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ADMISSION TRENDS AND TREATMENT OUTCOMES OF MDR AND XDR-TB PATIENTS AT SIZWE HOSPITAL IN GAUTENG PROVINCE

Maria Cornelia Louw

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Public Health in the field of Hospital Management

Johannesburg, November 2012

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DECLARATION

I, Maria Cornelia Louw, declare that this research report is my own work. It is being submitted for the degree of Master of Public Health in the field of Hospital Management at the University of the Witwatersrand, Johannesburg. It has not been submitted before, for any degree or for any examination at this or any other University.

_____

November 2012

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DEDICATION

This research is dedicated to my precious children Hanri, Su-Mari and Liezl.

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ACKNOWLEDGEMENT

Sincere appreciation is extended to all my colleagues in Sizwe Hospital, who contributed to the successful completion of this study. The assistance of the following people deserves a special acknowledgement:

- My supervisor, Professor S. Naidoo for expert guidance, support, availability and encouragement.
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- Ms. G. Vukeya for support with data collection.
- Dr. X. Padanilam, Chief Medical Officer, for clinical input.
- The Gauteng Department of Health and Social Development for allowing me to conduct the study.

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Introduction: Tuberculosis (TB) control is included in the eight Millennium Development Goals, with the aim to halve the prevalence and death rate associated with TB by 2015 compared to 1990. TB is a global public health crisis aggravated by the emergence of multidrug-resistance (MDR) and extensively drug-resistance (XDR). South Africa is currently ranked as the country with the third highest TB and fifth highest MDR-TB burden in the world. Sizwe Hospital is the only specialised TB hospital in the Gauteng Province, responsible for the management of MDR and XDR-TB. The number of admissions has increased since 2007, poor outcomes were reported, the treatment is expensive and patients stay for long periods in hospital. Risk factors and MDR-TB outcomes have not been well described in South Africa. Information on admission trends, demographic and clinical profiles as well as treatment outcomes are lacking and is critical to evaluate and strengthen the management of MDR and XDR-TB at Sizwe Hospital.

Aim: The aim of the study is to describe and compare the admission trends and treatment outcomes of MDR and XDR-TB patients at Sizwe Hospital in Gauteng Province for the period January 2008 to December 2009.

Methodology: The study design was an analytical cross-sectional study based on a record review of all adult MDR and XDR-TB patients admitted at Sizwe Hospital. Information was extracted from the medical records and drug-resistant registers. Excel and Epi-info was used to record and analyse the data respectively. The variables: admissions, demographic profile, clinical profile and treatment outcomes, were analysed through descriptive statistics and statistical tests were used for the comparison analysis. Logistic regression was performed to determine factors influencing death. Ethical approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand.

Results: The total number of adult admissions for the period was 891 with an increased admission over the two years. MDR-TB accounted for 95.3% (849) of the admissions and XDR-TB for 4.7% (42). The male admissions were higher (55.8%) than the female admissions in both years. The majority of patients were in the age

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age was 36 years and increased from 35 years to od. Most patients (75.9%, n=676), had a previous history of TB and a higher proportion of XDR-TB patients (95.2%, n=40) had a history of previous TB. A high proportion of 74.9% (655) of patients were HIV positive, with a higher proportion in females (81.5%, n=317) as compared to males (69.5%, n=338). Culture conversion decreased from 80.8% (308) to 76.7% (391) over the two years and was higher (79.2%, n=672) in MDR-TB compared to XDR-TB (64.3%, n=27). No statistical significance was found in the treatment outcomes comparing HIV positive and negative patients. Low cure (2.4%) was achieved and treatment completed decreased from 42% (160) to 13.5% (69), when comparing 2008 figures with 2009, as a result of a higher proportion (33.3%, n=170) of patients still on treatment in 2009. Age, TB diagnosis and HIV were significantly associated with death.

Discussion: The majority of admissions were males, between 28-32 years of age who were MDR-TB patients for the study periods January 2008 to December 2009. The increase in the number of admissions over the study period was not significant, however could be due to non adherence of TB treatment. XDR-TB was significantly ($p<0.01$) associated with a previous history of TB treatment and female gender with HIV infection ($p<0.0001$). High culture conversion was achieved in both years as a result of monitoring and support while in hospital. HIV infection did not influence treatment outcomes. Low cure however was observed mostly due to the lack of documented culture results from the clinics. The decrease in treatment success over the two years might be due to high default rate after discharge from hospital, increase in mortality and being still on treatment during the study period. Risk factors associated with the high mortality were age, HIV and XDR-TB.

Conclusions: The study identified the need for a comprehensive integrated HIV/AIDS care. Hospitalisation contributed to early success and an intervention is needed to strengthen TB control management from prevention and early detection to case holding and follow up to improve community care. Further studies are necessary to identify risk factors for deaths and treatment default.

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Drug-resistant TB is a disease (usually pulmonary) caused by *Mycobacterium tuberculosis* strains resistant to one or more anti-TB drugs (NDOH, 2011).

MDR-TB is defined as resistance to rifampicin and isoniazid, with or without resistance to other first-line anti-TB drugs (NDOH, 2011).

XDR-TB is defined as resistance to rifampicin, isoniazid, any fluoroquinolone and resistance to one or more of the following injectable anti-TB drugs: kanamycin, amikacin, capreomycin (NDOH, 2011).

Interim treatment outcome: Outcome recorded at the end of hospitalization. (Note that this definition is specific for the study to evaluate hospital outcomes).

Still in hospital: Interim treatment outcome when a patient was not discharged from hospital as on the 31th of May 2011. (Note that this definition is specific for the study as patients were followed up as per approved protocol until this date).

Culture conversion: A negative culture result on discharge from hospital. (Note that this definition is specific for the study as interim outcome was documented at the end of hospitalisation).

Treatment outcome: Outcome as on 31st May 2011. (Note that this definition is specific for the study as patients were followed up as per approved protocol until this date).

Treatment outcome definitions: The outcome definitions are based on bacteriological culture as a monitoring tool:

- **Cure**: A patient who has completed treatment and has been consistently culture-negative for five consecutive months in the final twelve months of treatment. If one positive culture is reported during that time and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures, taken at least thirty days apart (NDOH, 2011).
- **Treatment completed**: A patient who has completed treatment but does not meet the definition for cure due to lack of bacteriologic results (i.e. less than

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ned in the final twelve months of treatment) (NDOH,

- **Treatment failure**: A patient who has had two or more of the five consecutive cultures taken in the final twelve months which are positive, or if any one of the final three cultures are positive (NDOH, 2011).
- **Death:** A patient who dies from any cause while on DR-TB treatment (NDOH, 2011).
- **Treatment default:** A patient who interrupts DR-TB treatment for two or more consecutive months for any reason (NDOH, 2011).
- **Transfer out:** A patient who has been transferred to a reporting unit in another province and for whom the treatment outcome is unknown (NDOH, 2011).
- **Still on treatment**: A patient who for any reason is still on treatment at the time of submission of treatment outcome report (NDOH, 2011).
- **Successful treatment completed:** Cure and treatment completed combined (NDOH, 2011).

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AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
CDC	Centre for Disease Control and Prevention
CI	Confidence interval
DOT	Directly Observed Therapy
DOTS	Directly Observed Therapy Short course
DR-TB	Drug- Resistant Tuberculosis
DST	Drug Susceptibility Testing
HIV	Human Immunodeficiency Virus
IQR	Interquartile range
MDR-TB	Multidrug -Resistant Tuberculosis
NDOH	National Department of Health
NHLS	National Health Laboratory Services
SA	South Africa
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant Tuberculosis

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CHAPTER 1
INTRODUCTION

This chapter will cover the background to the study, statement of the problem and the aims and objectives will de defined.

1.1 BACKGROUND

Tuberculosis (TB) control is included in the eight Millennium Development Goals, with the aim to halve the prevalence and death rate associated with TB by 2015 compared to 1990 (World Health Organization, 2010). Tuberculosis was declared a global emergency by the World Health Organization (WHO) in April 1993 (WHO, 2003). TB remains a worldwide health crisis and the leading cause of death among people living with HIV/AIDS (Small, 2009). According to the WHO there were an estimated 9.4 million new TB cases in 2008 with 1.8 million deaths (WHO, 2010). South Africa (SA) has the third highest TB burden and the fifth highest burden of multidrug- resistant (MDR) TB in the world (National Department of Health, 2011). The emergence of drug-resistant (DR) TB is an additional major threat to public health worldwide, with 440 000 MDR-TB cases reported in 2008, of which a third of these patients died (WHO, 2010). Extensively Drug-resistant (XDR) TB is a growing public health problem worldwide associated with high mortality (Raviglione & Smith, 2007). MDR-TB is defined as resistance to at least two powerful drugs, rifampicin and isoniazid. XDR-TB is a huge concern since resistance exists for the same drugs with additional resistance to the fluoroquinolones and one or more injectables (amikacin, kanamycin or capreomycin). Both these forms of TB are difficult and expensive to treat (National Department of Health, 2011).

Sizwe Hospital is a specialised TB hospital responsible for the management of MDR and XDR-TB. The Hospital is situated in Gauteng Province and has 266 approved beds. All diagnosed, laboratory confirmed cases in the province are referred and admitted at Sizwe Hospital, and discharged only after a negative culture result. The

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vided with hospital transport to the clinic nearest to under supervision. Patients come for follow up with organized transport to the hospital on a monthly to three monthly bases and have to bring their culture results to monitor progress. The hospital provides the treatment and is also responsible for keeping the drug-resistant register. .

MDR-TB patients were treated mainly with the standardised regimen consisting of at least six months intensive phase with kanamycin, pyrazinamide, ofloxacin, ethionamide and terizidone or ethambutol, followed by eighteen months continuation phase after culture conversion, with ofloxacin, ethionamide and terizidone or ethambutol. XDR-TB patients were treated with at least four to seven drugs expected to be effective (capreomycin, ofloxacin later substituted with moxifloxacin, ethionamide, terizidone, pyrazinamide, high dose isoniazid, p-aminosalicylic acid, clarithromycin, clofazimine, azithromycin and amoxicillin-clavulanate) for eighteen to twenty four months (National Department of Health, 2010). One hundred and eleven XDR-TB patients have been admitted since the emergence of the disease late in 2006 until 2010. Almost one thousand nine hundred MDR-TB cases have been admitted from 2007 to 2010 according to the drug-resistant registers at Sizwe Hospital (Gauteng Department of Health, 2011).

The management of MDR and XDR-TB in South Africa is in accordance with the National Tuberculosis Control Programme guidelines and Directly Observed Therapy Short course (DOTS) expansion and enhancement strategy. A decentralized MDR-TB management approach has been incorporated in the updated National guidelines as a policy framework. Decentralisation of MDR-TB management is a community-based treatment model providing for shorter hospitalization and includes the management of DR-TB in decentralized MDR-TB units, satellite MDR-TB units, or in the community primary health care clinics, mobile MDR-TB injection teams and/or community health care workers and households (National Department of Health, 2011).

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According to Wood, Lawn, Johnstone-Robertson, et al. (2011), TB control in South Africa has failed and it is time to reappraise its strategy. Drug-resistant TB is a growing epidemic with high mortality, requiring expensive treatment. The number of admissions at Sizwe hospital has increased over the past years since 2007, the length of stay in hospital is long with an average of four months, the cost of treatment increased and poor treatment outcomes were reported (Gauteng Department of Health, 2011). Information on MDR and XDR-TB admission trends, demographic and clinical profiles as well as treatment outcomes are lacking and is critical to understand the admission patterns as well as to measure and evaluate treatment outcomes for effective MDR and XDR-TB management .

1.3 JUSTIFICATION FOR THE STUDY

Limited studies were conducted on MDR and XDR-TB treatment outcomes in South Africa and risk factors such as the impact of HIV and outcomes of MDR-TB treatment, have not been well described (Farley, Ram, Pam, et al., 2011). Studies that have investigated trends and outcomes of MDR-TB in Sizwe Hospital are lacking. As the only specialized TB Hospital in Gauteng Province, expert management and advice should be based on accurate information.

This research therefore attempts to analyse the differences in the caseload, demographic and clinical profiles as well as treatment outcomes for two years at Sizwe Hospital. This information could assist Hospital management, TB control programmes of National and Provincial Departments of Health and senior management of other specialised TB institutions to strengthen MDR and XDR-TB management and control.

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This study aimed to describe and compare the difference in admission trends and treatment outcomes between MDR and XDR-TB patients at Sizwe Hospital in Gauteng Province, for the period January 2008 to December 2009.

1.5 AIM AND OBJECTIVES

1.5.1 AIM

The aim of the study is to describe and compare the admission trends and treatment outcomes of MDR and XDR-TB patients at Sizwe Hospital in Gauteng Province, for the period January 2008 to December 2009.

1.5.2 OBJECTIVES

The objectives are as follows:

- To describe and compare admission trends for MDR and XDR-TB in Sizwe Hospital for the study period January 2008 to December 2009.
- To describe and compare demographics of these patients between the periods January to December 2008 and January to December 2009.
- To determine changes in treatment outcomes for these patients for the study period.

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CHAPTER 2
LITERATURE REVIEW

In this chapter, relevant literatures on MDR and XDR-TB in South Africa and worldwide are discussed.

2.1 DISTRIBUTION OF DISEASE

Increasing numbers of cases of drug-resistant TB, as stated by Jassal and Bishai, 2009, is due to inadequate regimens and non adherence to therapy. Several epidemiological factors such as HIV infection and inadequate case detection and treatment completion have contributed to the increase in XDR-TB (Jassal & Bishai, 2009). This necessitates a comprehensive, universal approach that can reverse the current trends of drug resistance.

2.1.1 MDR-TB WORLDWIDE

The burden of MDR-TB disease varies significantly from country to country and region to region (Dias-Baptista, Uso, Marcondes- Machado, 2008). MDR-TB prevalence of 7.9% (361) was found in a study done by Migliori, Besozzi, Girardi et al. (2007) from cases analysed in Estonia, Germany, Italy and the Russian Federation, and 16.9% (196) MDR-TB prevalence was found in another study by Kliiman and Altraja (2009) only in Estonia. According to the WHO (2010), 3.6% (440,000) of TB cases globally in 2008 were estimated to have MDR-TB with cases documented in nearly 90 countries and regions worldwide. The highest prevalence of cases was reported in Asia, which contributes 50% of the global burden of MDR-TB (WHO, 2010). Worldwide the proportion of MDR-TB reported to the WHO, ranges from 0% to 28.3% among new TB cases. The highest proportions of MDR-TB ever documented were from Russia ranging from 23.8% to 28.3%; Tajikistan, with 61.6% MDR-TB among previously treated TB patients

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strict (WHO, 2010). China reported 5.7% among ose previously treated (WHO, 2010).

2.1.2 WORLDWIDE XDR-TB

XDR-TB was reported in fifty nine countries and confirms that this is a global public health threat (Sotgiu, Ferrara, Matteelli, et al., 2009). WHO estimates 40,000 annual XDR-TB cases with many cases still unreported and 772 cases reported from 28 countries in 2007. Surveillance data on testing for XDR-TB from 46 countries found that 5.4% of MDR-TB cases were XDR-TB (WHO, 2008). The Centers for Disease Control (CDC) and the WHO surveyed an international network of TB laboratories during 2000ï 2004 and of 17,690 TB isolates, 2% were XDR. In addition, population-based MDR-TB data were obtained from the United States (1993ï 2004), Latvia (2000ï 2002), and South Korea (2004). In these cases it was found that 4%, 19%, and 15% respectively, were XDR (CDC, 2006). Kim, Kim, Park, et al. (2008) and Mitnick, Shin, Sueng, et al. (2008), found that 5.3% and 7.4% of TB cases were XDR in South Korea and Peru respectively.

2.1.3 TB DRUG RESISTANCE IN SA

According to the National Department of Health (NDOH, 2011) 45,196 MDR-TB and 3,128 XDR-TB cases were confirmed by the National Health Laboratory Services (NHLS) between 2004 and 2010. A total 1,296 XDR-TB cases and 16,821 MDR-TB cases were started on treatment during 2007 to 2010. South Africa has the fifth highest burden of MDR-TB in the world (NDOH, 2011). In Gauteng 2,030 and 140 patients were started on MDR-TB and XDR-TB treatment respectively during the period 2007-2010. These numbers differed slightly from the Provincial report (2011) of 1,931 and 106 for MDR and XDR-TB respectively. This is the fourth largest number of South African provinces, and the largest number was reported in KwaZulu-Natal (NDOH, 2011).

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3% of newly diagnosed TB cases and 6.7% of MDR-TB. In studies done in South Africa, 6% of MDR-TB isolates were found to have XDR-TB (Mlambo, Warren, Poswa, et al., 2008) and in another study done in Kwazulu-Natal by Gandhi, Moll, Sturm, et al. (2006), 39% (185) of confirmed TB cases were MDR-TB and 6% (30) XDR-TB. This data confirms the existence of the MDR and XDR-TB challenge in South Africa.

2.2 DEMOGRAPHIC PROFILE

2.2.1 AGE

TB cases predominantly occur (approximately 6 million out of 8 million) in the economically most productive 15- to 49-year-old age group (Dias-Baptista, et al., 2008). Patients in age groups older than 14 and younger than 65, were more likely to acquire MDR- TB according to Espinal, Laserson, Camacho, et al. (2001) and Kliiman, et al.(2009). A median age of 32, 6 years for MDR-TB and a mean age of 33 years in XDR-TB were found in studies in Oman and in South Africa respectively (Mohammadi, Nassor, Behlim, et al., 2008; Dheda , Shean, Zumla, et al., 2010). Other studies in South Africa found a median age of 36 years for XDR-TB (Mlambo, et al., 2008) and a median age of 35 years in a study by Gandhi et al. (2006) in Kwazulu-Natal. This shows that drug-resistant TB occurs mostly in the younger age group.

2.2.2 GENDER

Studies on MDR and XDR-TB showed a higher percentage in males (Espinal, et al., 2001; Kliiman, et al., 2009). A WHO report (2010) that looked at data from different countries showed that females worldwide had a higher likelihood of harboring MDR-TB. However, no association was seen between MDR-TB and the sex of the TB patient. In South Africa, although a higher number of male than

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eported; female TB cases were 1.2 times more than male TB cases (WHO, 2010). The study by Kliiman et al. (2009) in Estonia showed a six fold increased risk of MDR-TB in females younger than 25 years.

2.3 CLINICAL PROFILE

XDR-TB frequently follows TB or MDR-TB treatment and rates of acquisition of primarily XDR-TB differ from setting to setting (Dheda, et al., 2010; WHO, 2010). Seventy two percent of XDR-TB patients had MDR-TB in a South African study by, Dheda, et al. (2010). Kliiman et al. (2009) found that the odds of MDR-TB among the previously treated TB patients was 4.11 times (95% CI 2.77 to 6.08) than the risk of MDR-TB among patients who never had TB and a higher odds of 10.54 times (95% CI 5.97 to 6.08) among XDR-TB in the previously treated TB patients than the risk of XDR-TB among patients who never had TB. Espinal et al. (2001) showed ineffective treatment as a strong predictor of drug resistance. Studies in South Africa showed that TB not effectively treated and cured, contributes towards drug-resistant TB (Holtz, Lancaster, Laserson, et al., 2006; Mlambo, et al., 2008). Prior exposure to anti-TB drugs according to data is a well-established risk factor for drug resistance, although the contribution of previous treatment to outcomes is unclear (Cox, Ford, McDermid, et al., 2010).

It is evident from the epidemiological overlap that a high prevalence of HIV/AIDS fuels the TB epidemic; however, the literature is not consistent about HIV as a co-factor for MDR or XDR-TB (Dias-Baptista, et al., 2008; WHO, 2010). Some studies have found that MDR-TB is not more common among people infected with HIV and that HIV infection *per se* does not appear to be a predisposing factor for the development of MDR-TB (Dias-Baptista, et al., 2008). A significant association however, was shown in a WHO report (2010) for specific countries. For example in Estonia, HIV was found to be an independent predictor of XDR-TB (Kliiman et al., 2009), however other studies did not show any significant

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M/XDR-TB (Espinal, et al., 2001; Blaas, et al., ed among HIV co-infected individuals (Gandhi, et al., 2006; Migliori, et al., 2007; Farley, et al., 2011).

2.4 TREATMENT OUTCOMES

2.4.1 MDR-TB

From the data of 71 countries, the WHO reported on treatment success in 60% of patients overall and contributed low treatment success even in well-resourced settings due to a high frequency of death, default and treatment failure, as well as many cases reported without definitive outcomes (WHO, 2010). Treatment success in studies done ranged from 48% to 66%, death rates were between 7% and 12% and default rates 12% to 29% (Dias-Baptista, et al., 2008). In a study done by Brust, Gandhi, Carrara, et al. (2010) in KwaZulu-Natal, the success rate was 44%, 21% defaulted, mortality rate 18% and the failure rate was high at 17%. Previous TB treatment was a risk factor for the high treatment failure, HIV and males for default and HIV for death (Brust, et al., 2010). WHO estimated the number of MDR-TB deaths excluding those with HIV infection as 97 000. MDR-TB case fatality in HIV-negative cases was estimated at 26%. There is however very little data providing direct measurements of MDR-TB case fatality (WHO, 2010). The outcomes differed worldwide and factors contributing to poor outcomes need further exploration in different settings to plan interventions.

2.4.2 XDR-TB

XDR-TB is found to have worse and poorer clinical outcomes than MDR-TB (Migliori, et al., 2007; Jassal, et al., 2009). In Peru 46% (17) were cured, 22% (8) died and 30% (11) failed or defaulted treatment (Bonilla, et al., 2008). Successful treatment of 60% and 65% was however reported in HIV negative patients (Mitnick, et al., 2008; Sotgiu, et al., 2009). It should be noted that these studies

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ll sample size included. In another study done in (2010) a high proportion of 36% (62) died. The CDC United States reported in 2000 that 64% of patients died (Thaver, et al., 2006). The largest outbreak of XDR-TB was in KwaZulu-Natal South Africa with a mortality rate of 98% (52) amongst HIV-positive patients (Gandhi et al., 2006). However, Dheda et al. (2010) did not find HIV to be a predictor of death in XDR-TB in South Africa. Data suggests that death contributes towards the poorer outcomes and interim outcomes could be evaluated to assess the early and late impact of deaths.

In a comparative study by Kim et al. (2008) in South Korea, the default rate was found to be high (453/1407; 32%), and patients with XDR-TB had lower treatment success (29.3% vs. 46.2%; P=0.004) and higher all-cause (49.3 % vs.19.4%; P<0.001) and TB-related disease mortality (41.3% vs. 11.8%; P<0.001) than other patients with MDR-TB. The presence of XDR-TB significantly affected treatment success (odds ratio, 0.23; 95% confidence interval [CI], 0.08ï 0.64; P= 0.005), all-cause mortality (hazards ratio, 3.25; 95% CI, 1.91ï 5.53; P<0.001), and TB-related mortality (hazards ratio, 4.45; 95% CI, 2.48ï 8.00; P< 0.001) on multivariate analyses. XDR-TB was found to be the strongest predictor of treatment outcome and long term survival.

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CHAPTER 3
METHODOLOGY

The methodology for this study was selected on the basis of its aims and objectives. In this chapter the following are described: study design, setting, period, scope and research tools.

3.1 STUDY DESIGN

This was an analytical cross sectional study based on a retrospective record review conducted at Sizwe Hospital in the Gauteng Province.

3.2 STUDY SETTING

The study setting was Sizwe Hospital and all adult patient records for the period 1st of January 2008 to the 31st of December 2009 were reviewed. Sizwe Hospital is a provincial public hospital, situated in the Greater Johannesburg Metropolitan Municipal area and is the only Specialised TB Hospital for the entire Gauteng Province. The hospital has 266 beds, is responsible for the management of MDR and XDR-TB patients, and receives referrals from the six districts in the province, as indicated in figure 3.1. The six health districts of Gauteng Province are Johannesburg Metropolitan, Ekurhuleni Metropolitan, Tshwane Metropolitan, West Rand, Sedibeng and Metsweding Districts. Patients are referred back to the District clinics with organized transport for directly observed therapy (DOT) after culture conversion and followed up at the hospital outpatient department for monitoring and recording. Gauteng Province is the smallest, most densely populated province in South Africa, and has the second highest population of 11 million (almost 25% of the total population of the country).

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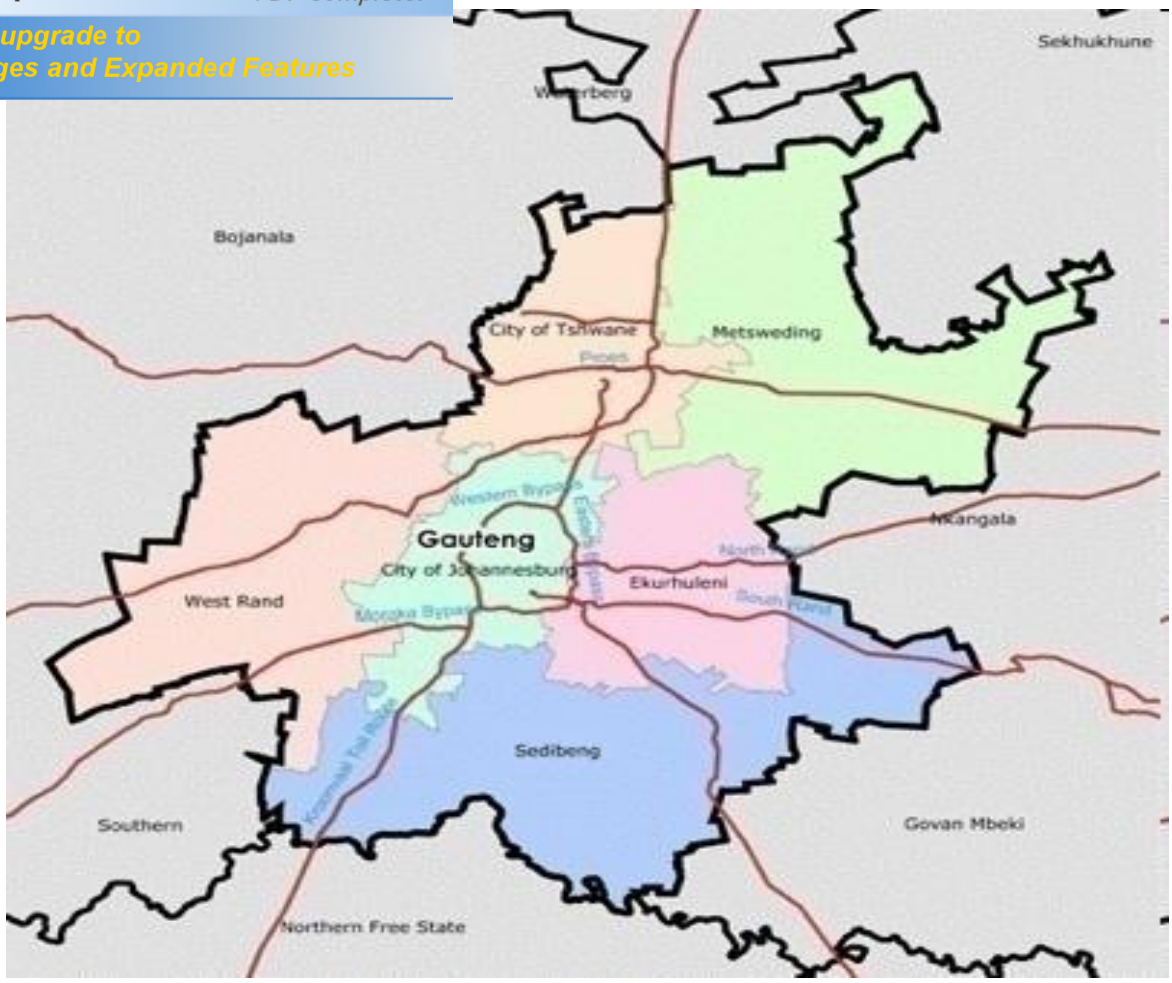

Figure 3.1: Gauteng Province

3.3 STUDY SCOPE

The study involved secondary data collected retrospective from the medical records of adult MDR and XDR-TB patients admitted in Sizwe Hospital during the study period.

3.4 STUDY PERIOD

The study reviewed the relevant records for the two year periods from 1 January 2008 to 31 December 2009.

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The study population was TB patients admitted at Sizwe Hospital. A total of 891 records for the period 1 January 2008 to 31 December 2009 were reviewed. All records were reviewed hence no specific sample size was used. Patients 15 years of age or older were included.

3.6 DATA MANAGEMENT

3.6.1 VARIABLES

The variables measured with their indicators for each objective are listed in the table below.

Table 3.1: Objectives and study variables

Objective	Variables	Indicators
To describe and compare admission trends.	Admissions.	No. of MDR and XDR-TB patients admitted.
To describe and compare demographics.	Demographic profile: Age, gender. Clinical profile: HIV, previous TB treatment	Age (in years). Gender (male/female). HIV status (pos/neg/unknown). Previous TB treatment (yes/no).
To determine changes in treatment outcomes.	Interim treatment outcome. Treatment outcome.	MDR/XDR-TB: Death, treatment default, still in hospital, transferred out and culture conversion. Treatment completed, transfer out, death, treatment default, treatment failure, still on treatment and cured.

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Data for this study was collected from the routine medical records including the drug-resistant TB registers. Data were collected for the following variables: admissions, age, gender, HIV status, previous TB treatment, interim treatment outcome and treatment outcome. The interim treatment outcome data were collected for the duration of hospitalisation and treatment outcome data was as on the 31st of May 2011. Data was extracted from the registers and entered in MS Excel spreadsheet. The tool was designed for this study (Appendix A). The data were cleaned and quality of data was ensured by going back to the records to check for missing information.

3.6.3 DATA ANALYSIS

The data were analysed using EPI-Info software version 3.4.1. The following descriptive statistics were reported:

- For numerical variables (age): Median and interquartile range was used to analyse the skewed distribution.
- For categorical variables (admissions, gender, HIV status, previous TB treatment, interim treatment outcome and treatment outcome): the data were analysed as proportions and presented in tables and graphs.

Statistical analysis to compare the two years was done using the Mann-Whitney U test for the numerical variable and the Chi-square test for the categorical variables. The statistical significance was calculated at the 95% confidence level. Logistic regression was performed to determine factors influencing death as an outcome variable.

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RATIONS

The protocol for this study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand for approval (see appendix B).

Permission to conduct the study and access to medical records at Sizwe Hospital was received from the Gauteng Department of Health and Social Development (see appendix C).

The study had no potential risk for subjects as the information for this study was based on retrospective review of routine collected hospital information. No primary data collection was done. The information was extracted anonymously on the data collection tool without patientôs identification (such as name and hospital number). A separate list coded the name of the patient and was kept by the researcher to ensure confidentiality.

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CHAPTER 4
RESULTS

The main results obtained from the analysis of the study data are described in this chapter. Admission trends, demographic characteristics, clinical profiles and treatment outcomes of MDR and XDR-TB are presented in this chapter.

4.1 ADMISSION TRENDS

The total number of adult admissions for the period 1 January 2008 to 31 December 2009 was 891. The number of patients admitted to the hospital during 2008 and 2009 was 381 and 510 respectively. The adult MDR-TB admissions accounted for 95.3% of the total admissions and XDR-TB for 4.7% as illustrated in Table 4.1.

Table 4.1: Comparison of MDR and XDR-TB admissions between 2008 and 2009.

Diagnosis	Total	2008	2009	p- value
MDR	849 (95.3%)	364 (95.5%)	485 (95.1%)	0.75
XDR	42 (4.7%)	17 (4.5%)	25 (4.9%)	
Total	891 (100%)	381 (100%)	510 (100%)	

Although there was a 33% increase in MDR-TB and a 47% increase in XDR-TB between 2008 and 2009, there was no statistical significant difference between the years (Chi-square test, p- value = 0.75).

4.2 DEMOGRAPHIC PROFILE OF PATIENTS

The demographic distribution according to gender and age between the study groups was as follows:

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Four hundred and ninety seven (55.8%) of the total admissions were males. In 2008, 56.4% (215) of admissions were males and 43.6% (166) were females, resulting in a male to female ratio of 1:0.77. In 2009, 55.3% (282) of the patients admitted were males and 44.7% (228) were females resulting in a male to female ratio of 1:0.81 as indicated in table 4.2.

Table 4.2: Gender comparison between 2008 and 2009.

Gender	Total	2008	2009	p- value
Female	394 (44.2%)	166 (43.6%)	228 (44.7%)	0.73
Male	497 (55.8%)	215 (56.4%)	282 (55.3%)	
Total	891 (100%)	381 (100%)	510 (100%)	

A slightly higher proportion was noted for female admissions in 2009 compared to 2008, but a higher proportion of males was admitted in both years, with no significant difference (Chi-square test, p-value = 0.73).

In table 4.3 below, gender in MDR and XDR-TB was compared. A higher proportion of males was also diagnosed with both MDR-TB and XDR-TB. The proportion of males with XDR-TB was slightly higher compared to males with MDR-TB (57.1% vs. 55.7 %), however, this was not statistically significant (Chi-square test, p-value = 0.85).

Table 4.3: Comparison of gender between MDR and XDR-TB.

Gender	Total	MDR	XDR	p- value
Female	394 (44.2%)	376 (44.3%)	18 (42.9%)	0.85
Male	497 (55.8%)	473 (55.7%)	24 (57.1%)	
Total	891 (100%)	849 (100%)	42 (100%)	

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The ages ranged from 15 to 79 years. The median age was 36 years overall (IQR 29-54), with a median age of 35 years (IQR 29-43.5) and 36.5 years (IQR 29-44) for 2008 and 2009 respectively (Table 4.4).

Table 4.4: Age comparison between 2008 and 2009 in years.

Age	Total	2008	2009	p-value
Median (IQR)	36 (29-54)	35 (29-43.5)	36.5 (29-44)	0.42
Minimum	15	15	15	
Maximum	79	79	76	

The median age of 36.5 was higher in 2009 than the 35 of 2008. No significant difference however, was found using the Mann Whitneyôs test (p-value= 0.42), when the median age was compared between the different years. The histogram of age in figure 4.1 shows a distribution curve with the majority of patients lying in the productive ages between 28 and 32 years. The data is skewed. The test for skewness, using DôAgostinosôtest, gave a probability of 0.001.

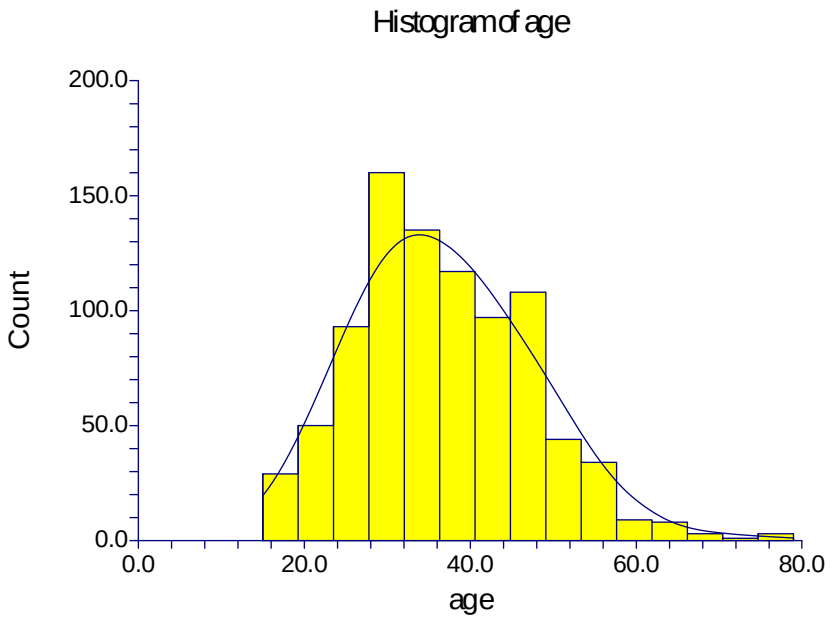

Figure 4.1: Histogram of age

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MDR and XDR-TB in table 4.5 shows a bigger
ars) compared to XDR-TB (18-62 years). The median age for MDR and XDR-TB was 36 years (IQR 29-54) and 35 years (IQR 27-40.5) respectively with no significant difference (Mann Whitney's test, p-value = 0.32).

Table 4.5: Age comparison between MDR and XDR-TB in years.

Age	Total	MDR	XDR	p-value
Median (IQR)	36 (29-54)	36 (29-44)	35(27-40.5)	0.32
Minimum	15	15	18	
Maximum	79	79	62	

4.3 CLINICAL PROFILE

4.3.1 PREVIOUS TB HISTORY

The majority of patients had a history of previous TB (75.9%), with 295 (77.4%) in 2008 and 381 (74.7%) in 2009, as reflected in table 4.6. There was an increase in the proportion of patients with no previous TB history from 22.6% to 25.3%. This difference was however, not statistically significant using the Chi-square test (p-value = 0.34).

Table 4.6: History of previous TB in the study groups.

Previous TB	Total	2008	2009	p-value
No	215 (24.1%)	86 (22.6%)	129 (25.3%)	0.34
Yes	676 (75.9%)	295 (77.4%)	381 (74.7%)	
Total	891 (100%)	381 (100%)	510 (100%)	

Six hundred and thirty six (74.9%) and 40 (95.2%) of MDR and XDR-TB patients respectively had a previous history of TB, as outlined in table 4.7. The 33% increase between 2008 and 2009 with no previous history, was not significant.

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ant association between diagnosis and previous st, p<0.01). The previous history of TB was significantly associated with XDR- TB.

Table 4.7: History of previous TB between MDR and XDR-TB.

Previous TB	Total	MDR	XDR	p-value
No	215 (24.1%)	213 (25.1%)	2 (4.8%)	p< 0.01
Yes	676 (75.9%)	636 (74.9%)	40 (95.2%)	
Total	891 (100%)	849 (100%)	42 (100%)	

Figure 4.2 below illustrates that the majority of patients had a history of previous TB with a higher proportion of XDR-TB compared to MDR-TB.

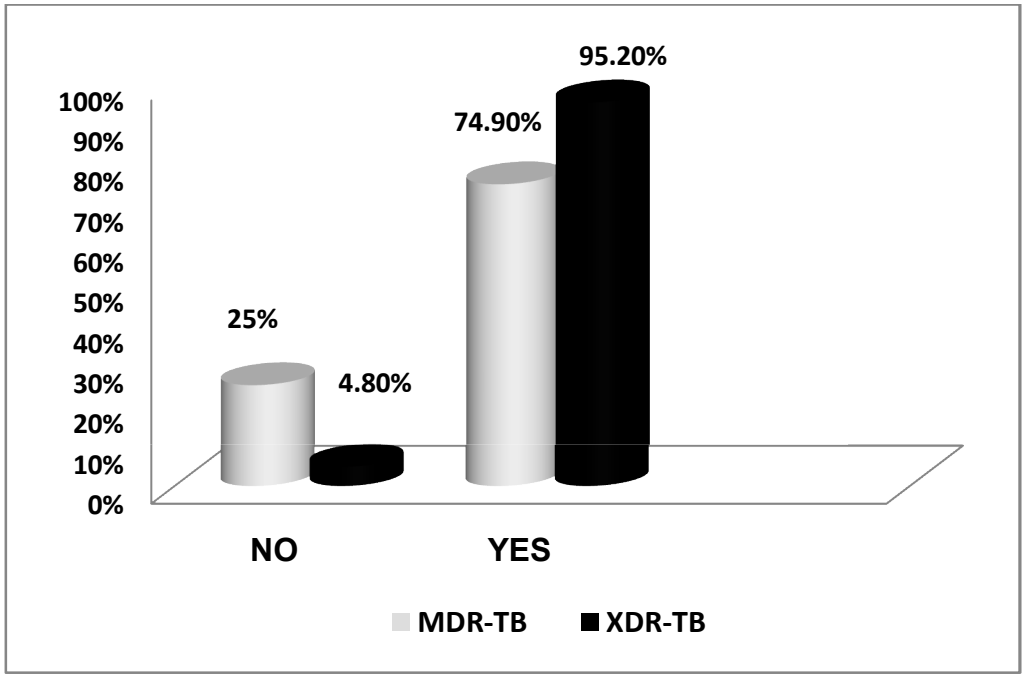

Figure 4.2: Previous history of TB in MDR and XDR-TB.

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A high proportion of 74.9% (655) of the patients were HIV positive as indicated in table 4.8. Two hundred seventy three (73.2%) of the patients were HIV positive in 2008 and 382 (76.1%) in 2009, however, there was no statistically significant difference between the years (Chi-square test, p-value =0.33).

Table 4.8: Comparison of HIV status between 2008 and 2009.

HIV status	Total	2008	2009	p-value
Negative	220 (25.1%)	100 (26.8%)	120 (23.9%)	0.33
Positive	655 (74.9%)	273 (73.2%)	382 (76.1%)	
Total	875 (100%)	373 (100%)	502 (100%)	

Table 4.9 is a summary of the HIV status in MDR and XDR-TB. A higher proportion of XDR-TB patients were HIV positive (78%) compared to the 74.7% of MDR-TB HIV positive patients. The difference was not statistically significant between the two groups (Chi-square test, p-value = 0.62).

Table 4.9: HIV status in MDR and XDR-TB.

HIV status	Total	MDR	XDR	p-value
Negative	220 (25.1%)	211 (25.3%)	9 (22.0%)	0.62
Positive	655 (74.9%)	623 (74.7%)	32 (78.0%)	
Total	875 (100%)	834 (100%)	41 (100%)	

As illustrated in table 4.10, a higher proportion of females (81.5%) compared to males (69.5%) were HIV positive, with a significant association between gender and HIV status (Chi-square test, p-value <0.0001). A positive HIV status in these patients is significantly associated with female gender.

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der.

		Female	Male	p-value
Negative	220 (25.1%)	72 (18.5%)	148 (30.5%)	<0.0001
Positive	655 (74.9%)	317 (81.5%)	338 (69.5%)	
Total	875 (100%)	389 (100%)	486 (100%)	

4.4 TREATMENT OUTCOME

4.4.1 INTERIM TREATMENT OUTCOME

Interim treatment outcomes for this study were outcomes reported for the duration of hospitalisation. Table 4.11 compares the interim treatment outcomes between 2008 and 2009 combined for MDR and XDR-TB. High culture conversion was achieved. In 2008, 308 (80.8%) had sputum culture conversion, with 46 (12.1%) deaths, 13 (3.4%) treatment defaulters, 7 (1.8%) still in hospital and 7 (1.8%) transferred out. In 2009, 391 (76.7%) culture converted, 82 (16.1%) died, 18 (3.5%) defaulted treatment, 15 (2.9%) were still in hospital and 4 (0.8%) were transferred out. Culture conversion decreased in 2009 (76.7% vs. 80.8% in 2008) mainly as a result of increased death rate (16.1% vs. 12.1%) and more patients still in hospital (2.9% vs.1.8%) during 2009. Early deaths result from late referrals. There was no significant difference in the interim treatment outcomes between the two years (Chi-square test, p-value = 0.20).

Table 4.11: Comparison of interim treatment outcomes between 2008 and 2009. (combined for MDR and XDR-TB)

Interim treatment outcome	Total	2008	2009	p-value
Culture conversion	699 (78.5%)	308 (80.8%)	391 (76.7%)	0.20
Death	128 (14.4%)	46 (12.1%)	82 (16.1%)	
Still in hospital	22 (2.5%)	7 (1.8%)	15 (2.9%)	
Treatment default	31 (3.5%)	13 (3.4%)	18 (3.5%)	

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	%)	7 (1.8%)	4 (0.8%)	
	%)	381 (100%)	510 (100%)	

The interim treatment outcomes of MDR and XDR-TB are compared in table 4.12 for the study period. The 79.2% (672) culture conversion for MDR-TB was higher compared to the 64.3% (27) of XDR-TB. The possible reasons could be that more XDR-TB patients died (26.2%, n=11) compared to the 13.8% (117) of MDR-TB patients and 4.8% (2) XDR-TB patients defaulted treatment compared to 3.4% (29) MDR-TB patients. No statistical significant difference between the interim treatment outcomes of MDR and XDR-TB was found (Chi-square test, p-value = 0.19).

Table 4.12: Interim treatment outcomes comparison between MDR and XDR-TB.

Interim treatment outcome	Total	MDR	XDR	p-value
Culture conversion	699 (78.5%)	672 (79.2%)	27 (64.3%)	0.19
Death	128 (14.4%)	117 (13.8%)	11 (26.2%)	
Still in hospital	22 (2.5%)	21 (2.5%)	1 (2.4%)	
Treatment default	31 (3.5%)	29 (3.4%)	2 (4.8%)	
Transfer out	11 (1.2%)	10 (1.2%)	1 (2.4%)	
Total	891 (100%)	849 (100%)	42 (100%)	

The interim treatment outcomes for MDR and XDR-TB in 2008 are illustrated in figures 4.3 and 4.4. Culture conversion for MDR-TB (364) was higher than XDR-TB (17) and was 81.3% (296) and 70.6% (12) respectively. The other outcomes for MDR-TB were 11.5% (42) deaths, 3.6% (13) treatment default, 1.9% (7) still in hospital and 1.7% (6) transferred out. XDR-TB patients had 23.6% (4) deaths, 5.8% (1) transfer out and no patients defaulted treatment or were sill in hospital. The results were an indication of interim treatment success achieved.

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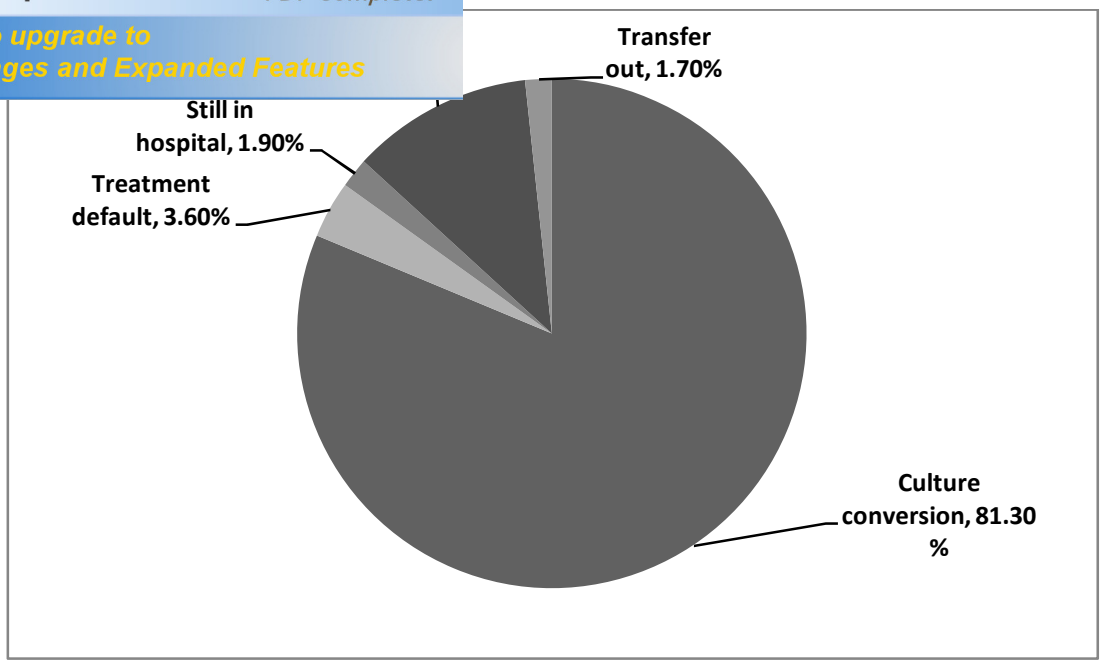

Figure 4.3: Interim outcomes for MDR-TB in 2008.

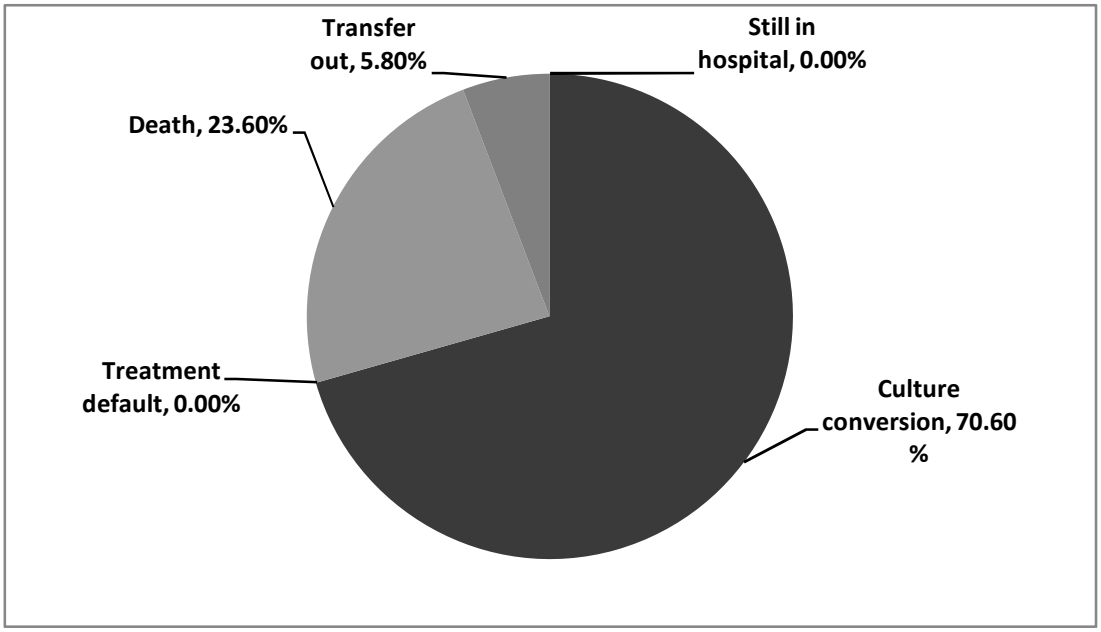

Figure 4.4: Interim outcomes for XDR-TB in 2008

Figures 4.5 and 4.6 indicate the interim treatment outcomes for MDR (485) and XDR-TB (25) in 2009. Culture conversion was 77.5% (376) and 60% (15) for

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ively. Again, culture conversion was higher in in XDR-TB, similar to the findings of 2008.

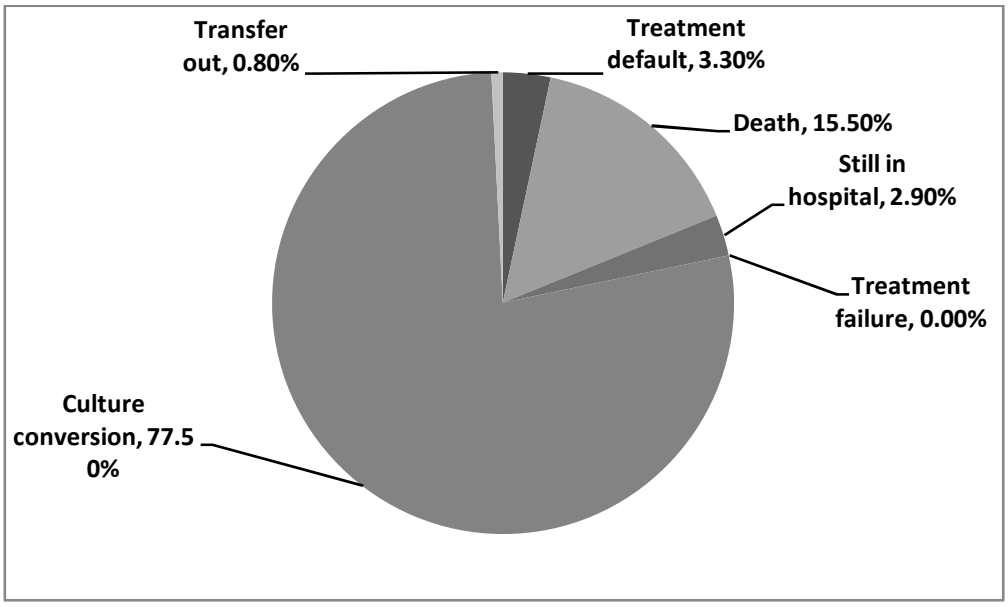

Figure 4.5: Interim treatment outcomes for MDR-TB in 2009.

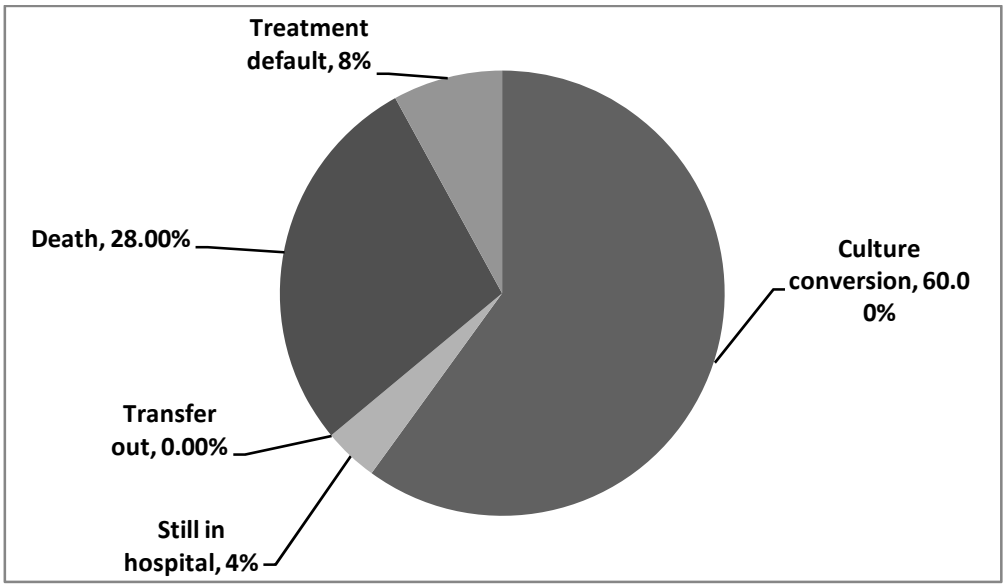

Figure 4.6: Interim treatment outcomes for XDR-TB in 2009.

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atment outcomes between HIV positive and HIV ble 4.13. Eighty four percent (185) HIV negative compared to 76.9% (504) HIV positive patients achieved culture conversion. More [15.9% (104)] HIV positive, than the 9.5% (21) HIV negative patients died. Three percent (20) and 4.1% (9) HIV positive and HIV negative patients defaulted treatment respectively. Although culture conversion is higher in the HIV negative patients and the death rate and still in hospital higher in HIV positive patients, no statistically significant difference was observed between the two groups for the study period (Chi-square test. p-value = 0.05).

Table 4.13: Comparison of interim treatment outcomes and HIV status.

Interim treatment outcome	Total	HIV negative	HIV positive	p-value
Culture conversion	689 (78.7%)	185 (84.1%)	504 (76.9%)	0.05
Death	125 (14.3%)	21 (9.5%)	104 (15.9%)	
Still in hospital	22 (2.5%)	2 (0.9%)	20 (3.1%)	
Treatment default	29 (3.3%)	9 (4.1%)	20 (3.1%)	
Transfer out	10 (1.1%)	3 (1.4%)	7 (1.1%)	
Total	875 (100%)	220 (100%)	655 (100%)	

The interim treatment outcomes for HIV positive MDR and XDR -TB patients is summarised in table 4.14. Seventy eight percent (486) HIV positive MDR-TB patients culture converted compared to 56.3% (18) HIV positive XDR-TB patients. Although higher culture conversion was achieved in HIV positive MDR-TB patients, deaths (31.3%), treatment default (6.3%) and still in hospital (3.1%) were higher in HIV positive XDR -TB patients. The difference in interim treatment outcomes between HIV positive MDR and XDR- TB HIV positive patients was not significant (Chi-square test, p-value = 0.05).

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outcomes in HIV positive patients compared between MDR and XDR-TB.

Interim treatment outcome	Total	MDR	XDR	p-value
Culture conversion	504 (76.9%)	486 (78%)	18 (56.3%)	0.05
Death	104 (15.9%)	94 (15.1%)	10 (31.3%)	
Still in hospital	20 (3.1%)	19 (3%)	1 (3.1%)	
Treatment default	20 (3.1%)	18 (2.9%)	2 (6.3%)	
Transfer out	7 (1.1%)	6 (1.0%)	1 (3.1%)	
Total	655 (100%)	623 (100%)	32 (100%)	

4.4.2 TREATMENT OUTCOME

Treatment outcome for this study was for all adult MDR and XDR-TB patients registered in 2008 and 2009 as at the end of May 2011. Cure was achieved only when a patient had five consecutive monthly negative sputum culture results documented in the last twelve months. For the total study population, a low cure rate of 2.4% (21) was achieved, with treatment completion of 25.7% (229). The high number of patients still on treatment [21.5%, (n=192)], as a result of the long period of treatment for 18- 24 months, contributed to the low success rate of 28.1% (cure and completed). Deaths were 22% (196) and treatment default 20.8% (158). Treatment failure was low at 3.1% (28). A comparison between the treatment outcomes for 2008 and 2009 is illustrated in table 4.15.

Cure was low at 2.1% (8) and 2.5% (13) in 2008 and 2009 respectively. Treatment completion was higher at 42% (160) in 2008 than the 13.5% (69) in 2009. The treatment success rate (cure and completion) therefore, was 44.1% in 2008 and 16% in 2009. Nineteen percent (74) died in 2008 and 23. 9% (122) died in 2009. Treatment failure was low, 2.6 % (10) and 3.5% (18) in 2008 and

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tment default of 22.6% (86) in 2008 and 19.4 % More deaths and more patients still on treatment were in the 2009 cohort, and this was statistically significant (Chi-square test, p-value <0.01).

Table 4.15: Comparison of treatment outcomes between 2008 and 2009.

Treatment outcome	Total	2008	2009	p-value
Cure	21 (2.4%)	8 (2.1%)	13 (2.5%)	<0.01
Death	196 (22%)	74 (19.4%)	122 (23.9%)	
Still on treatment	192 (21.5%)	22 (5.8%)	170 (33.3%)	
Treatment completed	229 (25.7%)	160 (42%)	69 (13.5%)	
Treatment default	185 (20.8%)	86 (22.6%)	99 (19.4%)	
Treatment failure	28 (3.1%)	10 (2.6%)	18 (3.5%)	
Transfer out	40 (4.5%)	21 (5.5%)	19 (3.7%)	
Total	891 (100%)	381 (100%)	510 (100%)	

Table 4.16 compares the treatment outcomes between HIV positive and HIV negative patients. Four percent (9) HIV negative patients were cured compared to 1, 8% (12) HIV positive patients. Higher cure and treatment completion rates were achieved in the HIV negative patients. Deaths and treatment default was higher in the HIV positive patients, with no significant difference. (Chi-square test, p-value = 0.05)`

Table 4.16: Treatment outcomes compared with HIV status.

Treatment outcome	Total	HIV negative	HIV positive	p-value
Cure	21 (2.4%)	9 (4.1%)	12 (1.8%)	0.05
Death	192 (21.9%)	33 (15.0%)	159 (24.3%)	
Still on treatment	190 (21.7%)	54 (24.5%)	136 (20.8%)	

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	25.5%)	61 (27.7%)	162 (24.7%)	
	20.9%)	44 (20%)	139 (21.2%)	
Treatment failure	28 (3.2%)	7 (3.2%)	21 (3.2%)	
Transfer out	38 (4.3%)	12 (5.5%)	26 (4.0%)	
Total	875 (100%)	220 (100%)	655 (100%)	

Treatment outcomes for male and female are shown in table 4.17. The deaths, treatment completion and transfer outs were slightly higher in females and still on treatment and treatment default were higher in males. The difference was not statistically significant (Chi square test, p-value =0.58).

Table 4.17: Comparison of treatment outcomes and gender.

Treatment outcome	Total	Female	Male	p-value
Cure	21 (2.4%)	9 (2.3%)	12 (2.4%)	0.58
Death	196 (22%)	91 (23.1%)	105 (21.1%)	
Still on treatment	192 (21.5%)	74 (18.8%)	118 (23.7%)	
Treatment completed	229 (25.7%)	107 (27.2%)	122 (24.5)	
Treatment default	185 (20.8%)	80 (20.3%)	105 (21.1%)	
Treatment failure	28 (3.1%)	12 (3%)	16 (3.2%)	
Transfer out	40 (4.5%)	21 (5.3%)	19 (3.8%)	
Total	891 (100%)	394 (100%)	497 (100%)	

As shown in table 4.18, the treatment outcomes for MDR-TB were 2.5% (21) cure, 26.7% (227) treatment completed, 21.3% (181) deaths, 21% (178) still on treatment, treatment default 21 % (178), treatment failure 3.2 % (27) and 4.4% (37) were transfer out.

The treatment outcomes for XDR-TB were 0% cure, 4.8% (2) treatment completed, 35.7% (15) deaths, 33.3% (14) still on treatment, 16.7% (7) treatment default, 2.4% (1) treatment failure and 7.1% (3) transfer out. Cure, treatment

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d treatment failures were higher in MDR-TB. The
were, however, higher in XDR-TB compared to MDR-TB and this was statistically significant (Chi-square test, p-value<0.01). Death and still on treatment was significantly associated with XDR-TB.

Table 4.18: Treatment outcomes comparison in MDR and XDR-TB.

Treatment outcome	Total	MDR	XDR	p-value
Cure	21 (2.4%)	21 (2.5%)	0 (0%)	<0.01
Death	196 (22%)	181 (21.3%)	15 (35.7%)	
Still on treatment	192 (21.5%)	178 (21%)	14 (33.3%)	
Treatment completed	229 (25.7%)	227 (26.7%)	2 (4.8%)	
Treatment default	185 (20.8%)	178 (21%)	7 (16.7%)	
Treatment failure	28 (3.1%)	27 (3.2%)	1 (2.4%)	
Transfer out	40 (4.5%)	37 (4.4%)	3 (7.1%)	
Total	891 (100%)	849 (100%)	42 (100%)	

The treatment outcomes for MDR-TB and XDR-TB in 2008 are illustrated in figures 4.7 and 4.8 respectively. MDR-TB outcomes were as follows: 2.2% (8) cure, 43.4% (158) treatment completed, 18.4% (67) deaths, 23.4% (85) treatment default, 2.8% (10) treatment failure, 4.9% (18) transfer out and 4.9% (18) still on treatment. No XDR-TB patients were cured. Other outcomes were 11.8% (2) treatment completed, 41.2% (7) death, 5.9% (1) treatment default, 17.6% (3) transfer out and 23.5% (4) still on treatment. The successful treatment completion rate achieved for MDR-TB was 45.6% (166) and low for of XDR-TB [11.8% (n=2)]. The death and defaulter rates were high for MDR and XDR-TB.

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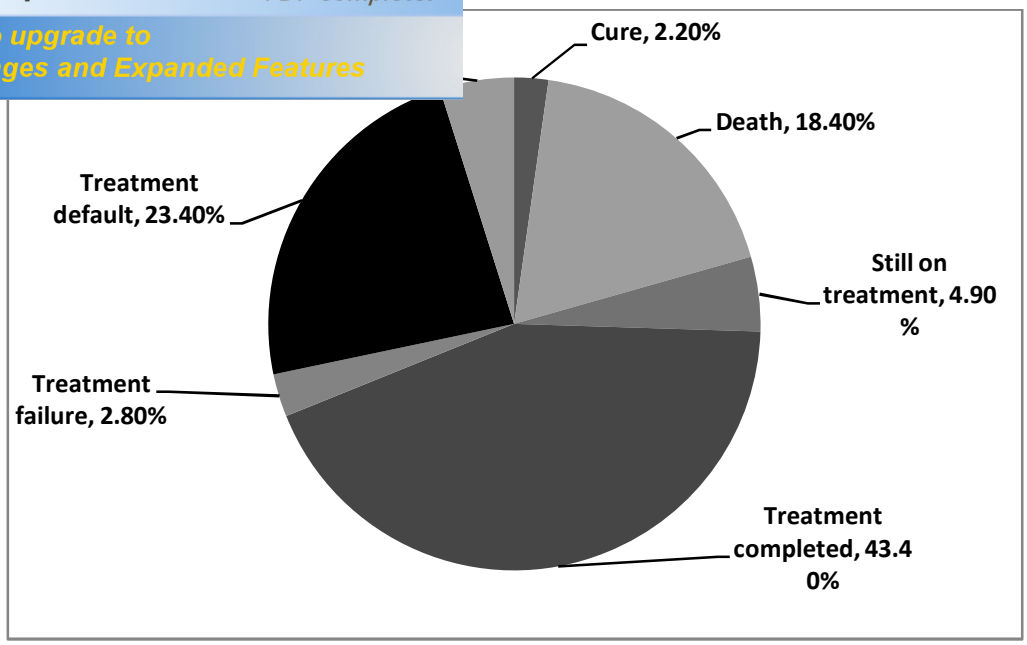

Figure 4.7 MDR-TB treatment outcomes 2008.

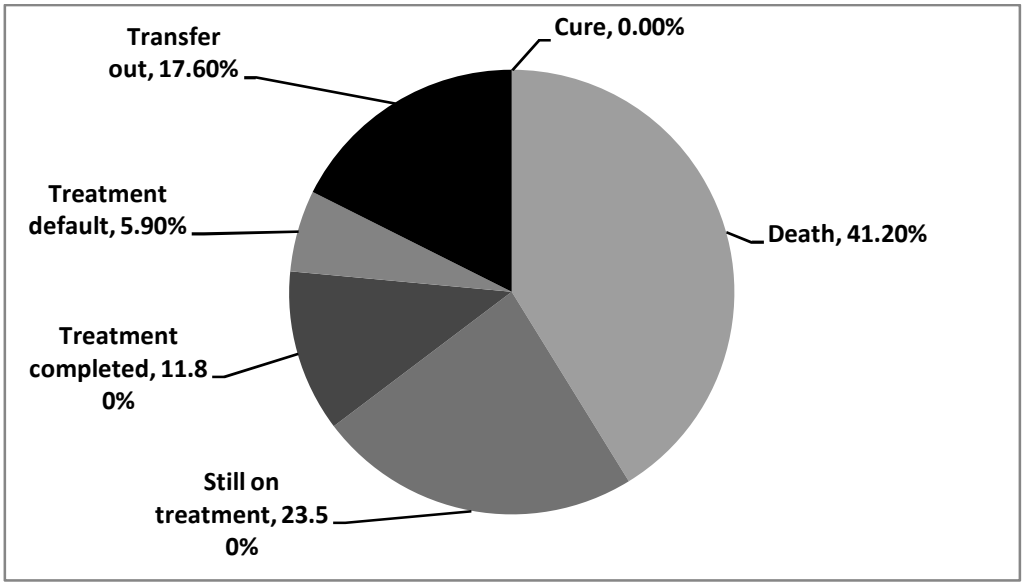

Figure 4.8 XDR-TB treatment outcomes 2008.

The treatment outcomes for MDR-TB and XDR-TB in 2009 are shown in figures 4.9 and 4.10 respectively. Thirty three percent (160) MDR-TB patients and 40% (10) XDR-TB patients were still on treatment due to the duration of treatment.

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and only 2.7% (13) MDR-TB patients were cured, ..2% (69) MDR-TB patients completed treatment. Other outcomes for MDR-TB were 23.5% (114) deaths, 19.2% (93) treatment default, 3.9% (19) transfer out and 3.9% (19) treatment failure. 24% (6) of XDR-TB patients defaulted treatment, 32% (8) died and 45 (1) failed treatment.

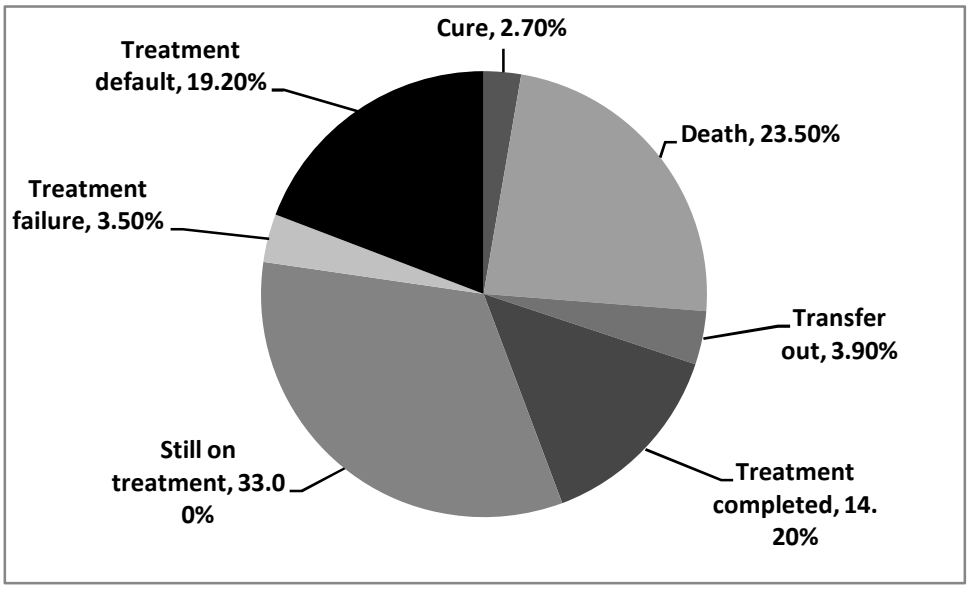

Figure 4.9 MDR-TB treatment outcomes 2009.

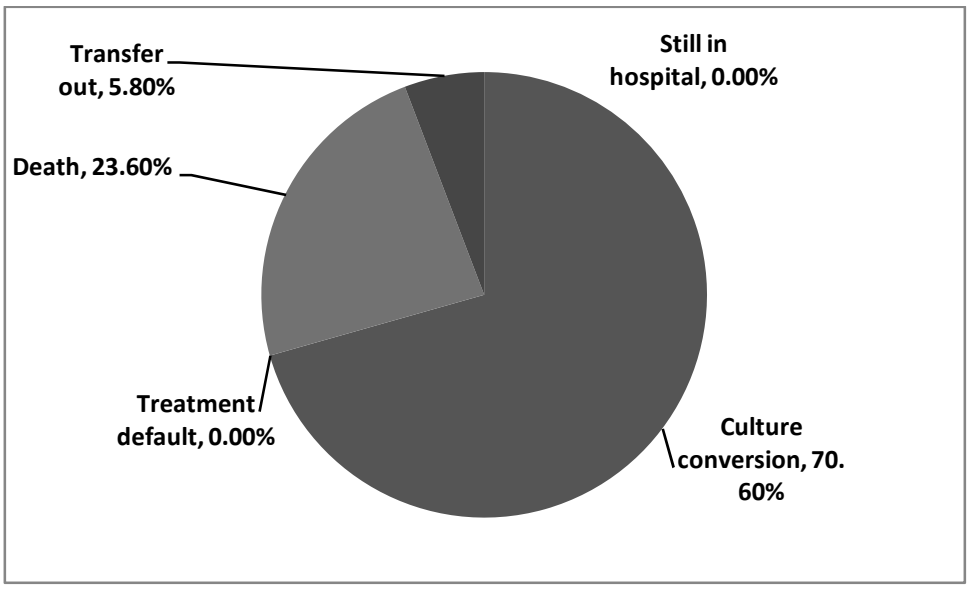

Figure 4.10 XDR-TB treatment outcomes 2009.

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MDR and XDR-TB HIV positive patients are
e HIV positive patients, the MDR-TB treatment outcomes were as follows: 1.9% (12) was cured, 26% (162) completed treatment, 23.3% (145) died, 20.2% (126) were still on treatment, 21.5% (134) defaulted treatment, 3.2% (20) failed treatment and 3.9% (24) were transferred out. In the HIV positive XDR-TB patients, none were cured or completed treatment. Other treatment outcomes were 43.8% (14) deaths, 31.3% (10) still on treatment, 15.6% (5) treatment default, 3.1% (1) treatment failure and 6.3% (2) transfer out.

Higher cure and treatment completion was achieved in MDR-TB HIV positive patients compared to XDR-TB HIV patients, despite the higher treatment default in MDR-TB HIV positive patients. Deaths and still on treatment were higher amongst XDR-TB HIV patients, with statistical significance (Chi-square test, p-value < 0.01). Death and still on treatment was significantly associated with HIV positive XDR-TB patients.

Table 4.19: Treatment outcomes comparison in HIV positive patients between MDR and XDR-TB.

Treatment outcome	Total	MDR	XDR	p-value
Cure	12 (1.8%)	12 (1.9%)	0 (0.0%)	< 0.01
Death	159 (24.3%)	145 (23.3%)	14 (43.8%)	
Still on treatment	136 (20.8%)	126 (20.2%)	10 (31.3%)	
Treatment completed	162 (24.7%)	162 (26.0%)	0 (0.0%)	
Treatment default	139 (21.2%)	134 (21.5%)	5 (15.6%)	
Treatment failure	21 (3.2%)	20 (3.2%)	1 (3.1%)	
Transfer out	26 (4.0%)	24 (3.9%)	2 (6.3%)	
Total	655 (100%)	623 (100%)	32 (100%)	

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o determine the factors influencing death as an
n table 4.20. The following variables were tested for the model: age, gender, diagnosis, HIV status and previous history of TB. The model was significant for age ($p<0.02$), diagnosis ($p<0.03$) and HIV status ($p< 0.04$). Age, diagnosis and HIV were significantly associated with death ($p<0.05$). The adjusted odds ratio was 0.15 (95% CI of 0.07 to 0.30) which was statistically significant (p-value<0.01).

Table 4.20: Logistic regression for factors influencing death as an outcome variable.

Term omitted	Odds ratio	95% Confidence Interval	p-value
Age	1.02	1.00-1.03	<0.01
Diagnosis	0.46	0.23-0.89	0.02
Gender	1.16	0.83-1.62	0.37
HIV	0.55	0.36-0.83	0.03
Previous TB	1.14	0.78-1.66	0.49

The logistic regression performed for MDR-TB patients gave an odds ratio of 0.12 (95% CI 0.05-0.24; $p<0.01$) which was statistically significant. However, it was not possible to perform a logistic regression separately for XDR-TB patients due to the small number.

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CHAPTER 5
DISCUSSION

In this chapter, the results obtained from the analysis of the data are discussed with reference to other published studies. The limitations of the study are listed. Conclusions are drawn and relevant recommendations and suggestions for future research are made based on the findings of the study.

5.1 INTRODUCTION

This study was done in order to describe and compare the admission trends and treatment outcomes of MDR and XDR-TB at Sizwe Hospital in Gauteng Province during the study period 1st of January 2008 to 31st of December 2009. Limited studies have been conducted on MDR and XDR-TB treatment outcomes in South Africa and risk factors such as the impact of HIV and outcomes of MDR-TB treatment, have not been well described (Farley, et al., 2011). This information is needed to plan and strengthen the management of MDR and XDR-TB.

5.2 ADMISSION TRENDS

Out of the total study population of 891 admissions, 95.3% were MDR-TB. There was an increase in both MDR-TB and XDR-TB admissions between 2008 and 2009. Previous studies have cited factors contributing to an increase in MDR-TB as poverty, poor drug compliance and HIV co-infection (Thaver, et al., 2006). The reasons for increased numbers of XDR-TB could presumably be the high number of MDR-TB defaulters, high HIV prevalence, inadequate regimens, non adherence to TB treatment and delay in case detection (Mlambo, et al., 2008; Jassal & Bishai, 2009). Increasing numbers of MDR and XDR-TB indicate a failing TB control programme and necessitate a comprehensive, integrated and universal approach to address poverty, HIV prevention and care as well as early

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order to reverse the current trends of MDR and

5.3 DEMOGRAPHIC PROFILE OF PATIENTS

5.3.1 GENDER

The higher proportion of male admissions found in this study for both study groups, correlated with the findings of other studies (Espinal et al., 2001; Kliiman, et al., 2009). The proportion of MDR-TB males (55.7%) in this study was much lower than 65.4% found in a previous study done by Njaramba and Naidoo (2007), indicating an increase in the proportion of females with MDR-TB over the years. However, there was no significant difference between genders in terms of admissions to hospital.

5.3.2 AGE

The majority of patients were in the age group of 28-32 years in this study; this was lower than the 35-54 age group in the study by Kliiman, et al. (2009) in Estonia but within the age group of 15-44 years in a study by Anderson, Laurenson, Blatchford, et al. (2009) in Scotland. The median age for MDR-TB of 36 years correlated with another South African study by Farley, et al. (2011), but was higher than the finding in the study by Mohammadi et al. (2008) of 32.6 years in Oman. A median age of 35 years for XDR-TB was also shown by another study by Gandhi et al. (2006) in KwaZulu-Natal and was lower than the 36 years shown earlier in South Africa by Mlambo et al. (2008) but higher than the median age in another South African study (Dheda, et al., 2010). Although MDR and XDR-TB affects all age groups, the majority are in the productive age group. This has a huge socio-economic impact on families.

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5.4.1 PREVIOUS TB HISTORY

The analysis of study data showed that the majority of patients previously received TB treatment (75.9%) which indicates that ineffective TB management contribute towards drug resistance. Previous treatment was found to be a predictor of resistance in a study by Frieden, Sterling, Pablos-Mendez et al. (1993). A higher proportion of patients with XDR-TB (95.2%) than MDR-TB (74.9%) had a previous history and XDR-TB was significantly ($P<0.01$) associated with previous TB treatment in this study. Kliman, et al. (2009) found a higher association between XDR-TB and previously treated patients than for MDR-TB. Effective TB and MDR-TB management is therefore critical to prevent XDR-TB as studies in SA showed that TB not effectively treated and cured contributes towards development of drug resistance (Holtz, et al., 2006; Mlambo, et al., 2008).

TB drug resistance occurs in patients as a result of inadequate therapy (acquired resistance) or by infection with a drug-resistant strain (primary resistance) (Andrews, Shah, Gandhi, et al., 2007). Although there was an insignificant decrease in the history of previous TB treatment, the increase in primary resistance is a concern and indicates transmission of the disease in the community, which could be as a result of late diagnosis. Health education and strategies to improve infection control in the community need urgent attention.

5.4.2 HIV STATUS

A high proportion (74.9%) of the study population was HIV infected with an increase in the proportion of HIV infected patients for the study period. The HIV prevalence differs from country to country. Previous studies done in South Africa showed 80% co-infection rate (Brust, et al., 2011), 47% in a study by Dheda, et

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s tested in a study conducted in KwaZulu-Natal o the 0% in a study done by Mitnick et al. (2008) in Peru. The findings of HIV as an independent risk factor are not consistent. Kliiman, et al. (2009) found HIV as an independent risk factor for XDR-TB, whereas other studies did not find a significant association between HIV and drug resistance (Espinal, et al., 2001; Blaas et al., 2008). A significant association ($p<0.0001$) between HIV positive status and female gender (81%) was found in this study. The high HIV proportion found among MDR and XDR-TB patients in this study necessitates integration of treatment for drug-resistant TB and HIV/AIDS and justifies the current hospital policy for all HIV positive patients to receive antiretroviral therapy (ARV).

5.5 TREATMENT OUTCOME

5.5.1 INTERIM TREATMENT OUTCOME

High sputum culture conversion was achieved where patients converted from positive to negative in hospital, a very important finding indicating early success, similar to findings in other studies in South Africa and Southern Africa (Holtz, Sternberg, Kammerer, et al., 2006; Seung, Omatayo, Keshavjee, et al., 2009; Brust, Lygizos, Chaiyachati, et al., 2011). The MDR-TB culture conversion rate of 79.2% is much higher than the 41.9% achieved in a previous study done in the hospital by Njaramba, et al. (2007). Culture conversion in XDR-TB of 64.3% correlates with a 67% culture conversion rate achieved in a study by Mitnick et al. (2008) in Peru. However, a lower culture conversion for XDR-TB (19%) was reported by Dheda et al. (2010) in South Africa. A higher conversion rate as shown at Sizwe Hospital might have been due to the introduction of moxifloxacin. Similar to the study by Brust et al. (2011) in Tugela Ferry, KwaZulu-Natal, no difference was found in the culture conversion between HIV negative and HIV positive patients and the status therefore should have no impact on interim treatment outcomes.

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ant interim indicator of treatment success in TB errals of patients are among the reasons for early deaths in hospital. Therefore earlier detection is needed to improve outcomes through the use of new rapid diagnostic tests. Low treatment default rate in the intensive treatment phase could be as a result of the in hospital monitoring where comprehensive care, treatment under supervision and support is effectively provided.

5.5.2 TREATMENT OUTCOME

5.5.2.1 CURE AND TREATMENT COMPLETION

Patients are discharged from hospital to their respective clinics and provided with hospital transport. The clinics are then responsible for the continuation of treatment, monitoring of progress and transport arrangements for patients follow up at the hospital. Patient culture results from the clinics are needed for recording thereof in the hospital drug resistant register to report treatment outcomes.

The measure of treatment success is cure and treatment completion according to National Policy. Cure is achieved when five consecutive negative cultures are obtained in the last year of treatment. Treatment completed lack bacteriologic results of sputum culture and therefore does not meet the definition of cure. The cure rates were low compared to other studies (Dias-Baptista, et al., 2008; Brust, et al., 2010). This could have been due to unavailable sputum culture results from the clinics as a result of system failure. Culture results were entered into the hospital register as patients are followed up at the hospital. The decrease in treatment completion in 2009 was mainly as a result of the significant (p-value<0.01) increase in deaths and the high proportion of patients still on treatment in 2009. Because of the long period of treatment with at least 18 months following culture conversion, it was expected that some 2009 patients

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result of data collection as on the 31st of May

The successful treatment completion rate (cure and treatment completed as a proportion of the total cases) of 45.6% achieved for MDR-TB in 2008 was higher than the 11.8% for XDR-TB in 2008 and MDR-TB (16.9%) in 2009. A similar finding of 44% MDR-TB success was reported by Brust et al. (2010) from a study done in KwaZulu-Natal. Generally studies reported poor treatment outcomes for MDR-TB (Schaaf, et al., 2001; Dias -Baptista, et al., 2008) and worse outcomes in XDR-TB (Gandhi, et al., 2006; Migliori, et al., 2007; Kim, et al., 2008; Jassal, et al., 2009). MDR-TB was not found to be a predictor of poor treatment outcome (Solomon, Periman, Friedman, et al., 1995), however, XDR-TB was found to be a strong predictor of poor treatment outcome (Kim, et al., 2008). The WHO reported 60% success in MDR-TB and stated reasons for poor success as deaths, defaulters and treatment failure (WHO, 2010).

5.5.2.2 TREATMENT DEFAULT

One out of five patients defaulted treatment. Factors associated with treatment default revealed in the study by Holtz et al. (2006) were, the use of alcohol, smoking of marijuana or mandrax, being born outside of South Africa, spending time in prison during treatment, not owning a radio, having an unsatisfactory opinion of the HCWôs and changing residence during treatment. These factors could have contributed to the high default rate in this study. Patients, however, may have died as Holtz et al. (2006) found in their study, a significant mortality amongst MDR-TB patients thought to have defaulted. Treatment default of XDR-TB patients (16.7%) was lower than the 32% reported in the study by Kim, et al. (2008) in South Korea and this could be due to the fact that patients are hospitalised longer. Of concern is the increased defaulter rate from 3.5% to 20.8% after discharge from hospital. This is probably due to the long duration of treatment, but also indicates a failing community DOT system which is a major

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of the low success rate of 44% following the to the 78.5% culture conversion rate achieved during hospitalisation.

The findings of the study have severe implications regarding the implementation of the National Decentralization Policy (NDOH, 2011). The purpose of the policy is to provide community MDR-TB care the policy provides for smear negative patients to be treated in the community and for shorter hospital stay until smear conversion. Admission of all MDR and XDR-TB cases until culture conversion is current hospital policy. Management of MDR-TB in decentralized sites is also recommended. Implementation within a challenged system might result in worse outcomes in future

5.5.5.3 MORTALITY

The deaths were slightly higher in females, but gender had no impact on treatment outcome. Mortality in this study was significantly higher (p-value<0.01) in XDR-TB compared to MDR-TB (35.7% vs. 21.35%) and correlated with the finding of 36% deaths in the study by Dheda et al. (2010) in South Africa. HIV and age were other risk factors in this study significantly associated (p-value<0.05) with death. HIV, however, was not shown to be a predictor of death in XDR-TB in the study by Dheda et al. (2010). Although the number of deaths in this study was higher in HIV positive patients, no significant difference (p-value=0.05) was noted in treatment outcomes similar to the study by Dheda et al. (2010).

5.6 LIMITATIONS OF THE STUDY

The following limitations experienced in conducting this study were:

- Culture results not available from the clinics resulted in defining patients as treatment completed and not cured. This seems to be a major problem that

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available, as a result of treatment continued for longer than two years for some patients in 2008 and for many of the patients who started therapy in 2009 due to the fact that they were still on treatment at the time of data collection as on 31st May 2011, limited comparative analysis between the two years for treatment outcomes.

5.8 CONCLUSIONS

The main conclusions from the study are as follows:

- The co-infection rate is high and warrants comprehensive integrated HIV/AIDS care.
- The high proportion of patients with previous TB reflects ineffective TB management and non adherence to treatment in the community.
- High culture conversion is an indication of early treatment success achieved with in hospital care.
- Low treatment success following discharge has severe implications for a decentralized approach within a challenged system.
- High default and death rates might indicate a failing community TB control programme.

5.8 RECOMMENDATIONS

5.8.1 FOLLOW-UP

In line with findings documented earlier, the following recommendations are put forward to improve effective management and control of MDR and XDR-TB and to improve outcomes in future. Corrective measures are needed to improve the system failure to collect and record culture results at the clinics. The electronic drug register to link with the laboratory for culture results and to provide treatment outcome results. These results to be utilized as a management tool for

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rug-resistant TB. Data collection tool to be tion of data to assist with treatment outcome analysis. A comprehensive and integrated approach to combat MDR and XDR-TB is essential, which include increased awareness and education, integrated HIV/TB care and support, the provision of ARV, new technology rapid testing for early diagnosis, social support and patients follow up at clinics following discharge. The TB control programme needs to be strengthened from early detection to case holding, to prevent further drug resistance. Community infection control practices needs to be developed through health education. Hospitalisation until culture conversion is recommended to sustain early success as well as hospital follow up visits until systems are in place. Specialized outreach, training and support are recommended to strengthen and ensure community MDR-TB care following discharge. Availability of drugs including ARVs and DOT care is requirements for community care.

It is evident that systems need to be put in place to improve strengthen community care and support to improve on treatment outcomes.

5.8.2 FUTURE RESEARCH AND DISSEMENATION

Based on findings of this study, the researcher would like to suggest the following future studies:

(a) There is a need to conduct a study to identify risk factors associated with defaulting of treatment.

(b) A follow up study is needed after treatment completion of the 2009 cohort for comparative analysis.

(c) Research is needed to further explore and identify risk factors contributing to the high mortality rate.

The findings will be communicated through a formal presentation to the hospital staff and the Provincial TB Control Programme, the National Department of

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B hospitals in South Africa to assist with future

e presented in a local conference and published in a peer review.

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: DATA COLLECTION TOOL

DATA COLLECTION TOOL

Year	Number	Gender	Age	Previous TB	Diagnosis	HIV status	Interim outcome	Treatment outcome

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HICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Maria Cornelia Louw

CLEARANCE CERTIFICATE	M110807
PROJECT	Admissions Trends and Treatment Outcomes of Multi-Drug-Resistant (MDR-TB) and Extensively Drug Resistant Tuberculosis (XDR-TB) at Sizwe Hospital in Gauteng
INVESTIGATORS	Dr Maria Cornelia Louw.
DEPARTMENT	School o Public Health
DATE CONSIDERED	26/08/2011
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 26/08/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Professor Shan Naidoo

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 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...

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C: LETTERS OF APPROVAL

Appendix C

health and social development
Department: Health and Social Development
GAUTENG PROVINCE

To	:	Dr. P. Mazamisa Chief Director: TBCP
From	:	Dr. M.C. Louw CEO: Sizwe Hospital
Date	:	14 February 2011
RE	:	Approval for research

I hereby request approval to conduct research at Sizwe Hospital. The research will be towards my MPH hospital management. To assist in planning and management of MDR/XDR-TB resources, my research topic will be on admission trends, health outcomes and selected expenditure patterns.

I will proceed with my formal application to Mrs. Le Roux for final approval by the HOD and I will apply for WITS ethical approval before conducting the research.

Dr. M.C. Louw
CEO: Sizwe Hospital

GAUTENG HEALTH DEPARTMENT
Sizwe Hospital
Private Bag X2
Sandringham
2131
DR. M. C. LOUW
Chief Executive Officer
Date: 14/02/2011

Approved/ not approved/ approved as amended

Dr. P. Mazamisa

Director: Hospital Services
Date 21/02/2011

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Appendix C

CONDITIONS OF APPROVAL OF A RESEARCH STUDY PROPOSAL

health and social development
Department: Health and Social Development
GAUTENG PROVINCE

Vision of the Department

"To be the best provider of quality health and social services to the people in Gauteng"

POLICY, PLANNING AND RESEARCH (PPR)
Enquiries: Dr B Ikalafeng
Tel: +2711 355 3500
Fax: +2711 355 3675 Email: Bridget.Ikalafeng@gauteng.gov.za

CONTACT DETAILS OF THE RESEARCHER	
Date	21 October 2011
Contact number	N/A
Email	N/A
Researcher /Principal investigator (PI)	Dr M C Louw
Supervisor	Prof Naidoo
Institution	University of the Witwatersrand
Research title	Admission trends and treatment outcomes of MDR and XDR-TB patients at Sizwe hospital in Gauteng Province

This approval is granted only for a research proposal submitted to GDHSD by Dr M C Louw entitled "Admission trends and treatment outcomes of MDR and XDR-TB patients at Sizwe hospital in Gauteng Province."

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Aim

To describe and compare the admission trends and treatment outcomes of MDR and XDR-TB patients at Sizwe hospital in Gauteng Province, for the period January 2008 to December 2009.

Objectives

- To describe and compare admission trends for MDR and XDR-TB in Sizwe hospital for the study period January 2008 to December 2009.
- To describe and compare demographics of these patients between the periods January to December 2008 and January to December 2009.
- To determine changes in treatment outcomes for these patients for the study period.

METHODS

An analytical cross sectional study will be conducted at Sizwe hospital. Approximately 1000 adults (≥15 years) MDR and XDR patient records will be drawn and information for the 2 years will be extracted from the medical records and drug-resistant registers. Excel and Epi-info will be used to record and analyze the data respectively. The variables: admissions, demographic profile, clinical profile and treatment outcomes, will be analyzed through descriptive statistics and statistical tests will be used for the comparison analysis.

REVIEWER'S FINAL CONCLUSION

This study is recommended; it will strengthen management and planning for drug-resistant TB and may be useful for hospital management, Provincial and National Department of Health as well as other specialized TB hospitals in SA.

Reviewed and Recommended by

Dr Bridget Ikalafeng

Date: 2011/10/26

Approved/ ~~not approved by~~

S. le Roux, Director PPR

Date: 31/10/2011

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Faculty of Sciences
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Reference: Mrs Mathikhui Moshabesha
Email: Mathikhui.moshabesha@wits.ac.za
11 July 2011
Person No: 403876
TAA

Dr Maria Cornelia Louw
P.O. Box 203
Meyerton
South Africa
1960

Dear Dr Louw

Master of Public Health (Hospital Management): Approval of change of title

We have pleasure in advising that your proposal entitled "Admission trends and treatment outcomes of MDR and XDR - TB patients at Sizwe Hospital in Gauteng Province". Please note that any changes to this title have to be endorsed by the Faculty's Higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences