PREVALENCE OF MULTI-DRUG RESISTANT TUBERCULOSIS AND THE ASSOCIATED RISK FACTORS AT A TUBERCULOSIS OUTPATIENT FACILITY IN DURBAN, SOUTH AFRICA

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BY

RENU GAJEE

SUPERVISOR: Dr Stephen Knight

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SUMMARY

Introduction

Tuberculosis (TB) is a major cause of death worldwide. Control of Tuberculosis is a serious challenge to global health. A new and potentially devastating threat to TB control is the emergence of multi-drug resistant TB (MDR-TB). South Africa was ranked fourth among the countries with the highest number of confirmed MDR-TB cases.

Aim

The aim was to investigate the annual MDR-TB prevalence and associated risk factors for MDR-TB from 2001 to 2007 at the Prince Cyril Zulu Communicable Disease Centre. To investigate previous TB treatment duration, previous TB treatment outcome, and duration of previous TB treatment interruption in a subgroup of patients who were previously treated for TB. To determine the average length of time from diagnosis of TB to diagnosis of MDR-TB and commencement of MDR-TB treatment.

Methods

An observational analytic nested case-control study design was used. All patients who were diagnosed with pulmonary TB and who had a sputum culture performed between 2001 and 2007 were included in the study. The cases were all MDR-TB cases diagnosed on sputum culture between 2001 and 2007. The controls were drug susceptible TB cases which had a sputum culture done at diagnosis, and were diagnosed in the same month as the MDR-TB case

Results

There were 10 205 sputum cultures performed from 2001 to 2007. MDR-TB was found in 445 patients. An increase in the prevalence of MDR-TB occurred in 2007, due to a significant increase in prevalence among new TB cases. The MDR-TB prevalence was 11.7% among new TB cases and 4.7% among previously treated

TB cases in 2007. There was no significant association between demographic characteristics and MDR-TB. Previous TB treatment failure and a duration of previous TB treatment of greater than 32 weeks was found to be significantly associated with MDR-TB. The median time from TB diagnosis to MDR-TB diagnosis was 98 day and from MDR-TB diagnosis to MDR-TB treatment 10 days.

Discussion

Delays in the diagnosis of MDR-TB, long waiting times before MDR-TB treatment commencement and lack of isolation have contributed to the spread of primary MDR-TB and was most likely responsible for the increase in prevalence of MDR-TB among new TB cases.

Recommendations

It was suggested that a sputum specimen should be obtained for culture and sensitivity from all new TB patients in areas which have an MDR-TB prevalence of greater than 3% among new TB patients.

Ensure patient education on basic infection control measures.

Improve MDR-TB diagnosis and reduce waiting times for MDR-TB treatment.

DECLARATION

I, Renu Gajee declare that

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Renu Gajee
Department of Public Health Medicine,
Nelson R Mandela School of Medicine
University of KwaZulu Natal South Africa

Date: 30 February 11, 2012

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ACRONYMS AND ABBREVIATIONS

TB	-	Tuberculosis
MDR-TB	-	Multi-drug resistant tuberculosis
XDR-TB	-	Extensively drug resistant tuberculosis
DOTS	-	Directly observed treatment short course
HIV	-	Human Immunodeficiency Virus
WHO	-	World Health Organization

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CHAPTER 1. INTRODUCTION

1.1. INTRODUCTION

Tuberculosis (TB) is a major cause of death worldwide. Globally the incidence risk for TB was 139 per 100 000 population in 2007.[1] An estimated 20 deaths per 100 000 population occurred globally in 2007 among Human Immunodeficiency Virus (HIV) uninfected incident TB cases.[1] There were 456 000 (33%) deaths among HIV infected incident cases of TB.[1] South Africa was ranked fifth among the 22 high burden tuberculosis countries in terms of overall TB burden in 2007.[1] Among the 15 countries which had the highest estimated TB incidence per capita, South Africa was ranked second in 2007.[1] The Internationally recommended directly observed treatment, short course (DOTS) strategy was implemented in South Africa in 1996 after TB was declared a national emergency. [2] Despite these efforts, TB incidence and case-fatality have increased threefold in South Africa during the decade from 1994 to 2004.[3] More than 400 000 cases of TB are treated annually in South Africa but only 60% are cured.[1]

Control of TB is a serious challenge to global health. A new and potentially devastating threat to TB control is the emergence of multi-drug resistant TB (MDR-TB).[4] MDR-TB is defined as, “resistance to isoniazid and rifampicin”[3] (the two most potent anti-TB drugs).

Multi-drug resistant tuberculosis was identified as a problem in all the regions under the World Health Organization (WHO) surveillance. MDR-TB isolates constitute 1 to 3% of global isolates.[7] Each year over 400 000 people develop MDR-TB world wide. In 2007 among the 10.4 million cases of TB globally, an estimated 4.9% or 511 000 were cases of MDR-TB. Of these 511 000 cases of MDR-TB, 289 000 were among new cases (3.1% of all new cases) and 221 000 were among cases that had been previously treated for TB (19% of all previously treated cases).[1] According to the WHO, in 2007 South Africa ranked fourth among the 30 countries with the highest

number of MDR-TB cases.[1] South Africa reported the highest number of confirmed MDR-TB and extensively drug resistant tuberculosis (XDR-TB) cases in the African region.[1] The prevalence of MDR-TB in South Africa in 2007 was 1.8% among all new TB cases and 6.7% among previously treated TB cases.[1]

MDR-TB can be as a result of failure of drug sensitive TB treatment with development of resistance (acquired MDR-TB) or as a result of direct transmission of a multi-drug resistant strain (primary MDR-TB).[5] The development of MDR-TB, with subsequent transmission of drug resistant strains in the community, may be the result of many factors. Globally, these factors have included programme related factors such as inadequate management of patient's treatment, absence of directly observed treatment, shortages of drug supply, suboptimal drug quality, uncontrolled availability of anti-tuberculosis drugs without prescription, lack of uniformity between the public and private health sector treatment guidelines , and poorly managed and supported national TB control programmes.[6]. In addition, patient characteristics including age, HIV infection and poor adherence to treatment have also been implicated to influence the transmission of drug resistant organisms.

Multi-drug resistant tuberculosis is difficult and expensive to treat. The economic burden of this problem is already evident in South Africa where in 2009, the drug costs for treating a case of drug susceptible TB was R110 in comparison to the drug costs for treating a case of MDR-TB was which was R1866.[9] In South Africa in 2009, the average district hospital cost per MDR-TB patient per day was R850 and the average regional hospital or MDR-TB hospital cost per MDR-TB patient per day was R1100.[10] These hospital costs exclude drug costs. The cost of community based injection teams was estimated to be R86 per day excluding the cost of drugs.[1] Patients with MDR-TB remain infectious for much longer, both in the community and in hospital.[11] In addition to this, patients need to be hospitalized for much longer

[1] Community based injection teams is based on the on the Church of Scotland Hospital model which uses four injection teams to manage thirty patients. The cost includes the salaries of staff, running costs of vehicle, and the purchase price of vehicle built in on a three year purchase amount. The cost excludes the cost of drugs.

periods of 4 to 6 months and treatment is required for up to 24 months.[12] Less effective and more toxic second line drugs have to be used to treat MDR-TB[11] Many laboratory investigations are required (monthly bacteriology cultures) and drug toxicity necessitates additional laboratory screening tests such as liver and kidney function tests.[12] MDR-TB often culminates in incurable disease.[7] The MDR-TB case-fatality is estimated to range from 40% to 60%, which is similar to the mortality of patients with untreated tuberculosis.[7]

The problem of MDR-TB is further compounded by the current HIV epidemic.[25] A systematic review of studies assessing HIV infection and risk factors for MDR-TB found that in a study in the United Kingdom, MDR-TB patients who were HIV infected were nine times more likely to die than those who were HIV uninfected, and in a study in Peru, 50% of MDR-TB patients who were HIV infected died.[5] The systematic review reported that several countries with longer follow-up observed case-fatality ranging from 72% to 89% in patients co-infected with MDR-TB and HIV.[5] In South Africa it was estimated that 55% of drug susceptible TB cases and 60% of MDR-TB cases were co-infected with HIV.[13]

Table 1: TB treatment outcomes for South Africa 2006 – 2007 (n = 182 741)

	New smear positive TB cases	***Re-treatment smear positive TB cases***
Number of smear positive TB cases	*139 516*	*43 225*
TB Treatment outcome (%)		
Cured	*63*	*56*
Treatment completed	*11*	*10*
Died	*7.3*	*5.1*
Treatment failed	*1.7*	*9*
Treatment defaulted	*9.1*	*12*

Source: Global Tuberculosis Control – Epidemiology, Strategy and Financing, World health Organization, 2009

1.2. BACKGROUND

In South Africa, in 2006 there were 139 516 new sputum smear positive and 43 225 re-treatment smear positive TB cases registered in the DOTS programme nationally. These cases were followed up through 2007. The reported treatment outcomes in the cohort of new cases found that 63% of cases were cured, a further 11% of cases completed treatment, but were not proven to be cured, 7.3% of TB cases died, 1.7% of cases failed treatment and 9.1% of cases defaulted TB treatment (Table 1). The TB treatment outcomes in the cohort of re-treatment cases found that 56% of cases were cured, 10% of cases completed treatment, 5.1% of cases died, 9.0% of cases failed treatment and 12% of cases defaulted treatment.[1] (Table 1)

One of the objectives of tuberculosis control programmes is to minimize the emergence of drug resistance. In South Africa, due to limited resources the National Tuberculosis Control Programme does not recommend sputum culture and drug susceptibility testing for all TB patients. Drug susceptibility testing is used selectively for patients at risk for MDR-TB. Culture and drug susceptibility testing is recommended for the following groups of patients[14]:

- All re-treatment TB patients;
- New TB patients who remain sputum smear-positive after two months (new cases) or three months (re-treatment cases) of first-line treatment;
- Symptomatic close contacts of confirmed MDR-TB patients; and
- Symptomatic patients from known high risk groups, including health care workers, laboratory workers, prisoners and HIV infected patients.

This study was conducted at the Prince Cyril Zulu Communicable Disease Centre, situated in the centre of the city of Durban in the province of KwaZulu-Natal, South Africa. The Prince Cyril Zulu Communicable Disease Centre provides outpatient services which include investigation, diagnosis and management of patients with TB, and sexually transmitted infections. Voluntary counseling and testing for HIV (VCT) services are also provided at the Prince Cyril Zulu Communicable Disease Centre. The centre does not serve a well defined catchment population. The Prince Cyril

Zulu Communicable Disease Centre is situated adjacent to the taxi rank which is the main transport node for the city. It therefore provides services to the entire eThekwini Metropolitan Municipality. Walk-in patients and patients referred from primary health clinics and hospitals are accepted at the centre. Patients with MDR-TB are diagnosed at the Prince Cyril Zulu Communicable Disease Centre and then referred to the hospitals designated to manage MDR-TB for therapy. There are an increasing number of MDR-TB cases diagnosed at the Prince Cyril Zulu Communicable Disease Centre.

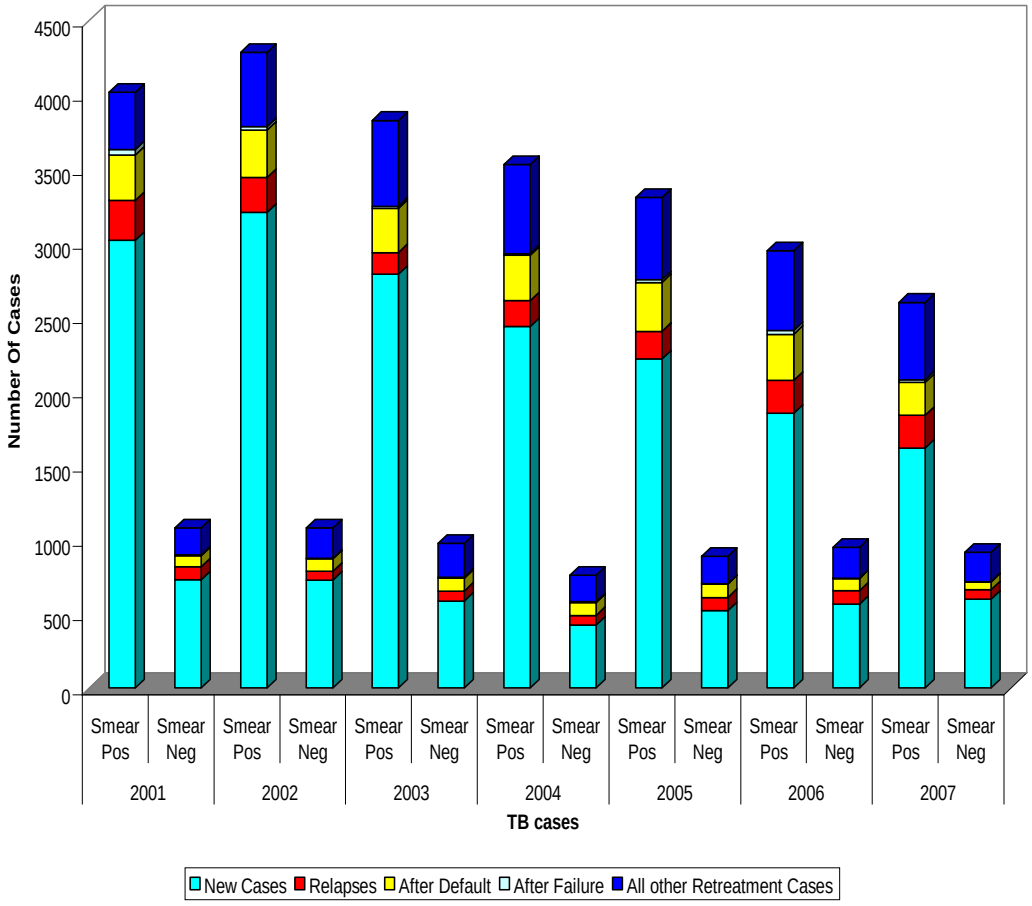

Figure 1: Number of pulmonary tuberculosis cases registered at Prince Cyril Zulu Communicable Disease Centre from 2001 to 2007[2]

[2] Information was sourced from the Prince Cyril Zulu Communicable Disease Centre database.

The number of patients with pulmonary TB diagnosed and managed at the Prince Cyril Zulu Communicable Disease Centre had decreased from 5096 in 2001 to 3504 in 2007 (Figure 1). This decrease was due the decentralization of TB services to Primary Health clinics. Patients were referred to their local primary health clinics before registration. The Prince Cyril Zulu Communicable Disease Centre registers over 3000 pulmonary TB cases annually. In 2007 the Prince Cyril Zulu Communicable Disease Centre registered 3514 pulmonary TB cases, 62% of smear positive cases were new cases and 38% were re-treatment cases. From the smear positive re-treatment cases 22% were relapses, 23% after defaulting treatment and 1.9% after having failed treatment.

The trend in TB treatment outcomes at the Prince Cyril Zulu Communicable Disease Centre from 2001 to 2007 (Figure 2) showed that the proportion of all TB cases successfully treated had improved to 63% among cases who commenced treatment in 2007. Sixty per cent of the new smear positive cases were cured in 2007, which was compatible to the national cure rate of 63% in 2007.[1]The treatment failure rate at the Prince Cyril Zulu Communicable Disease Centre was 1.7% in 2007, which was similar to the national treatment failure rate of 1.7% in 2007.[1] In 2007, 25% of new smear positive TB cases defaulted treatment. The Prince Cyril Zulu Communicable Disease Centre has had a consistently high number of cases defaulting from treatment which was more than twice the national treatment defaulter rate of 9.1% in 2007.[1] Among the re-treatment smear positive cases (Figure 3), 52% of cases were cured in 2007. This was slightly lower than the national cure rate of 56%.[1] The Prince Cyril Zulu Communicable Disease Centre has had improvement in cure rates over the seven year period, but for both new and re-treatment cases the cure rates at the Prince Cyril Zulu Communicable Disease Centre remain below the target for South Africa which is 85%.[18] In 2007, 2.2% of re-treatment smear positive cases failed treatment, this was lower than the national treatment failure rate of 9% in 2007. [1] The Prince Cyril Zulu Communicable Disease Centre has had a consistently high number of treatment defaulters among re-treatment cases. In 2007, 31.3% of re-treatment cases defaulted from treatment. This was much higher than the national re-treatment defaulter rate of 12%.[1]

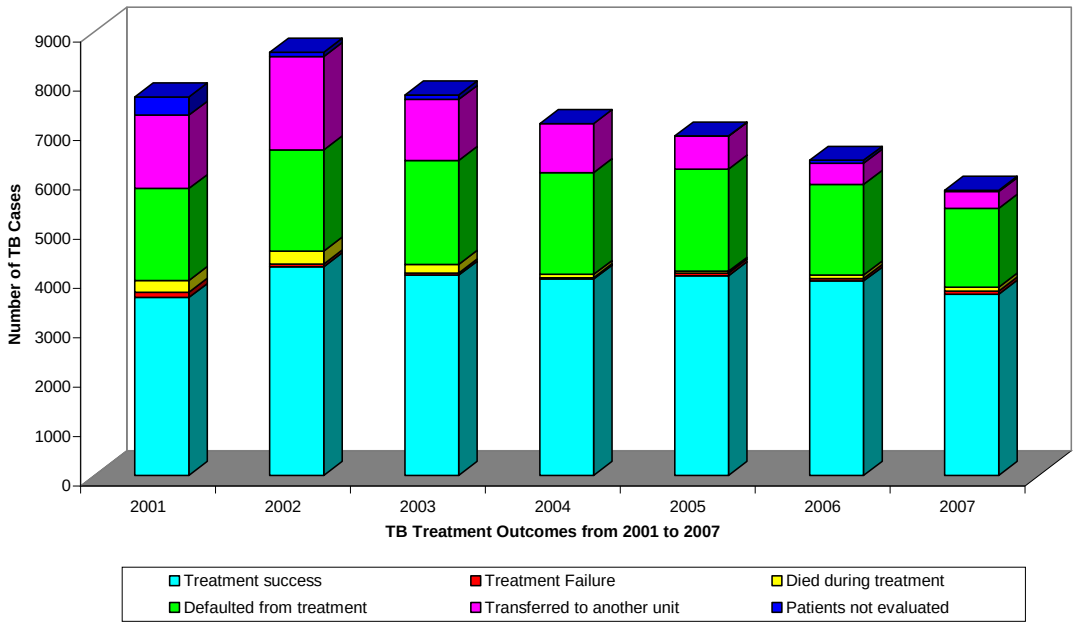

Figure 2: Number and category of TB treatment outcomes for all TB cases at Prince Cyril Zulu Communicable Disease Centre from 2001 to 2007[2]

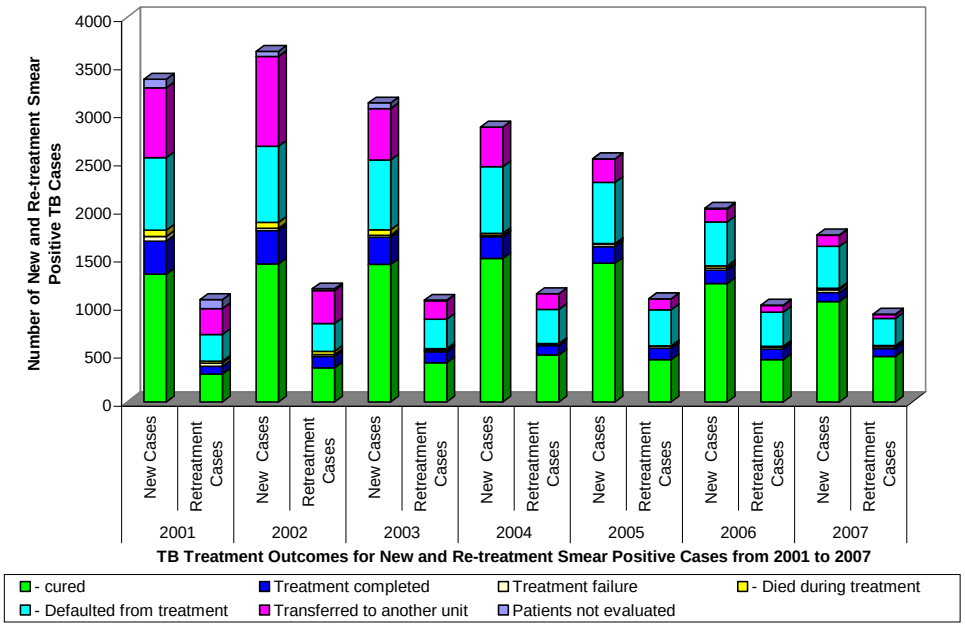

Figure 3: Treatment Outcomes for New and Re-Treatments Smear Positive Cases at the Cyril Zulu Communicable Disease Centre from 2001 to 2007[2]

1.3. THE PROBLEM

The problem is MDR-TB. The prevalence of MDR-TB varies considerably throughout the world and between regions, with outbreaks isolated to some areas and institutions. There is limited epidemiological data on patients with MDR-TB from most of the developing world. In South Africa, the prevalence of MDR-TB varies between provinces. The burden of MDR-TB at district or facility level is relatively unknown. KwaZulu-Natal was the province with the highest TB caseload in 2006, accounting for 31% of all TB cases nationally.[15] The eThekwini district in KwaZulu-Natal was identified as one of the four districts which have a quarter of the national TB caseload. [16] The Prince Cyril Zulu Communicable Disease Centre is a facility with one of the highest TB caseloads. MDR-TB cases have been identified at this facility but the extent of the problem of MDR-TB is unknown. MDR-TB is an infectious condition with associated morbidity and mortality. The burden of MDR-TB needs to be quantified and factors that are contributing to the development and spread of MDR-TB need to be determined. A greater understanding of the scale of the problem would enable appropriate interventions to improve diagnosis and reduce transmission of MDR-TB.

1.4. AIM

This study aimed to investigate the annual MDR-TB prevalence and associated risk factors for MDR-TB from 2001 to 2007 at the Prince Cyril Zulu Communicable Disease Centre.

1.5. OBJECTIVES

Primary Objectives

The primary objectives of the study were:

1. To describe the annual trend in MDR-TB prevalence from 2001 to 2007 at the Prince Cyril Zulu Communicable Disease Centre, eThekwini;

2. To identify and describe the association between demographic characteristics, a past history of previous TB treatment, HIV status, referral type and an outcome of MDR-TB; and
3. To determine the mean length of time from TB diagnosis to MDR-TB diagnosis and MDR-TB treatment commencement.

Secondary Objectives (Subgroup analysis of MDR-TB and TB patients with a history of previous TB treatment)

The secondary objectives were:

a. To identify and describe the association between previous TB treatment duration, previous TB treatment outcome, duration of previous TB treatment interruption and an outcome of MDR-TB.
b. To establish the mean length of time from previous TB diagnosis to current MDR-TB diagnosis.

Hypothesis

- There is a significant association between risk factors, namely: demographic characteristics, a history of previous TB treatment, HIV status, referral type and MDR-TB.
- There is a significant association between risk factors from previous TB treatment, namely: previous TB treatment outcome, previous TB treatment duration, previous TB treatment interruption and MDR-TB.

1.6. DEFINITIONS

Multi-drug resistant TB (MDR-TB)

"Multi-drug resistant tuberculosis is defined as *Mycobacterium tuberculosis* where there is *in vitro* resistance to at least isoniazid and rifampicin with or without resistance to any other tuberculosis drugs." [18]

Extensively drug resistant TB (XDR-TB)

"MDR-TB in association with *in vitro* resistance to any of the fluoroquinolones plus one or more of the injectable second line TB drugs."[15]

New case of TB

"A patient who has never had treatment for TB or who has taken anti tuberculosis drugs for less than four weeks."[18]

Re-treatment case

"A patient who has taken treatment for TB before and either relapsed, defaulted or had treatment failure."[18]

Treatment failure

"A pulmonary TB patient who is still sputum smear positive at the end of the standard treatment period."[18]

Treatment default

"A patient who completed at least one month of treatment, and returns after having interrupted treatment for two months or more."[18]

Drug sensitive TB

"Mycobacterium tuberculosis that is sensitive to all anti-TB drugs." [18]

Pulmonary TB

"Pulmonary tuberculosis refers to disease involving the lung parenchyma."[18]

Extra-pulmonary TB

"Extra-pulmonary tuberculosis covers all forms of tuberculosis in which the disease process occurs outside the lung parenchyma."[18]

Primary resistance

"Resistance in cultures from patients with no history of previous tuberculosis treatment."[19]

Acquired resistance

"Resistance in cultures from patients with one or more previous tuberculosis treatment episode totaling more than one month."[19]

Treatment interruption

"Treatment interruption was defined as a patient whose treatment was interrupted for more than two consecutive months before the end of the treatment period.[15]

Cure

"Client who is smear negative at, one month prior to the completion of treatment, and also on at least one previous occasion at least 30 days prior" [15]

Treatment completed

"Client who has completed treatment but does not meet the criteria to be classified as cured or treatment failure"[15]

Died

"Client who dies for any reason during the course of TB treatment."[15]

1.7. SUMMARY OUTLINE PER CHAPTER

This dissertation is presented in the form of six chapters. A short description of each chapter is outlined below:

Chapter 1

In chapter 1 an introduction to the study is given and the importance of MDR-TB is outlined. In this chapter the background for the study is provided, the problem and purpose of the study are highlighted. The primary and secondary objectives of the study are stated in chapter 1.

Chapter 2

In chapter 2 a review of the literature is provided. In this chapter a theoretical review of the development of drug resistance is given. An empirical review of other studies on the prevalence of MDR-TB and the risk factors associated with MDR-TB is included

Chapter 3

In chapter 3 the methods undertaken to conduct the research are outlined. The study design, study population, data collection and sampling method are explained. The statistical methods used to analyze the data are described in chapter 3.

Chapter 4

In chapter 4 the results are presented in the form of graphs and tables. It reports on the findings of the study and the significance of the results obtained is discussed.

Chapter 5

In chapter 5 the results that were presented in chapter 4 are analyzed. Comparison of the results is made with results from other studies. The findings are discussed in relation to the national and provincial picture.

Chapter 6

In chapter 6 the conclusions that are drawn from the research study are provided. In this chapter recommendations that are specific to the Prince Cyril Zulu Communicable Disease Centre and general recommendations that can benefit TB control initiatives are offered. Suggestions for further research are made.

1.8. CHAPTER SUMMARY

In this introductory chapter a background to the problem of TB and the development of MDR-TB was provided. MDR-TB, its importance and associated morbidity and mortality was discussed. The status of TB at the Prince Cyril Zulu Communicable Disease Centre from 2001 to 2007 was described. The aims and the objectives of the study were stated and a brief outline of the content of the chapters that will follow was given.

CHAPTER 2. LITERATURE REVIEW

2.1. INTRODUCTION

A review of the literature was undertaken to provide an understanding of the development of tuberculosis drug resistance and the extent of multi-drug resistant tuberculosis globally, regionally and in South Africa. There are many factors that contribute to the development of tuberculosis drug resistance including client related and management factors. Previous studies have investigated various risk factors, to test their association with MDR-TB. The risk factors that are relevant to South Africa and the Prince Cyril Zulu Communicable Disease Centre, specifically, are explored in this chapter.

2.2. THE HISTORY OF DRUG RESISTANCE

Reports on TB drug resistance started more than 60 years ago, shortly after the use of the first TB drugs commenced.[39] By 1961 there were tests available for detecting drug susceptibility.[39] During the 1960s, "the common feature of data from developing countries was a much higher prevalence of drug-resistant TB than in developed countries." [39] With the introduction of rifampicin and short-course chemotherapy, a decrease in TB was seen during the 1970s which resulted in may countries stopping TB drug resistance surveillance.[39] There was an increase in TB in the 1980s with associated outbreaks of MDR-TB mainly attributed to, "HIV and deteriorating TB programmes" [39] Global TB drug resistance surveillance projects were initiated in 1994. [39]

2.3. MECHANISM OF TURBERCULOSIS DRUG RESISTANCE

2.3.1. Natural Resistance

Spontaneous slow mutation can occur in the genome of *Mycobacterium tuberculosis* leading to the development of resistant mutant organisms.[20] The phenomenon of

spontaneous mutation is genetically determined and varies from drug to drug.[14] With regard to anti-tuberculosis drugs the probability of spontaneous resistance to isoniazid is 1 in every 10^6 cell divisions and the probability of spontaneous resistance to rifampicin is 1 in every 10^9 cell divisions. [14] It is not common for spontaneously occurring multi-drug resistance to occur because the chromosomal loci responsible for resistance to different drugs is not linked.[14] For MDR-TB to occur a double spontaneous mutation to both isoniazid and rifampicin has to occur. The probability of spontaneous resistance to both isoniazid and rifampicin is 10^{-15} because the probability of spontaneous mutation resulting in resistance to isoniazid is 10^{-6} and the probability of a spontaneous mutation to rifampicin is 10^{-9}. The risk of spontaneously developing resistant mutants is very low because a large bacterial load which occurs in lung cavities is required for MDR-TB strains to emerge.[14] Primary resistance refers to "resistance in cultures from patients with no history of previous tuberculosis treatment".[19]

Acquired resistance

"Drug resistance occurs as a result of selection of resistant mutants in the bacterial population, due to killing of susceptible bacilli by tuberculosis drugs."[19] Suboptimal anti-TB treatment has been implicated as a contributor to the selection of resistant mutants. This situation can arise when monotherapy is used, either as result of ingestion of a single anti-tuberculosis drug or from the ingestion of a combination of drugs where the minimal inhibitory concentration of only one drug may be optimal.[19] The result is that susceptible bacteria are killed rapidly and the resistant mutants are then able to multiply.[19] Resistance to rifampicin can develop within 2 to 5 months and resistance to streptomycin can develop within 45 days. [19] "Acquired resistance refers to resistance in cultures from patients with one or more previous tuberculosis treatment episode totaling more than one month." [19]

2.3.3. Exogenous Re-infection

One study suggests that in an area with a high TB incidence and a high prevalence of HIV infection, combined with the lack of airborne infection control measures,

resistance due to exogenous re-infection is an important mechanism for the development of MDR-TB.[38] A study in KwaZulu-Natal, South Africa identified patients who developed MDR or XDR-TB after initially being diagnosed and treated for a less resistant form of TB. The study used spoligotyping to compare TB isolates obtained at the time of treatment initiation with follow-up isolates that were identified as MDR-TB or XDR-TB. The study found that 74% of patients who developed MDR-TB or XDR-TB, did so as a result of exogenous re-infection with a drug-resistant TB strain (primary resistance) rather than the result of inadequate drug therapy (acquired drug resistance). [38]

Table 2: Countries with the of the highest numbers of estimated MDR-TB cases in 2007

	Number of MDR-TB Cases	***Proportion of MDR-TB among new TB cases (%)***	***Proportion of MDR-TB among previously treated TB cases (%)***
Country			
India	99 639	2.8	17
China	76 154	5	26
Russian Federation	31 397	13	49
South Africa	10 708	1.8	6.7
Bangladesh	7 694	3.5	20

Source: Global Tuberculosis Control – Epidemiology, Strategy and Financing, World health Organization, 2009

2.3. PREVALENCE OF MDR-TB

Global

Estimates of the burden of MDR-TB are provided by the World Health Organization (WHO) Global Project on Drug Resistance Surveillance.[1]The information about the proportion of TB cases with MDR-TB was obtained from drug susceptibility testing of samples from patients in whom MDR-TB was diagnosed in public health facilities.[1] Data was available for new TB cases for 113 countries and for TB re-treatment cases for 102 countries. [1] India, China, Russian Federation; South Africa and

Bangladesh ranked from first to fifth in terms of the highest numbers of estimated MDR-TB cases in 2007(Table 2). Of the 511 000 estimated MDR-TB cases, South Africa had 10 708 MDR-TB cases (1.8% MDR-TB among new TB cases and 6.7% MDR-TB among previously treated TB cases).[1]The proportion of MDR-TB among new cases was much lower in South Africa compared to the other countries (Table2). Earlier literature had reported that MDR-TB isolates constitute 1 to 3% of global isolates.[7] The findings of the WHO surveillance in 2007 estimated that 4.9% of global isolates were MDR-TB.[1]

The population weighted mean[3] of MDR-TB among all TB cases from 114 countries that reported to a global project was 5.3% (95% CI: 3.9 to 6.6), but ranges from 0% in some Western European countries to over 35% in some countries of the former Soviet Union.[21]

Data from India found that the prevalence of primary MDR-TB varied between 0 to 5% and for acquired MDR-TB it was between 9.6 to 80.6%.[7] A study conducted in the Lucknow District in India found that the prevalence of MDR-TB was 20% (n = 686), primary and acquired being 13,2% (95% CI: 9.5 to 16.9) and 25% (95% CI: 21 to 30) respectively.[7] These results for the Lucknow district varied considerably from the national MDR-TB prevalence of 2.8% among new TB cases in India. Another study in Chennai, India detected an MDR-TB prevalence of 34% (n = 618).[22] .An expanded global survey on tuberculosis drug resistance found that the prevalence of MDR-TB in the Zhejiang Province, China was 4.5% and 10.8% in the Henan Province, China.[23] The prevalence of MDR-TB in Tomsk, Russia was 6.5% and in Ivanova, Russia 9.0%.[23]

[3] The drug resistance among all TB cases was reported for countries conducting routine surveillance. In the majority of survey settings the number of previously treated TB cases was small and did not reflect the proportion of re-treatment cases within the TB programme. Therefore when estimating proportions of resistance among combined cases proportions were weighted by their population within the TB programme.

Africa

The MDR-TB case load and prevalence varies within regions of the WHO, including the African region. South Africa had the largest number of confirmed MDR-TB and XDR-TB cases (10 708) in Africa in 2007.[1] South Africa's neighbouring countries Botswana, Lesotho and Swaziland had less than 150 cases each of MDR-TB in 2007. Namibia had 270 MDR-TB cases, Mozambique 1464 MDR-TB cases and Zimbabwe 1620 MDR-TB cases.[1]

In the Global MDR-TB and XDR-TB Response Plan (2007 to 2008), WHO estimated a 2% prevalence of MDR-TB for the African region as a whole, with Cote D'Ivoire, Democratic Republic of the Congo and Mozambique showing much higher proportion of TB drug resistance.[8] The low prevalence of resistance was fairly consistent in WHO surveys, however, it was likely that smaller epidemics of MDR-TB were going undetected due to poor laboratory capacity.[8] The MDR-TB epidemic in Tugela Ferry, a district in KwaZulu-Natal, South Africa is evidence of these smaller epidemics of MDR-TB in the African region.[29] At a hospital in Tugela Ferry 41% of 544 TB patients had MDR-TB.[33]

A study in Rwanda found that 3% of 616 new TB cases had MDR-TB and 9.4% of 85 previously treated TB cases had MDR-TB.[24] In the West African country of Benin, the prevalence of MDR-TB was 1.6% in new TB cases (n = 244) and 11.1% in previously treated TB cases (n = 226).[24]

South Africa

A national survey of TB drug resistance commissioned by the National Department of Health between 2001 and 2002 was conducted by the Medical Research Council. In South Africa the overall prevalence of MDR-TB in 2002 was 2.9% (n = 4 358), arising from 1.6% in new cases and 6.6% in previously treated TB cases.[4] Provincial differences in drug resistance ranged from 1.0% to 2.7% in newly diagnosed TB cases and from 4.0% to 13.9% in TB re-treatment cases.[4]

In 2006, KwaZulu-Natal was the province with the highest total TB caseload, accounting for 31% (n = 342 315) of all TB cases in South Africa.[15] A study conducted at a TB referral hospital in Durban from 1998 to 2001 found that the proportion of MDR-TB patients admitted rose from 7.6% (n = 740) in 1998 to 14% (n = 1212) in 2001.[26]

The national survey of TB drug resistance also provided a report for each province. The survey of tuberculosis drug resistance in KwaZulu-Natal found that the total MDR-TB caseload for KwaZulu-Natal in 2001 was estimated to be between 1385 and 2616 cases consisting of 538 to 1016 new cases and 847 to 1600 re-treatment cases.[35] The prevalence of MDR-TB in KwaZulu-Natal n 2001 was 1.7% among new cases and 7.7% among patients with a prior history of TB treatment.[35] With regard to MDR-TB prevalence among new cases, KwaZulu-Natal (1.7%) was the province with the fourth highest MDR-TB prevalence. Mpumalanga (2.6%), Limpopo (2.4%) and North West Province (2.2%) were the three provinces with the highest MDR-TB prevalence among new cases. With regard to MDR-TB prevalence among previously treated TB cases, KwaZulu-Natal (7.7%) was the province with the second highest MDR-TB prevalence. Mpumalanga was the province with the highest MDR-TB prevalence of 13.7% among previously treated TB cases.[25] KwaZulu-Natal was however the province with the highest estimated MDR-TB burden based on cases.[25]

A study conducted at a TB referral hospital in Durban from 1998 to 2001 found that the proportion of MDR-TB patients admitted rose from 7.6% (n = 740) in 1998 to 14% (n = 1212) in 2001. [26]

2.5. MDR-TB INCIDENCE

There is a very high incidence of tuberculosis in the African region which suggests that the number of MDR-TB cases within the population and the consequent risk of transmission may also be high.[4] The WHO Global Surveillance Project reports that the prevalence MDR-TB and the incidence of MDR-TB remains largely unknown.[4] Zager and McNerney (2008) did a re-analysis of the WHO Global Surveillance

Project data and calculated estimates of the incidence of MDR-TB in previously untreated cases.[4] Data from 97 geographical settings was compiled and it was found that 25 settings had an estimated incidence of greater than 3 per 100 000.[4] Karakalpakstan had the highest estimated incidence of MDR-TB (35 cases per 100 000), Kazakhstan was second (22 cases per 100 000), Mpumalanga Province (South Africa) was third (15 cases per 100 000) and KwaZulu-Natal Province (South Africa) had the fourth highest (14 cases per 100 000) estimated incidence of transmitted MDR-TB.[4] Countries like South Africa with high MDR-TB incidence should prioritize measures to address the control of MDR-TB transmission.

2.6. FACTORS CONTRIBUTING TO MDR-TB IN SOUTH AFRICA

Many factors have been implicated as contributing to the development of MDR-TB. According to the South African National Tuberculosis Guidelines, "MDR-TB is considered to be a man-made problem, which has arisen because of human error resulting in the poor management of drug supply, poor client management and other client related factors."[15] These contributory factors are explored below.[15]

Uninterrupted Drug Supply

The most common errors observed in the management of drug supply were[15]:

- Poor management of supply of first line anti-tuberculosis drugs due to poor stock management and / or procurement problems.[15,19]
- Use of tuberculosis drugs (or drug combinations) of unproven bioavailability.[15,19]

The use of single first line drugs instead of fixed-dose combination tablets.[15] Single first line drugs were used in South Africa until 1999/2000, this enabled patients to discontinue individual drugs that were causing side effects.[26]

Poor Client Management

Health system failures that lead to poor client management, inadequate or inappropriate treatment and poor adherence all contribute to MDR-TB, including[15]:

- Uncaring and unfriendly staff attitudes.[15,19] Lack of support and failure to adopt a problem solving approach to address challenges contribute to poor relationships between clients and health care workers.[15]
- Poor counseling of client's resulting in a lack of knowledge and poor understanding of what is expected of the client. [15,19]
- Ineffective systems, including absence of directly observed therapy, unsupervised clients, poor referral, inadequate record keeping and follow-up of clients.[15]
- Insufficient or absent contact tracing and follow-up of MDR-TB cases. [15]
- Low staff morale, lack of regular support and supervision and low accountability of staff for programme outcomes. [15,19]
- Prescription errors including[1]:
    - The use of two or three drugs when four or five first line drugs should be used; [15,19] and
    - Adding one extra drug in the case of treatment failure. [15,19]

Client-Related Factors

Client adherence is most often a problem when:

- The client is homeless, has a substance abuse problem, or is unemployed. [15,19] A family member has been unsuccessfully treated previously. [15,19]
- Access to health care is difficult. [15,19]

2.7. RISK FACTORS FOR MDR-TB

The WHO has identified elements in the patient's history that suggest an increased risk for drug resistance as listed below.[14] This study will not investigate all identified risk factors.

List of Risk Factors for MDR-TB

Risk factor	Comments
Failure of re-treatment regimens and chronic TB cases	These patients have the highest MDR-TB rates of any other group, often greater than 80%.
Exposure to a known MDR-TB case	Most studies have shown close contacts of MDR-TB patients to have very high rates of MDR-TB.
Failure of first-time short course chemotherapy	Failures for short course chemotherapy are patients who, while on treatment, are sputum smear positive at 5 months or later during the course of treatment.
Relapse and return after default	Erratic drug intake or early relapse may point to possible MDR-TB. Relapses within the first six months post-treatment may have similar MDR-TB rates as failures.
History of using poor or unknown quality TB drugs	The percentage of MDR-TB caused by use of poor quality drugs is unknown but considered significant.
History of other medications that interfere with TB drug absorption	Antacids containing aluminium or magnesium selectively compete with TB drugs, particularly with isoniazid and fluoroquinolones.
Use of drugs that alter the metabolism of TB drugs, resulting in reduced serum levels	Antifungal agents in the azoles family interfere with each other; rifampicin will lower azole levels. In addition, ketoconazole can lower rifampicin levels by 40% to 50%.
Treatment in poorly-performing / operating control programmes	These are usually non-DOTS programs or DOTS programs with poor patient adherence or drug management and distribution systems.
Co-morbid conditions example mal-absorption or rapid transit diarrhoea	Mal-absorption may result in selective low serum drug levels and may occur in either HIV uninfected or HIV infected patients.
HIV	Numerous MDR-TB outbreaks have been documented in HIV positive individuals, and XDR-TB outbreaks in HIV positive individuals have been documented in South Africa.

Source: World Health Organization. Guidelines for the Programmatic Management of drug-resistant Tuberculosis (WHO/HTM/TB/2005.361), World Health Organization: Geneva, Switzerland, 2006

2.8. RISK FACTORS FOR MDR-TB UNDER INVESTIGATION

DEMOGRAPHIC CHARACTERISTICS

Age and sex

Data on drug resistance stratified by age and sex were reported by 42 settings in 36 countries from all World Health Organization Regions. MDR-TB among combined cases was found to be associated with the male sex and younger age groups (25 to 44 years old) in most of the WHO regions. [21]

In a survey with 10 374 TB patients from 11 countries, patients aged 35 to 44 years (OR 4.6; 95% CI: 1.1 to 18.9; *p = 0.03*) and 55 to 64 years (OR 4.4; 95% CI: 1.1 to 18.4; *p = 0.04*) were more likely to have MDR-TB.[6] There were no significant differences between males and females (OR 0.9; 95% CI: 0.7 to 1.1; *p = 0.43*). [6] A study in Taiwan (n = 611) found that the overall proportion of drug resistance was significantly higher in those aged less than 25years (79%; *p=0.031*) compared to those aged 25 to 45 years (61%) and greater than 65 years (55.2%).[27]There was no significant difference between males and females. [27]

In South Africa, the National Survey of Tuberculosis Drug Resistance found that for both new and re-treatment patients, there was no significant association between MDR-TB and sex (OR 0.8; 95% CI; 0.6 to 1.1; *p = 0.19*) or age (*p = 0.4*). [25] A study in Durban also found that there was no significant association between MDR-TB and sex (OR 1.1*; p = 0.2*) or age (*p = 0.6*). [26]

Race

In the United Kingdom, special risk groups for MDR-TB included being of Black African, Indian, Pakistani, Bangladeshi or Chinese ethnicity. [28] In Durban, South Africa it was found that there was no racial difference in prevalence between MDR-TB and drug susceptible TB. [26] The South African national survey of tuberculosis drug resistance did not investigate racial differences.[25]

Geographical Location

There are wide variations in the proportions of TB drug resistance within all WHO regions and all regions have reported outliers. [21] In South Africa, at a hospital in Tugela Ferry, 41% of 544 culture positive TB patients were found to have MDR-TB (n = 1539). [30]

A study in Lucknow, India (n = 1162), found that only two isolates came from patients who were residents of the same geographical locality. [7] The study was unable to establish any geographical connection with MDR-TB.

REFERRAL TYPE

The literature is limited with regard to MDR-TB in different levels of care, and the private or public sectors. A study in Lucknow, India (n = 1162) found that the prevalence of MDR-TB at tertiary level healthcare (27%) and secondary level healthcare (20%) were significantly higher than at primary level healthcare (7.2%). A study in Brazil found that statistically significant differences were found in the group with drug resistance compared to the group with no resistance with respect to prior hospitalization (51% versus 14%; *p<0.001).* [32]

The South African National Survey of Tuberculosis Drug Resistance also found that previous hospitalization was a significant determinant of drug resistance, both for any drug resistance (OR 2.0; 95% CI: 1.3 to 3.1; *p = 0.002*) and for MDR-TB (OR 2.8; 95% CI: 1.6 to 4.9*; p = 0.001*). [25]

In South Africa, TB treatment is available in the private sector but published literature on MDR-TB in the private sector could not be found.

PREVIOUS TB TREATMENT OUTCOMES

A history of previous TB treatment has been demonstrated to be the single most important predictor of MDR-TB. [26] Those patients with a previous history of receiving anti-tuberculosis therapy are more likely to have MDR-TB than those patients who had no history of receiving anti-tuberculosis therapy (OR=4.4; CI: 3.2 to 5.9) ($p < 0.05$). [26]

A study in Thailand (n = 1590) found that the prevalence of MDR-TB among all patients was 10%, and the prevalence of MDR-TB among patients with a history of previous TB treatment was 34%.[31] The prevalence of MDR-TB was 75% in the group, treatment after failure. In the group of patients who had relapsed, the prevalence of MDR-TB was 78%.[31]

In Brazil, a study where primary resistance was 7.0% and acquired resistance was 43%, found that there was a statistically significant association between history of previous TB treatment and drug resistant TB (76%; $p < 0.001$). [32] The study also found that having previously defaulted anti -TB treatment was strongly associated with drug resistance (OR 7.2; 95% CI: 3.3 to 15.9; $p < 0.001$). [32]

The South African National survey of Tuberculosis Drug Resistance investigated MDR-TB among the four conventional previous TB treatment outcome categories, namely: cured, treatment completion, treatment default and treatment failure. Treatment failure was strongly associated with increased risk for MDR-TB (OR 13.3; 95% CI: 4.9 to 36.0; $p < 0.001$). [25] Patients who had previously defaulted from treatment were also at higher risk for MDR-TB (OR 3.3; 95% CI: 1.3 to 8.1). Drug resistance was twice as high when the previous TB outcome was defined as 'treatment completed' versus bacteriologically proven 'cure' (OR 2.1; 95% CI: 1.3 to 3.4; $p < 0.001$). [25]

In a study on drug resistant tuberculosis among South African gold miners it was found that previous treatment outcome was significantly associated with acquired drug resistance in patients with re-treatment TB ($p = 0.01$)[33]. Patients who had

previously failed primary TB treatment had a significantly higher risk of MDR-TB (OR18.7; 95% CI: 1.76 to 475) compared to those who had completed TB treatment (OR 2.2; 95% CI: 0.3 to 0.5). [33]

The survey of tuberculosis drug resistance in KwaZulu-Natal analyzed drug resistance among the different categories of re-treatment cases. Drug resistance was detected in 25.9% of cases with a previously unsuccessful treatment outcome (failure or interrupted), compared to 14.9% of patients with a successful treatment outcome (cured or treatment completed). These differences were not statistically significant (*p = 0.07*), but indicated that patients who fail or interrupt treatment are at a higher risk for drug resistance. [35]

PREVIOUS TB TREATMENT DURATION

A study involving 11 countries found that as the total duration of prior anti-tuberculosis treatment increased, so did the likelihood of having MDR-TB *(p < 0.001*). [6] When compared with individuals without prior anti-tuberculosis treatment, the study found that having received TB drugs for an overall period of time totaling 6 to 11 months (OR 7.6; 95% CI: 2.6 to 22.4*; p < 0.001*) or 12 months or greater (OR 13.7; 95% CI: 4.5 to 41.6; *p < 0.001*) was associated with MDR-TB. [6]

A study in the Philippines found that there was an increased risk of acquiring resistance with longer but incomplete anti-tuberculosis treatment. [37] The effect of duration of previous anti-tuberculosis treatment on the resistance pattern showed increasing odds of developing MDR-TB if treatment was taken for longer than 3 months but less than 6 months (OR = 4.6; *p < 0.001*). [37]

The South African National Survey of Tuberculosis Drug Resistance found that the duration of previous treatment was not significantly associated with drug resistance, neither when testing for trend (1 month increase in treatment duration) nor when treatment duration was dichotomized (less than 2 months versus 2 months or longer), although trend analysis suggested a higher risk for any resistance with prolonged treatment duration (OR 1.2; 95% CI: 1.0 to 1.5; *p = 0.05*). [25]

HIV and MDR-TB

The association between HIV and drug resistance is complex. “HIV co-infection is not believed to increase the rate at which spontaneous resistance conferring mutations occur”. [43] HIV co-infection might increase selection for spontaneous mutations due to diminished adherence because of increased pill burden or toxic effects, and sub-therapeutic concentrations of TB drugs because of malabsorption or drug interactions. [43] Patients with HIV are more likely to progress to active disease than HIV uninfected patients. HIV infection itself does not cause an increase in the rate of drug resistant mutations but can increase the number of individuals who select for drug resistance, or manifest active disease from resistant organisms thereby accelerating the spread of drug resistant disease. [43]

TB is the most common opportunistic infection and cause of death among HIV infected patients in resource limited settings. [42] HIV infected patients are vulnerable to primary disease following infection with TB and therefore at high risk of illness and mortality when exposed to drug resistant TB strains. [42] HIV infected patients on therapy still have a more than 5 fold increased risk of developing TB compared to individuals without HIV infection.[42]

A systematic review of 32 studies assessing HIV infection as a risk factor for MDR-TB was unable to demonstrate an overall association between HIV prevalence and MDR-TB (prevalence ratio $r = 0.209$).[5] The pooled prevalence ratio for acquired MDR-TB and HIV was 1.17 (95% CI: 0.86 to 1.6; $p = 0.19$), and the pooled prevalence ratio for primary MDR-TB and HIV was 2.72 (95% CI: 2.03 to 3.66; $p = 0.36$). [5] The results did suggest that HIV infection is associated with primary MDR-TB. [5]

A study in Northern Thailand found an association between HIV infection and primary MDR-TB (OR 2.0; 95% CI: 1.1 to 3.5), but not acquired MDR-TB (OR 1.4; 95% CI: 0.7 to 2.9).[31] A small study in India (n = 70), observed similar rates of MDR-TB in HIV co-infected (10%) and HIV uninfected patients (2.5%).[5]

Three studies in South Africa also found no association between HIV infection and MDR-TB. In a retrospective study in Durban, 2.4% of 42 HIV co-infected and 11% of HIV uninfected patients had MDR-TB.[5] A prospective study of hospitalized TB patients in Cape Town found a MDR-TB prevalence of 3.2% in 93 HIV co-infected patients, compared to 2.6% in 115 HIV uninfected patients.[5] In a study on gold miners, the MDR-TB rate was 5.3% among 207 HIV co-infected and 6.5% among 215 HIV uninfected miners. [5] A study at a hospital in Tugela Ferry found that HIV was a risk factor for XDR-TB (OR 8.2; CI: 1.3 – 52.6), but not for MDR-TB. [40]

Contrary to the above findings the South African National Survey of Tuberculosis Drug Resistance found that HIV infected patients tended to have a higher risk for MDR-TB (OR 1.3; 95% CI: 1.0 to 1.7; $p = 0.05$). [25] The survey for KwaZulu-Natal however, found that the association between HIV and MDR-TB was non-significant ($p = 0.18$). [35]

LENGTH OF TIME FROM TB DIAGNOSIS TO MDR-TB DIAGNOSIS

A study in South Africa enrolled patients who developed MDR-TB after being diagnosed and treated for an initial infection with drug susceptible TB. The study found that the median number of days between the collection of initial sputum (drug susceptible) and second sputum (drug resistant) was 154 days (range: 68 to 321 days). [38] The study did not report on any association between the time from collection of initial sputum to collection of second sputum, and MDR-TB. [38] At the time of submission of this dissertation there were no other published studies found investigation the length of time from TB diagnosis to MDR-TB diagnosis.

2.9. GAPS IN THE LITERATURE

The review of the current literature did not find any published studies investigating the following:

- The association between MDR-TB and employment status;
- Duration of previous TB treatment interruption;

- Length of time from previous episode of TB to current diagnosis of MDR-TB; and
- Average length of time from MDR-TB diagnosis to MDR-TB treatment commencement.

2.9. CHAPTER SUMMARY

Anti-tuberculosis drugs are effective for the treatment of TB, however, if they are inappropriately used they can also lead to the selection of resistant mutants for which the same drugs then become ineffective.[20]

The variability in the prevalence of MDR-TB between and within countries, and the changes in MDR-TB prevalence over time, highlights the need for monitoring MDR-TB prevalence at facilities were a large numbers of TB patients are managed. The literature review has shown that various risk factors have been identified and investigated, but not all risk factors have been found to be significantly associated with MDR-TB, and there have been differences in association across studies. There has been general consensus that the risk factors most frequently associated with MDR-TB are previous TB treatment, previous TB treatment failure and previous TB treatment default. This study will test the associations with the risk factors discussed and MDR-TB at the Prince Cyril Zulu Communicable Disease Centre. The study will also attempt to investigate aspects related to MDR-TB which have been identified as gaps in the literature.

CHAPTER 3. RESEARCH METHODS

3.1. INTRODUCTION

In this chapter, a comprehensive description of the research methods used in this research project is presented. The design that was most appropriate to achieve the objectives was used. The study population that was identified and the sampling strategy that was used are described in detail. The data management and statistical methods that were employed are also presented.

3.2. TYPE OF RESEARCH

This research project was categorized as health systems research.

3.3. STUDY DESIGN

An observational analytic nested case-control study design was used.

3.4. STUDY POPULATION

All patients who were diagnosed with pulmonary TB[4], and who had a sputum culture[5] performed, at the Prince Cyril Zulu Communicable Disease Centre between

[4] The South African National Tuberculosis Control Programme definition of pulmonary TB was used:

- If there are at least 2 sputum smears positive for acid fast bacilli, or
- 1 sputum smear positive for acid fast bacilli and chest X-ray abnormalities consistent with active TB, or
- Sputum culture positive for TB, or
- Chest X-ray abnormalities that are consistent with active TB although 2 sputum smears are negative for acid fast bacilli

[5] Sputum is obtained from all TB suspects at the Prince Cyril Zulu Communicable Disease Centre. Microscopy for acid fast bacilli is done at the Prince Cyril Zulu Communicable Disease Centre. If a culture is requested then the sputum is transported to Inkosi Albert Luthuli hospital TB culture laboratory where sputum culture and drug susceptibility testing is done. The Inkosi Albert Luthuli Laboratory uses the modified proportion method for susceptibility testing for slow growing bacteria, which is considered the gold standard, and is performed on 7H11 agar. Dilutions of inoculums are seeded on both control and drug containing media so that countable colonies are obtained on at least

2001 and 2007 constituted the study cohort and formed the denominator for the calculation of prevalence which was the measure of disease occurrence used.

3.5. STUDY SITE

The study site was the Prince Cyril Zulu Communicable Disease Centre, located in the city of Durban, KwaZulu-Natal, South Africa.

The Prince Cyril Zulu Communicable Disease Centre provides outpatient services which include investigation, diagnosis and management of patients with TB, and sexually transmitted infections. Voluntary counseling and testing for HIV (VCT) services are also provided. The centre had an average of 3 to 5 doctors and 4 to 6 professional nurses during the study period.

All self referred patients are screened by primary healthcare trained professional nurses. Patients with symptoms of TB have 2 sputum smears done on 2 consecutive days, one of which is an early morning sputum. The turnaround time for sputum smear results at this facility has remained between 2 to 4 hours. Patients who have 2 positive smears are commenced on TB treatment.

A Chest X-ray is done for the following patients who have symptoms of TB and:-

- 1 positive smear and 1 negative smear
- 2 negative smears
- Chest pain
- Signs of respiratory distress.
- All patients referred from primary health clinics, hospitals or the private sector

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one of the control media. The numbers of CFU that grow on a drug medium is then compared with the number on the control media. From this the proportion of acid fast bacilli resistant to a given drug can be calculated. The Inkosi Albert Luthuli Laboratory defines resistance as 1% or more growth against critical drug concentration: 0.2ug/ml for isoniazid, 49ug/ml for rifampicin, 5ug/ml for streptomycin and 2ug/ml for ethambutol.

Sputum culture is performed for the following patients:-

- New patients who are symptomatic but sputum smear negative;
- New patients who are sputum smear positive with extensive changes on chest X-Ray;
- New patients who do not have radiological improvement after 2 months of anti-TB treatment;
- New patients who remain sputum smear positive after 2 months of anti-TB - treatment; and
- All patients who have a history of previous TB treatment, which is all re-treatment cases.

3.6. SAMPLE POPULATION:

Inclusion criteria

The inclusion criteria were:

- All patients diagnosed with pulmonary TB who had a sputum specimen taken for culture at the time of TB diagnosis
- Patients older than 8 years[6] of age; and
- All cases of MDR-TB[7].

Exclusion criteria

The exclusion criteria were:

- Patients who had extra-pulmonary TB; and
- Patients who had pulmonary TB but who did not have a sputum culture performed.

[6] Children under 8 years are unable to produce an adequate sputum specimen to confirm diagnosis of MDR-TB

[7] Cases of XDR-TB were included as MDR-TB cases because they adhere to the definition criteria of MDR-TB. A separate analysis of XDR-TB was not an objective of this study.

3.7. STUDY SAMPLE

Cases

The cases in this study were all MDR-TB cases diagnosed on sputum culture between 2001 and 2007

Controls

The controls were drug susceptible TB cases which had a sputum culture done at diagnosis, and were diagnosed in the same month as the MDR-TB case

Sampling process

If a patient was diagnosed with MDR-TB more than once during the period 2001 to 2007 each event would be counted separately and included in the analysis. The inclusion criteria were all cases of MDR-TB. The XDR-TB cases were included as MDR-TB cases. A separate analysis of XDR-TB was not an objective of this study.

One control was randomly selected for each case. Systematic random sampling was done to select the controls. Each 100th pulmonary TB case after the MDR TB case was selected. If the selected pulmonary TB patient did not satisfy the inclusion criteria then the next 100th pulmonary TB case was selected as a control. The selection from the electronic database was done manually. The controls were only matched to cases with regard to the time of diagnosis. The controls had to be diagnosed in the same month as the MDR-TB case. The controls were not matched for age and sex because the investigator wanted to analyze for these demographic characteristics. A similar case control study conducted at a hospital in Tugela Ferry, South Africa used the same ratio of 1: 1 for selection of controls and controls were not matched. [40]

If a TB case was diagnosed more than once with TB during the study period, the case would have been included more than once in the sample population. The electronic database was automatically updated when a patient was diagnosed with

TB. Therefore, although rare, the possibility did exist for a TB patient to be randomly selected more than once as a control.

Subgroup

A subgroup of patients who had a history of previous TB treatment was selected from the sample population.
The cases in the subgroup were MDR-TB cases which had a history of previous TB treatment.
The controls in the subgroup were TB cases which had a history of previous TB treatment.

3.8. DATA SOURCES

The Prince Cyril Zulu Communicable Disease Centre has had an electronic database[8] on which data for all patients since 2001 has been recorded. The cohort of patients from which cases and controls were extracted were from this database.

Variables

The variables that were measured in this study were divided into independent and dependent variables.

[8] The database comprises of specific data elements which include patient demographic characteristics (age, sex, location, occupation), previous TB treatment outcomes, current symptoms, sputum smear results, sputum culture results, chest X-rays, current TB case category (new or re-treatment), site of TB, TB treatment given (dose, duration, quantity), type of DOTS, treatment commencement dates, treatment completion dates, TB treatment outcome (cured, treatment completed, died, treatment failure, defaulted, transferred out, moved out), HIV status.
The database also includes medical notes of every clinical consultation with the patient, which documents clinical information including chest X-ray findings, duration of treatment interruption, side effects of TB treatment, other medical conditions and any other relevant medical information. Patients who return to the Prince Cyril Zulu Communicable Disease Centre for subsequent episodes of TB are linked to their previous TB records through their patient identification numbers by limited, password protected access to patient names and dates of birth, to enable continued follow-up of patients.

- **Independent variables**

The independent variables measured included the following:

- Age

When data was collected, age was a continuous variable. Age was discretised into categories (< 25 years; 25 – 45 years; 46 – 65 years; > 65 years). Age was changed to a categorical variable for analysis.

- Sex

Sex was defined as male or female. Sex was a categorical variable

- Race

Race was defined as African, Indian, Coloured or White. If data was missing for race the category unknown was used. Race was a categorical variable.

- Geographical area

Geographical area was defined as North, South, West or Out of eThekwini. Geographical area was a categorical variable.

- Employment status

Employment status was defined as being employed, unemployed, a scholar / student or a pensioner. If data was missing for employment status then the category unknown was used. Employment status was a categorical variable. The database has specific data elements related to employment which included whether employed (yes or no) and if employed what occupation.

- Previous TB treatment

The categories were defined as either yes, (there was a history was previous TB treatment or no (there was no history or previous TB treatment). Previous TB treatment was a categorical variable

- Duration of previous TB treatment

When data was collected, duration of previous TB treatment was a continuous variable. Duration of previous TB treatment was discretised into categories (< 24 weeks; 24 – 32 weeks; > 32 weeks). Duration of previous TB treatment was changed to a categorical variable for analysis.

- Previous TB treatment outcome

Previous TB treatment outcome was defined as previous TB cured; previous TB treatment failure; previous TB treatment completed or previous TB treatment defaulted. If data was missing for the previous TB treatment outcome then the category unknown was used. Previous TB treatment outcome was a categorical variable.

- Duration of previous TB treatment interruption

TB treatment interruption was defined as a patient whose treatment was interrupted for more than two consecutive months before the end of the treatment period. [15] When data was collected, duration of previous TB treatment interruption was a continuous variable. Duration of previous TB treatment interruption was discretised into categories (8 - 16 weeks; 16 – 24 weeks; > 24 weeks). Duration of previous TB treatment interruption was changed to a categorical variable for analysis.

- HIV status

HIV status was defined as HIV infected or HIV uninfected. If data was missing for HIV status then the term unknown was used. HIV status was a categorical variable.

- Referral Type

Referral type was defined as referral from a primary health clinic, a public hospital, the private sector or a self referral. If data was missing for the referral type then the term unknown was used. Referral type was a categorical variable.

The database has specific data elements related to referral. The database has a data element: referred (yes or no) and a second data element where one of the following categories has to be ticked: Primary health clinic, hospital, private.

- Timelines.

The study design enabled follow-up of MDR-TB cases from previous TB to current TB diagnosis and MDR-TB diagnosis. The study design also allowed for follow-up of the MDR-TB cases until MDR-TB treatment commencement or death before MDR-TB treatment commencement.

There were 4 different timelines defined:

- Time from previous TB diagnosis to MDR-TB diagnosis.
- Time from current TB diagnosis to MDR-TB diagnosis
- Time from MDR-TB diagnosis to MDR-TB treatment
- Time from current TB diagnosis to death for MDR-TB cases

Timelines were continuous variables.

The date of registration of the TB case was taken as the date of diagnosis of the TB case. The database has a data element where this date has to be entered for every TB case.

Similarly there is a data element where the date of registration of an MDR-TB case is entered. This corresponds to the date the MDR-TB culture results were received.

The date that the MDR-TB treatment was commenced is the same as the date that the patient was admitted to the MDR-TB referral hospital where MDR-TB treatment is commenced. MDR-TB patients visit the Prince Cyril Zulu Communicable Disease Centre on the day of their admission to the MDR-TB referral hospital because they are transported in hospital transport. An entry is made on the database indicating the date of admission.

Death among MDR-TB patients, refers to death before MDR-TB treatment is commenced. The South African National Tuberculosis guideline definition of died was used, “client who dies for any reason during the course of TB treatment”. Every MDR-TB patient is followed up on a monthly basis while they are awaiting

a bed for admission to hospital. If the patient does not return for their follow-up visit then the patient is contacted or traced. If death is reported an entry is made in the database where there is a data element on death.

- **Dependent variable**

The dependent variable measured was MDR-TB.

3.9. RELIABILITY

The reliability of the data was ensured by the use of the following procedures:

- All patient data recorded in the database was initially obtained by clerks at the point of entry to the facility. Data was then rechecked and corrected by the doctors during the patient's medical consultation. If the doctors did not check that all the relevant information that was captured was correct and there were errors or missing data then the doctors would not have been able to move to the next page of the electronic database. Missing information, incorrect information entered that does not correlate would prevent the doctors from completing the patients TB registration, TB notification and prescription, which are all automatically generated provided all the information has been correctly entered into the database. This would cause delays, so to ensure efficiency the doctors routinely cross check the information captured on each electronic page before moving to the next page to ensure that delays do not occur.

- The database utilized the computer programme Access ("Datacare") which had automatic checks and re-checks to ensure that data had been correctly entered.

3.10. VALIDITY

The validity of the study was established through the utilization of an appropriate study design and through the random selection of controls.

3.11. REDUCTION OF BIAS

Different forms of bias were reduced in the following ways:

- Information bias was reduced by obtaining information on risk factors before the cases were identified. The information was obtained at the patient's first visit to the Prince Cyril Zulu Communicable Disease Centre, this was before the diagnosis of MDR-TB.
- Sampling bias was reduced by selecting all cases of MDR-TB and through the random selection of controls.

3.12. DATA COLLECTION AND HANDLING

The following processes outline how data was collected and handled:

- Data was obtained from the database by the researcher.
- Data was cleaned and verified by cross checking data elements in the database with patient's medical notes[9] and laboratory results[10] in the database. If data was missing in the database the investigator informed the Prince Cyril Zulu Communicable Disease Centre Information Technology Support Specialist (Mrs. Sally Chetty), who then accessed the hard copies of

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9 Patient's medical notes are recorded in the database under patient identification numbers. Patient's medical notes in the database are not linked to patient names or South African Identity Numbers. In addition to the database, a hard copy of patient's medical notes is kept at the Prince Cyril Zulu Communicable Disease Centre. These hard copies contain the patient names in addition to the patient identification numbers.

10 Laboratory results are recorded in the database under patient identification numbers. Patient's laboratory results which appear in the database are not linked to patient names or South African Identity Numbers. Hard copies of laboratory results, which have patient names and Prince Cyril Zulu Communicable Disease Centre patient identification numbers, are received from the TB culture laboratory (Inkosi Albert Luthuli Laboratory) by the Prince Cyril Zulu Communicable Disease Centre laboratory staff. The full culture result is entered into the database by the Prince Cyril Zulu Communicable Disease Centre laboratory staff under the patient identification numbers.

patient's medical notes and laboratory results and populated the database with the missing data.

- Confidentiality was maintained at all times. Data was not linked to individual patients. Access to match patient names and identification numbers was password protected and limited to 3 users at the Prince Cyril Zulu Communicable Disease Centre. The investigator was not given access to any data that contained patient names. The researcher did not disclose the password to the database to anyone and therefore maintained confidentiality.
- All datasheets and flash discs that contained information from the database were stored in a lock-up cabinet to avoid third persons unrelated to the study gaining access to said materials. At the end of the study, all datasheets containing information from the database were shredded and destroyed by the investigator. Electronic copies of the datasheets were deleted.
- Individual patient data was not shared with the statistician, only summarized data was shared.
- Analysis of the data was done by the researcher under the direction of a statistician (Dr Gaetan Kabera).
- The investigator used the information obtained from the database solely for the purpose of the above study.

3.13. STATISTICAL METHODS

The statistical methods used were both descriptive and analytic. These methods are described below:

Descriptive

- Data was captured using the statistical package STATA, IC version 11. The distribution of the data was not uniformly distributed and therefore the median and the inter-quartile range were calculated.
- Summarized data will be presented in tabular and graphical form in the next chapter.

Analytic

- Inferential statistics namely, Chi-square test, logistic regression, Wilcoxon rank sum test, and Kaplan-Meier survival analysis were used to reach conclusions about how the data related to the research objectives.
- Data analysis was done using the statistical package STATA, IC version 11 and 17.
- Analysis of bivariate data was done as follows:
    - Data was grouped in the form of tables and cross tabulation was done to examine if the variables were significantly associated with the case or control status using Pearsons chi square tests for categorical variables.
    - The measure of association was also statistically tested using logistic regression and reporting odds ratios for categorical data.
    - A 5% level of significance was used.
    - The measure of association between a binary response variable and a continuous variable was assessed using binary logistic regression model, odds ratios with an associated 95% confidence interval and p-value were reported.
    - For comparing continuous data across categories of a binary factor the Wilcoxon rank sum test was used.
- Multivariate logistic regression analysis was performed to assess the independent effects of each risk factor while controlling for confounding factors.
- Kaplan-Meier survival analysis was used to determine time to event between independent groups for continuous variables. Kaplan-Meier was used because survival function and survival probability had to be investigated. The log rank test was not used because the survival analysis was only done for the cases. There were no controls for these variables so a comparison of 2 curves could not be made.

- Subgroup analysis was done using Chi square test, logistic regression and Wilcoxon rank sum test to assess measures of association for categorical data. Odds ratios with a 95% confidence interval were reported on.

Confounders

Age, sex, HIV infection and employment status were identified as possible confounders

Associations measured

The list of associations that were explored is tabulated below:

Age	MDR-TB
Sex	MDR-TB
Race	MDR-TB
Geographical Location	MDR-TB
Employment status	MDR-TB
Previous TB treatment	MDR-TB
Duration of previous treatment	MDR-TB
Previous TB cured	MDR-TB
Previous TB treatment failure	MDR-TB
Previous TB treatment completed	MDR-TB
Previous TB treatment defaulted	MDR-TB
Duration of previous treatment interruption	MDR-TB
HIV status	MDR-TB
Referral Type	MDR-TB

3.14. LIMITATIONS OF THE RESEARCH METHOD

The limitations of the research method used were:

- The study was retrospective and therefore limited to the data that was available in the existing database.
- The study was limited to those patients who had a sputum culture performed at the Prince Cyril Zulu Communicable Disease Centre.

These limitations did not affect the quality of the data. Although retrospective, the data for most variables was complete. For most demographic characteristics data was missing for less than 5 cases or controls. The variable most affected by unknown data was HIV status, but this was due to patients not having tested and not due to missing data. An adequate number of patients had sputum culture performed, 10 205 and this did not affect the quality of the data.

3.15. CHAPTER SUMMARY

The details of the research process were described in this chapter. The contents of this chapter showed that scientifically acceptable research methods were used to investigate the MDR-TB prevalence and associated risk factors for MDR-TB at the Prince Cyril Zulu Communicable Disease Centre.

CHAPTER 4. RESULTS

4.1. INTRODUCTION

The results of the analysis of the data are presented in his chapter. The results are presented in tabular and graphical form according to MDR-TB prevalence, demographic characteristics, previous TB treatment (subgroup), TB and MDR-TB timelines.

4.2. PREVALENCE OF MDR-TB

During the period from 2001 to 2007 the Prince Cyril Zulu Communicable Disease Centre performed 10 205 sputum cultures from pulmonary TB cases. Multi-drug resistant tuberculosis was found in 445 of these TB cases. The prevalence of MDR-TB for the period 2001 to 2007 was 4.4% (n = 10 205); 4.3% (n = 3308) MDR-TB cases among new TB cases and 4.4% (n = 6897) MDR-TB cases among previously treated TB cases (Table 3). All MDR-TB cases had a single episode of MDR-TB diagnosed at the Prince Cyril Zulu Communicable Disease Centre between 2001 and 2007. Each MDR-TB case was counted once. (For total MDR-TB prevalence: numerator = total number of MDR-TB cases and denominator = total TB cases with sputum culture. For MDR-TB prevalence among new TB cases: numerator = MDR-TB cases among new TB cases, and denominator = total number of new TB cases with sputum culture. For MDR-TB prevalence among previously treated TB cases: numerator = MDR-TB cases among previously treated TB cases and denominator = total number of previously TB cases with sputum culture.)

Table 3: Prevalence of MDR-TB at the Prince Cyril Zulu Communicable Disease Centre from 2001 to 2007 (n = 10 205)

	All cases			*New TB cases*				*Previously treated TB cases*			
Year	*Cultures*	*MDR-TB cases*	*MDR-TB Prevalence*	*Cultures*	*MDR-TB cases*	*Prevalence of MDR-TB*	*OR (CI)*	*Cultures*	*MDR-TB cases*	*Prevalence of MDR-TB*	*OR(CI)*
2001	1116	17	1.5	346	8	2.3	1(Ref)	770	9	1.2	1 (Ref)
2002	1305	41	3.1	418	12	2.9	1.2 (0.5 - 3.9)	887	29	3.3	2.9 (1.3 - 6.1)
2003	1510	74	4.9	519	16	3.1	1.3 (0.6 - 3.2)	991	58	5.8	5.3 (2.6 - 10.7)
2004	1574	67	4.2	488	15	3.1	1.3 (0.6 - 3.2)	1086	52	4.8	4.3 (2.1 - 8.7)
2005	1433	63	4.3	459	10	2.2	0.9 (0.4 - 2.4)	974	53	5.4	4.9 (2.4 - 9.9)
2006	1586	65	4.1	523	17	3.2	1.4 (0.6 - 3.3)	1063	48	4.5	4.0 (2.0 - 8.2)
2007	1681	118	7.0	555	65	11.7	5.6 (2.7 -11.8)	1126	53	4.7	4.2 (2.0 - 8.5)
	10 205	445	4.4	3308	143	4.3		6897	302	4.4	

OR = Odds ratio

CI = 95% Confidence Interval

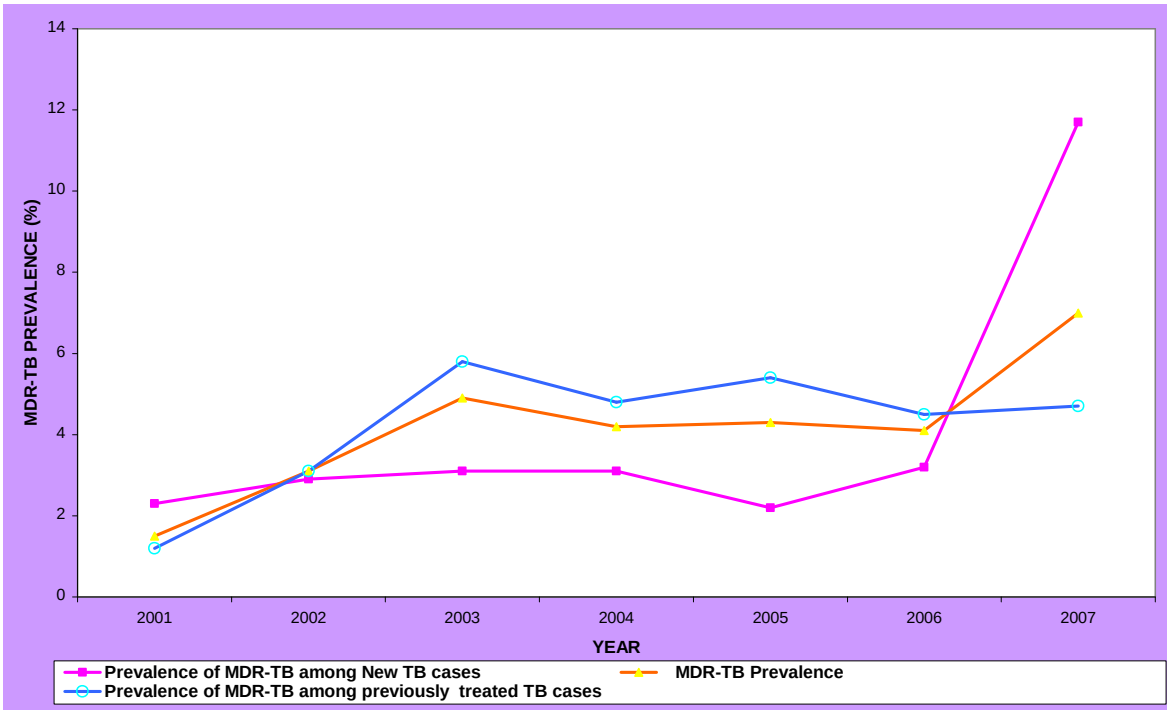

Figure 4: Prevalence of MDR-TB at the Prince Cyril Zulu Communicable Disease Centre from 2001 to 2007

The prevalence of Multi-drug resistant tuberculosis at the Prince Cyril Zulu Communicable Disease Centre was 1.5% (n = 1116) in 2001(Figure 4). The prevalence of MDR-TB increased to 4.9% (n = 1510) in 2003 and remained stable at around 4% for the next three years. There was an increase in the prevalence of MDR-TB after 2006 with an MDR-TB prevalence of 7% (n = 1681) in 2007 (Figure 4).

There was an increase in the prevalence of MDR-TB among new cases from 3.2% (n= 523) in 2006 to 11.7% (n = 555) in 2007 (Table 3). The increase in prevalence of MDR-TB among new cases in 2007 relative to 2001 was significant (OR 5.6; 95% CI: 2.7 to 11.8) (Table 3). The prevalence of MDR-TB among previously treated TB cases was low, 1.2% (n = 770) in 2001 with an increase to 4.7% (n = 1126) in 2007 (Table 3).

From 2002 to 2006 the prevalence of MDR-TB has had a trend of being higher among previously treated TB cases when compared to new TB cases. This trend changed in 2007 when the prevalence of MDR-TB cases was higher (11.7%) (n = 555) among new TB cases when compared to previously treated TB cases (4.7%) (n = 1126) (Figure 4).

4.3. DEMOGRAPHIC CHARACTERISTICSS

During the period 2001 to 2007, the Prince Cyril Zulu Communicable disease Centre had 445 culture confirmed cases of MDR-TB. The study sample population was therefore 890 (Table 4), which comprised of 445 cases (MDR-TB cases) and 445 controls (drug susceptible TB cases).

Table 4: Demographic characteristics of study sample population at the Prince Cyril Zulu Communicable Disease Centre from 2001 to 2007. (n = 890)

	Chi square test			*Logistic regression*	
	Cases (%)	***Controls (%)***	***P-value***	***OR (95%CI)***	***P- value***
N (890)	445(50)	445(50)			
Age			0.3		
Median (IQR)	35 (29 - 43)	13 - 80			
< 25 years	53(12)	67(15)		1 (Ref)	
25 - 45 years	293(66)	287(65)		1.3 (0.9 - 1.9)	0.2
46 - 65 years	94(21)	86(19)		1.4 (0.9 - 2.2)	0.2
> 65 years	5(1)	5(1)		1.3 (0.4 - 4.6)	0.7
Sex			0.2		
Male	260(58)	279(63)		1 (Ref)	
Female	185(42)	166(37)		1.2 (0.9 - 1.6)	0.2
Race			0.4		
African	406(91)	395(89)		1 (Ref)	
Indian	22(5)	33(7)		0.6 (0.4 - 1.1)	0.1
Coloured	11(2.5)	12(3)		0.9 (0.4 - 2.0)	0.8
White	2(0.5)	0		_	
Unknown	4(1)	5(1)		_	
Geographic Area			0.6		
Out of eThekwini	5(1)	6(1.5)		1 (Ref)	
North	130(29)	112(25)		1.3 (0.4 - 4.7)	0.6
South	289(65)	305(68.5)		1.1 (0.3 - 3.8)	0.8
West	21(5)	22(5)		1.1 (0.3 - 4.3)	0.8
Employment status			0.7		
Employed	150(33)	155(35)		1 (Ref)	
Unemployed	289(65)	283(63.6)		1.0 (0.8 - 1.4)	0.7
Scholar / student	3(1)	5(1)		0.6 (0.2- 2.6)	0.5
Pensioner	0	1(0.2)		_	
Unknown	3(1)	1(0.2)		_	
Referral Type			0.4		
Primary Health Clinic	29(6.5)	31(7)		1 (Ref)	
Public Hospital	133(30)	152(34)		0.9 (0.5 - 1.6)	0.8
Private Sector	38(8.5)	42(9.5)		0.9 (0.5 - 1.9)	0.9
Self Referral	136(30)	134(30)		1.0 (0.6 - 1.9)	0.8
Unknown	109(25)	86(19.5)		_	
HIV Status					
HIV Uninfected	9(2)	6(1)	0.9	1 (Ref)	
HIV Infected	92(21)	62(14)		1.0 (0.3 - 2.9)	0.9
Unknown	344(77)	377(85)		_	

4.3.1. Age

The median age among the MDR-TB cases was 35 years with an inter-quartile range of 29 to 43 years. The median age among the controls was 34 years with an inter-quartile range of 29 to 42 years (Table 4). There was no significant difference in age between the MDR-TB cases and controls (*p = 0.3*). Almost 80% (n = 445) of cases with MDR-TB were less than 45 years old.

4.3.2. Sex

There was no significant difference in sex between the MDR-TB cases and the controls (OR 1.2; 95% CI: 0.9 to 1.6; *p = 0.2*) (Table 4).

4.3.3. Race

There was no significant difference between the different race groups among the MDR-TB cases and the controls, *p = 0.4* (Table 4). The proportion of MDR-TB cases was highest among the African race group, but this was not significant when compared to the Indian race group (OR 0.6; 95% CI: 0.4 to 1.1; *p = 0.1*) or when compared to the Coloured race group (OR 0.9; 95% CI: 0.4 to 2.0; *p = 0.8)*) (Table 4). Comparison with the White race group was not possible due to the small numbers.

4.3.4. Geographical area

There was no significant difference between the different geographical areas among the MDR-TB cases and the drug susceptible TB cases, *p = 0.6* (Table 4). A high proportion of MDR-TB cases, 65% (n = 445) and controls, 69% (n = 445) came from the South Sub-district but this was not significant (OR 1.1; 95% CI: 0.3 to 3.8; *p = 0.8)* (Table 4).

4.3.5. Employment status

A high proportion, 65.0% (n = 445) of MDR-TB cases and 63.5% (n = 445) of controls where unemployed but there was no significant difference between being employed and unemployed among the MDR-TB cases and the controls, (OR 1.0; 95% CI: 0.8 to 1.4; *p = 0.7*) (Table 4).

4.4. REFERRAL TYPE

Among the MDR-TB cases, the highest proportion of cases where referrals from public hospitals, 30% (n = 445) and self referrals, 30% (n = 445). The private sector contributed, 8.5% (n = 445) of the MDR-TB cases, this was higher than the referrals from the primary health care clinics, 6.5% (n = 445) (Table 4).

There was no significant difference between the origin of referral namely: self referral, private sector, public hospital and primary health care clinic among the MDR-TB cases and the controls, *p = 0.4* (Table 4).

The highest proportion of referrals came from public hospitals but this was not significant (OR 0.9; 95% CI: 0.5 to 1.6; *p = 0.8*) (Table 4). Similarly self referrals were not significant (OR 1.0; 95% CI: 0.6 to 1.9; *p = 0.8*) (Table 4).

4.5. HIV STATUS

There was no significant difference in HIV status between MDR-TB cases and controls, (OR 0.1, 95% CI 0.3 to 2.9; *p = 0.9*) (Table 4). The HIV status of a large proportion of cases, 75% (n = 445) and controls, 85% (n = 445) was unknown Due to the small number of cases with a known HIV status a breakdown of HIV status among new MDR-TB cases and previously treated MDR-TB cases was not possible.

4.6. PREVIOUS TB

The subgroup analysis found that 603 patients from the 890 patients in the sample population had previous TB (Table 5). This was a high proportion, 67.8% (n = 603) of previous TB treatment. The 603 patients with previous TB comprised of 302 cases (MDR-TB cases) and 301 controls (drug susceptible TB cases). There was no significant difference in previous TB treatment between the MDR-TB cases and the controls, *p = 0.9* (OR 1; 95% CI: 0.7 to 1.3) (Table 5).

Table 5: Subgroup analysis of cases with previous TB at the Prince Cyril Zulu Communicable Disease Centre from 2001 to 2007.

	Chi square test			*Logistic regression*	
	Cases (%)	***Controls (%)***	***P-value***	***OR (95%CI)***	***P-value***
	n = 445	n = 445			
Previous TB treatment			0.9	1 (0.7 - 1.3)	
Yes	302(68)	301(68)			
No	143(32)	144(32)			
Previous TB treatment outcome (n=603)			0.004		
Treatment completed	97(32)	129(43)		1 (Ref)	
Cured	84(28)	55(18)		2.0 (1.3 - 3.1)	0.001
Treatment failure	61(20)	42(14)		1.9 (1.2 - 3.1)	0.006
Treatment defaulted	60(20)	73(24)		1.1 (0.7 - 1.7)	0.7
Unknown	0	2(1)		_	_
***Duration of previous TB treatment in weeks* (n=603)**			0.005		
Median	28	28			
Inter quartile range	28 - 34	24 - 28			
< 24 weeks	59(20)	72(24)		1 (Ref)	
24 - 32 weeks	160(53)	179(59)		1.1 (0.7 - 1.6)	0.7
> 32 weeks	83(27)	50(59)		2.0 (1.2 - 3.3)	0.005
***Duration of previous TB treatment interruption in weeks* (n=243)**			0.3		
Median	20	18			
Inter quartile range	14 - 24	16 - 22			
8 - 16 weeks	18(16)	16(12)		1 (Ref)	
16 - 24 weeks	28(25)	41(32)		0.6 (0.3 - 1.4)	0.2
>24 week	67(59)	73(56)		1.2 (0.5 - 2.9)	0.7

4.6.1. Previous TB treatment outcome

Previous TB treatment outcome between MDR-TB cases and controls was significant, *p = 0.004* (Table 5). A previous TB treatment outcome of treatment failure was significantly associated with MDR-TB (OR 1.9; 95% CI: 1.2 to 3.1; *p = 0.006*) (Table 5). A previous TB treatment outcome of cure was significantly associated with MDR-TB (OR 2.0; 95% CI: 1.3 to 3.1; *p = 0.001*), when compared to treatment completed. A previous TB treatment outcome of treatment default among MDR-TB cases and controls was not significant (OR 1.1; 95% CI: 0.7 to 1.7; *p = 0.7*), when compared to treatment completed. (Table 5)

4.6.2. Duration of previous TB treatment

The median duration of previous TB treatment among MDR-TB cases was 28 weeks, inter-quartile range from 28 to 34. The median duration of previous TB treatment among the controls was 28 weeks, inter-quartile range from 24 to 28 (Table 5). There was significant difference in the duration of previous TB treatment between the MDR-TB cases and the controls, *p = 0.005* (Table 5). A duration of previous TB treatment of greater than 32 weeks was significantly associated with MDR-TB (OR 2.0; 95% CI: 1.2 to 3.3; *p = 0.005*) (Table 5). A duration of previous TB treatment of 24 to 32 weeks was not significantly associated with MDR-TB (OR 1.1; 95% CI: 0.7 to 1.6; *p = 0.07*). (Table 5)

4.6.3. Duration of previous TB treatment interruption

The median duration of previous TB treatment interruption among the MDR-TB cases (n = 113) was 20 weeks with an inter-quartile range from 14 to 24 weeks (Table 5). The median duration of previous TB treatment interruption among the controls (n = 130) was 18 weeks with an inter-quartile range from 16 to 22 weeks (Table 5). There was no significant difference in the duration of previous TB

treatment interruption between the MDR-TB cases and the controls (*p = 0.3*) (Table 5).

Table 6: Multiple regression models for MDR-TB patients with previous TB treatment (n = 603)

Model 1: MDR-TB versus age group and duration of previous TB treatment (n = 603)			
	Odds Ratio	***95% CI***	***P-value***
Age			
< 25 years	1 (Ref)		
25 - 45 years	1.7	(1.00 - 2.99)	0.05
> 46 years	2.0	(1.1 - 3.6)	0.03
Duration previous TB treatment			
<24 weeks	1 (Ref)		
24-32 weeks	1.1	(0.7 - 1.6)	0.81
>32 weeks	2.0	(1.2 - 3.2)	0.01
Model 2: MDR-TB versus age group and previous TB treatment outcome (n = 601)			
Age			
< 25 years	1 (Ref)		
25 - 45 years	1.8	(1.0 - 3.2)	0.03
> 46 years	2.0	(1.1 - 3.7)	0.03
Previous TB treatment outcome			
Treatment completed	1 (Ref)		
Cured	1.9	(1.3 - 3.0)	0.003
Treatment failure	2.1	(1.3 - 3.4)	0.003
Treatment defaulted	1.1	(0.7 - 1.7)	0.58

4.7. MULTIVARIATE ANALYSIS

The multivariate analysis was done using logistic regression (Table 6). No significant variables were found when the full dataset was used. When the analysis was restricted to the subgroup of previously treated cases, 2 multiple logistic regression models had significant findings. In the multiple regression models for previously treated TB cases, age was found to be significantly associated with MDR-TB.

In model 1: age group and duration of previous TB treatment were associated with MDR-TB. There was a significant association between the age group > 46 years and MDR-TB (OR 2.0; 95 % CI: 1.1 to 3.6, *p = 0.03*).
In model 2: The age groups 25 – 45 years (OR 1.8; 95% CI: 1.0 to 3.2; (*p = 0.03*) and the age group > 46 years (OR 2.0; 95% CI: 1.1 to 3.7; *p = 0.03*) were significantly associated with MDR-TB. (Table 6)

Table 7: Timelines from TB diagnosis to MDR-TB diagnosis, treatment and death at the Prince Cyril Zulu Communicable Disease Centre from 2001 to 2007.

	N	*Median*	*IQR*
Time from previous TB to MDR-TB diagnosis (Days)	212	560	392 - 1092
Time from current TB diagnosis to MDR-TB diagnosis (Days)	445	98	77 - 140
Time from MDR-TB diagnosis to MDR-TB treatment (Days)	192	10	1 - 32
Time from current TB diagnosis to death for MDR-TB cases (Days)	27	87	29 - 159

4.8. MDR-TB TIMELINES

The data was not uniformly distributed therefore medians and the inter quartile range (IQR) are reported (Table 7). All MDR-TB cases had a single episode of MDR-TB diagnosed at the Prince Cyril Zulu Communicable Disease Centre between 2001 and 2007. All MDR-TB cases were only counted once. If there were more than one previous episodes of TB, then the time lines were calculated from the last previous episode of TB.

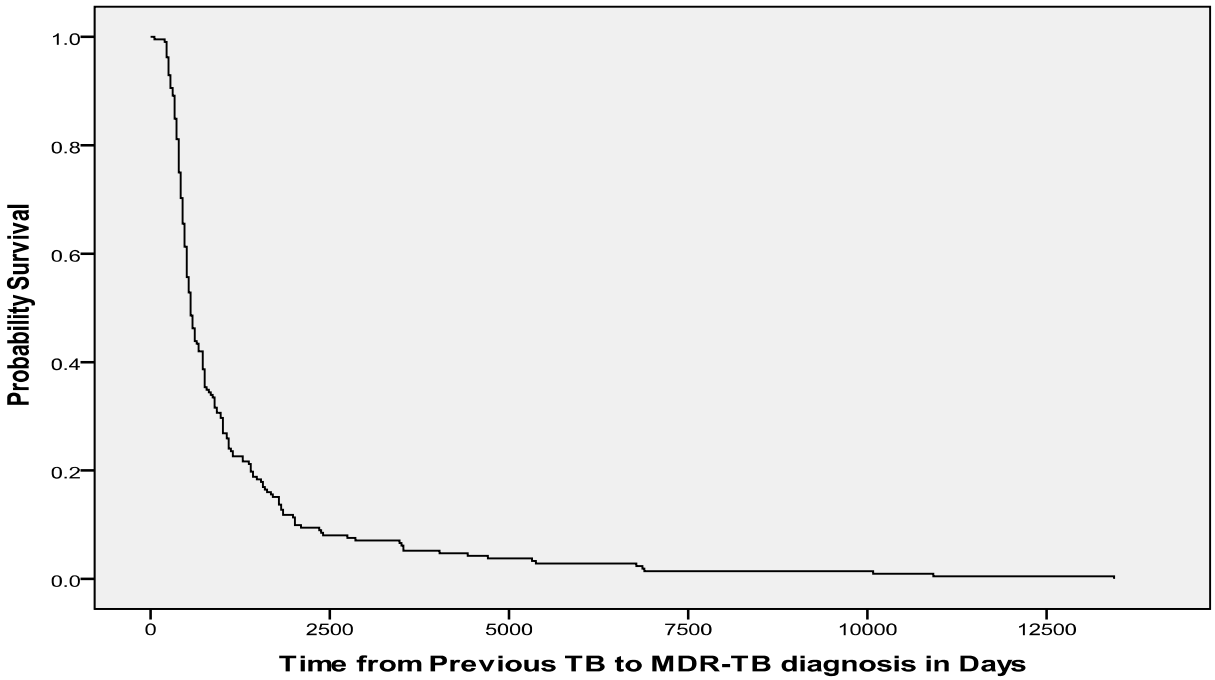

Figure 5: Time from previous TB to MDR-TB diagnosis at the Prince Cyril Zulu Communicable Disease Centre from 2001 to 2007 (n = 212)

4.8.1. Time from previous TB to MDR-TB diagnosis

The median time from previous TB to MDR-TB diagnosis was 560 days, inter quartile range 392 to 1092 days (n = 212) (Table 7). With an increase in time beyond 2500 days after a previous episode of TB the probability of developing MDR-TB decreased to less than 10% (Figure 5).

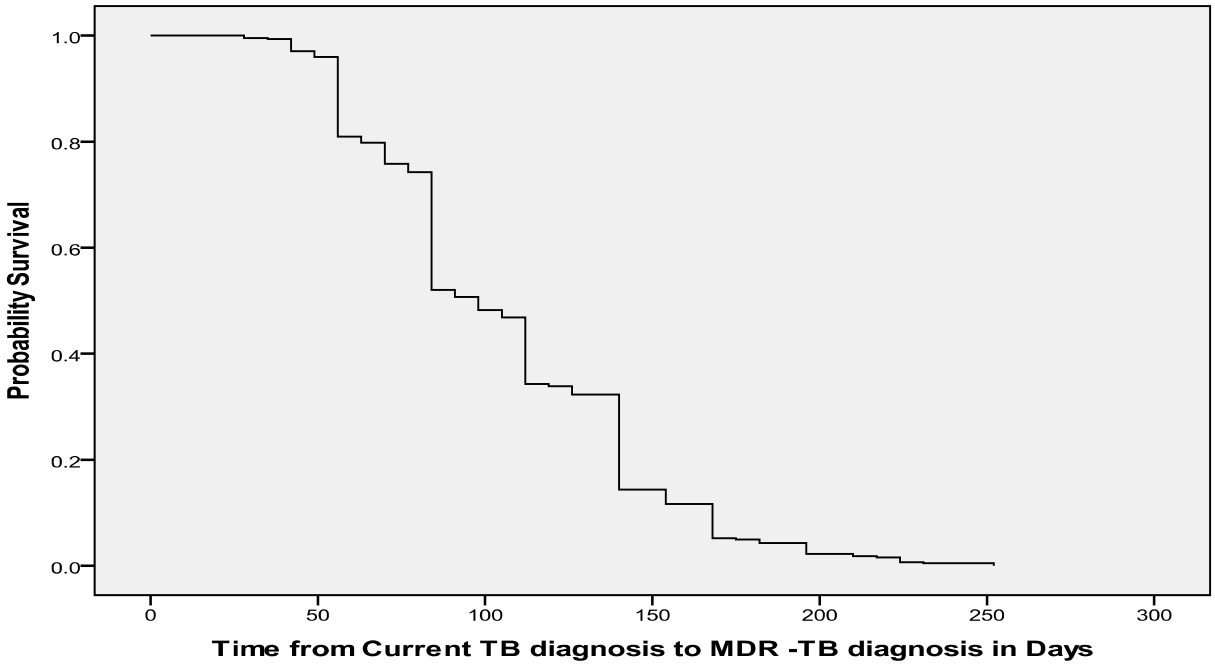

Figure 6: Time from current TB diagnosis to MDR-TB diagnosis at the Prince Cyril Zulu Communicable Disease Centre from 2001 to 2007 (n = 445)

4.8.2. Time from current TB diagnosis to MDR-TB diagnosis

The median time from current TB diagnosis to MDR-TB diagnosis was 98 days, inter quartile range 77 to 140 days (n = 445) (Table 7).

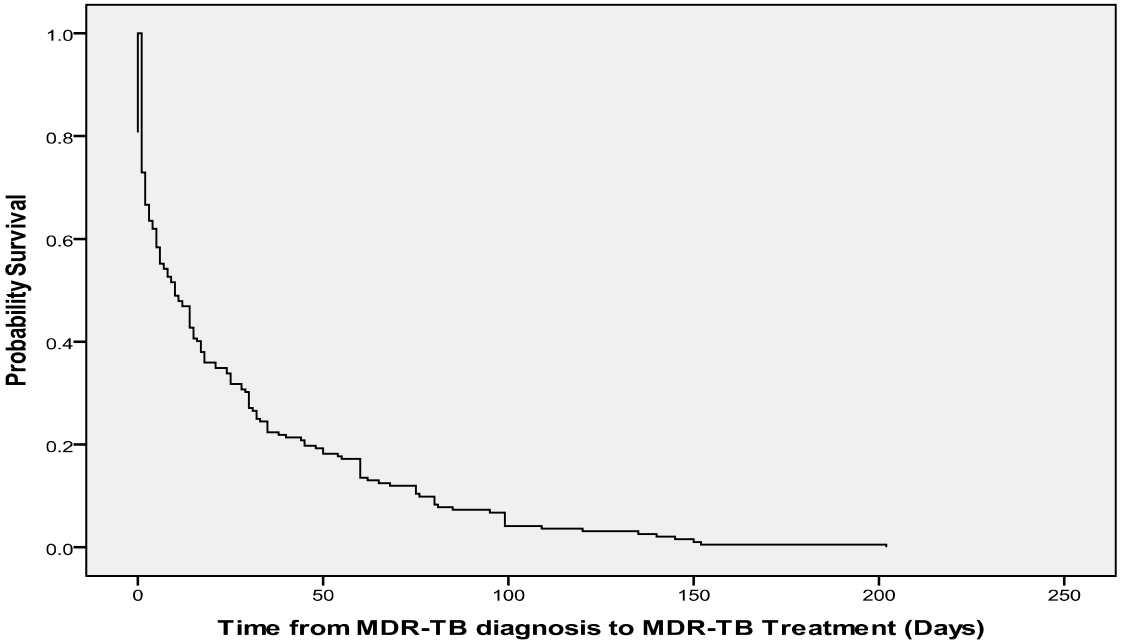

Figure 7: Time from MDR-TB diagnosis to MDR-TB treatment at the Prince Cyril Zulu Communicable Disease Centre from 2001 to 2007 (n = 192)

4.8.3. Time from MDR-TB diagnosis to MDR-TB treatment

The median time from MDR-TB diagnosis to MDR-TB treatment was 10 days, inter quartile range 1 to 32 days (n = 192) (Table 7).

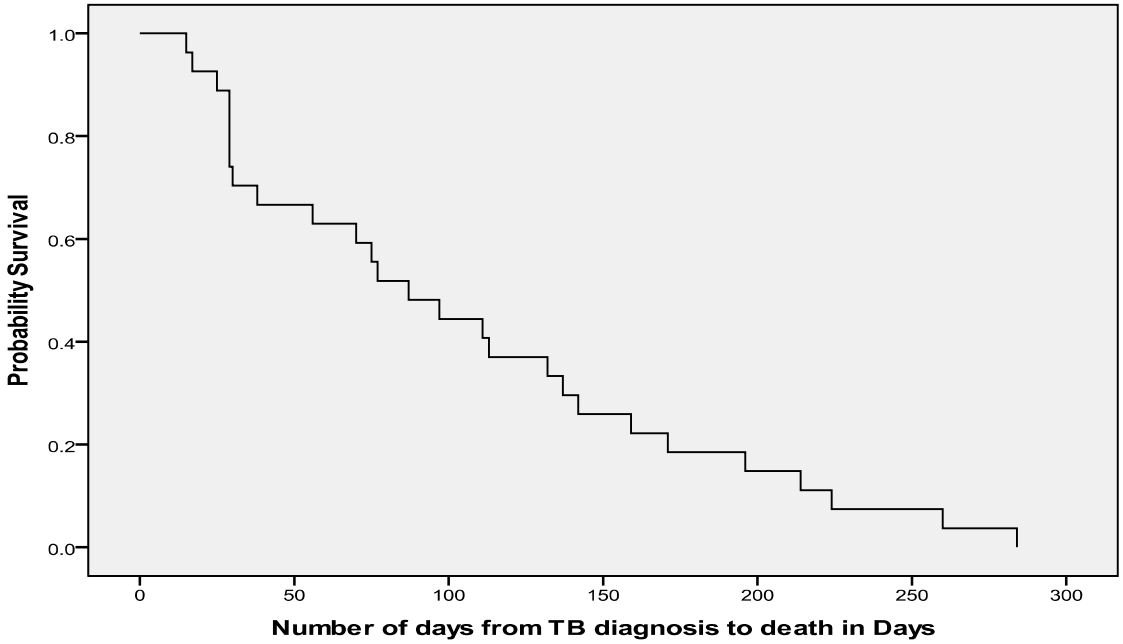

Figure 8: Time from current TB diagnosis to death at the Prince Cyril Zulu Communicable Disease Centre from 2001 to 2007 (n = 27)

4.8.4. Time from current TB diagnosis to death

The MDR-TB cases were followed up until MDR-TB treatment was commenced. The results from this study that relate to death, refers to patients who died before starting MDR-TB treatment. MDR-TB cases that died were included in the analysis. The median time from current TB diagnosis to death for MDR-TB cases was 87 days, inter quartile range 29 to 159 (n = 27), (Table 7). The Kaplan-Meier curve demonstrates that the probability of death decreases as length of from the current TB diagnosis increases. (Figure 8)

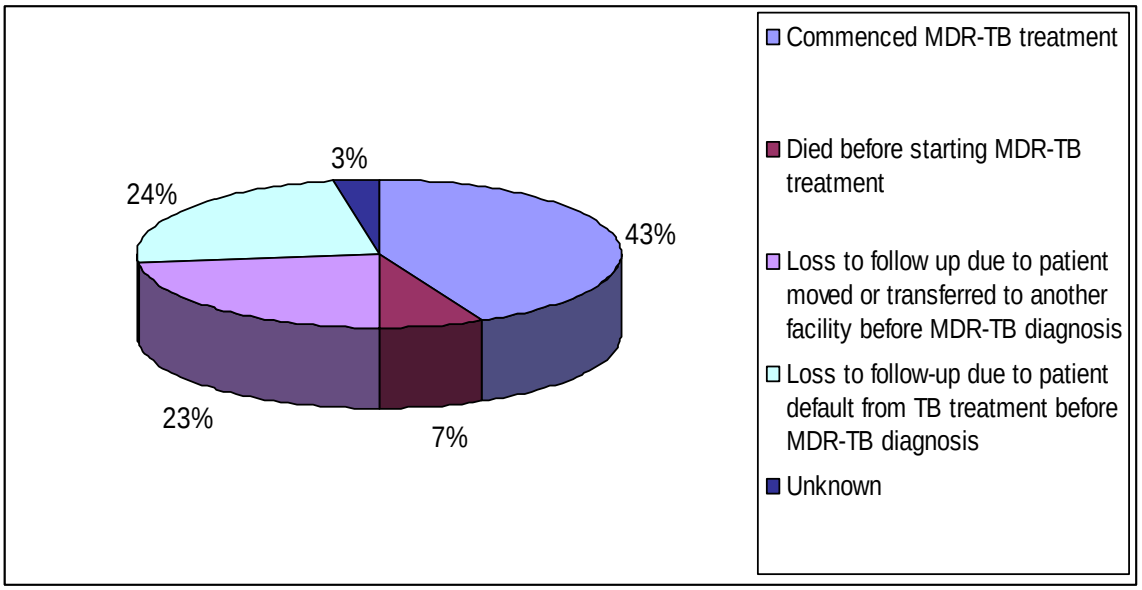

Figure 9: MDR-TB outcomes at the Prince Cyril Zulu Communicable Disease Centre between 2001 and 2007 (n = 445)

4.9. MDR-TB FOLLOW-UP OUTCOMES

Analysis was done of the outcome of the 445 MDR-TB cases that were diagnosed at the Prince Cyril Zulu Communicable Disease Centre between 2001 and 2007 (Figure 9). It was confirmed that 43% (n = 445) of MDR-TB cases had commenced MDR-TB treatment at the MDR-TB referral hospital. A large proportion, 47% (n = 445) were lost to study follow-up. From the MDR-TB cases that were lost to follow-up, 23% (n = 209) of the cases were lost to study follow-up because the patients were moved or transferred to another facility and 24% (n = 209) of the cases were lost to study follow-up because the patients defaulted from TB treatment before the MDR-TB diagnosis was made (Figure 9). A concerning finding was that 7% (n = 445) of MDR-TB cases died before they started MDR-TB treatment (Figure 9).

4.10. CHAPTER SUMMARY

The important finding of this study was that the Prince Cyril Zulu Communicable Disease Centre experienced an increase in the prevalence of MDR-TB in 2007 which was largely due to the increase in prevalence of MDR-TB among new TB cases. The MDR-TB prevalence increased to 11.7% among new TB cases in 2007, this increase in prevalence of MDR-TB among new TB cases was significant. The study found that there was no significant association between age, sex, race, geographic area, employment status, referral type, HIV status and MDR-TB. The subgroup analysis of patients with previous TB found that there was a significant association with a previous TB treatment outcome of treatment failure and MDR-TB. A duration of previous TB treatment of greater than 32 weeks was also found to be significantly associated with MDR-TB. Among patients with previous TB treatment, age > 46 years was significantly associated with MDR-TB. The median time from TB diagnosis to MDR-TB diagnosis was 98 days and from current TB diagnosis to MDR-TB treatment 10 days. It was confirmed that 43% of MDR-TB cases commenced MDR-TB treatment and 47% of MDR-TB cases were lost to study follow-up. Seven percent of MDR-TB cases died before commencing MDR-TB treatment. The median time from current TB diagnosis to death was 87 days. These findings of the study will be discussed further in the next chapter.

CHAPTER 5. DISCUSSION

5.1. INTRODUCTION

The results that were presented in the previous chapter are discussed in this chapter. The prevalence of MDR-TB at the Prince Cyril Zulu Communicable Disease Centre is discussed in relation to the provincial, national and global prevalence of MDR-TB. Risk factors associated with MDR-TB are compared with the results from other studies. MDR-TB timelines and outcomes are discussed. Possible explanations for some of the results are provided.

5.2. PREVALENCE OF MDR-TB

The prevalence of MDR-TB at the Prince Cyril Zulu Communicable Disease Centre in 2001 (1.5%: 0.7% among new cases and 0.8% among previously treated TB cases) was lower than the prevalence of MDR-TB in KwaZulu-Natal (2001: 1.7% among new cases and 7.7% in previously treated TB cases).[35] The prevalence of MDR-TB at Prince Cyril Zulu Communicable Disease Centre was also lower than the national prevalence of MDR-TB in South Africa in 2002 (2.9%: 1.6% in new cases and 6.6% in previously treated TB cases).[25] For the period 2001 to 2002 the prevalence of MDR-TB was also similar to the global picture where MDR-TB isolates constituted 1 to 3% of global isolates.[7].

The increase in MDR-TB prevalence at the Prince Cyril Zulu Communicable Disease Centre to 4.9% in 2003 may have been due to increased staff awareness following the national drug resistance survey in 2002 which could have led to improved case detection and reporting The number of sputum cultures done by the Prince Cyril Zulu Communicable Disease Centre in 2003 increased by 15% compared to the number of sputum cultures done in 2002 (Table 3). It has been reported in the United States,

that with increased awareness and earlier diagnosis, mortality among HIV infected MDR-TB cases improved from 100% to 50%.

The consistency of the prevalence of MDR-TB at the Prince Cyril Zulu Communicable Disease Centre from 2003 to 2006, remaining around 4% was probably due to the stability of the performance of the tuberculosis programme at the facility. The treatment success, treatment failures and treatment defaulters remained consistent over this period (Figure 3).

The sudden increase in the prevalence of MDR-TB at the Prince Cyril Zulu Communicable Disease Centre from 4.1% in 2006 to 7% in 2007 was an important finding. The importance of this finding is that is that most of this increase occurred among new TB cases (Figure 4). The increase in MDR-TB prevalence among new cases to 11.7 % in 2007 was significant (OR 5.6; 95% CI 2.65 to 11.83) .This implies that the risk of new TB patients developing MDR-TB was 5 times greater in 2007 compared to 2001. For South Africa the MDR-TB prevalence among new TB cases was 1.8% in 2007.[1] A MDR-TB prevalence of 11.7% among new TB cases is high. There was no available data for the provinces for 2007.

A possible explanation for the increase in prevalence of MDR-TB among new TB cases is increased awareness around drug resistance and therefore increased case detection. The XDR-TB outbreak in Tugela Ferry occurred in 2005, but information about the outbreak was released in 2006. There was a large amount of media coverage in 2006 of the XDR-TB outbreak in Tugela Ferry, [30] which may have contributed to increased awareness and a higher index of suspicion for MDR-TB and XDR-TB. If improved awareness and increased case detection was the explanation for the increased prevalence of MDR-TB among new TB cases, there would have been an increase in the number of sputum cultures done by the Prince Cyril Zulu Communicable Disease Centre in 2007. The results however show that there was only a 6% (95) increase in the number of sputum cultures done from 2006 to 2007

(Table 3), compared to the 11% (153) increase in the number of sputum cultures done from 2005 to 2006.

"High defaulter rates for drug susceptible TB treatment, likely resulted in the creation of large numbers of MDR-TB strains." [41] The Prince Cyril Zulu Communicable Disease Centre does have a high defaulter rate contributing to the development of MDR-TB. The defaulter rate for 2001, 2006 and 2007 was 24.3%, 28.7% and 27.6% respectively (figure 2). This does not explain the exponential rise in MDR-TB cases.

The most likely explanation for the increase in prevalence of MDR-TB among new TB cases is that there was increased transmission of MDR-TB in 2007. The transmission of drug resistant TB is the same as for drug susceptible strains, transmission of TB occurs through droplet nuclei, aerosolized by patients with infectious pulmonary TB and inhaled by another individual. [43] The Prince Cyril Zulu Communicable Disease Centre is an outpatient facility, so confirmed MDR-TB patients are sent home, back into the community while waiting for MDR-TB treatment. The finding that patients with confirmed MDR-TB waited a median time of 98 days for diagnosis and an additional 10 days before treatment commencement is probably the biggest contributory factor (Table 7). This does not include the time from the start of symptoms until attending the clinic. The Prince Cyril Zulu Communicable Disease Centre does limit patients diagnosed with MDR-TB from working, but no other restrictions are placed on patients while they are waiting for MDR-TB treatment. Patients are informed of basic infection control measures (cough practices, natural ventilation) but masks are not issued to patients and patients are not restricted from using public transport or attending community gatherings. The Prince Cyril Zulu Communicable Disease Centre has adequate infection control measures with regard to the structure of the building; waiting area design and a negative pressure ventilation system to reduce transmission of TB within the facility. Infection control measures at a facility level are well documented

but there is limited literature on infection control in a household and community setting.[41]

A MDR-TB 'hot spot' is defined by the World Health Organization as a geographical setting where the prevalence of MDR-TB among new patients exceeds 3%.[25] A MDR-TB prevalence of 11.7% in 2007 among new TB cases at the Prince Cyril Zulu Communicable Disease Centre should raise concerns as to whether the eThekwini district is an MDR-TB 'hot spot'. This finding also raises the concern that there are most likely other districts in South Africa with high MDR-TB prevalence among new TB cases. "Primary resistance is usually 5% or less in good National programmes" [19]

The findings of this study imply that there is deterioration in the performance of the TB control programme at the Prince Cyril Zulu Communicable Disease Centre and in the eThekwini district. There is an urgent need to address the issues of infection control and delays in diagnosis and treatment of MDR-TB on order to reduce the transmission of MDR-TB.

5.3. DEMOGRAPHIC CHARACTERISTICS

5.3.1. Age

The finding that age was not significantly associated with MDR-TB was similar to the South African national survey of tuberculosis drug resistance and the Durban study.[25, 26] The multivariate analysis finding that among previously treated TB cases, the risk of MDR-TB increased as age increased is supported by the survey of 11 countries [6] where patients aged 35 to 44 years and 55 to 64 years were more likely to have MDR-TB.[6] This implies that for new TB cases age is not a risk factor for MDR-TB and this can be generalized for Durban. However a history of previous TB treatment increased the risk of MDR-TB for patients older that 46 years (OR 2.0; 95% CI: 1.1 to 3.0*; p = 0.03*) (Table 6).

5.3.2. Sex

Sex was not significantly associated with MDR-TB. This finding was the same as the South African national survey of tuberculosis drug resistance and several other studies.[6,25,26,27] This differed from the WHO regions were MDR-TB was associated with the male sex.[21] The similarity of the results to the South African national survey implies that the results could only be generalized for South Africa, but not for other countries. Sex was not a confounder for MDR-TB.

5.3.3. Race

The finding that MDR-TB was not significantly associated with any race group was the same as the Durban study.[26] The proportion of MDR-TB among the different race groups was in keeping with the demographic characteristics of the eThekwini district were 68% of the population were African, 20% Indian, 9% White and 3%, Coloured. The importance is that the results of this study can then be generalized for Durban. This implies that, if living in Durban, the risk of getting MDR-TB is the same across the different race groups.

5.3.4. Geographical Area

This study was unable to establish an association between MDR-TB and geographical area. This finding was similar to the findings of a study in India.[7] The fact that 65% of MDR-TB cases come from the South Sub-district of eThekwini is due to the fact that the Prince Cyril Zulu Communicable Disease Centre is located in the South Sub-district. The South Sub-district is also the largest sub district in the eThekwini District with the highest population when compared to the North and West Sub-districts.

5.3.5. Employment Status

Employment status was not significantly associated with MDR-TB. However, 65% of MDR-TB cases and 64% of drug susceptible TB cases were unemployed. A study at a TB referral hospital in Durban found that 58.2% (n = 1209) of MDR-TB patients were unemployed and 22.9% (n = 1209) were employed[41]. Unemployment rates were high among MDR-TB patients in Durban. “Deteriorating socioeconomic conditions” [44] was identified as a contributor to the worsening TB epidemic in South Africa. “A poor diet”[12] was also implicated in the development of active MDR-TB. Unemployment does not necessarily reflect poor diet or socioeconomic status but these aspects could be closely related and can suggest the need for further research in this area.

5.4. REFERRAL TYPE

There was no significant association between MDR-TB and the type of referral namely: self referral, private sector, public hospital and primary health clinic. This finding differed from the findings of 2 South African and a Brazilian study which found that prior hospitalization was significantly associated with MDR-TB.[25, 32, 40] This finding refutes the possible explanation that the high prevalence of MDR-TB at this facility is because of referrals from hospitals and primary health clinics. The same proportion of MDR-TB cases were from hospital, 30% (n= 445) and self referrals, 30% (n = 445). The private sector was not included in the South African national survey. Information on MDR-TB in the private sector is limited or non-existent. The finding that 8.5% (n = 445) of MDR-TB cases were referred from the private sector suggest that MDR-TB is prevalent in the private sector and the private sector should be included in the surveillance of MDR-TB.

5.5. HIV STATUS

There was no significant association between HIV and MDR-TB. This finding was similar to the systematic review of 32 studies which included 3 South African studies.[5, 34] It is a concern that for a large proportion of MDR-TB cases (75%) the HIV status was unknown. HIV was not a confounder for MDR-TB. The case-fatality among patients co-infected with HIV and MDR-TB is 72 to 89%.[5] Having a high number of MDR-TB patients with unknown HIV status would delay the commencement of anti-retroviral therapy and contribute to the morbidity and mortality associated with MDR-TB and HIV co-infection.

The MDR-TB prevalence was high among new TB cases in 2007 (11.7%). The evidence shows that HIV is associated with primary MDR-TB.[5] It was not possible to do a breakdown of HIV status between MDR-TB among new TB cases and MDR-TB among previously treated TB cases because of the small number of MDR-TB cases with a known HIV status.

5.6. PREVIOUS TB

5.6.1. Previous TB Treatment

Many studies have demonstrated that previous TB treatment was an important predictor of MDR-TB.[25, 26, 31, 32, 33] This study found that there was no significant association between previous TB treatment and MDR-TB. A possible explanation for this could be that some patients may have received previous TB treatment but were misclassified as not having had previous TB treatment. “Patients don’t always reveal previous TB treatment history”[25] Information on previous TB treatment was collected as part of the routine data collection at the Prince Cyril Zulu Communicable Disease Centre, and not by trained research interviewers so misclassification could have occurred. The misclassification bias was not quantified. The assumption was

made that misclassification of previous treatment would be minimal as majority of patients previous TB records would be available to confirm previous TB treatment.

5.6.2. Previous TB Treatment Outcome

A previous TB treatment outcome of treatment failure was significantly associated with MDR-TB. This finding was similar to the South African national survey and the study on South African gold miners.[25, 33] A surprising finding was that a previous TB treatment outcome of treatment default was not significantly associated with MDR-TB. This differed from most literature and the South African national survey on drug resistance. [25] An unexpected finding which is contrary to current evidence on MDR-TB was that a previous TB treatment outcome of cured was significantly associated with MDR-TB. The most likely explanation for these contrary findings would be misclassification of previous TB treatment outcomes.

The survey of tuberculosis drug resistance KwaZulu-Natal survey reported, that “a considerable proportion of patients seemed to be misclassified by the routine health services”.[35] The consequence of misclassification would be that misclassified patients would receive the wrong treatment regimen. [35]

Another explanation for the finding could be that although many MDR-TB cases were previously treated for TB their current MDR-TB was due to exogenous re-infection (primary resistance) and was not the result of inadequate drug therapy (acquired resistance). Therefore the previous TB treatment outcome would have no relation with the current TB and MDR-TB infection.

The Prince Cyril Zulu Communicable Disease Centre is in a Province with highest TB caseload[15] and a high prevalence of HIV. The exogenous re-infection possibility is supported by the study conducted in KwaZulu-Natal which confirmed that 74% of

previously treated TB patients developed MDR or XDR-TB as a result of exogenous re-infection (primary resistance). [38]

5.6.3. Duration of Previous TB Treatment

A duration of previous TB treatment of greater than 32 weeks was significantly associated with MDR-TB (OR 2.0; 95% CI: 1.2 to 3.3; *p = 0.005*) (Table 5). This finding was similar to a study involving 11 countries which found that as the total duration of prior tuberculosis treatment increased so to did the likelihood of having MDR-TB.[6] That study showed that receiving TB drugs for a period of time greater than 6 months increased the risk of MDR-TB. [6] It was found that 27% (n = 302) of MDR-TB cases at the Prince Cyril Zulu Communicable Disease Centre received more than 32 weeks of TB treatment during the previous episode of TB. The TB control programme recommends 24 weeks of TB treatment for new TB cases and 32 weeks of TB treatment for re-treatment cases. The Prince Cyril Zulu Communicable Disease Centre, while adhering to these recommendations, does extend TB treatment beyond the recommended duration if there is radiological evidence that the TB has not fully resolved. In these situations TB treatment is extended even if sputum analysis indicates cure.

5.6.4. Duration of Previous TB Treatment Interruption

The duration of previous TB treatment interruption was not significantly associated with MDR-TB. No current literature was found which investigated the duration of previous TB treatment interruption, therefore the finding of this study could not be compared with other studies. For the Prince Cyril Zulu Communicable Disease Centre, this finding, together with the finding that previous TB treatment default was not significantly associated with MDR-TB, may suggest that although treatment adherence should remain central to TB control, this strategy alone may be insufficient to stop the increase in MDR-TB.

5.7. MDR-TB TIMELINES

5.7.1. Time from previous TB to MDR-TB diagnosis

The Kaplan- Meier curve demonstrated that 75% (n = 212) of MDR-TB cases developed MDR-TB within 1092 days from the previous. The results imply that the probability of getting MDR-TB after previous TB decreases with time. There was no literature available on time from previous TB to MDR-TB diagnosis.

5.7.2. Time from current TB diagnosis to MDR-TB diagnosis

The median time from current TB diagnosis to MDR-TB diagnosis was 98 days. The duration of the process of sputum culture and sensitivity to confirm MDR-TB is 6 weeks (42 days) [46] This is similar to other laboratories in South Africa, where most commonly used culture and drug susceptibility testing methodologies require 6 to 8 weeks for results. [40] The Inkosi Albert Luthuli Laboratory informs the Prince Cyril Zulu Communicable Disease Centre immediately when resistance to isoniazid and rifampicin is detected. If sputum was sent for culture and sensitivity at the time of TB diagnosis then the majority of MDR-TB cases would have been diagnosed by 42 days. The median time was 98 days from current TB diagnosis to MDR-TB diagnosis. This result implies that 50% of MDR-TB cases did not have sputum sent for culture and sensitivity at the time of TB diagnosis. This implies that 50% (n = 445) of the MDR-TB patients had sputum sent for culture and sensitivity at their 2 month follow up visit. Indications for sending a sputum specimen for culture and sensitivity at a 2 month follow-up visit would have been; radiological deterioration or a 2 month positive smear. “Delays in diagnosis lead to clinical deterioration of patients and ongoing drug-resistant TB transmission in the community or hospital.” [40]

5.7.3. Time from MDR-TB diagnosis to MDR-TB treatment

MDR-TB patients waited a median time of 10 days from MDR-TB diagnosis to MDR-TB treatment. This delay is due to the lack of beds for admission of patients to the MDR-TB referral hospital for MDR-TB treatment initiation. This reason for delay in MDR-TB treatment commencement is also experienced in other countries where there is also "insufficient hospital capacity and long waiting lists for treatment."[43]. A study at a MDR-TB referral hospital in Durban did Kaplan–Meier curves for time from XDR-B diagnosis to XDR-TB treatment initiation.[45] The median time between diagnosis and initiation of therapy for patients who died was 88days, the median time between diagnosis and initiation of therapy for patients who survived was120 days.[45] Comparatively, a median time of 10 days from MDR-TB diagnosis to MDR-TB treatment may not appear to be long, however in the context of the situation where these patients are not isolated, it raises the concern of increased risk of MDR-TB transmission. This concern is supported by literature which confirms that appropriate isolation of suspected MDR-TB cases until disproved or appropriately treated is important because of nosocomial and community outbreaks.[11]

5.7.4. Time from current TB diagnosis to death

The time from MDR-TB diagnosis to death was not calculated. This was because of the study design (nested case control), the results of the study found that 46% of the 27 deaths among the MDR-TB cases had occurred before bacteriological confirmation of the MDR-TB. Deaths before confirmation of MDR-TB has been documented elsewhere, "Overall outcomes are substantially worsened with HIV co-infection, largely owing to very high mortality in both MDR and XDR tuberculosis within the first 2 months, before patients can be diagnosed and started on treatment."[43]

The finding that 25% of deaths among the MDR-TB cases occurred within 29 days from TB diagnosis and 50% of deaths occurred within 87 days from TB diagnosis suggests that the progression to death in untreated MDR-TB cases is short. Survival times for MDR-TB were not found, but the literature on survival times for XDR-TB showed that the median survival from the time of sputum collection to death was 16 days (IQR 6 – 37) [42]

A comparison of the median time from current TB diagnosis to MDR-TB diagnosis of 98 days with the median time from current TB diagnosis to death of 87 days, together with the finding that 46% (n = 27) of deaths occurred before bacteriological confirmation of MDR-TB shows that MDR-TB patients are dying before the diagnosis of MDR-TB. This raises the concern that other TB deaths may be MDR –TB related and may be occurring before MDR-TB was suspected because not all new TB cases have sputum sent for culture and sensitivity at the time of TB diagnosis. The current TB guidelines for South Africa do not recommend sputum culture for all TB patients.[15]The results of his study support the need for sputum culture for all TB patients in areas where the MDR-TB prevalence among new TB cases is high (> 3%). “To provide universal drug susceptibility testing for all patients with suspected tuberculosis,” has been identified as an important strategy to prevent new cases and manage existing cases of MDR-TB. [43] The challenge that routine cultures for all TB suspects is not feasible due to limited laboratory capacity and cost is known. [40] However, in view of the high costs of MDR-TB, resources need to be allocated to establish laboratory capacity capable of undertaking culture and drug susceptibility testing for all TB patients to ensure early diagnosis, and to assess prevalence of drug resistance, in resource limited settings. [42]

The finding that 25% of deaths among MDR-TB cases occurred within 29 days of TB diagnosis supports the concern that many TB deaths among new TB cases may be MDR-TB related and may be occurring before MDR-TB was suspected or diagnosed. These deaths would also be missed cases of MDR-TB. They would

contribute to the increased transmission of MDR-TB in the community. Missed cases of MDR-TB imply that there is underestimation of the prevalence of MDR-TB.

5.8. MDR-TB FOLLOW-UP OUTCOMES

The outcomes of the MDR-TB diagnosis at the Prince Cyril Zulu Communicable Disease Centre could not be compared to other studies because what was presented in this study was not the MDR-TB treatment outcome but the follow-up outcome of each patient diagnosed with MDR-TB until MDR-TB treatment commencement. Although it could be confirmed that only 43% (n = 445) of patients diagnosed with MDR-TB commenced MDR-TB treatment at the MDR-TB referral hospital, it is possible that many of the 23% (n = 445) of patients who were lost to study follow-up because they were moved or transferred to other facilities, did actually commence treatment for MDR-TB. The staff at the Prince Cyril Zulu Communicable Disease Centre ensure that bacteriological results of drug resistance are forwarded to the facilities to which patients have been transferred.[11] This however, cannot be quantified and the possibility that a proportion of these patients could be dying at home or defaulting treatment has to be considered.

The finding that 24% (n = 445) of patients diagnosed with MDR-TB were lost to follow-up due to the fact that the patients defaulted from TB treatment was similar to the findings of a study at a MDR-TB referral hospital in Durban where 21% (n = 1209) on MDR-TB treatment defaulted from treatment.[41] High defaulter rates for drug susceptible TB and MDR-TB have most likely resulted in the creation of large numbers of drug resistant strains.[41] It has been recommended that to reduce the number of MDR-TB patients defaulting, decentralization of MDR-TB treatment should be considered, by creating community- based treatment programmes or satellite in-patient centres.[41] The benefit of decentralization of MDR-TB treatment is

[11] Information obtained from the manager of the Prince Cyril Zulu Communicable Disease Centre. It is routine procedure that medical staff at the Prince Cyril Zulu Communicable Disease Centre forward bacteriological results of drug resistance to the facilities to which patients have been transferred.

that it will reduce the current patient load at MDR-TB referral hospitals and therefore reduce the delays in MDR-TB treatment initiation.

The finding that 7% of MDR-TB cases died before they started MDR-TB treatment is concerning because patients are waiting a median time of 10 days from MDR-TB diagnosis to commencing MDR-TB treatment. This raises the issue of whether MDR-TB patients are dying because of delays in receiving treatment for MDR-TB. The Prince Cyril Zulu Communicable Disease Centre does not initiate MDR-TB treatment. MDR-TB patients are referred to the designated MDR-TB referral hospital in the district for commencement of MDR-TB treatment. The Prince Cyril Zulu Communicable Disease Centre is only able to refer MDR-TB patients for commencement of MDR-TB treatment when there are beds available at the MDR-TB referral hospital. The delay in commencement of MDR-TB treatment is therefore due to the lack of availability of beds at the MDR-TB referral hospital.

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5.10. LIMITATIONS

- Information bias may have occurred and could have been responsible for misclassification of previous TB treatment. It is possible that patients did not reveal that they had previous TB treatment if they had not completed their previous TB treatment. The reason for this would have been to avoid a negative reaction from the healthcare worker obtaining the history. Information bias was reduced by cross checking information obtained from patients current visit with records from patients previous visits to the Prince Cyril Zulu Communicable Disease Centre.

- Death before diagnosis was included in the analysis and may have been contributed to possible bias.

- The results on MDR-TB prevalence from this study are limited to the Prince Cyril Zulu Communicable Disease Centre. The prevalence results do not reflect the prevalence of MDR-TB for the province or other cities in South Africa. However due to the high number of TB patients seen at this facility, these results could be generalized to the eThekwini district.

- The waiting times for MDR-TB diagnosis and MDR-TB treatment commencement are limited to the Prince Cyril Zulu Communicable Disease Centre as they are dependent on the laboratory and MDR-TB referral hospital used by this facility. Other facilities using the same laboratory and hospital may be experiencing similar delays but these delays do not reflect the situation in other areas in the Province or in South Africa.

5.10. CHAPTER SUMMARY

The important issues arising from the discussion of the results are that there are delays in the diagnosis of MDR-TB at the Prince Cyril Zulu Communicable Disease Centre. Patients diagnosed with MDR-TB are experiencing further delays before MDR-TB treatment is commenced. Due to the delayed diagnosis and lack of isolation, patients spent more than 100 days in the community with MDR-TB. This was probably the main contributor to the spread of MDR-TB among new TB cases in the eThekwini District and was most likely responsible for the significant increase in prevalence of MDR-TB among new TB cases at the Prince Cyril Zulu Communicable Disease Centre in 2007. It is a concern that the prevalence of MDR-TB among new TB cases was 11.7% at the Prince Cyril Zulu Communicable Disease Centre in 2007 when the national prevalence of MDR-TB among new TB cases in South Africa was 1.8% in 2007. Recommendations to address some of the findings and concerns raised will be provided in the next chapter.

CHAPTER 6. CONCLUSIONS AND RECOMMENDATIONS

6.1. INTRODUCTION

This chapter provides the conclusions of the study based on the findings and discussion presented in the previous two chapters. Recommendations to reduce the transmission and spread of MDR-TB are offered to the Prince Cyril Zulu Communicable Disease Centre and to the TB control programme. Suggestions for further research are also made.

6.2. CONCLUSIONS

The most important finding of this study was that the Prince Cyril Zulu Communicable Disease Centre experienced an increase in the prevalence of MDR-TB in 2007 which was largely due to a significant increase in prevalence of MDR-TB among new TB cases. The MDR-TB prevalence was 11.7% among new TB cases and 4.7% among previously treated TB cases in 2007. The study found that there was no significant association between demographic characteristics and MDR-TB. There was no significant association between HIV status and MDR-TB. The subgroup analysis of patients with previous TB found that there was a significant association with a previous TB treatment outcome of treatment failure and MDR-TB. A duration of previous TB treatment of greater than 32 weeks was also found to be significantly associated with MDR-TB. Among MDR-TB patients with previous TB, age > 46 years was significantly associated with MDR-TB. There were delays in the diagnosis of MDR-TB at the Prince Cyril Zulu Communicable Disease Centre. Patients diagnosed with MDR-TB were waiting a median time of 10 days before MDR-TB treatment was commenced. Due to the delayed diagnosis and lack of isolation, patients spent over 100 days in the community with MDR-TB. This was probably the main contributor to the spread of MDR-TB in the eThekwini District. It was confirmed that 43% of MDR-TB cases commenced MDR-TB treatment, 23% of

the cases were lost to study follow-up because the patients were moved or transferred to another facility, 24% of the cases were lost to follow-up because the patients defaulted from TB treatment before the MDR-TB diagnosis was made and 7% of MDR-TB cases died before they started MDR-TB treatment. The Prince Cyril Zulu Communicable Disease centre needs to take urgent steps to reduce the delays in diagnosis of MDR-TB, reduce the waiting time for MDR-TB treatment commencement and improve infection control measures to reduce the spread of MDR-TB.

Recommendations to the Prince Cyril Zulu Communicable Disease Centre and TB control programme to reduce the spread of MDR-TB will follow.

6.3. RECOMMENDATIONS

6.3.1. Recommendations for Prince Cyril Zulu Communicable Disease Centre

- The Prince Cyril Zulu Communicable Disease Centre should develop a routine monitoring system to determine the incidence and prevalence of MDR-TB at the facility on an annual basis. This should include distinguishing between primary and acquired drug resistance so that emphasis can be placed on the appropriate strategy to address the drug resistance problem. If the majority of the cases of MDR-TB develop as a result of acquired resistance then emphasis must be placed on strengthening directly observed treatment short course (DOTS) and improving treatment cure rates. If primary resistance is a major factor then the creation and implementation of infection control measures at household and community level must be added as a critical component of the control strategy in order to curb the ongoing transmission of drug resistant strains.[38] The responsibility for this intervention lies with the Prince Cyril Zulu Communicable Disease Centre manager and with the eThekwini District TB Control Programme coordinator.

- In response to the MDR-TB prevalence of 11.7% among new TB cases the Prince Cyril Zulu Communicable Disease Centre should consider performing sputum culture and sensitivity on all new TB cases. This would prevent delays in MDR-TB diagnosis and MDR-TB treatment commencement.

- In response to the delays in diagnosing MDR-TB the Prince Cyril Zulu Communicable Disease Centre should in conjunction with the TB culture laboratory explore other options to detect TB drug resistance in a shorter time instead of waiting six weeks for culture and sensitivity results. An option that could be considered is the Line Probe Assay which is used for smear positive sputum and determines resistance to isoniazid and rifampicin in 24 hours (Not in use at the Inkosi Albert Luthuli TB Laboratory in 2007). An alternative option is the Gene Expert which could be used for sputum that is smear positive or negative and determines resistance to rifampicin in two hours.

- Isolation of MDR-TB patients at other hospitals while awaiting MDR-TB treatment commencement is an appropriate recommendation but unlikely to be practical due to resource constraints and the lack of availability of beds in public hospitals. Therefore improving and ensuring patient education on basic infection control measures for MDR-TB patients is essential. Measures should include: safe coughing and sputum disposal, separate sleeping place, ventilation and sunlight. Some consideration should be given to the issuing of masks to patients for home use to reduce the spread of infection.

- In view of the delays in the commencement of MDR-TB treatment, the Prince Cyril Zulu Communicable Disease Centre should consider commencing MDR-TB treatment at the facility on an out-patient basis for selected patients who are at a lower risk for complications. This could be done if a doctor from the MDR-TB referral hospital rotated through the Prince Cyril Zulu Communicable

Disease Centre and initiated MDR-TB patients on MDR-TB treatment as out patients or the doctors at the Prince Cyril Zulu Communicable Disease Centre could be trained on MDR-TB treatment. The latter option may be more feasible.

- Accelerate voluntary counselling and testing programmes for HIV to ensure that all TB and MDR-TB cases are tested for HIV. To ensure that all MDR-TB cases are commenced on anti-retroviral therapy as recommended by the South African HIV treatment guidelines. The integration of HIV and TB service should be prioritized.

- Training of staff on obtaining more accurate information with regard to previous TB treatment and previous TB treatment outcome.

- The National Tuberculosis Control Programme (NTCP) Guidelines stipulate that TB treatment should be for six months. This study has shown that treatment longer than 32 weeks increases the risk of MDR-TB significantly, Prince Cyril Zulu Communicable Disease Centre must treat TB patients according to the TB guidelines,

- Ensure that all TB treatment defaulters are traced with special emphasis on tracing defaulters who have sputum confirmed MDR-TB. These defaulters should be encouraged to return to the Prince Cyril Zulu Communicable Disease Centre for appropriate counselling on MDR-TB even if they refuse treatment.

- Strengthen and improve directly observed treatment short course (DOTS) to ensure patient adherence to treatment and improve cure rates.

6.3.2. Recommendations for the TB control programme

- The South African TB control programme should encourage all facilities to monitor their MDR-TB incidence and prevalence in order to detect changes in trends and to determine 'hot spots' where the MDR-TB prevalence among new TB cases exceeds 3%.

- It is suggested that for those facilities were the MDR-TB prevalence among new TB cases exceeds 3% all new TB cases must have sputum culture and sensitivity performed. This would prevent delays in MDR-TB diagnosis and MDR-TB treatment commencement.

- In view of the delays in the commencement of MDR-TB treatment due to the lack of availability of beds at the MDR-TB referral hospital the South African TB control programme should consider increasing the number of MDR-TB referral hospitals providing MDR-TB treatment in the eThekwini district to reduce the waiting times for MDR-TB treatment. Alternatively, consideration should be given to the use of community based injection teams in the eThekwini district were the need for MDR-TB treatment is high and the MDR-TB referral hospital is unable to cope with the demand for beds.

6.3.3. Recommendations for further research

- Further investigation should be conducted at the Prince Cyril Zulu Communicable Disease Centre to determine what the continued trend in MDR-TB prevalence among new TB cases was from 2008 to 2010.

- Future investigations and surveillance activities should be extended to include the incidence of MDR-TB in addition to the prevalence of MDR-TB.

- MDR-TB prevalence studies should be conducted in the private sector and the private sector must be included in all drug resistance surveillance.

- A study to determine the role of exogenous re-infection as a cause of MDR-TB among previously treated TB cases will provide important information on the mechanism of MDR-TB at the Prince Cyril Zulu Communicable Disease Centre. This would enable the implementation of appropriate strategies to reduce the prevalence of MDR-TB at the Prince Cyril Zulu Communicable Disease Centre.

REFERENCES

1. Global Tuberculosis Control 2009: Epidemiology, Strategy, Financing Switzerland: World Health Organization. 2009.

2. Weyer K. Case study: South Africa. *Bulletin of the World Health Organization* May 2007; **85**(5)**:** A-419.

3. Global Tuberculosis Control: Surveillance, Planning, Financing: World Health Organization. Geneva. 2007

4. Zager EM. McNerney R. Multidrug-resistant tuberculosis. *BMC Infectious Diseases* 2008; **8**(10).

5. Suchindran S. Brouwer ES. Van Rie A. Is HIV infection a risk factor for multidrug resistant tuberculosis? A systematic review. *Plos One* **4**(5). 0005561. http:www.pubmedcentral.nih.gov/articlerenderfcgi?tool=pubmed

6. Espinal M A. Laserson K. Camacho M. Fusheng Z. Kim SJ. Determinants of drug resistant tuberculosis: analysis of 11 countries. *Int J of Tuberc and Lung Dis.* October 2001; **5**(10)**:**887-893.

7. Jain A. Mondal R. Prasad R. Singh K. Ahuja RC. Prevalence of multidrug resistant *Mycobacterium tuberculosis* in Lucknow India. *Indian J of Med Res.* September 2008, **128:** 300-306.

8. The Global MDR-TB and XDR-TB Response Plan 2007-2008. Geneva: World Health Organization, Stop TB Partnership. 2007.

9. Masters I. Cost of anti-tuberculosis drugs (Presentation to Department of Health by Dr Masters) - King George V Hospital. Durban. 2010.

10. Margot B. Cost of MDR TB in South Africa - KwaZulu-Natal Department of Health (Personal Communication). Pietermaritzburg. 2010.

11. Ormerod LP. Multidrug-resistant tuberculosis: epidemiology, prevention and treatment. *British Medical Bulletin* 2005; **73-74**(1)**:**17-24.

12. Weyer K. Van der Walt M. Kantar P. Managing drug resistant tuberculosis - Legal implications: MRC Policy Brief, Medical Research Council of South Africa. January 2006

13. Holtz TH. Lancaster J. Laserson KF. Wells CD. Thorpe L. Weyer K. Risk factors associated with default from multi drug resistant tuberculosis treatment, South Africa, 1999-2001. *Int J Tuber C Lung Dis* 2006; **10**(6)**:** 649-655.

14. Management of Drug Resistant Tuberculosis in South Africa - Policy Guidelines. Pretoria: National Department of Health, 2007.

15. South African National Tuberculosis Guideline - 2007. Department of Health Pretoria, South Africa, 2007.

16. Report on TB, including XDR-TB in South Africa National Department of Health South Africa - Presentation to Ethekwini District by J Dalton. September 2006.

17. Lee JH. Chang JH. Drug-resistant tuberculosis in a tertiary referral teaching hospital of Korea. *Korean J Intern Med* 2001; **16**(3)**:** 173-178.

18. The South African National Tuberculosis Control Program - Practical Guidelines Department of Health - Republic of South Africa. 2004.

19. The Management of Drug Resistant Tuberculosis in South Africa. 2nd Edition:Department of Health - Republic of South Africa. 1999.

20. Johnson R. Streicher EM. Louw GE. Warren RM. Van Helden PD. Victor TC. Drug resistance in *Mycobacterium tuberculosis*. Curr. Issues Mol. Biol. January 2009 (8): 97 -112. www.cimb.org .

21. World Health Organization. Anti-tuberculosis Drug Resistance in the World (2002 - 2007). Switzerland: The WHO / IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance. 2008.

22. Deivanayagam CN. Rajesekaran S. Venkatesan R. Mahilmaran A. Ahmed PR. Annadurai S. Kumar S. Chandrasekar C. Ravichandran N. Pencillaiah R. Prevalence of acquired MDR-TB and HIV co-infection. *Indian J Chest Dis Allied Sci.* 2002; **44**(4)**:** 237-242.

23. Espinal MA. Laszlo A. Simonson L. Boulahbal F. Kim SJ. Reniero A. Hoffner S. Rieder HL. Binkin N. Dye C. Williams R. Raviglione MC. Global trends in resistance to anti-tuberculosis drugs. *N Engl J Med*; April 2001. **344**(17)**:** 1294-1303.

24. Umubyeyi AN. Vandebriel G. Gasana M. Basinga P. Zawadi JP. Gatabazi J. Pauwels P.Nzabintwali F. Nyiramasarabwe L. Fissette K. Rogouts L. Struelens MJ. Portaels F. Results of a national survey on drug resistance among pulmonary tuberculosis patients in Rwanda. *Int J Tuberc Lung Dis*. 2007. **11**(2)**:** 189 - 194.

25. Weyer K. Brand J. Lancaster J. Levin J. Van der Walt M. Determinants of multi-drug resistant tuberculosis in South Africa: Result from a national survey. *S Afri Med J.* November 2007; **97**(11).

26. Padayatchi N. Trends in tuberculosis susceptibility: factors influencing resistance in Durban, South Africa. New York: Unpublished Masters Dissertation - Mailman School of Public Health 2002.

27. Su W. Feng J. Huang C. Perng R. Increasing drug resistance of *Mycobacterium tuberculosis* isolates in a medical centre in Northern Taiwan. *J Formos Med Assoc.* 2008. **107**(3)**:**259-264.

28. Anderson LF. Laurenson IF. Blatchford O. Shak E. Stevenson J. Trends in multi-drug resistant tuberculosis in Scotland. *Eurosurveillance.* March 2009. **14**(11).

29. Report of the second meeting of the WHO Task Force on the WHO Task Force on XDR-TB. Geneva, Switzerland: World health Organization.9 - 10 April 2008.

30. MDR-TB and XDR-TB - Presentation: National Department of Health - South Africa. 4 October 2006.

31. Yoshiyama T. Supawitkul S. Kunyanone N. Riengthong D. Yanai H. Abe C. Ishikawa N. Akarasewi P. Payanandana V. Mori T. Prevalence of drug resistance tuberculosis in an HIV endemic area in Northern Thailand. *Int J Tuberc Lung Dis*; 2001. **5**(1)**:** 32-39.

32. Matos ED. Lemos ACM. Bittencourt C. Mesquita L. Anti-tuberculosis drug resistance in strains of *Mycobacterium tuberculosis* isolated from patients in a tertiary hospital in Bahia. *Brazilian J Infect Dis*; June 2007. **11**(3).

33. Churchyard GJ. Corbett EL. Kleinschmidt I. Mulder D. De Cock KM. Drug resistant tuberculosis in South African gold miners: Incidence and associated risk factors. *Int J Tuberc Lung Dis*; 2000. **4**(5)**:** 433-440.

34. Anastasis D. Pillai G. Rambiritch V. Abdool Karim SS. A retrospective study of human immunodeficiency virus infection and drug-resistant tuberculosis in Durban, South Africa. *Int J Tuberc Lung Dis*; 1997. **1**(3)**:** 220-224.

35. Weyer K. Lancaster J. Brand J. Van der walt M. Levin J. Survey of tuberculosis drug resistance in KwaZulu-Natal 2001-2002 - Medical Research Council, Pretoria, South Africa, June 2003.

36. Keane VP. De Klerk N. Krieng T. Hammond G. Musk WA. Risk factors for the development of non-response to first-line treatment for tuberculosis in Southern Vietnam. *Int J Epidem* 1997; **26**(5)**:** 1115-1120.

37. Mendoza MT. Gonzaga AJ. Roa C. Velmonte MA. Jorge M. Montoya JC. Tan Torres T. Ong M. Barez MYC. Ang CF. Nature of drug resistance and predictors of multi-drug resistant tuberculosis among patients seen at the Philippine General Hospital, Manila, Philippines. *Int J Tuberc Lung Dis.* 1997. **1**(1)**:**59-63.

38. Andrews JR. Gandhi NR. Moodley P. Shah NS. Bohlken L. Moll AP. Pillay M. Friedland G. Sturm WA. Exogenous reinfection as a cause of multidrug resistant and extensively-drug resistant tuberculosis in rural South Africa. *J Infect Dis*. December 2008. **198:** 1582-1589.

39. Espinal M A. The Global Situation of MDR-TB. Tuberculosis, 2003. (83), 44 - 51

40. Andrews JR. Shah SR. Weissman D. Moll A. Friedland G. Gandhi NR. Predictors of multidrug and extensively drug resistant tuberculosis in a high HIV

prevalence community. December 2010. Plos ONE 5(12): e15735.doi;10.1371/jornal.pone.0015735

41. Brust JCM. Gandhi NR. Carrara H. Osborn G. Padayatchi N. High treatment failure and default rates for patients with multidrug reistant tuberculosis in KwaZulu-Nata, South Africa, 2002 - 2003. Int J Tuberc Lung Dis. 2010. 14(4): 413-419

42. Gandhi N. Moll A. Sturm A. Pawinski R. Govender T. et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in·a rural area of South Africa, Lancet 2006; 368:1575-80.

43. Gandhi N. Nunn P. Dheda K, Scaaf SH. Zignol M et al. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. Lancet 2010; 375:1830 - 43.

44. Weyer K. Case study of South Africa. Bulletin of the World Health Organization. May 2007. 85(5). A-419.

45. O'Donnell M. Padayatchi N. Master I. Osburn G. Horsburgh C. Improved early results for patients with extensively drug-resistant tuberculosis and HIV in South Africa. Int J Tuberc Lung Dis. 2009. 13(7): 855-8861,

46. Standard Operating Procedures, Inkosi Albert Luthuli Hospital , TB laboratory. 2002