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**A RETROSPECTIVE ANALYSIS OF DRUG-RESISTANT
TUBERCULOSIS TRENDS AND CAUSAL FACTORS IN THE
PERIOD BETWEEN 2016 AND 2020 IN THE SARAH BAARTMAN
DISTRICT OF THE EASTERN CAPE PROVINCE, SOUTH AFRICA**

BY

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**A MINI DISSERTATION SUBMITTED TO THE FACULTY OF HEALTH
SCIENCES IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR A
MASTER OF PUBLIC HEALTH DEGREE**

**FACULTY OF HEALTH SCIENCES
UNIVERSITY OF FORT HARE**

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12 March 2025

DECLARATION

I, **Salmoné Jordania Petrus**, student number 201821277, hereby declare that this mini dissertation is a product of my own work and is being submitted to the University of Fort Hare in partial fulfilment of the requirements for the degree of Master of Public Health. It has not been submitted before to any other institution, by me, or any other person, for the purposes of fulfilling the requirements for attaining any other qualifications. I further cede the copyright of this research in favour of the University of Fort Hare.

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DEDICATION

This mini dissertation is dedicated to my family, who supported my dream of pursuing post-graduate studies.

Firstly, to my loving husband, Shirage, without whose support I would not have enrolled in this programme.

To my daughters, Layla, Isabella, Zara and Nazley, for keeping me motivated to improve myself continuously.

To my mother, Maria January, and late father, Hendrik Marthinus January, who shaped me into who I am today, for which I will forever be grateful.

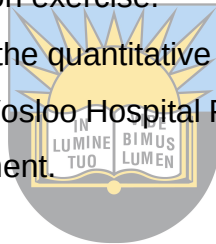


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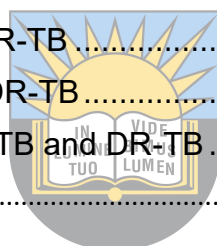
- Professor X.T. Maluleke, my supervisor, thank you for your impeccable engagement and guidance throughout the execution of this research study.
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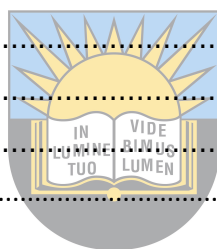
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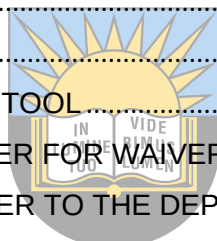
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LIST OF ACRONYMS AND ABBREVIATIONS

AIDS – Acquired Immunodeficiency Syndrome

APP – Annual Performance Plan

DOTS – Direct observed Therapy Short course

DR – Drug Resistant

EDoH – Eastern Cape Department of Health

eDR-web – electronic Drug-resistant web application

HIV – Human Immunodeficiency Virus

INH - Isoniazid

MDR-TB – Multi-drug resistant Tuberculosis

PLHIV – People living with HIV

Rif – Rifampicin

RR-TB – Rifampicin resistant TB

SA – South Africa

TB - Tuberculosis

WBOTs – Ward-based outreach teams

webDHIS – web application of District Health Information System

WHO – World Health Organization

XDR-TB – Extensive drug-resistant Tuberculosis



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ABSTRACT

Introduction

Resistance to anti-tuberculosis (TB) medication is a challenge that TB control practitioners have seen increasing in recent years. Drug-resistant (DR) TB can be caused by many factors, among them non-adherence to medication, substandard medication, inadequate patient care and airborne transmission. The prevalence of DR-TB was high, and there was a significant spike in the number of Rifampicin-resistant cases in the Sarah Baartman district. This study aimed to conduct a retrospective analysis of trends and causal factors to Drug-Resistant Tuberculosis in the Sarah Baartman district from 2016 to 2020 using EDR-web, the Drug-resistant Tuberculosis Register.

Methods

A retrospective, descriptive and quantitative study design was used. Data were collected from files of 100 TB adult patients' records who had been treated and admitted at the Margery Parkes TB Hospital in Graaf-Reinet. A data extraction tool was used to collect data from the EDR-web register, which was later captured onto a Microsoft Excel® spreadsheet for further analysis.

Results

Almost two-thirds of the patients in the study were males (60%) and had an average age of 40.8 years. Of the 100 participants, 54% were infected with HIV, and they had a mean CD4 count of 226 with a 95% confidence interval of (161.8 290.2). Sixty-six percent had previously been treated for TB, and 59.1% had been cured. In relation to the current DR-TB diagnosis, 49% had RR-TB, 46% had MDR-TB, and 5% had pre-XDR. The time taken to initiate patients on treatment was around 15 days, and the treatment duration was an average of 10.8 months. The treatment used was consistent with the WHO guidelines. Most of the patients were on Pyrazinamide PZA (100%), High dose Isoniazid at 89%, Bedaquiline at 82%, Ethambutol at 79%, Clofazimine at 78%, and Levofloxacin at 74%. Thirteen per cent of the participants reported side effects due to the treatment. Concerning treatment outcome, a 60% treatment success rate was achieved and 19% of the participants died.

Conclusion

The prevalence of DR-TB was found to be high, and an alarming spike in the number of Rifampicin-resistant cases was observed. DR-TB and TB, in general, are more common in males and affect the economically active age group. People living with HIV are at a higher risk of contracting DR-TB because of their weakened immune systems. Treatment compliance will positively affect CD4 count and treatment outcomes. There is a high risk of developing DR-TB or Pre-XDR-TB, without having been previously exposed to TB or TB treatment. RR-TB is emerging fast and is more prevalent than MDR-TB. DR-TB has a high mortality rate when treatment is delayed. Community mobilisation and patient education aimed at improving health-seeking behaviour and basic household infection control mechanisms would be recommended as interventions to curb the spread of DR-TB.

KEYWORD: Drug-resistant Tuberculosis; Adherence; retrospective; South Africa



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CHAPTER ONE: INTRODUCTION

1.1 Introduction

Tuberculosis (TB) is one of the leading causes of mortality globally. The disease has the highest mortality from a single organism *Mycobacterium Tuberculosis* (World Health Organization (WHO), 2017). It has a co-epidemic relationship with HIV/AIDS, with one disease exacerbating the effects of the other. Deaths attributable to TB exceeded those attributable to HIV/AIDS alone and contributed 40% to all HIV-related mortalities in 2016 (WHO, 2017). In 2016, 10.4 million patients were diagnosed with TB globally and of these 1 674 000 died and of these mortalities, 22.3% were living with HIV. Globally, TB incidence decreased by about 2% per year between 2015 and 2020, with a cumulative reduction of about 11%. This decrease could have been the result of the End TB Strategy. South Africa is one of the 86 high-burden countries that achieved the 2020 goal of the End TB Strategy. The goal was a 20% reduction in the TB incidence rate (WHO, 2021). Furthermore, the burden of TB disease is highest in low to middle-income countries. According to the WHO, the South East Asian Region constitute 45% of the global burden of TB disease, followed by the African Region at 25%, and other regions share the remaining 30%. The TB incidence varied from 10 per 100,000 population in high-income countries to more than 500 per 100,000 population in a few countries, including South Africa. The TB incidence rate in South Africa was 805 per 100 000 population in 2016, 738 per 100 000 population in 2017, 677 per 100 000 population in 2018, 615 per 100 000 population in 2019 and 554 per 100 000 population in 2020 (World Health Organization, 2021). In 2019, 13 005 patients were diagnosed with RR-TB of which 9 040 including 406 X-DR TB patients were initiated on treatment (Massyn, Day, Ndlovu; et al. 2020.)

Although TB is a curable disease, many infected patients are not cured because they do not complete their treatment cycle. One of the risk factors of drug-resistant (DR)-TB was found to be non-adherence to first-line TB treatment (Matteelli, Roggi & Carvalho, 2014). In 2014 primary infection with Multidrug-resistant (MDR) or Extensively Drug-resistant (XDR) TB accounted for one-third of all TB cases (WHO, 2014). Multidrug-resistant TB (MDR-TB) can result from multiple factors, including improper treatment of patients, poor drug supply management, and airborne transmission of bacteria in public places (WHO, 2014).

1.2 Study background

Resistance to anti-TB medication is increasingly becoming a challenge for TB control practitioners globally. The trends in the incidence of resistance to anti-TB medication form an essential reference for developing TB control strategies. The HIV/AIDS epidemic and the associated low immunity in the population led to the rise in MDR and XDR TB infections before 2016. In 2016, 156 119 new cases of drug-resistant TB were registered, and this number steadily increased to a peak of 201 997 in 2019 before dropping to 157 903 in 2020 (WHO, 2017; WHO, 2021). Literature suggests that non-adherence to and non-completion of first-line TB treatment contributes to the increased prevalence of DR-TB (WHO, 2014; WHO, 2017; Hayes, 2014).

1.2.1 Classification of Drug-resistant Tuberculosis

Drug-resistant TB is classified into five groups, namely, INH-resistant, Rif-resistant (RR), Multi-drug Resistant (MDR), pre-extensive drug-resistant (pre-X-DR) and Extensive drug-resistant (XDR). With a diagnosis of MDR-TB, resistance is shown against the two most potent first-line treatment agents, Rifampicin (R and Isoniazid (H). Pre-XDR TB occurs when the TB displays resistance to Rifampicin and one of the fluoroquinolones used in the second-line treatment of TB. X-DR TB involves resistance to either Rif or INH, a fluoroquinolone, and Bedaquiline or Linezolid. Therefore, the most potent drugs used to treat TB are rendered ineffective, and second-line and third-line treatments are necessary to treat the disease effectively. Previously, Drug-resistant TB was classified into two groups, namely, MDR and XDR (WHO, 2021).

1.2.2 Aetiology of Drug-Resistant Tuberculosis

There are two distinct pathways for developing drug-resistant TB (WHO, 2014). These are multifactorial and distinct. It is known as acquired drug resistance and primary drug resistance. Primary drug resistance occurs when a person exposed to drug-resistant strains of TB develops DR-TB. Resistance can be defined as primary resistance when the patient has no documented or proven previous exposure to TB treatment, whether first-line or DR-TB treatment. Therefore, it is assumed that this patient is infected with an already resistant strain of TB (Sharma, et al.,2017). The transmission mode is the same as with drug-sensitive TB. It is spread through droplet transmission that is, coughing and sneezing. Co-infection with HIV/AIDS makes this

population more vulnerable to contracting DR-TB due to their compromised immune system (Matteelli, et al., 2014).

On the other hand, acquired drug resistance can be described as a process through which a person previously infected with drug-sensitive TB strains develops resistant strains due to several factors. These factors can be divided into three groups, namely, patient, health care provider, and pharmaceutical.

Pharmaceutical factors include wrong drugs, incorrect doses, inadequate quality, and unavailability of medication used to treat DR-TB. Healthcare worker (HCW) factors include no monitoring of treatment, insufficient information given to patients, sub-optimal knowledge of guidelines for the treatment of TB, weak treatment support, and poor training of healthcare workers (Saravanan, et al., 2018; Matteelliet al., 2014; Shah et al.,2007). Patient factors are usually the most decisive ones in the development of DR-TB. These include non-adherence to treatment, stigma, lack of education and social risk factors such as unemployment and drug and alcohol abuse (Kigozi et al.,2017; Daftary et al., 2015). Factors that contribute to non-adherence to TB treatment among patients include crowded living spaces, poor economic state and poor food security (Gugssa et al., 2017). In the Eastern Cape context, the factors that enhance the development and spread of DR-TB, are not clearly understood (Klopper et al.,2013).

Adherence to anti-tuberculosis treatment is the cornerstone of treatment success. When patients become non-adherent, the level of the anti-tuberculosis medication in their bodies falls to levels where it cannot inhibit or sterilize the bacteria. Non-adherence results in the bacteria becoming resistant to the drug and multiplying in the presence of suboptimal medication levels. Previous treatment of TB disease is the most prominent risk factor for developing DR-TB while substance abuse (alcohol and drugs) is one of the determinants of non-adherence (Sharma et al.,2011). The abuse of substances is not restricted to TB treatment but spreads across all areas of other disease states (Gugssa et al., 2017).

Drug-resistant TB poses a significant threat to public health and puts tremendous financial strain on the national fiscus. The cost of treatment for DR-TB is exponentially higher than the first-line TB treatment. These exorbitant but preventable public health

expenses further strain many low and middle-income countries' dwindling economic and healthcare resources, including South Africa. The South African Department of Health spent over R15 billion in 2016/2017 through its Comprehensive HIV and TB conditional grant, and this expenditure was estimated to increase to R22 billion by 2019/2020 due to non-adherence to treatment (National Development Plan 2030,, 2017).

1.2.3 Strategies to Counteract DR-TB

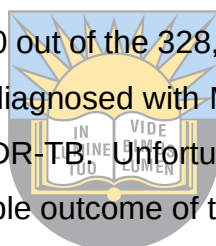
Different countries developed different strategies for treating and managing MDR and XDR TB. However, South Africa has adopted the End TB strategy developed by the World Health Organization in 2015. The End TB Strategy is an expansion of the Sustainable Development Goals backed by the United Nations. The goals of the End TB strategy include a 75% reduction in deaths related to TB and a 50% reduction in TB incidence rate by 2025 (WHO, 2014). As a result, South Africa has implemented strategies to increase adherence as a way of reducing the disease burden. In the South African context, a reduction in TB-related deaths was found to be a real possibility as evidenced by a decrease in the TB death rate from 8.6% in 2011 to 6.6% in 2015. In addition, the treatment success rate increased from 75.4% in 2011 to 81.0% in 2015 (Massyn, et al., 2017). Strategies to counteract DR-TB include improving the accessibility of TB treatment centres, availability of medication, operation of the Direct Observed treatment short-course (DOTS) strategy, and implementation of ward-based outreach teams (WBOTs) that make home visits to selected patients. These methods have been effective but may be limited when resources are stretched by a high disease burden (Out, 2013).

Other strategies employed to curb the spread of DR-TB were based on the WHO consolidated guidelines on drug-resistant tuberculosis treatment. These included taking steps in technical support, research, drug resistance surveillance, diagnosis, and cooperation (WHO, 2019). In 2019, the South Africa National Department of Health introduced the MDR-TB policy framework that put more emphasis on decentralised and deinstitutionalised TB management as a way of dealing with the burden of MDR and XDR TB in the country. According to this policy framework, South Africa had increased the amount of designated MDR-TB initiation centres to six-hundred and fifty-eight (658) sites in eighty-nine per cent (89%) of sub-districts.

Simultaneously, the RR/MDR-TB treatment success rate improved from forty percent to fifty-five per cent from 2011 to May 2019 (Department of Health, 2019). These MDR and XDR treatment sites are run by a doctor, a clinical associate or a primary health care nurse practitioner. In addition, each treatment initiation site had to meet the minimum requirements which included quality-assured medicines, laboratory services and Electrocardiogram devices (ECGs), and a data recording and reporting system (Department of Health, 2019).

1.2.4 Current Trends in TB and DR-TB

Globally, it was estimated that 127 per 100,000 population would be infected with TB in 2020. In Africa, this number was estimated to be 220 per 100,000 population. With its population of 59 Million, South Africa is estimated to have 554 cases per 100,000 population infected with TB. Co-infection with HIV remains the main challenge faced by most people diagnosed with TB. In South Africa, the incidence of TB is higher among male patients, with 195,000 out of the 328,000 patients diagnosed. In 2020, in South Africa, 6900 patients were diagnosed with MDR/RR-TB and 733 patients were diagnosed with pre-XDR and XDR-TB. Unfortunately, only sixty-five per cent of MDR/RR-TB cases had a favourable outcome of treatment success.



As mentioned earlier, there has been a significant reduction in the incidence of TB and DR-TB. However, it is essential to consider the effect of interferences caused by the COVID-19 pandemic on vital TB services at the country level. These disruptions could have caused delays and a lack of monthly and quarterly notifications of people diagnosed with TB (WHO, 2021). The WHO predicts that the COVID-19 pandemic might have pushed the global strides against TB back to pre-2017 levels with expected increases in TB and DR-TB cases from 2022 onwards. The arrival of the COVID-19 pandemic negatively affected the treatment and management of TB, with patients not having access to health facilities for treatment and diagnosis. There was also a decrease in the expenditure related to TB and DR-TB, possibly subsidising the fight against COVID-19. As a result, DR-TB continues to be a public health crisis and health security threat because only a third of people with drug-resistant TB accessed treatment in 2020 (WHO, 2021; Ou et al., 2021).

1.2.5 Gaps In the Knowledge of TB and DR-TB

The impact of COVID-19 on the diagnosis, treatment and cure of TB and DR-TB should be explored. Locally, districts with a high prevalence of TB and DR-TB should explore the knowledge, attitudes and perceptions of patients defaulting on their treatment to develop informed local mitigation strategies to combat TB and DR-TB.

1.3 Problem statement

The 2017 statistics indicated that the highest burden of MDR-TB was reported in China, India, Russia, and South Africa. These countries have more than 60% of all cases of MDR-TB worldwide. The challenge with the increasing MDR-TB problems is the decreasing cure rates and dwindling survival rates. Furthermore, the MDR-TB prevalence has increased the expenses for responding to anti-TB programs by about 47% and strained local health resources in many low and middle-income countries. Therefore, there is a high need to ensure adherence to TB treatment and control of Drug-resistant TB. (Ou, et al., 2021).

According to Massyn, et al., (2017), the incidence of TB in the Eastern Cape is high, and the burden of TB disease is classified as very high in some districts, including the Sarah Baartman District, as reported in the District Health Barometer of 2016/2017. The Sarah Baartman District falls below all the Annual Performance Plan (APP) targets of the National Department of Health as shown in Table 1.1, below.

Table 1. 1: TB Indicators - Achievement by Sarah Baartman 2016/17

Indicator	APP target	Sarah Baartman
Treatment success rate	84%	77.2%
TB client loss to follow-up (defaulters)	5.4%	10.9%
TB death rate	5%	8%
Drug-resistant T.B. death rate	12%	33.3%

Source: (Massyn, et al., 2017)

In 2016, there were 159 patients enrolled on treatment within the Sarah Baartman district, as reported on EDR-web, the electronic drug-resistant TB register. Between 2015 and 2017, the Sarah Baartman District showed an MDR treatment success rate

of between fifty-nine and sixty-five percent. This low treatment success rate was documented for patients utilising the long-term treatment plan of over 24 months.

However, the causes of this highly drug-resistant TB are not clear. Sarah Baartman is a district with a very high unemployment rate, with around fifty-one per cent of its population living in poverty. Consequently, about 168,000 people in this district rely on one or other government grants. Therefore, this study wants to determine the factors contributing to these high numbers of DR-TB patients in the Sarah Baartman District and the trends of the disease over five years.

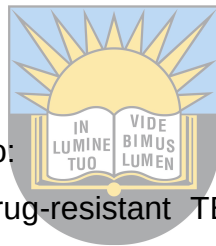
1.4 Purpose of the study

The purpose of the study was to conduct a retrospective analysis of drug-resistant TB patients' medical records to determine trends and factors contributing to drug-resistant TB during the period between 2016 and 2020 in the Sarah Baartman District.

1.5 Objectives of the study

The objectives of the study were to:

- Describe the trends of Drug-resistant TB in the Sarah Baartman District between 2016 and 2020.
- Identify the factors contributing to drug-resistant TB between 2016 and 2020 at Sarah Baartman District.



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1.6 Research questions

- What were the trends of drug-resistant TB in the Sarah Baartman District between 2016 and 2020?
- What were the factors contributing to the occurrence of Drug-resistant TB in the Sarah Baartman District between 2016 and 2020?

1.6 Significance of the study

The results and recommendations from this study could assist in the prevention of the spread of DR-TB and improve the care of patients with drug-resistant TB in the Eastern Cape. They might strengthen the knowledge and skills of the healthcare professionals in drug-resistant care and encourage the patients to adhere to their treatment. In

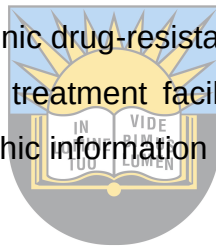
addition, the findings might be used to teach communities and families of patients with drug-resistant TB to assist the patients with adhering to their treatment and preventing the spread of TB in the community.

1.7 Limitations of the study

The main limitation of the study is that it was carried using data from one centre in one district of the Eastern Cape province and this limits the generalizability of the results to the whole province, let alone nationally.

1.8 Delimitations of the study

Delimitations can be explained as the boundaries that the researcher will set to control the range and scope of the study to make the study achievable (Theofandis & Fountouki, 2019). This study was limited to medical records of adult patients diagnosed with drug-resistant TB at Sarah Baartman District between 2016 and 2020 using data contained in the electronic drug-resistant (EDR) T.B. register. EDR-web is a database populated by DR-TB treatment facilities in the Eastern Cape with all relevant healthcare and demographic information of patients diagnosed with DR-TB.



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1.9 Definition and operationalisation of concepts

Adverse drug reactions: The South African Health Product Regulatory authority defines adverse drug reactions or side effects as any unfavourable or unexpected medical occurrence presenting during treatment with a health product (SAHPRA, 2020)

Drug-resistant Tuberculosis: Tuberculosis that can no longer be treated by conventional first-line drugs due to the patients having developed resistance to one or more of the first-line drugs.

Drug susceptibility: The ability of the drug to inhibit the growth of mycobacterium.

Outcome of previous TB treatment: According to the RR-TB Clinical Guidelines (National Department of Health, 2023) the following are outcomes that may be utilised to describe the end result of TB treatment:

Cured: A pulmonary patient with bacteriologically confirmed DR-TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response and no evidence of failure (clinical deterioration).

Loss to follow up: A patient who has interrupted their treatment for more than consecutive months

Died: A patient who dies for any reason during treatment

Treatment failure: A patient whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy (change of 2 or more drugs).

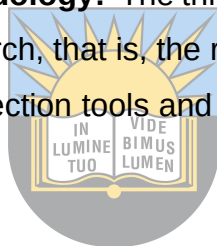
Retrospective analysis: Retrospective analysis utilises data collected for reasons other than the current research. In this study, the researcher utilised the data of drug-resistant TB patients collected as part of the national TB notification system. TB and DR-TB are notifiable conditions, and all health facilities treating such patients should report this to the national health authorities.

1.10 CHAPTERS LAYOUT

Chapter One: Introduction: This chapter provides a brief overview and introduction of the study. It discusses the problem statement, purpose of the study, research questions and objectives of the study. Finally, the concepts contained in the study are operationalised.

Chapter Two: Literature review: The second chapter explores the research problem in relation to published research. Drug-resistant tuberculosis is defined, and the aetiology is discussed. Finally, the strategies used to counteract drug-resistant tuberculosis and the current trends experienced within the field of drug-resistant tuberculosis are explored.

Chapter Three: Research Methodology: The third chapter outlines the methodology employed in conducting the research, that is, the research design, setting, population size, sampling methods, data collection tools and techniques, data analysis methods and ethical considerations.



Chapter Four: Research findings, presentation and discussion of results: This chapter contains the research results and a discussion thereof. This chapter discusses the findings of the study in relation to the available literature.

Chapter Five: Conclusions and recommendations: Represented in this chapter is an overview of the strengths and limitations of the study as well as conclusions and recommendations that can be drawn from the findings.

1.11 Chapter Summary

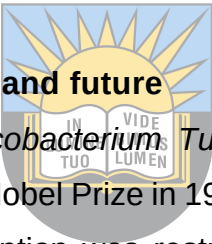
This chapter presented the background to the study, the prevalence and impact of tuberculosis and drug-resistant tuberculosis, as well as the research questions and objectives. The study aimed to describe the observed trends of drug-resistant TB and identify possible contributory factors. In addition, the research objectives and research questions were presented. In the next chapter, a review of published literature is presented.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

A literature review is a process by which the researcher gathers in-depth, critical knowledge regarding a subject or topic. It is based on published evidence and makes up the body of established knowledge. A literature review is secondary information and relies on the researcher to make a personal summary. Therefore, it should be an unbiased appraisal (Winchester & Salji, 2016). For the literature review in this study, electronic data searches were conducted. Databases such as Pubmed, MEDLINE and ScienceDirect were utilised as well as online sites such as Google Scholar. In addition, published dissertations and theses from students in South African universities were also accessed through the University of Fort Hare website. In the literature review, the researcher expands on the evolution of tuberculosis treatment, the emergence of drug resistance, causal factors and trends regarding TB and MDR TB.

2.2 Tuberculosis: past, present and future



Robert Koch first discovered *Mycobacterium Tuberculosis* in 1822, for which the acclaimed physician received the Nobel Prize in 1905. During his time, the placement of patients suffering from consumption was restricted to living in sanatoriums and isolation from the community (Murray et al., 2015). Medications used to treat TB were slowly developed, and the first ones to be used were Streptomycin and PAS (Para-amino salicylic acid) in the 1940s (WHO, 2022). The combination of the two worked better than one individual treatment. With the discovery of Isoniazid in the 1950s, the use of triple combination therapy in the treatment of tuberculosis continued. The next drug to enter the TB treatment sphere was Ethambutol, initially used in patients who showed re-emergence of tuberculosis after treatment with the other agents. Rifampicin was first used in 1966, with Pyrazinamide later introduced after establishing the least toxic and most effective dose. Some drugs currently used in drug-resistant tuberculosis were also discovered in the late 1960s and 1970s (Murray, et al., 2015); (Cohen, et al. 2015).

More than 50 years later, the same medication is still used as the first-line treatment against tuberculosis. Although historically, patients were treated for a more extended period, many changes and interventions led to decreased treatment time, reduced side

effects, and more rapid initiation of treatment. With the advent of modern technology, there is the convenience of GeneXpert® which can diagnose TB and resistance to Rifampicin within a few hours, depending on laboratory availability (WHO, 2022). This innovation has strengthened the fight against tuberculosis and has impacted survival rates due to the prompt initiation of appropriate treatment. In addition, the roll-out of the TB Lam test, a point-of-care urine test that can identify Extra-pulmonary TB in immune-compromised patients, has led to improvements in rapid diagnosis (NDoH, 2021). Currently, prophylactic TB treatment, INH, is given to people living with HIV and those in close contact with active DS-TB cases.

The World Health Organization recognises that great strides must be made to decrease the disease burden by 2025. Therefore, the last pillar of the End TB strategy is to "intensify research and innovation". The focus is developing a vaccine that could be used before and after exposure to tuberculosis and affordable rapid point-of-care diagnostics, eliminating the need for laboratory diagnosis of tuberculosis (WHO, 2020). Although TB diagnosis, treatment and management have come a long way, many obstacles still exist, and drug resistance is just but one of them.

2.3 Prevalence of DR-TB

"Responding to drug-resistant TB is probably one of the most profound challenges facing global health" (Gandhi, Nunn, Dheda, Schaaf, Zignol & van Soolingen, 2010). The World Health Organization's Global Tuberculosis Report of 2020 states that in 2019, globally, 465 000 people were infected and diagnosed with DR-TB. Although this number shows a decrease of 3.69% from the previous year, it is still unclear what effect the COVID-19 pandemic had on treatment and access to care worldwide.

The three world regions with the highest DR-TB burden are South East Asia (171 000), Western Pacific (101 000) and Africa (77 000). The Americas have the lowest burden, with only 11 000 infections. The countries with the highest number of drug-resistant tuberculosis cases are India, China and the Russian Federation with 27%, 14% and 8% of global cases, respectively. In Africa, Nigeria leads with an estimated 21 000 infections, followed by South Africa with 14 000 infections. The African country with the lowest number of DR-TB infections is Zimbabwe, with 1 200 infections. In the

Eastern Cape, 1 791 DR-TB infections were recorded in 2019. Out of this number, 155 were in the Sarah Baartman District.

2.4. Risk factors associated with DR-TB infection.

2.4.1 Adherence

Treatment adherence was identified as a critical factor in curing tuberculosis (Bristow, et al.,(2013). Matteelli, et al.,2014 concur with this statement and reiterates that adherence to the correct treatment regimen is the cornerstone in controlling and preventing DR-TB (Matteelli, et al., 2014). Treatment failure remains an obstacle in attaining the WHO goal of a TB incidence rate of less than 10%. Inadequate adherence to TB treatment leads to the emergence of DR-TB and worsens symptoms and increases TB morbidity and mortality (Craig & Zumla, 2015).

In a qualitative study done in Kwazulu-Natal (KZN) province of South Africa, regarding perceptions of patients co-infected with HIV and TB and their treatment adherence, participants preferred taking anti-retroviral treatment over DR-TB treatment. The participants indicated that the pill burden of up to 32 tablets a day-for DR-TB, having to take their treatment under the supervision of a health care worker and mostly the stigmatisation surrounding taking this treatment often contributes to non-adherence (Daftary, et al., 2014). However, a similar study in Addis Ababa, Ethiopia, showed that patients had no problems with adhering to their medication due to their awareness of the risks of non-adherence to treatment (Sahile, et al., 2018). A prominent feature of the study done in KZN was that 91% of the participating patients were unemployed. In contrast, the participants in the study in Addis Ababa showed an eighty percent employment rate. The study in Addis Ababa did not mention the HIV status of participants, which was one of the criteria for inclusion in the KZN study.

In a quantitative study focusing on HCWs involved in TB care in different health districts of South Africa, respondents to a self-administered questionnaire mentioned that patients defaulted to treatment because they felt better (Bristow, et al., 2013). In the study in Addis Ababa, Ethiopia, participants believed that tuberculosis is caused by cold air while others believed it is caused by contaminated foods (Sahile, et al., 2018). The participants in a study in KZN felt that the intensive counselling they

received regarding their adherence to ARVs caused them to be more adherent and accountable to their treatment. Regarding TB treatment, the responsibility is transferred chiefly to the administering HCW (Sahile, et al., 2018). MDR-TB patients shared experiences of social exclusion following diagnosis of DR-TB with community members being scared of being infected by the patient (Daftary, et al., 2014). About two fifths (39%) of health care workers participating in a study identified stigma as a factor that plays a significant role in patients defaulting TB treatment (Bristow, et al., 2013).

2.4.2 Human Immunodeficiency Virus (HIV) and DR-TB co-infection

TB and HIV co-infection has been named as one of the deadliest co-morbidities. Each by itself is just as dangerous, but the combination is deadly. HIV infection already reduces the immune response of the body to suboptimal levels. In this state, the body is most susceptible to Mycobacterium tuberculosis infection (Gandhi, et al., 2010). The disadvantage is that when the body is infected, it loses its ability to counteract or fight other infections and to speedily and uneventfully recover. The TB-HIV coinfection death toll is highest in people infected with HIV who are not yet on anti-retroviral treatment and have a meagre CD4 count (Nair, Velayutham, Kannan, Tripathy, Harries, Natrajan & Swaminathan, 2017). The CD4 count measures the ability of the body to elicit an immune response.

A patient co-infected with HIV will initiate anti-tuberculosis medication and only be initiated on anti-retroviral medication around eight weeks later. The reasoning is that when the body is exposed to ARVs, the immune system recovers very well and may lead to immune reconstitution inflammatory syndrome (IRIS). IRIS leads to an over-stimulated immune response which can be fatal. Initiation of ARVs has been found to positively influence adherence to ARVs and TB medications (Daftary, et al., 2015). However, following a retrospective study by Anastasis and colleagues on HIV and DR-TB in Durban, South Africa, they found that an HIV diagnosis did not necessarily indicate a predisposition for infection with DR-TB. Furthermore, they concluded that HIV did not exacerbate the rate of DR-TB infection (Anastasis, Pillai, Rambiricht, & Abdool Karim, 1997).

2.4.3 Gender

In some studies, the patients infected with DR-TB were found to be predominantly males (Oostvogels, et al., 2022). Researchers speculate on the reason behind this phenomenon. Males are 60% more likely to default on TB treatment than females (Kigozi, et al., 2017). Positive health-seeking behaviour by males is not commonplace in South Africa. Furthermore, males are prone to late presentation for illness; they are usually the breadwinners and prefer not to miss work (Skinner & Claassens, 2016); (Wrohan, et al., 2022). In addition, males tend to be less compliant with medication when they feel better. Males are also more prone to other risk factors for TB and DRTB, such as alcohol abuse and smoking (Nair, et al., 2017). The distribution of infections was equal between the two genders (Merza, et al., 2011). Conversely, in the study entitled Epidemiological Trends of Drug-Resistant Tuberculosis in China from 2007 to 2014, females were found to be more likely to be diagnosed with DR-TB than males.

2.4.4 Adverse Reaction to DR-TB medication

In a univariate analysis done in China, one of the predisposing factors to developing DR-TB is the presence of adverse reaction during the treatment of DS-TB. This resulted in patients not completing treatment and developing resistance. Adverse reactions and unfavourable outcomes for DR-TB patients are caused by their reluctance to take the offending medication (Chen, et al., 2013)

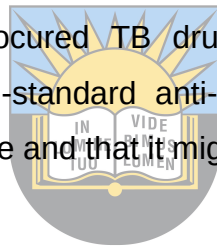
2.4.5 Age

Globally, the incidence of TB is the highest in the age category of 25 – 34 years in both males and females (WHO, 2020). A retrospective study in Iran shows that the median age of people infected with TB was lower than 40 years (Merza, et al., 2011). According to Skrahina, et al., (2012), patients below 35 years showed an odd ratio of double that for patients over 35 years of age. In Ethiopia in 2020, the mortality rate in patients diagnosed with DR-TB was the highest in the age group above 60 years (Alemu, Bitew & Worku, 2021). In Asia, Eastern Europe and Latin America it was reported that males above 40 years showed a higher mortality rate for DR-TB than any other group (Nair, et al., 2017).

2.4.6 Inferior quality medication

Treatment for DR-TB has exponential costs. In some low to middle-income countries, the patients must carry the costs of treatment of TB and DR-TB. The drugs used to treat DR-TB are extremely expensive and given the extended duration of treatment with these drugs, it is safe to assume that it might lead to potential financial hardship for families. The treatment cost for a course of drug-sensitive TB was US\$40 (R655) in 2020 vs US\$1000 (R16 393.44) for drug-resistant TB (WHO, 2020). The WHO recognises this risk, and one of the aims of the End TB strategy, is to have 0% of households that face catastrophic costs due to TB. The ultimate goal is for all to have Universal Access to Healthcare (WHO, 2021).

The unaffordability of quality drugs opens up an opportunity for unscrupulous drug manufacturers to supply sub-standard medication. These medications do not comply with international standards, such as the active pharmaceutical ingredient (API) levels. Researchers tested privately procured TB drugs in 19 different countries and concluded that falsified and sub-standard anti-tuberculosis medication is readily available in the private marketplace and that it might contribute to the development of DR-TB (Bate, et al., 2013).



Conversely, in South Africa, TB and DR-TB diagnoses and treatment is free of charge and subsidised by the government through budget allocations and conditional grants from sponsors. Indirect costs related to TB care and treatment, such as transport fees, affected the poorest and most economically vulnerable people the most (Foster, et al., 2015).

2.5 Acquired DR-TB versus primary drug resistance

As mentioned in the introduction, DR-TB infection develops in two distinct pathways. One pathway is infection with the primary drug resistance and the other is acquiring resistant mutations following assumed non-adherence to TB treatment. Currently, the two schools of thought around the emergence of drug-resistant TB are competing for relevance. Resistance can be attributed to incomplete treatment, non-adherence or poor quality of medication (Shah, et al., 2017; Matteelli, et al., 2014). On the other hand, (Sun, et al., 2018) did extensive genetic testing in Myanmar's high TB burden

area. They found that most drug-resistant strains resulted from improper treatment of possibly drug-sensitive TB. However, a few cases could be linked to direct transmission. Transmission of the resistant strain by genetic sequencing and confirmed no household contact with XDR (Gandhi, et al., 2010). However, all patients diagnosed with XDR-TB visited the same rural hospital where two health workers were also diagnosed with XDR-TB, which suggests possibility of nosocomial infection.

The first recorded outbreak of extensively drug-resistant TB happened in Kwa-Zulu Natal, in South Africa in 2006. That is when the world was alerted to the involvement of a disease that had been a part of humanity for centuries into a major public health risk (Oostvogels, et al., 2022). Over time, it has remained one of the diseases with the highest morbidity and mortality rates. In 2019, the WHO estimated that 3.3% of new cases and 18% of the previously treated case showed drug-resistant tuberculosis. The MDR/R-RTB incidence cases in 2019 are estimated at 465 000, with around 14 000 recorded in South Africa (WHO, 2020). Resistance to first-line anti-tuberculosis medication infers that the patient will use treatment that consists of more expensive, toxic, and possibly inaccessible second and third-line medication.

As reported by Mlambo, et al. (2008), both pathways of drug-resistant tuberculosis development have been seen in South African settings, and both play an equally important role. Therefore, by acknowledging the possibility of both pathways, interventions can be more effective in curbing the spread of drug-resistant tuberculosis.

2.6 Predictors of mortality and treatment success

Before the introduction of anti-tuberculosis medications, the mortality rates from TB were as high as 70% of patients diagnosed. DR-TB has historically been associated with adverse clinical outcomes, especially in resource-limited settings. Globally, the reported number of patients who succumbed to DR-TB in 2017 was fifteen percent which has steadily decreased since 2012 (WHO, 2020). Different factors were found to be associated with higher mortality rates, such as HIV co-infection, gender, age, complications of TB infections, type of drug resistance (MDR-TB lower mortality rate than X-DRTB), malnutrition and substance abuse (smoking, alcohol and illegal substances) (Alemu, et al., 2021). These same demographics and characteristics lead

to the most unfavourable outcomes. Another indicator of mortality in DR-TB patients was the long delay in the initiation of treatment of DR-TB (Nair, et al., 2017).

2.7 Evolution of treatment guidelines for DR-TB

Drug-susceptible tuberculosis is treated with a simple six-month regime of first-line anti-tuberculosis medication available in a fixed dose combination, that is, four different anti-tuberculosis medications contained within one tablet. Patients are treated according to weight with the fixed-dose combination. DR-TB presents a challenge, as it is usually resistant to one or more active ingredients in first-line treatment (WHO, 2019).

Treatment of DR-TB consists of using more than four different agents, depending on the resistance profile. The combination is individualised for each patient and can be adjusted depending on response and possible adverse reactions experienced. The duration of treatment for DR-TB lasts for up to 18 months.

Bedaquiline and Linezolid are medications previously used as antibiotics but are now repurposed for use as anti-TB drugs. There had been an associated increased risk of death during Phase 2b trials, so the WHO added a caution to the use of Bedaquiline. However, since South Africa is a high-burden country, South Africa received approval to use Bedaquiline as a part of treatment for DR-TB in patients not responding to other second-line treatments. This programme was named the Bedaquiline Compassionate Access Programme. This programme, which was run in a few countries, showed reduced mortality and effective treatment of DR-TB (Schnippel, et al., 2015). In 2016, the World Health Organization recommended a shorter regime for DR-TB in some instances. The duration would now be shortened to between nine and twelve months. This shortened regime included new drugs such as Bedaquiline and Linezolid.

2.8 Summary

In this chapter, a literature review and an in-depth review of published articles were presented. The background to the discovery of tuberculosis and its evolution to DR-TB was given. It is shown that TB is still as relevant and deadly as it was upon discovery in 1905. South Africa remains a high TB and DR-TB burden country. It is ranked the second highest in infections on the African continent. The discussion of risk

factors associated with DR-TB showed that non-adherence to treatment is central to the development of DR-TB. Gender, age and TB treatment experiences were identified as factors associated with the development of DR-TB. Transmission of a resistant infection or other factors such as non-adherence form part of the pathways leading to DR-TB development. According to the research, a higher mortality rate is seen among patients with HIV co-infection, males, of old age and non-compliant to TB treatment. Finally, the changes in DR-TB guidelines show repurposed medication as a backbone of current treatment guidelines. In chapter three, the methodology used to carry out the study will be presented.



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CHAPTER THREE: RESEARCH METHODOLOGY

3.1 Introduction

Research methodology is deciding on the most appropriate and ethical way to satisfy or answer a research question. Research methodology can be divided into qualitative, quantitative and a combination of the two, the mixed-method approach. The choice of the research method is the most crucial step in the research process. It involves selecting the most appropriate research design based on the research questions to be answered and availability of participants (Goyal, 2013). The quantitative observational study design was chosen for this study since no intervention was being tested (Mann, 2003).

3.2 Study design

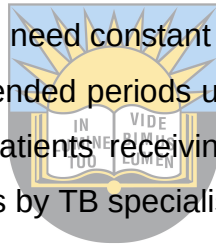
This quantitative study is descriptive and retrospective. A retrospective study is one that utilises data already collected for purposes other than research. In this study, the data source were medical records. A cross-sectional study involves a predefined population at a specific time, documenting them simultaneously and measuring all variables and outcomes simultaneously (Goyal, 2013). The study investigated the trends and causal factors of DR-TB in the Sarah Baartman district from 2016 to 2020. There are many advantages to using this study design, such as it is relatively easy and quick to complete. In addition, it monitors and evaluates public health strategies and can help indicate prevalence. A disadvantage of this type of study is that it is not in-depth and can not elaborate on the "why". There is also a limitation in identifying the cause-and-effect relationship between variables (Rezigalla, 2020; Mann, 2003). The retrospective design was used because the study focused on reviewing patient medical records from 2016 to 2020.

3.3 Study setting

Sarah Baartman district is the largest of all districts in the Eastern Cape. In 2015, the Eastern Cape had a TB incidence rate of 692 per 100 000 and, in the same year, Sarah Baartman district had the highest incidence rate of 1022 per 100 000 population, almost double the national incidence rate of 520 per 100 000 population (Massyn, et al., 2017). In 2016, the Sarah Baartman district enrolled 159 patients on

DR-TB treatment. These patients were known to have the experience of defaulting or not completing their TB treatment.

This study was conducted in the Cambedoo health sub-district of the Sarah Baartman district of the Eastern Cape Province of South Africa. This health sub-district was selected because there is a specialised DR-TB hospital called Margery Parkes TB Hospital situated in Graaf-Reinet. The health sub-district is made up of the Dr Beyers Naude and the Blue Crane Route municipalities. The population in this sub-district is 115 293 and spreads over nine rural towns, including Graaf-Reinet and Somerset East. There are 24 clinics, one Community Health Centre (CHC) and five district hospitals, and active mobile clinics to visit outlying farming areas. Care for patients diagnosed with tuberculosis is rendered from all these facilities, and patients are usually allocated to one facility to ensure accurate data management in this sub-district is the Margery Parkes TB Hospital. This facility houses patients who are at risk of defaulting treatment and therefore, need constant surveillance. Patients are admitted at this specialised hospital for extended periods until culture conversion or treatment completion. Ambulatory DR-TB patients receiving outpatient care are followed up monthly through outreach activities by TB specialists, CHC and clinics.



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3.4 Study population

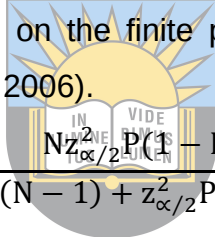
A study population is a set of individuals from which a sample is taken. A population in research does not necessarily have any bearing on the physical or geographic location of the study. Therefore, observations made by a study are not always generalisable to all other populations. However, a population will exhibit common characteristics among the group and satisfy the criteria set out by the researcher (Banerjee & Chaudhury, 2010). The population of this study were records of all adult patients enrolled on DR-TB treatment in the Cambedoo health sub-district of the Sarah Baartman district between January 2016 and January 2020.

3.5 Sampling

Sampling is a process through which participants are selected to conduct a study. Accurate inferences can be drawn when the sample best represents the population. In this study, simple random sampling was employed (Banerjee & Chaudhury, 2010). The available records and datasets of patients diagnosed with DR-TB from 1 January

2016 to 30 December 2020 in the Camdeboo sub-district were accessed from the EDR-web for patients on DR-TB treatment in the Sarah Baartman district. Unique numbers were allocated to the records on a spreadsheet. This was used on the random number generator in Microsoft Excel® to select the records that participated in the study. Available patient records based on the inclusion criteria were included in the study. The participating records were selected from available records and data sets retrieved from EDR-web for patients on DR-TB treatment in the Sarah Baartman district.

The justification of sample size is an integral part of the design of a study. Calculating an adequate number of participants is critical in detecting significant results (Pourhoseingholi, et al.,2013). This study aimed at approximating the prevalence of drug-resistant TB among TB patients in the Sarah Baartman district. The population of TB patients during the 2016-2020 period was 17 671. The required sample size for this study was determined based on the finite population sample size calculation formula given below (Naing, et al., 2006).



$$n = \frac{Nz_{\alpha/2}^2 P(1 - P)}{d^2(N - 1) + z_{\alpha/2}^2 P(1 - P)}$$

where n is the required sample size, N is the population size, α is the significance level, P is the hypothesised drug-resistant TB prevalence, $z_{\alpha/2}$ is the two-tailed Z test critical value and d is the margin of error.

Based on a population size of 17671 patients, a 5% significance level, a 5% margin of error, and a 5% hypothesised drug-resistant TB prevalence; the minimum sample size was estimated to be 72 patients. However, in order to cater for the possibility of incomplete information on some patient records, a sample of size of 100 patients' records was used in this study.

3.6 Inclusion criteria

Inclusion criteria identify participants in the study in a reliable, uniform, objective and consistent manner (Garg, 2016). In this study, all adult patients' records on the EDR-

web from January 2016 to January 2020 in the Sarah Baartman District were eligible for inclusion in the study.

3.7 Exclusion criteria

Exclusion criteria are the distinguishing traits that render the participants unfavourable for inclusion in the study. In addition, any factor that pre-exists and that might confound the outcome must be excluded (Garg, 2016). In this study, all adult patients' records on the EDR-web from January 2016 to January 2020 in the Sarah Baartman District with missing or incomplete data represented on EDR-Web were excluded from the study. Duplicate entries of participants were also excluded. All patients under 18 years were excluded from the study.

3.8 Data collection

Data collection is the process through which a researcher collates information about the research question using different sources and techniques (Hox & Boeije, 2005). The researcher utilised secondary data captured from the medical records and other relevant documents on the EDR web. Data were collected by reviewing and analysing the patients' records and relevant documents in the Department of Health through EDR-web. A data collection checklist was used to review patient medical records. Using secondary data can be especially helpful for the researcher with time constraints and limited funding.

3.8.1 Research instrument

The researcher adopted a standardised checklist to extract the information from the medical records captured on the EDR web. The checklist included a section dedicated to demographic information, then a section related to all relevant medical history, such as results, and medication used. The final section was aimed at assessing the treatment outcome. The initial data collection tool was verified and populated into a Microsoft Excel spreadsheet.

3.8.2 Pre-testing

Pre-testing was conducted to ensure that the data collection tool, design of the study and analysis thereof would lead to the desired outcome (Polit & Beck, 2004). Pre-testing of the checklist was done with 12 patient files that did not form part of the actual

study. The results from the pre-testing allowed the researcher to analyse whether the appropriate questions were asked. It assisted in developing the researcher's data collection skills and streamlining the questions to adapt to the data extraction tool. Reliability and validity were proved through the pre-testing.

3.8.3 Data collection procedure

Data collection allows us to collect and analyse the information we need for research purposes. Therefore, systematic and accurate data collection is integral to completing the research process. In this study, the researcher used information from the Eastern Cape Department of Health on DR-TB, a notifiable condition in South Africa. Data collected by all institutions that treat patients with DR-TB are captured on a web-based program called EDR-web. Information such as demographics, dates of initiation and completion of treatment, previous treatment history, all results of blood work done, and reported side effects are captured on this web-based database.

3.9 Data analysis

Statistical analysis allows the researcher to summarise, organise and communicate numeric data (Polit & Beck, 2004). Initially, the researcher populated a Microsoft Excel spreadsheet with the data extracted from patient medical records. Then, with the help of a statistician, frequency distribution tables were used to summarise the categorical variables. At the same time, descriptive summary statistics were used for the numerical/quantitative variables, namely, age (years), CD4 count, diagnosis to treatment delay (days) and treatment duration (months).

3.10 Ethical considerations

The ultimate purpose of research ethics is to protect the research participants at all costs (Terre Blanche et al., 2006). Research should not do more harm than good whenever it is conducted. Ethical clearance for the study was obtained from the University of Fort Hare and approval was obtained from the Eastern Cape Department of Health research directorate. The Sarah Baartman District Manager approved and granted permission to access patient records.

Participant information was protected and kept confidential by restricting access to the information to no one else except the researcher. In addition, all information that might be used in determining a patient's identity was de-identified. De-identification was done by assigning a sequential number of unique numbers to each participant instead of having any names, identity numbers and addresses. The personal information collected from records was kept safe and secure on a password-protected personal desktop computer in a locked office that was only accessible to the researcher. The information shared with the statistician for analysis purposes was de-identified to protect the participants' identities.

For research involving the collection of identifiable data from databases, consent was given for the collection, storage and analysis of such data (WMA, 2013). The research study did not involve human participants and did not require explicit informed consent. The researcher applied to the ethics committee for the waiver of consent to analyse medical records and received permission from the Eastern Cape Department of Health (ECDoH) to use data from webDHIS, EDRweb, and other facility-held patient records.

According to the Declaration of Helsinki (2013), gaining new knowledge through research can never take preference over the rights and interests of participants. Participants had minimal risk involved since they were not actively involved in the process. Minimal risk is no more risk than is encountered in daily activities and tasks (Polit & Beck, 2004). At most, there could be the risk of loss of data with identifiable information included. The researcher took every precaution to guard against such losses by keeping information secure on a password-protected personal desktop computer in a locked office used by the researcher with no unauthorised access. There were also no direct benefits to any participant or organisation giving consent for the use of medical records.

3.11 Validity and reliability

Validity is the ability to generalise the study results to different samples or settings (Hart & Aithal, 2022). The results will stay the same even when a different researcher conducts the study. Validity indicates whether the study results are well-grounded, irrefutable and persuasive. In this study, the researcher utilised content validity. The method has to cover all relevant issues related to the subject to produce relevant

results. Standardised checklist was used to collect the data and pre-testing was done during analysis to validate the results. The expertise of the academic supervisor and inputs of a statistician were incorporated into the execution of the study. The expertise of medical officers at the drug-resistant tuberculosis hospital and the study supervisor ensured face validity.

Reliability indicates whether the information contained in a study is accurate and consistent, and statistical reliability means that it can also be generalised to a broader sample (HR, Aithal 2020);(Polit & Beck, 2004). It should also be noted that the researcher used a standardised instrument to extract factual information from patient medical records and secondary data was checked for errors during collection and analysis.

3.12 Chapter Summary

This chapter explored the methodology related to the study, including the study design and setting. The study was quantitative and descriptive. The study setting was in the Cambedoo health sub-district in the Sarah Baartman district of the Eastern Cape. The calculated sample size was 72, but 100 participants were randomly selected to be part of the study in order to cater for possibility of missing information on some records. Data collection was done via a standardised tool to extract information from EDR-web and was forwarded for statistical analysis. Special attention was paid to all ethical issues during data collection and analysis. The next chapter presents and discusses the data analysis results and study findings.

CHAPTER FOUR: PRESENTATION AND DISCUSSION OF RESULTS

4.1 Preamble

In the previous chapter, the research methodology and data collection were discussed. This chapter presents and discusses the findings following the data analysis. The results illustrate the DR-TB trends observed in the Cambedoo health sub-district. The contributing factors and pre-disposing factors observed are presented in this chapter.

4.2 Demographic characteristics

4.2.1 Age

The age distribution of the 100 participating patients' records of adult patients aged between 22 and 83, with an average age of 40.8 years and a median of 39 years. Therefore, it implies that half of the participants were at least 39 years old. The results show that the age groups 31 to 40 years had the highest number of participants at 31%, followed by those aged between 21 and 30 at 25% and those aged 41 to 50 at 23%. Comparatively, a study done in Khaylethisa in the Western Cape, the mean age of participants infected with DR-TB was 32.99 ± 14.52 years. This result concurs with (Merza, et al., 2011) who conducted a study on DR-TB in Iran found that the median age of participants in Iran was 40 years. A retrospective cohort study in Kwazulu Natal shows that 62% of the DR-TB cases were in the age group of 38-39 years (Anastasis, et al., 1997). The median age of patients diagnosed with DR-TB was 33 years (Anderson, Pietersen, Shepherd, Bian, Dheda, Warren, Sterling & van der Heijden, 2022). Global statistics also show that younger patients are more prone to infection with DR-TB, but mortality due to DR-TB increases with age (WHO, 2020). A study conducted by He, et al., (2017), states that MDR-TB and XDR-TB cases were significantly more likely to occur among the older age groups of 42years and above. Whilst Mphande-Nyasulu, et al., (2022) in their study found that the mean age of the MDR-TB and XDR-TB was 50years.

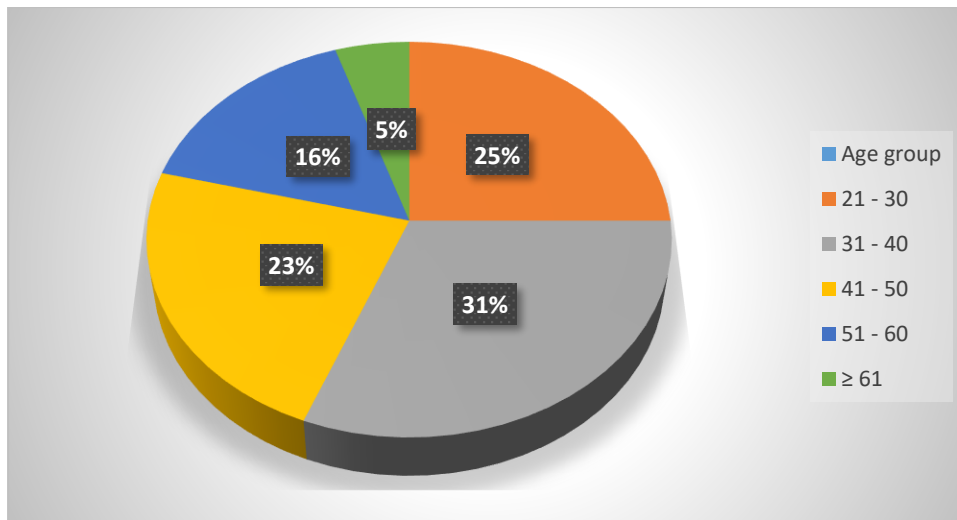


Figure 4.2.1: Age distribution of participants

4.2.2 Gender and HIV history and health profiles

More than half 54 (54.0%) of the patients were living with HIV and 60% of the participating patients were males. The results in the table below show that, of the 54 who were HIV positive, 51 (94.4%) started on antiretroviral treatment. Out of 51 participants who started on ART, 26 (51.0%) were on the first-line regimen, followed by 14 (27.4%) on the second line 5 (9.8%) were on an unknown regimen.

Of the 100 patients, 87 (87.0%) had no other illness, while the remaining 13 (13.0%) had comorbidities such as asthma, diabetes, hypertension, epilepsy and combinations of these illnesses. Diabetes is regarded as one of the risk factors associated with TB and DR-TB (Duarte, et al., 2018). A study done in rural India, found that 31.8% of patients had diabetes and that this higher than the proportion of TB patients with HIV co-infection (Gupta, et al., 2011). In a South African cross-sectional study, it was reported that 16.7% of patients had hypertension and 5.2% of had diabetes (Whitehouse, et al., 2019).

Table 4.1: Distribution of patients by demographic and health characteristics

Characteristic	Category	Frequency	Percentage
Gender	Female	40	40.0
	Male	60	60.0
HIV status	Negative	46	46.0
	Positive	54	54.0
ART started (n=54)	Unknown	2	3.7
	No	1	1.9
	Yes	51	94.4
ART regimen (n=51)	First line	26	51.0
	Renal	5	9.8
	Second line	14	27.4
	Third line	1	2.0
	Unknown	5	9.8
Pregnancy (n=40)	No	40	100.0
Comorbidities	None	87	87.0
	Asthma	1	1.0
	Diabetes	1	1.0
	Hypertension	5	5.0
	Hypertension, Diabetes	4	4.0
	Hypertension, Diabetes, Epilepsy	1	1.0
	Epilepsy	1	1.0

Males, globally, account for more of the TB diagnoses(WHO,2022). They are more likely to acquire they also have a higher incidence of TB than females (WHO, 2022). Males accounted for most of the patients diagnosed with DR-TB (Wrohan, et al, 2022). Males had 42% increased odds of being diagnosed with Rif-resistant TB than females (Coovadia, et al., 2013). In a study looking into the transmission, distribution and resistance-conferring mutations of XDR-TB in the Western Cape, it was found that 54.7% of patients diagnosed with XDR-TB were males (Oostvogels, et al., 2022).

Similarly, Anderson, et al., (2022) also found that most patients diagnosed with DR-TB were male (54%). However, in the Chinese study context, females were more prone to DR-TB infection than males (He, et al., 2016).

DR-TB and HIV co-infection is a significant concern and driver of mortality, globally and in South Africa. In this study ~~shows that~~ most participants (54%) were HIV positive. This is in keeping with global statistics and local studies done on DR-TB which state that HIV co-infection is a driver of DR-TB infection. In a KZN study of the XDR-TB outbreak, 100% of the participants tested positive for HIV. All patients in this study died within 16 days of diagnosis (Mlambo, et al, 2008). Another retrospective cohort study conducted in South Africa found that 47% of the DR-TB patients enrolled were HIV-positive (Geiger, et al., 2021). Two South African studies conducted at different times found no differences between the groups, suggesting that HIV infection may not have a significant link to DR-TB (Anastasis, et al., 2022).

A retrospective cohort study in Vietnam concluded that people living with HIV are at a greater risk of unfavourable treatment outcomes when diagnosed with DR-TB (Wrohan, et al., 2022). There is evidence to suggest that people living with HIV who are on ART have a higher survival rate than those not on treatment (Dheda, et al., 2010).

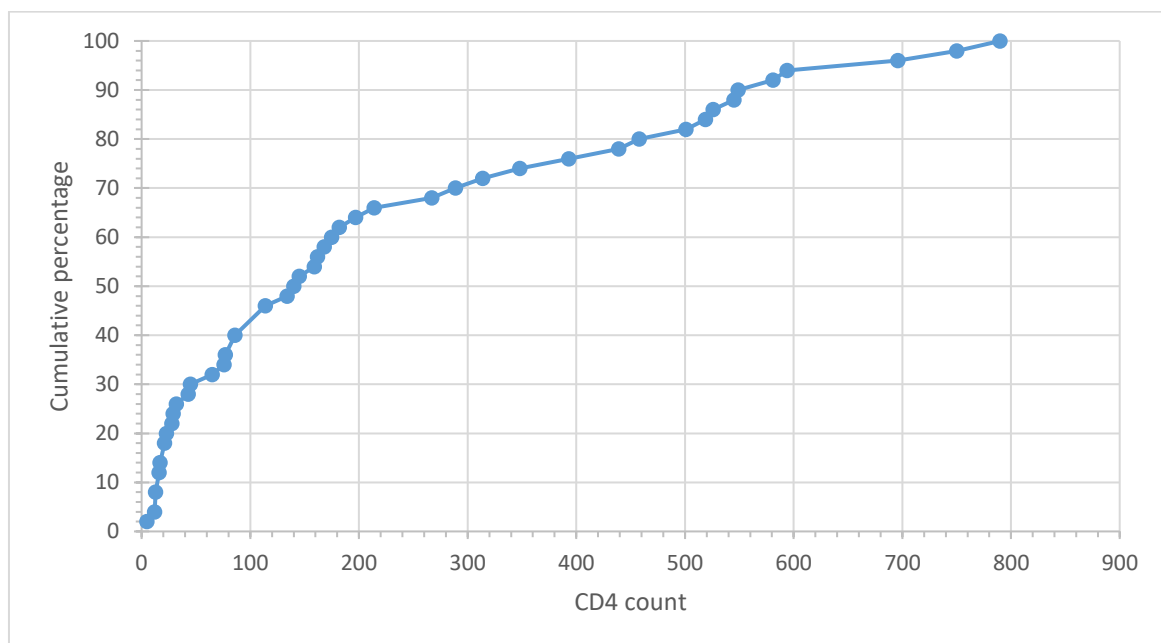


Figure 4.2.2: Cumulative distribution of CD4 count of participants

The CD4 count of HIV-positive participants ranged between 5 and 790, with a mean CD4 count of 226 and a 95% confidence interval of (161.8; 290.2). In another study in South Africa, (Dheda, et al., 2010) found a median CD4 count of 237 (IQR 169: 396) and Kvasnovsky, Cegielski, Peter, Erasmus, Siwisa, Thomas and van Der Walt (2011) found a median CD4 count of 215.

The median CD4 count was found to be 142.5, which means half of the HIV-positive patients had a CD4 count of at least 142.5. The mean was much higher than the median, suggesting that the CD4 counts were skewed to the left. That is, most of the participants had CD4 counts lower than the average value of 226. The upper quartile of the CD4 count was 393, which means that 75% of the HIV-positive patients had CD4 counts of, at most, 393. Figure 4.2.2 above shows the cumulative distribution of the CD4 counts of the patients, and based on that plot, about 70% of patients had CD4 counts less than 300.



There is a limited number of studies reporting on CD4 levels at the baseline of DR-TB initiation and it is recommended complete record keeping so as to improve the response and treatment of co-infected patients (Geiger, et al., 2021). Most patients had baseline CD4 counts in the higher range of at most 393. This could be due to most patients having been on ART long before diagnosis of DR-TB. High baseline CD4 count is a positive indicator of treatment success and favourable outcomes (Wu, et al., 2022). However, in a South African study, it was concluded that CD4 count did not have a significant bearing on survival rate in DR-TB patients (Dheda, et al., 2010).

4.3 Tuberculosis treatment history

4.3.1 Distribution of patients by a previous TB treatment regime

With regard to TB treatment history, 66 (66.0%) of patients had had previous TB treatment and 55 (83.3%) of them had Rifampicin-sensitive TB, 8 (12.1%) had MDR-TB and 3 (4.6%) had Rifampicin-resistant-TB. Thirty-four patients had no previous exposure to TB drugs and were classified as new patients.

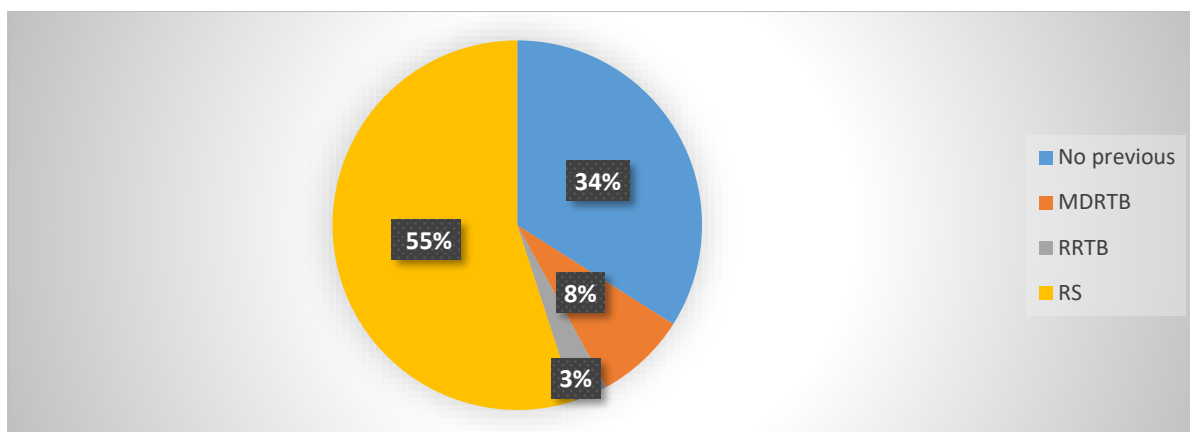


Figure 4.3.1: Distribution of patients by previous regime

Sixty-six percent of participants had previously received treatment for TB. Of these, 83.3% were treated for drug-sensitive TB, 12.1% were treated for multidrug-resistant TB and only 4.6% for Rifampicin-resistant TB. Previous exposure to TB treatment is one of the risk factors in the development of drug-resistant TB (Kvasnovsky, et al., 2011; Merza, et al., 2011)). In Vietnam, previous treatment with anti-TB drugs was reported for 82.7% of the participants (Wrohan, et al., 2022). A study in Belarus indicated that 76.5% of DR-TB patients had a history of previous TB treatment (Skrahina, et al., 2012). About 6.7% of participants who were previously enrolled on TB treatment were diagnosed with DR-TB in South Africa in 2013 (Klopper, et al., 2013).

4.3.2 Outcome of previous TB treatment

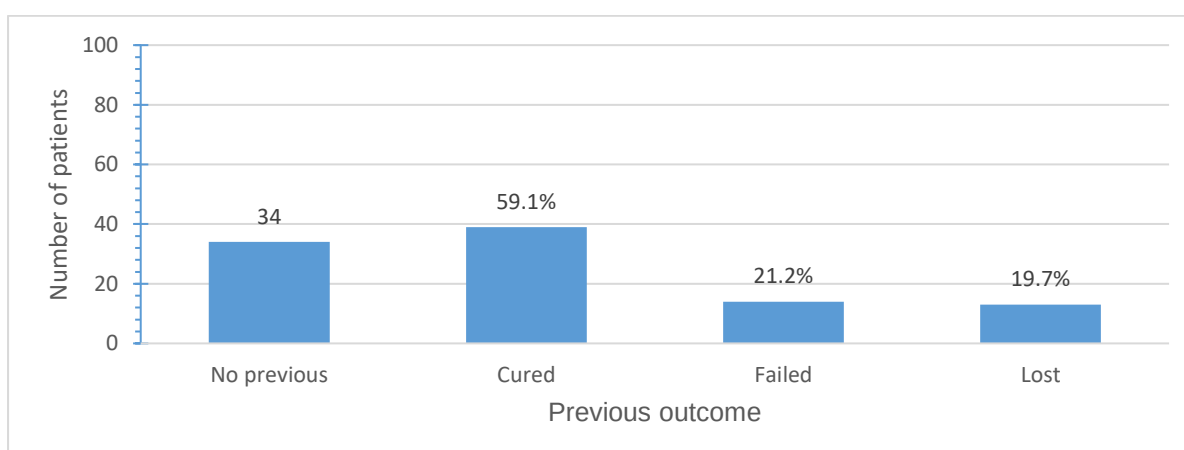


Figure 4.3.2: Distribution of patients by previous outcome

Following the diagnosis of these patients with previous treatment history (n=66), 59,1% were cured, 21,2% failed the treatment regime, and 19.7% were lost to follow-up. Failure of the regime is defined as non-conversion of sputum to negative in the last three cultures. Therefore, treatment failure can be ascribed to non-adherence (Tesfahuneygn, et al., 2015). Thirty-four percent of participants had no history of previous TB treatment and are therefore assumed to display primary resistance. This group was therefore assumed to be infected with an already resistant strain and this is mainly due to transmission and exposure to an infected person.

4.4 Current DR-TB infection

4.4.1 Site of Infection

The majority (97%) of patients were diagnosed with MDR-TB of pulmonary origin. This is in keeping with trends observed in other studies (Schnippel, et al., 2015). It is the most common site of TB infection. This suggests that literature on extra-pulmonary DR-TB is scarce. In an Indian study on extra-pulmonary DR-TB, it was found that only 4.4% of the enrolled DR-TB patients suffered from extra-pulmonary DR-TB (Desai & Joshi, 2019). In Iran, 7.3% of enrolled patients had extra-pulmonary DR-TB (Merza, et al., 2011).

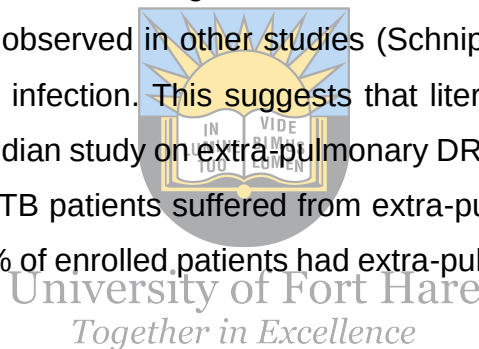


Table 4.2: Site of current DR-TB infection

Characteristic	Category	Frequency	Percentage
Current TB site (n=100)	Extra-pulmonary	3	3.0
	Pulmonary	97	97.0

4.4.2 Drug susceptibility results

The DST results of the 100 patients used in this study show that 49 (49.0%) had RR, 46 (46.0%) had MDR and 5 (5.0%) pre-XDR. In a retrospective study in China, 5,6% of patients were diagnosed with RR-TB and 4% had MDR-TB (Shen, et al., 2009).

The World Health Organization reports that the incidence of MDR-TB and RR-TB remained stable from 2015 to 2020 but showed a marked increase in 2021. Unfortunately, the numbers for MDR-TB and RR-TB have been clumped together and not reported separately. It is reported as a combined 3.6% in new cases and 18% among previously treated cases (WHO, 2022). In a South African study, the prevalence of RR-TB was reported as 8.8% (Coovadia, et al., 2013).

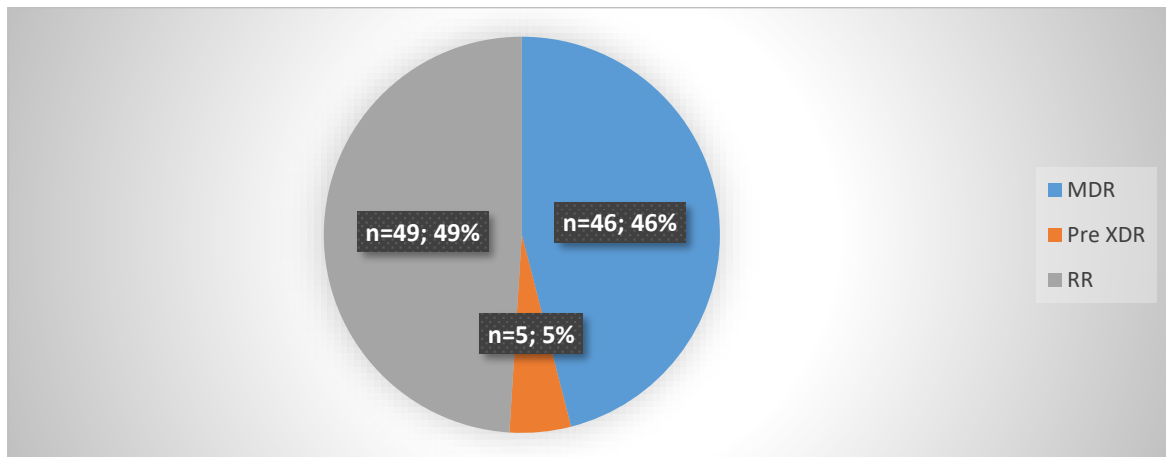


Figure 4.4.1: Distribution of patients by DST result

The five patients diagnosed with pre-XDR were previously treated for TB. Of concern in this instance is that 3 of the five were previously Rifampicin sensitive and were considered cured. Cured is defined as completed treatment and showing negative sputum at the end of the treatment period. From this, it could be suggested that they could have been re-infected with a pre-XDR strain of TB. The same trend can be seen in 14 patients diagnosed with MDR-TB who were also cured after Rif-sensitive TB episodes. Another 14 patients were primarily infected with a resistant strain of MDR-TB since they had no previous history of TB treatment.

The same observation was made in retrospective studies done in China (Shen, et al., 2009; He, et al., 2016). In the Eastern Cape Province, it was found that pre-XDR-TB and XDR-TB evolved from a single origin after DNA sequencing (Klopper, et al., 2013). Therefore, a suggestion can be made that it was spread through the transmission of a resistant organism. The high incidence of initial MDR-TB is attributable to recent transmission of resistant strains (Merza, et al., 2011).

4.4.3 Delay in initiation of DR-TB treatment

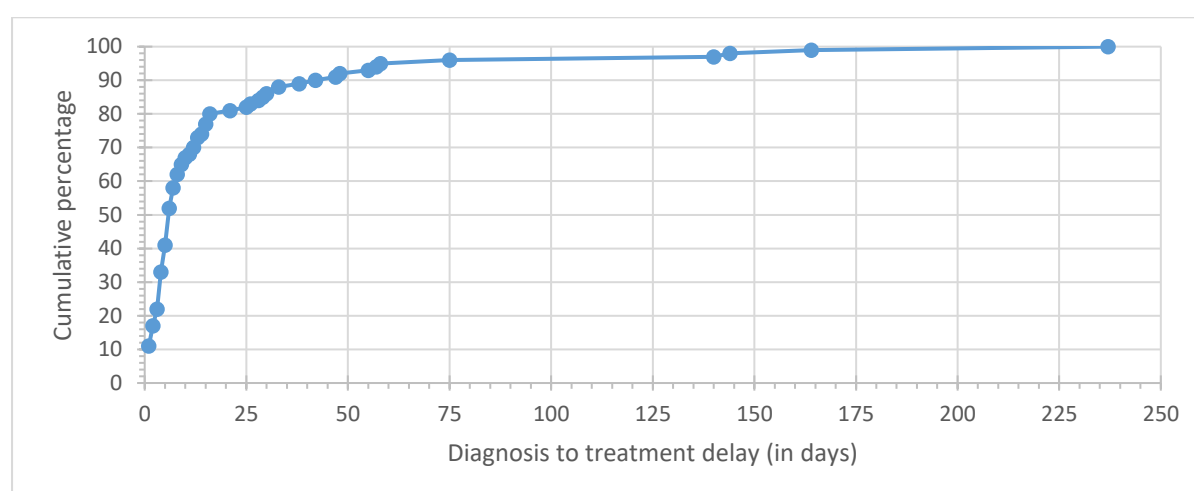


Figure 4.4.2: Cumulative distribution of diagnosis to treatment delay

The cumulative distribution curve of the diagnosis to treatment delay in Figure 4.4.2 shows that almost 90% of the patients waited for less than 50 days before starting treatment, and 80% waited at most two weeks before starting treatment.

The descriptive statistics for the diagnosis to treatment delay show that the delay lies between 1 and 237 days, with a median of 6 days and an upper quartile of 15 days. These results show that half of the patients started treatment within six days of diagnosis, and 75% started treatment within 15 days. This means only a quarter of patients were delayed for more than 15 days before initiating treatment. A South African cohort study done shows a decrease in diagnosis to treatment delays from 44 days in 2011 to 22 days in 2013 (Cox, et al., 2017). A similar study done in a rural area in the Western Cape, South Africa, found that the median time to start DR-TB treatment was 55 days in 2011 (Jacobson, Theron, Kendall, Franke, Barnard, van Helden, Victor, Streicher, Murray & Warren, 2013). Other studies have reported median delays of 128 days before starting of treatment (Nair, et al., 2017).

Any delay in the start of DR-TB treatment could have an adverse effect on the outcome. However, starting incorrect treatment, especially with extensive resistance, can perpetuate the resistance profile. It is essential to define the start date as the day on which the most appropriate regime for the displayed drug resistance profile is started (Anderson, et al., 2022). In this study, the shortest initiation delay was one day and the longest was 237 days. The patient initiated after 237 days refused treatment,

then was lost to follow up and eventually started on DR-TB treatment when presented again to the facility.

4.4.4 Duration of DR-TB treatment

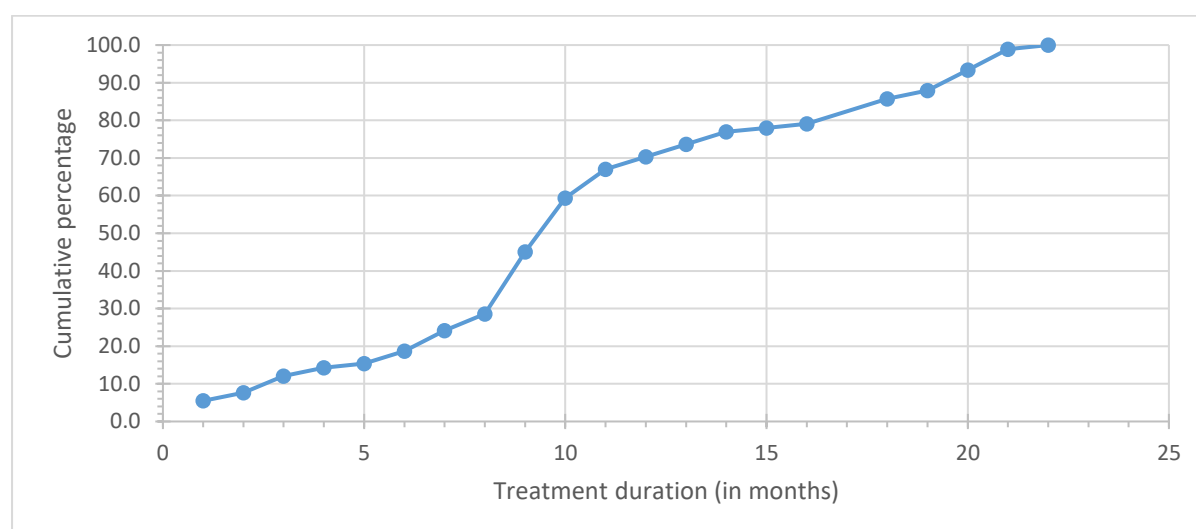


Figure 4.4.3: Cumulative distribution of treatment duration

Once on treatment, the patients had treatment durations ranging between one month and 22 months, with an average treatment duration of 10.8 months and a 95% confidence interval of (9.6; 12.0). The median was ten months, which means half of the patients spent at most ten months on treatment. Figure 6 below shows the cumulative distribution of treatment duration, suggesting that 80% of the patients spent at most 15 months on treatment. The fact that the mean and the median are close to each other suggests that the treatment durations are evenly distributed on either side of the mean, showing no signs of skewness.

The most extended duration of treatment was 22 months, with the shortest being one month. This participant died within one month of treatment initiation. The WHO maintains that newer treatments against DR-TB can reduce treatment time to 6 months, whilst the older regimes could last up to 20 months or more. Another study reported a median total treatment duration of 19 months (Wrohan, et al., 2022). As per the WHO guideline on DR-TB treatment, the shorter regime lasts 9 –12 months, with the older regimes lasting 18 months or more (WHO, 2019). In a South African cohort study, it was found that the median was 6.9 months with oral treatment and 13.4 months with injectable drugs (Dheda, et al., 2010).

4.4.5 Drugs used during treatment of DR-TB

Table 4. 3: Distribution of TB drugs taken by patients

Drugs taken	Frequency	Percentage
Amikacin	36	36.0
Bedaquiline	82	82.0
Clofazamine	78	78.0
Ethambutol	79	79.0
Ethionamide	57	57.0
Isoniazid	89	89.0
Levofloxacin	74	74.0
Linezolid	48	48.0
Moxifloxacin	45	45.0
PAS	24	24.0
Pyrazinamide	100	100.0
Terizidone	49	49.0
Other	5	5.0

Table 4.3 above shows the distribution of patients by the TB drugs they were taking as part of their DR-TB treatment. The results of this study show that all of the DR-TB patients used Pyrazinamide (Z). The majority used high dose Isoniazid (Hh) at 89%; Bedaquiline (Bdq) at 82%; Ethambutol (E) at 79%; Clofazmine (Cfz) at 78%, and Levofloxacin (Lfx) at 74%. The other anti-TB drugs were used to a lesser extent and these included Ethionamide (Eto) at 57%; Terizidone (Trd) at 49%; Linezolid (Lzd) at 48%, Moxifloxacin (Mfx) at 45%, Amikacin (Am) at 36%; para-aminosalicylic acid (PAS) at 24%. The other 5% include Delamanid (Dlm).

These results align with the DR-TB guidelines from WHO that recommend at least four effective second-line agents, plus Z (WHO, 2019). Individualised treatment options, different resistance profiles, or adverse reactions to medication may cause the use of other agents. Patients, who are not cured by a first line regime, should not receive any of the drugs contained in that regime as part of DR-TB regime (Seung, et al., 2015).

Only 4% of patients diagnosed with MDR-TB/RR-TB and 25.4 % of patients diagnosed with XDR-TB were initiated on a regime containing Bdq (Schnippel, et al., 2015).

A study conducted in South Africa found that the standard MDR-TB treatment regime is Kanamycin, Ofloxacin, Ethionamide, Ethambutol and Pyrazinamide (Dheda, et al., 2010). The XDR-TB treatment regime is reported as being customised according to the resistance profile shown upon drug susceptibility testing. The most commonly used treatment agents for XDR-TB were Capreomycin (93%), PAS (90%), Trd (84%), Z (80%), Eto (61%), E (59%). Figure 4.4.4 below shows a graphic representation of the DR-TB drugs used in this study.

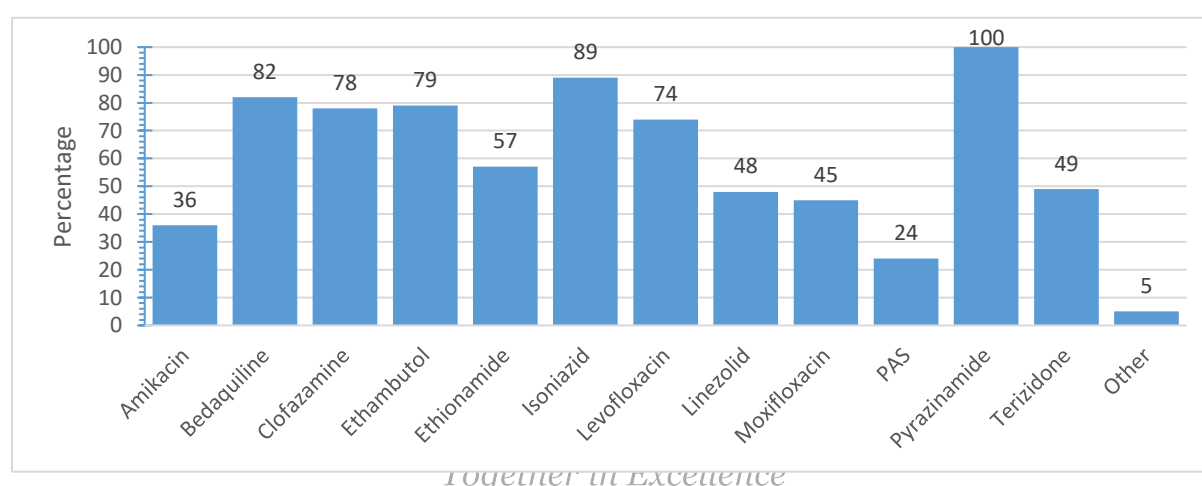


Figure 4.4.4: Distribution of patients by TB drugs used

4.5 DR-TB treatment experience and outcome

The treatment experience comprises of several variables including, but not limited to, whether the patient had a negative sputum date within six months of starting treatment, side effects, treatment interruption, loss to follow-up and treatment outcome. The distribution of the patients according to these variables is shown in Table 4.4 below. Each of the variables will be discussed separately.

Table 4.4: Distribution of patients by treatment experience

Variable	Category	Frequency	Percentage
First negative sputum	Died	17	17.00
	Within 6 months	74	74.00
	Lost	5	5.00
	Transferred out	1	1.00
	Unknown	3	3.00
Treatment interruption	No information.	97	97.00
	Yes	3	3.00
Side effects	Anaemia	9	9.00
	QT-prolongation	3	3.00
	Nil reported	87	87.00
	Renal impairment	1	1.00
	Peripheral Neuropathy	3	3.00
	Dizziness	1	1.00
	Diarrhoea	1	1.00
Treatment outcome	Cured	58	58.00
	Died	18	18.00
	Lost	19	19.00
	Treatment completed	2	2.00
	Treatment failure	3	3.00
Reason for loss to follow-up	Not lost	86	86.00
	Refusal	7	7.00
	Relocation	7	7.00

4.5.1 Sputum conversion

Sputum culture conversion is usually an indicator of treatment success at the end of the treatment course. Sputum conversion should occur within the first few months of treatment to show the efficacy of the treatment regime. This is also an indicator of less

infectiousness of the individual (WHO, 2019). The results show that most of the patients had the first negative sputum within six months (74%) and that 17% of the patients had died, and the remaining 9% were lost (5%) or transferred out (1%), or no information is available (3%). Furthermore, only 3% of the patients had a record of having interrupted their treatment, and none of the rest had a record of treatment interruption duration.

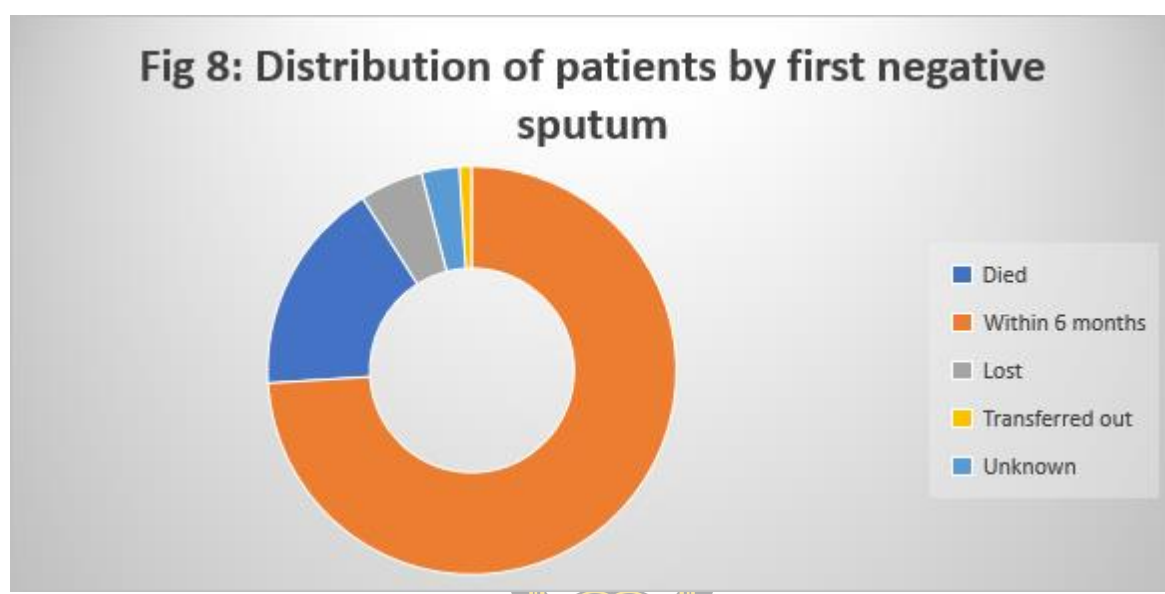


Figure 4.5.1: Distribution of patients by sputum conversion

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Most of the participants in the study group showed sputum conversion by the sixth month (74%), 17% had died by the sixth month, and the rest had relocated or were lost to follow-up. Sputum conversion by month six can serve as an early predictor of treatment success (Kurbatova, et al., 2015); (Abubakar, et al., 2022).

4.5.2 Adverse drug reactions experienced by participants

Regarding side effects, 9% had anaemia, 3% developed QT prolongation, 3% reported peripheral neuropathy, 1% suffered from diarrhoea, and 1% had renal problems. The rest of them never reported side effects (87%). However, it should be noted that patients could experience more than one side effect.

Most of the DR-TB patients did not report any adverse drug reactions experienced (87%, n=100). The other 13% reported at least one adverse drug reaction and it should be noted that some of the patients experienced more than one adverse drug reaction. The adverse drug reactions reported on the EDR-web application resulted in a change

of treatment for the patient. It is therefore suggested that other side effects may have been experienced but not reported since it was transient and did not result in a change in treatment.

The anaemia that was reported for the nine participants could have been caused by Linezolid. Linezolid is known for causing bone marrow depression, leading to anaemia requiring blood transfusion in many instances (Cox & Ford, 2012). QT-prolongation was reported for three patients and this could have been caused by Bedaquiline. Patients using Bdq reported prolongation of the QT interval (Tanneau, et al., 2022). Peripheral neuropathy was reported for three patients and could be attributed to Terizidone, High dose Isoniazid and Linezolid. Diabetic patients have a higher risk of developing peripheral neuropathy (Lange, et al., 2014).

Adverse drug reactions could be life-threatening and detrimental to the treatment outcomes. It often leads to non-compliance and could result in further development of resistance (Shean, et al., 2013). In this study, all but two participants who complained of adverse drug reactions were cured. Patients receiving ART could be at a higher risk for the development of side effects due to more complex treatment regimens or possible drug interactions.

4.5.3 DR-TB treatment outcome

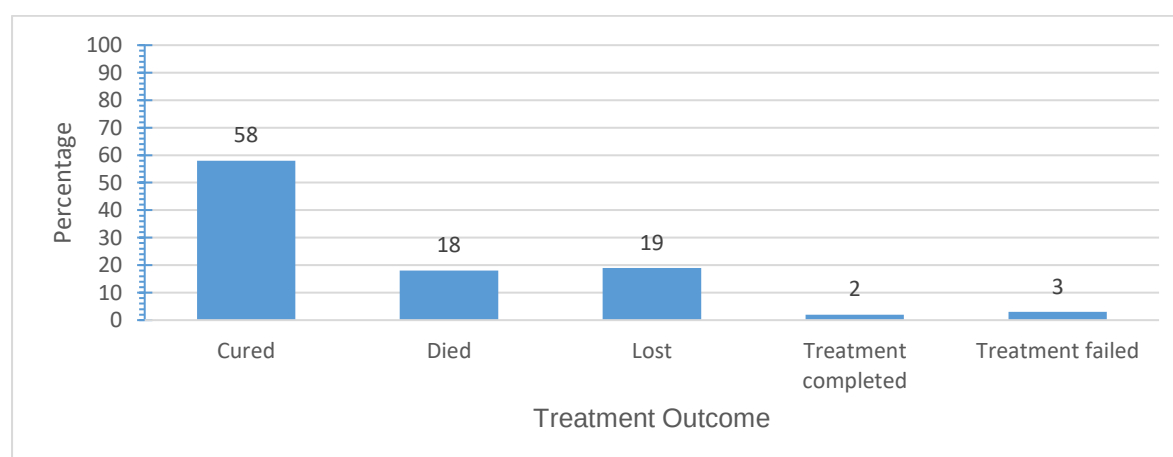
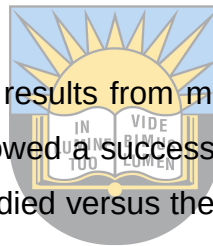


Figure 4.5.2: Distribution of patients by treatment outcome

Of the 100 patients, 19% were lost to follow-up, and the reasons for the loss to follow-up were either treatment refusal or relocation. However, most of them were not lost, and their treatment outcomes were either cured (58%) or died (18%), or the treatment was completed or failed.

In this study, 58% of all patients were cured of DR-TB, 19% of were lost to follow-up due to relocation and refusing treatment and 18% of died during treatment. Cured is defined as completed treatment and showed three consecutive negative cultures. Died is defined as death for any reason while receiving treatment for DR-TB. Three had treatment failure, which is defined as having two or more positive cultures out of five sputum cultures within the 12 – 15 months treatment period or the final three sputa being positive. Two completed the treatment which is defined as completion of the course of treatment but does not have the bacteriological sample to prove cure (Nair, et al., 2017).

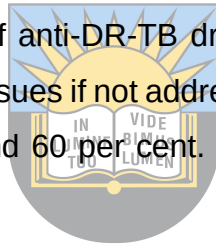
These results are consistent with results from more extensive studies that reported that less than 70% of patients showed a successful outcome (Wrohan, et al., 2022). In other studies, 7.5% of patients died versus the 18% death rate found in this study (Wrohan, et al., 2022). The WHO 2022 reports a treatment success rate of 60%, which was not achieved in this study.



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4.6 Chapter Summary

The results presented and discussed in this chapter show the trends observed regarding DR-TB in the Sarah Baartman District of the Eastern Cape. It shows that the sample was predominantly males (60%) and that the average age was 40.8 years which suggests that this gender and that age group are more prone to infection with DR-TB. Slightly more than half of the participants were HIV positive (54%) and about 70% of them had a CD4 count of less than 300. About two-thirds of the patients had previously been on TB treatment (66%) with 59.1% having been previously cured. With respect to the current DR-TB diagnosis, most patients had Rifampicin resistant-TB (49%), followed by MDR-TB (46%) and 5% pre-XDR-TB. In the study setting, the time taken to initiate DR-TB treatment was acceptable as most patients started treatment within 15 days. The treatment duration in this study setting was 10.8 months which is within the recommended treatment duration by the WHO. The anti-TB agents used are in line with what is recommended by the WHO in their DR-TB guidelines. Despite the life-saving potential of anti-DR-TB drugs, they can cause adverse drug reactions, leading to compliance issues if not addressed timeously. This study showed a treatment success rate of around 60 per cent. However, it showed a higher-than-expected mortality rate of 19%.



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CHAPTER FIVE: CONCLUSIONS AND RECOMMENDATIONS

5.1 Preamble

The preceding chapter presented the findings and results of the study. This final chapter presents the recommendations, study limitations and conclusions regarding trends and casual factors observed in the Sarah Baartman District.

5.2 Summary of the study

The leading cause of death globally is TB despite the fact that it is a curable disease. This happens because many TB-infected patients are not cured because they do not complete their treatment cycle leading to the development of DR-TB and MDR-TB. The Sarah Baartman District in the Eastern Cape Province is one of the areas in South Africa that experience high numbers of DR-TB and MDR-TB.

This study was a retrospective analysis that utilised data from the Electronic Drug Resistant TB. The study's purpose was to conduct a retrospective analysis of Drug-resistant TB patients' medical records to determine trends, causes, and contributory factors to Drug-resistant TB during the period 2016 and 2020 at Sarah Baartman District. The Camdeboo sub-district of Sara Baartman District was selected for the study. This was done to achieve the following objectives:

- To describe the trends of Drug-resistant TB that occurred in the Sarah Baartman District between 2016 and 2020.
- To identify the contributing factors to Drug-resistant TB between 2016 and 2020 at Sarah Baartman District.

Hundred adult patients' records were randomly selected from the EDR-web. The age distribution of the selected patients' records ranged between 22 and 83, with a mean age of 40.8 years. The majority (97%) of patients were diagnosed with MDR-TB of pulmonary origin with about half 54 of the patients living with HIV which is in line with the trends observed in other studies.

The majority (97%) of the records belonged to patients who were diagnosed with MDR-TB of pulmonary origin. Half of the participants were at least 39 years old with males more likely to acquire DR-TB. Sixty-six percent of participants had previously

received treatment for TB and might have experienced treatment defaults or lost to follow-up during their TB treatment period.

5.3 Conclusions of the study

The conclusions of this study are discussed according to the objectives of the study as a way of checking if this study has achieved its purpose and objectives.

5.3.1 Trends of Drug Resistant TB that occurred in the Sarah Baartman District between 2016 and 2020

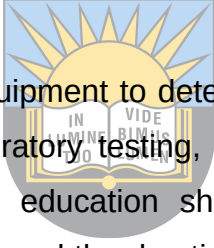
In this study, the researcher described the epidemiological trends of drug-resistant tuberculosis in Sarah Baartman District. The indicators used to describe this were age, gender, treatment history, the number of cases, the treatment outcomes, HIV history, treatment initiation delay, the treatment regimens, adverse drug reactions and treatment outcomes. The data in relation to this were collected over a five-year period, from 1st January 2016 to 31st December 2020.

The prevalence of DR-TB is high, and there was a spike in the number of Rifampicin-resistant cases in this setting. DR-TB and TB, in general, are more common among the males. The age group most affected is around 40 years, the group most economically active and more likely to be breadwinners in their households. There is a very high risk of developing DR-TB from a resistant strain, meaning that there is a possibility of infection with pre-XDR even though one might have never had any other TB exposure and treatment. RR-TB is emerging fast and is more prevalent than MDR-TB. The study results show that there has not been a very long delay in treatment initiation for DR-TB patients.

The treatment duration of patients with DR-TB is within the guidelines of the World Health Organization at 10.8 months on average. Most of the patients treated for DR-TB did not experience adverse drug reactions. The sputum conversion rate in this study is indicative of effective treatment. In this study, 58% of participants had been cured. The mortality rate in the study is high at 19%, but as seen from the results, most of the deaths occurred within the first six months, suggesting that there might have been a delay in seeking healthcare.

5.3.2 The contributing factors to Drug-Resistant TB between 2016 and 2020 in Sarah Baartman District.

The study showed that people living with HIV are at a higher risk of contracting DR-TB because of their weakened immune system. Treatment compliance is likely to positively affect CD4 count and treatment outcomes. Previous exposure to TB treatment increases the risk of development to DR-TB even if there was treatment completion and cure. Non-adherence to first line TB treatment increases the risk of relapse and DR-TB. The Rifampicin resistance profile can be immediately available through TB diagnosis with GenXpert®. However, this rapid result may lead to immediate treatment initiation without susceptibility testing for other anti-TB agents yet incorrect treatment may exacerbate resistance. Delays in initiation of DR-TB can lead to poor treatment outcomes as well as further transmission of DR-TB. There is always a possibility to experience adverse drug reactions, but early intervention is beneficial for treatment adherence.



The availability of rapid testing equipment to detect resistance to first-line treatment could eliminate the need for laboratory testing, leading to more rapid initiation of treatment of DR-TB. Community education should be prioritised regarding the transmission and spread of DR-TB and the de-stigmatisation thereof. Health seeking behaviour can be positively influenced by community mobilisation and patient education. DR-TB is a real threat to public health since there is potential emergence of totally drug-resistant TB that could ultimately be spread by a single cough.

5.4 Study limitation

This retrospective study was done to extract information with regards to DR-TB from the EDR-web. As such, the study findings cannot be extrapolated to the general public. Furthermore, the reliance on programmatic data could have a negative effect on the outcomes since there was no corroboration of information with other sources. Furthermore, the information in the available records could be inaccurate and/or incomplete, leading to less accurate estimates.

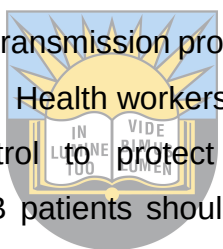
5.5 Strength of the study

The results of this study provide a reflection of the DR-TB situation in the Sarah Baartman district. Furthermore, the study could provide insight into the extent of DR-TB in the study area and provides a platform for future studies, especially those focussing on DR-TB transmission and genetic profiling.

5.6 Recommendations

5.6.1 Recommendation for the health sector

Based on this study, it is recommended that all facilities treating DR-TB patients adopt newer agents such as Bedaquiline and Linezolid. This shift could result in shorter treatment durations and less economic burden for households. Health education should be done at every interaction with the community, explaining the signs and symptoms as well as risks and precautions that should be known with regard to TB and DR-TB. Careful monitoring of transmission profiles of DR-TB strains will be crucial in preventing outbreaks of DR-TB. Health workers in facilities treating DR-TB should practise excellent infection control to protect themselves and their patients. Decentralisation of care of DR-TB patients should go hand in hand with adequate information sharing and education of the family and community of patients to ensure the negligibly low risk of transmission.



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5.6.2 Recommendations for patients and communities

Patients should be empowered to accept responsibility for their healthcare and to exhibit better health-seeking behaviour, especially men. This study showed that compliance with prescribed medication, whether for diabetes, HIV or TB, will positively affect the treatment outcomes. Furthermore, patients diagnosed with DR-TB should consider the safety of their community. Since DR-TB is transmissible, taking adequate precautions is paramount to preventing outbreaks.

5.6.3 Recommendation for research

For future research, developing newer agents to treat DR-TB should be hastened since total drug-resistant TB will be a reality sooner than is thought. In addition, more prevention strategies should be considered, such as vaccines as well as other methods to prevent occurrence of drug resistant TB strains.

5.7 Chapter Summary

This final chapter briefly outlined the study by giving a summary of it. The purpose and objectives of the study are indicated, and the conclusions of the study are discussed using its objectives. This study reflected the DR-TB situation in the Sarah Baartman district. Delays in the initiation of DR-TB were found to lead to poor treatment outcomes as well as further transmission of DR-TB. It also showed that there has not been a very long delay in treatment initiation for DR-TB patients. Early intervention could have been more beneficial for treatment adherence. There is therefore a need that all facilities treating DR-TB patients to adopt newer agents and ensure better treatment outcomes.



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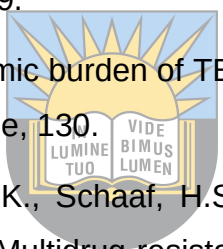
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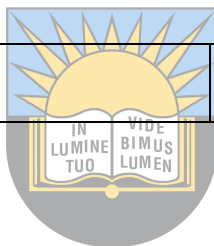
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ANNEXURE A: DATA COLLECTION TOOL

Data extraction Tool		
Section A - Demographic Information		
Age		
Gender	M	F
Sub-District	Camdeboo	Kouga
	Other(specify)	
Section B - Medical and Patient history		
HIV status	Positive	Negative
If HIV Positive answer the following		
Include CD4 count		Unknown
ART start date		
ART regimen	First line	
	Second line	
	Third line	
	Renal friendly	
	Unknown	
Pregnant	Yes	No
Other co-morbidities	None	Diabetes
	Mental illness	Asthma
	Other (Specify)	
Section C - TB Diagnosis and History		

Previously treated for TB.	Yes	No
Previous regime	Rif Sensitive	RR-TB
If previously treated, please state outcome:	Cured	Failed
	Loss to follow up	
Details of current TB Diagnosis		
Date of TB diagnosis		
Date of DST result		
Interpretation of DST result	RR	MDR
Indicate site of TB.	Pulmonary	extra-pulmonary (specify)
TB Treatment start date:		
Duration between TB diagnosis and start date		
Drugs used in treatment	Moxifloxacin	Ethionamide
Clofazamine	Pyrazinamide	Ethambutol
Bedaquiline	Levofloxacin	Amikacin
Terizidone	Delamanide	
Duration of treatment (months)		
Date of first negative sputum		
Any interruption of treatment	Yes	No
Side Effects reported	Hearing Loss (Amikacin)	Anemia

	Cardiac problems/QT prolongation (Bedaquiline)	Diarrhoea
	Renal impairment	
	Liver impairment	
Other(specify)		
Treatment outcome		
Cured	Loss to follow up	Died
Transferred out		
Reason for Loss to follow up		
Refusal of treatment	Relocation	



University of Fort Hare
Together in Excellence

ANNEXURE B: APPLICATION LETTER FOR WAIVER OF CONSENT FORM

4 End Street

Somerset East

5850

31 August 2022

Research Ethics Committee

University of Fort Hare

P. Bag 5200

East London

5201

Dear Sir / Madam

RE: REQUEST PERMISSION FOR A WAIVER OF CONSENT FORM

I am Salmoné Petrus, a student studying for a master's degree in Public Health at Fort Hare University. I am requesting a waiver of informed consent for a retrospective analysis of drug-resistant tuberculosis in Sarah Baartman district from 2016 and 2020 in the Eastern Cape province. No human participants will be used for this study.

The study will be a quantitative, descriptive, retrospective design based on the information extracted from patients' files as captured on the eDR-web (Electronic Drug Resistant TB web application). Information will be extracted from medical records of patients diagnosed with and treated for Drug-Resistant TB at the Sarah Baartman District for five years (from 01 January 2016 to 31 December 2020). This information will be entered on a structured information collection sheet.

A qualified statistician will be consulted to discuss this study's objectives, sampling technique, questionnaire and relevant data analysis procedure. Data will be entered into a statistical software package for social sciences (SPSS 21), cleaned and analysed. Anonymity and confidentiality will be protected by not recording patients' names and removing all details, which could lead to the identification of individuals. Only a research number will be assigned, representing each patient's record information. Furthermore, the information obtained from data collection will not be divulged to anybody.

Lastly, extracted data will be stored electronically on a password-protected computer. In addition, hard copies of structured information collection sheets with information obtained from patients' records will be stored in a locked cupboard in my office.

Yours sincerely



Mrs Salmoné Petrus

Cell no: 0783756084

ANNEXURE C: APPLICATION LETTER TO THE DEPARTMENT OF HEALTH

4 End Street
Somerset East
5850
31 August 2022

Eastern Cape Health Research Committee
Health Systems Trust
Online submission at nhrd.health.gov.za

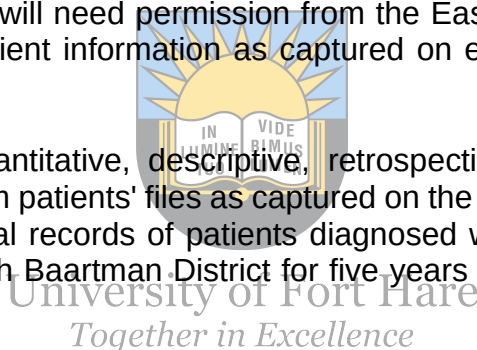
Dear Sir / Madam

RE: REQUEST ETHICAL APPROVAL FOR CONDUCTING OF RESEARCH

I am Salmoné Petrus, a full-time pharmacist of the Eastern Cape Department of Health, at Andries Vosloo Hospital in Sarah Baartman District. I am currently pursuing a master's degree in Public Health at Fort Hare University. My proposed study is a retrospective analysis of drug-resistant tuberculosis in Sarah Baartman district from 2016 to 2020.

To complete the study, I will need permission from the Eastern Cape Department of Health for the use of patient information as captured on eDR-web (Electronic Drug Resistant TB program)

The study will be a quantitative, descriptive, retrospective design based on the information extracted from patients' files as captured on the eDR-web. Information will be extracted from medical records of patients diagnosed with and treated for Drug-Resistant TB at the Sarah Baartman District for five years (from 01 January 2016 to 31 December 2020).



Anonymity and confidentiality will be protected by not recording patients' names and removing all details, which could lead to the identification of individuals. Only a research number will be assigned, representing each patient's record information. Furthermore, the information obtained from data collection will not be divulged to anybody.

Extracted data will be stored electronically on a password-protected computer. In addition, hard copies of structured information collection sheets with information obtained from patients' records will be stored in a locked cupboard in my office.

All results will be submitted in a written report to the ECDOH.

I trust that this request will be favourably considered.

Yours sincerely

Mrs Salmoné Petrus

ANNEXURE D: APPLICATION LETTER TO ACCESS DOCUMENTS AT THE SARAH BAARTMAN DISTRICT

4 End Street
Somerset East
5850
31 August 2022

District Manager
Sarah Baartman District Office
8th Floor
Port Elizabeth
6000

Dear Sir / Madam

RE: REQUEST ETHICAL APPROVAL FOR UTILISATION OF PATIENT RECORDS

I am Salmoné Petrus, a full-time Eastern Cape Department of Health pharmacist at Andries Vosloo Hospital in Sarah Baartman District. I am pursuing a master's degree in Public Health at Fort Hare University. My proposed study is a retrospective analysis of drug-resistant tuberculosis in Sarah Baartman district from 2016 to 2020.

To complete the study, I will need permission from the Eastern Cape Department of Health, Sarah Baartman District for the use of patient information as captured on eDR-web (Electronic Drug Resistant TB program). As the extraction of information can be tedious since I will be accessing information for five years, I am humbly requesting authorised access for a limited period to download all necessary information to not impede on the time of other officials who need to carry on daily duties. My research is mainly done outside of working hours.

The study will be a quantitative, descriptive, retrospective design based on the information extracted from patients' files as captured on the eDR-web. Information will be extracted from medical records of patients diagnosed with and treated for Drug-Resistant TB at the Sarah Baartman District for five years (from 01 January 2016 to 31 December 2020).

Anonymity and confidentiality will be protected by assigning research numbers. Furthermore, the information obtained from data collection will not be divulged. Security of data will be ensured.

All results will be submitted in a written report to the ECDOH.

I trust that this request will be favourably considered.

Yours sincerely



Mrs Salmoné Petrus

ANNEXURE E: ETHICS APPROVAL LETTERS

 University of Fort Hare <i>Together in Excellence</i>	HEALTH RESEARCH ETHICS COMMITTEE P.O Box 1054 East London 5200 Tel: +27 (0) 43 704 7368 E-mail: dgoon@ufh.ac.za
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ETHICAL CLEARANCE CERTIFICATE
REC-100118-054

Certificate Reference Number:	Ref#2022=06=10=PetrusSJ
Project title:	A retrospective analysis of drug-resistant tuberculosis in the period 2016 and 2020 at Sarah Baartman district in the Eastern Cape province, South Africa
Nature of Project:	Masters of Public Health
Principal Researcher:	Petrus, Salmoné Jordania
Student number	201821277
Supervisor:	Prof XT Maluleke

On behalf of the University of Fort Hare Health Research Ethics Committee (HREC), I hereby give ethical approval in respect of the undertakings contained in the above-mentioned project and research instruments(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 HREC 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 HREC in the prescribed format, where applicable, annually, and at the end of the project, in respect of ethical compliance.

The HREC retains the right to

- Withdraw or amend this Ethical Clearance Certificate if
 - Any unethical principles 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.

📧 @ufh1916 📍 ufh1916 🌐 www.ufh.ac.za



Province of the
EASTERN CAPE
HEALTH

Enquiries: Yvonne N. Gixela

TEL: 043 605 4540/4518

Email: ncebaxela22@gmail.com

Date: 01 November 2022

**A RETROSPECTIVE ANALYSIS OF DRUG-RESISTANT
TUBERCULOSIS TRENDS AND CASUAL FACTORS IN THE PERIOD
2016 AND 2020 AT SARAH BAARTMAN DISTRICT IN THE
EASTERN CAPE PROVINCE, SOUTH AFRICA. (EC_202210_026)**

Dear Mrs S.J. Petrus

The department would like to inform you that your application for the above mentioned research topic has been approved based on the following conditions:

1. During your study, you will follow the submitted protocol with ethical approval and can only deviate from it after having a written approval from the Ethics Research Committee.
2. You are advised to ensure, observe and respect the rights and culture of your research participants and maintain confidentiality of their identities and shall remove or not collect any information which can be used to link the participants.
3. The Department of Health expects you to provide a progress update on your study every 3 months (from date you received this letter) in writing.
4. At the end of your study, you will be expected to send a full written report with your findings and implementable recommendations to the Eastern Cape Health Research Committee secretariat. You may also be invited to the department to come and present your research findings with your implementable recommendations.
5. Your results on the Eastern Cape will not be presented anywhere unless you have shared them with the Department of Health as indicated above.

Your compliance in this regard will be highly appreciated.

SECRETARIAT: EASTERN CAPE HEALTH RESEARCH COMMITTEE



TOGETHER, MOVING THE HEALTH SYSTEM FORWARD

ANNEXURE F: LANGUAGE EDITOR'S LETTER

StatAnalysis Consulting
5 Boqwana Place, Lolo Park, Bhisho 5605
Tel: +27-40-635 0278
Cell: +27-78-966 6219

To whom it may concern

RE: Confirmation of Provision of Research Services

This serves to confirm that _SALMONé JORDANIA PETRUS_UFH Student No: 201821277_ received the following research services from us.

Services: Statistical Analysis and Language Editing

Statistician: A. Mandeya (BScEd Maths, MSc Biostatistics)

Editor: H. Mutsvairo (Dip Ed, BEd, MEd English)

Project: *A Retrospective Analysis of Drug-Resistant Tuberculosis Trends and Causal Factors in the period between 2016 and 2020 in the Sarah Baartman District of The Eastern Cape Province, South Africa*

In the event that you need further details of the services, feel free to contact the Statistician and /or Language Editor on the contact details provided above.

Regards

AMandeya

