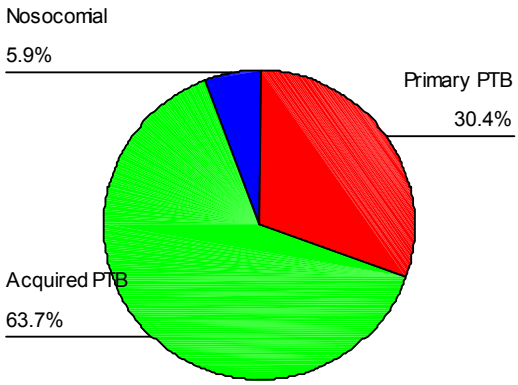

Figure 3: Pie Chart of Type of MDR-TB

Cross-tabulation of gender and type of MDR-TB revealed that while nosocomial and primary MDR-TB are almost evenly distributed across both sexes, more males with acquired MDR-TB (70.9%, n=107) were admitted when compared to females (29.1%, n=44). Since failure to adhere to treatment is a major cause of MDR-TB, then male gender can tentatively be associated with non-adherence to TB treatment. The following table shows the distribution of the type MDR-TB across gender.

Table 3: Type of MDR-TB and Gender

Patients Gender		Type of MDR-TB			Total
		Primary PTB	Nosocomial	Acquired PTB	
Male	Count	40	8	107	155
	% within TYPEMDR	55.60%	57.10%	70.90%	65.40%
Female	Count	32	6	44	82
	% within TYPEMDR	44.40%	42.90%	29.10%	34.60%
Total	Count	72	14	151	237
	% within TYPEMDR	100.00%	100.00%	100.00%	100.00%

4.9.2.2. TB Contacts

History of the patients' contact with other tuberculosis patients was recorded in 70% (n=166) of the files that were studied. Out of these valid cases, 45.2% (n=75) reported having had contact with a patient suffering from TB. It is important to note that most contact transmissions of TB that occurred in congregate settings like workplaces, churches, public transport and prisons were unlikely to have been reported.

Most of the reported contacts were close relatives. For example, a young girl of five years, whose uncle died of TB, developed active susceptible TB, was treated and cured. A year later she was diagnosed with primary MDR-TB. This time the contact was suspected to be her father.

4.9.2.3. Previous TB Treatment and Duration

Acquired MDR-TB was suspected in patients who had history of prior treatment for susceptible TB. Duration of previous treatment *before admission* ranged from 0 months (30.4%) for those diagnosed with primary MDR-TB to 48 months for those with acquired TB. The majority of the patients had been treated for 10 months or less prior to hospitalization with MDR-TB. Figure 4 shows a plot of the number of patients against the duration of treatment. This plot revealed a

positively skewed distribution with majority of the patients having being previously treated for 10 months and below.

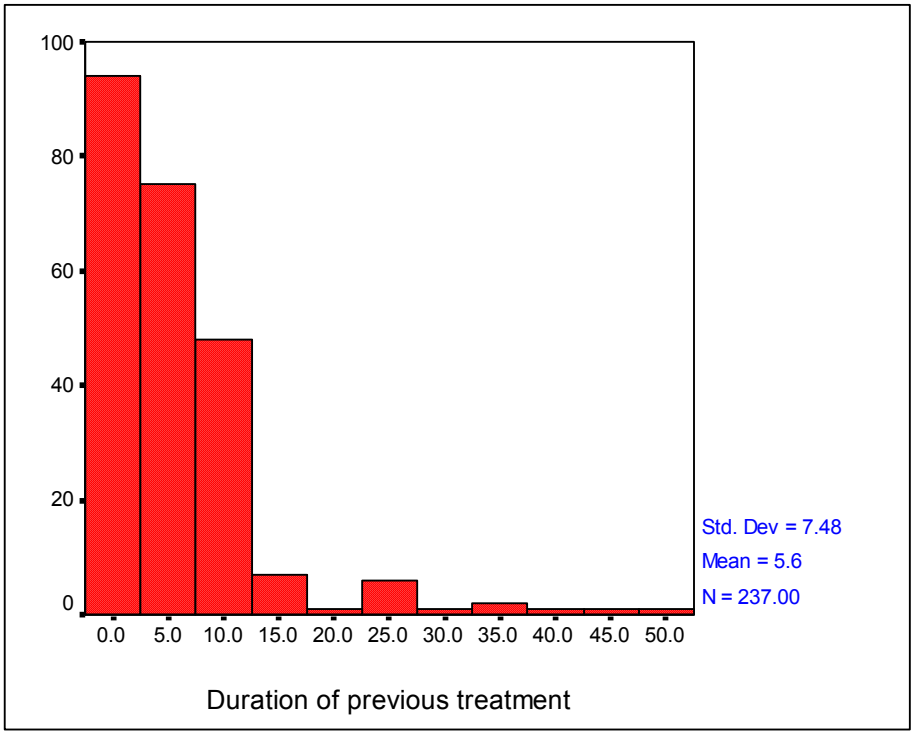

Figure 4: Duration of Previous TB Treatment

Patients who had received less than one month of treatment for susceptible TB were deemed to have been treated for 0 months. The mean duration of previous treatment was 5.6 months while the median was 4 months. Duration of previous treatment was on average higher in males (mean=6.31, 95% C.I. 5.03 - 7.59) than in females (mean=4.3, 95% C.I. 2.97 - 5.64). Given the skewed distribution of the data the median is a better estimator of the central tendency.

4.9.2.4. HIV Status

Over 59% (n=140) of the patients were HIV positive, 32.5% (n=77) were negative while 8.4 % (n=20) had no records of HIV status. Among the patients who were HIV positive, 62.9% (n=88) were males and 37.1 % (n=52) were females.

Table 4: HIV Status across Gender

			HIVSTAT			Total
			Positive	Negative	Missing	
SEX	Male n=155	% within gender	56.8%	34.2%	9.0%	100.0%
	Female n=82	% within gender	63.4%	29.3%	7.3%	100.0%
Total n=237		% within gender	59.1%	32.5%	8.4%	100.0%

The percentage of HIV positive patients who were admitted increased sharply with time to peak at about 73% in year 2002. This is illustrated by the following scatter plot.

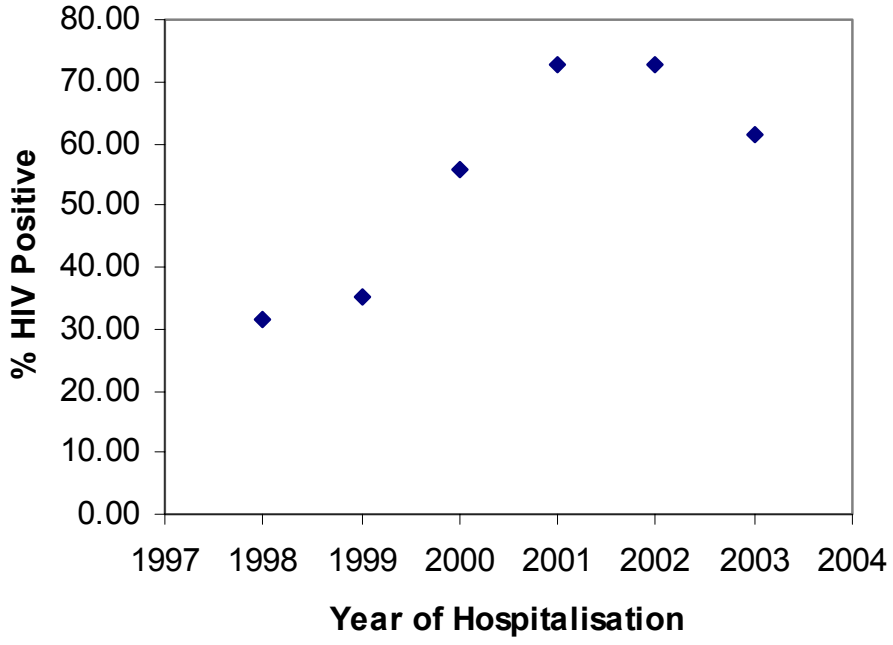

Figure 5: Scatter Plot Showing the HIV Trend of Hospitalized Patients

4.9.2.5. Co-morbidity

The most common complications seen in MDR-TB patients at the time of admission included those conditions commonly associated with HIV/AIDS. These signs included oral thrush in 11.4 % (n=27) of the patients, herpes 2.5% (n=6), Pneumocystis carinii pneumonia (PCP) 1.7 % (n=4), and Kaposi lesions in less than1% (n=1).

