PROFILE OF MULTI DRUG RESISTANT-TUBERCULOSIS (MDR-TB) PATIENTS AT SIZWE HOSPITAL: 2001-2002

Dr. Mupata Lelwi Likibi

A research report submitted to the School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment of the requirements for the Master of Public Health (MPH) degree in the field of Health Measurement.

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DECLARATION

I, Mupata Lelwi Likibi, declare that this research report, which is my own work, is a unique submission for the degree of Master of Public Health in the field of Health Measurement at the University of Witwatersrand, Johannesburg, South Africa.

Signed at Johannesburg, this 20-September 2011

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Mupata Lelwi Likibi

ABSTRACT

Background: In Gauteng Province, South Africa, Sizwe Tropical Hospital (STH) is the designated centre for the specialized management of MDR-TB. But during the period covered by this study (2001-2002), all cases of TB (MDR-TB and NMDR-TB) were treated at STH. This was not according to the prescript of the National guidelines. This study describes the socio-demographic, treatment profile and treatment outcomes of MDR-TB patients seen and treated at STH during 2001 and 2002.

Method: This was a cross sectional study involving retrospective review of records at STH. 281 systematically-sampled MDR-TB patient records were included in this study. Descriptive statistics were used to summarize the socio-demographic and treatment history characteristics and these were further analyzed to evaluate their relationship with MDR-TB treatment outcomes using Chi squared test of association. Means were compared using simple t-test.

Results: The patients were majority black, unemployed, and living in townships and informal settlements. Sputum tests alone or combined with x-ray were most commonly used to diagnose MDR-TB (98%) at referring facilities; and the majority of patients arrived at STH with a referral note (98%). The median duration of stay at STH was 56 weeks (IQR 21-89). The majority of patients had a successful treatment outcome (75%); and amongst those with unsuccessful outcomes, a significant number had died (17%). Factors associated with poor

outcomes in terms of death, default, treatment failure and transfer out were age groups (1-9 and 30-39), race, employment status, place of residence, housing structure, referral systems (referral note and feedback procedures) and HIV status.

Discussion: The patients in this study had socio-demographic characteristics that facilitate TB transmission. There is a commendable referral system but various methods used to confirm MDR-TB and unjustified long duration of treatment prior to referral.

Although in general the majority of patients have successful treatment outcomes, the policy guidelines of the management of MDR-TB are not implemented fully, and several factors associated to poor outcome are related to the health service and referral system.

Recommendation: Effective adherence to the policy guidelines by health care providers and patients is recommended to improve treatment outcomes.

DEDICATION

This work is dedicated to:

My father who passed away in June 1992;

My mother, Ngala Francisque, mother of eleven children, all alive;

All my six brothers and four sisters;

All my nieces and nephews;

My children Meda, Cephas, Joshua and Ruth; and

My life companion and wife, Bifele Viviane

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ABBREVIATIONS

a) GENERAL

AFB	Acid-Alcohol Fast Bacilli
AIDS	Acquired Immuno Deficiency Syndrome
BAAR	Bacilus acido- alcholo-resistant
CDC	Centre for Disease Control
CEO	Chief Executive Officer
DOH	Department of Health
DOTS	Directly Observed Treatment Short Course
DST	Drug Susceptibility Testing
ETR	Electronic TB Register
HIV	Human immuno-deficiency Virus
IUATLD	International Union against Tuberculosis and Lung Disease
KZN	KwaZulu-Natal Province
MDR-TB	Multi-Drug Resistant Tuberculosis
NMDR-TB	Non Multi-Drug Resistant Tuberculosis
NTBCP	National Tuberculosis Control Program

PHC	Primary Health Care
PHIS	Provincial Health Information System
PTB	Pulmonary Tuberculosis
RSA	Republic of South Africa
SANTA	South African National Tuberculosis Association
SANTBG	South African National Tuberculosis guidelines
STH	Sizwe Tropical Hospital
TB	Tuberculosis
TBCP	Tuberculosis Control Program
VCT	Voluntary Counseling and Testing
WHO	World Health Organization

b) ANTITUBERCULOSIS DRUG ABREVIATIONS

AM	Amikacin
Amx/Clv	Amoxicillin/Clavulanate
Cfx	Ciprofloxacin

Cfz	Clofazimine
Clr	Clarthromycin
Cm	Capreomycin
Cs	Cycloserine
E	Ethambutol
Eto	Etionamide
Gfx	Gatifloxacin
H	Isoniazid
HR	Isoniazid+Rifampicin
HRE	Isoniazid+Rifampicin+Ethambutol
HRZE	Isoniazid+Rifampicin+Pyrazinamide+Ethambutol
Km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
Mfx	Moxifloxacin
O	Ofloxacin
PAS	P-aminosalicylic acid

Pto	Protionamide
R	Rifampicine
S	Streptomycin
SHR	Streptomycin/Isoniazid/Rifampicin
SHRZE	Streptomycin/Isoniazid/Rifampicin/Pyrazinamide/Ethambutol
Th	Thioacetazone
Trd	Terizidone
Vi	Viomycin
Z	Pyrazinamide

CHAPTER 1: INTRODUCTION

1.1 Background

Tuberculosis (TB) is a critical public health problem globally. It is the leading cause of death among curable infectious diseases. The International Union Against TB and Lung Diseases (IUATLD) reports that Mycobacterium tuberculosis, the microbe that causes TB, is responsible for about 8.8 million cases of TB and nearly 2 million TB deaths each year, most of them in low-income countries (IUATLD, 2009).

Generally, the main reasons for the increasing global TB burden include: poverty and the widening gap between the rich and poor in various populations; poor program management in terms of inadequate case detection, diagnosis and cure; the impact of the Human Immuno-deficiency Virus (HIV) pandemic; and the collapse of infrastructure in countries experiencing deep economic crises or civil unrest. (National Department of Health [NDoH], 2004).

Multi drug-resistant TB (MDR-TB), a disease caused by Mycobacterium tuberculosis strains that are resistant to at least Rifampicin and Isoniazid, is a serious global public health problem because it entails extended treatment, expensive and toxic regimens, and reflects higher rates of treatment failure and death (Chan et al., 2004). In 2004 it was reported that the global number of incidence cases of MDR-TB of all new and previously treated TB cases nearly doubled from 2000 (272,906) to 2004 (424,203) (Zignol et al., 2006). In the same year (2004), a total of 181,408 MDR-TB cases were estimated to have occurred among previously treated TB cases alone (Zignol et al., 2006).

In 2008, there were 29,423 MDR-TB cases reported throughout the world by 127 countries. These cases only represent about seven percent of the MDR-TB cases estimated to have emerged that year (WHO, 2010). In South Africa, a country with a high burden of TB, a high prevalence of HIV and Acquired Immuno-deficiency Syndrome (AIDS) co-infection rate, HIV/AIDS has further exacerbated MDR-TB. The number of laboratory confirmed cases of MDR-TB more than tripled from 2,000 in 2005 to 7,350 in 2007 (WHO, 2008). Furthermore, South Africa has seen an increasing number of reported patients with XDR-TB since 2007 (from 74 cases in 2004 to 536 in 2007) (NDoH, 2008).

It is recommended that the best way to control MDR-TB is to ensure effective control of TB. The National Tuberculosis Control Program (NTBCP) guidelines in South Africa recommend the following strategies for TB control (NDOH, 2004):

1) The integration of services for TB control into primary health care (PHC) to ensure its effectiveness and its sustainability. At this first level, access to diagnosis and to TB treatment (using the DOTS system) should be made available to the population through strong community participation.

2) The decentralization of the management of TB cases to the local facilities (clinics, SANTA or TB hospitals) to promote the DOT strategy. At that level sputum can be collected and sent to the nearest laboratory facility. Once the result is diagnosed as positive, treatment (first line) can be initiated at the same level. (SANTA stands for South African National Tuberculosis Association and had in the past years managed many TB hospitals.

3) The referral of TB complications to district, regional and tertiary hospitals.

4) The transfer of all confirmed MDR-TB (sputum culture sensitive to at least both INH and RIF) to a specialized centre where trained staff will initiate standardized MDR-TB treatment.

The 2004 South African National Tuberculosis control program guidelines (SANTBCPG) and the MDR-TB policy guidelines of June 2007 clearly outline the management of TB and TB associated conditions, including MDR-TB, XDR-TB (extremely or extensively drug resistant-TB) and TB complications in South Africa. These guidelines require that all MDR-TB and other complicated TB cases be referred to a specialized centre where they can be fully assessed and managed by experts. The policy guideline for the management of MDR-TB in Gauteng recommends a standardized treatment regimen for 4 months (initial intensive phase) followed by 12-18 months of the continuation phase. Individualized treatment is given based on the results of drug susceptibility tests (NDoH, 2007).

Recently, the emergence of XDR-TB cases in the province has presented treatment challenges and highlighted why it is important to correctly and quickly diagnose and treat MDR-TB. In Gauteng Province of SA, in order to adhere to national policy, the Sizwe Tropical Hospital (STH), a 220 bed specialized hospital, was chosen to fulfill the role of a specialized MDR-TB treatment hospital. This is because of its past experience of being a tropical disease hospital, having isolation facilities and staff who are skilled and experienced to handle complicated cases, including MDR-TB. A specialized unit

was established at STH with the aim of evaluating the effectiveness of treating MDR-TB patients using a standardized regimen of second line anti-TB drugs and of monitoring the reduction of the burden and spread of multi-drug resistant.

There are two main categories of TB that are managed at STH at present. The first category includes TB cases falling into the WHO definition of MDR-TB comprising the commonly called MDR-TB (established resistance to both INH and RIF), poly resistant TB (laboratory confirmed resistance to INH, RIF and Ethambutol), high grade resistant TB (confirmed resistance to at least 4 first line anti-TB drugs) and XDR-TB (confirmed resistance to at least RIF and INH, in addition to any Fluoroquinolone, and at least one of the three following injectables drugs: Apreomycin, kanamycin and Amikacin).The second category includes non-MDR-TB (NMDR-TB) cases including all pulmonary TB, extra pulmonary TB, all TB complications such as TB meningitis, TB lymphadenitis, Miliary tuberculosis, TB pleural effusion, Tuberculous Empyema, Tuberculous pericardial effusion, Ascitis, TB of the bones as well as all cases of drug resistance not falling into the WHO definition of MDR-TB. The correct procedures for diagnosis and treatment of these conditions are reflected in the SA national policy guidelines; and it is essential to adhere to these guidelines to ensure effective TB control (NDoH, 2007).

The NTBCP recommendations have been adopted by the TB program in Gauteng. The control of TB in Gauteng has however been a challenge. The TB co-ordination team that has been set up at provincial level to oversee TB control has experienced challenges in each of the following steps in the control of TB: correct diagnostic process

at health facilities (a positive sputum result is diagnostic); starting first line TB treatment as early as possible, supported by the DOT strategy; and the monitoring of treatment progress by monthly sputum tests. There have also been challenges in referral and management of MDR-TB (NDoH, 2004).

At STH, all cases are admitted in the program through the gate way clinic which is a triage facility within the hospital. After being seen by dedicated doctors and staff, critical patients are admitted into hospital wards and less serious ones followed in ambulatory care or sent back to the referring facility with a management guide. Those who are admitted will have one of the following outcomes: cured, these will be sent to the referring facility with a specific follow up treatment plan; died these will be discharged to the undertaker. Some will default treatment, will be transfer out or will fail treatment. Nevertheless there was no appropriately written operational discharge policy at that time.

1.2 Problem statement

The management of MDR-TB is one of the most critical public health issues today, especially in the context of the fast-growing HIV and AIDS epidemic and the emergence of a new resistant strain of TB, the XDR-TB (WHO, 2010). In Gauteng, at the time of the implementation of the TB electronic register, annual reports demonstrated that there were 27453 and 31784 cases of TB reported in 2001 and 2002, respectively. During this period MDR-TB data was not being collated. But statistics from STH show that there

were 446 and 400 cases of MDR-TB in 2001 and 2002 respectively (Gauteng Department of Health (GDoH), 2001; GDoH, 2002).

In Gauteng, proper routine data collection for MDR-TB cases only started in March 2003 and by 2008 the electronic register for MDR-TB was not yet developed. Many questions arose about what was happening at STH with the implementation of the national policy guidelines on TB and MDR-TB. These questions include:

a) Who were the patients who were referred to STH for MDR-TB treatment?

b) Were the patients on MDR-TB treatment were indeed confirmed MDR-TB cases (based on WHO definition of MDR-TB);

c) Were clinicians at health facilities (facilities where MDR-TB diagnosis was made) adhering to the guidelines for diagnosis, referral and the management of MDR?

d) How were patients managed, and what were their treatment outcomes at STH?

This study addresses these questions, with a focus on STH. The study which covers the period from 2001 to 2002, describes the demographic and socio-economic profile of MDR-TB patients admitted at STH during this period, the processes for their diagnosis and referral to STH, and their MDR-TB treatment characteristics, and treatment outcomes.

1.3 Justification for the study

This study explores the way in which national TB guidelines for MDR-TB have been implemented in Gauteng by identifying how MDR patients are diagnosed and managed (i.e. their route through the health system from referral facility to STH). This will help in

identifying gaps in management of MDR-TB, and identify whether there is proper adherence to MDR-TB guidelines. The study is also useful for the provincial TB program in other ways. By providing information on the performance of the MDR-TB treatment program at STH, the study findings can assist TB control program managers with planning and program management, and assist clinicians to improve treatment of MDR-TB patients at STH. By trying to determine the treatment outcomes of patients with confirmed MDR-TB, this study provides baseline data that could be used for future monitoring. This is further important since no similar study has been done. Finally, this being a descriptive study, it raises issues that can be investigated further in other analytical studies.

1.4 Literature review.

The following issues are considered in the literature review: the burden of the disease; adherence to policy guidelines in managing TB and the importance for TB control; determinants of treatment outcomes; experiences with managing MDR-TB in various settings; and outcomes of MDR-TB treatment. As a point of clarification preference has been first given to more recent publications (2005-2010). Publications before 2005 were considered for review only in cases where more recent articles were not available to illustrate specific issues specially referring to the South African publications going as far as 1997.

1.4.1 Burden of TB

Tuberculosis (TB) is still a major global health problem today despite treatment having been available for over 50 years. Furthermore, TB remains a serious public health challenge and is the leading cause of death in people living with AIDS, as well as the most important infectious disease causing death in all ages in the general population (IUATLD, 2009). In 2008 WHO reported an estimate of 9.4 million incident cases of TB, 11.1 million prevalent cases of TB, 1.3 million deaths among HIV negative TB patients and 0.52 million deaths among HIV positive TB patients (WHO, 2008). Recently Multidrug-resistant -tuberculosis (MDR-TB) has emerged as a global epidemic, with 425,000 new cases estimated to occur annually (Wells et al., 2007). The WHO has released a new report on anti-TB extensively drug resistant TB (M/XDR-TB) stating that in 2008, an estimated 440 000 cases of MDR-TB emerged globally with 150 000 deaths. (WHO, 2010)

The emergences of MDR-TB and thereafter of XDR-TB are the most critical aspect of the TB epidemic in South Africa (SA). WHO declared SA to have one of the worst recorded TB epidemics in the world due to the high TB rate, the rise of HIV, and the emergence of MDR-TB. According to a 2009 WHO report, among the twenty two countries classified with the highest TB burden globally, eight are in Africa and SA is ranked fifth with 948 cases per 100 000 population, a major increase from 338 cases per 100 000 population in 1998 (WHO/IUATLD, 2009). A drug resistance survey found that in South Africa, about 1.6% of new TB cases and about 6.7% of previously treated

cases were MDR-TB. This translates into at least 6000 new cases of MDR-TB in SA each year (Blumberg, 2003).

The need to address the problem of TB and MDR-TB in SA became urgent since the emergence of the epidemics of XDR-TB cases in KZN Tugela Ferry. Dr Friedland of FIDSA indicated that generally, 50% of patients newly infected with HIV in sub-Saharan Africa are also TB infected; but in Tugela Ferry 90 % of these HIV infected are co-infected with TB. The TB case rate is more than 1000 per 100 000 people. By the end of 2009, nearly 1000 cases of XDR-TB and MDR-TB had been diagnosed, with more than a half being XDR-TB (IDSA News-Nov. /Dec. 2010).

1.4.2 Guidelines for TB control

It is critical to acknowledge that poor TB management will facilitate the development of MDR-TB, and also to recognize that MDR-TB is a threat to TB control (Prasad, 2007). Generally, prevention and control of MDR-TB is obtained through implementation of a good TB control program operating under the DOTS strategy (Yew & Leung., 2008; Blöndal., 2007).

In 1991, the 44th World Health Assembly set two key targets for global TB control to be reached by 2000: 70% case detection of acid-fast bacilli smear-positive TB patients under the DOTS strategy recommended by WHO and 85% treatment success of those detected to be smear-positive (Laserson and Wells. 2007). WHO, in support of

countries affected with the TB epidemic, has developed policy guidelines to help these countries to achieve efficient and effective management of TB and MDR-TB.

South Africa has implemented WHO guidelines in the form of practical guidelines which have outlined how TB and MD R-TB should be diagnosed and managed. The guidelines indicate clearly that the treatment of smear- positive patients is the most important way to control TB and prevent complications, and MDR-TB. The guidelines also state that sputum testing is the appropriate method for making a diagnosis of TB, and that too much reliance on chest X-ray in the diagnosis of TB results in unnecessary treatment, because chest X-ray is not a reliable predictor of active TB (DoH, 2004). The guidelines insist that TB culture for drug susceptibility testing is done on all patients who continue to have positive sputum smears in spite of correct treatment. In this way, MDR-TB can be detected early and appropriate treatment started.

1.4.3 MDR-TB treatment outcomes

The following are commonly recorded outcomes of TB treatment: successful treatment (cure), relapse, failure, transfer out, death, default or loss during follow up (Palmero et al., 2004). Successful outcomes will also include treatment completion, sputum conversion, disappearance of X-ray lesions; while relapse, failure, transfer out, death, default (loss during follow up), remain on treatment, referred to surgery constitute what is also called unsuccessful outcomes (Masjedi et al., 2008; Laserson et al., 2005; Shean et al., 2008; Dhingra et al., 2008).

Treatment outcomes are often unsuccessful in multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB), and successful outcomes are generally low (Shean et al., 2008). Experience with MDR-TB treatment outcomes varies in different settings. For example, a descriptive study conducted in 1996 in Santa Cruz, Bolivia revealed that a successful outcome was achieved in 28% of patients, while 48% defaulted, and 13% died and 10% were still under treatment (Olle-Goig & Sandy, 2005). Another study by Tupaisi et al (2003) in the Phillipines showed a cure rate of 73.4%, a failure rate of 3.8% and a likely failure rate of 6.3%; while death occurred in 3.8% and defaulting was observed in 11.4 %).

Latvia has one of the highest rates of MDR-TB in the world. In a study conducted there to assess treatment outcomes for the first full cohort of MDR-TB patients treated under Latvia 's DOTS-Plus strategy following WHO guidelines, it was demonstrated that of the 204 patients assessed, 55 (27%) had been newly diagnosed with MDR-TB, and 149 (73%) had earlier been treated with first-line or second-line drugs for this disease. Assessment of treatment outcomes showed that 135 (66%) patients were cured or had completed therapy, 14 (7%) had died, 26 (13%) had defaulted, and 29 (14%) had treatment failure. Of the 178 adherent patients, 135 (76%) achieved a cure or treatment completion which is an example of a good outcome (Leimane et al., 2005).

1.4.4 Determinants of MDR-TB treatment outcome

According to literature TB treatment outcomes are influenced directly or indirectly by a number of factors, including: socio-demographic characteristics (age, sex, education

level and economic status), treatment delay, inappropriate prior TB treatment with poor adherence (inefficient DOTS strategy and referral system), poor prescription and provision of drugs, staffs' bad attitude, the HIV sero-positive status, previous TB treatment for more than 4 weeks, smoking (for Isoniazid resistance), the presence of cavitations on the chest radiograph, and imprisonment (Ekaterina et al., 2006).

a) Socio-demographic factors

There are very few studies that have looked at the socio-demographic characteristics of TB and MDR-TB patients in international literature and especially in South Africa. The following are the most reported socio-demographic characteristics of TB and MDR-TB patients in the literature: age group, sex, race, employment status, area of residence and housing (DoH, 2004; Amin et al., 2009). For instance in Abidjan, Ivory Coast, among MDR-TB patients, those aged 20-40 years are the most commonly-affected group (72%), with a clear male predominance (sex ratio 3:1), and most of them living in dwellings with a common yard (Kouassi et al., 2004). Furthermore, a South African study by Rawlinson et al (2000) on MDR-TB explains that unemployment is a contributing factor leading to poverty, which is an important social determinant of TB and MDR-TB (Rawlison et al., 2000).

b) Previous TB treatment

Prior ineffective treatment is a strong predictor of drug resistance (Espinal et al, 2001). It has been shown that the high rates of MDR-TB are associated with previous anti-tuberculosis treatment, and that the chance of developing MDR-TB is significantly increased when inadequate TB treatment is given for more than three months (Mendoza et al., 1997). Other factors to consider in relation to previous treatment are the effectiveness of the treatment, the duration of treatment, the delay in starting treatment, the outcome of that treatment (e.g. previous treatment failure), and multiple previous TB episodes (Espinal et al., 2001).

c) Clinical and treatment features

Delay in starting appropriate MDR-TB treatment after the diagnosis has been made also has potentially serious consequences, and increases the risk of developing MDR. Predictors of good outcomes regarding treatment include: resistance to not more than three anti-tubercular drugs, use of less than or up to three second line drugs in treatment, and no change of regimen during treatment (Dhingra et al., 2008). Predictors of poor outcomes include: previous treatment for MDR-TB, the use of five or fewer drugs for three months or more, and resistance to ofloxacin (Leimane et al., 2005)

Clinical features such as cavities present on chest X-rays are factors associated with MDR-TB development, and are high risk mostly in low-income countries (Temple et al., 2008). A body mass index of less than 18.5 at the start of treatment is also associated with MDR-TB development (Leimane et al., 2005). Clinical predictors of good MDR-TB

treatment outcome include: weight gain at six months of treatment, culture conversion, and radiologic improvement during treatment (Dhingra et al., 2008).

d) HIV/AIDS

HIV infection is one of the most common determinants of poor TB/MDR-TB outcomes (Kliiman & Altraja, 2009). The global HIV epidemic is associated with significant increases in TB incidence and may be contributing to increases in MDR-TB (IUATLD, 2009). Institutional outbreaks of MDR-TB have primarily affected HIV-infected persons. Delayed diagnosis of TB, inadequate initial TB treatment, and prolonged periods of infectiousness with TB have led to extraordinary TB attack rates and case-fatality rates among HIV-infected persons. HIV infection is also associated with mal absorption of anti-TB drugs and acquired Rifampicin resistance. HIV-infected patients with MDR-TB have high mortality rate; both antiretroviral and anti mycobacterial treatment are necessary (Wells et al., 2007).

A study of patients in HIV prevalent areas of sub-Saharan Africa reveals that with a mere 0.7 % percent of the world's population, South Africa is home to 19 percent of human immunodeficiency virus (HIV) and tuberculosis co-infected people, the highest co-infection rate in the world. The rest of Africa accounts for 61 percent of global co-infected patients. Furthermore this same study also found that the risk of tuberculosis was 8.3 times higher for those who were infected with HIV than for those who were HIV negative (Corbert et al., 2006).

It is projected that HIV/AIDS will delay the global control of the TB epidemic over the next few years (ref). Globally it is estimated that 73% of new TB patients are co-infected with HIV; and an estimated 31% of all TB-HIV cases in Africa are in SA (WHO, 2008). Churchyard et al (2000) revealed that the HIV epidemic has lead to increased TB incidence in South African miners. Very few studies have found no relationship between HIV and MDR-TB. One example is the study in the Ivory Coast which showed No link between HIV infection and MDR--TB. (Kouassi et al., 2004).

But in general, the HIV and MDR-TB relationship is strongly supported in literature, and confirms that strong TB control - in particular, to ensure control of drug-resistant TB - will be facilitated by scaling-up WHO-recommended TB/HIV collaborative activities such as HIV counseling and testing of all TB patients, greater use and acceptance of Isoniazid as a preventive treatment in HIV-infected individuals, screening for active TB in HIV-care settings, and provision of universal access to antiretroviral treatment for all HIV-infected individuals eligible for such treatment; and by improving coordination between HIV and TB control programmes (Laserson and Wells, 2007)

A retrospective cohort study by Dheda et al. (2010) investigating the association between HIV and XDR-TB in Kwazulu-Natal (KZN) suggested that, contrary to the findings of earlier studies in KZN (during 2006-2009) which suggested that XDR-TB in SA was predominantly associated with HIV infection, a majority (53%) of South African XDR-TB patients outside KZN province are HIV negative. The same study also shows that the number of deaths among HIV positive and HIV negative patients was not

significantly different, patients with XDR-TB have poorer management outcomes regardless of their HIV status, and sputum-culture conversion was not found to be associated with sex, ethnic group, or the numbers of previous episodes of MDR-TB. However low body weight (< 50 kg) before treatment was associated with conversion failure.

In summary, various studies have shown that MDR-TB is a serious public health problem. It has also been demonstrated that socio-demographic characteristics and treatment profile including HIV positivity are important determinants in acquiring MDR-TB and attaining MDR-TB treatment outcomes. Understanding these characteristics of MDR-TB patients at STH is thus an important first step in exploring the determinants of MDR-TB acquisition and treatment outcome in Gauteng. These few characteristics that have been described in this study will give a baseline on the profile of MDR-TB patients before and after admission at STH.

1.5 Aim and objectives

1.5.1 Aim

The aim of this study is to describe the profile of MDR-TB patients treated at STH during 2001-2002; and to determine their MDR-TB treatment outcomes, with a view to also to formulating recommendations based on the findings. In the context of this study, the word profile refers to the socio-demographic and treatment characteristics of these MDR-TB patients.

1.5.2 Objectives

The objectives of this study were:

a) To describe the socio-demographic characteristics of MDR-TB patients treated at STH during 2001 to 2002

b) To describe their treatment history at the referring facility level (past medical history before admission at STH)

c) To determine the HIV prevalence among these MDR-TB patients.

d) To describe these MDR-TB patients' treatment history at Sizwe Tropical Hospital.

e) To describe MDR-TB patients' treatment outcomes.

f) To evaluate associations between socio-demographic and clinical factors with their treatment outcomes.

1.6 Definition of terms used in the study

Multi-Drug Resistant-Tuberculosis (MDR-TB)

In this study, MDR-TB is defined as the disease caused by TB bacilli resistant to at least Isoniazid (H) and Rifampicin (R). Drug resistance is further classified into "primary" or "acquired" according to the patient's history of previous tuberculosis treatment.

- Primary resistance: Resistance in cultures from patients with no history of previous TB treatment.
- Acquired resistance: Resistance in cultures from patients with one or more previous TB treatment episodes (totaling more than one month).

- Initial resistance: Drug resistance in new TB patients, allowing for undisclosed previous treatment, i.e. “initial resistance” refers to primary and undisclosed acquired resistance. This rate may be up to twice the rate for true primary resistance and the term is preferred by some authors when dealing with population-based studies.

Re-treatment case

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

Smear negative Pulmonary Tuberculosis case

At least 2 sputum smears are negative for AFBs. Chest X-ray abnormalities are consistent with active TB.

Smear-positive Pulmonary Tuberculosis case

There are at least 2 sputum smears positive for AFBs or 1 sputum smear positive for AFBs and chest X-ray abnormalities consistent with active TB or culture positive TB, or 1 sputum smear and clinically ill.

Treatment standardized

It is a recommended regimen for 4 months for the treatment of MDR-TB cases. It is comprised of Kanamycin, Pyrazinamide, Ethambutol (or Terizidone), Ofloxacin (or ciprofloxacin) and Ethionamide during the initial intensive phase. This phase is followed

by 12-18 months of Ethambutol, Ofloxacin and Ethionamide in the continuation phase. Cycloserine is used as Ethambutol replacement when resistance to Ethambutol is detected (Department of Health (DoH), 2004).

Treatment Individualized

Individualized treatment is given to MDR-TB patients based on the results of drug susceptibility tests. If drug susceptibility test results are not yet available, the TB treatment is to be delayed and patients are started on the standardized regimen while awaiting drug susceptibility results (Department of Health (DoH), 2004).

Regimen 1 TB treatment

This treatment, which is given to TB patients as fist line treatment, includes R, H and E and Z.

Ajunction of surgical treatment

In case of pneumothorax and empyema, intra costal drains are inserted and washing performed. Sometimes artificial desh is done to demolish the space between the two pleural layers so to avoid recurrence of pleural effusions and finally patient will be referred to other tertiary hospitals for major procedures like lobectomies or pneumectomies.

CHAPTER 2: MATERIALS AND METHODS

2.1 Study Design

This is a cross sectional study conducted at STH involving retrospective review of records of MDR-TB patients seen and admitted at STH during 2001-2002.

2.2 Study Setting

The study was conducted at STH in Gauteng Province, South Africa. The STH is a 220-bed hospital which functions as a centre for complicated tropical diseases, including malaria, trypanosomiasis, and yellow fever. It also plays an important role in the TB control program in the Gauteng Province as it was chosen as a referral hospital to handle complicated cases and also drug-resistant cases of tuberculosis. According to Gauteng guidelines, every MDR-TB patient should be referred to STH with a referral letter specifying the reason for referral, the name of the referring facility, the investigations used, the duration of treatment and HIV status if possible, and the result of sputum culture and sensitivity test.

2.3 Study Population

The study population for this research includes all patients seen and admitted at STH with a diagnosis of MDR-TB during 1 January 2001 to 31 December 2002. In this report, the following definition of MDR-TB was used to identify MDR-TB patient records for inclusion in the study: “Drug sensitivity tests for both INH and Rifampicin show

resistance". In this study, NMDR-TB will refer to any TB patient whose sensitivity test does not demonstrate any resistance to both INH and Rifampicin, with or without resistance to other anti-TB drugs. This will included all PTB cases, extra-pulmonary cases and TB complications.

2.4 Sampling

Sampling strategy: Out of 3,706 TB cases seen and admitted at STH during the study period, 845 (23%) were MDR-TB patients. Of these 845 MDR-TB patients, 281 (33%) were selected by systematic sampling – starting from a random point, every third patient record listed in an admission register, was sampled and included in the study.

Sample Size: Epi-info's Stat calc function (version 9.2) was used to calculate the sample size for this study. At the confidence level of 95% a sample of at least 205 MDR-TB records was required. 281 MDR-TB records (which represented one third of all cases) were systematically selected; oversampling was done in order to be on the safe side, in case some records were incomplete.

2.5 Data Collection

Data were extracted from patient records which were kept in 3 separate storerooms and filed in ascending order following patient file numbers. A data collection sheet (Appendix 1) was used to extract and capture data from hospital records. The following variables were extracted from the records and captured on the data collection sheet:

Socio-demographic variables:

- Age, sex and race
- Employment status: this was recorded as occupation. Those who had any defined occupation were taken as employed; those without any defined occupation were “unemployed”.
- Housing structure: this was classified as a formal structure (flat, hotel, hostel, prison, private house; or an informal structure (shack and other non specific).
- Place of residence: this was recorded in the files as “address” – it was categorized in this study as town, suburb, township and informal settlement.
- District of residence: Gauteng had five Districts at that time namely Sedibeng, West rand, city of Johannesburg, Ekurhuleni and Tshwane-Medsweding.

Treatment history at referring facility:

- Referring facility means: any health facility [e.g. clinic, hospital] which at any time in the provision of TB care refers a patient to the referral facility [STH]).
- Investigations done to diagnose TB at referring facility: this refers to types of investigations that were done to make the diagnosis of TB.
- Type of referring facility: clinics and community health centers were classified as PHC, others were hospitals.
- Reason for the referral to STH: the reason that was mentioned in the referral note from the referring facility was captured (e.g. MRD-TB, E-PTB, TB complications etc).

- Past treatment history (duration of TB treatment (if any) before referral to STH: This refers to the time between treatment for normal TB till the time the sputum culture reveals MDR-TB.

HIV status: this was categorized as ‘positive’, ‘negative’ or ‘unknown’. HIV status was extracted from referral letters or from the laboratory report.

Treatment history at STH was measured by the following:

- Drug resistance patterns
- Treatment received at STH
- Duration of treatment (admission) at STH
- Whether feedback letter to referral facility was issued on discharge
- Types of TB complications treated while at STH.

Drug resistance pattern: this refers to the classification of MDR-TB according to the WHO definition; Patients will be found to be resistant to one, two or more anti-TB drugs. The importance was to check resistance to the two major anti-TB drugs (H and R)

Treatment received at STH: this refers to:

- the clinical management provided during admission (see ‘definition of terms’ above for clinical management options)
- whether clinical management was in line with policy guidelines

- duration of treatment – which refers to the period between admission at STH till the patient died, was discharged, or absconded; and
- whether feedback letters were given upon discharge (in accordance with guidelines).

MDR-TB treatment outcomes were categorized as:

- Successful outcome: cure, sputum conversion and treatment completion; or
- Unsuccessful outcome: defaulted, died, failed treatment (treatment failure), loss during follow up, relapsed and transferred out.

Cure was defined as a patient who is smear-negative at one month prior to the completion of treatment and also on at least one previous occasion. Sputum conversion was defined as the fact that positive smear detected by microscopy has become negative under the effect of an appropriate treatment during a period of normally 9 months. Treatment completed is when the patient has completed treatment but without proof of cure (i.e. smear results are not available on at least two occasions prior to the completion of treatment).

Variable for unsuccessful outcome were defined as follows: default referred to a case where treatment was interrupted for a period of time mostly due to patient related reasons; died referred to a patient who died for any reason during MDR-TB treatment; failed treatment (treatment failure) was a patient who remained positive or was again smear positive five months after starting treatment; loss during follow up was defined as

a patient who did not return for treatment during the period after starting his TB/MDR-TB treatment. Relapsed was a sputum smear positive pulmonary TB patient who received treatment and was declared cured (sputum smear negative) at the end of the treatment period and has now developed sputum smear positive pulmonary TB again; and transferred out is when a patient already registered for treatment in one district and who had been transferred to another to continue treatment (treatment outcome not known).

Data was extracted from the records by two trained field workers, the principal investigator and one retired professional nurse. The principal investigator also verified the data by randomly rechecking 100 cases from the patient register. Patient details were linked to the data collection sheet with the hospital number only, and no patient names were entered onto the data collection sheet.

2.6 Data management and analysis

Data were captured electronically onto a Microsoft Excel spreadsheet, and this was imported into Epi-Info Version 9.2 for quantitative analysis. Descriptive statistics (minimum and maximum, mean and standard deviation, and median and inter-quartile range) were used to describe numeric data (age, and duration of treatment). Proportions were used to summarize categorical data and determine frequency distributions of the variables of interest.

The one sample t-test (Student's t-test) statistic was used to perform test of association between numerical data (to compare mean age) and MDR-TB treatment outcome; and

chi squared test was used to assess association between socio-demographic, treatment history characteristics with treatment outcome. These tests of association were done using Epi-info and a probability value (p-value) of less than 0.05 was considered to be statistically significant, and confidence limits were set at 95%.

2.7 Ethical Considerations

The permission of the Gauteng Health Department was obtained to conduct the study in the province. Ethics clearance (number M030816 – see attached) was obtained from the Wits Ethics Committee. Permission was granted by the Chief Executive Officer (CEO) of STH to access hospital records, including information from referring facilities. Information was treated confidentially. No patient's names were collected and records were identifiable through a unique study record number only. While there was no direct benefit to individual patients, it is hoped that the result of this study will influence policy making and health service delivery at STH and the referring facilities, and thus may in the future indirectly benefit patients at STH.

CHAPTER 3: RESULTS

During January 2001 to December 2002, 3,706 TB cases were seen at STH (845 MDR and 2,861 non-MDRTB patients). Of the 845 MDR-TB bases, 281 were reviewed in this study. The results are presented in this chapter, according to the objectives of the study.

3.1 Patient's socio-demographic profile

The mean age of MDR-TB patients was 37 years (SD 11.4), the median 36 (IQR 30-44); the means age by sex were 38.3 for male, 34.3 for female. Furthermore, the majority of MDR-TB was males (62%), black (94%), unemployed (72%), living in formal housing structures (91%) and residing in township (62%). Except the mean age, these descriptive data are summarized in Table 3.1.1.

Table 3.1.1: Socio-demographic profile of MDR-TB patients at STH: 2001-2002.

Characteristics		N	%	95% CI
Sex	Male	175	62	56.5-68.1
	Female	106	38	31.9-43.5
	Total	**281**	**100**	
Race	Black	264	94	90.5-96.4
	Colored	11	4	2.0-6.9
	Indian	2	1	0.1-2.5
	White	4	1	0.4-3.6
	Total	**281**	**100**	
Employment status	Employed	79	28	23.2-34.0
	Unemployed	202	72	66.0-76.8
	Total	**281**	**100**	
Place of Residence	Township	173	62	55.4-67.1
	Town and suburb	107	38	32.6-44.2
	Informal settlement	1	0	0.0-2.0
	Total	**281**	**100**	
Housing type	*Formal housing*			
	Private house	202	71.9	67.2-81.7
	Flat	25	8.9	5.8-12.8
	Hotel	14	5.0	??
	Hostel	13	4.6	2.7-8.2
	Prison	3	1.1	1.2-5.5
	Informal housing			
	Shack	10	3.6	2.5-7.8
	Not specified			
	Not indicated on record	14	5.0	1.9-9.5
	Total	**281**	**100**	

3.2: Patient treatment history at the referring facilities

Patients treatment history at the referring facilities included the duration of treatment at facilities level, the investigations used to diagnose MDR-TB, the referral characteristics. Sputum tests alone or in combination with x-ray were most commonly used to investigate and diagnose MDR-TB (98%) at referring facilities (Table 3.2.1).

Table 3.2.1: Investigations used to diagnose MDR-TB at referring facilities.

Type of investigation used	**MDR-TB patients**		
	N	**%**	**95% CI**
Sputum test with routine X-ray together	255	91	86.8-93.9
Sputum test alone (sputum culture and sensitivity)	21	7	3.8-13.2
Only X-ray	4	2	0.4-3.6
No sputum and no X-ray done	1	0	0.0-2.0
Total	**281**	**100**	

The mean duration of TB treatment at referring facilities (recorded as past treatment history) was 32 weeks (SD: 38.11) and a median of 24 weeks (IQR 12-39). The majority of patients arrived at STH with a referral note (98%); most referred from clinics/CHC (81%) and the major reason for referral was confirmed MDR-TB. These referral characteristics are summarized on table 3.2.2.

Table 3.2.2: Referral characteristics of MDR-TB patients: 2001-2002

Referral characteristics		MDR-TB patients		
Variable		N	%	95% CI
Referral letter	Had a referral letter	276	98	95.9-99.4
	No referral letter	5	2	0.4-5.6
	Total	**281**	**100**	
Reason for referral	TB contact	1	0	0.0-2.0
	PTB	21	8	4.7-11.2
	Extra pulmonary TB	1	0	0.0-2.0
	TB complications	2	1	0.1-2.5
	Suspected MDR-TB	7	2	1.0-5.0
	Confirmed MDR-TB	249	89	84.4-92.1
	Total	**281**	**100**	
Referring Facility	Self referral	3	1	0.2-3.1
	Clinic/CHC	228	81	72.3-89.8
	Private sector	4	2	0.4-5.6
	Public hospital	10	4	1.7-6.4
	SANTA hospital	20	7	4.4-10.7
	Tertiary hospital	15	5	3.0-8.6
	Other/NGOs	1	0	0.0-2.0
	Total	**281**	**100**	

3.3 HIV status of MDR-TB patients

Over a third of MDR-TB patients (39%) in this study were HIV positive and 124 (44%) did not know their HIV status as depicted in table 3.3.1. The proportion of HIV positive

cases was statistically significantly higher (more than double) than HIV negative cases (17%).

Table 3.3.1: HIV status of MDR-TB patients admitted to STH: 2001-2002

HIV status of MDR-TB patients	**N**	**%**	**95% CI**
HIV Positive	110	39.2	33.6-45.3
HIV Negative	47	16.7	12.5-21.5
HIV Unknown	124	44.1	38.1-50.0
Total	**281**	**100**	

3.4 MDR-TB Patients treatment characteristics while admitted at STH

The treatment characteristics included the following: duration of stay at STH, drug resistance profile, treatment received at STH, and feedback note. The mean duration of stay at STH was 64 weeks for all patients in general (SD 51) with a median of 56 weeks (IQR 21-89, but in HIV positive cases the mean duration of stay was 58 weeks (SD 51) with a median of 48 weeks (IQR 13-88).

The other treatment characteristics showed that all patients (100%) were resistant to at least both H and R, of which 77% (N= 217) received standardized treatment, 22% (N= 60) received individualized treatment, 1% (N=3) received an adjunction of surgical

treatment and 90% received feedback on discharge. A summary of these results is displayed in Table 3.4.1

Table 3.4.1: Treatment characteristics of MDR-TB patients at STH: 2001-2002.

Characteristics		**N**	**%**	**95% CI**
Drug resistance profile	INH+ RIF only	120	43	36.7-48.6
	INH + RIF + 1 other drug	83	30	24.2-35.1
	INH+RIF+STREPT+EMB	77	27	22.2-32.9
	INH+RIF+STREPT+EMB +more other drugs	1	0	0.0-2.0
	Total	**281**	**100**	
Treatment received at STH	Individualized treatment	60	22	16.6-26.5
	Standard treatment	217	77	72.0-82.1
	Adjunction of surgical treatment	3	1	0.2-3.1
	TB treatment Regimen 1	1	0	0.0-2.0
	Total	**281**	**100**	
Feedback note	Feedback note	253	90.0	86.0- 93.3
	No feedback note	27	9.6	6.4-15.6
	Missing	1	0.4	
	Total	**281**	**100**	

3.5 MDR-TB treatment outcomes at STH

The majority of patients had a successful treatment outcome (75%); and amongst those with unsuccessful outcomes, a significant number had died (17%). It was noticed that some outcomes were not recorded in patients files e.g. relapse, remained on treatment, and referred to surgery. This descriptive data is summarized in table 3.5.1.

Table 3.5.1 Treatment outcomes for MDR-TB patients at STH: 2001-2002.

Treatment outcomes	**N**	**%**	**95% C.I**
Successful outcomes			
Conversion at 9 months	174	61.9	56.5-68.1
Cured	36	12.8	9.1-17.2
Subtotal of successful outcomes	210	74.7	
Unsuccessful outcomes			
Defaulted	15	5.3	2.3-10.5
Death	46	16.4	12.2-21.2
Transfer out	1	0.4	0.0-2.0
Treatment failure	8	2.8	1.2-5.5
Subtotal of unsuccessful outcomes	70	24.9	
Missing	1	0.4	
Total	**281**	**100**	

The study explored the association between socio-demographic characteristics (age, sex, race, employment status, area of residence, district of residence, housing structures) and treatment outcomes as well as between clinical characteristics (duration of treatment at facility level, MDR-TB resistance profile, treatment received at STH, feedback note received and duration of treatment at STH and HIV status) and treatment outcomes at STH. These associations were calculated using a Chi-squared test of association. The results are summarized in the table below. Only associations which are statistically significant ($p< 0.05$) are represented in the tables.

The factors that are statistically significantly associated with MDR-TB treatment outcomes at STH were feedback given to the referring facility, HIV Status and housing type, as shown in table 3.5.2.1. Those patients for whom formal feedback was given by STH to their referring facility were more likely to achieve better outcomes (sputum conversion at 9 months and cure) than those who did not have referral feedback. Death as a poor outcome was more likely to occur in patients for whom no feedback was provided to referring facilities. The findings also show that HIV negative patients were more likely to achieve better outcomes; and patients living in formal houses (hostel, private house, flats and hotel) had better outcomes than those living in shack and prison.

Table 3.5.2.1: Association between MDR-TB treatment outcomes and socio-demographic and treatment characteristics of patients at STH: 2001-2002

	MDR-TB Treatment outcomes [No. (%)]						p-value
Explanatory variables	Sputum conversion at 9 months	Cure	Death	Default	Transfer out	Treatment failure	
Feedback given to referring facilities							0.0000
Yes	172 (68,3)	34 (13.5)	23 (9.1)	14 (5.6)	1 (0.4)	8 (3.2)	
No	2 (7.4)	1 (3.7)	23 (85.2)	1(3.7)	0 (0.0)	0 (0.0)	
HIV Status							0.0000
Positive	60 (54.5)	8 (7.3)	35 (31.8)	4 (3.6)	0 (0.0)	3 (2.7)	
Negative	33 (70.2)	7 (14.9)	4 (8.5)	0 (0.00	0 (0.0)	3 (6.4)	
House type							0.015
Hostel	10 (76.9)	0 (0.0)	3 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Private house	122 (60.4)	29 (14.4)	37 (18.3)	6 (3.0)	1 (0.4)	7 (3.5)	
Flat	19 (76.0)	3 (12.0)	2 (8.0)	1 (4.0)	0 (0.0)	0 (0.0)	
Hotel	10 (71.4)	0 (0.0)	1 (7.1)	3 (21.4)	0 (0.0)	0 (0.00	
Shack	5 (50.0)	0 (0.0)	1 (10.0)	4 (40.0)	0 (0.0)	0 (0.0)	
Prison	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

The study further found that amongst the 46 patients who died, over three-quarters of them (76.1%) were HIV positive, 15.2% had an unknown HIV status, and 8.7% were HIV negative. These findings are summarized in the Figure 3.5.1 below.

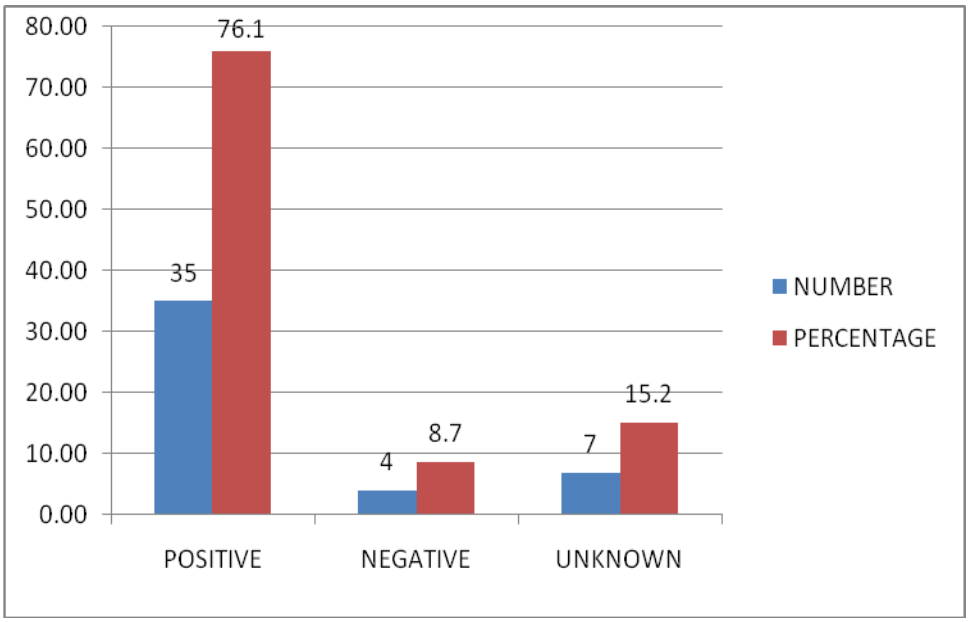

Figure 3.5.1 Distribution of HIV status among the deceased (n=46)

CHAPTER 4: DISCUSSION AND LIMITATIONS

4.1. Discussion

This study describes the socio-demographic characteristics, diagnostic and treatment history at referring facility level, HIV status, treatment history at STH and treatment outcomes at STH of MDR-TB patients, and factors associated with treatment outcomes. The findings of the study reveal that there are issues around areas which have serious influence on MDR-TB management in Gauteng. The issues pertain to socio-demographic characteristics of the patients, non compliance to MDR-TB management policies, HIV and TB co-infection, and MDR-TB treatment outcomes. These issues are discussed below.

4.1.1 Socio-demographic profile

This study has shown that the mean age for MDR-TB patients was relatively young at 37 years. The result is quite comparable with the study in Iran where the mean age was found to be 44.38 +/- 19.05 years (Masjedi at al., 2008). Likewise, other studies in Taipei, Taiwan and at Santa Cruz in Bolivia, found quite comparable mean ages (43.3 years and 33.9 years respectively) to the mean age found in this study (Chiang et al.,2006; Ollé-Goiget al., 2005). In South Africa a study at Ngwelezane hospital in the Northern Kwazulu Natal found that the mean age of TB patients was 29.6 years, with the highest notification age ranging between 25 and 34 years old, still in the comparable limit if one considers that naturally a person would suffer from TB first and then later develop MDR-TB as a complication if TB is not well managed (Lin et al., 2004). This

age group represents the working force in South Africa, thus the negative socio-economic impact of TB and MDR-TB in our society.

It was also found that the majority of MDR-TB patients were male. This finding is in accordance with literature that reveals that there are generally more males than females suffering from TB and MDR-TB worldwide (Masjedi et al., 2008; Dhingra et al., 2008; Chiang et al., 2006; Ollé-Goig et al., 2005; Lin et al., 2004). In addition more MDR-TB patients were black, probably because the users of STH are mainly black people since traditionally public hospitals cater largely for the black catchment population representing the majority population in SA, and therefore this result is not surprising. However, generally social inequalities related to race are a real issue in South Africa and the rest of Africa and this has great influence on TB/MDR-TB acquisition especially in the context of poor living conditions associated with poor nutrition and overcrowding (Nhlema et al., 2003). In South Africa the majority of black people live in poor conditions where they are vulnerable to contract TB and MDR-TB. .

The study further revealed that the majority of patients were unemployed, living in formal types of houses, and residing in townships. Employment status, types of housing and the area of residence are commonly used to determine the socio-economic status of individuals in the community as poverty is strongly associated with TB and MDR-TB. (Nhlema et al., 2003)

4.1.2 Compliance with policies (Referral and Diagnosis of MDR-TB)

In this section focus will be placed on compliance with organizational structural policy on the one hand and MDR-TB management policy guidelines on the other hand. Organizational structure means that in principle, STH was designated as a specialized centre for the treatment of MDR-TB patients in Gauteng, but in practice, this centre was functioning like a normal TB hospital with an extension ward for MDR-TB patients. For instance this study reported that in the period between 2001 and 2002, from a total of 3706 TB patients seen at STH only 845 (23%) were MDR-TB cases.

The mean duration of MDR-TB treatment or stay at the referral facility level (STH) was 64 weeks which is quite long. The study also showed a long mean duration of treatment at referral facility level of about 31 weeks, before referral to STH. According to national policy the duration of normal TB treatment is six months for new cases and 8 months for re-treatment cases divided into an initial and continuation phases (NDoH, 2004). Newly diagnosed MDR-TB patients at a referring facility should be transferred to STH immediately after a diagnosis of MDR-TB has been made (NDoH, 2007) to start MDR-TB treatment since the delay in starting MDR-TB treatment has a serious effect on the treatment outcome (Schaaf et al; 2003). But this study showed that patients waited 31 weeks on average to be transferred to STH. Such a situation could be related to delays in obtaining laboratory results and/or the fact of commencement of a TB treatment on the basis of an X-ray or clinical features.

A further finding was that 98% of patients were sent to STH with a referral note, a good indication of adherence to national policy guidelines on referral. Moreover generally more patients (80%) were referred to STH from clinics than other facilities. Further investigation needs to be initiated to check with other referring facilities whether they do adhere completely to the policy that stipulates that STH is the provincial specialized centre for the treatment of MDR-TB patients or whether these facilities have fewer cases of MDR-TB or are perhaps treating them themselves. Another explanation could be that staff in clinics and CHCs is more exposed to training than those from other facilities. Also, hospitals and most especially at tertiary level, might be treating MDR-TB themselves which is against protocol. The study further discovered a few cases of self referral to STH (1%) which again is against the protocol.

In assessing a reason for referral, it was found that the majority of patients (89%) referred to STH were confirmed MDR-TB. There is no indication in the records as to whether the referring facilities or STH did the sputum culture tests. The policy guideline recommends that the laboratory results should come from the referring facilities. Any delay in referring patients will cause delays in commencing treatment.

In terms of the diagnosis of MDR-TB, this study demonstrated that 91% of patients who had laboratory tests to confirm MDR-TB, had also an X-ray done, and that laboratory tests alone were only done in 7% of cases. A laboratory sputum test is a clear indicator of adherence to national policy and a measure of the quality of a diagnosis. The policy states clearly that a laboratory test is the first choice diagnostic method in the diagnosis

of TB and a tool to monitor treatment progress after five months. A sputum for culture and susceptibility testing is only required if the patient still remains positive at the end of the intensive phase. The policy also defines clear guidelines of the use of X-rays in the diagnosis of TB and MDR-TB. These are: suspicion of complications (Pneumothorax, pleural effusion); frequent or severe Hemoptysis; diagnosis of other lung diseases; clinical TB after a negative smear; and treatment progress (NDoH, 2004). No check was made as to whether or not these two investigations were done simultaneously. Or given an indication as to whether the X-rays were taken according to protocol or not. On the other hand the guidelines also state that too much reliance on chest X-ray in the diagnosis of TB results in unnecessary treatment, because chest X-ray is not a reliable predictor of active TB (DoH), 2004). Furthermore, the study showed that 1% MDR-TB (4 cases) had no laboratory tests done; 1 case of MDR-TB had not been investigated at all. The above gives some indication of non- adherence to policy. Further study needs to be conducted to assess the reason for this and too much use of chest X-ray in this facility.

The treatment received at STH was relatively in accordance with the policy in exception of two elements. Firstly the study showed a serious concern about the one patient who being diagnosed MDR-TB as others (100%) but received TB regimen one treatment! Secondly, the study could not determine the MDR-TB treatment received by the three MDR-TB patients who were on adjunction of surgical treatment. There is a policy issue there as well.

In summary the study has found that referral facilities are not following the correct procedure to diagnose MDR-TB as stipulated in the National TB guidelines. The consequence of this malpractice has led to a situation where some cases who have ended up at STH as MDR-TB are actually not infected (11%), but many of these patients are actually TB cases or have TB complications.

4.1.3 Treatment of MDR-TB at STH

The duration of treatment/stay at STH is an important factor to consider. On average, MDR-TB patients stayed 63.59 weeks (about 16 months). Considering the time these patients have spent at a referring facility it can be concluded that up to a total of 94.58 weeks (about 24 months) for MDR-TB is spent in treatment, which is too long. These findings are quite similar to a study by Edgington et al. where it was found that the mean duration of patients stay at STH was 28 months (Edginton & Joffe, 2004). As stated previously, national policy has specified that the total duration of MDR-TB treatment should be 19 months (76 weeks). The mean duration of stay found in this study was also comparable to the study by Ward et al in Vietnam where the mean duration of treatment for MDR-TB was 23.0 (SD+/-11.4) months (Ward et al., 2005).

Length of stay or duration of treatment at STH is showing how long the patients are taken into charge by the referral facility. This is a very important socio economic parameter. The attempt to assess predictors of “duration of stay at STH” showed no significant association but it is not clear at this moment how this influence can be evaluated.

This policy states clearly that the diagnosis to confirm a MDR-TB case should be made at facility level before the patient is referred to STH. In that case the laboratory test should show a sputum resistant to at least the two powerful anti TB drugs: H and R (NDoH, 2007).

The study has revealed that confirmed MDR-TB cases at Sizwe were classified into four groups: those resistant to the two major TB drugs, H and R (43%), those who were resistant to three TB drugs including H and R(30%) also called "poly-resistant-TB" by STH staff, those who are resistant to all 4 first line TB drugs (SHRE) (27%) locally called " high grade resistant-TB" by the staff at STH and finally one case resistance to 6 drugs after 9 months treatment and was , classified as "treatment failure" by the local staff. Recently, another group was added to the MDR-TB cases. These are the XDR-TB (Extremely or Extensively Drug Resistant Tuberculosis) defined by WHO as resistance to at least Rifampicin and Isoniazid (MDR-TB), in addition to any Fluoroquinolone, and at least one of the three following injectable drugs Capreomycin, kanamycin, and Amikacin over and above resistance to INH and RIF (DoH, 2004). A precise classification of cases is therefore important and will consequently determine appropriate treatment .This study demonstrated that the majority of MDR-TB received standardized treatment (77%) while a few others received individualized treatment (21%), only 1% received surgical treatment and one case of treatment misclassification who received TB treatment regimen 1. This shows that at STH, the protocol for the treatment of MDR-TB is commendable. At STH poly-resistant TB patients, all high grade

resistant-TB and all treatment failure cases are given individual treatment after drug susceptibility test results are obtained which is good practice.

4.1.4 Treatment Outcomes of MDR-TB

Generally in literature, MDR-TB treatment outcomes are measured in terms of success or non success (unsuccessful). Successful outcomes will be cure, treatment completion, good conversion rate while unsuccessful outcomes which are most common in MDR-TB treatment are death, default, failure and absconding (Laserson et al., 2005). Non compliance to policy guidelines by the provider as well as by the patient will lead to poor or unsuccessful outcomes.

The conversion rate at 9 months in this study was low 62% which is low. These findings in the study by Holtz et al (2006) in Latvia revealed that among 167 patients who were sputum culture-positive at initiation of second-line therapy, 129 (77%) converted in a median time of 60 days (range, 4 to 462 days) and 38 (23%) did not convert (Holtz et al., 2006). Other studies have revealed cases of poor MDR-TB treatment outcomes in different setting including the Western Cape, Estonia, Germany, Italy, Russia federal and Srilanka (Shean et al., 2008; Migliori et al., 2008 ;Ollé-Goig, 2005 ; Senaratne, 2004;Mishkinis et al., 2000.)

Good outcomes have been reported by Masjedi et al in their study on the outcome of treatment of MDR-TB patients with standardised regimens in Iran during 2002-2006 where 67.5% had a successful outcome (Masjedi et al., 2008). Another situation of

successful outcomes is reported in the study on monitoring tuberculosis treatment outcome: analysis of national surveillance data from a clinical perspective study by Ditah et al where the success rate was 76.8% using WHO/IUATLD criteria or 87.5% success rate when applying the new criteria (Ditah et al., 2008). Good outcomes in terms of cure or treatment completion were achieved with the MDR-TB treatment as was the case all over the world: (Chiang et al., 2006; Leimane et al., 2005; Chan et al., 2004;Toungoussova et al., 2004).

This study has shown the importance of giving feedback by the referral facility to the referring facilities about their patients. The feedback would include the final diagnosis, the proposed treatment and the follow up schedule as well as some instructions on DOT, and non interruption of the treatment. According to this study, giving feedback will improve outcomes and not giving feedback will lead to poor outcome especially death.

In general HIV was demonstrated to have an association with MDR-TB treatment outcomes in this study; but the limitation is that HIV data were not available on all patients. HIV negative patients were more likely to achieve better outcomes. It was difficult to comment about the association between HIV positivity with either good or poor outcomes. But HIV positive was more likely to be associated with death than HIV negative. In contrast, the study by Dedha revealed no association between death and HIV positive or negative status(Dheda et al., 2010).

Finally, this study revealed a significant relationship between types of house and treatment outcomes, and living in formal houses (hostel, private house, flats and hotel) has influence in achieving better outcomes than living in shack and prison.

The literature previously confirmed that experience with MDR-TB treatment outcomes varies in different settings. For example, a descriptive study conducted in 1996 in Santa Cruz, Bolivia revealed that a successful outcome was achieved in 28% of patients, while 48% defaulted, and 13% died and 10% were still under treatment in 1996 (Olle-Goig and Sandy., 2005). Another study by Tupaisi et al in the Phillipines showed a cure rate of 73.4%, a failure rate of 3.8% and a likely failure rate of 6.3%; while death occurred in 3.8% and defaulting was observed in 11.4 % (Tupaisi et al., 2003). Latvia has one of the highest rates of multidrug-resistant tuberculosis (MDR-TB). In a study conducted there to assess treatment outcomes for the first full cohort of MDR-TB patients treated under Latvia 's DOTS-Plus strategy following WHO guidelines, it was demonstrated that of the 204 patients assessed, 55 (27%) had been newly diagnosed with MDR-TB, and 149 (73%) had earlier been treated with first-line or second-line drugs for this disease. Assessment of treatment outcomes showed that 135 (66%) patients were cured or had completed therapy, 14 (7%) had died, 26 (13%) had defaulted, and 29 (14%) had treatment failure. Of the 178 adherent patients, 135 (76%) achieved a cure or treatment completion which is an example of a good outcome (Leimane et al., 2005). In this study, death rate is also high (16%) which is equivalent to 16000 deaths per 100 000 population.

In this study receiving feedback letters, HIV status and type of housing seem be most associated with treatment outcomes. According to published literature TB treatment outcomes are influenced directly or indirectly by a number of factors, including socio-demographic characteristics (age, sex, education level and economic status), treatment delay, inappropriate prior TB treatment with poor adherence (inefficient DOTS strategy and referral system), poor prescription and provision of drugs, staff bad attitude, HIV sero-positive status, previous TB treatment for more than 4 weeks, smoking (for Isoniazid resistance), the presence of cavitations on the chest radiograph, and imprisonment (Ekaterina et al., 2006). Other literature stresses predictors of good outcomes as weight gain at six months, culture conversion, radiologic improvement during treatment, resistance to less than or up to the three anti-tubercular drugs, use of less than or up to three second line drugs in treatment and no change of regimen during treatment (Dhingra et al., 2008).

HIV infection is one of the most common determinants of poor outcomes in TB/MDR-TB with negative influence on the incidence alongside with previous TB treatment, resistance to Ofloxacin and the positive start of treatment (Kliiman, K and Altraja, A., 2009). In 2008 WHO reported an estimate of 9.4 million incidence cases of TB, 11.1 million prevalence cases of TB, 1.3 million deaths among HIV negative TB patients and 0.52 million deaths among HIV positive TB patients (WHO, 2008). In 2008 WHO reported an estimate of 9.4 million incidence cases of TB, 11.1 million prevalence cases of TB, 1.3 million deaths among HIV negative TB patients and 0.52 million deaths among HIV positive TB patients (WHO, 2008).

4.1.5 TB/HIV co-infection

This study revealed that the prevalence of HIV amongst MDR-TB patients was 39%. It also found that there is more HIV infection in male patients than in females with MDR-TB. One reason could be that there were more males than females under review. This is a challenge in S.A where it has been found that more females than males are HIV positive; but in the context of TB/MDR-TB, there are more male than female HIV positive cases mostly because the male gender is more affected by this condition. Literature indicates that in general, HIV infection is significantly associated with TB/ MDR-TB and TB is a leading cause of death among people who are HIV positive since HIV is the single most important factor determining the increased incidence of TB in Africa. (Espinal et al., 2001; Fujita, 1998).

In SA, HIV testing is generally not compulsory. VCT is being used for individuals to find out their HIV status. In the context of the HIV-TB co-infection it would be recommended that VCT be offered to all TB/MDR-TB patients. But a policy of compulsory HIV testing (even if this was legal) of TB patients in general would be counterproductive. This type of policy may result in patients deterred from seeking care, decreased case-finding in at-risk groups and reduced credibility of health services. A notable achievement is the fact that all Gauteng TB hospitals and most community health clinics are VCT and ARV sites.

Another issue was to evaluate association of HIV status with duration of stay in hospital. This study found that in the HIV positive population the average duration of

stay/treatment at STH was shorter; at 58 weeks (14 months) for MDR-TB patientough there was no significant difference. Endeavoring to establish whether HIV was a contributing factor to death, the study revealed that amongst the 46 patients who died, over three-quarters of them (76.1%) were HIV positive, above the rate found in a study by Quy et al where death during treatment occurred in 15 of 50 HIV-infected patients (30%) (Quy et al, 2006). HIV infection may lead to mal-absorption of anti-TB drugs and acquired Rifampicin resistance. HIV-infected patients with MDR-TB have a high mortality take, thus the necessity of both anti-retroviral and anti-myco bacterial treatment. Surveillance data suggests that in several countries HIV infection and MDR-TB may converge. Furthermore institutional outbreaks, overwhelmed public health program, and complex clinical management issues may contribute to the convergence of the MDR-TB and HIV infection epidemics. Thus infection control, rapid case detection, effective treatment, and an expanded program capacity are needed urgently (Wells et al., 2007).

Finally drug resistance, specifically multidrug resistance and extensive drug resistance, is a serious threat to public health in all countries. For instance in the Russian Federation the highest rates of multidrug resistance are presently accompanied by a rapid increase in HIV infection. The collaborative effort of different organizations, professionals and communities is needed to address the development and spread of multidrug resistance and extensive drug resistance, which combined with the epidemic of HIV infection is one of the barriers to dealing effectively with TB. This effort should be directed towards facilitating the diagnosis and treatment of TB patients, in particular by

improving access to drug susceptibility testing and strengthening treatment delivery by rigorous adherence to DOTS as outlined by the Stop TB Partnership (Blöndal et al., 2007). Strong TB control will be facilitated by scaling-up WHO-recommended TB/HIV collaborative activities and by improving coordination between HIV and TB control programs, in particular, to ensure control of drug-resistant TB. The study concluded that integrating the care and treatment of TB and HIV in high prevalence areas is a necessary strategy as confirmed by the recently completed Starting Antiretroviral Therapy at Three Point in Tuberculosis Therapy (SAPIT) trial which showed that integrated treatment of HIV and TB in an urban African setting improves outcomes, reduces mortality, and is more effective than sequential treatment (IDSA News, 2010).

4.2 Limitations

- The research team was unaware of how representative the cases at STH were of the MDR-TB population. From the distribution of cases, it seems that other cases were missing.
- The study was a record review from a facility and relies on the accuracy of record keeping. Other cases of MDR-TB in the region may have been referred to the facility and not arrived, or they may not have been referred to the facility at all. Some patients may have died prior to arriving at the facility.
- A case control study would have had to be used to determine the association between MDR-TB and each of the factors being studies in this project.
- Incomplete records made it difficult to obtain the full information needed.

- The study was not able to assess the relationship between MDR-TB and the previous treatment.
- The study did not go as far as using mutli-variate regression analysis to measure the relationship between each sub category of independent variables with each outcome.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

The study demonstrated that treatment given at STH was not always standardized. Individual treatment was given in some cases of high grade MDR-TB, poly-resistance TB and treatment failure. It has also shown that socio-demographic characteristics of patients described favor TB development and were clearly evident of the majority of the community dealt with (black majority, unemployed, living in township and in the informal settlement.

In general the treatment characteristics were equivocal (commendable referral system with unclear methods used to confirm MDR-TB and unjustified long duration of treatment prior to referral). Past treatment history was explored and revealed that there was no compliance to the organizational policy given the fact that STH was used for treatment of all type of TB infections (MDR-TB, XDR-TB, PTB and extra-PTB). Although in general the majority of patients had successful treatment outcomes, the policy guidelines of the management of MDR-TB were not implemented fully and that led to some cases of mismanagement resulting in poor outcomes. Finally predictors of poor outcomes in terms of death and default were not giving feedback, HIV status and housing types.

5.2 Recommendations

The Provincial TB control policy stipulates that all Gauteng MDR-TB patients should be referred to STH. But there was no written policy about the role to be played by STH in the management of TB and MDR-TB patients. The following are direct recommendations from this study:

- There is an urgent need to define clearly the role of STH as a MDR-TB hospital only with clear admission and discharge criteria taking into account staff workload (including the burden of XDR-TB), and the existence of a number of TB hospitals around Gauteng.
- Private sector should also conform to the policy guidelines. Currently it is not known where this sector sends its MDR-TB cases.
- Staff in the referring facilities needs to be trained to understand that TB/MDR-TB is diagnosed by a laboratory test first, except those cases where an X-ray or other investigations are indicated.
- There is a need to conduct further studies to check what causes delays in laboratory investigations. It is time to explore the possibility of developing rapid testing for MDR-TB.
- It is important to check what the hospital policy is regarding HIV testing, to know whether it is a routine test for those who give consent or not. In the light of antiretroviral treatment (ART), it is particularly important that every person with MDR-TB is tested for HIV.

- The reporting or notification system should be improved to allow for accurate calculations, and also for conducting other statistical analysis in terms of the relationship between various contributing factors.
- It is important to tackle predictors of poor MDR-TB treatment outcomes in future: stronger study designs like case-control studies may be needed to do this.
- There is a need to trace where other racial groups have been treated for MDR-TB by conducting further studies.
- It is important to tackle predictors of poor outcomes in future: well defining the role of STH as related to the treatment of MDR-TB patients, improve feedback mechanisms, and improve VCT policies for MDR-TB patients.
- It is also recommended that patients should be hospitalized for at least the first few months until they have produced three consecutive monthly cultures of-negative sputa.

Generally, early diagnosis and treatment of TB cases, a well-implemented DOT system, well-planned follow up of patients (laboratory and X-ray tests), well-trained and dedicated health care professionals; and an informed and adherent population are key elements for preventing the occurrence of MDR-TB and improving TB control. Given the impacts of HIV, integration of TB and HIV services should be encouraged, especially at the outlying areas. This is important to effectively treat those infected with both diseases, to prolong their survival and to maximize limited human resources. Globally, renewed attention to TB/HIV collaborative activities is recommended, combined with committed political will (Laserson et al., 2007; Quy et al., 2006).

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APPENDICES

Appendix 1: Data Collection Sheet

FILE NUMBER _____ Entry no:_____

1. SOCIO-DEMOGRAPHIC CHARACTERISTICS:

1.1 YEAR of admission:

1.2 AGE/DOB:

1.3 SEX: F / M

1.4 RACE: Black Coloured Indian White

1.5 PLACE OF RESIDENCE (address): Informal settlement,

Township,

Suburb

and Town

DISTRICT OF RESIDENCE (part of address) : Johannesburg

West Rand

Ekurhuleni

Sedibeng

Tshwane

Metsweding

1.7 EMPLOYED: Yes / No

1.8 TYPE OF HOUSING (or housing structure if available)

Informal Housing structure: (shack and other non specific)(

Formal housing structure: (flat, hotel, hostel, prison, private house)

2. TREATMENT HISTORY AT REFERRING FACILITY

2.1 TYPE OF REFERRING FACILITY: Self

Clinic

CHC

Private Doctor

Hospital (public)

Hospital (SANTA)

Hospital (private)

Hospital (tertiary)

Other (specify) e.g. NGO

2.2 ACCOMPANYING REFERRAL NOTE: Yes / No

2.3 DURATION OF TB TREATMENT AT REFERRING FACILITY in weeks (from the period between the time the sputum AFB results were obtained (the patient is then put on TB treatment regimen) and the time the referral letter to STH was written (when the sputum culture result is positive)

2.4 INVESTIGATION DONE to diagnose TB at referring facility:

Laboratory alone

Laboratory and X-Ray

Clinical

X-RAY alone

2.5 DIAGNOSIS AT TIME OF REFERRAL: ----------

2.6 HIV STATUS: Positive

Negative

Unknown

3. TREATMENT HISTORY AT SIZWE HOSPITAL

3.1 MDR-TB RESISTANT TO: ----------

3.2 CONFIRMED DIAGNOSIS at STH

3.3 CLASSIFICATION: MDR-TB

NON-MDR-TB

3.4 TREATMENT RECEIVED AT SIZWE HOSPITAL:

3.5 DURATION OF TREATMENT at Sizwe Hospital (refers to the period between the start of treatment at STH till the patient died, was discharged, or absconded): ----------

---

3.6 FEEDBACK NOTE from Sizwe Hospital: Yes / No / Unknown

3.7 TYPE OF TB COMPLICATIONS: ----------

3.8 MDR-TB TREATMENT OUTCOMES:

CURED

CONVERTED AT 9MONTHS

COMPLETED

TREATMENT FAILURE

DEFAULT

DEATH

TRANSFER OUT

OTHER (SPECIFY):

Appendix 2: Ethics Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)
Ref: R14/49 Likibi

CLEARANCE CERTIFICATE **PROTOCOL NUMBER** M03-06-16

PROJECT Profile of MDR-TB Patients at Sizwe Hospital 2001-2002

INVESTIGATORS Dr ML Likibi

DEPARTMENT School of Public Health, Wits Medical School

DATE CONSIDERED 03-06-27

DECISION OF THE COMMITTEE Approved unconditionaliy

Unles otherwise specified the ethical clearance is valid for 5 years but may be renewed upon application This ethical clearance will expire on 1 January 2008.

DATE 03-06-30 CHAIRMAN Mokhachane 27/06/03 (Professor P E Cleaton-Jones)

* Guidelines for written "informed consent" attached where applicable.

c c Supervisor: R Weiner
Dept of School of Public Health, Wits Medical School
Works2\lain0015\HumEth97.wdb\M 03-06-16

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DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10001, 10th Floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress form. I/we agree to inform the Committee once the study is completed.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES