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FACTORS CONTRIBUTING TO TUBERCULOSIS MORTALITY AMONG NEW TUBERCULOSIS PATIENTS IN ZULULAND HEALTH DISTRICT

BY

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DECLARATION

I, **Khulekani Zakheleni Dlamini**, hereby declare at the best of my knowledge, that this research project submitted at the University of Fort Hare for the Degree of Masters in Public, has never been previously submitted by me for a degree at this or any other university; and that this is my original work in design and execution; and that all material contained therein has been acknowledged through proper referencing.

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I, **Khulekani Zakheleni Dlamini**, student number: 201415819 hereby declare that I am fully aware of the University of Fort Hare's policy on plagiarism and I have taken every precaution to comply with the regulations.

Signature…… Date…….

DEDICATION

I wish to dedicate this work to my family who have been a pillar of strength to me during difficult times, which assisted me to keep focused to the task of developing this work without failure.

My children Sphamandla Dlamini and Bongumusa Dlamini for their unfailing love, which kept me, going forward despite all odds in pursuit of my studies. My young daughter, Aphiwe Dlamini, for she had been my friend and my source of inspiration.

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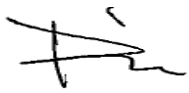
CERTIFICATION

This mini-dissertation entitled “Factors Contributing to Tuberculosis Mortality among New Tuberculosis Patients in Zululand Health District, KwaZulu-Natal, South Africa” meets the regulation governing the award of the degree of Masters of Public Health of the University of Fort Hare, and its approval for the contribution to scientific knowledge literary presentation.



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ABSTRACT

During the period ranging from 2011 to 2013, Zululand Health District reported tuberculosis (TB) related mortality cases above the WHO's norm of 10%. This raised concerns because TB is curable even if the person is HIV positive. The overall performance of TB programme in South Africa concealed the actual problem of TB related mortality in the country and most particularly in Zululand Health District. The aim of the study was to examine factors contributing to TB mortality, and the extent of TB related mortality in Zululand Health District.

A retrospective, descriptive study was conducted to review records of data on the electronic TB register at the district level in order to ascertain the relationship between TB mortality and the contributory factors associated with TB mortality. The TB data was analysed using descriptive and inferential statistics to test the null hypothesis at the significance level of $p< 0.05$. The study was limited to only new patients enrolled between the periods from the 1st January 2012 to the 31 December 2013.

The study found that TB/HIV comorbidity was a main factor contributing to mortality among new TB patients. Eighty percent (80%) of all patients who died were HIV positive. Poor CD4 monitoring, delays or failure to initiate TB/HIV comorbid patients was one of the factors associated with mortality ($p < 0.0001$, OR 0.51) among this cohort of patients. Poor DOT support system significantly ($p< 0.0008$, OR 0.81) contributed to mortality in this district. The study also found significant association between mortality and failure to initiate comorbid patient on co-trimoxazole prophylaxis (Chi-square =9.1; df=1; p=0.0025).

Tuberculosis and HIV comorbidity, and delays or failure to providing antiretroviral therapy to HIV positive patients were the main factors responsible for TB mortality in Zululand Health District. The whole phenomenon was attributable to health worker related factors. Good TB/HIV clinical management guidelines and protocols developed by the Department of Health, and distributed to all health facilities did not alleviate the problem. Support and supervision could translate policies and protocols to action.

LIST OF FIGURES AND TABLES

LIST OF ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
AFB	Acid-Fast Bacilli
ART	Antiretroviral Therapy
CHC	Community Health Centre
CD4	Cluster of Differentiation 4
DOT	Directly Observed Treatment
DOTS	Direct Observed Treatment, Short-Course
ETR	Electronic TB Register
GXP	GeneXpert
HIV	Human Immune Deficiency Virus
LPA	Line Probe Assay
MDG	Millennium Development Goal
NGO	Non-Governmental Organization
UNAID	The Joint United Nations Programme on HIV and AIDS
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensive Drug-Resistance Tuberculosis

CONTENTS

CHAPTER 1: BACKGROUND

1.1. INTRODUCTION

The reports from Statistics South Africa in 2013 showed that tuberculosis (TB) was the leading cause of mortality in South Africa. According to the report, TB accounted for 11% of all deaths in South Africa on average, between 2008 and 2011 (Statistics South Africa, 2013). South African TB treatment regimen is one of the aggressive regimens compared to other countries, since it consists of two most effective drugs namely Isoniazid and Rifampicin combined Ethambutol and Pyrazinamide in a four-drug regimen.

Isoniazid and Rifampicin are highly effective drugs against micro-bacterium tuberculosis (Reider, 2002). Despite the use of the most efficacious drugs in TB management, improvement in documented TB outcomes does not translate to improved TB mortality in the whole country and, Zululand Health District in particular. Tuberculosis is curable even if the patient is HIV infected. ideally no change for treatment failure as a cause of TB related mortality mainly in HIV comorbid patients.

The study pursues the exploration of factors responsible for the occurrence of TB mortality in a well performing TB program, with the aim of solving the myth associated with TB related mortality, and propose remedial action in mitigation phenomenon. South Africa as a third world country is vulnerable to factors fuelling TB epidemic which are: overcrowding, poverty and unemployment, stigma associated with TB and HIV and AIDS and migrant labour system.

The reported deaths are not justifiable where there are signs of improvement in TB outcomes, especially the case holding rate. The TB cure rate of Zululand district was 76% in 2011 and improved to 84% in 2013, which is just one digit below the national norm of 85%. Despite the impressive TB control program performance in Zululand Health District, TB related mortality of 19.9% was reported in 2011, above norm of less than 10% (WHO, 2013).

The TB control program in South Africa is based on the World Health Organization recommended direct observation of treatment short course (DOTS) strategy introduced by Dr Karel Styblo in 1970 and adopted by the WHO is golden standard against which TB management program in any county can be measured (NDOH, 2009). South Africa observes all five pillars of the DOTS strategy in line with the World Health Organisation set norms. The district is implementing the national TB /HIV integrated management protocols, providing for the testing of HIV to all TB patients and starting of antiretroviral drug 2 to 8 weeks of TB treatment (National Department of Health, 2014).

The study conducted in Johannesburg Academic Hospital among newly initiated ART patients based on post-mortem revealed that TB was a leading cause of mortality among TB/HIV comorbid patients (Wong, 2012). Similar sentiments were shared by Statistics South Africa and United Nations Global TB report of 2013. This bears hard evidence that TB/HIV increase mortality among TB patients. While HIV increases the risk of death among TB patients, South African health system is well equipped with well-trained clinicians, good policies and protocols to effectively manage TB HIV comorbidity.

1.2 PROBLEM STATEMENT

During the period ranging from 2011 to 2013, Zululand Health District reported TB related mortality cases above the norm of 10%. This raises concerns since TB is curable even if the person is HIV positive. TB is a global crisis especially in South Sahara Africa (WHO, 2013). Improvement of general TB programme indicators in South Africa mask the actual problem of TB related mortality in the country and most particularly in Zululand Health District. Examining the contributory factors to TB mortality in Zululand Health District would inform future intervention to improve TB related mortality in this district.

The Treatment Action Campaign (TAC) presented the position paper at the TB conference held in Durban ICC on the 4th of July 2008 in which they implicated Government and Health department as responsible for the TB related mortality by perpetuating poor TB programme management.

The following paragraph is the direct quotation from their paper. "How does a preventable, curable disease become the leading cause of all-natural deaths in SA, and the leading cause of all AIDS-related mortalities on our continent? Well, first we take drug-sensitive TB, a perfectly curable form of tuberculosis, and mismanage it for decades in health structures with poor infection control, weak diagnostic capacity, insufficient education on TB, inadequate resources and minimal political commitment. We observe substandard cure rates and increasing mortality figures. Over time, our poorly functioning TB programs are manufacturing drug-resistant TB strains, the result of inadequate or incomplete TB treatment, but we don't worry about this too much until multidrug-resistant (MDR) TB" (TAC, 2008). The

amount of resources allocated to the South African TB control program and South African Government's commitment to fight the scourge of HIV and AIDS on face value, nullifies the statement by TAC, notwithstanding the fact that TB related mortality remains high.

1.3 PURPOSE OF THE STUDY

The main purpose of the study was to explore factors contributing to TB mortality in Zululand Health District in order to inform public health policy concerning the strategies and priority areas of intervention to reduce TB related mortality and improve clinical management of TB in Zululand Health District.

1.4 OBJECTIVES OF THE STUDY

The specific objectives of the study were:

- To explore health worker related factors (non-adherence to protocols) as a contributory factor to TB mortality in Zululand Health District
- To discover health system factors (poor implementation DOTS strategy) as a contributory factor to TB mortality in Zululand Health District
- To ascertain patient related factors (treatment default, poor health seeking behaviour) as a contributory factor to TB mortality in Zululand Health District

1.5 RESEARCH QUESTIONS

The following research questions were framed for the study:

- What is the health worker related factors contributing to TB mortality in Zululand Health District?
- What are the health systems factors contributing to TB mortality in Zululand Health District?
- What are patients related factors contributing to TB mortality in Zululand Health District?
- What is the relationship between HIV infection and TB related mortality among TB patients in Zululand Health District?

1.6 NULL HYPOTHESIS

The following null hypotheses were framed to guide the study:

- Health worker related factors would not contribute to TB mortality in Zululand Health District
- Health systems factors would not contribute to TB mortality in Zululand Health District
- Patient related factors would not contribute to TB mortality in Zululand Health District
- There will be no significant relationship between HIV infection and mortality among TB patients in Zululand Health District.

1.7 SIGNFICANCE OF THE STUDY

The study analyses existing data using 100% sample frame of applicable data extracted on the electronic tuberculosis database at the District level. The study could produce credible report on the state of TB program implementation in Zululand Health district. It is a vital operational research using management information to explore challenges in TB program implementation. This will give the opportunity for the proposal of the remedial action which will improve the implementation of TB program in Zululand Health District. The inferences drawn from the study would be used to influence both patient and health care worker behaviour, and review TB management policies and protocols.

1.8 SCOPE OR DELIMITATION OF THE STUDY

This study was delimitated to Zululand Health District. The specific contributory factors of interest was, health worker, health system, and patient related factors associated with TB mortality in Zululand Health District.

1.9 THEORETICAL FRAMEWORK

The study is premise on the theories of behaviour change by Glanz & Lewis. (1990) and Social Behaviour Theory by Bandura (1986). Bandura, (1986) and Perry et al., (1990) proposed a triad analogy of behavioural interaction between personal factors and

environment which they called reciprocal determinism. The environment is defined as milieu providing context at which behaviour is performed. Personal intrinsic factors like traits, personal drivers and other motivational forces determine individual behaviour. Self-efficacy, perceptions of outcomes expected, and ability to enhance self-control are described as key determinants of individual behaviours. Reinforcements determine kinds of behaviours people engage in.

The missed match between clinical management protocols and implementation is the significant lethal indicator of none compliant by both clinicians and patients themselves. Adherence counselling of patients by health care workers at each visit is a protagonist factor for patient survival. It would increase patient self-efficacy and enable them to channel their behaviour to what will promote their health. The benefit of involving patients on chronic medication to support groups would enhance their emotional coping with stimuli and observational learning from peers would serve as the motivator for compliance treatment regimen.

The Health Care Worker's behaviour in adhering to treatment protocols and patient adherence tendencies to treatment regimen mediates between infirmity and mortality. The theory defines threat, as is the harmful event which people may or may not be aware of, which determine people behaviour and actions (Perry et al., 1990; Witte, 1997). Health care workers fear for the risk of litigation and consequences of none adherence to guidelines and protocols, and patient's perception of risks associated with none adherence and treatment default could be describing as the threat.

Delays in anti-retroviral treatment initiations to eligible patients, multiple drug resistant Tuberculosis and extreme drug resistant tuberculosis are programmatic errors man made by both patients and health care workers is a threat to patient's life. The theory describes fear as an emotional arousal caused by perception of significance and personally relevance of a threat, while efficacy is a perception that recommended response would prevent a threat from occurring. One needs to be empowered with skills to develop self-efficacy, which would develop confidence in their ability to perform recommended responses to avert the threat.

Bandura (1986) and Perry et al. (1990) proposed a triad analogy of behavioural interaction of personal factors with environment which they called reciprocal determinism. The analogy describes the environment as providing context for performing behaviour while personal intrinsic factors like traits, personal drivers and other motivational forces determine behaviour. According to the theory, self-efficacy is perceptions of outcomes expected, and ability to enhance self-control.

Reinforcements determine kinds of behaviours people engage in. Applied the theory, could explains the importance consistent adherence counselling of patients by health care workers at each visit would increase their self-efficacy and enable them to channel their behaviour to what will promote their health. The benefit of involving patients on chronic medication to support groups would enhance their emotional coping with stimuli and observational learning from peers would serve as the motivator for compliance treatment regimen.

1.10 DEFINITIONS OF TERMS

Tuberculosis is the disease of the lung capable of migrating to all parts of the body, caused by bacteria called *mycobacterium tuberculosis.*

New TB patient is a patient who has not taken TB treatment before, or has taken treatment for less than a month.

TB mortality refers to death of TB patients from any cause while on treatment

TB Cured refers to a patient who was sputum- positive at the beginning of treatment, converted to negative after two months and was discharge with negative sputum at the end of treatment period.

Treatment Default refers to interruption of the course of treatment for more than month in successive days.

Prophylaxis is the use of one drug or more as preventive therapy for people who are not yet sick of a particular disease.

Vaccination is an inoculation use to stimulate antibodies to fight invading infections in body of a living organism.

CD4 is the marker of the body's ability to defend itself from HIV disease and opportunistic infection.

Direct Observed Treatment is a daily supervision or observation of treatment consumption between the TB patient and a DOT supporter.

Direct Observation of Treatment Short Course is the strategy to ensure the sustainability of the TB control programme.

Multiple Drug Resistant -**TB** is a TB strains which resistant to the first line anti-mycobacterial agents including isoniazid and or rifampicin.

Post-mortem is an autopsy done on human body to establish the cause of death.

Gene-Expert is the machine which analyses specimen collected on human body to detect mycobacteria resistant to a TB drug rifampicin.

1.11 CHAPTER OUTLINE

Chapter 1: covers the background to the study, problem statement, aim, objectives, research questions, null hypothesis, and significance of the study, theoretical framework and the definitions of key operational terms are described and presented in Chapter 1. The chapter also describes the division of the study.

Chapter 2: covers the Literature Review, the global view of TB epidemic, epidemiology of TB in South Africa, context of TB management, global principles of TB treatment, TB/HIV co-morbidity, treatment interruption, drug resistant TB, tuberculosis infection control were reviewed.

Chapter 3 provides the detail plan of the research through the research design and methodology. This covers the research approach, the details of the research setting, population, inclusion and exclusion criteria, research tools and instruments, data collecting procedures, reliability and validity and ethical considerations.

Chapter 4: presents the results of the study and discusses them.

Chapter 5, presents a summary of the pertinent findings, together with the limitations of the study are, presented. This is followed by the conclusions and recommendations.

CHAPTER 2: LITERATURE REVIEW

2.1. INTRODUCTION

Tuberculosis is the disease of the lung caused by a bacterium called mycobacterium tuberculosis. TB bacteria are transmitted through airborne route, when a person with TB coughs or sneezes into the air. People with HIV have 50% chances of developing TB disease (National Depatment of Health, 2009).Tuberculosis infection differs from TB disease in that not all people infected with TB is likely to develop disease in their life lime.

In South Africa about 88% of the adult population is infected with TB be but not sick of a TB disease (NDOH, 2012). Under normal circumstances, 10% of people infected with TB would develop TB in their lifetime. Factors like age, immunological status, malnutrition and stress determine the susceptibility of TB infected people to TB disease (NDOH, 2009). TB is curable even if a person is HIV positive.

2.2. THE GLOBAL VIEW OF TB EPIDEMIC

Globally, about 8.6 million people were suffering from TB disease in 2012, and 1.1 million were people living with HIV (Statistic South Africa, 2013). In 2012, TB accounted for 1.3 million deaths, where 50% of patients who died were HIV positive women. TB is the top killer of women of reproductive age (World Health Organization, 2014). Global statistics showed 45% decrease in TB mortality since 1990. The world achieved the MDG target of 50% reduction of TB mortality by 2015 as projected by the Word Health Organization. The report

painted a good picture of improving trends in TB management in the world, whereas the reality was that significant people died of the curable TB disease. The number of people diagnosed with multiple drug resistant Tuberculosis (MDR) in the world doubled between 2011 and 2012. That further increased the risk for TB related mortality. The introduction of Gene X pert (MTB/Rif) in the baseline screening algorithms for TB in 2013, improved early detection of TB diseases among new TB patients. According to the World Health Organisation report, management of TB programme remained poor in the third world countries (WHO, 2014).

In 2013, most countries adopted a molecular TB diagnostic test with on spot detection of rifampicin resistance. This is one of the attempts by governments to reduce mortality related to TB and MDR in particular. The world is moving toward development of efficacious short cause new anti TB drugs to reduce the pill burden in an effort to improve compliance with treatment. The setback in TB management was a slow decline of 2% in TB incidence in all six WHO regions (WHO, 2014). Early detection of TB disease should help reduce infectious cases in the community, thus reduce TB incidence.

According to the report by WHO, the prevalence of TB in the community decreased by 37% globally since 1990 compared to the aspired MDG target of 50% in 2015. Countries of the world needed to put more effort to reduce the prevalence of TB. The World Health organization proposed five priorities to intensify the fight against TB which are to reach the missed cases, (ii) address MDR- TB as a public health crisis, (iii) to accelerant the response to TB/HIV, (iv)to increase financing to close resource gap and (v) to assure rapid innovations

prevention of all forms of TB (WHO, 2014). The countries commitment towards control of the TB scourge would be majored by adherence to the above proposed interventions.

2.3. EPIDEMIOLOGY OF TB IN SOUTH AFRICA

South Africa has a third highest incidence of TB after India and China (NDOH, 2009). Considering that South Africa has the small population compared to these countries, this country has the highest incidence of TB in the world. According to the Department of Health of South Africa, 73% of TB patients were HIV positive in 2012 (NDOH, 2012). WHO reported in 2013 that 80% of the population of South Africa were infected with TB bacilli and 88% of which were between ages 30-39 year living in township and informal settlements. Tuberculosis accounted for 11.6% of death in the country in 2012. The TB incidence in South Africa was 802/100 000 in 2012 (Health, 2009). World Health Organization reported the incidence rate for TB/HIV infection of 650/100 000 in South Africa only 44% were put on ART therapy (WHO, 2013).

In 2009, the President of South Africa announced the changes in ART guidelines allowing all TB patients co-infected with HIV to be initiated on anti-retroviral therapy. According to the WHO global TB report of 2013, 65% of eligible HIV positive patients were put on co-trimoxazole preventive therapy (CPT) in South Africa in 2011. Failure to achieve 100% CPT coverage among these cohort of patients is the glaring example of programmatic failures.

The Department of Health annual Report of 2012 shows that the health system failed to put all HIV positive patients to isoniazid prophylaxis according to TB/HIV management guidelines (NDOH, 2012). KwaZulu-Natal Province reported TB mortality of 18, 2% and the hardest hit district was Zululand Health District with 19, 9%. Tuberculosis was the leading cause of death in 10 of 52 districts in South Africa (WHO, 2013).

The government of South Africa spends reasonable portion of its gross domestic product on infrastructure and spatial development to reverse the legacy of apartheid and under development with the hope of improving housing, eliminate slums and reduce overcrowding. This expenditure would be a waste, if TB related mortality continues in such magnitude. The incidence of TB in Zululand Health District and the country at large is suggestive of the need to step up community mobilization strategies to promote adequate household ventilation, avoidance of overcrowding and HIV prevention, to make a desired impact in the fight against TB and HIV.

2.4 THE SOUTH AFRICAN TB PROGRAMME

Factors fuelling TB epidemic in third world countries are overcrowding, poverty and unemployment, treatment default and poor patient tracking mechanisms, stigma associated with TB and HIV and AIDS, migrant labour, and poor program management (NDOH, 2009). The TB cure rate of Zululand district was 76% in 2011 and improved to 84% in 2013.This was one digit below the national norm of 85% and was good improvement of overall TB outcomes. Zululand Health on the contrary continued to TB report death of 19, 9% in 2011 (WHO, 2013).

South Africa is one of the countries with good TB control programme in the world despite high burden of TB. The TB control programme in the whole South Africa is based on the World Health Organization recommended DOTS strategy introduced by Dr Karel Styblo in 1970 (Reider, 2002). South Africa observes all five pillars of the DOTS strategy in line with WHO recommendations. Zululand health district subscribe to the national TB /HIV integrated management protocols, providing for the testing of HIV to all TB patients and starting of antiretroviral drugs, 2 to 8 weeks of TB treatment (NDOH, 2014).

The 2009, National TB management protocols provided for the screening and TB testing of all positively screened TB suspects for signs of active TB. TB programme in South Africa created opportunities for early detection and management of TB cases according to National TB management protocols. Despite all these impressive policies, TB related mortality remained high in Zululand Health District. The study conducted in Johannesburg Academic Hospital among newly initiated ART patients based on post-mortem, revealed that TB was a leading cause of death for HIV patients (Wong et al., 2012). This study supported Statistic South Africa and United Nations Global TB report 2013, in identifying TB as a leading cause of mortality in South Africa.

National Department of Health propose five strategies to deal with TB in South Africa (NDOH, 2014). These are the following:

- Reduce transmission of TB infection in the country.
- Diagnose drug sensitive TB and drug resistant TB early.
- Initiate treatment to all people diagnosed with TB early.

- Retain patients on treatment and care until completion of treatment.
- Initiating all eligible HIV positive people on ART and Isoniazid prophylactic treatment, to protect them against TB.

The National Department of Health developed and distributed clinical protocols on management of TB to all health facilities for implementation. In 2013, The National Department of Health introduced the Gene X pert as the first line screening test for all TB suspects followed by compulsory smear microscopy in line with program management strategies (NDOH, 2013). Stringent TB program monitoring system based on TB registers, transcribed into electronic TB register, monitors TB program outcomes.

There is a clear and unambiguous political will to tackle TB in South Africa. National Department of Health introduced new TB guidelines to formalise the realignment HIV guideline with TB guidelines to promote integration. The new guideline incorporates the following strategies (National Department of Health, 2014):

- Targeted TB screening intervention in all point of care to increase case detection
- The use of gene X pert in the 1st line TB testing algorithm
- The revised treatment regimen for retreatment patients
- The protocols for management of adverse drug event
- Initiation of ART to all HIV positive TB patients where the is no contra indication

South Africa adopted a decentralized TB management models to mitigate the effect of overcrowding in health facilities. Rigorous training of nurses on TB management protocols

enabled them to manage smear positive TB patients at clinic level. Hospitals diagnosed and initiates treatment to smear negative and extra pulmonary tuberculosis cases. Doctors at hospital refer stable patients for further management at clinics. Specialized MDR-TB hospital manages and stabilise MDR-TB patient, then transfer these to the satellite MDR sites for further management. Ambulant MDR patients on injectable drugs are linked to community care by tracer and injection teams (NDOH, 2013).

The country's commitment translated into good TB and HIV clinical management guidelines, which led to a decline in TB incidence and mortality rates in the country. The ART program in South Africa is biggest program in the world catering for more than two and half million people compared to any country in the world. This has proven to be not enough. The reality still haunted the health system, that people are still dying of TB and HIV in spite of the tremendous amount resources allocated to improve the health status of the population. It is of vital importance to understanding factors responsible for TB mortality in the country.

2.5. PRINCIPLES OF TB TREATMENT

There has been sluggish progress in research and innovation to discover new drugs in the world since 1940 when first ant-tuberculosis drugs were discovered (Schaaf, et al., 2011). This is against the emergence of resistant patterns against many TB drugs and the challenge of adverse effects of certain drugs like ototoxicity and liver problems. The principles underpinning the fundamentals of TB treatment remained the same in the world and South Africa is no exception.

The golden standard of TB management is to use drug combinations in treatment regimens. There is empirical data to support that this is effective in achieving tissue sterilization, prevent relapse and drug resistance. The paramount properties of TB drug's efficacy are that of bactericidal and bacteriostatic effect to the anti-bodies. Rifampicin and Isoniazid are champion drugs, which anchor the TB regimen, and the other two ethambutol and pyrazinamide are supportive drugs. The combine effect of the champion and support drugs achieves tissue sterilization and prevents resistance (Falzon, et al., 2011).

Figure 2.5 (A) below is an illustration table showing the classification of all anti TB drugs according to (Caminero, 2012), borrowed from URC TB presentations in South Africa 2013.

Figure 2.5A below, is a classical illustration of the properties of anti-TB drugs according to their pharmacological activates and related toxicity.

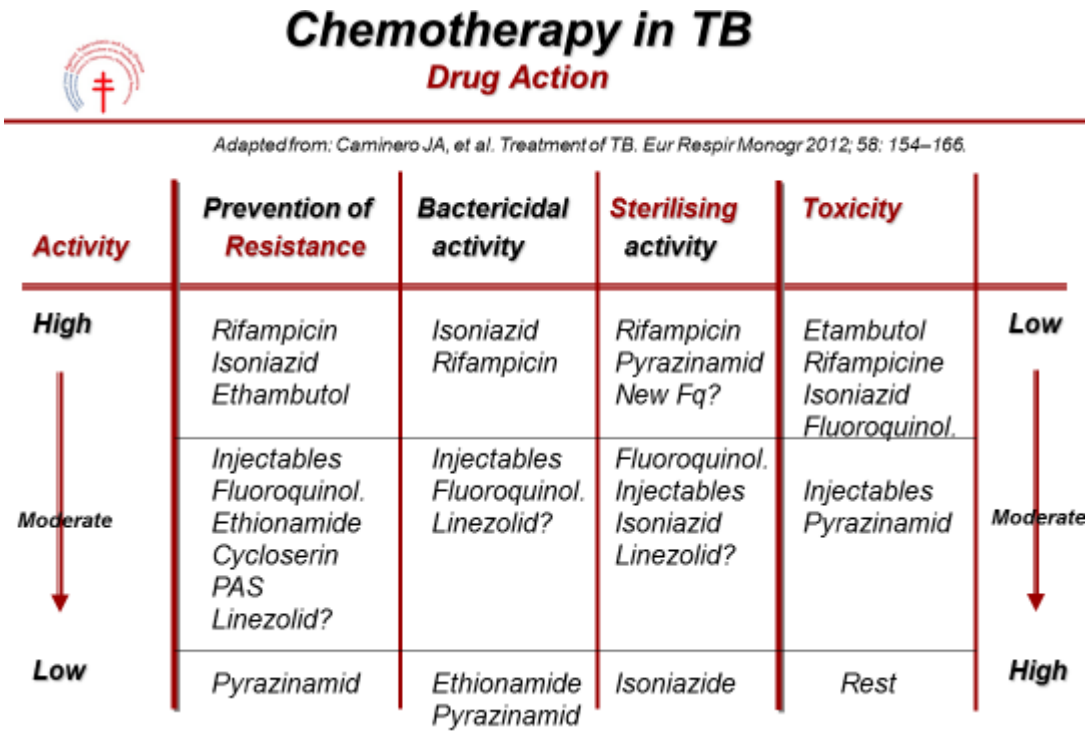

Figure 2.5(A): Chemotherapy in TB

Second line drugs are only used in the regiment if core drugs are contra indicated due to resistance or toxicity. Equally, efficacious drugs at second or third line range of drugs may be used to construct TB regimen as both add on or substitutes drugs. There are five 5 groups of anti-TB drugs used in different regimens to achieve cure, avoid relapse and prevent MDR in any TB disease form (Caminero, 2013).

Figure 2.5(B) illustrates the classification of all ant TB drugs, borrowed from the adaptation from (Caminero, 2006) by URC in 2013

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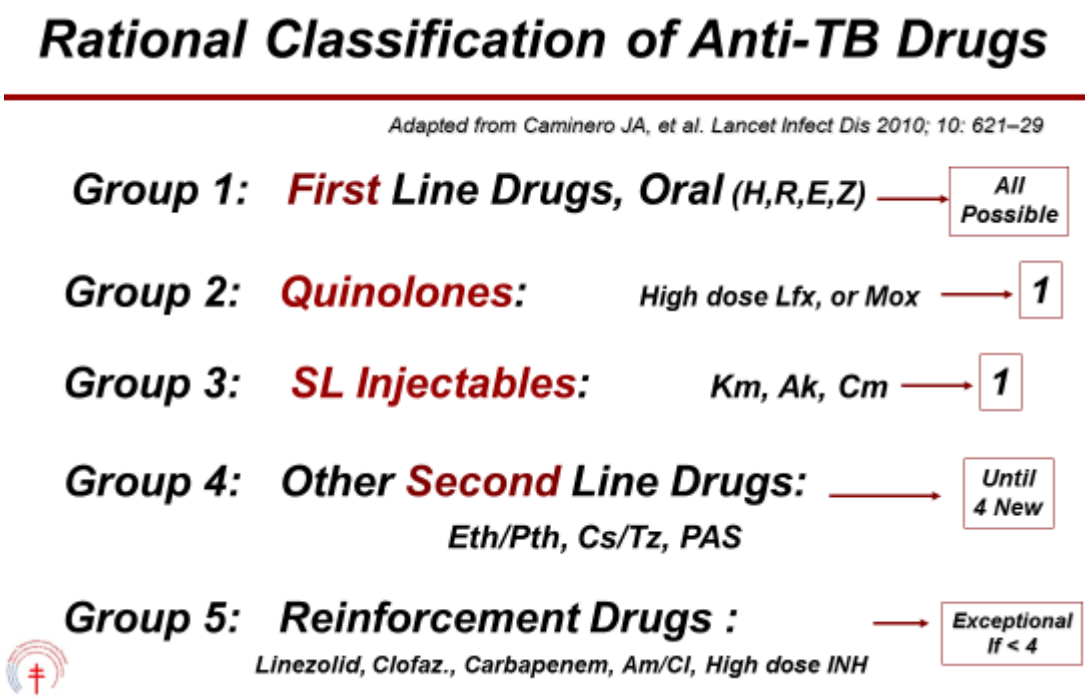

Figure 2.5(B): Rational classifications of anti-TB drugs

Group 1 are first line drugs, group 2 -5 are second line drugs while group 5 are TB drugs whose efficacy is not clinically proven, used mainly to construct regimen for extreme drug resistant Tuberculosis (Caminero & Scardingli, 2015). Second line drugs are used in secondary regimen to achieve favourable outcomes to multi-drug resistant tuberculosis. National TB guideline incorporate these international renown treatment protocol that ideally leaves no chance for treatment failure, yet people continue to die of tuberculosis.

2.6 TB/HIV CO-MORBIDITY

WHO report, stated that HIV/AIDS pandemic is fuelling TB in South Africa (WHO, 2013). According this report about 73% of TB patient in South Africa has HIV. It is now common knowledge that in the absence of HIV about 10% of people infected with TB will develop TB disease. A six month of isoniazid prophylaxis treatment has a potential reverse TB infection but not effective to treat TB disease. HIV positive adults and children benefits from Isoniazid prophylaxis since their immune system are weak to protect them from developing TB disease.

The Joint United Nations Programme on HIV and AIDS (UNAIDS), The United States Census Bureau, and United States centre for disease control and prevention, reported in 2003 that HIV pandemic presents a massive challenge to global TB control. The study found that HIV cause TB in adults aged 15 -49 years. Studies have shown that TB is the leading cause of death among HIV positive people (Corbett, 2003). TB is curable with the same anti TB drug on both the HIV infected people and people who are HIV negative. There is no obvious reason why so many HIV positive patients die of TB. Ismail & Bulgiba, (2013) conducted a study on predictors of death during TB treatment in TB/HIV co-infected patients in Malaysia, which revealed that HIV positive patients have a high fatality rate during TB treatment. This study recommended initiation of ART therapy to these patients to improve survival by restoring immune function and prevent opportunistic infections.

South Africa has since adopted a protocol, which provides for initiation of anti- retroviral therapy (ART) to all patients who has a history of TB or is sick of TB. The study conducted in

Brazil with the objective to determine the different characteristics of HIV positive and negative patients treated for tuberculosis at central hospital in Brazil, found that TB disease manifest differently in HIV positive patients compared to HIV negative patients (Henn, et al., 1999). According to this study HIV positive patients has poorer outcomes, which are death and treatment default compared to negative patients.

This critical finding was in addition to the distinguishable clinical features between the mention groups of patients, which is diffuse cavitation compatible with generalize TB and extra pulmonary TB among HIV positive compared to localized cavitation and mainly pulmonary tuberculosis among the HIV negative patients. TB disease accelerates the deterioration of CD4 lymphocytes affecting the competency of the body immune system. The immune system became less able to prevent the growth and spread of mycobacteria tuberculosis. TB in HIV positive people present as smear negative, extra pulmonary and disseminated tuberculosis. This form of TB is more difficult to diagnose with conventional smear microscopy. There are most diagnosed with chest X ray, biopsy and in some instances ultra-sonic scans. Most of these patients remain with undiagnosed TB and die of disseminated generalized TB (NDOH, 2014).

According to Blanc and Sok (2011), Tuberculosis causes death among HIV patients. The most important finding of this study is that initiating ART 2 weeks after the start of ART improves chances of survival among HIV infected adult with the CD4 count of 200 cubic millimetres or less. The study conducted in Khuzestan on cause and risk factors associated with tuberculosis deaths, revealed that people were dying of TB because of shortcomings in TB control programme (Alavi & Salami, 2009). The study recommended revision of TB surveillance strategies, to promote active TB surveillance, active surveillance of HIV in

prisons and maintenance of a stable systematic approach to screening and treatment of TB-HIV comorbid patients. TB mortality remained 11,2 %. The reported change was the reduction of TB incidence by 21% in 2018 and the improvement in the countries ranking among the 20 countries with high TB burden (WHO, 2018). HIV and alcohol abuse were major risk factors for TB in south Africa according to the global TB report 2018. Notwithstanding a significant increase in ART initiations reported in 2018, non- adherence to protocols. TB/HIV comorbidity are significant factors influencing TB mortality in South Africa.

South Africa introduced TB/HIV management guidelines promoting an integrated approach to TB/HIV management with ART and TB drugs, to decrease the burden of TB among HIV positive people with isoniazid prophylaxis. Patients with CD4 count less than 100 are most likely to have TB while their TB has increased likelihood of being misdiagnosed compared to those with CD4 above 200 cubic millimetres, as they are most likely to have few bacillary TB and generalized TB (Kufa et al., 2012). In view of the difficulty experience by clinicians in diagnosing TB among HIV patients at some incidences empirical initiation of TB treatment for HIV positive patients is recommended (NDOH, 2009, Lawn et al., 2011).

A challenge in TB management in South Africa points out gaps in the implementation of TB and HIV guidelines and poor health seeking tendencies by some patients. Isoniazid prophylaxis has been shown to decrease the risk of TB disease among people infected with HIV, while it is critical to exclude active TB before starting INH prophylaxis because of a risk of development of multiple drug resistance TB if only one drug is used to treat active TB. It is rewarding to know that recent TB/ HIV management protocols recommends universal test

and treat. The 90,90,90 program monitoring framework reduces chances of treatment default and TB mortality.

2.7. TREATMENT INTERRUPTION

South Africa has a decentralized TB management program. All health facilities have facility-based TB programme mainly for smear positive TB cases. Tracer and Injection teams care for patients on injectable drugs. A mobile base service visits their homes on daily bases, to inject patient on initial phase of treatment with injectable anti TB drugs. In some instances, population distribution and topographic factors negatively influence accessibility of these patients by injection teams on daily basis, where daily dosing of anti-TB treatment is the golden standard in TB management (NDOH, 2009). These are some of the challenges with this model.

The study conducted in Estonia Russia on predictors of mortality associated with treatment default revealed that alcohol consumption and unemployment were independent predictors of mortality among TB patients (Kliiman & Altraja, 2010). The study found that the burden of daily injection associated with MDR treatment was a factor contributing to treatment default ((Kliiman & Altraja, 2010). Tocque et al. (2005) established the relationship between history of TB disease and increased mortality from diseases like cancers of the lung and bronchi-pneumonia. It is clear that retreatment patients do not only have poor outcomes but also are susceptible to other deadly disease like cancer. Proper dosing of patients and adherence counselling at each visit can reduce unnecessary death resulting from treatment failure, MDR and XDR.

Clinicians have a role to provide favourable conditions for patients to adhere to treatment through routine counselling and linking of patients to DOT supporters. This proposed intervention would deal with the aspect of treatment interruptions, which leaves the bigger chunk of intervention dealing with proper dosing according to weight bands, which has a potential of reducing relapse and resultant drug resistance. Patients themselves have a role of accepting the treatment plan, avoiding alcohol and substance abuse and cooperating fully with their treatment plan.

Zhang and Yew (2015) shared the sentiments of the Treatment action campaign when arguing that drug resistance is wholly man-made phenomenon resulting from suboptimal physician prescription and poor patient adherence. Human error acts as impediment to the prevention of genotypic and phenotypic resistance (Zhang & Yew, 2015).

2.8. DRUG RESISTANT –TB

Multiple-drug resistant tuberculosis is the type of TB disease, which is resistant to two most efficacious first line drugs, which are isoniazid and Rifampicin. Drug resistant tuberculosis is synthetic problem caused by both clinician and patients. The factors responsible for the emergence of MDR TB are (i) intermittent supply of anti TB drug, (ii) poor patient management habits, (iii) errors in prescription and patient adherence. In 2010, KwaZulu-Natal alone had 2032 cases of drug resist TB (NDOH, 2013).

According to Scardingil and Camonero, (2013), multidrug-resistant tuberculosis (MDR-TB), defined as tuberculosis (TB) that is resistant to at least rifampicin and isoniazid, and extensively drug-resistant TB (XDR-TB). MDR-TB is also resistant to fluoroquinolone and any second-line injectable anti-TB drug, have become tremendous challenges for clinical and programmatic TB management as well as an enormous threat to global TB control.

The inadequate management of patients with susceptible TB, poor TB infection control measures, and the persistent high prevalence of HIV in some settings have allowed the number of M-XDR/TB cases to increase year after year.

Figure 2.8 below illustrates genetic alterations in isoniazid resistance, which is the vital resistance in MDR- TB. The figure is borrowed from URC presentation at Richards bay south Africa in 2013. (URC, 2013).

Cross Resistance with Ethambutol

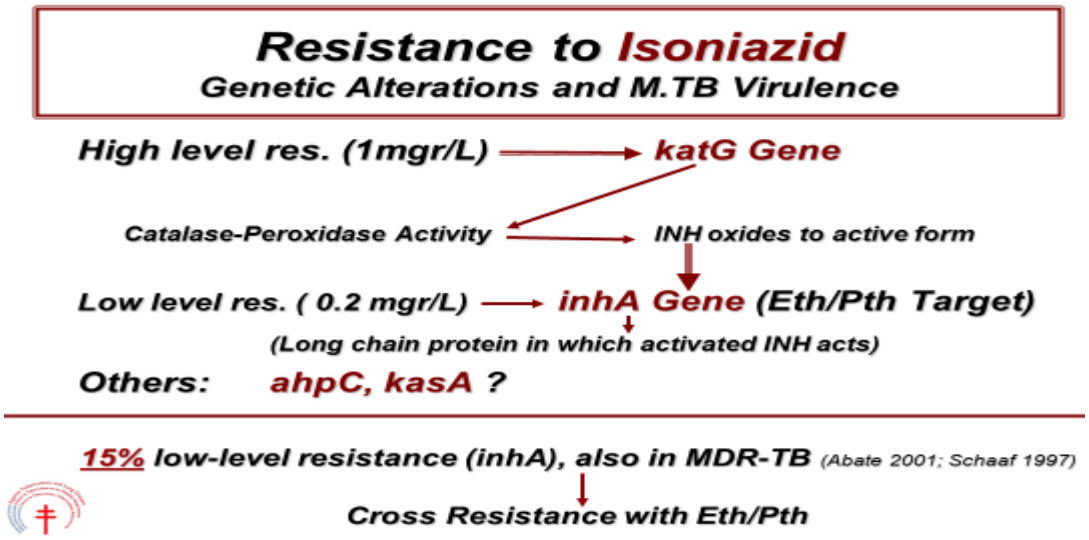

Figure 2.8 Cross Resistance with Ethambutol

According to Zhang and Yew (2015), both MDR and XDR –TB are posing significant challenge to effective treatment and control of tuberculosis in the world. They argue that the use of multiple drugs in TB treatment has proven to be beneficial to the cure of tuberculosis but does not absolutely guarantee against development of MDR and XDR-TB. Drug resistant TB is two folds: genetic and phenotypic resistance (Schaaf et al., 2011; Zhang & Yew, 2005) Genotypic resistance result from a mutation in chromosomal genes of growing bacteria while phenotypic resistance is caused by factors outside the genetic make-up of the cells of TB bacteria. Phenotypic resistance results from the modification of bacterial protein, causing changes in the genetic expression thus affecting drug tolerance by persistence bacteria. It manifests as sputum conversion failure, prolonged treatment and post treatment relapse (Caminero, 2010).

Natural resistance is as a random genomic mutation accruing to all living species. When reach certain number of divisions, giving rise to organism with certain antlered foundation (Caminero, 2006). Selection of drug resistant mutant organism occurs if smear positive TB, is treated with one drug, one individual microorganism (a resistant mutant organism) will escape untreated. The mutant organisms multiply into a colony of mutant organism. Mutation is not cause by drugs themselves but each drug selects mutant organism.

The combination of drugs in a treatment regime prevents the appearance of resistance because it avoids the selection of naturally resistant mutant organism (Caminero, 2006; Reider, 2002). The increase in MDR cases result from the initial resistance to Rifampicin

before the introduction of gene Expert in the screen algorithm for TB. The most difficult resistance is resistance to both isoniazid and Rifampicin which is called MDR. Resistance in previously untreated patient is primary or initial resistance. According to Andrews et al. (2012) drug resistant and extreme drug resistant TB is most likely to be caused by regiment failure compare to treatment default. This points a finger to the health care worker related factors associated with misdiagnosis and under dosing of patients.

Genotypic or selective mutations are a natural phenomenon responsible for the emergence of MDR and XDR mostly. Researchers also suggest that the two types of resistance may overlap and interconvert. Sub therapeutic levels of drugs in the patient may cause phenotypic resistance, which by produce genotypic modification of TB bacteria to certain patients, giving raise to MDR and XDR.

According to Zhang and Yew (2015), selective mutation which is a genetic phenomenon responsible for resistance may cause the persistent bacteria in phenotypic resistant. Deductive reasoning could suggest the relationship between TB programmatic deficiencies and both phenotypic and genotypic resistance. Prescription errors, under dosing and none adherence to treatment regime are the direct cause of MDR and XDR (Zhang & Yew, 2015).

South African National Health Laboratory Services statistics for 2009 revealed that on 50% of MDR-TB diagnosed cases did not receive treatment (NDOH, 2012). The rest of the cases were diagnosed by laboratories but not identified by unsuspecting clinicians and were missed. The first priority to fight against MDR/XDR -TB is to strengthen the NTP with good management of the susceptible. TB studies conducted in South Africa show that the strains

predominating in XDR-TB in western, Eastern Cape and KwaZulu-Natal were strongly association with harbouring and inhA promoter mutation, potentially suggestion or role of this mutation in XDR-TB development in SA (Chihota, et al., 2012).

According to National TB guidelines (2009) a patient has defaulted treatment if he or she returns for treatment with a bacteriological positive sputum smear after stopping treatment for more than 2 months (NDOH, 2009). Poor treatment for adherence is a high-risk factor for selecting resistance to TB. An investigation into the emergence of increase resistance and extensively drug-resistant TB despite treatment adherence conducted among HIV co-infected at a gold mine of South Africa; established that the then existing TB control measures were not adequate to control the spread of drug resistant TB in this category of patients (Calver, et al., 2010)

Delays in diagnosis and treatment with inappropriate therapy facilitate disease transmission and drug resistance. The study recommended improvement of infection control strategies, implementation of rapid diagnostic tests and enhances active screening strategies (Calver, et al., 2010). The study on extreme drug resistant TB conducted in rural areas of South Africa, published by The Lancet in 2006, revealed that XDR was the leading courses of mortality among HIV/TB comorbid patients (Sandhi et al. 2006).

Changes in diagnostic algorithms introduced by the South African Health Department in 2013 significantly improved the health outcomes of TB /HIV comorbid patients. The introduction of Gene X pert and Line Probe Assay fast tracked the diagnosis of MDR-TB and XDR-TB. TB/HIV comorbid patient management improved significantly since these patients are most susceptible MDR-TB and XDR-TB. The number of comorbid patients started on

ART increased to 89%. Sixty-six (66%) of new TB patients were tested with GeneXpert and 53 % of HIV patients diagnosed with TB while on INH prophylaxis (WHO, 2018).

2.9. TB INFECTION CONTROL

Infection control is the vital component of the TB control programme. The deadly strain of TB bacteria is mainly transmissible through primary infection compared to normal drug susceptible TB bacteria. This is mainly because TB bacteria becomes less infections after 4 weeks of treatment with anti- TB drugs (NDOH, 2009). Deductive reasoning suggests that the best way to control TB infection is early detection of cases of active TB, prompt treatment and isolation of TB suspects. Active surveillance of TB cases, cough etiquette and segregation of TB suspects are golden standards of TB control.

Inadequately treated MDR TB patients co-infected with HIV are highly infectious compared to ordinary TB patients (Escombe, et al., 2008). This highlights the importance of rapid TB drug-susceptibility testing to allow prompt initiation of effective treatment among drug resistant patients. This has prompted The Department of Health to introduce Gene Expert in basic TB testing algorithms in 2013 (NDOH, 2013).

The study conducted in Khayelitsha, Cape Town, found that low cost interventions like wind driven high roof turbines combine with natural ventilation, are more effective than negative pressure mechanism of mechanical ventilation and ultra violet lights-based radiation (Cox et

al, 2012). The findings of this study agree with the study on natural ventilation conducted in Peru, looking at natural ventilation.

This study proposed natural ventilation as the alternative to mechanical ventilation in resource constraint settings (Escombe et al, 2007). According to this study, natural ventilation offers by far the best air exchanges compared to the recommended 12 exchanges of mechanically ventilated negative pressure systems installed in modern building of the 21st century. This is an important finding for health facilities in Zululand, which are predominantly not equipped with the negative pressure technology. Cox et al. (2012) and Escombe et al. (2007) stated that opening windows and door maximize allowing cross ventilation maximize natural ventilation and eliminate the risk of airborne infectious diseases in hospitals.

CHAPTER 3: RESEARCH METHODOLOGY

3.1. RESEARCH DESIGN

The study was a retrospective, descriptive survey reviewing electronic TB records at the district level. The study was confined to electronic TB data base, aimed at identify contributory factors influencing TB mortality among newly diagnosed TB patients in the Zululand Health District, Kwa-Zulu Natal Province, South Africa.

3.2 RESEARCH SETTING

The study was conducted in Zululand Health District situated in northern KwaZulu-Natal Province of South Africa. Zululand Health District is Presidential rural node area characterized by poverty and high unemployment rate where 73% of the population leaves on less than R283 a day (Statistics South Africa, 2011). The district comprises 5 district hospitals, 1 Community Health Centres (CHC) and 68 clinics. Each facility report TB cases to district using the paper-based TB register. The papers based transcribe information into the electronic register kept at district level.

All the five sub-districts obtain their outcomes each quarter and anytime on request from The District TB Coordinator. Patients TB records are kept at each health facility, either a district hospital or clinics for 5 years. Each facility reports TB cases to a district manager using the paper-based TB registers which are transcribed into the electronic register kept at district level. All patients on the data base, who met population characteristics of interest to the research project, were considered. The sample frame was the district electronic TB register, which is a consolidated record of sub-district tuberculosis registers for all patients on the database enrolled between January 2012 and December 2013.

3.3 RESEARCH POPULATION AND SAMPLING

The researcher chose a convenient sample of all patients who meets population characteristics of interest to the research project, to avoid visiting the health facilities for data verification. The sample frame was the district electronic TB register, which is a consolidated record of sub-district tuberculosis registers. According to Bobbie and Mouton (2001) sampling is done to generalise findings about people and events which have not been observed. The sample frame was adequate to generalise findings since only patients with incomplete data entries were excluded among those which met the criterion of new TB patients,

Kumar (2005) describes sampling as the process of selecting a few cases from a bigger group to become the basis for estimating or predicting the prevalence of an unknown piece of information, situation or outcome regarding the bigger group. All patients on the database enrolled between January 2012 and December 2013 were sampled. Convenient sampling was applied to select all patients on the database who meet the inclusion criteria for selection.

3.4 INCLUSION AND EXCLUSION CRITERIA

The study focused on new all new TB patients with complete key research information captured on the electronic TB register. Patients were included if they were enrolled for treatment between January 2012 and December 2013. However, patients who were exposed to TB treatment for a month or more before the current treatment episode; had incomplete data on the district database; and were transferred in or transferred out of the district were excluded from the study.

3.5 DATA COLLECTION TOOLS

The original Microsoft access electronic TB database, which enabled exportation of data to Microsoft excel spread sheet, was the data collection tool for this study. The tool contains detailed transcription of paper-based TB registers. The registers cover population characteristics like: demographic data, TB case finding, smear conversion, treatment outcomes and HIV information. The HIV information comprises diagnostic parameters, treatment and information on patient outcomes. The TB data comprises diagnostic information, patients' categorizations or patient's descriptive data and information on treatment regimen.

Descriptive and inferential statistics were used for data analysis. Descriptive statistics (frequency and percentages) were applied to the category variables. All statistical analyses were performed with the Statistical Package for Social Science (SPSS) version 21.0 for Windows (SPSS Inc., Chicago, IL, USA).

3.6 DATA COLLECTION PROCEDURES

Authority was obtained from the Provincial department of Health and The District director for Zululand Health District. The district based electronic TB register was used as the primary source of information. The Microsoft access data base was exported to the Microsoft excel for ease of analysis. The Microsoft excel spread sheet was used to select all new TB patients on the electronic data base. Population characteristics of interest to the Researcher ware explored and patients with incomplete data were eliminated. Extracted data was subjected to further analysis using excel spread sheet, Descriptive and inferential statistics were used for data analysis. Descriptive statistics (frequency and percentages) were applied to the category variables.

3.7 DATA ANALYSIS

Data were analysed using a combination of descriptive and inferential statistics. Descriptive statistics (frequency, percentages, mean and standard deviation) were used for categorical variables to summarise entire sets of data. Inferential statistics (bivariate and multivariate logistic regression) were used to identify the significant associated risk factors of HIV comorbidity, CD4 count, ART initiation, pre-exposure prophylaxis against TB for HIV positive patients and post HIV exposure prophylaxis against TB.

The confidence interval of (95% CI). Chi-square was used to determine the association between the variables. The logistic regression was also adjusted for confounding factors to determine which of the demographic variables between sex and age, would independently

and significantly predict the risk of mortality among participants. Descriptive statistics (frequency and percentages) were applied to the category variables. Chi-square was used to determine the associations of SMEAR, CPT, DOT, HIV testing and HIV status with a Survival indicator (patient is alive or dead).

A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed with the Statistical Package for Social Science (SPSS) version 21.0 for windows (SPSS Inc., Chicago, IL, USA)

3.8 ETHICAL CONSIDERATIONS

The study was approved by the Ethical committee of the University of Fort Hare (Appendix A). The Provincial Department of Health of KwaZulu-Natal Knowledge Management Unit granted ethics approval to conduct the study (Appendix B). The study received approval from the District Director for Zululand Health District (Appendix C). The aim and the nature of the study were explained to the various health facility managers indicating the privacy, confidentiality and anonymity of the data extracted. The right to anonymity and confidentially was observed by not identifying patient by names. The study did not have direct interference with patients' lives since it was mainly a desktop research. The research principle of beneficence guided handling sensitive information on the HIV status of the patients by avoiding the use of patient's names and file numbers for study purposes.

CHAPTER 4: RESULTS AND DISCUSSION

4.1 INTRODUCTION

This chapter presents the results of the study and a discussion of the results. Results are presented in tables.

4.2 DEMOGRAPHIC PROFILE OF PARTICIPANTS

Table 4.1 shows gender and age groups of all participants. TB mortality was most prevalent between ages 25 to 45 years. Males had high mortality between ages 25 years and 65 years; and this age bracket had the highest burden of TB disease across all genders contributing 53% of all TB cases. Among the females, TB infection and mortality was high between ages 15 and 24 years more significantly affecting females compared to males in the same age category.

Table 4.1: Demographic profile of TB patients stratified by age and gender.

Variables	Survived patients (n=14567)		Died patients (n=1318)		Total (n=15885)	
Age (years)	Females n (%)	Males n (%)	Females n (%)	Males n (%)	Female n (%)	Males n (%)
0-5	507(3)	532(4)	6(04)	13(09)	513(3)	545(3)
14-Jun	341(2)	357(2)	14(1	6(0.4)	355(2)	363(2)
15-24	1143(8)	581(4)	59(5)	20(2)	1202(8)	601(4)
25-45	3333(23)	3422(23)	356(27)	399(30)	3689(23)	3821(24)
46-65	904(6)	1264(9)	115(.9)	204(15)	1019(6)	1468(9)
66-99	1939(13)	244(2)	60(5)	66(5)	1999(13)	310(2)
Total	8167(56)	6400(44)	610(44)	708(54)	8777(55)	7108(45)

4.3. MULTIPLE DRUG RESISTANT TUBERCULOSIS

Table 4.2 reflect treatment outcomes of interest to the TB program. It could be deduced from the table that the TB control program in Zululand Health district performs well, whereas the only outlier is the scourge in the number of deaths which warranted investigation.

Table 4.2: Multiple drug resistant tuberculosis

Patients Outcome	All patients11467 n (100%)	Males 6400 n (44%)	Females 8167 n (56%)
Turned to MDR	161(1.2)	69(1.1)	92(1.1)
TX Failure	12(0.09)	9(0.1)	3(0.03)

4.4 ASSOCIATION BETWEEN TB AND MORTALITY

The Table 4.3 indicates the associations among the variables: gender and survival for each of the tests of interest, namely, SMEAR, CPT, DOT, HIV testing and HIV status.

Table 4.3: Bivariate and multivariate logistic regression analysis of factors contributing to TB mortality among patients.

Table 2: Associations of SMEAR, CPT, DOT.

Test	Association	χ^2	p-value	Comparison	Response level	OR	95% CI
Smear	Result and Survival	20.5; df=2	<0.0001	Not done vs. Positive	Alive	0.81	0.75-0.91
				Negative vs. Positive	Alive	2.57	2.38-2.79
CPT	Result and Survival	9.1; df=1	0.0025	Not started vs. Started	Alive	0.73	0.59-0.89
DOT	Result and Survival	11.3; df=1	0.0008	Not on DOT vs. on DOT	Alive	0.81	0.71-0.91
HIV testing	Gender and Result	8.3; df=1	0.0039	Female vs. Males	Not tested	0.70	0.55-0.89
	Gender and Survival	7.3; df=1	0.0067	Female vs. Males	Alive	1.17	1.05-1.31
	Result and Survival	2.6; df=1	0.1091	Not tested vs. Tested	Alive	1.48	0.91-2.39
	Result and Survival (Females)	0.1; df=1	0.7833	Not tested vs. Tested	Alive	1.10	0.55-2.19
	Result and Survival (Males)	3.6; df=1	0.0577	Not tested vs. Tested	Alive	1.90	0.97-3.75

CPT= Cotrimoxazole prophylactic therapy, DOT= Direct observation of treatment; HIV=Human immuno-virus.

Table 3: Associations of HIV testing and HIV status.

Test	Association	χ^2	p-value	Comparison	Response Level	OR	95% CI
HIV status	Gender and Result	78.4; df= 1	<0.0001	Female vs. Males	Negative	0.72	0.67-0.77
	Gender and Survival	8.19; df= 1	0.0042	Female vs. Males	Alive	1.18	1.10-1.33
	Result and Survival	61.7; df= 1	<0.0001	Negative vs. Positive	Alive	1.75	1.52-2.02
	Result and Survival (Females)	28.1; df= 1	<0.0001	Negative vs. Positive	Alive	1.80	1.44-2.25
	Result and Survival (Males)	37.2; df= 1	<0.0001	Negative vs. Positive	Alive	1.78	1.47-2.13

Table 4: Association between survival, CD4 testing and antiretroviral therapy

Test	Association	χ^2	p-value	Comparison	Response Level	OR	95% CI
CD4 testing	Gender and Result	13.6; df=1	0.0002	Female vs. Males	Not tested	0.83	0.76-0.92
	Gender and Survival	5.3; df=1	0.0212	Female vs. Males	Alive	1.20	1.02-1.35
	Result and Survival	22.1; df=1	<0.0001	Not tested vs. Tested	Alive	0.71	0.59-0.81
CD4 count levels	Gender and Result	1.1; df=1	0.2845	Female vs. Males	<100	0.93	0.83-1.06
	Gender and Survival	0.2; df=1	0.9615	Female vs. Males	Alive	1.00	0.83-1.22

	Result and Survival	32.8; df=1	<0.0001	CD4<100 vs. 100<CD4<200	Alive	0.50	0.44-0.68
Antiretroviral therapy	Result and Survival	6.8; df=1	0.0090	Not Started vs. Started	Alive	1.30	1.07-1.56

CD4= white blood cells, ART =anti-retroviral therapy

Result refers to the outcome of the test/screening (positive or negative, yes or no); Survival refers to whether the patient is alive or dead. There is a statistically significant association between screening result and survival for smear (Chisq=20.5; df=2; p<0.0001). Those who did not have smear screening/testing were significantly less likely to survive compared to those who were smear positive (OR=0.81; 95% CI (0.75; 0.91)). Those who do not take the smear test have 19% lower chances of survival. Those who tested negative have a significantly much higher chance of survival than those who tested positive. The odds of survival for the smear negative are 157% higher than for smear positive.

There is a significant association between starting CPT and survival (Chisq=9.1; df=1; p=0.0025). Those who did not start on CPT are less likely to survive compared to those who have started on CPT (OR=0.73). The upper limit of the 95% confidence interval of the odds ratio is less than 1 indicating the odds of survival are lower in the non-CPT group. Similarly, patients not on DOT had lower chances of survival compared to those on DOT (OR=0.81).

Concerning HIV testing, the odds of not testing for HIV are significantly lower for females than for males (OR=0.70; 95% CI (0.55; 0.89)). This means, females were more likely to test for HIV and to survive (OR=1.17; 95% CI (1.05; 1.31)) than males. The odds of survival

were 17% higher among the females than for males. There was no statistically significant association between testing for HIV testing and survival, for females and females separately. The Breslow-Day test for homogeneity of odds ratios was carried out and it showed that the odds of survival for those who tested for HIV and those who did not were the same for males and females (Chisq=1.3; df=1; p=0.2605). It could be deduced that, regardless of gender, the odds of survival did not depend on whether one tested for HIV or not.

The results for HIV by status show that females are significantly less likely to be HIV negative (OR=0.72; 95% CI (0.67; 0.77)), that is, the odds of being negative were 28% lower among females. However, the odds of survival are 18% higher among females than males (OR=1.18; 95% CI (1.10; 1.33)).

Considering HIV status and survival, the results show that HIV negative patients have a higher chance of survival, in general and among the males and females, separately. This is evidenced by odds ratios greater than 1 with confidence limits above 1 and p-values less than 5%. The Breslow-Day test for homogeneity of odds ratios showed that there is no gender effect on the association between HIV status and survival (Chisq=0.015; df=1; p=0.9037).

4.5 DISCUSSION

4.5.1 PATIENTS RELATED FACTORS

The finding of the study indicated TB is most prevalent among patients between 25 and 45 years; and TB related deaths occurred mostly in this age bracket, across all genders. Similarly, female between 15-24 years were most vulnerable to TB and TB related deaths compared to their male counterparts. Interestingly, the highest prevalence of TB and related deaths among males was between ages 25 and 45 years.

The literature has shown that TB/HIV comorbid patients presents with negative sputum smears (Corbett et al., 2003, Ismail & Bulgiba, 2013; Blanc & Sok, 2011; Alavi & Salami, 2009). The finding that HIV was a major contributor to TB mortality in Zululand Health District is supported by several studies (Corbett et al., 2003, Ismail & Bulgiba, 2013; Blanc & Sok, 2011; Alavi & Salami, 2009). Empirical studies point to HIV association with negative smears in clinically TB patients (Henn et al., 1999; Kufa et al., 2012).

The study also found odds of not testing for HIV to be significantly lower for females than for males. Females were more likely to test for HIV and to survive than males. The odds of survival were 17% higher among the females than for males. There was no statistically significant association between testing for HIV and survival, for males and females. The results showed that females were significantly less likely to be HIV negative. The odds of being negative are 28% lower among females. However, the odds of survival are 18% higher among females than males. One plausible reason could be that females have better health seeking behaviour compared to males.

Changes in diagnostic algorithms introduced by the South African Health Department in 2013 significantly improved the health outcomes of TB /HIV comorbid patients. The introduction of Gene X pert and Line Probe Assay fast tracked the diagnosis of MDR-TB and XDR-TB. TB/HIV comorbid patient management improved significantly since these patients are most susceptible MDR-TB and XDR-TB. TB mortality remained 11,2 %.

The reported change was the reduction of TB incidence by 21% in 2018 and the improvement in the countries ranking among the 20 countries with high TB burden (WHO, 2018). The number of comorbid patients started on ART increased to 89%. Sixty-six (66%) of new TB patients were tested with GeneXpert and 53 % of HIV patients diagnosed with TB while on INH prophylaxis (WHO, 2018). HIV and alcohol abuse were major risk factors for TB in south Africa according to the global TB report 2018. Notwithstanding a significant increase in ART initiations reported in 2018, non- adherence to protocols. TB/HIV comorbidity are significant factors influencing TB mortality in South Africa.

4.5.2 HEALTH WORKER RELATED FACTOR

The study found significant association between starting co-trimoxazole prophylaxis and survival for TB/HIV comorbid patients. The association is such that those who did not start on co-trimoxazole prophylactic treatment, were less likely to survive compared to those who had started on CPT. The upper limit of the 95% confidence interval of the odds ratio is less than 1, which means the odds of survival are lower in the non-CPT group. TB/HIV management protocols provide for the initiation of co-trimoxazole prophylaxis to all TB patients co-infected with HIV more especially those with low CD4 test result. The statistics has shown that in 2012 only 65 % of TB patients were on CPT prophylaxis (WHO, 2013; National Department of Health, 2012).

The results also show that there is a statistically significant association between TB bacteriological test result and survival. The association is such that those who did not have TB smear testing were significantly less likely to survive compared to those who were TB smear positive. Comparing all patients under study, those who did not do the smear test had 19% lower chances of survival than the tested positive.

Those who tested negative had a significantly much higher chance of survival than those who tested positive for TB. The odds of survival for the smear negative are 157% higher than for smear positive. The diagnosed of these patients was clinically by chest x ray or treatment would have been started based on empirical reasons. Although this finding does not relate to objectives of the study, it is significant in highlighting the importance of bacteriology in the diagnosis of TB disease.

The finding of the study shows an increase in mortality among patients without CD4 tests. This holds true even though CD4 was not a criterion for initiation of ART for TB HIV co-infected patients. This finding concurs with several studies (Alavi & Salami, 2009; Andrew et al., 2012; Henn et al., 1999; Ismail & Bulgiba, 2011 and Lawn et al., 2011) conducted elsewhere. The non-integration of TB and HIV service points leading to poor tracking of TB patients for initiation of ART at the HIV service point. There is need to study the operational dynamics of integration of TB and HIV service points I order to effectively track TB patients for ART initiation.

4.5.3 HEALTH SYSTEMS FACTORS

Direct observation of treatment, as a health systems factor, is a factor influencing TB mortality. The finding of this present study indicates that patients who were not under direct observation of treatment had lower chances of survival compared to those on DOT. It should be noted that resource constraints by the Zululand Health District has contributed immensely to the failure of TB programme in the implementation of DOT.

CHAPTER5: SUMMARY, CONCLUSION AND RECOMMENDATIONS

5.1 SUMMARY

During the period ranging from January 2011 to December 2013, Zululand Health District reported tuberculosis (TB) related mortality cases above the WHO's norm of 10%. This raised concerns because TB is curable even if the person is HIV positive. The overall performance of TB programme in South Africa concealed the actual problem of TB related mortality in the country and most particularly in Zululand Health District. The aim of the study was to examine factors contributing to TB mortality, and the extent of TB related mortality in Zululand Health District.

Specifically, the objectives of the study were:

- To examine health worker related factors (non-adherence to protocols) as a contributory factor to TB mortality in Zululand Health District
- To examine health system factors (poor implementation DOTS strategy) as a contributory factor to TB mortality in Zululand Health District
- To examine patient related factors (treatment default, poor health seeking behaviour) as a contributory factor to TB mortality in Zululand Health District
- To ascertain the extent of TB related mortality rate among TB patients of Zululand Health District.

The following research questions were framed:

- What are health worker related factors contributing to TB mortality in Zululand Health District?
- What are health systems factors contributing to TB mortality in Zululand Health District?
- What are patient related factors contributing to TB mortality in Zululand Health District?
- What is the relationship between TB and TB related mortality among TB patients in Zululand Health District?

This was a retrospective, descriptive study to review medical records pertaining to TB data at the district level in order to identify contributory factors associated with TB mortality among TB patients at Zululand Health District.

All patients on the database enrolled between January 2012 and December 2013 were conveniently sampled. All new TB patients with complete key research information were captured on the electronic TB register. Patients were included if they were enrolled for treatment between January 2012 and December 2013. However, patients who were exposed to TB treatment for a month or more before the current treatment episode; had incomplete data on the district database; and were transferred in or transferred out of the district were excluded from the study. A data sheet was developed to record information extracted from the medical records. The medical records of TB patients were examined for data extraction, with the help and permission of the health facility manager or assistant.

The study was approved by the Ethical committee of the University of Fort Hare. The aim and the nature of the study were explained to the various health facility managers indicating the privacy, confidentiality and anonymity of the data extracted. The right to anonymity and confidentially was observed by not identifying patient by names.

Data were analysed using a combination of descriptive and inferential statistics. Descriptive statistics (frequency, percentages) were used to summarise entire sets of data. Chi-square was used to determine the association between TB and mortality. Inferential statistics (bivariate and multivariate logistic regression) were used to identify the significant associated factors of TB mortality among TB patients and their 95% confidence interval (95% CI). A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed with the Statistical Package for Social Science (SPSS) version 21.0 for windows (SPSS Inc., Chicago, IL, USA.

5.1.1 MAJOR FINDINGS

- The study found that TB/HIV co-morbidity was a main factor contributing to mortality among TB patients resulting from poor CD4 monitoring and poor management of TB/HIV comorbid patients, thus suggesting that HIV related factors are the main contributor to mortality among TB patients.
- There is poor implementation of co-trimoxazole prophylactic treatment protocols to TB/HIV comorbid patients.

- The study found no association between delays in ART initiation and mortality. This finding is supported by the Global tb report of 2018 which shows that 89% of TB/HIV comorbid patients are initiated on ART in South Africa.
- The study found association between TB mortality and demographic patient's related factor.
- Patient factors related to health seeking behaviour were not associated with mortality. This is attributed to the limitations in both methodology and reference data.
- The health systems factor was poor DOT support, which also showed significant statistical association with TB mortality.

5.2.1 HYPOTHESIS TEST

Health worker related factors would not contribute to TB mortality in Zululand Health District. This hypothesis was rejected. Data presented suggested that failure to initiate patients on co-trimoxazole prophylaxis, poor HIV screening and CD4 monitoring contributed to mortality among TB/HIV comorbid patients. Poor implementation of TB/HIV management policies and protocol and none integration of TB and HIV services points are the underlying cause of identified factors associated with TB mortality in Zululand Health District.

Patient related factors would not contribute to TB mortality in Zululand Health District. This hypothesis was rejected. The study found that patients related factors of demographic origin contributed to TB mortality, notwithstanding the case holding rate of above 85%,

default rate, transfers out and none evaluated cased which contributed only 15% of patients on the data base. The inference drawn from the later statistics suggests, patients presented themselves for treatment but were not treated according to protocols at some instances.

Health systems factors would not contribute to TB mortality in Zululand Health District. The null hypothesis is rejected. Poor DOT implementation is the health systems factor which was significantly associated with mortality among TB patients. The effectiveness of the health systems can be measured in terms of its ability to provide leadership and effective clinical governance structure to drive policy implementation. The health worker related factors mention in this study may be a symptom of health systems factors contributing to TB mortality in Zululand health district.

5.2 LIMITATIONS

Limitations of the study are that actual patients could not be interviewed to collect more information on health systems factors and their health seeking behaviours. The database was incomplete with missing data elements, which led to exclusion of some patients, but this did not affect the study because the sample size was big enough to generalise findings. The use of data base does not eliminate the risk of poor quality date, but not withstanding these possible challenges, the study is an operational research which analyse the data bank and produce information with the potential to influence policies, protocols and health worker behaviour and positively impact on health outcomes.

5.3 CONCLUSIONS

The findings of the study point to a mismatch between TB management protocols and implementation thereof. The study identifies health systems gaps and poor clinical governance in regards to TB/HIV management as the underlying source of factors contributing to mortality among TB patients. Patient demographic factors were associated with both mortally and susceptibility to TB and HIV. There was no data to support patient's health seeking behaviours as a factor contributing to TB mortality among new patients of Zululand Health Districts. Government committed significant amount of resources to TB control in south Africa. Ninety percent (90%) of TB funding is sourced from the country's GDP, and only 8% from donor funding and WHO identified the funding gap of 2% (WHO, 2018).

5.4. RECOMMENDATIONS

Based on the results and findings of the study, the following recommendations were made:

- The health system has to develop re-engineered mechanism to step up clinical governance system linked to performance management to ensure that clinical protocols are followed at each encounter with patients.

- The health system needs to prioritise multiskilling of the heath work force to enable integration of tuberculosis and HIV service points, without posing the risk of

combining the two services point, in avoidance of the disastrous effect of cross-infection among patients.

- Mobilization and re- affirmation of the role of none government organization should be coupled with mobilization of resource to support community DOT system to ensure that each TB patient is linked to a DOT support.

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ANNEXURES

ANNEXURE A: ETHICAL CLEARANCE CERTIFICATE FROM UNIVERSITY OF FORT HARE

University of Fort Hare
Together in Excellence

ETHICAL CLEARANCE CERTIFICATE
REC-270710-028-RA Level 01

Certificate Reference Number:	GOO101SDLA01
Project title:	**Factors Contribution to TB Mortality among new TB patients in Zululand Health between 2012 and 2013.**
Nature of Project:	Masters
Principal Researcher:	Khulekani Dlamini
Supervisor:	Prof T.D Goon
Co-supervisor:	N/A

On behalf of the University of Fort Hare's Research Ethics Committee (UREC) I hereby give ethical approval in respect of the undertakings contained in the above-mentioned project and research instrument(s). Should any other instruments be used, these require separate authorization. The Researcher may therefore commence with the research as from the date of this certificate, using the reference number indicated above.

Please note that the UREC must be informed immediately of

- Any material change in the conditions or undertakings mentioned in the document
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research

The Principal Researcher must report to the UREC in the prescribed format, where applicable, annually, and at the end of the project, in respect of ethical compliance.

Special conditions: Research that includes children as per the official regulations of the act must take the following into account:

Note: The UREC is aware of the provisions of s71 of the National Health Act 61 of 2003 and that matters pertaining to obtaining the Minister's consent are under discussion and remain unresolved. Nonetheless, as was decided at a meeting between the National Health Research Ethics Committee and stakeholders on 6 June 2013, university ethics committees may continue to grant ethical clearance for research involving children without the Minister's consent, provided that the prescripts of the previous rules have been met. This certificate is granted in terms of this agreement.

The UREC retains the right to

- Withdrew or amend this Ethical Clearance Certificate if
  - Any unethical principal or practices are revealed or suspected
  - Relevant information has been withheld or misrepresented
  - Regulatory changes of whatsoever nature so require
  - The conditions contained in the Certificate have not been adhered to

- Request access to any information or data at any time during the course or after completion of the project.

- In addition to the need to comply with the highest level of ethical conduct principle investigators must report back annually as an evaluation and monitoring mechanism on the progress being made by the research. Such a report must be sent to the Dean of Research's office

The Ethics Committee wished you well in your research.

Yours sincerely

Professor Gideon de Wet
Dean of Research

21 June 2016

ANNEXURE B: REQUEST TO CONDUCT RESEARCH FROM ZULULAND HEALTH DISTRICT

P.O. Box 1374
Pongola
3170
18 August 2016

The Research Unit
KZN Department of Health
330 Langaliballele Street
P/ Bag x 9051
Pietermaritzburg
3200

Dear Sir / Madam

Request to Conduct Research in Zululand Health District and to Use Patients Records for Purposes of Clinical Research.

The research will be conducted in fulfilment of the academic requirement for the master's program in public health offered by the University of Fort Hare in collaboration with Harvard School of Public Health and University of Pretoria School of Public Health. The course is in pursuit of the Albertina Sisulu Executive Leadership Course in Public Health.

The reports from statistic South African in 2013 show that tuberculosis is still the leading course of mortality in South Africa. According to the report TB account for 11% of all deaths in South Africa, on average between 2008 and 2011 (Statistic South Africa 2013). The TB cure rate of Zululand district was is 76% in 2011 and improved to 84% below the national norm of 85% in 2013. Despite the impressive TB control program performance in Zululand Health District, TB related mortality was 19.9% in 2011 above norm of less than 10% (World Health Organisation 2013).

The circumstances surrounding TB mortality in Zululand Health District motivated The Researcher to conduct a retrospective record survey to investigate factors influencing TB mortality in Zululand Health District. The scope of research will cover a random sample of 5 clinics per sub- district, all five district hospitals and one community health centre. The total number of facilities under review will be 31of 74 facilities. The research will review 5 patents record from each health facility.

The request is hereby made for the researcher to access and utilize patient's information on files for research purpose .Confidentiality will be maintained by allocating study numbers as patient identifier .Access to information will be limited to the researcher and Research Assistants who will be TB Coordinators of each sub district participating in the study.

Thank You

Mr. K.Z. Dlamini
The Researcher

ANNEXURE C: LETTER OF APPROVAL BY THE DISTRICT DIRECTOR

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE: ZULULAND HEALTH DISTRICT
Physical Address: King Dinuzulu Highway, Administrative Building, Ulundi 3838
Postal Address: Private Bag x 81, Ulundi, 3838
Tel: 035 874 0602 Fax: 035 874 0662 Email: mumsy.cebekhulu@kznhealth.gov.za
www.kznhealth.gov.za

Enquiries: S.M Cebekhulu
Extension: 0602
Date: 23 August 2016

To:
Mr. K.Z Dlamini

Subject: Request to conduct research in Zululand Health District and to use patients' records for the purpose of clinical research

Your letter dated 18 August 2016 is hereby referenced; the Health District Office therefore grants you the permission to conduct the as per your request. You are requested to please share your findings and recommendation with this office for the purpose of improving service delivery and promoting quality patient care.

Good luck with your studies

Regards

Ms. S.M Cebekhulu
DD: P; M&E

23/8/2016
Acting District/Director – Zululand Health District

ANNEXURE D: REQUEST FOR WAIVER OF INFORMED CONSENT

P.O. Box 1374

Pongola

3170

30 August 2015

The Dean for Faculty of Research

Ethics Committee

University of Fort Hare

Alice

Sir / Madam

REQUEST FOR AWAIVER OF INFORMED CONSENT

I am currently a Masters student under Albertina Sisulu Executive Leadership Programme (ASELPH) at the University of Fort Hare in the faculty of Health sciences and Agriculture. A request is hereby submitted to be granted permission to waive informed consent "Factors Contributing to TB mortality Among New TB Patients of Zululand Health District. The research project will be a retrospective record survey conducted under the supervision of Professor. Daniel Goon from the University of Fort Hare in East London.

Tile of the Study: Factors Contributing to TB mortality Among New TB Patients of Zululand Health District.

Statement of Problem: During the period ranging from 2011 to 2013, tuberculosis related mortality cases above the norm 10% in Zululand Health District have been reported. That raises concerns since tuberculosis is curable even if the person is HIV positive.

Purpose of the Study: The main purpose of the study is to establish the extent to which patient's factors, health worker related factors and health systems factors influence TB mortality among TB patients in Zululand Health District.

Research Objectives:

The specific objectives of the study were:

- To explore health worker related factors (non-adherence to protocols) as a contributory factor to TB mortality in Zululand Health District

- To discover health system factors (poor implementation DOTS strategy) as a contributory factor to TB mortality in Zululand Health District
- To ascertain patient related factors (treatment default, poor health seeking behaviour) as a contributory factor to TB mortality in Zululand Health District

Study Design: The study shall be a cross-sectional retrospective record survey.

Confidentiality: Confidentiality and anonymity will be maintained by not using patient's names and limiting accesses to patient's records to only the researcher.

Contact details: Contact details for my supervisor are as follows: E-mail: Daniel. Goon @ufh.ac.za, phone Number 0437047359.

My contact details are as follows: kdlamini54@gmail.com, cell number being 082300110and land line 0358317000.

Attachments: Checklist

Ethics forms

Synopsis of the study

Researcher CV

Research Instrument &

Research Proposal

Letter to the Head of Department for Health

Letter to the District Manager

Thanking you in advance and also hoping that my application will meet your favourable consideration.

Yours faithfully

Mr Khulekani Zakheleni Dlamini

ANNEXURE E: ETHICAL CLEARANCE CERTIFICATEFROM KZN DOH ETHICS COMMITTEE

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Health Research & Knowledge Management

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

HRKM Ref: 284/16
NHRD Ref: KZ_2016RP34_259

Date: 9 September 2016
Dear Mr K. Dlamini

Approval of research

1. The research proposal titled **'Factors contributing to TB mortality among new TB patients of Zululand Health District'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Zululand District Office using electronic TB data.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 12/09/16

Fighting Disease, Fighting Poverty, Giving Hope

ANNEXURE F PROFESSIONAL EDITING CERTIFICATE

TO WHOM IT MAY CONCERN

I have 42 years' experience in the teaching profession, both at high school and tertiary level. In my last position before retiring in December 2016, I was a Teaching and Learning Consultant and Acting Manager of the Teaching and Learning Centre (TLC) of the University of Fort Hare. As such, I facilitated modules on the Post Graduate Diploma in Higher Education and Training (PGDHET) and also evaluated lecturers' teaching and their courses. My skills set allowed me to focus on management, language, research and student development. Activities which speak to this included being the Co-ordinator of the Language and Writing Advancement Programme (LWAP) and the Supplemental Instruction Programme (SI) for two years plus being the editor of the TLC's bi-annual newsletter for approximately eight years.

I hereby certify that I have proofread an academic journal article submitted to me by Khulekani Z Dlamini of the Public Health Department at the University of Fort Hare. His research topic is:

` Factors contributing to mortality among new tuberculosis patients in the Zululand Health District, South Africa: A retrospective study'.

I have corrected superficial errors in spelling, grammar, syntax and punctuation. Furthermore, I trust that the language used accurately reflects the intended meaning of the data tabulated and that the narrative aligns with the aforementioned. Every effort has been made to avoid confusion or misunderstanding. The principles of anonymity, confidentiality, accountability and reliability were respected by all parties. Mr Dlamini elected to take responsibility himself for all the referencing (in-text and end referencing) so that aspect of the journal article has not been checked by me.

Should there be any questions that arise from this exercise, kindly contact me on lscheckle@gmail.com.

Linda Scheckle (Private Editing Service) 15 May 2018

Address:
Flat 2 Riverview Heights
6 Riverview Terrace
Beacon Bay
East London
5241