TB related complications ranked second in terms of occurrence. There were 21 cases (8.9%) of empyema, 2 cases (0.8%) of TB Meningitis and a further 2 cases (0.8%) of TB of the bowel. One case (0.4%) of a disease due to *Mycobacteria scrofulaceum*, a MOTT, was noted.

Signs commonly associated with effects of anti-TB drugs were also recorded. These included two cases (0.8%) of peripheral neuropathy, one case (0.4%) of hepatitis, five cases (2.0%) of gastrointestinal tract symptoms, one case (0.4%) of allergy to aminoglycosides and three cases (1.2%) of renal failure.

One female patient was pregnant. Although pregnancy is not a co-morbid state it nevertheless poses a number of clinical and ethical challenges during treatment as second line drugs are highly toxic to both the mother and the foetus.

4.9.3. Hospitalization of MDR-TB Patients

In this section that details how patients were hospitalized, four variables that comprised three nominal and one scale variables were analysed. The variables covered data on how patients were managed after being diagnosed with MDR-TB.

4.9.3.1. Management after Diagnosis

Management soon after diagnosis was either as inpatient or outpatient. Over half of the patients (74.2%) were hospitalized soon after MDR-TB was culture-confirmed, compared to 25.8 % who were managed as outpatients. More patients

with primary MDR-TB (62.5%) were hospitalized soon after diagnosis compared to newly diagnosed acquired MDR-TB patients (51.0%) (χ^2 =7.546, p=0.023).

4.9.3.2. Time before Admission

With regard to time interval between culture confirmation of MDR-TB and hospitalization, four groups of patients were evident:

- Patients admitted due to susceptible TB complications but later confirmed MDR-TB patients after a period of hospitalization. This could happen after contracting nosocomial MDR-TB infections or through the progression of single drug-resistant tuberculosis to full-blown MDR-TB disease.
- Patients admitted to Sizwe hospital on suspicion of MDR-TB. Culture-confirmation occurred while the patients were already hospitalized.
- Patients newly diagnosed and referred to Sizwe hospital as proven MDR-TB. After evaluation the patients were hospitalized. For some patients the referral process or lack of beds could have delayed hospitalization.
- Patients diagnosed and then managed as outpatients only to be hospitalized later due to disease complication or relapse.

Table 5 : Groups of Hospitalized Patients

Mode of Management	Count	Percent
Diagnosed during treatment for susceptible TB or single drug resistant TB	32	13.5%
Admitted on suspicion of MDR-TB	116	48.9%
Referred as newly proven MDR-TB patients	28	11.8%
Managed initially as MDR-TB Outpatients	61	25.8%
Total	**237**	**100%**

Figure 6 below shows the time taken to admit patients to Sizwe hospital after MDR-TB confirmation. Time interval before admission that is depicted in the negative refers to time patients spent in hospital prior to their being confirmed with MDR-TB.

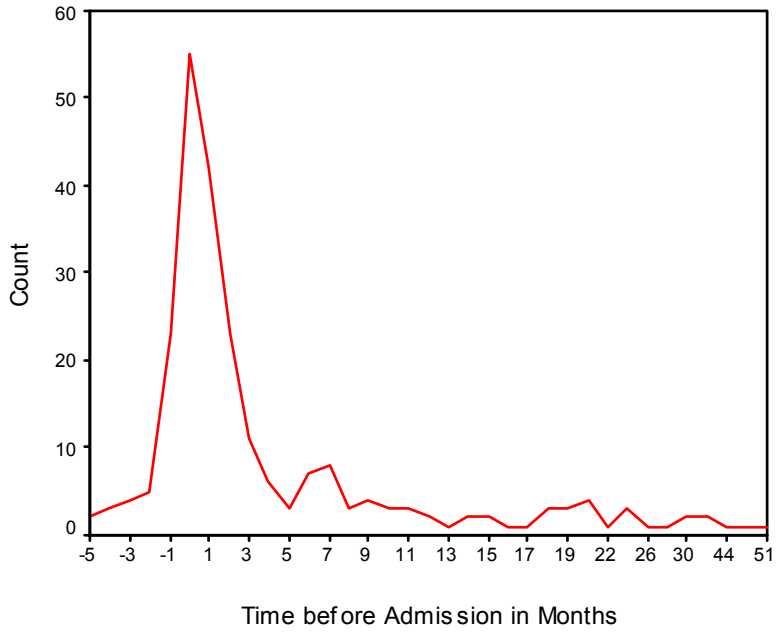

Figure 6: Period before Admission after MDR-TB Confirmation

4.9.3.3. Admission Criteria

A number of criteria were used to decide on whether or not to hospitalize the patients. A total of 49.0% of the patients were hospitalized on suspicion of MDR-TB. Suspicion of MDR-TB was based on persistency of positive sputum despite adequate treatment for drug susceptible tuberculosis (32.5%), and consistent defaulting in first line drugs (16.5%).

For those patients hospitalized with proven MDR-TB, 30.8 % of the cases were hospitalized based on either confirmation or complications of MDR-TB. Another 6.8% of the patients were hospitalized due to the twin reasons of MDR-TB and poor social circumstances. Out of those who were hospitalized due to disease

severity 95.5% had been managed as outpatients soon after diagnosis of MDR-TB. Table 6 illustrates criteria used during admission.

Table 6: Admission Criteria

Admission Criteria	Count	Percentage
Suspicion=49.0%		
a) Persistency of Sputum	77	32.50%
b) Defaulting first line drugs	39	16.50%
Proven MDR-TB=37.6%		
a) MDR-TB +Disease Complications	73	30.80%
b) MDR-TB + Poor Social circumstances	16	6.80%
Other Criteria=13.4%		
a) Single Drug Resistance	18	7.50%
b) Ordinary TB Complications	14	5.90%
Total	**237**	**100.00%**

Other reasons leading to hospitalization were cases of single drug resistance (7.5%) that were unresponsive to treatment. A further percentage of 5.9% of the hospitalization was due to severe or complicated susceptible TB disease.

The average number of patients admitted every six months was 23.7. Of the total number of patients studied, 11% (n=26) of them were readmitted at Sizwe. The following figure shows a six monthly admission trend.

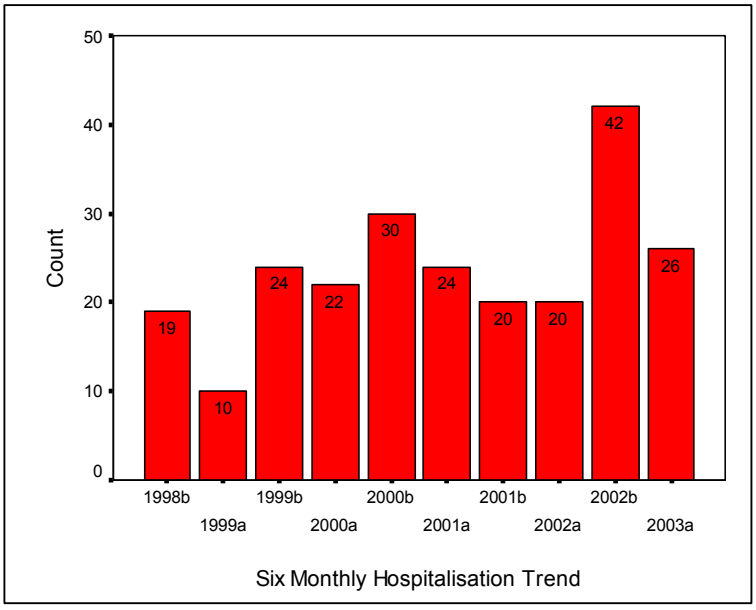

Figure 7: Bar Graph Showing Six Monthly Hospitalization Rates

4.9.4. Baseline Tests

Upon admission, a number of baseline tests were performed on the patients. Initial tests performed in all those who were hospitalized included liver function tests, measurement of urea and electrolytes, and visual and auditory tests. Other baseline tests were; determination of body weights and examination of chest x-rays.

Bacteriological tests were also done to confirm MDR-TB diagnosis and determine the drug sensitivity patterns of the mycobacteria. Sputum smear and culture results as well as patterns of drug resistance were measured on nominal scale. Sputum smear and culture turnaround times were determined on a ratio scale.

4.9.4.1. Sputum Smear Results and Turnaround Times

Of the total number of patients admitted, 97.9% (n=231) percent had their sputum microscopy tests recorded on admission. Positive smears that ranged from scanty to heavily positive were found in 81.8%, (n=189) of the cases. Sputum smear turnaround time was on average less than a day, with a median of one day.

Almost a fifth of the patients (18.2%, n=42) were hospitalized when the sputum smear was negative for acid fast bacilli (AFB).

Table 7: Sputum Results on Admission

		Frequency	Percent
Valid	Scanty positive+	59	25.6
	Moderate Positive ++	68	29.4
	Heavy Positive+++	62	26.8
	Negative	42	18.2
	Total	231	100

4.9.4.2. Sputum Culture Results and Turnaround Times

Of all the admitted patients, 91.6% (n=217) had sputum culture results recorded around the time of admission. Out of these 217 patients a total of 191 (88%) had

positive culture results while the rest turned out negative (12%, n=26). The average culture turnaround time was 19 days (calculated Mean=18.51, 95% C.I. 17.46 - 19.56).

While all patients who were admitted were reported to have TB resistant to both rifampicin and isoniazid, records of resistance patterns were only found for 217 patients. The resistance rate for the combination of rifampicin and isoniazid alone was found to be 54.9% (n=119). In 40.5% (n=88) of the patients resistance to either one or more of the other first line drugs could be demonstrated. Second line drugs were not spared as resistance to ofloxacin, ethionamide or cycloserine occurred at a rate of 4.6%, (n=10).

4.9.5. Prescribing Patterns

Prescribing patterns were measured for both the initial and continuation phase. A total of six nominal variables were analysed to describe the types of drugs that were prescribed on admission. Changes in prescribing that occurred during the course of hospitalization were not captured. While the use of standard MDR TB regimens was the recommended practice at the hospital, availability of culture and sensitivity results enabled the physicians to tailor the regimens to suit the susceptibility results. In 1.7% (n=4) of the cases MDR-TB therapy had not been commenced by the time the patients died.

The most frequently used aminoglycoside on admission was streptomycin injection (48.9%, n=116) followed by kanamycin (40.1%, n=95). Amikacin was rarely used (4.2%, n=10). A fraction of the patients (6.3%, n=15) did not receive any aminoglycoside possibly due to allergy, side-effects or abscess formation at sites of injections. The following pie chart depicts the type of injections used at the time of admission.

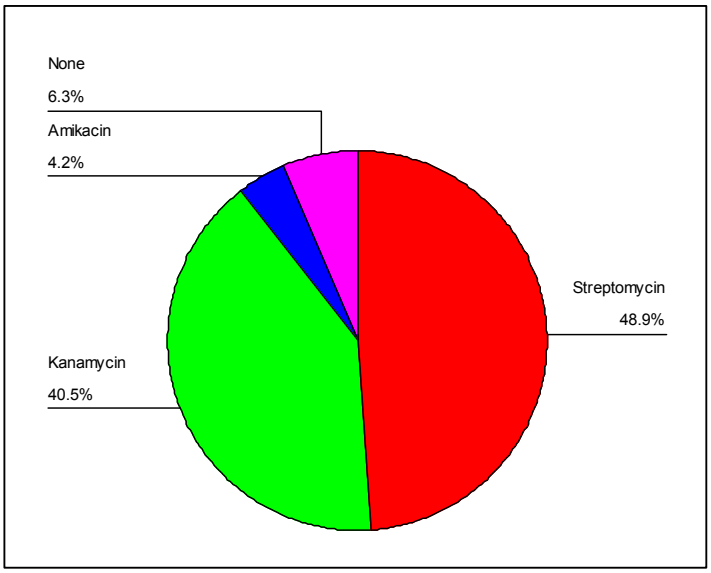

Figure 8: Pie Chart of Type of Injection

Ethambutol was used 52.7% (n=125) of the time compared to 40.1% (n=95) for cycloserine. Other drugs that were used include the macrolides, clofazimine and thiacetazone. Of all the admitted patients, 40.1% (n=95) used a macrolide, with clarithromycin and roxithromycin being equally prescribed. Thiacetazone, in combination with isoniazid (INAT), was used more often (11.3%, n=27) than clofazimine (4.2%, n=10).

In all HIV positive cases sulfamethoxazole - trimethoprim combination was administered as a prophylactic against Pneumocystis carinii pneumonia (PCP). The hospital did not provide antiretroviral drugs for the HIV positive patients. However, referral services to pilot government run antiretroviral programmes and private pharmacies were offered to some of these patients.

Non-tuberculosis drugs that were used often were pyridoxine, amitriptyline, metoclopramide, vitamin B complex, paracetamol and antacid gel. Most of these

non-tuberculosis drugs were used to counteract the unwanted effects of administered MDR-TB drugs.

4.9.6. Treatment Monitoring Practices

Besides the baseline tests discussed in section 4.9.4 above, follow up tests were subsequently done to monitor response to therapy.

4.9.6.1. Laboratory Based Monitoring

To monitor response to therapy after initiating treatment, monthly sputum microscopy and sputum culture were done in 78.1% and 73.0% of the patients respectively. Another commonly performed monitoring practice was chest x-rays with 73.0% of the patients having had an x-ray taken at least once during the hospital stay. Monthly body weight measure (the least expensive of monitoring practices) was done in 59.5% of the patients.

Table 8: Results of Monitoring Practices

Monitoring Tests	Count	Frequency of Tests
Monthly sputum	185	78.1%
Monthly culture	173	73.0%
Chest x-ray	173	73.0%
Monthly weight measures	141	59.5%
Liver function test	45	19.0%
Urea and electrolytes	45	19.0%
Auditory tests	33	13.9%
Visual tests	27	11.4%

Liver function tests and determination of urea and electrolytes were done in 19% of the patients after initiating treatment. The least performed follow up tests were auditory and visual tests performed at the rate of 13.9% and 11.4% respectively for all the patients who were hospitalized.

4.9.6.2. Pharmacotherapeutic Monitoring

Determination of the number of prescribed drugs and the presence of drug interactions, followed by the description of occurrence and management of subsequent adverse drug effects are the key areas covered in this section of pharmacotherapeutic monitoring. The only ratio scale variable analysed was the number of drugs prescribed while the rest were all measured as categorical (nominal) variables.

The mean number of drugs prescribed per patient was about 8 (calculated. Mean=8.10, 95% C.I. 7.94 - 8.25). A minimum of 6 to a maximum 12 drugs were prescribed per patient. Cases of detected drug interactions were directly related to the total number of prescribed drugs as shown in Table 9:

Table 9: Prescribed Drugs and Drug Interactions

			DRGINTXN		
			Yes	No	Total
NUMBDRUG	6	Count	1	12	13
		% within NUMBDRUG	7.7%	92.3%	100.0%
	7	Count	4	61	65
		% within NUMBDRUG	6.2%	93.8%	100.0%
	8	Count	8	77	85
		% within NUMBDRUG	9.4%	90.6%	100.0%
	9	Count	9	42	51
		% within NUMBDRUG	17.6%	82.4%	100.0%
	10	Count	6	6	12
		% within NUMBDRUG	50.0%	50.0%	100.0%
	11	Count	4	1	5
		% within NUMBDRUG	80.0%	20.0%	100.0%
	12	Count	5	1	6
		% within NUMBDRUG	83.3%	16.7%	100.0%
Total		Count	37	200	237
		% within NUMBDRUG	15.6%	84.4%	100.0%

One patient whose condition was deteriorating despite treatment was reported to have been caught hiding pills instead of taking them. Common drugs that the patients explicitly refused to utilize were streptomycin due to pain on injection, and ethionamide due to vomiting. The powerful aversion to the ethionamide was due its severe gastrointestinal effect. Gastritis was the most frequent adverse effect

with 26.1% (n=62) of the hospitalized patients suffering from nausea, vomiting, heartburn and/or diarrhoea. Peripheral neuropathy was the second most suffered drug reaction (16.9%, n=40). Abscess formation at the site of injection occurred in 11.8% (n=28) of the cases. Other adverse effects suffered were deafness at 3.4% (n=8), dizziness (1.7%, n=4) and dermatitis (1.7%, n=4).

Rare side effects were also noted with four patients (1.7%) suffering from central nervous system disturbances, two from gout (0.8%) and one from hepatotoxicity (0.4%). The most common method of managing the side effects was adding another drug to the regimen.

In all cases that adverse drug effects were addressed, another drug was added in 60.8% (n=144) of the cases. The offending drug was withdrawn in 25.3% (n=59) of the patients while in 7.0% (n=17) of the cases the drug was replaced with another. In another 7.0% (n=17) of the cases nothing was done possibly because the side effects were minor.

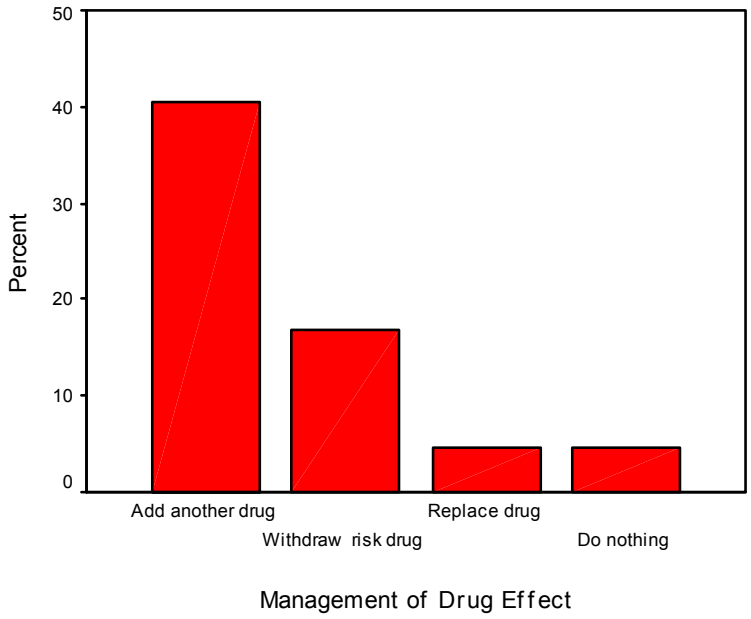

Figure 9: Management of Adverse Drug Effects

To counteract symptoms of gastritis and neuropathy, other drugs were prescribed. Drugs were added in cases of heartburn (75.0%, n=18), nausea and vomiting (70.0%, n=24), and for patients with peripheral neuropathy (80.0%, n=32).

Withdrawal of the offending drug with no alternative replacement was done after observation of pain on injection (39.3%, n=11), deafness (62.5%, n=5), and psychosis (50%, n=1). Replacement of drugs was effected after complaints of allergy (50%, n=1) and gout caused by pyrazinamide (100%, n=2). In 14.3% (n=4) of cases suffering pain on injections and 12.5% (n=3) of heartburn, no action was taken.

4.9.7. Surgical Interventions

Only two categorical variables were analysed for this section. In all the hospitalized patients, 78.5% (n=186) did not need any surgical intervention during their hospitalisation. For those who required some type of surgical intervention (n=51), insertion of an intercostal drainage tube (ICD) was the most frequently performed procedure with 23 (9.7%) of the total patients having had an ICD inserted during their inpatient management. All the ICD insertions were performed at Sizwe hospital.

Table 10: Table of Surgical Interventions

Type of Surgery	Place of Operation	Count n=51	%of all Operations	% of all Patients
Insertion of ICD Tube	Sizwe Hospital	23	45%	9.7%
Lobectomy	Johannesburg Hospital	5	10%	2.1%
Pneumonectomy	Johannesburg Hospital	2	4%	0.8%
Unsuitable for Major Surgery	Johannesburg Hospital	4	8%	1.7%
Transferred before Surgery		10	19%	4.3%
Died before Surgery		1	2%	0.4%
Absconded before Surgery		1	2%	0.4%
Refuses Major Surgery		5	10%	2.1%
Total		**51**	**100%**	**21.5%**

The percentage of the patients operated on was 2.9% with 7 patients undergoing major surgical resection of the lungs. All major surgical operations were carried out at the Johannesburg Hospital. Such major operations require adequately equipped operating theatres, Intensive Care Units, and qualified Surgeons. These resources were not fully available at Sizwe Hospital.

For another 21 patients (15.3%) for whom surgical procedures were recommended by the treating doctors, 10 of them (4.3%) were transferred before the procedures had been carried out. Another 5 patients refused the operation (2.1%), while 4 were willing to undergo the operation but surgeons found them inoperable (1.7%). One patient absconded (0.8%) while another one died (0.8%) before the operation could be done. The surgical outcomes were often fatal as 57% (n=4) of those who had surgical resections died.

4.9.8. Hospitalization Outcomes

To determine hospitalization outcomes six variables were analysed. Three of the six were nominal variables whilst the rest were measured on the ratio scale. The continuous variables measured the duration of hospitalization, time interval to the first smear conversion, and time interval to the first culture conversion. The nominal variables measured the outcomes on discharge, and the smear and culture status of the patients at the end of the hospital stay.

4.9.8.1. Duration of Hospitalization

The duration of hospitalization ranged from a few days, for those who were critically ill and died soon after admission, to a maximum of 18 months. There was no significant difference ($t=0.030$, $df=235$, $p=0.976$) in the duration of hospitalization between males and females with the mean hospital stay being 3.53 (95% C.I. 3.11 - 3.94) and 3.52 (95% C.I. 2.92 - 4.11) months respectively.

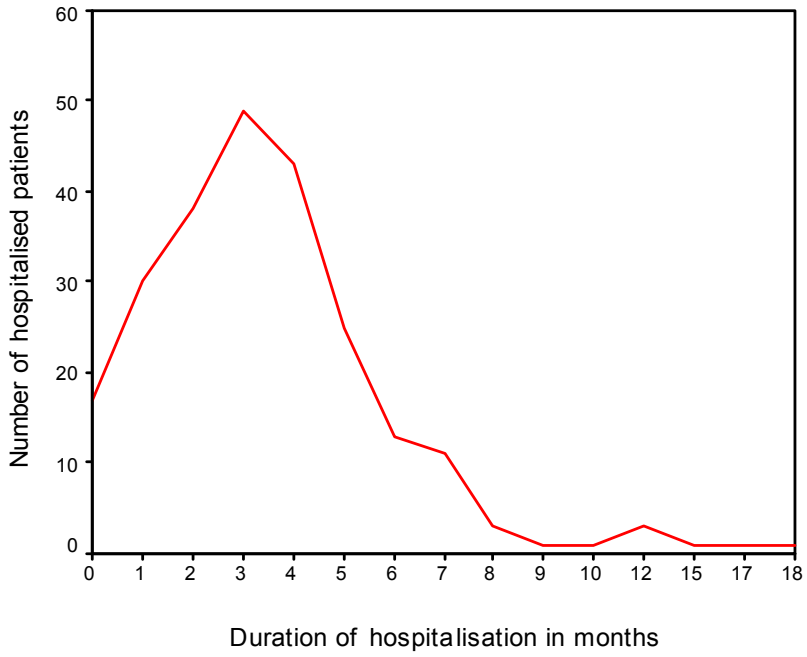

Figure 10: Duration of Hospitalization

The mean length of hospital stay for primary, acquired and nosocomial MDR-TB patients was 3.73, 3.37, and 4.14 months respectively. The higher mean for nosocomial MDR-TB patients is expected as the duration of hospitalization for these patients included time spent in hospital on treatment for non-MDR-TB conditions.

The mode of management of MDR-TB patients soon after diagnosis did not affect the length of hospital stay. The mean duration of hospitalization for patients managed as inpatients soon after diagnosis was 3.56 months while for those managed as outpatients was 3.74 months (t= -0.508, df=223, p=0.612). Neither the length of time spent before admission nor the duration of previous treatment affected the duration of hospitalization.

4.9.8.2. Sputum Conversion Rates

The proportion of those patients who converted; the time interval to conversion, and the number of consecutive months the patients remained negative were recorded. For the purposes of this study only a single conversion was used as an early marker of progress. Normally the point of conversion is the first of a series of two or three consecutive negative cultures. However, due to the short hospital stay most patients were discharged with only one negative culture.

4.9.8.2.1. Sputum Smear Conversion

For patients whose smear conversion records were available (N= 216), 62.5% of the patients converted sputum smears to negative by the time they were discharged from hospital. Patients with one negative smear results comprised 44.4% of those with available smear conversion records. A further 15.3% were discharged with two consecutive negative monthly smear results. A small fraction, 2.8%, had 3 consecutive negative smears taken a month from each other. The time interval to smear conversion ranged from 1 to 17 months with the mean period being 2.57 months. Figure 11 shows the time taken to both smear and culture convert.

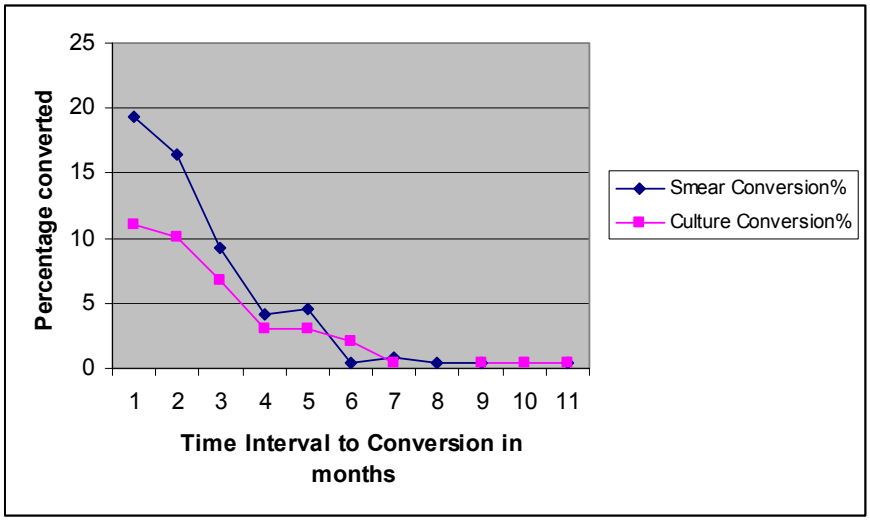

Figure 11: Time to Conversion

4.9.8.2.2. Sputum Culture Conversion

Interim culture conversion rate was lower than that of smear conversion with only 41.9% (89 of 212) of the patients culture converting compared to 62.5% (135 of 216) who smear converted. Sputum culture is more sensitive and is regarded as the gold standard for sputum conversion.

About a third of the patients (34%) were discharged after achieving one negative smear result, 7.5% had achieved two consecutive monthly smear results while a negligible 0.5% had three negative monthly results in a row.

The time to culture conversion was similar to that of smear conversion with the time ranging from a minimum of 1 to a maximum of 17 months with an average period of 2.96 (95% C.I 2.41 – 3.50) months. Over half of the patients, 58.1 %, were discharged with positive culture results.

4.9.8.3. Transfer Out Rate

Further treatment outcomes were determined which included transfer out rates, hospital treatment refusal rates, default rates, failure rates and mortality rates. Table 11 below shows the frequency of these outcomes during the hospitalization period.

Table 11: Treatment Outcomes

		Frequency	Percent
Valid	Transferred	164	69.2
	Refused Hospital Treatment	16	6.8
	Failed	7	3.0
	Died	46	19.4
	Absconded	4	1.7
	Total	237	100.0

Of the total number of admitted patients, 69.2% were transferred out to clinics, after varying periods of inpatient care, to continue treatment as outpatients. The

time period between hospitalization and transfer out ranged from below one month to 18 months with most transfers taking place after 3 months of hospitalization.

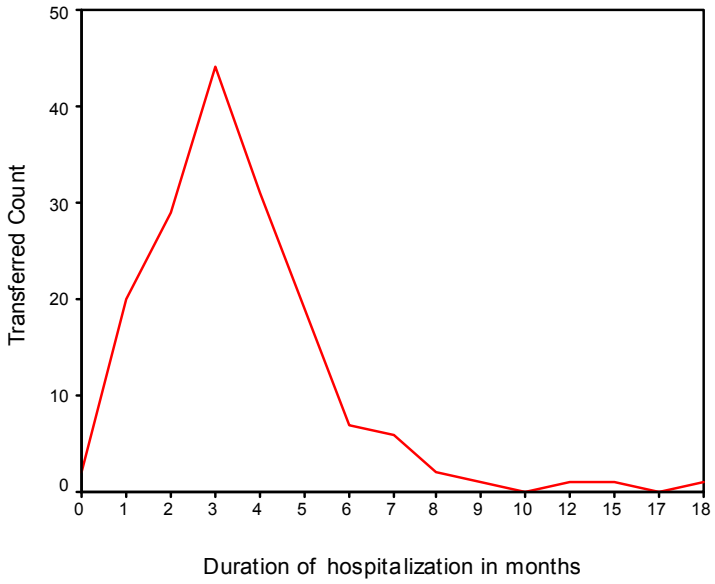

Figure 12: Time Period before Transfer out

4.9.8.4. Hospital Treatment Refusal Rate

All patients who refused hospitalization but were willing to continue with treatment as outpatients were required to sign a refuse hospital treatment (RHT) form. A total of 16 patients (6.8%) signed out to continue treatment on outpatient basis. The largest percentage of refusals occurred after two months of hospital treatment. The likelihood to refuse hospital treatment was similar for both males (n=8) and females (n=8).

4.9.8.5. Default Rate

Default rate during hospitalization was defined as treatment suspension due to absconding. A total of four patients, two females and two males, absconded. Two patients absconded before one month of hospitalization was over. Two other patients escaped after four months of treatment. All the patients who absconded were unemployed.

4.9.8.6. Failure Rate

A failure rate was defined as the occurrence of persistently positive sputum culture despite hospitalization and treatment for six months with second line drugs. Interim failure rate was low, at 2.95%. Three patients remained sputum positive regardless of six months of treatment. Another three persisted even after seven months of medication with second line drugs. One patient was still sputum positive after 17 months of hospitalization. Of those who failed treatment 85.7% were HIV positive.

4.9.8.7. Mortality Rate

Mortality was defined as death of the hospitalized patients due to any cause. Almost a fifth of the hospitalized patients (n=46, 19.4%) died. Among those who died, 23 (50%) of the deaths occurred during the first month of treatment. This may indicate that patients were hospitalized while critically ill. Males were more likely to die than females. This conclusion was arrived at after 60.8% (n=28) of males died compared to 39.2% (n=18) females. A large percentage (73.9%) of those who died was HIV positive.

4.9.9. Regression Analysis

Regression analysis was done to determine predictors of poor hospitalization outcomes. Poor hospitalization outcomes were defined as protracted hospitalization periods, interruption of treatment through absconding, treatment failure and mortality.

Independent or explanatory variables that were entered in the regression analysis were HIV status, age, gender, period before admission, type of MDR-TB, and management method soon after diagnosis. Variables measured at the nominal scale were recoded to produce dichotomous independent variables with values of 0 and 1.

HIV status was found to be a strong predictor of poor hospitalization outcomes of treatment failure and mortality (Coefficient=0.126, Constant=0.117, R^2=0.023, p=0.013). Age, gender, time period before admission, type of MDR-TB, and the method of management soon after culture-confirmation of MDR-TB had no significant influence on poor hospitalization outcomes.

4.10. Discussions

More males than females were hospitalized during this study period. Past studies[59] in various parts of the world have shown that more men than women are diagnosed with TB. This could be due to physiological, socioeconomic or cultural differences between males and females that determine the risk of getting infected, the speed of progression to active disease and ultimately death. While men are more likely to frequent congregate settings which are fertile grounds for transmission of the mycobacteria, progression from infection to disease and case fatalities are extremely high among girls and young women.[60]

The study demonstrated more Africans being hospitalized for MDR-TB, an indication of Africans bearing the brunt of this disease. A possible explanation for this could be the socioeconomic inequalities existing between the racial groups with the Africans being less privileged due to neglect of past regime. While TB is fuelled by poverty it also, in turn, increases poverty as it disables the economically productive fraction of the population.

Acquired MDR-TB patients were hospitalized more often than those with primary MDR-TB. Results of a South African study of drug resistance concluded in year 2002 showed that primary MDR-TB occurred in 1.6% of new TB cases while acquired MDR-TB was more common at 6.7 % of previously treated cases.[22,61]

Patients with primary MDR-TB, who had no history of non-adherence to treatment, were paradoxically more likely to be hospitalized shortly after diagnosis. Acquired MDR-TB patients were mostly managed as outpatients immediately after diagnosis only to be hospitalized later due to non-adherence or disease severity. As non-adherence to first-line drugs is a major cause of acquired MDR-TB, a higher proportion of acquired MDR-TB patients theoretically deserve to be hospitalized soon after diagnosis compared to patients with primary MDR-TB.

The median smear turnaround time was found to be one day while culture turnaround time was on average 19 days. One day is normally required to process raw sputum and concentrate the bacilli load in order to enhance sensitivity of smear microscopy. Culture turnaround time is dependent on culture technique used, the load and viability of the inoculated bacilli.

The study indicated that almost a fifth of the patients (17.8%) were hospitalized when the sputum was negative for acid fast bacilli (AFB). This could be due to

lower positive predictive value of sputum microscopy that has been found to be about 90%. To be detected by smear microscopy, TB bacilli must exceed the cut-off bacilli level of 10,000 per mm^3 of sputum.[5] Inability to produce adequate bacillary load could arise due to either non-cavitary disease, partial response to ongoing therapy or to poor sputum collection techniques.

Over half of the patients were admitted on suspicion of MDR-TB. These patients were mostly treated in the admission ward pending confirmatory tests. Prompt detection of MDR-TB facilitates early transfers of the confirmed MDR-TB patients to MDR-TB wards thereby preventing spread of MDR bacillus. Early diagnosis also enables patients to be treated with the right drugs that the bacilli are susceptible to. In a study in Western Cape, South Africa, delay in appropriate treatment for MDR-TB and lack of detailed contact history was associated with poor outcomes in management of MDR-TB in children.[62]

On average, the mean number of drugs that were prescribed was 8 per patient. While aggressive treatment of MDR-TB is the norm, unnecessary prescribing was noted where more than one drug from the same pharmacotherapeutic class was prescribed. The most affected classes were antibiotics, analgesics and vitamins. Specific examples included co-prescribing amoxycillin and Augmentin® (combination of amoxycillin and clavulanic acid), paracetamol and ibuprofen, and morphine with either codeine or pethidine. Non-adherence to treatment while being hospitalized was an unexpected finding of the study as the close observation of the patients is expected to ensure adherence.

A large percentage of hospitalized patients were HIV positive. HIV infection increases the chance of developing active TB disease by 10% annually. HIV care and support was incomplete as antiretroviral drugs were not available at the

hospital despite the findings that the percentage of HIV positive MDR-TB patients has been increasing with time reaching a high of about 73% in 2001 and 2002. In a report by Blumberg, a similar figure was reported for year 2003.[22] This study found that HIV status had powerful contribution to poor hospitalization outcomes of failure and mortality. A similar finding was made by Cohn DL with profound immunossupression being one reason for poor outcomes.[63]

Close monitoring of specific organ function tests and serum chemistry facilitates identification of potential adverse reactions. Baseline measurements of liver enzymes, bilirubin, serum creatinine, complete blood count and platelet were done in all the hospitalized patients. After initiation of treatment, liver function tests and renal tests were done in only 19% of the patients. This not surprising, since routine laboratory monitoring is not recommended if baseline findings were normal at time of admission.

Evaluations of auditory and vestibular functions detected otovestibular toxicities in about 5% of the patients with subsequent withdrawal of the aminoglycosides. Monitoring of desirable response to therapy was done through monthly sputum microscopy and culture tests, monthly body weight measures and chest x-rays. Despite body weight measure being the least expensive of the monitoring practices it was less frequently done.

Only 7 of the 28 patients for whom surgical resection was recommended underwent the operation. Lack of beds in the intensive care unit of the hospital where surgery was to be done was often quoted as hindrance to timely operation. Delayed removal of cavitary lesions may enhance pulmonary spread leading to total lung destruction. More than half of the patients who underwent surgical operations died possibly due to late interventions.

Shortage of hospital beds was noted as a main reason for not admitting deserving patients at Sizwe hospital. However in a study done by Pronyk et al in South Africa, median total delay to hospitalization was 10 weeks, with patient delay contributing a greater proportion than service provider delay.[64]

The mean duration of hospitalization, 3.52 months, correlated favourably with the time interval to first culture conversion of 2.96 months. Goble et al, in a study done at the National Jewish Centre, revealed that median time for cultures to become negative was two months with majority becoming negative by 4 months.[32] The mean duration of hospitalization at Sizwe hospital of 3.52 months was found ideal. Lengthy hospital stays impact negatively on the patient's social and economic life ultimately forcing many of them to seek temporary discharge from hospital, refuse hospital treatment or simply abscond.

Discharge from hospital is based on a number of factors that include conversion of sputum microscopy and culture, patients' clinical condition and radiological improvement. The overall culture conversion rate of the hospitalized patients was 41.9%. Standardized treatment for MDR-TB patients in South Africa has been shown to have high culture conversion rates of greater than 70% although subsequent high default rates reduce the overall culture conversion rates to nearly 50%.[61]

About 7% of the patients refused hospital treatment. The main reasons given for refusing hospital treatment were visiting traditional healers, solving family and other socioeconomic problems.

The study had limitations. Due to the large number of patients' involved in the study, minute details of patient management could not be captured. These details included clinical observations, nursing reports and patients self reports. A major drawback of the study was its reliance on the TB register to pick up MDR-TB patients and then following up to confirm whether the patients had been hospitalized. This not only slowed down the data collection process but also failed to determine conclusively the total number of hospitalized MDR-TB patients within this period.

The TB register produced several false leads as some patients were diagnosed MDR-TB patients after discharge or death. Some single drug resistant cases had been misclassified as MDR-TB patients. A further shortfall in the study could have arisen due to inaccessibility of some earmarked files as they were untraceable. The existing file tracking system was inadequate. Some of the records that were accessed were incomplete while some files had missing sections. Finally, post-discharge treatment outcomes of the hospitalized patients were not captured due to the limitations imposed by the scope of the study.

CHAPTER 5: RECOMMENDATIONS AND CONCLUSIONS

"TB and drug resistance are global problems.... An effective response calls for resources, for an informed society and a functioning health system in its widest sense." WHO Director-General, Dr Gro Brundtland, 2001[65]

The burden of hospitalizing MDR-TB patients in this setting was found to involve high numbers of patients for whom the allocated hospital beds were not adequate. Irrational prescribing was observed and cases of drug toxicity often occurred. There were low rates of culture conversion with concomitant protracted hospitalization periods. Hospitalization did not guarantee total treatment adherence. Patients frequently needed time off to solve socioeconomic problems and to visit traditional healers. Many patients were co-infected with HIV, no antiretroviral (ARVs) drugs were available and mortality rates were high. Misclassification of MDR-TB cases was evident and some records were untraceable. The following recommendations can be made to address this burden:

5.1. Preventing Emergence and Spread of MDR-TB

In order to minimize the relatively high numbers of MDR-TB patients prevalent in Gauteng province efforts at preventing the emergence and transmission of MDR-TB should be stepped up as it is easier to prevent the occurrence of MDR-TB than to treat it. Strategies to deter emergence of acquired MDR-TB should include enhancement of DOTS for drug susceptible TB patients, counseling on importance of adherence, and offering suitable incentives for those who complete treatment. To block the transmission of MDR-TB on contact, infection control at both the community level and at the health institutions should be vigorously promoted. Early suspicion, swift evaluation and accurate detection of MDR-TB, followed by isolation and personal hygiene instructions to the patients will reduce the transmission of MDR-TB.

5.2. Diagnosis of MDR-TB

Apart from curtailing the spread of MDR-TB, early and accurate detection of MDR is of high clinical importance. Early diagnosis of MDR-TB before extensive lung damage occurs improves the chances of treatment success as extensive lung destruction impedes delivery of drugs to the cavities, where the bacilli are concentrated. Misclassification of single drug resistant cases as MDR-TB denies these patients the benefits of powerful drugs. Early suspicion of MDR-TB and the use of standardized definitions and laboratory procedures will enhance timely and accurate diagnosis of MDR-TB.

5.3. Hospitalization of MDR-TB Patients

The hospital should formulate admission and discharge guidelines that will ensure adequate beds are reserved for deserving patients. Acquired MDR-TB patients should be given preference over those with primary MDR-TB as the former mainly arises from non-adherence to treatment. Failure to hospitalize notoriously non-adherent MDR-TB patients may lead to further transmission of MDR-TB in the community. An extra MDR-TB ward has, since year 2004, been made available at Sizwe. This additional ward will certainly ease the demand of hospital beds.

5.4. Drug Administration

Continuing education for service providers on aggressive but rational prescribing of the second line drugs at high-end dosages will lower instances of side effects, drug interactions and aversion to drugs by patients. Unnecessary prescribing and attendant costs will be minimized. Continuing education for nurses will enhance adherence through motivating patients, observed therapy, improved injection techniques, and better administration of the numerous pills. Therapeutic drug monitoring should be recommended in all patients who do not smear convert after six months of aggressive

treatment. This monitoring of blood levels of second line drugs will facilitate fine tuning of the optimal dosages that will achieve cure without inflicting undue harm to the patients.

5.5. HIV Care and Support

Given the dynamics between HIV and TB, it is apparent that treatment of HIV in co-infected MDR-TB patients with antiretroviral (ARV) drugs will greatly enhance the patients' response to MDR-TB therapy. ARVs reduce the viral load with improvement of patients' immunity. The reconstituted immunity subsequently helps in clearing the MDR-TB bacilli from the patients' lungs. The high numbers of MDR-TB patients co-infected with HIV/AIDS further emphasize the necessity of stocking and prescribing ARVs at Sizwe hospital.

5.6. Social Support Issues

Some patients expressed desire to consult with traditional healers at some point during their hospitalization. Traditional healers need to be trained on MDR-TB management issues so that they don't discourage patients from adhering to therapy. Treatment of MDR-TB is a lengthy process and the patients and their relatives should be adequately and regularly counselled. Patients should be granted compassionate leave on request, maintaining a patient centered approach in the whole hospitalization process. Application and processing of disability grant should be made easy for deprived patients.

5.7. Monitoring and Evaluation

Processed information regarding patient management should be made readily available to the health workers in the hospital. An improved file tracking system that facilitates filing and tracking of medical records needs to be put in place. This especially important since MDR-TB treatment takes a long time with files being

handled by various wards, doctors, nurses, and even researchers. Guidelines on filing and discarding of old x-ray films are also needed since accumulated x-ray films make medical records unwieldy and take up a lot of filing space.

A study that compares treatment outcomes of partially hospitalized patients with outcomes of patient solely treated as outpatients would be an interesting future undertaking. Such a study would compellingly demonstrate the advantages of hospitalizing MDR-TB patients.

To maximize public benefit, every effort will be exerted to disseminate the findings and recommendations emanating from this study. Copies of this report will be forwarded to the Sizwe hospital, the Gauteng Department of Health and University of the Witwatersrand Health Sciences Library. Editors of reputable journals will be contacted in an endeavour to publish the work.

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APPENDIX A: DATA CAPTURE FORM

Section I: Patient Demographic Variables

1. **Study Number:** ☐☐☐
2. **Age on Admission (Yrs):** ☐☐
3. **Sex:** O Male O Female
4. **Weight on Admission (Kg):** ☐☐
5. **Race:** O African O Indian O Coloured O White
6. **Occupation:** _____

Section II: Treatment History

7. **TB Contacts** O Yes O No O Not Available
8. **Previous TB treatment** O Yes O No O Not Available
9. **Type of MDR-TB:** O Pulmonary O Extra-pulmonary
10. **Date of diagnosis with MDR-TB:** ☐☐/☐☐/☐☐
11. **Management of MDR-TB soon after Diagnosis:**
    O In-patient O Out-patient
12. **Previous admission at Sizwe:** O Yes O No
13. **If yes, duration of hospitalization:** ☐☐
14. **Date Admission at Sizwe:** ☐☐/☐☐/☐☐
15. **Criteria for Hospitalizing Patient:**

O Defaulting O Persistency of positive sputum O Severity of MDR-TB disease O Poor social circumstances O Other_____

16. **HIV Status:** O Positive O Negative O Not Available
17. **Co-morbidity:** O Asthma O Hypertension O Specify other _____

Section IV: Baseline Tests on Last Admission

18. Facility where bacteriological tests were done:

_____

19. Sputum Microscopy and Culture:

Test	Date of Specimen			Date of Results			Test Characteristics					
							Negative	Scanty	Moderate	Advanced	Spoilt	Not Available
Smear1							O	O	O	O	O	O
Smear2							O	O	O	O	O	O
Culture							O	O	O	O	O	O

20. Drug Susceptibility tests :

	Resistant	Susceptible	Not available
Rifampicin	O	O	O
Isoniazid	O	O	O
Ethambutol	O	O	O
Streptomycin	O	O	O
Pyrazinamide	O	O	O
Pyrazinamide	O	O	O
Ethionamide1	O	O	O
Ofloxacin	O	O	O
Cycloserine	O	O	O

21. Liver function Tests: O **Yes** O **No** O **Not available**

22. Visual Tests: O **Yes** O **No** O **Not available**

23. Audiometry Test: O **Yes** O **No** O **Not available**

24. Renal Tests: O **Yes** O **No** O **Not available**

25. Other Tests: _____

Section V: Initial Phase of Treatment

26. Date of starting the Initial phase: | | | / | | | / | | |

27. Initial phase treatment:

Drug	Dose	Freq	No. of days in a week	Duration	Therapeutic category
Pyrazinamide					
Kanamycin					
Ofloxacin					
Ethionamide					
Cycloserine					
Ethambutol					

Section VI: Therapeutic Monitoring

28. Noted adverse effects during Initial Phase: O Nephrotoxicity
O Neurotoxicity O Hepatotoxicity O Skin symptoms
O GIT symptoms O Behavioural symptoms Specify Other: _____

29. Facility where monthly smears and culture were done during Initial Phase treatment monitoring. _____

30. Monthly smears and culture:

Month	Test	Date of Specimen			Date of Results			Test Characteristics					
								Negative	Scanty	Moderate	Advanced	Spoilt	Not Available
First	Smear1							O	O	O	O	O	O
	Smear2							O	O	O	O	O	O
	Culture							O	O	O	O	O	O
Second	Smear1							O	O	O	O	O	O
	Smear2							O	O	O	O	O	O
	Culture							O	O	O	O	O	O
Third	Smear1							O	O	O	O	O	O
	Smear2							O	O	O	O	O	O
	Culture							O	O	O	O	O	O
Fourth	Smear1							O	O	O	O	O	O
	Smear2							O	O	O	O	O	O
	Culture							O	O	O	O	O	O
Fifth	Smear1							O	O	O	O	O	O
	Smear2							O	O	O	O	O	O
	Culture							O	O	O	O	O	O
Sixth	Smear1							O	O	O	O	O	O
	Smear2							O	O	O	O	O	O
	Culture							O	O	O	O	O	O

31. Other treatment monitoring Practices: _____

Section VII: Continuation Phase of Treatment

32. Date of starting continuation phase: | | | / | | | / | | |

33. Drugs used in continuation phase:

Drug	Dose	Freq	Duration	Therapeutic Category
Ofloxacin				
Ethionamide				
Cycloserine				
Ethambutol				

Section VII: Therapeutic Monitoring During Continuation Phase

34. Noted adverse effects –Continuation phase: ONephrotoxicity ONeurotoxicity OHepatotoxicity O Skin symptoms O GIT symptoms O Behavioral symptoms Specify Other:_____

35. Facility where quarterly smears and culture tests were done: _____

36. Monthly smears and culture:

Month	Test	Date of Specimen			Date of Results			Test Characteristics					
								Negative	Scanty	Moderate	Advanced	Spoilt	Not Available
First	Smear1							O	O	O	O	O	O
	Smear2							O	O	O	O	O	O
	Culture							O	O	O	O	O	O
Second	Smear1							O	O	O	O	O	O
	Smear2							O	O	O	O	O	O
	Culture							O	O	O	O	O	O
Third	Smear1							O	O	O	O	O	O
	Smear2							O	O	O	O	O	O
	Culture							O	O	O	O	O	O
Fourth	Smear1							O	O	O	O	O	O
	Smear2							O	O	O	O	O	O
	Culture							O	O	O	O	O	O
Fifth	Smear1							O	O	O	O	O	O
	Smear2							O	O	O	O	O	O
	Culture							O	O	O	O	O	O
Sixth	Smear1							O	O	O	O	O	O
	Smear2							O	O	O	O	O	O
	Culture							O	O	O	O	O	O

37. Other monitoring Practices: _____

38. Surgical Intervention O Yes O No

39. Date of surgical intervention | | | / | | | / | | |

40. Facility where done: O Sizwe Hospital O Joburg Gen O Other:_____

41. Type of Surgical Intervention: O Pneumonectomy O Lobectomy O Intercostal drainage Other:_____

42. Treatment outcomes:

Outcome	Date						Discharged to Clinic	Weight on discharge
Culture converted								
Interrupted								
Failed								
Died								

APPENDIX B: ANALYSIS PLAN

Coding and Cleaning of Raw Data

- Work out variable names for each item in the data capture sheet and then code the values associated with each variable.
- Prepare an MS Excel spreadsheet with the variables as columns
- Enter raw data in the MS Excel spreadsheet with each case studied entered in the rows
- Check for typing errors after entering data for each case
- Check for coding errors after entering all the cases by running through the columns
- Check for obvious range errors.

Transformation and Processing of Raw Data

1. Calculate and enter the following continuous variables:
    - Age on Admission,
    - Duration of previous treatment,
    - Period before admission,
    - Smear turnaround time,
    - Culture turnaround time,
    - Duration of Hospitalization,
    - Smear conversion time and
    - Culture conversion time.
2. Determine pharmacokinetic and pharmacodynamic drug interactions based on the pharmacological activities of the prescribed drugs using Martindale 31st Edition for confirmation.
3. Export the data into SPSS Version 12 software

Analysis of Processed Data

Table 1: Analysis Plan for Demographic Section

Variables Used	Variable Labels	Type of Data	Analytical Procedures	Graphic Display
Gender	Gender of the patients	Nominal	1. Frequencies 2. Chi Square test	Narrative
Race	Race	Nominal	Frequencies	Narrative
Ageoadmn	Age on admission	Ratio	1. Descriptives 2.T test with Gender 3. Recode to Ageodmn5	Narrative
Ageodmn5	Age groups of admitted patients	Ordinal	Frequencies	Bar chart
Occupatn	Occupation	Nominal	Frequencies	Narrative

Table 2: Analysis Plan for Clinical Characteristics

Variables Used	Variable Labels	Type of Data	Analytical Procedures	Graphic Display
Typemdr	Type of MDR-TB diagnosed	Nominal	1.Frequencies 2.Crosstab with Gender	Pie chart
Contacts	Previous contact with TB patients	Nominal	1.Frequencies 2. Crosstab with typemdr	Narrative
Prevtbrx	Previous treatment of TB	Nominal	Frequencies	Narrative
Durnprvx	Duration of previous treatment	Ratio	1.Descriptives 2.Explore	Histogram
Hivstat	HIV status	Nominal	1.Frequencies 2.Crosstab with Gender 3.Crosstab with typemdr 4.Correlation with year of admission	Table
Comorbid	Other diseases that MDR-TB patients suffer	Nominal	Frequencies	Narrative

Table 3: Analysis Plan for Hospitalization

Variables Used	Variable Labels	Type of Data	Analytical Procedures	Graphic Display
Mangsnad	Management of Patients soon after diagnosis of MDR-TB	Nominal	1.Frequencies 2.Crosstab with typemdr	Narrative
Peribadmn	Time spent before hospitalization after diagnosis	Ratio	1.Descriptives 2.Correlation with durnhos 3. Crosstab with outcomod	Line graph
Critadmn	Admission criteria	Nominal	1.Frequencies 2.Crostab with mangsnad 3. Crosstab with typemdr	Table
Readmn	Readmission	Nominal	Frequencies	Narrative

Table 4: Analysis Plan for Bacteriological Tests

Variables Used	Variable Labels	Type of Data	Analytical Procedures	Graphic Display
Sputoadm	Smear results on admission	Nominal	Frequencies	Narrative
Sputime	Smear turn around time	Ratio	1.Descriptives 2.Explore	Narrative
Cultodmn	Culture results on admission	Nominal	Frequencies	Narrative
Cultime	Culture turn around time	Ratio	1.Descriptives 2.Explore	Narrative
Resitans	Resistance patterns	Nominal	Frequencies	Narrative

Table 5: Analysis Plan for Prescribing Patterns

Variables Used	Variable Labels	Type of Data	Analytical Procedures	Graphic Display
Inject	Type of injection used	Nominal	Frequencies	Pie chart
Regimen	Type of regimen used	Nominal	Frequencies	Narrative
Macrolide	Type of macrolide used	Nominal	Frequencies	Narrative
Othertb	Other tuberculosis drugs used	Nominal	Frequencies	Narrative
Contpha6	Continuous phase after six months?	Nominal	Frequencies	Narrative
Hivcare	Was HIV care done	Nominal	Frequencies	Narrative
Othrdrug	Other non tuberculosis drugs.	Nominal	Frequencies	Narrative

Table 6: Analysis Plan and Results for Laboratory Based Monitoring

Variables Used	Variable Labels	Type of Data	Analytical Procedures	Graphic Display
Mthlyspt	Monthly sputum	Nominal	Frequencies	Narrative
Mthlycult	Monthly culture	Nominal	Frequencies	Narrative
Chstxray	Chest x-ray	Nominal	Frequencies	Narrative
Mthlywt	Monthly weight measures	Nominal	Frequencies	Narrative
Liverfts	Liver function test	Nominal	Frequencies	Narrative
Urealect	Urea and electrolytes	Nominal	Frequencies	Narrative
Auditest	Auditory tests	Nominal	Frequencies	Narrative
Visutest	Visual tests	Nominal	Frequencies	Narrative

Table 7: Analysis Plan for Pharmacotherapeutic Monitoring

Variables Used	Variable Labels	Type of Data	Analytical Procedures	Graphic Display
Numbdrug	Number of drugs prescribed	Ratio	Descriptives	Narrative
Drgintxn	Drug interaction	Nominal	Frequencies	Table
Adveffct	Adverse effects	Nominal	Frequencies	Narrative
Mngeffct	Management of adverse effects	Nominal	1.Descriptives 2.Crosstab with Adveffct	Graph

Table 8: Analysis Plan for Surgical Interventions

Variables Used	Variable Labels	Type of Data	Analytical Procedures	Graphic Display
Typesurg	Type of surgery	Nominal	Frequencies	Table
Placoper	Place of operation	Nominal	1.Frequencies 2. Crosstab with Type of surgery	Narrative

Table 9: Analysis Plan for Hospitalization Outcomes

Variables Used	Variable Labels	Type of Data	Analytical Procedures	Graphic Display
Durnhos	Duration of hospitalization	Ratio	1. Desriptives 2. T-test for Durnhos x Gender 3. F-test for Durnhos x Typemdr 4. F-test for Durnhos x Mangsnad 5. Correlation coefficient for Durnhos x Peribadmn 6. T-test with Hivstat	Line graph
Sputaod	Sputum on discharge	Nominal	Frequencies	Narrative
Cultod	Culture on discharge	Nominal	Frequencies	Narrative
Smecontm	Smear conversion time	Ratio	Desriptives	Line graph
Culcontm	Culture conversion time	Ratio	1.Descriptives	Line graph
Outcomod	Outcome on discharge	Nominal	1.Frequencies 2.Crosstab with Durnhos 3.Cross tab with typemdr 4.Crosstab with gender 5.crosstab with Hivstat	Narrative

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Njaramba

CLEARANCE CERTIFICATE **PROTOCOL NUMBER M040239**

PROJECT Managing multidrug-resistant tuberculosis in hospitalized patients at Sizwe Tropical diseases hospital: A 5 year review of treatment outcomes.

INVESTIGATORS Mr P J Njaramba

DEPARTMENT School of Public Health

DATE CONSIDERED 04.02.27

DECISION OF THE COMMITTEE* Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr S Naidoo

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES