Factors Affecting Treatment Outcomes in Tuberculosis (TB) Patients in the Limpopo Province, South Africa.

By

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Declaration:

I declare that the dissertation submitted to the University of Limpopo for the degree of masters in Pharmacy (M Pharm), has not been previously submitted by me for a degree at this or any other University; that it is my work in design and in execution, and all material contained therein has been dully acknowledge.

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Gafar Mohammed Mergni

Date……

Dedication

I dedicate this work to my father´s soul for passing to me all the experiences that he acquired during his lifetime, and my mother who kept praying for me. And finally to my wife and my kids who endured the suffering of being apart during my study time.

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Operational definitions of commonly used terms and concepts (ETR.net)

Age group 0- 2 years: from birth to two years.

Completed treatment: TB patient who has completed the intensive and continuation phases of TB treatment; may be cured or not.

Cure rate: the sum of bacteriological and completion of the TB treatment.

Death: refers to the death while on the TB treatment with confirmed TB at the time of the death; regardless of cause.

Demographic factors: refers to the age and gender.

Directly Observed Therapy Short-course (DOTS): strategy of tuberculosis treatment recommended by WHO which involves direct observation and recording of the patient taking the medication, standardized regimens, and proper diagnostic and referral systems.

Disease classification : is based on the site of TB, may be pulmonary TB, extra- pulmonary TB or both.

Extensive- Drug Resistance TB (XDR- TB): resistance to rifampin, isoniazid and at least one of the other (second line) anti-TB drugs.

Extra- pulmonary TB: refers to TB of organs other than the lungs e.g. pleura, lymph nodes, abdomen, genti- urinary tracts, skin, joints and bones and meninges.

Multi- Drug Resistance TB (MDR- TB): resistance at least to the two most effective first line TB drugs (rifampin and isoniazid).

New Patient: a patient who never had treatment for TB or who has taken anti-TB treatment for less than one month, or patient previously treated and cured (two or more years ago) who is diagnosed with TB again.

Other diagnostic category: TB patients who have smear negative test or are HIV sero-positive

Patient category: refers to new patient or retreatment patient (relapse).

Patients starting treatment: all patients (including new patients, moved- in, transferred- in) who have started treatment during selected period.

Pulmonary TB: refers to the disease involving the lung parenchyma.

Regimen: refers to standardized treatment combinations used by National TB Programme (South Africa), e.g. 2RHZE+4RH (4 drugs in first two months – rifampicin, isoniazid, pyrazinamide and ethambutol, followed by 2 drugs in the next four months – rifampicin and isoniazid).

Retreatment patient (relapse): a patient previously treated for TB (three years ago or less ago) who has been declared cured or treatment completed, and is diagnosed with bacteriology positive TB.

Successful treatment: either cured or completed the treatment.

The patient's address: refers to the physical address where the patient receives TB services.

Treatment failure: is a treatment outcome for active TB patients who have not smear converted and are still smear positive at the end of treatment.

Treatment interruption (default): is a treatment outcome for TB patient who returned to health facility for treatment and is diagnosed with positive bacteriology, following interruption of the treatment for two months or more.

Treatment outcomes: as recorded on the ETR.net database include-completed treatment, default, death, sputum smear conversion and treatment failure.

Unsuccessful treatment: either died, failed or defaulted the treatment.

Abbreviations

ABC:	Abacavir
AFB:	Acid- Fast Bacilli
AIDS:	Acquired immune deficiency syndrome
ARDS:	Acute Respiratory Distress Syndrome
ART:	Anti-retroviral therapy
ATS	American Thoracic Society
BMI:	Body Mass Index
CDC:	Center for Disease Control and Prevention
CHC:	Community Health Care
CI:	Confidence Interval
CMI:	Cell-Mediated Immunity

COPD:	Chronic Obstructive Pulmonary Disease
CPT:	Co-trimoxazole preventive therapy
CST:	Chi Square Test
CXR:	Chest X- Ray
DM:	Diabetes Mellitus
DOTS:	Directly observed therapy short Course
DST:	Drug Susceptibility Testing
E:	Ethambutol
EAP:	Economically active population
EFV:	Efavirenz
ETR.net:	Electronic TB Register
ESR:	Erythrocytes Sedimentation Rate
FTC	Emtricitabine
H:	Isoniazid
HAST:	HIV and AIDS, STI and TB
HBCs:	High- Burden Countries
HIV:	Human immunodeficiency virus
HAART:	Highly active anti-retroviral therapy
IDUs	Injecting Drug Users
IRIS:	Immune Reconstitution Inflammatory Syndrome
IUATLD:	International Union Against, TB and Lung Disease
LP:	Limpopo Province
LPV/r:	Lopinavir
MBGT:	Mycobacterium Beijing Genotype
MDR-TB:	Multi-drug resistant tuberculosis
MTB:	*Mycobacterium tuberculosis*
NACP:	National AIDS Control Programme
NHLS:	National Health Laboratories Services
NICD:	National Infectious Communicable Diseases
NTCP:	National Tuberculosis Control Programmed
OSS:	One Stop Strategy
PCP:	*Pneumocystis carinii*pneumonia (*now P.jiroveci* pneumonia)
PTB:	Pulmonary tuberculosis
R:	Rifampin
RAD:	Retreatment after Default
SANTA:	South African National Tuberculosis Association
SPSS:	Statistical Package Social Science
SSC	Sputum- smearconversion
ST:	Streptomycin
STI:	Sexually Transmitted Infections
TB:	Tuberculosis
3TC:	Lamivudine

TST:	Tuberculin Skin Test
USAID:	United States Agency for International Development
WHO:	World Health Organization
XDR-TB:	Extreme/extensively drug resistant tuberculosis
Z:	Pyrazinamide
ZN stain:	Ziel-Nielsen staining technique

Abstract

Background

Tuberculosis (TB) threatens the public health all over the world. South Africa is ranked fifth on the list of 22 high burden countries. SA has not achieved the international targets for cure rate and default rate yet. This is attributed to high HIV/AIDS prevalence and emergence of multi- drug resistant TB. Limpopo Province experiences poor TB treatment outcome, in spite of the adoption of strategies that proved globally that they can improve the outcome. The factors affecting treatment outcome in Limpopo Province are as yet undocumented. The specific objectives of this study were to determine the demographic profile of TB patients in the Limpopo Province; to investigate the treatment outcomes and to establish the relationship between age, gender, HIV status, treatment regimen and health facility level and the treatment outcomes in patients diagnosed with pulmonaryTB for period between 2006- 2010, inclusive, in Limpopo Province.

Method

Retrospective data for the period between 2006 and 2010 (inclusive) were reviewed, and 1200 records of cases of confirmed TB patients were sampled from the ETR.net provincial database. All these patients were diagnosed and treated according to guidelines adopted by the national TB control programme. Standard WHO definitions were used to classify the TB treatment outcome. Chi squire test was used to investigate the association between age, gender, diagnostic category and treatment regimen and treatment outcome.

Results

Of the 1200 TB cases sampled, 656 (54%) were male. Most of them fell within the age group 22- 55 years (n=871; 72.5%)). According to diagnostic category, 1035 (86.2%) were new cases; 962 (80.1%) cases received regimen I (two months of rifampicin [R], isoniazid [H], pyrazinamide [Z} and ethambutol [E] followed by four months of rifampicin and isoniazid, 2RHZE+ 4RH); 893 (74.4%) cases had successful treatment; 118 (9.8%) defaulted on treatment; 26 (2.2%) had treatment failure, and 163 (13.6%) died. There was a strong association between age ($P < 0.001$), diagnostic category ($P < 0.001$), treatment regimen ($P < 0.001$), and health facility level ($P < 0.001$) and treatment outcome. The success treatment was highly significant ($P < 0.001$) for the cases that fell within the age group 3- 6 years, those that were diagnosed as new cases, those that received treatment at mine health facilities or were

treated with regimen III (2RHZ + 4RH). While the default rate was highly significant (P< 0.05) for the cases aged 7- 12 or 22- 55 years, patients that had history of defaulting, and those that received treatment at a community health centre or village health facilities – .treatment failure was highly significant (P< .05) for Those fell within age group 22-55 or 56- 74 years, those had initial treatment failure, those that received treatment at hospital or mobile health facilities or treated with regimen II (3RHZES + 5RH) while the death rate was highly significant (P< 0.05) for the cases either fall within age group 0-2, 22- 55 or 56- 74 years, had initial failure, received treatment at hospital or village health facilities or treated with regimen). The un success rate was very highly significant (P< 0.001) for those either characterized by; fall within age group 22- 55 years, had initial failure, received treatment at hospital or village health facilities or treated with regimen II.

Conclusion

TB treatment outcome are poor in the Limpopo Province, particularly among patients with previous history of TB treatment, those receiving treatment in hospitals, or those being treated with first line regimen II. This situation requires that the TB control programme and other relevant programmes be strengthened, for instance through integration at facility level, towards more effective response to the challenges which hamper progress towards international targets on TB. Further studies are needed to address the effect of HIV status and AIDS, $CD4^+$ cell counts, anti-retroviral therapy (ART), cotrimoxazole preventive therapy (CPT) and radiological presentation, and their effect on TB treatment outcome in Limpopo Province. Those data are not routinely captured on ETR.net, hence were not included in the present study.

Chapter I: Introduction

1.1 TB in South Africa

Tuberculosis is a major health problem in South Africa, with South Africa ranked fifth on the list of 22high burden tuberculosis in the world *(WHO Report, 2008).* According to the WHO GlobalReport 2009, South Africa had nearly 460 000 new TB cases in 2007 with incidence rate of 948 cases per 100 000 population in 1998 *(WHO Global Report, 2008)*, and TB prevalence was 692 per 100 000 population per year *(WHO Global Report, 2009)*. Although TB is a notifiable disease in South Africa, the quality of notification and reporting varies. The case detection rate of smear-positive cases in 2007 for directly observed treatment short course (DOTS) programme was 78%in South Africa *(WHO Global Report, 2009).* Constraining the progress to combat TB in South Africa is high TB/HIV co-infection rate, with 44% of new TB cases, testing positive for HIV *(WHO Report 2008).* This burden of TB/HIV co-infection is worsened in rural communities by poverty *(WHO report, 2008),* and the emergence of high levels of multi- drug resistant TB (MDR-TB) and extensively drug resistant TB (XDR- TB) *(Robert et al 2007).*

1.1.1 TB treatment in South Africa

According to South African *Clinical Guidelines (2001),* new TB patients are treated with TB standard treatment regimen I two months of rifampicin [R], isoniazid [H], pyrazinamide [Z} and ethambutol [E] followed by four months of rifampicin and isoniazid, 2RHZE+ 4RH), while regimen II which included streptomycin (S) in the first three months (3RHZES+ 5RH) is dedicated to retreatment patients and regimen III (2RHZ +4RH) is designed for infants and children.

Countrywide, the health facilities are uniformly geographically distributed, and provide most of the patients home- health facility which is not far from their localities. TB services are found in different levels (hospitals, clinics, mobile, community health clinic (CHC), mine health facilities and village health facilities). In response to One Stop Strategy (OSS), that was recommended by WHO to manage TB and HIV/AIDS simultaneously, health authorities provide HIV services for TB patients (testing and counseling) or have already PCP or toxoplasmosis.

1.1.2 TB treatment outcomes in South Africa

Since South Africa rolled out DOTS in 1996, TB treatments outcome have improved in people who take the therapy under the support of DOTS *(Daavies et al, 1999),* and 84% of people who take TB/HIV treatment reportedly complete treatment (*Gandhi, 2009).* Despite improved treatment completion and low mortality presented by a previous study conducted in Kwazulu Natal Province of South Africa *(Gandhi, 2009),*death due to TB in HIV co-infected persons is still high in rural South Africa *(MacPherson, 2009).* In addition, it has been shown that demographic factors, social factors, life style factors and clinical factors may contribute to death due to TB among people co- infected with HIV and those infected with TB only *(Ciglenecki, 2007).* However, the National Tuberculosis Control Programme (NTCP) attributes low TB cure rates in South Africa to poor patient compliance *(National Department of Health SA, 2000).*

Interruption of TB treatment increases the risk of development of drug resistance strains of TB, which are hard and expensive to treat *(Daavies, 2007).* A study conducted in Wardha District (India) identified several factors such as barriers to patient compliance with TB treatment, including leaving home, transport costs, inadequately informed patient, ill-informed helpers, unclear instructions about drug regimens and absence of supporting person *(Barhoorn and Adriaanse, 1992).* It is not clear to what extent such a situation obtains in South Africa, and the Limpopo Province in particular.

Multi- drug resistance is a further concern in South Africa, especially in the northern part of the country (i.e., North West and Limpopo provinces) where the greatest incidence of MDR-TB occurs *(Rawlinson et Al., 2001).* In 2006 researchers reported that an outbreak of extensively drug-resistant (XDR) TB had claimed over 50 lives in less than a year in one hospital in Kwazulu-Natal Province *(International Council of Nurses, 2008).* Since that report, drug sensitivity of TB bacteria isolates in Kwazulu-Natal Province has revealed that in 2006 alone 2476 patients had MDR –TB, compared with just 124 cases in the whole of the United States in 2006; 539 cases of MDR- TB were reported between June 2005 and August 2007, from one hospital alone - the Church of Scotland Hospital in Tugela Ferry - a small town in rural Kwazulu- Natal *(Gandhi, 2008).* That level of MDR- TB was attributed by WHO to poor adherence to the six months' regimen of TB drugs required to cure the disease.

In an attempt to improve patients' adherence to TB drugs, WHO advised the institution of the DOTS strategy.

1.1.3 Limpopo Province Background

Limpopo Province is situated in the northern part of the Republic of South Africa. The province covers an area of 123 910 km² with a population of 5,357,923 million according to midyear estimations for 2008. The province is divided into five administrative districts namely Capricon, Sekhukhune, Mopani, Vhembe and Waterberg, with a total number of 455 health centres *(Provincial Profile, 2004).* Forty-seven percent of the population is concentrated in Vhembe and Capricon districts. Females consistently outnumber the male population in all districts *(SA Census, 2001).*The province is 89.3% rural, with 71.8% unemployment rate, and with 37.3% of the population being children under the age of 15 years, while the elderly make up 4.7% of the province population. The remaining proportion (58%) falls into the economically active population (EAP) segment *(Provincial Profile, 2004).* The EAP migrate to more urban areas seeking employment. About 97% of the total population is Black African, 0.2% Coloured, 0.2% Indian and 2.4% White. In 2000 the deaths in Limpopo Province were estimated at 5,3815, 49.1% were females, and 50% of the causes of the deaths were attributed to Group 1, including HIV/AIDS. Death due to HIV/AIDS alone was higher among females (28%) than males (21%) and death due TB was 4.1%; two- thirds of this percentage were male. The capital of the province, Polokwane, is in Capricorn District, which is the most central of the five districts. Health facilities are well distributed throughout the province.

1.1.4 TB in Limpopo Province (South Africa)

Within the nine provinces of South Africa, Limpopo Province is one of most affected by TB. Compared to national TB incidence (645/100 000) Limpopo Province's TB incidence was 237/100000, *(Limpopo profile 2004).* Approximately 55% of TB patients are HIV positive *(Limpopo profile 2004).* National antenatal survey revealed the Limpopo provincial prevalence of HIV was an insignificant increase of 0.5%, which resulted in 21.9% provincial HIV prevalence, the highest prevalence ever reported by the province since the inception of the survey *(NICD & NHLS, 2010).* National HIV prevalence has also returned to its highest

pick of 30.2% which was noted in 2005. The percentage of men and women aged15 – 49 years who have had sexual intercourse with more than one partner in the last 12 months rose from 9.5% in 2005 to 10.8% in 2008 respectively *(Limpopo Provincial Strategic Plan for HIV, STI and TB 2012 – 2016)*. TB and HIV integration were not well defined in the 2007-2011*(Provincial Strategic Plan for HIV, STI and TB 2012 – 2016)* and insufficient progress has been made in TB integration even after restructuring of Limpopo Provincial Strategic Plan for HIV and AIDS, STIs and TB (HAST). This remains a challenge as interventions are still running parallel.

Figure 1: Map of, South Africa (2004)

1.2 Rationale for the study

TB spreads at a high rate in Limpopo Province, due to emergence of high prevalence of HIV/AIDS and MDR-TB*(SANTA, 2009)* ; the number of TB cases increased from 6, 286 cases in 2000, to 22, 292 in 2009 *(SANTA, 2009).* This situation is worsened by poor TB treatment outcomes; until 2008 the TB cure rate in the province was 62.4%, defaulter rate 7.6% and death rate 9.2%. MDR-TB cases increased from 60 cases in 2004 to 826 in 2010 *(NICD, NHLS, 2010).* All these figures and percentages reflect the modest efficiency of the TB control programme, and indicate that the province is far from WHO targets of 85% cure rate and less than 5% defaulter rate. The factors contributing to the treatment failure, and treatment interruption, as common outcomes, remain undocumented in Limpopo Province. This study established the relationship between the effect of some of the demographic factors (namely age, sex), in addition to diagnostic category, level of health facility and treatment regimens on the TB treatment outcomes.

1.3 The aim of the study

To investigate the factors that influence pulmonary TB treatment outcomes and how these factors are related.

1.4 Objectives

The specific objectives of the study were:

i. To determine the demographic profile of the pulmonary tuberculosis patients for the period between 2006-2010, inclusive, in Limpopo Province.

ii. To investigate the treatment outcomes among tuberculosis patients for the period between 2006-2010, inclusive, in Limpopo Province.

iii. To establish the relationship between age, gender, HIV status, and treatment regimen and health facility level and the TB treatment outcomes in patients diagnosed with pulmonary TB for the period between 2006-2010, inclusive, in Limpopo Province.

1.5 Research Question

What factors influenced treatment outcomes among pulmonary TB patient in Limpopo Province for the period 2006 to 2010?

Chapter II: Literature Review

This chapter is divided into two sections: Section 2.1on TB treatment outcome, and Section2.2 deals with the relationship between TB and HIV.

2.1 TB morbidity and mortality

TB remains a major source of morbidity and mortality throughout the world.
Globally, TB caused 1.8 million deaths in 2007 (*WHO Report 2009)* and TB is among the top ten causes of death worldwide, especially in Asia and Africa *(WHO Report2008).* Information about the determinants of death among TB patients could help identify individuals who are at higher risk so that targeted interventions can be implemented to improve TB treatment outcomes can be improved.

Co-morbidity was previously reported as an important predictor of on-treatment mortality among TB patients(*Hansel et al., 2004, Oursler et al., 2002 , Walpola et al., 2003*). The most common diseases that were listed with TB as the cause of death included HIV/AIDS, renal diseases, liver disease, cardiovascular disease, cancer, chronic obstructive pulmonary disease (COPD), and diabetes *(Mathew et al., 2006,Sterling et al., 2006,Borgdorff et al., 1998;Oursler et al., 2002, Walpola et al., 2003,White et al., 1996*). However, the effect of underlying diseases other than HIV/AIDS on the risk of death due to TB has not been as well explained, sometimes the actual disease that caused death is unknown.(*Xin et al., 2009*). Some diseases, such as renal disease and liver disease, may change the presentation of TB, making it more difficult to diagnose and treat and they may be associated with increased risk of toxicity caused by anti-TB drugs (*Blumberg et al., 2003*). TB screening among patients with other conditions which increase the risk of death might be helpful to detect TB early and to improve TB treatment outcomes (*Xin et al., 2009*).

Risk factors such as older age *(Mathew et al., 2006, Hansel et al., 2000),* a history of prior TB treatment, MDR-TB*(Mathew et al., 2006, Lefebvre, Falzon, 2008),* intravenous drugs used *(Sterling et al., 2006, Borgdorff et al., 1998),*co-morbidity *(Oursler et al., 2002),* and incomplete treatment *(Kolappan et al., 2008)* are known to increase the mortality associated with TB. Disseminated disease, usually in the setting of HIV infection, has been recognized as an important predictor of death *(Danise et al., 2010, Burton et al., 2011).* Other factors that

can influence mortality rates are extensive fibro-cavitatory disease and consolidations on chest radiographs *(Lee et al., 2007).* Acute respiratory distress syndrome (ARDS), sepsis and multiple organ failure also carry a very high mortality *(Lee et al., 2007, Ryu et al., 2007).*

The relationship between HIV and TB associated mortality is cause for concern. Several studies reported a higher mortality rate among HIV infected TB patients compared to HIV negative TB patients (*Lawn& Cheampong 1999, Connolly et al., 1998, Webeter et al., 1999, Anunnatsiri et al 2005, Burton et al., 2011, Alain et al., 1995, Bewire, 1999, Quy et al., 2006).* However, a study from South Africa found no significant difference between the mortality rate in HIV infected and non-HIV infected TB patients (*Das et al.,2010*). In HIV-infected patients who started ART at low CD4 cell counts, tuberculosis at baseline was a predictor of death *(Komati et al., 2010,),* but was not independent of other factors indicating poor baseline health status. Tuberculosis during follow-up was, in contrast, an independent predictor of death even after adjustments for baseline risk factors, including CD4 cell count and viral load *(Komati et al., 2010).* Virologic failure (HIV RNA level > 400 copies\ ml) during ART was associated with a 55% increase in risk of tuberculosis. Thus, tuberculosis is a major marker for poor outcome both at baseline and during ART and is not completely eliminated by fully suppressive ART.

In HIV/ TB co-infected patients, residence in rural areas, sputum smear negative disease and prolonged symptoms, pose risk factors for mortality, while in HIV infected and non-HIV infected TB patients, low body mass index (BMI) and low haemoglobin were reported to be predictors of death (*Webeser et al., 1999*). In contrast, a study from Shanghai, China reported sputum smear positivity as significant independent risk factors for mortality during anti-TB treatment (*Xin et al., 2009*).

Malegender was significantly associated with mortality among TB patients in some earlier studies *(Lefebvre & Falzon 2008, Borgdorff et al., 1998, Vasankari et al., 2007, Tessema et al., 2009, Zwang et al., 2007*). A recent analysis of European surveillance data showed that male TB patients had approximately 50% higher risk of death than female TB patients *(Lefebvre &, Falzon, 2008).* However, other studies failed to detect a significant association between male gender and death among TB patients *(Sterling et al., 2006, Hansel et al., 2004, Walpola et al., 2003*). The higher risk in male patients was explained by some researchers as the consequence of low compliance with anti-TB therapy, leading to repeated, short interruptions of treatment, or a greater occurrence of defaulting from treatment (Xin *et*

al.,2009). Better case-holding strategies, such as DOTS, may improve treatment outcomes (*Lefebvre & Falzon 2008, Balasubramanian et al., 2004*).

In some studies, advanced age was strongly associated with on-treatment mortality and is a likely confounder of the association of male sex, sputum smear status and co-morbidities with on-treatment mortality (*Xin et al., 2009, Lawn& Cheampong 1999, Connolly et al., 1998, Webeser et al., 1999, Anunnatsiri et al., 2005*). TB mortality among the elderly has been an enormous concern in Shanghai,China, wherethe aging population could be one of the reasons why the case fatality rate of TB cases was high (Xin *et al.,* 2009). Generally, older patients experience unfavourable living conditions, malnutrition, co-morbidities and less access to health care, any of which could increase the risk of death *(Doherty et al., 1995)*. In addition, elderly people may present with more extensive TB disease, based on the initial chest radiograph *(Perez-Guzman et al., 1999, Leung et al., 2002).*It is possible that older TB patients had a high mortality rate because they were more likely to present with nonspecific symptoms, which may contribute to delays in diagnosis and treatment of TB and, ultimately, a higher risk of death *(Perez-Guzman et al., 1999, Doherty et al., 1995).* More vigorous clinical management and prevention strategies including earlier suspicion, diagnosis and treatment of TB may reduce deaths among older patients.

Antiretroviral therapy (ART) has been found to improve the survival in HIV infected TB patients (*Girardi et al., 2001*) and to reduce the mortality rate when initiated earlier (*Girardi et al., 2001, Tabarsi et al., 2009, Akkslip et al., 2007).* In contrast, initiation of ART is sometimes associated with the development of immune reconstitution inflammatory syndrome (IRIS) and drug- drug interaction which in turn inversely affects the treatment outcome.

The association between co- trimoxazole prevention therapy(CPT) and mortality among HIV positive patients has been documented by several studies. Dialy co- trimoxazole at dose of 960 mg has been found considerably to reduce the mortality rate among HIV infected TB patients (*Nunn et al., 2008, Witor et al., 1999, Mwaungulu et al., 2004)* therefore adding CPT to routine care of HIV infected TB cases is highly recommended (*Mwaungulu et al., 2004).*

2.1.1 TB treatment defaulting

Completing tuberculosis treatment is challenging for patients, because treatment takes a minimum of six months, may require frequent clinic visits for drugs refilling and monitoring, and treatment may cause unpleasant side effects *(WHO Report, 2004)*. TB treatment default is an important public health problem, because patients who default may continue to transmit infection to healthy people or acquire drug- resistance TB strains and consequently treatment failure *(WHO Report, 2004)*. Factors affecting default have been extensively studied.
Adherence to long- term therapy is a multidimensional phenomenon, determined by interplay of five sets of factors namely: social and economic factors, health care team and system related factors, condition related factors, therapy, and patient- related factors *(WHO, Report 2003)*. Improving treatment outcome and designing effective interventions require understanding of the factors that prevent people from adhering to treatment and those that help in treatment completion *(Muture et al., 2011).*

Several social and economic factors such as low income, lack of social support, low education, financial problems and inability to afford services, have been linked to TB treatment adherence (*Demissie & Kabede, 1994, Dodor &Afenyadu 2005, Ai et al.,2010, Rabahi et al., 2002).*

Old age, the male gender, ignorance on need for treatment compliance and stigma are among reported patient- related factors that influence default in different parts of the world, particularly in the sub-Saharan Africa region *(Comolet et al., 1998, Demissie &Kabede, 1994, Muture et al 2011, Belay et al., 2009, Dodor& Afenyadu,2005, Jakubowiak et al., 2008, Liefooghe & Muynk 2001, Zellweger & Coulin, 1997*). In contrast, a study from Madagascar found that there was no relationship between the patient´s age and defaulting from TB treatment *(Rakotonirina et al.,2009).*

Reported health care system- related factors for default include: poor service provider attitudes, negative attitudes by TB patients toward treatment centre, running out of drugs, access to health services and living near treatment centre (*Wasonga,2006, Comolet et al., 1998, Demissie & Kabede, 1994, Mweemba et al., 2008, Holtz et al., 2006).*
Side effects, drugs too strong, and feeling better are among therapy related factors that influence TBtreatment default (*Demissie & Kabede, 1994, Jaiswal et al., 2003,*

Wasonga,2006, Vajay et al.,2010,Tekle et al., 2002) while HIV comorbidity is among the condition-related factors reported as predictor of TB treatment default *(Daniel et al.,2006, Ai et al., 2010).*That could be because HIV co-infected TB patientsoften have to attend separate clinics or facilities for the two conditions, thus increasing transport and other opportunity costs for instance missing of workday (*Daniel et al., 2006; Muture et al., 2011).* Furthermore, the side-effects profile of TB chemotherapy is magnified in patients with concurrent HIV treatment. Besides, combining anti-retroviral and TB drugs increases the pill burden and can be difficult and challenging to a patient *(Fry et al, 2005).* Patients with HIV comorbidity are significantly more likely to default, which suggests that HIV and TB care should be integrated *(Muture et al., 2011).* In contrast, a study from Nigeria found no difference between HIV infected and non-infected TB patients with regard to treatment default *(Amoran et al., 2011).*

Incarceration has been frequently reported as a risk factor for TB treatment defaulting *(Jakbowiak et al., 2008, Wanitchaya et al., 2009)* and this may be attributed to factors related to the prisoner or lack of components (e.g. DOTS, patient education and counseling)which play a role in improvement of compliance (*Wanitchaya et al., 2009).*

Several studies compared the default rate between citizens and immigrants and found higher default among immigrants *(Zellweger & Coulon, 1997, Wanitchaya et al., 2009).* The findings of these studies may applies to illegal immigrants who experience malnutrition, lack of dwelling and medical insurance, and therefore have poor access to health services.
A study from Brazil showed that lack of appetite as initial symptom, diagnosis of TB outside the governmental health facilities, missing re- examination during treatmentand prescription of drugs other than standard first- linewere strongly associated with noncompliance*(Rabahi et al., 2002).*

Alcoholism has been identified as an important predictor of noncompliance in several studies in different parts of the world (*Zellweger & Coulin, 1997, Vajay et al, 2010,Muture et al 2011*). Recurrent use of alcohol (alcohol abuse) leads the patient to forget to take drugs regularly and eventually default treatment*(Muture et al 2011).*Establishing a history of alcoholism prior to treatment initiation may help in identifying potential defaulter needing special attention during treatment *(Muture et al 2011).*

Dissatisfaction with treatment services and poor patient provider interaction were apparent determinants of default and barriers in utilization of services *(Nyurebda et al., 2003, Hane et al., 2007, Vajay et al, 2010, Dodor &Afenyadu 2005, Holtz et al., 2006)*. Reasons for dissatisfaction were lack of personalattention, rude behaviour of staff, inconvenient DOT timings and long waiting hours for refilling drugs *(Muture et al., 2011)*.Some social habits including tobacco, and abuse of marijuana or mandrox during treatment for TB have been found to be associated with defaulting *(Holtz et al., 2006, Wanitchaya et al, 2009)*.

2.1.2 TB treatment failure

TB treatment failure is a serious problem facing some TB control programmes. Irregularity of treatment and MDR-TB are factors that can lead to treatment failure *(WHO, 2004)*.
Several studies that have investigated the factors affecting treatment failure have found that HIV status, gender, age, education level, un-employment, extra- pulmonary TB, tobacco smoking, co-morbidity, for instance with diabetes mellitus, sputum culture and delayed diagnosis were strongly associated with failure *(Morsy et al., 2003, Babker et al., 2010, Nik N et al., 2011)*. In contrast, studies from Vietnam reported TB treatment failure associated with drug resistant but not with HIV status *(Quy et al., 2006; Buu et al., 2010).* Some patient- and health care provider-related factors include non- compliance to treatment, deficient health education to patients, poor knowledge regarding disease, and these have been identified as risk factors for TB treatment failure *(Morsy et al., 2003).*There does not seem to be a link between TB treatment failure and mycobacterium Beijing genotype (MBGT), however, there seems to an apparently strong association between MBGT and MDR- TB *(Buu et al., 2010)*.

2.1.3 Unsuccessful TB treatment

A study found among all the associated factors studied, only age, chest X-ray (CXR) findings and HIV co-infection were significantly associated with treatment outcomes *(Nik et al., 2011).* This is consistent with findings from previous studies in which older age increased the risk of unfavorable treatment outcomes(*Nik et al., 2011*). A study by *Nunnatsiri et al. (*2005*)*showed that age over 60 years was significantly associated with treatment interruption and treatment failure. Another study by *Talay et al. (2008)* stated that age more than 46 years was found to be a significant risk factor for unsuccessful treatment outcome. The lowering of

the immune system level with increasing age would be the reason for unsuccessful TB treatment (*Nik et al., 2011*).

Some previous studies observed generally low treatment success rates among smear positive re-treatment TB patients treated with the category II regimen *(Menzies et al., 2009, Jones-Lopez et al., 2011).* Given the poor treatment outcomes also observed in the ‘‘other’’ re-treatment groups (negative TB smear with HIV sero- positive), it is certainly worthwhile and important to review the current category II regimen for re-treatment of TB patients. These patients may be at high risk of drug resistance and of developing MDR-TB, as was reported in South Africa *(Basu et al., 2009).*

The categorization of TB patients as “other” is, according to the WHO, TB patients who have smear negative test or are HIV sero- positive, and may indicate poor patient management. According to WHO Global Tuberculosis Control report on relapse, failure, retreatment after default (RAD) and “other” TB cases for Africa, South-East Asia and Western Pacific regions in 2007, about 35% of 581,000 TB re-treatment cases were registered as “other” *(WHOReport 2009).*Although the WHO report provides information on the number of patients categorized as “other”, there are limited data on treatment regimens or treatment outcomes for this group. A study conducted in India found that TB patients categorized as “other” were treated with regimen II and had better treatment outcomes compared to relapse, failure and RAD cases *(Srinath et al., 2011).*

Concerning chest X-ray findings, a study showed that patients with advanced lesions will have more than six times the risk of unsuccessful treatment outcome compared to those who have minimal chest X-ray findings *(Nik et al., 2011).* This is in line with findings by *Bao et al.(2007)* who reported that treatment success outcomes among patients with cavitations was 0.7 times less likely than among the patients without cavitations. Similarly, another study by *Talay et al. (2007)* showed that successful treatments outcome among patients with extensive lesions on chest X-rays was 0.5 times less likely than among those with non-extensive lesions. Extensive lesion on chest X-ray might represent some delay for diagnosis in seeking TB treatment and finally contribute to the unsuccessful TB treatment *(Nik et al., 2011).*
The implication of female gender as risk factor for poor treatment outcome was reported by *Vinod & Anna (1999)* who found that female gender was a predictor for unsuccessful TB

outcome due to limited access to health care facilities, causing delayed in diagnosis and treatment as well as more social stigma for women with TB (*Vinod & Anna, 1999)*.

2.1.4 TB treatment regimens

Despite the fact that designing retreatment regimens for patients with TB and a history of category I treatment is a cornerstone in TB management, few studies have addressed this issue. Currently, WHO recommendations are based on category II regimen for retreatment of these cases. However, the successful outcome of this regimen is relatively low; according to a study in Morocco showed that the mean retreatment success rates of the category II regimen were, 58.0% and 51.4% respectively, among failure and default cases *(Ottmani et al., 2006, Tabarsi et al., 2008).* The prevalence of MDR TB in patients with CAT I failure or a history of more than one course of an irregular category I anti-TB regimen, which were 56% and 55%, respectively. Therefore, it is evident that introducing treatment regardless of drug susceptibility test (DST) pattern may be an improper approach to patients, especially those who failed or had irregular category I treatment *(Tabarsi et al 2008).*

A retreatment strategy based on DST and replacing the category II regimen may improve clinical outcomes among category I treatment failures, a great part of whom are patients with MDR TB *(Tabarsi et al., 2008).* This strategy significantly reduces delays inarriving at MDR TB diagnosis and the initiation of MDR TB therapy *(Tabarsi et al., 2008).* The success rate of based on DST is 62.2% and 72% in MDR TB and overall CAT I failure and irregular treatment cases, respectively *(Tabarsi et al., 2008).*

The management of children with TB should be in line with the Stop TB Strategy, taking into consideration the particular epidemiology and clinical presentation of TB in children(*WHO, 2006*) Obtaining good treatment outcomes depends on the application of standardized treatment regimens according to the relevant diagnostic category, with support for the child and carer that maximises adherence to treatment. A recent development in treatment recommendations is that, following a comprehensive literature review, ethambutol is now considered safe in children at a dose of 20 mg/kg (range 15–25 mg/kg) daily *(WHO,2006).* Adverse events caused by anti-tuberculosis drugs are much less common in children than in adults *(WHO 2006),* in addition to TB treatment regimen dosing dedicated for infants and

children is more accurate because its calculation is based on body weight, so all these factors justify better treatment outcome in this group of patients *(WHO 2006).* The outcome of the standard retreatment regimen for TB is poor, particularly in those infected with both HIV and MDR-TB *(Jones Lopez et al., 2011).* This indicates that standard retreatment approach to TB as implemented in low and middle income setting with high prevalence HIV is inadequate and stresses the importance of new, more effective strategy *(Jones Lopez et al., 2011).*

2.1.4.1- Factors affecting TB drug resistance

TB drug resistance is a big challenge, particularly in regions with high prevalence of TB *(WHO report 2004).* A lot of attention has been focused on this hurdle globally, and by national TB control programmes. According to study of estimates launched by WHO and one of its partners, the median prevalence of multi- drug resistance was 1.1% in newly diagnosed cases(*WHO & IUATLD, 2004*) The proportion, however, was considerably high in patients who had previously received anti- TB treatment. Incomplete and inadequate treatment was the most important factor leading to development of MDR- TB *(WHO &IUATLD, 2004).*

A study from Europe reported that MDR- TB cases are more likely to be HIV positive, foreign born and younger than 65 years *(Faustini et al., 2005).* In contrast, several studies did not find significant association between MDR- TB and HIV status *(French et al., 2008, Suchindran et al., 2009, Balaji et al., 2010).* Alcoholism, smoking, number of previous TB treatment and lung cavities were found as risk factors for acquired MDR- *TB (Balaji et al., 2010).*

2.1.4.2 Factors affecting sputum smear conversion

There is substantial variability in response to therapy for tuberculosis, even in those fully drug sensitive isolates *(Abal et al., 2005).* The exact reason is not known, but they are suggested to be due to variability in the mycobacteria, host biological factors or host behavioural factors (*Waliset al.,* 2000). Several studies reported on factors that justified these variations to response to TB treatment(*Jaywardena & Samrathung, 2006; Hoe et al., 2007; Güler et al, 2007; Davis et al, 2010; Su et al, 2011*).

The erythrocytes sedimentation rate (ESR), advanced age , male gender and presence of cavitary disease have been reported as factors associated with a longer time to sputum smear conversion in patients with active pulmonary tuberculosis *(Jaywardena & Samarathung 2006, Hoe et al., 2007, Güler et al., 2007, Davis et al., 2010, Su et al., 2011,)*. However, HIV co-infection was associated with a shorter time to sputum conversion *(Domínguez-Castellano et al., 2003)* and the rate of conversion is higher among HIV infected comparing to non-HIV infected people *(Domínguez-Castellano et al., 2003)*. In contrast, some studies have demonstrated that HIV-seropositive status is not a principal factor in delaying sputum conversion among patients receiving intensive phase TB treatment or even that HIV co-infection is associated with a shorter time to sputum conversion*(Telzak et al., 1997, Bwire, 1999)*.A key factor is therefore the presence or absence of cavitation, independently of HIV infection (*Telzak et al., 1997)*. The presence of diabetes mellitus and extensive disease were determined as independent factors associated with persistent sputum smear and culture positivity at the end of intensive phase*(Domínguez-Castellano et al., 2003, Güler et al., 2007)*.The presence of diabetes mellitus and extensive disease were found to be independent risk factors influencing both sputum smear and culture conversion time in pulmonary TB. Sputum smear and culture examinations should be considered together to assess TB treatment outcomes in diabetic patients and in those with extensive disease (*Domínguez-Castellano et al., 2003)*.

Initial bacilliary load, indicated by smear grading, has been frequently associated with sputum conversion time in PTB patients *(Jaywardena & Samarathung 2006, Su et al., 2011, Davis et al., 2010)*and may be a useful predictor for programmatic planning and patient counseling *(Davis et al., 2010)*.

Several studies on the effect of tobacco smoking on sputum smear conversion time found significant association between smoking habits and delayed time to smear conversion *(Jose et al., 2007, Güler et al., 2007)*. In contrast, a study from Kuwait found no association between smear conversion time and smoking *(Abal et al., 2005)*.

The relationship between the medical staff and the culture conversion rate received some attention. Two studies from the USA found that patients treated by private physicians were less likely to have documentation of sputum culture conversion to negative than patients treated in the public TB programme *(Chaulk et al., 1995, Liu et al., 1999)*.

Sputum conversion at 2 months is associated with good treatment outcome and the possibility of reaching a cure is higher among patients whose sputum has converted than among those whose sputum remains positive at 2 months *(Dembele et al., 2007)*. These results are consistent with reports in the literature *(Kuaban et al; 2009, Abal et al; 2005, Jose et al 2007)*. In Madagascar, the majority of failures were observed in patients who were smear-positive at 2 months *(Dembele et al., 2007)*.Sputum conversion during the third month of treatment is an important predictor of treatment success, and failure to convert predicts treatment failure *(Zhao & Levy 1997)*.

For hospitalized patients with smear-positive pulmonary or laryngeal tuberculosis, the Centres for Disease Control and Prevention (CDC) recommends that three consecutive sputum samples be negative for acid-fast bacilli (AFB) before respiratory isolation is discontinued *(Telzak et al., 1997)*. Limited data are available on prediction of time required to obtain three negative sputum smears and cultures and to determine factors associated with a prolonged interval before sputum smear and culture conversion, especially among patients infected with HIV*(Telzak et al., 1997)*.

2.2 Relationship between TB and HIV

HIV affects the immune system and increases the likelihood of people acquiring new TB infection *(WHO, 2004)*.It also promotes both the progression of latent TB infection to active disease and relapse of the disease in previously treated patients *(WHO, 2004)*. TB is one of the leading causes of death in HIV-infected people *(WHO, 2004)*.

2.2.1- Effect of HIV infection on clinical and microbiological presentation of TB

HIV infection affects the clinical and microbiological presentation of TB in different ways. HIV positive patients have fewer myco-bacterial colony counts compared to HIV negative patients *(Aderaye et al., 2004; Mohamed & Naing2001)*. The reduction in colony counts and smear positivity rate in HIV infected patients make the diagnosis of TB complicated among this group of patients and may have a negative effect on TB cases detection process (*Aderaye et al., 2004)*. To avoid TB misdiagnosis *Aderaye et al (2004)* recommend the adoption of HIV\TB collaborative activities.

Tuberculosis can develop through progression of recently acquired infection (primary disease), reactivation of latent infection, or exogenous re-infection. Recent data suggest that in urban areaswithin the United States, recent transmission accounts for a larger proportion of cases than was realized previously (*Alland, et al., 1994, Small et al., 1994*). Molecular genotyping studies in San Francisco and New York reported that 30-40% of new cases were due to recent infection with rapid progression to disease (*Alland,et al., 1994, Small et al., 1994*). However, a more recent study in the same setting found that the progression of TB in 13.6% of new cases was attributed to HIV infection (Kathryn et al, 2007). In the earlier studies afore-cited (*Alland,et al., 1994, Small et al., 1994*), HIV infection or AIDS was an independent risk factor for recent acquisition of infection and rapid progression to disease. Although defects in macrophage function have been demonstrated in HIV-infected patients, there is no conclusive evidence that HIV sero- positive persons are more likely to acquire TB infection than HIV-seronegative individuals, given the same degree of exposure (*Meltzer et al., 1990*).

In other aspects, subclinical infection (positive acid bacilli stains or culture without symptoms and radiological findings) has been found to be most common among ambulatory HIV infected persons (*Mtei et al., 2005).* However WHO guidelines for screening for latent TB do not recommended sputum culture and therefore subclinical active TB may not detected in a substantial number of HIV infected persons (*Mtei et al., 2005).*

2.2.2- Effect of TB on HIV progression

Tuberculosis is the most frequently diagnosed disease in HIV infected patients world-wide *(Badri et al.,2001).* In vitro studies have shown that tuberculosis increases the ability of HIV to replicate by activating CD4- T-lymphocytes and macrophages harbouring latent HIV. The onset of tuberculosis in HIV-infected patients causes marked release of pro-inflammatory cytokines that activate lymphocytes and macrophages, and this results in an increased HIV viral load (*Day et al., 2004).* Transient increases in viral load occur with opportunistic infections (*Donovan et al., 1996*), but two large African studies of patients with tuberculosis and no access to antiretroviral therapy found that viral load did not decrease despite effective anti-tuberculosis therapy (*Lawn et al. 1999, Morris et al.,1998*) and cellular immune

activation markers persisted (*Lawn et al., 1999)*. Epidemiological studies assessing the effect of tuberculosis on HIV progression have shown inconsistent results *(Badri et al., 2001).* Some studies have concluded that there was no discernible decrease in survival or evidence of major acceleration of HIV disease attributable to tuberculosis in patients with HIV infection (*Horsburgh et al., 1993, Whalen et al., 1995*) while other studies have documented either a significantly reduced survival (*Leroy*or *et al., 1997, Pernegeret al., 1995*) or an increased frequency of AIDS-defining illness following the diagnosis of tuberculosis in HIV-infected patients (*Munsiff et al., 1998).* Furthermore, while prevention of active tuberculosis in HIV-infected patients was observed to reduce mortality in tuberculin skin test (TST), positive patients in one meta-analysis *(Ole et al., 2000),* no significant reduction was observed in another (*Bucher et al., 1999*).

The synergistic interaction between HIV and TB organisms increases with the level of P24, which suggests that TB and its components may activate HIV replication, while stimulation of HIV replication by TB exacerbates dysfunction of host immune response in dually infected individuals (*Zhang et al., 1995*). A study from South Africa suggested that another mechanism justifies the synergistic relationship between HIV and TB infection may be prolonged immune activation induced by tuberculosis lead to prolonged increased HIV replication and consequent accelerated disease progression *(Badri et al., 2001).*

TB infection reportedly elevates expression of HIV co-receptors (CXCR & CCR5) that help HIV infection progression, further supporting the idea that blocking these co-receptors may accelerate progression of HIV infection in TB/HIV co- infected patients *(Juffermans et al., 2001).*

2.2.3- Effect of HIV on TB incidence

HIV /AIDS has dramatically impacted on TB epidemiology, and this has increased the global burden, especially in populations where HIV is common and prevalence *(Corbett et al., 2003).* HIV infection has contributed to a significant increase in the worldwide incidence of tuberculosis *(AIDS CAP, 1996, Raviglione et al., 1992)*. By producing a progressive decline in cell-mediated immunity (CMI), HIV alters the pathogenesis of tuberculosis, greatly increasing the risk of developing disease in co-infected individuals and leading to more frequent extra-pulmonary involvement and atypical radiographic manifestations. Although

HIV-related TB is both treatable and preventable, incidence rates continue to rise in developing nations where HIV infection and TB are endemic and resources are limited. Worldwide, tuberculosis is the most common opportunistic infection affecting HIV-sero-positive individuals *(AIDS CAP 1996)* and it is the most common cause of death in patients with AIDS *(Raviglione et al., 1995).*

A study conducted in South Africa on gold miners with TB reported a linear relationship between TB incidence and HIV prevalence (*Sonnenberg et al., 2005*), which finding supports the synergistic action between these two infections *(Giradi et al., 2000).* However, the current predictive models of TB incidence underestimate the effect of HIV in areas where TB is endemic (*Sonnanberg et al., 2005*). Another study found that TB incidence was more strongly associated with HIV infection than the point prevalence of undiagnosed disease, and the researchers attributed that to rapid increase in TB disease prevalence*(Elizabeth et al., 2004).* Although the prevalence and incidence of TB infection is similar for both HIV sero-positive and HIV-sero-negative intra- venous drug users, the risk of active TB is higher in sero- positive subjects *(Selwyn et al., 1989).* These data suggest that in HIV positive persons TB most often results from reactivation of latent TB infection which warrant aggressive chemotherapy against TB in patients with HIV infection and positive purified derivative (PPD) test.

Chapter III: Methodology

3. 1 Study design

This was retrospective cross-sectional review of the ERT.net provincial data, based on records for all the patients with PTB between 2006 and 2010 inclusive. This study design was chosen due to its convenience, time saving and as the least costly alternative, although it has its own limitations which will be addressed later.

3. 2 Study setting

The study setting was Limpopo Province in South Africa (population 5.357 million). In the province, TB control programme services are available through a decentralized network of health care facilities which provide general health services including quality- assured smear microscopy, anti- TB drug dispensing and directly observed treatment through health facilities and community DOT providers. All TB patients initiated on treatment are registered trough five districts level TB programme management units. HIV counseling and testing services were offered through National AIDS Control Programme (NACP). The Limpopo Provincial TB Control Programme sends data to the national programme and hence contribute to the national reports. The provincial TB control programme depend s mainly on *ETR.net* to extract accurate data and tools for surveillance, TB programme management and supervision.

3.3 Study population

The study population were 80 530 patients' records. These were patients who were diagnosed with PTB and registered on ETR.net Provincial database between 2006 and 2010, the inclusive period. Inclusion criteria were any patient diagnosed with pulmonary TB between 2006 and 2010, with the diagnosis confirmed by sputum smear test and on anti-tuberculosis treatment, and complete record of such patient, including treatment outcomes.

The exclusion criteria were:

- any patient record with final treatment outcomes recorded as either moved out or transferred.
- any patient record with extra- pulmonary TB.
- any patient treated with second line TB treatment.
- any patient who died before starting the treatment.

3- 4 Study sampling

The procedure of sampling was done under guidance of a statistician who was assigned for this study.

The number of records which were transferred to Excel format (as indicated under data collection) was 80 530 records. The Excel data capture sheet was customized to reject any incomplete or any other records that did not meet the inclusion criteria (for instance those with EPTB, non-confirmed TB and those that died before starting the treatment). The sample size of 1200 was determined using an interactive formula:

$(n = t^2 \times (1 - p) \div m^2$

Where: t^2 is confidence interval at 99%, p: estimated prevalence of TB in research area, m: margin of error at 4% (standard value of 0.04) – adopted from *CustomInsight.com (*available at: http://www.custominsight.com/articles/random-sample-caculator.asp).

This was calculated to provide sufficient power for the study at 99% confident interval (CI) and less than 4% level of the error, and adequate distribution to the different strata (the years under review). The 1200 records were stratified to the five different years (2006- 2010). The percentage of each year patient population was calculated proportionally to the total number of records with complete data. The dataset for each year was then transferred separately to SPSS format version 20 and by utilizing random sampling function in SPSS, the system generated random sample for each year proportionate to their percentages (Table 1).

Table 1: Sample size and percentage drawn from each year (2006- 2010)

Year	No. of records	Sample size	Sample %
2006	8839	174	14.76
2007	11026	221	18.38
2008	13818	285	23.04
2009	17074	344	28.47
2010	9210	176	15.35
Total	**59967**	**1200**	**100%**

Note: No. of records refers to the records that met the inclusion criterion of the study.

3. 5 Data sources

The source of data for this study was the electronic TB register, ETR.net (refer to appendix 3), because it is considered most reliable database at provincial level. ETR.net provides relevant information on TB (demographic and clinical data) and is directly under supervision of Provincial TB Control Programme. The software is designed to generate various patient parameters, including personal patient information, health facilities and standard quarterly and annual reports on case finding and treatment outcome. Individual patient records are taken from standard manual facility TB register and entered into a district- based data entry programme. Due to confidentiality, ETR.net does not provide HIV patients' identifier information.

3.6 Data collection

The manual of ETR.net was reviewed to identify the site of targeted data. A list titled "patients in record" was identified as useful list which contained all the data needed to conduct this study. The data extracted from patients in record were:

- Year of registration.
- Gender.
- Age.
- Diagnostic category.
- Health facility.
- Treatment regimen.
- TB confirmatory.
- Final treatment outcome.

To facilitate the process of data collection, the list of patients in record for each year (2006-2010) was copied and pasted in Excel format (refer to appendix 1). The list of patients in record did not document data related to HIV/AIDS (e.g. HIV status, CD4 counts, HAART and CPT interventions); however, ETR.net provides these data in the form of quarterly and annual reports. These reports are used to explain the final results.

3.7 Study measurements

(i) Age is defined by years, the target population categorized according to the standard age grouping as follows:

- Group A: 0- 2 years (birth to two years).
- Group B: 3 – 6 years
- Group C: 7 – 12 years.
- Group D: 13 - 21 years.
- Group E: 22 - 55 years
- Group F: 56- 74 years
- Group G: 75+ years

(ii) Cases were diagnostically categorized to: new cases and retreatment cases which in turn are subdivided into: after default, after failure, relapse and all other retreatment cases.

(iii) TB treatment first line regimen divided into: regimen I, regimen II and regimen III as shown in (Table 2).

Table2: TB treatment first line treatment regimens

Regimen	Targeted group	Intensive phase	Continuation phase
I	Adult new cases	2RHZE	4RH
II	Adult retreatment	3RHZES	5RHE
III	Children	2RHZ	4RH

R= rifampin, H = isoniazid, Z = pyrazinamide, E = ethambutol, S = streptomycin, 2,3,4 and 5 refer number of months on treatment.

The indications for different regimen as follows:

- Regimen I: Is indicated for new smear positive and other serious pulmonary and extra pulmonary tuberculosis.(Table 2)
- Regimen II:Is indicated for retreatment cases.
- Regimen III:Is indicated for children cases.

(iv) Health facilities were divided into different levels, namely hospital, clinic, community health centre (CHC), mobile health facility, mine health facility, village health facility. Some health facilities' level is undocumented, and thus classified as "facility level unstated".

3.8 Outcomes

The treatment outcomes that were considered in this study based on available entries on the ETR.net database were:

(i) Successful treatment (if the patient was cured or completed the treatment or both)

(ii) Unsuccessful treatment :
- Defaulting.
- Treatment failure.
- Death

3.9 Data analysis

Data were entered into Microsoft Excel version 2007 to ease data management and for the eased with which data could be effectively transferred to other statistic programmes. The data then transferred to Statistic Package Social Science (SPSS) version 20 for analysis. Descriptive statistics test were used to describe the frequencies and percentage of gender, age diagnostic patient categories, TB treatment regimen, hospital facilities, outcome and treatment success status (successful and unsuccessful). The Chi Square Test firstly to test the association between outcome and different demographic (gender , age and health facility) and clinical variables (diagnostic category and treatment regimen) , and secondly to test association between treatment success status ((successful and successful) and the demographic and clinical variables outlined above (section 3.7). Threshold of significance was at $P< 0.05$, while Z Test (Bonferroni method) was used to identify the variable categories that were significantly different from each other at $P< 0.05$.

3.10 Ethical considerations

The study protocol was reviewed and approved by the School of Health Sciences (Turfloop Campus) Research and Senior Degrees Committee. Ethical clearance was granted by the Medunsa Campus Research Ethics Committee (MREC). In addition, approval for the study and permission to access the ETR.net data were obtained from Provincial Research Committee (Approval Number: Ref:4/2/2, Appendix 5). Patient information was captured anonymously, and all the data obtained were treated in the strictest confidence. Access to the

ETR.net by the student researcher was under the direct control of the supervisors and the Provincial Department TB Programme officers.

Chapter IV: Results

4.1 TB Patients between 2006- 2010

From 2006 through 2010, 80530 persons registered as confirmed TB patients in ETR.net Provincial data, of which 59967 (74%) had complete medical records, from which 1200 medical records drawn randomly for this study as shown in Table 3.

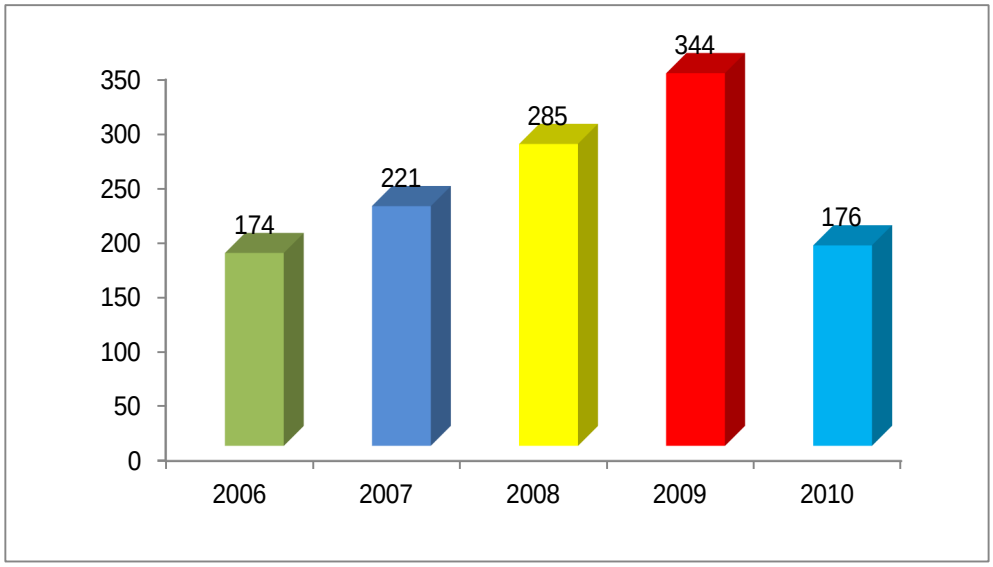
Table 3: ETR.net patients in record in Limpopo Province (2006- 2010)

Year	All records	complete records	% of complete records
2006	11454	8839	77.16%
2007	12961	11026	85%
2008	15698	13818	88%
2009	19898	17074	85%
2010	20519	9210	44.8%
Total	**80530**	**59967**	**74%**

Note: the overall percentage of incomplete records was 16%

Of the 1200 TB patients sampled, 174(14.5%) registered in 2006, 221 (18.4%) in 2007, 285 (23.7%),in 2008, 344 (28.6%) in 2009 and 176 (14.6%) in 2010. TB cases of the sample increased from 2006 to 2009 and decreased again in 2010 (Figure 2).

Figure 2: Distribution of the sample (1200cases) across years of study (2006- 2010 Limpopo Province)



4.2 Treatment outcomes

The treatment outcomes for the period under review (2006- 2010) of the 1200 patients were successful in 893(74.4%) of cases, while 307 (26.5%) had unsuccessful treatment outcome - 118 (9.8%) defaulted the treatment, 26 (2.2%) had treatment failure and 163 (13.6%) died. This is illustrated in Figure 3 and summarized by year in Table 4.

Figure 3: Treatment outcomes among the1200 TB patients (2006- 2010)

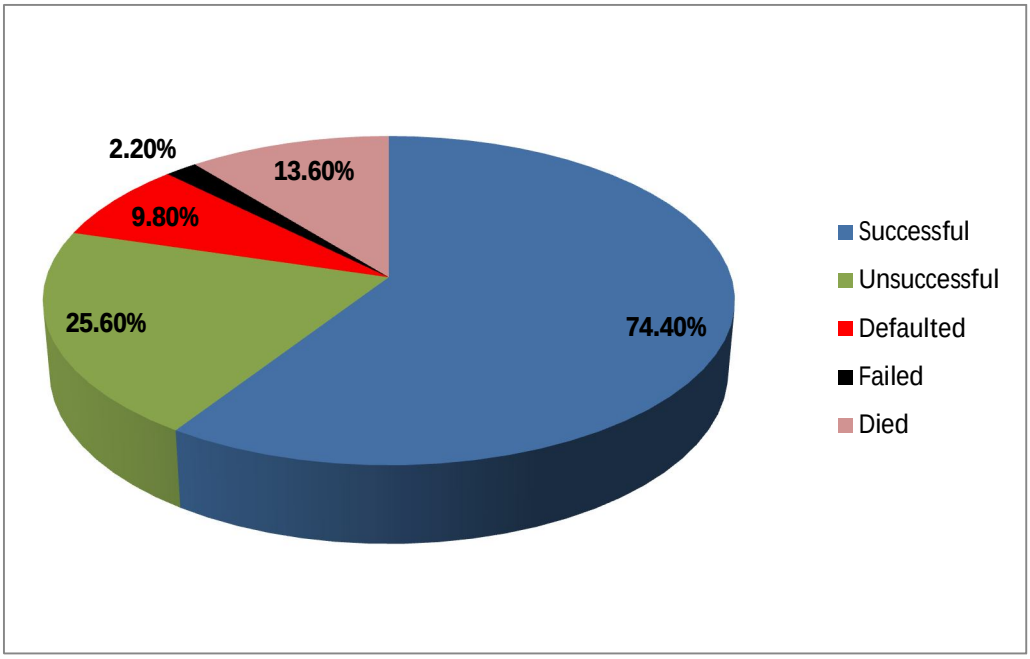


Table 4: Treatment outcome *Vs* years (Limpopo Province 2006- 2010)

year	Treatment outcome				
	Successful n (%)	Defaulted n (%)	Failed n (%)	Died n (%)	Total
2006	128 (73.6)	26 (14.6)	2 (1.1)	18 (10.3)	174
2007	171 (77.4)	14 (6.3)*	7 (3.2)	29 (13.1)	221
2008	225 (78.9)	23 (8.1)	5 (1.8)	32 (11.2)	285
2009	254 (73.8)	35 (10.2)	7 (2)	48 (14)	344
2010	115 (65.3)*	20 (11.4)*	5 (2.8)	36 (20.5)	176
Total	893 (74.4)	118 (9.8)	26 (2.2)	163 (13.6)	1200

Overall: $X^2 = 189.872$; df= 16, $P < 0.001$; *$P < 0.05$, (Bonferroni method)

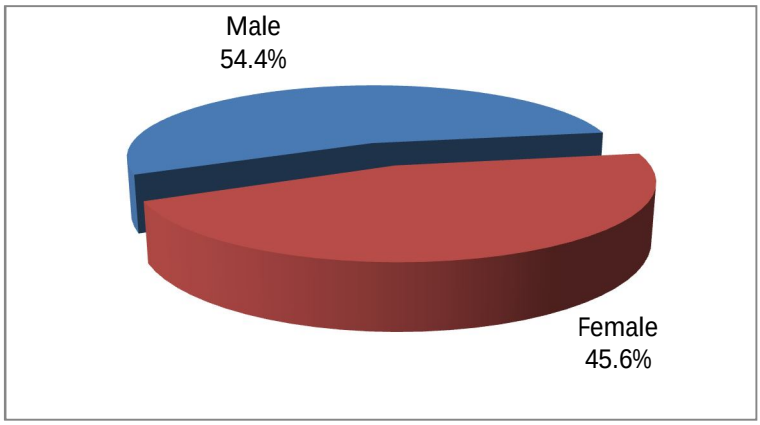
There was a highly significant difference in treatment outcome across the years of the study ($P < 0.001$) The proportion of cases with successful treatment outcome declined significantly

from 73.6% in 2006 to 65.3% in 2010 (P < 0.05), while the default rate was significantly increased from 6.3% in 2007 to 11.4% in 2010 (P < 0.05). The treatment failure rates across the years were not significantly different, though the proportion of deaths increased significantly over the years from10.3% in 2006 to 20.5% in 2010 (P< 0.05), with the overall death rate at 13.6%.

4.3 Gender

Of the 1200 cases, 656 (54.4%) were male (Figure 4).

Figure 4: Percentages of male and female in 1200 TB cases



The distribution of age groups between two genders was uniform except for age groups 13-21 years (female 68.3%) and 56- 74 years (male 59.7%), (Table 5).

Table 5: Distribution of age groups between two genders (N= 1200)

Age group /yrs	Male	Female	total
0- 2	19 (44.2%)	24 (55.8%)	43 (100%)
3- 6	14 (56%)	11 (44%)	25 (100%)
7- 12	14 (51.9%)	13 (48.1%)	27 (100%)
13- 21	32 (31.7)	69 (68.3%)	101 (100%)
22- 55	498 (57.2%)	373 (42.8%)	871 (100%)
56- 74	71 (59.7%)	48 (40.3%)	119 (100%)
75+	8(57.1%)	6 (42.9%)	14 (100%)

There was no significant association between the gender and treatment outcome (P > 0.05) (df = 4) (Table 6)

Table 6: Treatment outcome Vs Gender, (Limpopo 2006- 2010

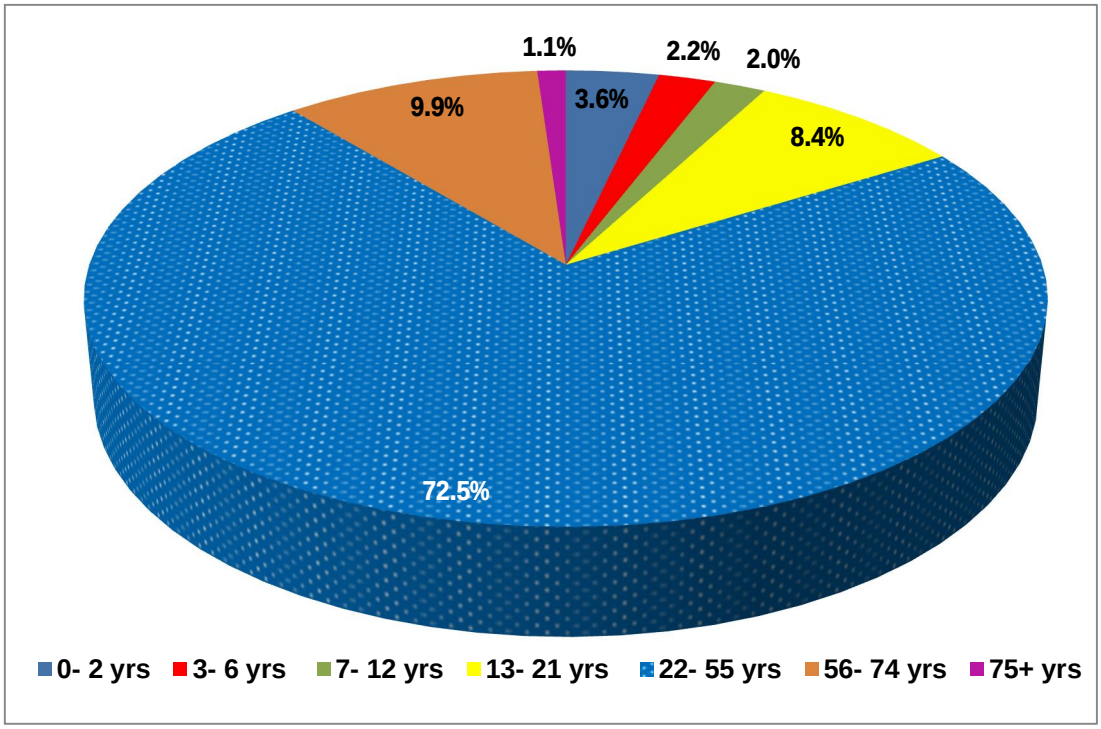
Gender	Treatment outcome					Total
	Successful n (%)	Un successful n (%)	Defaulted n (%)	Failed n (%)	Died n (%)	
Male	479(73)	177(27)	70(10.7)	16(2.4)	91(13.9)	653
Female	414(76.1)	130(23)	48(8.8)	10(1.8)	72(13.2)	547
Total	893(74.4)	307(25.6)	118(9.8)	26(2.2)	163(13.6)	1200

Overall: $X^2 = 2.363$; df =4; P > 0.05

4.4 Age groups

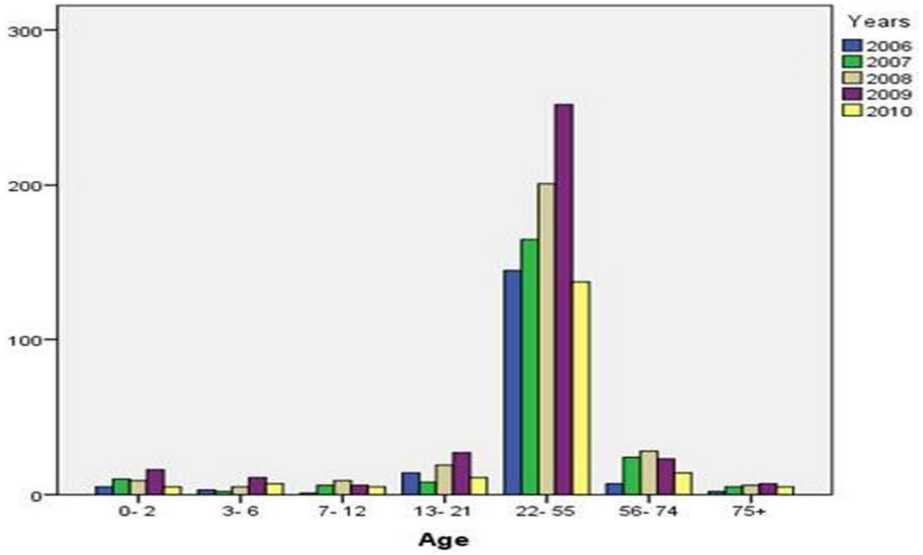
Of 1200 TB cases, the majority age group was 22- 55 years (N=871; 72.5%), while the 75+ years age group were the least 14 (1.1%) as shown in Figure 4.

Figure 5: Distribution of 1200 TB Cases between Age Groups.



For most of the age groups (0-2, 3-6, 13- 21 and 22- 55 years) the highest number of TB cases in the sample were in 2009, as illustrated in Figure 6.

Figure 6: Distribution of 1200 TB cases´ age ranges over the years



There was a significant association between the age groups and treatment outcome, as shown in Table 7.

Table 7: Treatment outcome Vs age group (Limpopo 2006- 2010)

Age group	Treatment outcome					
	Successful n (%)	Unsuccessful	Defaulted n (%)	Failed n (%)	Died n (%)	Total
0-2	36(83.7)	7(16.3	1(2.3)	0(0.0)	6(14)*	43
3- 6	23(92)*	2(8)	1(4)	0(0.0)	1(4)	25
7- 12	22(81.5)	5(18.5)	4(14.8)*	0(0.0)	1(3.7)	27
13- 21	90(89.1)	11(10.9)	8(7.9)	1(1)	2(2)	101
22- 55	619(71.2)	252(28.9)*	101(11.6)*	20(2.3)*	131(15)*	871
56- 74	27(77.3)	27(22.7)	2(1.7)	5(4.2)*	20(16.8)*	119
75+	3(78.6)	3(21.4)	1(7.1)	0(0.0)	2(14.4)	14
total	893(74.4)	307(25.6)	118(9.8)	26(2.2)	163(13.6)	1200

Overall: $X^2 = 91.882$, df = 24; P < 0.001;*P< 0.05, (Bonferroni method).

Treatment success was statistically significant for the cases aged 3- 6 years (92%; P<0.05), compared to other age groups (Table 7). Treatment failure was highly significant for age groups 56- 74 and 22- 55 years (4.2% and 2.3% respectively, P< 0.05), compared to other age groups. A general trend was that treatment failure rate increased with age. Defaulting from treatment was highly significant for the Age groups 7- 12 (14.8%) and 22-55 years (11.6%) (P < 0.05), if compared with the other age groups 0- 2 (2.3%), 3- 6 (4%), 13- 21 (7.9%), 56-74 (1.7%) and 75+ years (7.1%). There was significant association between age groups and

treatment success status, unsuccessful treatment was highly significant for 22- 55 years age group (28.9%; P< 0.05), compared to other age groups. In general adults were more likely to experience unsuccessful treatment than children (P< 0.05)

4.5 Patient diagnostic category

Of 1200 cases, 1035(86.26%) were new cases and 165 (13.75%) retreatment cases. Among the new cases, 764 (73.3%) were aged 22- 55. And among the retreatment cases, 52 (31.5%) returned after default the treatment, 39 (23.6%) returned after failed treatment, 62 (37.5%) after relapse and 12 (7.2%) returned for treatment for other reason as shown in Table 8.

Table 8: Reasons for retreatment (N=165)

Reason for retreatment	No	%
After default	52	31.5
After fail	39	23.6
relapse	62	37.5
other	12	7.2
total	165	100%

Most of the retreatment cases were aged 22- 55 (144/165, 87.2%), of which 49 were retreatment after default, 31were retreatment after fail, 55 were retreatment after relapse and 9 were cases retreated for other reasons. Age groups 0- 2, 3- 6 were more likely to be diagnosed as new cases (X^2 = 21.494 df=6; P< 0.05 and df = 6) – the details are shown in Table 9.

Table 9:Diagnostic category Vs age groups (N= 1200)

Age group/year	New cases	Retreatment subgroup				Total of Retreatment cases
		After default	After fail	relapse	other	
0- 2	42(97.7%)*	0	0	1	0	1(2.3%)
3- 6	24(96%)*	0	0	0	1	1(4%)
7- 12	27(100%)	0	0	0	0	0(0.0%)
13- 21	92(91%	3	2	3	1	9(9%)
22- 55	727(83.4%)	49	31	55	9	144((16.6%)
56- 74	109(91.5%)	0	6	3	1	10(8.5%)
75+	14(100%)	0	0	0	0	0(0.0%)
total	1035	52	39	62	12	165

Overall (X^2 = 21.494, df=6; P <0.005 and df = 6; * P< 0.05 (Bonferroni method)

There was no association between diagnostic category and the gender as shown in Table 10.

Table 10:Diagnostic category Vs gender(N = 1200)

Diagnostic category	gender		Total
	Male n (%)	Female n (%)	N(%)
New	548(52.9)	487(47.1)	1035(100)
After default	34(65.4)	18(34.6)	52(100)
After fail	25(64.1)	14(35.9)	39(100)
Relapse	41(66.1)	21(33.9)	62(100)
other	8(66.7)	4(33.3)	12(100)
Total	656	544	1200

Overall X2 = 12.035; df = 4; P > 0.05

There was, however, a strong significant association between treatment outcome and the diagnostic categories (P < 0.001, Table 11).

Table 11:Diagnostic category Vs treatment outcome (1200 TB cases) Limpopo, 2006 2010

Diagnostic category	Treatment outcome					
	Successful n (%)	Un successful n (%)	Defaulted n (%)	Failed n (%)	Died n (%)	Total
New case	787(76)*	248(24)	100(9.7)	17(1.6)	131(12.7)	1035
After default	34(65.4)	18(34.6)	9(17.3)*	2(3.8)	7(13.5)	52
After fail	21(53.8)	18(46.2)*	3(7.7)	5(12.8)*	10(25.6)*	39
Relapse	42(67.7)	20(32.3)	6(9.7)	2(3.2)	12(19.4)	62
Other	9(75)*	3(25)	0(0.0)	0(0.0)	3(25)	12
Total	893(74.4)	307(25.6)	118(9.8)	26(2.2)	163(13.6)	1200

Overall X^2 = 31.909; df=16; P<0.001; *P< 0.05, (Bonferroni method)

The likelihood of treatment success was statistically significant for the new cases and “other” diagnostic categories (76%and 75% respectively; P< 0.05) compared to other categories; while defaulting from treatment was more likely for the cases who returned for retreatment after having defaulted (17.3%; P< 0.05), compared to new cases and other retreatment subgroups (Table 11).Treatment failure and death were significantly higher for retreatment cases who had initial

treatment failure (12.8% and 25.6% respectively; P< 0.05), compared to other diagnostic categories. There was significant association between patient diagnostic category and treatment success status – successful and unsuccessful outcomes (P< 0.01). Unsuccessful treatment was highly significant for retreatment patients with initial treatment failure (46.2%; P< 0.05) compared to new cases and other retreatment subgroups (Table 11).

4.6 Health facilities

Of the 1200 patients, 95(7.9%) received the treatment at hospital, 171(14.3%) at clinic facility level, 69(5.8%) at community health centre, 17(1.4%) at mobile health facilities, 18(1.5%) at mine health facilities, 6 (0.5%) at village health facilities and for 824(68.7%) of the patients the level of health facilities where they received treatment was not recorded on the ETR.net. The distribution of patients by facility level is shown in Table 12.

Table 12: 1200 TB cases per health facility level (Limpopo Province. 2006- 2010)

Health facility level	Cases No	%
Hospital	95	7.9
Clinic	171	14.3
CHC	69	5.8
Mobile	17	1.4
Mine	18	1.5
Village	6	0.5
Unstated	824	68.7
Total	1200	100

As mentioned above, for most of the patients (824; 68.7%) the facility level at which the received treatment was not stated, which limits the interpretation of findings in this regard. The data show that significantly fewer children aged 0-2 years and cases aged 75+years received treatment at village health facilities (P< 0.05; Table 13). Male and female patients were however approximately uniformly distributed over all health facility levels.

Table 13: Age groups by Health facility level (N=1200)

Health facility level	Age group/yrs						
	Up to 2 n (%)	3- 6 n (%)	7- 12 n (%)	13- 21 n (%)	22- 55 n (%)	56- 74 n (%)	75+ No(%)
Hospital	1(2.3)	1(4)	0(0.0)	2(2)	79(9.1)	4(3.3)	2(14.3)
Clinic	5(11.6)	1(2.3)	2(7.2)	11(10.9)	132(15.2)	18(15.1)	0)0.0)
CHC	2(4.7)	1(4)	3(11.1)	4(4)	47(5.4)	11(9.2)	1(7.1)
Mobile	2(2.3)	1(4)	0(0.0)	2(2)	11(1.3)	2(1.7)	0(0.0)
Mine	0(0.0)	0(0.0)	0(0.0)	0(0.0)	17(2)	1(1.8)	0(0.0)
Village	0(0.0)*	1(2.3)	0(3.6)	2(2)	6(0.7)	4(3.3)	0(0.0)*
Un stated	34(79.1)	20(80)	21(77.8)	80(80)	579(66.5)	78(66.4)	11(78.6)
Total	43	25	27	101	871	119	14

* P<0.05 (Bonferroni method)

The majority of patient aged 22-55 tended to utilize either clinics or hospital. There was strong association between health facility level and outcome (X^2 = 81.059, df = 24, P<0.001; Table 13). Treatment success was highly significant for the cases who received treatment at mine health facilities (83.3%; P< 0.05) than other health facilities.

While defaulting from treatment was significantly high among those who received the treatment at Community Health Facilities (CHC) (21.7%) and village health facilities(16.7%) (21.7% and 16.7%, respectively; P< 0.05) compared to other levels, including the group for which the facility level was not stated. Treatment failure was highly significant for the cases who received the treatment at hospital and mobile health facilities, (5.9%) and (4.2%) (P< 0.05) respectively compared to other levels (Table 14).

Table 14:Health facility level Vs treatment outcome (N=1200)

Health facility level	Treatment Outcome					total
	Successful N (%)	Unsuccessful N (%)	Defaulted N (%)	Failed N (%)	Died N (%)	
Hospital	54(56.8)	41(43.2)*	5(5.3)	4(4.2)*	32(33.7)*	95
Clinic	138(8o.7)	33(19.3)	16(9.4)	5(2.9)	12(7)	171
Chc	43(62.3)	28(37.7)	15(21.7)*	1(1.4)	10(14.5)	69
Mobile	13(76.5)	4(23.5)	1(5.9)	1(5.9)*	2(11.8)	17
Mine	15(83.3)*	3(16.7)	0(0.0)	0(0.0)	3(16.7	18
Village	3(50)	3(50)*	1(16.7)*	0(0.0)	2(33.3)*	6
Un stated	627(76.1	197(23.9)	80(9.7)	15(1.8)	102(15)	824
Total	893(74.4)	307(25.6)	118(9.8)	26(2.2)	163(13.6)	1200

Overall X^2 = 81.059; df = 24, P<0.001; * P< 0.05 (Bonferroni method)

The death was highly significant for the cases that received treatment at hospital or village health facilities (33.7% and 33.3% respectively; P< 0.05), compared to the other health facility levels. There was strong association between health facility level and treatment success status (P< 0.001; Table 14). Successful treatment outcome was significantly higher for those cases who received TB treatment at mine health facilities compared to others (Table 15; 50% and 43.2% respectively; P < 0.05); while unsuccessful treatment was significantly more among the cases that received treatment at hospital and village health facilities (43.2%, 50% respectively; P< 0,05) compared to other health facility categories. The above results persisted even after health facilities with level unstated were excluded from the analysis (Table 15).

Table 15:Health facility level Vs treatment outcome Excluding those with health facilities level unstated

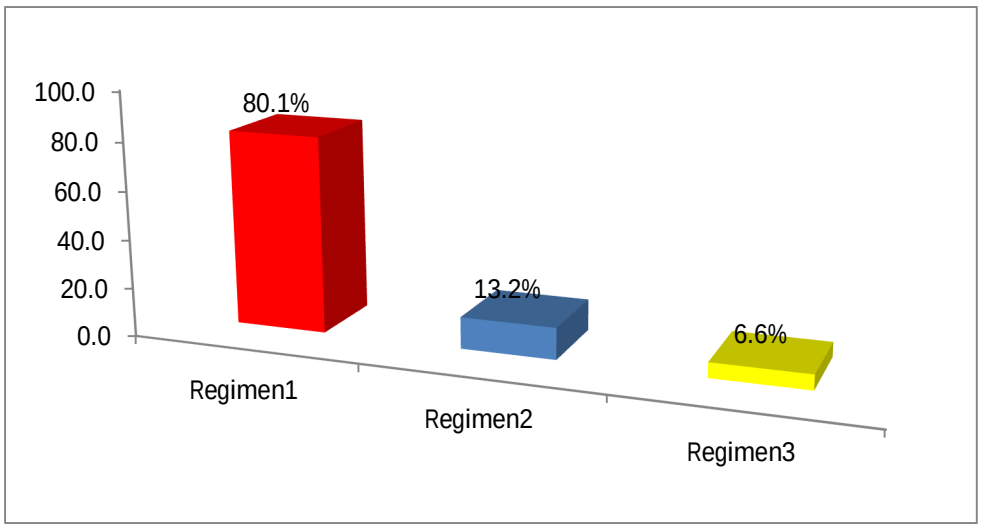
Health facility level	Successful N (%)	Unsuccessful N (%)	Defaulted N (%)	Failed N(%)	Died N (%)	Total
hospital	54(56.8)	41(43.2)*	5(5.3)	4(4.2)	32(33.7)*	95
clinic	138(80.7)	33(19.3)	16(9.4)	5(2.9)	12(7)	171
CHC	43(62.3)	28(37.7)	15(21.7)*	1(1.4)	10(14.5)	69
mobile	13(76.5)	4(23.5)	1(5.9)	1(5.9)*	2(11.8)	17
mine	15(83.3)*	3(16.7)	0(0.0)	0(0.0)	3(16.7	18
village	3(50)	3(50)*	1(16.7)*	0(0.0)	2(33.3)*	6
Un stated	0	0	0	0	0	0
total	266(74.4)	110(25.6)	38(9.8)	11(2.2)	61(13.6)	376

* Denotes significant at P< 0.05 (Bonferroni method)

4.7 Treatment regimens

Of the 1200 cases, 962(80.1%) were treated with regimen I, 159(13.2%) with regimen II and 79(6.6%) treated with regimen II, as shown in Figure 6.

Figure 7: 1200 TB cases per treatment regimens



The treatment regimens by age group are shown in Table 15. One new case aged 0-2 years, 2 new cases aged 3- 6 years and 14 new cases aged 7- 12 treated with regimen I. One new case aged 22- 55 years received regimen III. And two new cases aged 7- 12 received regimen II (Table 16).

Table 16: 1200 TB cases, regimens by age groups

Age group/ year	Diagnostic category	Regimen			Total
		I(2RHZE+4RH)	II(3RHZES+5RHE).	III(2RHZ+4RH)	
0- 2	new	1	0	42	43
	retreatment	0	0	1	1
3- 6	new	2	0	22	24
	retreatment	0	0	1	1
7- 12	new	14	0	13	27
	retreatment	1	0	0	1
13- 21	new	91	0	0	91
	retreatment	0	10	0	10
22- 55	new	726	1	0	727
	retreatment	5	129	1	135
56- 74	new	108	1	0	109
	retreatment	1	9	0	10
75+	new	14	0	0	14
	retreatment	0	0	0	0

There was observed a strong association between treatment regimen and treatment outcomes, Table 17).

Table 17: TB treatment regimen Vs outcome among 1200 TB cases

regimen	Treatment outcome					Total
	Successful n (%)	Unsuccessful n (%)	Defaulted n (%)	Failed n (%)	Died n (%)	
Regimen I	724(75.3)	238(24.7)	96(10)	17(1.8)	125(13)	962
Regimen II	100(62.9)	59(37.1)*	19(11.9)	9(5.7)*	31(19.5)*	159
Regimen III	69(87.3)*	10(12.7)	3(3.8)*	0(0.0)	7(8.9)	79
total	893(74.4)	307(25.6)	118(9.8)	26(2.2)	163(13.6)	1200

Overall X2= 72.328, df= 8; P<0.001; *P< 0.05 (Bonferroni method).

Treatment success was highly significantly for the cases that received regimen, compared with those who received regimen II (87.3% Vs 23.9%; P<0.05). Treatment failure was highly significant for the cases that received regimen II compared with those who received regimen I (5.7% Vs 1.8%; P<0.05). The deaths was highly significant for the cases who received regimen II (19.5%)(P< 0.05) than those who received regimen I(13%) or regimen III (19.5% Vs 8.9%; P<0.05; (Table 16). Similarly, there was a strong association between the treatment

regimen and successful treatment outcome; the successful treatment was highly significant for the cases that received regimen III, compared to the cases received regimen I and regimen II (87.3% Vs 75.3% and 62.9% respectively; $P<0.05$; Table 16).

Chapter V: Discussion and Conclusion

5.1 Discussion

The sample of 1200 TB cases had 656 (54%) males, and the majority of patients fell within the age group 22- 55 years (N= 871; 72.5%)). According to diagnostic category, 1035 (86.2%) were new cases; 962 (80.1%) cases received regimen I; 893 (74.4%) cases had successful treatment outcome; 118 (9.8%) defaulted the treatment; 26 had treatment failure, and 163 (13.6%)died. Cases within age group 3- 6 years, those diagnosed as new cases or other, those that received treatment at mine health facilities or those that were treated with regimen III were more likely to have successful treatment outcomes.

Patients within age groups 7- 12 years or 22- 55 years, those with history of defaulting, and those that received treatment at CHC or village health facilities were more likely to default the treatment. Patients within age group 22-55 or 56- 74 years, those that had initial failure, those that received treatment at hospital or mobile health facilities or those treated with regimen II were more likely to experience treatment failure. Death was proportionately more common among those within age group up to 2 years, 22- 55 or 56- 74 years, among those that had initial treatment failure, and those that received treatment at hospital or village health facilities and those treated with regimen II. Unsuccessful treatment outcomes were recorded more among those aged 22- 55 years, those who had history of treatment failure, those who received treatment at hospital or village health facilities and those treated with regimen II.

The high number of patients with incomplete data, especially treatment outcome information, on the ETR.net is noteworthy. As shown in Table 3, 15% of 80530 TB cases had incomplete records, particularly in 2010 where the percentage of incomplete records were 55.2% of 20519 records. This may reflect inadequate follow up services for TB treatment in Limpopo. However, where treatment outcomes could be assessed, the currently advocated re-treatment regimen achieved a high success rate. These observations point to an urgent need to improve TB documentation and follow up procedures within the public service in Limpopo in order to forestall the emergence and spread of drug resistant TB.

It was clear from the findings that the number of TB cases increased across years and this may be due to improvement in detection rate or the inadequacy of the measures taken to

control the spread of TB. The 2010 TB cases contributed to 15.3% of the sample of1200 . However, this value was uncertain because more than the half of the cases (56.2%) for that year were excluded from this study due to incomplete medical records, a potential source of bias in the study.

The majority (72.5%) of TB cases in Limpopo Province were among the economically productive age group (22- 55 years), which is similar to the findings of a study from Malaysia *(Nik Nar et al., 2011).* A high number of TB among this age group may be attributed to the fact that this age group accounts for 58% of the total population of Limpopo Province *(Provincial Profile 2004).* In addition this is the sexually active and at high risk for HIV/AIDS. Therefore, they easily contract TB infection and activate latent TB to active TB *(WHO report, 2004).* The provincial TB control programme revealed that 50% of HIV/AIDS cases fall in economic active age *(ETR.net Report 2010).*

Male TB cases (54.4%) were more than female cases, and yet SA Census 2001 reported that females outnumber males (54.6% vs 45.4%), this may imply that males are more vulnerable to TB infection than females. This is may be attributed to biological differences (i.e. gender differences) in the epidemiology of tuberculosis, differences in the societal roles of men and women (gender differences) that influence risk of exposure and/or gender differences in access to care. *(WHO report, 2001).*

Nine percent (9%) of TB cases were children, about 50% of whom were aged two years or less. Since the members of this age group most likely acquired the infection from their parents or other family members, this indicates a high transmission rate from adults to children, and may be due to poor knowledge about TB transmission and prevention. It may also suggest that patients with active TB are not subjected to isolation period to prevent further transmission.

The majority of patients (86.2%) were new TB cases. This is a considerably high percentage and indicates that in Limpopo Province the strategies applied to control the spreading of TB are ineffective or the delay in seeking treatment after symptoms have developed is common in this community. A high number of new cases may also be linked to a high default rate (9.8%) which is reported in this study, as patients who default may continue to transmit infection to healthy people *(WHO report 2004).* Another possible explanation may be that

high HIV/AIDS prevalence has dramatically impacted on TB epidemiology by increasing TB incidence (*Raviglione et al1992, AIDS CAP 1996, Corbet et al., 2002).*

Most of the 0-2 and 3- 6 years age groups were new cases (97.7% of 43 and 96% of 25 respectively). This finding may suggest inadequate BCG vaccine coverage, as reported in the Limpopo Profile 2004 there was a deterioration in infants/ children vaccination services (Limpopo Profile, 2004).Furthermore, in 2007 South Africa responded to a call by WHO, which recommended to stop the vaccination of TB /HIV co- infected children, since studies adopted by WHO found that BCG vaccine ineffective in this TB children group (*WHO Report, 2007*).

That cases two years or younger and those over 75 years were unlikely to have received TB services at village health facilities, may imply that people living in the villages do not trust TB services provided by these facilities, particularly for patients at age extremes, the very young and very old). According to the Limpopo Province TB Programme, health facilities at the villages are lower level (health centres or clinics),which are ran primarily by nurses with support of medical practitioners *(Limpopo profile, 2004).* It was not clear from the reviewed documents and records whether there are guidelines for referral of patients at extremes of age to higher level facilities; if that were so, it would explain why fewer patients in the two categories were treated at the lower level facilities.

The total number of 95 children (up to 12 years old) were diagnosed as new cases, while the number of cases receiving regimen III (dedicated for children) *(SA clinical guideline of TB and HIV/AID 2000)* was 79 cases. Since all cases in this study received TB treatment, it means 16 children received treatment that differs from the guidelines recommendations. Consequently two new cases, both children aged under two years and 14 new cases aged 7-12 years, received regimen I dedicated to adult new cases (*SA clinical Guidelines of TB and HIV/AID 2000).* Moreover, one adult new case aged 22-55 years received regimen III, and two new cases aged 7- 12 years, received regimen II which is indicated for adult retreatment cases *(SA clinical Guidelines of TB and HIV/AID 2000).* All these findings indicate that TB health facilities in Limpopo Province do not strictly adhere to TB treatment guidelines and recommendations adopted by the national and provincial TB control programmes.

According to the WHO 2005 report on global tuberculosis control *(WHO Report, 2005),* the treatment success rates under the DOTS programmes among the 22 high-burden countries (HBCs) varied from 60% in Uganda to 93% in China, with an average of 83%. Moreover, the study conducted by Shargie & Lindtjørn (2005) in Southern Ethiopia showed that the treatment success rate of all tuberculosis cases was 49% *(Shargie & Lindtjørn, 2005)*. The current study found that the success of treatment of tuberculosis was at a relatively acceptable 73.3%, although that is below the WHO target of 85%. Nevertheless, it is similar to the national successful treatment rate of 73% for 2006 *(SANTA, 2008).* The successful treatment was significantly high among the new cases, which indicates that first line regimen is still effective in Limpopo Province.

It was also observed in the current study that cases diagnosed as "other" were more likely to have successful treatment outcomes. This finding is consistent with a study conducted in India, which found that TB categorized as "others" and treated with a category II regimen, had better outcomes compared to relapse, failure and retreatment after default *(Srinath et al., 2011).* WHO has defined the "other" category as those TB patients who have negative smear test or who are HIV positive (*WHO Report, 2005*).

The default rate was 9.8% . This is approximately double the international target of less than 5%. Several studies have reported similar high default rate in Ghana (13.9%; *Dodor and Afenyadu, 2005),* India (11%); s*ingh et al., 2002)* and Iran (14%; *Tabarsi et al., 2009)*. This indicates that more needs to be done in Africa. Communities should be sensitized on need for treatment adherence in management of TB and other chronic illnesses.

Furthermore, the default rate was significantly high in two age groups, that is, 7- 12 and 22-55 years. Regarding high default rate among children age group 7- 12 years, and as stated earlier a number of children received inappropriate regimen. That may imply that some members of that category received regimen I (adult new cases) instead of regimen III. This could have exposed them to overdose due to inappropriate dose calculation; however, the common features of overdose such as itching, mental change and red- orange discoloration of the skin *(Holdiness , 1989)* were not recorded on the ETR.net. But such developments may lead to severe side effects, as reported in the literature as a factor that influences TB treatment default *(Demissie &Kabede, 1994, Jaiswal et a., 2003, Wasonga, 2006, Vajay et al.,2010).* It should be noted that reasons for defaulting treatment are not documented in

ETR.net. so there was no data to that effect. Another issue arising is that children received a regimen that contains ethambutol which is contra-indicated in children (*WHO, 2008*).

High default rate among 22- 55 age group may be explained by high HIV/AIDS among this sexually active group *(ETR.net Report, 2010)*. In literature review, TB/HIV co-morbidity is among the condition-related factors reported as predictor of TB treatment default *(Daniel et al., 2006, Ai et al., 2010).* However, a study from Nigeria *(Amoran et al., 2011)* found no association between HIV/AIDS and TB treatment default, but the Nigerian study included both pulmonary and extra- pulmonary TB cases, while the present study included only pulmonary TB cases. Some social habits are common among 22- 55 years age group (e.g., alcohol consumption, tobacco and drug abuse, and these habits reported by several studies as have association with TB treatment default *(Zellweger & Coulin, 1997, Vajay et al., 2010, Muture et al., 2011Holtz et al., 2006, Wanitchaya et al., 2009).*

The default rate was significantly higher among those who received regimen II compared to those treated with regimen 1. This finding maybe due to difficulties in adherence to this regimen because it includes an injectable drug in initial phase (streptomycin) and this route of administration is substantially inconvenient for most patients, *(Laurence et al., 2005).*

Health facilities in this study were classified to levels. However, in there were apparently no studies that used the same levels of health facilities, hence it was not possible to interpret the findings of the present study to others in this regard. It was noted that cases that received treatment at a health facility at the village level were more likely to default from the treatment than those treated at different facilities. This finding is consistent with previous study which reported that residing in rural areas is a risk factor for defaulting from the treatment *(Vijay et al., 2010).* On the other hand, counseling*(Liefooghe et al., 1999),* better supervision *(Harries et al., 1996),* home visits *(Jin et al., 1993),*patient motivation *(White et al., 1999)* and health education *(Dick et al., 1997)* are factors that reduce the default rate among TB patients. It is less likely that all these factors exist in village settings.

The default rate was significantly high in patients who received treatment in community health facilities. This could be partly due to however, these facilities provide dispensing services of anti- TB drugs only and lack other important TB services such as patient

education and counselling (*Limpopo Profile, 2004)* which play an important role in improving the patients' adherence to anti- TB drugs (*WHO, 2004*).

The default from retreatment was significantly more frequent among those who had defaulted from initial treatment, while treatment failure was significantly most common among those with previous failure. This supports earlier findings to the effect that initial treatment failure and defaulting are the risk factors for retreatment failure and defaulting, respectively *(Zignol et al., 2007, Dooley et al., 2011, Amoran et al., 2011).* Although retreatment guidelines are often the same for patients with failure, default or relapse after initial treatment *(WHO guidelines for national programs, 2003),*these results suggest these groups may benefit from different management strategies *(Zignol et al., 2007, Espinol, 2003).* For example, failure is commonly due to drug resistance, while recurrence may be due to poor treatment adherence, high*mycobacterial* burden or exogenous re-infection *(Zignol et al.,2007).*

The treatment failure rate varied from 0.1% in Zimbabwe to 9.1% in the Russian Federation, with an average of 1.5% in high burden countries (HBCs) (WHO report, 2005). The treatment failure rate in this study was 2.2%, which is higher than the average failure rate of the HBCs. This means Limpopo Province has considerable contribution to the national rate of TB treatment failure.

Treatment failure was significantly high among cases aged group 56- 74 years, which may be attributed to advanced age, which has been reported as a risk factor for treatment failure *(Ronaidi et al. 2011).* The absorption of anti-TB drugs is reduced in elderly patients, which in turn affects bioavailability and therefore inadequate drug concentration in the blood, resulting in treatment failure *(Laurence et al. 2005).*

Treatment failure was significantly high among the cases that received regimen II, than those treated with regimen 1. This can be explained in the context of retreatment, since regimen II is designed for retreatment cases. Retreatment TB cases who are treated with standard regimen II, according to WHO guidelines (applied to SA), are more likely to experience MDR- TB (WHO & IUATLD 2004), particularly in South Africa, where South Africa Profile 2011 reported ; MDR-TB infections significantly more common among retreatment cases than new cases (6.7% and 1.8% respectively) *(http://www.doh.gov.za/docsl2011/South African Tuberculosis Profile2011who.pdf).* MDR-TB is reported as a risk factor for TB

treatment failure *(Quy et al., 2006, Lew et al., 2008)*. The effectiveness of retreatment with regimen II has not been systemically evaluated *(Lopez et al., 2011)* and outcomes among patients receiving standard WHO category II retreatment regimen are suboptimal, with high rates of treatment failure and relapse, resulting in increased risk of morbidity, drug resistance and transmission. Previous studies found that retreatment with regimen II had unacceptably low treatment response rate in certain subgroups of TB patients and was associated with poor long- term outcomes particularly in MDR- TB and HIV infected patients *(Lopez et al 2011)*.The poor performance of regimen II may also be attributed to high background rates of drug resistance and prevalent HIV infection *(Mak, 2008)*. In this study the treatment default rate increased across the years (6.3% in 2007 to 11.4% in 2009), which may suggest that measures taken by Provincial TB control programme to improve adherence to anti- TB drugs were ineffective, or that recommendations (such as WHO ones) which aim to improve TB patients' compliance were not being optimally implemented in the province.

This pattern of increasing defaulting may also be linked to increase of HIV/AIDS cases across these years as reported by SA Collaborative Activities Report *2006- 2010 (*www.etrnet.info*)*. Previous studies reported significantly higher default rates among TB/HIV co-infected patients, compared to the patients only infected by TB (*Daniel et al.,*2006 *,Muture et al., 2004)*. The reports by Daniel at al (2006) and Muture et al (2004) explain the TB/HIV co-infection relationship by pointing out that HIV co- infected TB patients often had to attend separate clinic or health facility for TB and HIV care services, thus increasing transport and other costs (e.g. missing of work day). Besides, the side effect profile of patients is magnified in patients with concurrent HIV who combine anti- retroviral therapy (ART) and anti- TB drugs., *(Fry et al., 2005)*. Despite an increasing body of evidence on the effectiveness and feasibility of collaborative TB/HIV activities and recent improvements in TB/HIV integration, implementation remains below targets *(WHO,2011)*. This trend applies to South Africa as shown in a study carried out in 3 primary health care clinics in Johannesburg *(Page-Shipp et al., 2012)*.. Another study audited TB/HIV integration at 16 clinics in Cape Town, found poor capacity and weaknesses in quality and continuity of care *(Scott et al., 2010)*. The lack of standardised recording tools and incomplete documentation impede assessment at facility level and limit the accuracy of compiled data *(Page-Shipp et al., 2012)*

Treatment outcomes in children are generally good, even in young and immune-compromised children who are at a higher risk of disease progression and disseminated disease, provided that treatment starts promptly (*WHO, Geneva, Switzerland 2006)*. In the present study the success of treatment was significantly highest among cases of age ranging between 3 and 6 years. This result is expected because this group receives their treatment through their parents and this may be considered unplanned DOTS strategy which plays an important role in improvement of compliance *(WHO report 2004)*. In addition, there is a low risk of adverse effects associated with use of the recommended standardized treatment regimens III (*WHO, 2006).*

There was an overall death rate in Limpopo Province among TB patients of 13.6%. This is much higher than the WHO target rate of 3% *(World Health Organization WHO Tuberculosis Programme, 1994; International Union Against Tuberculosis and Lung Disease, 1996).*The percentage of deaths among TB patients increased significantly across the years From16.9%% in 2006 to 23.9% in 2010 (P< 0.001). This finding is consistent with a meta analysis study that reported a recent increase in TB deaths in Africa, after almost 40 years of decline *(WHO,2002)*. However, a study from Ethiopia reported a decline in TB deaths from 13.5% in 2004 to 5.1% in 2008 (Belay *et al*., 2009). Deterioration of survival over the years may be attributed to the increased prevalence of HIV /AIDS and MDR- TB *(NCID & NHLS, 2010)* which parallels TB incidence. Both HIV infection and MDR- TB have been frequently reported as risk factors for mortality during TB treatment (*Matthew et al., 2006;Sterling et al., 2006; Borgdorff et al., 1998; Oursler et al., 2002; Walpola et al., 2003;White et al., 1996).*

High mortality rates were observed among the 0- 2, 22- 55 and 56- 74 years age groups. With regard to high mortality among 0- 2 years old, Statistics South Africa *(Census 2001*) reported that high mortality among this age group was due to co- morbidity with HIV/AIDS, malnutrition and diarrhoea. HIV infection is responsible for 40% of deaths of children under 5 years *(Statistics South Africa, Census 2001)*. However, without figures on mother- to- child transmission programmes in Limpopo Province over the same period it is difficult t infer to what extent that may be a contributing factor.

High mortality rate among 22- 55 years age group, may be attributed to high prevalence of HIV infection among this group as stated before. The association between HIV infection and TB mortality has been reported by several studies *(Lawn & Cheampong 1999, Connolly et al., 1998, Webester et al., 1999, Anunnatsiri et al., 2005, Burton et al., 2011, Alain et al., 1995, Bewire, 1999, Quy et al., 2006),* while high mortality among 56-74 may be attributed to advanced age. Advanced age has been previously reported to be a risk factor for death, partly due to increasing co- morbidities as well as the general physiological deterioration with age *(Zellweger & Coulon 1998, Falzon et al., 2005, Belay et al., 2009, Anunnatsiri et al., 2005)* because of which close monitoring of treatment in older patients is necessary. Generally, older patients experience unfavorable living conditions, malnutrition, co- morbidities and less access to health care, any of which could increase the risk of death (*Falzon et al., 2005).* It is possible that older TB cases had a high mortality rate because they were more likely to present with nonspecific symptoms, which may contribute to delays in diagnosis and treatment of TB and ultimately a higher risk of death *(Perez- Guzman et al., 1999, Doherty et al., 1995).* In addition, elderly people may present with more extensive TB disease, based on the initial chest radiograph *(Xin et al., 2009, Lawn & Cheampong 1999, Connolly et al., 1998, Webester et al., 1999, Anunnatsiri et al., 2005)*

The death rate was significantly high among, retreatment cases particularly, among those who had initial treatment failure. This finding is consistent with the finding of Vasankari et al. *(2007)* who reported that previous TB treatment was associated with the risk of high death rate (17.2%). The high death rate among TB patients that received treatment at hospitals may be attributed to the fact that many of the very sick TB patients and those with complications were referred late for care to hospitals. However, this could not be established through the ETR.net data available

There was no association between gender treatment outcome. This is consistent with a study from Uganda which found that there was no difference between male and female patients in the likelihood of experiencing a favourable outcome *(Nsubuga et al., 2002).* In contrast, Vinod and Anna (1999) found that female gender was a predictor for unsuccessful TB outcome due to limited access to health care facilities causing delays in diagnosis and treatment as well as more social stigma for women with *TB (Vinod & Anna, 1999).*Similarly

Nik Nor et al. *(2011)* reported significant association between gender and unsuccessful treatment. Where differences have been reported in outcomes between the genders, the females were more likely to have successful treatment outcomes*(Belay et al., 2009, Doodley et al., 2011, Muture et al., 2011).*

The current study found similar degree of risk of unsuccessful treatment between two genders, contrary to the report by *Nik Nor* and colleagues (2011) where unsuccessful treatment outcomes among females surpassed those in males. According to Nik Nor et al (2011) in Kota Bharu, Kelantan , Malaysia females became substantially engaged in risk behaviors such alcohol, substances and tobacco abuse and crimes leading to imprisonment, all which had negative influence on their treatment outcomes*(Nik Nor 2011).*

The cases who received TB treatment at mine health facility had highly significant successful treatment outcomes, and this may be because health facilities may provide DOTS strategy or other support measures that improve the treatment outcome. TB is recognized as a disease that is highly prevalent among miners, and in some instances TB may be considered as an occupational disease among miners (*Dambisya and Modipa, 2007*). Hence the mines take TB treatment programmes very seriously, as an epidemic of TB could lead to a lot of lost time from work. Besides that, the presence of health facilities at the workplace is motivation to the patients to regularly refill the drugs and acquire knowledge about the disease and treatment and eventually satisfactory outcome and higher productivity among the workers.

5. 2 Limitations of the study

This study has several limitations. It was a retrospective study and based only on data that were available on ETR.net. It was not possible to analyze the effects of HIV status, CD4 and CPT on TB treatment outcomes in TB patients as these are not documented in ETR.net. It was also not possible independently to verify the accuracy of the records as captured on the database, nor was it possible to collect additional data to confirm or refute the findings of the present study. ETR.net did not consistently record the result of smear test, therefore these variables were not assessed in this study. The facility levels were not captured in ETR.net – only the names of the facility was given in most instances; hence analysis of the influence of level of care on treatment outcomes was confined to a relatively small proportion of the sample. At the time the data was extracted for the study, many of the records for 2010 were

incomplete, awaiting updating after inputs from the districts, hence some of the conclusions for 2010 may have been different with a more comprehensive record for that year as well.

Notwithstanding the above limitations, the large sample size (N=1200), and the length of the period reviewed conferred rigour to the analysis and make the inferences arising valid and relevant. The findings of this study may be extrapolated to the current situation of TB control in South Africa and African population, and may draw attention to major factors influencing TB treatment outcome in the management and control of TB.

5- 3 recommendations

- There needs to be a revision of the inputs into the ETR.net database to make it an even more reliable source of data, that can fully utilized in scholarly research. Additional inputs should include information on HIV status and treatment and follow-up indicators such as smear conversion results.

- There is need to identify those at high risk of unsuccessful treatment outcomes (e.g. through screening for age, patient diagnostic category or those with previous history of treatment defaulting)so special targeted measures, such as closer monitoring could be instituted.

- The high default rate recorded in village setting should be addressed through supportive measures such as raising the awareness levels and outreach programmes from higher levels of care to the community/village facilities and strengthened counselling and supervision during both the intensive and continuous phases and home visits along the principles of DOTS strategy.

    - Further studies are needed to investigate the effects of factors such as HIV status, level of CD4 counts, anti- retroviral therapy (ART) and co- trimothaxazole preventive therapy (CPT) on TB treatment outcome in the Limpopo Province.

    - Adherence to standard TB treatment regimens as recommended by international health authorities and the SA treatment guidelines for each patient diagnostic

category should be enforced to ensure acceptable outcomes, since deviation from these standards carries a risk of unfavourable outcomes.

- Given the lower than acceptable levels of successful treatment outcomes, there is need to review the treatment and support strategies being employed by the Province to identify bottlenecks.

5.4 Conclusion

The number of recorded PTB cases in the Limpopo Province increased during the period under review, with the increase attributed mainly to new cases. The males were apparently more vulnerable to contract TB than females. The rate of successful treatment outcomes was relatively acceptable, particularly among children aged between three and six years; however, the number of deaths and default rates were unacceptably higher. PTB in Limpopo Province is mainly a disease of the economically active population that accounted for most of the patients, most of the new cases, and most of those with poor treatment outcomes with high treatment failure rates and many deaths. This study supports previous findings of poorer survival among the very young and those advanced age with a diagnosis of TB. Similarly, poor survival was associated with high defaulting rate among retreatment cases which may point to inadequacies in performance of regimen II. History of previous treatment carried the risk of failure and defaulting. The high proportion of patients that died during the period under review is a serious public health concern that needs to be addressed urgently. Furthermore, the effects HIV status, level of CD4 counts, anti- retroviral therapy (ART) and co- trimethoxazole preventive therapy (CPT) on TB treatment outcomes in the Limpopo Province need to be studied urgently in order to benefit from synergies between TB and HIV services, given that the two infections often occur together.

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Appendix 1: Data collection sheet

Serial No	Gender	age	Diagnostic category	Health facility	Year of registration	Regimen	Outcome

Appendix 2: About ETR.net

The Electronic TB Register (ETR.net) is a Microsoftnet-based computer software programme, inspired by the World Health Organization (WHO) and International Union Against TB And Lung Disease (IUATLD) recording and reporting formats. Many of the features of ETR.net are derived from the electronic TB register (TBREG) software, a TB surveillance project in southern Africa that is supported by United States Agency for International Development (USAID) and the Centers for Disease Control and Prevention (CDC). The software was developed to provide for more efficient and useful collection, compilation, and analysis of TB data on an ongoing basis.

Individual patient records are taken from standard manual facility TB registers and entered into adistrict-based data entry programme that provide interactive guidance and support. The programme generated various patient listings such as lists of defaulters and standard quarterly and annual reports on cases finding, sputum conversion and treatment graphs (time trends) of key performance indicators. A mapping feature (geographic distribution) is under development.

(Summarised from the ETR.net Manual)

Appendix 3: Ethical Clearance

UNIVERSITY OF LIMPOPO
Medunsa Campus

MEDUNSA RESEARCH & ETHICS COMMITTEE

CLEARANCE CERTIFICATE

MEETING: 09/2011

PROJECT NUMBER: MREC/HS/193/2011: PG

PROJECT:

Title: Factors affecting treatment outcomes in Tuberculosis patients in the Limpopo Province.

Researcher: Mr M Gafar
Supervisor: YM Dambisya
Co-supervisor: NZ Nyazema
Department: Pharmacy
School: Health Sciences
Degree: Masters in Pharmacy

DECISION OF THE COMMITTEE:

MREC approved the project.

DATE: 15 November 2011

RESEARCH & POSTGRADUATE SUPPORT 2011 -11- 15 MEDUNSA CAMPUS

PROF GA OGUNBANJO
CHAIRPERSON MREC

Note:
i) Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee.
ii) The budget for the research will be considered separately from the protocol.
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.

Finding Solutions for Africa

Appendix 4: Permission from the Limpopo Province

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF HEALTH

Enquiries: Selamolela Donald

Ref:4/2/2

Gafar MM

University of Limpopo

Sovenga

0727

Greetings,

Re: Permission to conduct the study titled: Factors affecting treatment outcomes in Tuberculosis patients in the Limpopo Province.

1. The above matter refers.
2. Permission to conduct the above mentioned study is hereby granted.
3. Kindly be informed that:-
    - Further arrangement should be made with the targeted institutions.
    - In the course of your study there should be no action that disrupts the services.
    - After completion of the study, a copy should be submitted to the Department to serve as a resource.
    - The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.

Your cooperation will be highly appreciated.

Head of Department

24/02/12

Date

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