RESEARCH REPORT

THE BURDEN OF HEARING LOSS AMONGST MULTI-DRUG RESISTANT-TUBERCULOSIS PATIENTS ON BEDAQUILINE AT ZITHULELE HOSPITAL, EASTERN CAPE PROVINCE

by

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MINI- DISSERTATION

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DEDICATIONS

I dedicate this study to my parents and siblings for their tireless support and prayers, for being my shoulder to cry on, for being my number one cheerleader when I wanted to give. To myself, for being resilient and to God for being my source of strength.

DECLARATION

I declare that this dissertation has been composed solely by me and has never been submitted in any other institution in attempts to apply for a degree. Use of previous studies and other materials have been acknowledged by means of references.

Signature…….

ACKNOWLEDGEMENTS

I would like to extend my gratitude to my Supervisor Prof Maimela for going an extra mile in providing support through all the stages of writing this report. My mom Nobuntu Matikinca for providing solid emotional and financial support, Nosiphiwo Matikinca, Hlumela Matikinca, Mpendulo Kondlo for being my biggest cheerleaders. Linda Skaal for being such a good influence and my role model, your work ethic and determination are admirable.

Abstract

Background.

Multidrug-resistant tuberculosis (MDR-TB) has recently resulted to be in an emergence state globally and this of constitute a big challenge for TB control and the goals of the World Health Organization's End TB Strategy. Aminoglycosides (AG) were often used as part of treatment of life-threatening illnesses such as MDR-TB for decades, however their adverse effects are widely described and hearing loss is one of the major side effects. The risk factors for hearing loss in patients treated with AG include the dose and duration of AG, infection with human immunodeficiency virus (HIV), older age and persons exposed to a high level of noise while the damage can be total and permanent. Severe hearing impairment has been reported to occur among patients treated for MDR-TB with injectable drugs, especially among the elderly and patients infected with human immunodeficiency virus, however, Bedaquiline-containing regimens have demonstrated improved outcomes over injectable-containing regimens in the long-term treatment of MDR-TB.

Methods

The objective of the current study was to investigate the burden of hearing loss amongst MDR-TB patients on bedaquiline at Zithulele Hospital in Eastern Cape Province. Therefore, the current study followed a quantitative retrospective approach using simple random sampling to select MDR-TB patients treated with bedaquiline and having a baseline audiogram be the initiation of treatment. The data was captured in a Microsoft Excel spreadsheet and then transferred to Statistical Package for Social Sciences (SPSS) Version 20 for data analysis in which categorical variables were presented as percentages and frequencies, while continuous variables was presented as mean, median and standard deviation lastly, comparison of categorical variables was done using a Chi-Squared test, whereas continuous variables were compared using a t-test. P-value of <0.05 will be considered significant.

Results

The mean age for the participants was 39.2 years with standard deviation of 11.8 and there was no statistical significance difference between the age groups (*p value = 0.178*). There no was a statistical significance difference between the employment status (*p value = 0.794*), previous use of injectables (*p value = 0.360*) and type of hearing of loss (*p value = 0.536*). Majority of the MDR-TB patients on bedaquiline did not have hearing loss at 67% while those who had gradual hearing loss and sudden hearing loss were 26.8% and 6.2% respectively. There was no statistical significance difference between males and females in both the right and left ears, however, the right ear results appeared to be slightly worse than the left ear results. It was found that both males and females had a high frequency hearing loss in the left ears of 26.8% and 22.2% respectively as compared to the right ears with of 25.9% and 1.6% respectively. The was a statistical significance difference between the age groups in both ears for hearing loss at *p-value <0.001*.

The overall prevalence of hearing loss was found to be 32.9% and hearing loss at 20dB or more loss at any frequency was low at 11.9% while hearing loss at 10B or more loss at any frequency was the highest at 32.9% followed by loss response at 3 consecutive frequencies at 26.2%. Hearing loss was increasing with increasing age from 8.3% in age group and age was significantly associated with hearing loss as older patients were 2.2 times more likely to have a hearing loss at a degree of 20dB and 4.4 times more likely to have a hearing loss at a degree of 10dB. Previous use of injectables was also significantly associated with hearing loss as patients who used injectables previously were 11.5 times more likely to have a hearing loss at degree of 10dB, 5.6 and 11.3 times more likely to have a hearing loss at loss response at 3 consecutive frequencies and overall hearing loss respectively.

Conclusion

South Africa has a high burden of drug-resistant tuberculosis (DRTB) and until recently, ototoxic aminoglycosides were predominant in treatment regimens. Drug-resistant TB treatment with bedaquilines caused clinically and statistically significant deterioration of hearing loss in patients, most prominently at high frequencies.

Although public health interventions to prevent hearing loss have been deemed cost-effective and have meaningful individual and economic implications, hearing loss and its prevention consistently receive inadequate attention as a global public health priority. Despite the serious impacts of hearing loss, little is known regarding prevalence of ototoxic hearing loss after treatment for DR-TB. Therefore, when the use of injectable ototoxic medications is unavoidable, audiological ototoxicity monitoring is essential to optimise hearing-related outcomes.

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DEFINITION OF CONCEPTS

Patients

Patients are active recipients of health care services (WHO, 2016). In the context of this study, patients will be people who will be receiving treatment for tuberculosis at Zithulele hospital.

Effect

Effect is change as a result of an action, in this context taking drugs (WHO, 2013). In the context of this study, effect will be defined as change caused by bedaquine drugs to patients

Hearing loss

Hearing loss is the inability to hearing auditory stimulus from 20 decibels and better (WHO, 2016). In the context of this study, hearing loss will be defined as it is above.

Multi-drug-resistant tuberculosis (MDR-TB)

MDR- TB is defined as resistance to isoniazid and rifampicin, with or without resistance to other anti-tuberculosis drugs (WHO, 2013). In the context of this study, MDR-TB will be defined as it above.

Bedaquiline

It is a new drug that is presumed to have minimal to no effects on the hearing of MDR-TB patients that is specifically used to treat multi-drug-resistant tuberculosis (MDR-TB) (Mbuagbaw, 2017). In the context of this study, bedaquiline will be defined as it above.

ABBREVIATIONS

AG	Aminoglycosides
ADRs	Adverse drug reactions
BDQ	Bedaquiline
ECDOH	Eastern Cape Department of Health
FDA	Food & Drug Administration
INH	Isoniazid
MDR-TB	Multidrug-resistant Tuberculosis
MCC	Medicine Control Council
RMP	Rifampicin
SA	South African
SPSS	Statistical Package for Social Sciences
TB	Tuberculosis
TREC	Turf Loop Research Ethics Committee
US FDA	United State Food and Drug Administration
WHO	World Health Organization

1. CHAPTER 1: OVERVIEW

1.1. Introduction

This chapter serves to introduce the subject of the research study and describes the structure of the mini-dissertation. It gives background which help in providing context to the information that will be discussed throughout the study and justifies the research based on the problem statement. The identified problem then guides the research study. Chapter one lays out objectives of the study which determine what is going to be researched and excluded.

1.2. Introduction and background

The emergence of multidrug-resistant tuberculosis (MDR-TB) constitute a big challenge for TB control and the goals of the World Health Organization's End TB Strategy (Kashongwe, Anshambi, Maingowa, Aloni, Kaswa & Marie et al, 2020). For decades, aminoglycosides (AG) were often used as part of treatment of life-threatening illnesses such as MDR-TB (Brigden, Hewison & Varaine, 2015; WHO, 2015), however their adverse effects are widely described and hearing loss is one of the major side effects (Sagwa, Ruswa, Mavhunga, Rennie, Leufkens & Mantel-Teeuwisse, 2015; Kashongwe et al., 2020). This is related to the aminoglycosides toxicity that were used for decades for treatment of drug-susceptible TB and MDR-TB. The risk factors include the dose and duration of AG, infection with human immunodeficiency virus (HIV), older age and persons exposed to a high level of noise while the damage can be total and permanent (Seddon, Godfrey-Faussett, Jacobs, Ebrahim, Hesseling & Schaaf, 2012).

To date, the World Health Organization (WHO) recommended that bedaquiline (BDQ) could be added to the conventional WHO-recommended regimen in adult patients with pulmonary MDR-TB, when an adequate regimen was not feasible due to resistance or tolerability issues (WHO, 2013). Studies have shown that adding bedaquiline to background regimen improved the health outcomes of the patients and reduced the healthcare costs (Wirth, Dass & Hettle, 2017). However, of the persons estimated to need bedaquiline worldwide, only 15.7% were reported to have received it (Cox,

Brigden, Crespo, Lessem, Lynch & Rich et al., 2018). In 2015, countries such as Belarus, France, Georgia, South Africa, and Swaziland all started sizeable cohorts of patients on bedaquiline (Guglielmetti, Hewison, Avaliani, Hughes, Kiria & Lomtadze et al., 2017). In India, bedaquiline has been approved and used for the treatment of MDR-TB, but is currently recommended for MDR-TB patients who have failed initial treatment with standard regimens (Mehra, Kambili, Potluri, Rhines, Singh & Thomas., 2017). It is worth to note that, meta-analysis conducted in China, found that bedaquiline-containing regimen had a high culture conversion rate ranging from 65 to 100% and a satisfactory treatment outcome (Li, Sun & Zhang, 2019). In contrast, in France, a retrospective cohort study found that MDR-TB patients treated with bedaquiline are more likely to develop induced liver failure (Nguyen, Cao, Akkerman, Tiberi & Alffenaar, 2016).

Drugs such as kanamycin (G-KCIN), a second-line DR-TB injectable, used to treat patients with DR-TB have been shown to suppress cochlear activity, causing ototoxicity in the form of permanent, bilateral, mild-to-moderate and sensorineural hearing loss. Ototoxic hearing loss is typically bilateral and symmetrical; however, rare cases of asymmetrical hearing loss have been reported (Rachana & Shabnam, 2017). Hearing loss has been reported amongst TB patients who were put on drugs like bedaquiline and delamanid, and reposition of clofazimin and linezolid (Kashongwe, Anshambi, Maingowa, Aloni, Kaswa & Marie et al., 2020.

In South Africa, retrospective cohort studies found that adults receiving bedaquiline for MDR-TB treatment resulted in improved outcomes at 12 months (Zhao, Fox, Manning, Stewart, Tiffin & Khomo et al., 2019) and it reduced the MDR-TB patients mortality .Currently, one hospital in the Eastern Cape Province has given feedback on bedaquiline use in treatment of MDR-TB, which shown that the use of the bedaquiline improved success rate to 60% in 2017 (Ramangoaela, 2017). In sub-Saharan Africa, there is a little or no information on the burden of hearing amongst MDR-TB patients on bedaquiline.

1.3. Problem statement

MDR-TB is a major public health concern worldwide that affects families and thus society (Kyu, Maddison, Henry, Mumford, Barber, et al. 2018). Aminoglycosides are among the main anti-tuberculosis (TB) antibiotics used for the treatment of MDR-TB (WHO, 2011). However, a substantial number of patients treated with Aminoglycosides were found to develop hearing loss (Kranzer, Elamin, Cox, Seddon, Ford & Drobniewski, 2015) . Damage to the auditory and vestibular systems, caused by these drugs are most likely irreversible. Bedaquiline is considered an alternative treatment in patients with MDR-TB (Gras, 2013; Worley & Estrada, 2014; Chahine, Karaoui & Mansour, 2014). The registration of Bedaquiline by the South African Health Products Regulatory Authority (SAHPRA) has paved the way for the National Department of Health to make Bedaquiline part of its standard recommended treatment regimen for patients with MDR-TB.

The Eastern Cape Province is amongst the four provinces with the highest burden of MDR and XDR-TB (Hayes, 2014) and from a study conducted by Van de Water et al. (2021) at Zithulele Hospital, it was reported that it is difficult to measure improvements in care or gather baseline information due to poor collection of the necessary data to monitor steps in the TB prevention care cascade. This is an essential step in the improvement of quality of care for patients and contacts. The researcher in the current study has noted that there is little or no information about the burden of hearing loss amongst MDR-TB patients who are on Bedaquiline. Understanding this burden could therefore provide information to estimate the effect of Bedaquiline on MDR-TB patients hearing. Therefore, the current study aims to investigate the burden of hearing loss amongst patients who are diagnosed with MDR-TB and treated with bedaquiline.

1.4. Purpose of the study

The main purpose of this study is to investigate the burden of hearing loss amongst MDR-TB patients on bedaquiline at Zithulele Hospital in Eastern Cape Province.

1.4.1. Objectives

- To determine the prevalence of hearing loss in MDR-TB patients treated with bedaquiline at Zithulele Hospital

- To determine the type and onset of hearing loss in MDR-TB patients treated with Bedaquiline at Zithulele Hospital
- To determine association between selected demographics with hearing loss in MDR-TB patients with Bedaquiline at Zithulele Hospital

1.5. Research question

What is the burden of hearing loss amongst MDR-TB patients on bedaquiline at Zithulele Hospital in Eastern Cape Province of South Africa?

1.6. Research methodology

The current study followed a quantitative retrospective of MDR-TB patients' records on bedaquiline at Zithulele Hospital in the Eastern Cape Province, South Africa. All files of MDR-TB patients treated with bedaquiline and having a baseline audiogram be the initiation of treatment were included in the study using simple random sampling. The data was captured in a Microsoft Excel spreadsheet and then transferred to Statistical Package for Social Sciences (SPSS) Version 20 for data analysis in which categorical variables were presented as percentages and frequencies, while continuous variables was presented as mean, median and standard deviation lastly, comparison of categorical variables was done using a Chi-Squared test, whereas continuous variables were compared using a t-test. P-value of <0.05 will be considered significant. The proposal for this study was presented at the Department of Public Health Research Committee then submitted to the School of Healthcare Sciences Research Committee (SREC) and Faculty Higher Degree Committee (FHDC) for ethical reviews and ethical approval was requested from the Turfloop Ethics Research Committee (TREC) before the commencement of the study. A detailed methodology employed in the current study is presented in Chapter 3 below.

2. CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter assists in gaining familiarity and understanding of existing research that have been done in this field before carrying out a new research study. This assists in identifying what is unknown with in the same field of study. Existing literature and finding assisted with construction of the data collection tool and analysis of obtained data. In this section the researcher is going to discuss the global burden of hearing loss in MDR-TB patients, literature is sourced from various research engines such as google scholar, Pubmed and science direct. Medical heading used to source literature is: *the burden of hearing loss due to MDR-TB treatment*.

2.1 Prevalence of hearing loss on Multidrug Resistant-Tuberculosis Patients

2.1.1 Global burden of hearing loss due to MDR-TB treatment

Amikacin and kanamycin are mainly used for treating multidrug-resistant tuberculosis (MDR-TB), especially in developing countries where the burden of MDR-TB is highest. Their protracted use in MDR-TB treatment is known to cause dose-dependent irreversible hearing loss, requiring hearing aids, cochlear implants or rehabilitation (Sagwa, Ruswa, Mavhunga, Rennie, Leufkens & Mantel-Teeuwisse, 2015). A major safety concern of the aminoglycosides is their ability to induce ototoxicity, especially during their long-term use in MDR-TB treatment. Depending on the part of the inner ear that is affected as well as the selectivity of the aminoglycoside, the ototoxicity could be auditory or vestibular (Cianfrone, Pentangelo, Cianfrone, Mazzei, Turchetta & Orlando et al., 2011; Seddon, Godfrey-Faussett, Jacobs, Ebrahim, Hesseling & Schaaf, 2012).

In a study conducted in India, amongst drug susceptibility testing (DST) confirmed MDR-TB cases, hearing loss was found to be 50% (Dela, Tank, Singh & Piparva, 2017). This high incidence of hearing loss is almost 2–3 times higher than in high-resource countries, such as the US at 13%, the Netherlands at 18%, and the UK at 28% (Hong, Dooley, Starbird, Francis & Farley, 2019).

In another study conducted in the Netherlands, it was found that approximately 11% of MDR-TB patients treated with aminoglycosides developed hearing loss (van Altena et al., 2017). In Brazil, retrospective review study revealed that approximately 21.7% of MDR-TB patients treated with aminoglycosides found that audiometric testing confirmed hearing loss (Vasconcelos et al., 2017). In a prospective observational cohort study at a private tertiary care hospital in Mumbai, India amongst patients with DR-TB it was found that hearing loss was at 17 (Malu, Tornheim, Gupta, Girija & Udwadia, 2020).

2.1.2 The burden of hearing loss due to MDR-TB treatment in Africa

Adverse drug reactions (ADRs) continue to be one of the greatest challenges to treating MDR-TB especially in the high HIV burden among populations in sub-Saharan Africa (Kelly, Smith, Luo, Given, Wehrwein & Master et al., 2016). In a cohort study conducted in Ethiopia, majority of participants 88.9% had at least one reported adverse effect or toxicity during treatment and amongst these 6% had hearing loss which was very low however the self-reported hearing loss 14% (Meressa, Hurtado, Andrews, Diro, Abato & Daniel et al., 2015). In Namibia, a retrospective cohort study of MDR-TB patients treated with amikacin or kanamycin regimens found that 58% of the patients developed hearing loss (Sagwa et al., 2015). This study reported that amikacin use in the long-term MDR-TB treatment led to a higher risk of occurrence of the more severe forms of hearing loss compared to kanamycin use. In Botswana, of the MDR-TB patient's treatment with amikacin, 62% developed hearing loss (Modongo et al., 2014).

A longitudinal study performed in two hospitals, located in two different regions of Cameroon, assessed the outcome of anti-tuberculosis treatment in MDR-TB patients. Approximately 43% presented of the patients presented with hearing loss after a 4-month follow-up. A similar study performed in nine African countries (Cameroon, Burkina Faso, Burundi, Benin, Democratic Republic of Congo, Central Africa Republic, Ivory Coast, Niger, and Rwanda, assessed the adverse effects of anti-tuberculosis drugs in MDR-TB patients and approximately 11% of the patients had severe hearing deterioration at month 4 (Wonkam Tingang, Noubiap, Fokouo, Oluwole, Nguefack, Chimusa and

Wonkam, 2020). One of the most debilitating adverse outcomes from long-term use of AGs is ototoxicity and up to 69% of individuals with MDR-TB infection in sub-Saharan Africa experience hearing loss (Hong et al. 2018). A meta-analysis of studies conducted in South Africa, Botswana and Namibia found that individuals with MDR-TB and HIV co-infection had a 23% - 69% higher risk of developing aminoglycosides-induced hearing loss than non-HIV-infected individuals (Hong et al., 2018).

2.1.3 The burden of hearing loss due to MDR-TB treatment South Africa and Eastern Cape Province

A nested, prospective cohort study of 379 in South African adults treated for MDR-TB with aminoglycosides found that 63% developed hearing loss (Hong, Dowdy, Dooley, Francis, Budhathoki & Han et al., 2020). An earlier prospective cohort study of 153 MDR-TB patients at Brooklyn Chest Hospital in Cape Town found that 77% of patients treated with aminoglycoside developed high-frequency hearing loss (Harris, Bardien, Schaaf, Petersen, De Jong & Fagan., 2012). In a study conducted in an urban outpatient clinic in Durban, KwaZulu-Natal Province, South Africa which provides community-based treatment for drug-resistant TB for over 250 out-patient visits twice each week, it was found that hearing loss was amongst the most common adverse drug reactions (ADRs) at 26% (Kelly et al., 2016).

2.1.4 Public health interventions to prevent and reduce hearing loss due to MDR-TB treatment

Hearing loss can be progressive even after discontinuation of the IA and because it starts with loss of hearing at frequencies higher than those for human speech, it may be missed without rigorous audiology monitoring. What is alarming is that hearing loss may also develop after a single dose of the IA (although this is relatively uncommon). Hearing loss is usually permanent and there is limited access both to monitoring, which could detect hearing loss early, and to interventions such as cochlear implants, which could mitigate the impact of hearing loss on MDR-TB survivors (Reuter, Tisile, Von Delft, Cox, Cox & Ditiu et al., 2017). The standardized weekly AG dose may be used to identify individuals at high risk for AG-induced ototoxicity and guide healthcare

providers in developing personalized interventions to prevent AG-induced hearing loss in medically underserved settings. Specifically, for those at high risk for developing hearing loss, AG-sparing regimens, combined with close monitoring of drug safety, should be considered (Hong, Dowdy, Dooley, Francis, Budhathoki & Han et al., 2020).

2.2 Determinants of hearing loss in MDR-TB patients with Bedaquiline

The factors contributing to hearing loss in patients treated for MDR-TB with bedaquiline are a wide range of HIV-related variables, such as CD4 count, viral load, duration of living with HIV infection, as well as the specific ART combination given and its frequency. The time-dependent variables, such as weight, serum creatinine, and AG accumulation are believed to contribute to the risk of AG-induced hearing loss (Hong, Budhathoki, & Farley, 2018). Other contributing factors hearing loss include comorbidities, nutritional deficiencies, and substance use disorders. Furthermore, the most common side effects of bedaquiline were peripheral neuropathy 26.4%, electrolyte depletion 26.0%, and hearing loss 13.2%. Severe side effects related to linezolid and injectable drugs were more common than those related to bedaquiline and delamanid (Hewison, Khan, Bastard, Lachenal, Coutisson & Osso et al., 2022).

Ototoxicity and nephrotoxicity are both well-recognized adverse effects of injectable treatment. Ototoxicity can present with either hearing disturbance or vestibular symptoms. Hearing loss is classically irreversible, bilateral and high frequency, progressing to the lower frequencies in some patients, and is often accompanied by tinnitus. Both patient and drug factors influence ototoxicity, and in recent years there has been interest in the role of host genetics predisposing to ototoxicity, with the discovery that the A1555G mitochondrial DNA mutation is associated with some cases of aminoglycoside-induced hearing loss. Increased age, creatinine >44 μmol/L at any point and amikacin use were significantly associated with ototoxicity on analysis (Sturdy, Goodman, José, Loyse, O'Donoghue & Kon et al., 2011). The use of injectable antibiotics to treat multidrug-resistant TB (MDR-TB) is associated with substantial morbidity due to long-term hearing loss (Wrohan, Redwood, Ho, Velen,& Fox, 2021)

3. CHAPTER 3: RESEARCH METHODOLOGY

3.1. Introduction

This chapter explains the reasoning behind the research approach, it further lays out the collection and analysis methods, other keys aspects such as ethical considerations that have been observed by the researcher.

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3.2. Research design

A retrospective study of MDR-TB patients' on bedaquiline was conducted at Zithulele Hospital in the Eastern Cape Province, South Africa. Data was collected over the period of 49 months from July 1, 2018 until August 31, 2021.It evaluates outcomes on patients who have already been exposed to a suspected risk factor (Creswell, 2009)

3.3. Research method

The quantitative approach was used, it allows a collection of numerical data that can be measured and analysed using statistical procedures, the researcher used a survey by using a questionnaire to answer questions that were responded to by going through MDR-TB patient's files (Brink, van der Walt & Van Rensburg, 2012).

3.4. Setting

Setting refers to the place where data will be collected to conduct research (Bless et al., 2013). In this study data was collect at Zithulele Hospital MDR- TB ward using MDR-TB patients 'files, which is a district hospital situated in the rural areas of the Eastern Cape in a town called Mqanduli. It consists of out-patient department, general, maternity, paediatric and MDR-TB wards with a total number of 200 beds. The MDR-TB ward has 20 beds and 30 MDR-TB outpatients are reviewed every month or every 2 weeks where their hearing, heart and kidney functions are monitored (Personal communication with Information Officer).

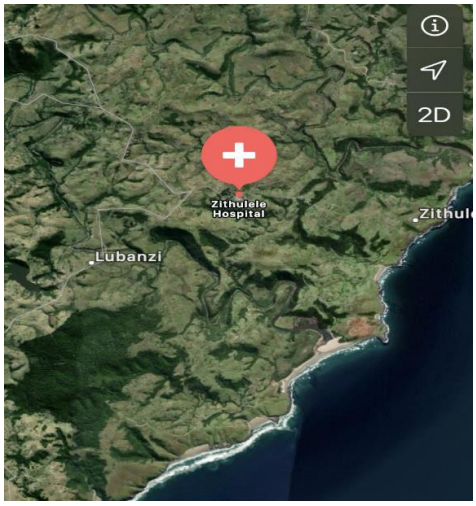

Figure 1: Map of Zithulele Hospital

3.5. Study population

Study population is a group of individuals taken from the general population who share a common characteristic (Friedman, Furberg & DeMets., 2010). The study population in the current study were patients files of all MDR- TB patients on bedaquiline seen at Zithulele Hospital in the Eastern Cape Province from July 1, 2018 to August 31, 2021.

3.5.1. Inclusion criteria

All files of MDR-TB patients treated with bedaquiline and have a baseline audiogram be the initiation of treatment at Zithulele Hospital were used in the study.

3.5.2. Exclusion criteria

As the purpose of the study is to investigate the burden of hearing loss and one of the objectives is also to determine the prevalence of hearing loss in MDR-TB patients treated with bedaquiline, the following patients files were excluded:

- Patient's files with pre-existing hearing loss were excluded.
- Patient's files without baseline audiogram during initiation of treatment at Zithulele Hospital
- Patient's files with evidence that patients have defaulted from treatment
- Patient's with inconsistent review audiograms

3.6. Sampling technique and sample size

The current study used the most basic method of sampling is called simple random sampling' (West, 2016). In this sampling technique, each and every member of a population (in this case patients diagnosed with MDR-TB and on treatment with bedaquiline) had the same chance of being included in the sample. Therefore, all possible samples of a given size below will have the same chance of selection. A sample size of 246 was required for the study which was calculated based on prevalence of 80% acquired hearing loss due to aminoglycosides (Hong et.al., 2018), 95% confidence interval and sampling error of 5%. The sample was calculated using the formula below:

$$\frac{n= Z^2pq}{d^2} \qquad \frac{(1.96)^2(0.\ 8)\ (1\text{-}0.\ 8)}{(0.05)^2} \qquad =246$$

Where:

n is the sample size

p is the prevalence of hearing loss post the use of injectable and aminoglycosides (Hong et.al., 2018)

Z is the 95% confidence interval

e is the sampling error of 5%

3.7. Data collection

Data collection refers to ways in which information will be gathered depending on the research design and can be done using strategies such as questioning, measuring etc. (Brink, van der Walt & Van Rensburg, 2012). Data was collected by a self-designed data collection sheet which was modified to best suit the study using previous studies (Harris, Bardien, Schaaf, Petersen, De Jong & Fagan., 2012; van Altena et al., 2017). It was collected directly from the patients' medical file by the researcher, there was interaction between the patients and researcher. The data collection sheet is divided into three sub-sections: socio-demographics, baseline and follow-up assessment (Appendix A).

3.8. Data analysis

Data analysis is defined as an intentional process whereby the researcher reports information obtained from the collected data whose checklist are to be used

(Guetterman, Fetters & Creswell 2015). The data was captured in a Microsoft Excel spreadsheet and then transferred to Statistical Package for Social Sciences (SPSS) Version 20 for data analysis. Assistance in analysing the results was sought from the statistician. Categorical variables were presented as percentages and frequencies, while continuous variables was presented as mean, median and standard deviation. Furthermore, comparison of categorical variables was done using a Chi-Squared test, whereas continuous variables were compared using a t-test. P-value of <0.05 will be considered significant.

3.9. Validity

Validity refers to the measures implemented to ensure that the data collection tool correctly measures what it is meant to measure, given the context in which it is applied (Brink et al. 2012). For this study, two forms of validity was used:

3.9.1. Content validity

Content validity refers to how accurately an assessment or measurement tool taps into the various aspects of the specific construct in question (Bless et al., 2013). In other words, do the questions really assess the construct in question, or are the responses by the person influenced by other factors. The researchers confirmed that the items measure the content they were intended to measure by assuring that concepts in the questionnaires are clearly stated to avoid confusion (Creswell, 2009).

3.9.2. Face validity

Another type of validity which will be addressed is face validity, which is defined by Gravetter and Forzano (2015) as an unscientific form of validity established when a measurement procedure superficially seems to measurer what it claims to measure. To secure face validity, the researcher provided the measurement tool to the supervisor to give feedback on the readability and clarity of the content and how well the questions measure the construct in the questionnaire. The tool was also be given to colleagues that are experts in this field of study to give their opinion about the validity of the tool.

3.10. Reliability

Reliability is the degree to which an instrument produces comparable results for repeated trials (Bless et al., 2013). For this study, internal consistency was utilised, to ensure that various items of an instrument measure the same construct even though there will be some variation between item scores, but they should vary in the same direction (Bless et al., 2013). To ensure internal consistency, the same check list was used to analyse patients' files. Reliability was ensured as the checklist was piloted to enhance the reliability of the instrument. The researcher used the checklist when going through patients' file to check if the items in the checklist are also in the patients' file to determine if more items need to be added or eliminated in the checklist.

3.11. Bias

Bias refers to an influence or situation that can falsify the data (Leedy & Ormrod, 2013). Selection bias - this refers to having participants in the sample who do not represent the population (Bless et al., 2013). In this study bias was avoided by analysing records of patients that meet all the inclusion criteria requirements.

3.12. Ethical considerations

3.12.1. Ethical clearance to conduct the study

The proposal for this study was presented at the Department of Public Health Research Committee then submitted to the School of Healthcare Sciences Research Committee (SREC) and Faculty Higher Degree Committee (FHDC) for ethical reviews and ethical approval was requested from the Turfloop Ethics Research Committee (TREC) before the commencement of the study. (Appendix C)

3.12.2. Permission to conduct the study

Permission to obtain and use data from patients file was requested from the Chief operating officer, clinical manager at Zithulele hospital and the Department of Health in the Eastern Cape Province (Appendix B).

3.12.3. Confidentiality and anonymity

From a legal perspective and research ethical considerations, the protection of privacy was linked to the processing of personal data. Thus, the current research was be conducted in accordance with basic considerations for data protection, such as personal integrity, privacy and responsible use and storage of personal data. According to Gray (2014) confidentiality refers to the respect of the information provided by other people as private by ensuring limited access to the information. The questionnaires were assigned unique identifier numbers to maintain confidentiality. However, the researcher ensured that the respondents were aware of all the people who will be handling the information for the purpose of the study. The respondents were informed about their rights of privacy. With regards to anonymity, the respondents were informed that they have the right to remain anonymous throughout the study and that the researcher will respect their choice of anonymity. Supportively, the data collection tool didn't have options were respondents should complete their identifying details.

3.12.4. Harm

No harm was done as the researcher did not interact with patients directly but with their files.

3.13. Summary

Chapter three discusses the research approach and design, data collection method, sampling design, research instrument, data analysis method, which were used in the current study. This chapter was about the definition of what the activity of the study is all about; measurement of progress and what constitute the success of the study.

Chapter four will give a detailed analytical understanding and illustration of the applied methodologies in chapter three.

4. CHAPTER 4: RESULTS

4.1. Introduction

The previous chapter of this study dealt with the methodology used in the current study, which included the research design, study population and method of sampling. This study is about investigating the burden of hearing loss amongst MDR-TB patients on bedaquiline at Zithulele Hospital in Eastern Cape Province. Quantitative cross-sectional study design which was retrospective in nature was used for data collection in this study and the current chapter deals with the findings of the study. In this chapter, the results are presented in a form of tables and graphs in order to highlight and interpret all statistical and descriptive associations. The study population consisted of a total of (N=194) patients whom their records were reviewed at Zithulele Hospital.

4.2 Characteristics of study population

Approximately forty-two percent of the participants were females and the mean age for the participants was 39.2 years with standard deviation of 11.8. There was no statistical significance difference between the age groups (*p value = 0.178*). There no was a statistical significance difference between the employment status (*p value = 0.794*), previous use of injectables (*p value = 0.360*) and type of hearing of loss (*p value = 0.536*) as presented in Table 4.1 below.

Table 4.1 below gives a more detailed review of the characteristics of the study population.

	Both sexes (n=194) n(%)	Female (n=82) n(%)	Male (n=112) n(%)	p-value for trend
Age in years				
18 – 24	28 (14.4)	16 (19.5)	12 (10.7)	0.178
25– 34	50 (25.8)	25 (30.5)	25 (22.3)	
35 – 44	43 (22.2)	15 (18.3)	28 (22.3)	
45 – 54	42 (21.7)	16 (19.5)	26 (23.2)	
≥55	31 (15.9)	10 (12.2)	21 (18.8)	
Employment status				

	Employed	76 (39.2)	33 (40.2)	43 (38.4)	0.794
	Unemployed	118 (60.8)	49 (59.8)	69 (61.6)	
Previous drug history					0.360
	Prev user of injectables	54 (27.8)	20 (24.4)	34 (30.4)	
	New on BDQ	140 (72.2)	62 (75.6)	78 (69.6)	
Type of hearing loss					0.536
	Normal hearing	129 (66.5)	58 (70.7)	58 (70.3)	
	Unilateral hearing loss	15 (7.7)	5 (6.1)	10 (8.9)	
	Bilateral hearing loss	50 (27.7)	19 (23.2)	31 (27.7)	

4.3 The onset of hearing loss in MDR-TB patients treated with Bedaquiline at Zithulele Hospital

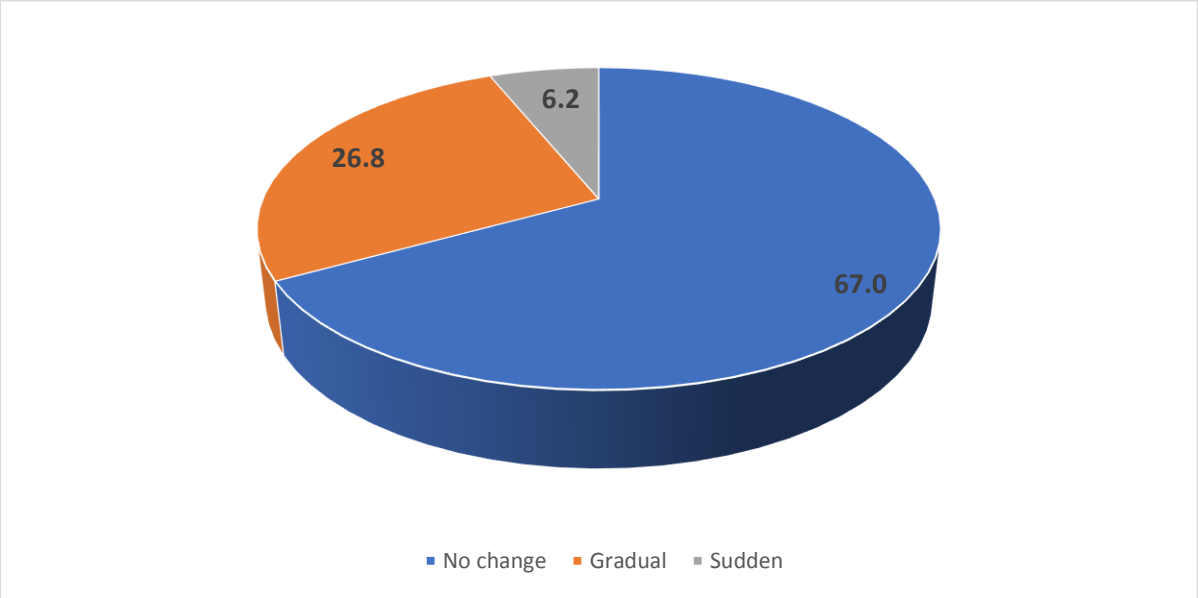

Figure 4.1: Description of hearing loss onset of study participants

Majority of the MDR-TB patients on bedaquiline at Zithulele Hospital in Eastern Cape Province did not have hearing loss at 67% while those who had gradual hearing loss

and sudden hearing loss were 26.8% and 6.2% respectively as presented in Figure 4.1 above.

In comparing the right and ears on the frequency of hearing loss, there was no statistical significance difference between males and females in both the right and left ears, however, the right ear results appeared to be slightly worse than the left ear results. It was found that both males and females had a high frequency of hearing loss in the left ears of 26.8% and 22.2% respectively as compared to the right ears with of 25.9% and 1.6% respectively. There was a statistical significance difference between the age groups in both ears for hearing loss at *p-value <0.001, and* hearing loss was reported more in elderly people as those in age group 45 – 54 years had high frequency hearing loss of 50% in both ears and those in age group 55 years and above had 74.2% of high frequency hearing loss also in both ears as presented in Table 4.2 below.

Table 4.2: Comparison of right and left ear hearing loss

		Frequency levels of hearing loss										
		high frequency hearing loss	low frequency hearing loss	mid frequency hearing loss	normal hearing	P-value		high frequency hearing loss	low frequency hearing loss	mid frequency hearing loss	normal hearing	P-value
		n (%)	n (%)	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	n (%)	n (%)
		Right ear						Left ear				
Gender												
	Males	29 (25.9)	3 (2.7)	8 (7.1)	72 (64.3)	0.561		30 (26.8)	-	-	82 (73.2)	0.397
	Females	19 (1.6)	1 (1.2)	3 (3.7)	59 (72.0)			18 (22.2)	1 (1.4)	-	62 (76.5)	
Age group in years												
	18 – 24	0 (0.0)	0 (0.0)	1 (3.6)	27 (96.4)	<0.001		0 (0.0)	0 (0.0)	-	27 (100)	<0.001
	25– 34	0 (0.0)	0 (0.0)	0 (0.0)	50 (100)			0 (0.0)	0 (0.0)	-	50 (100)	
	35 – 44	4 (9.3)	2 (4.7)	4 (9.3)	33 (76.4)			4 (9.3)	0 (0.0)	-	39 (90.7)	
	45 – 54	21 (50.0)	2 (4.8)	1 (2.4)	18 (42.9)			21 (50.0)	1 (2.4)	-	20 (47.6)	
	≥55	23 (74.2)	0 (0.0)	5 (16.1)	3 (9.7)			23 (74.2)	0 (0.0)	-	8 (25.8)	

4.4 The prevalence of hearing loss in MDR-TB patients treated with bedaquiline at Zithulele Hospital

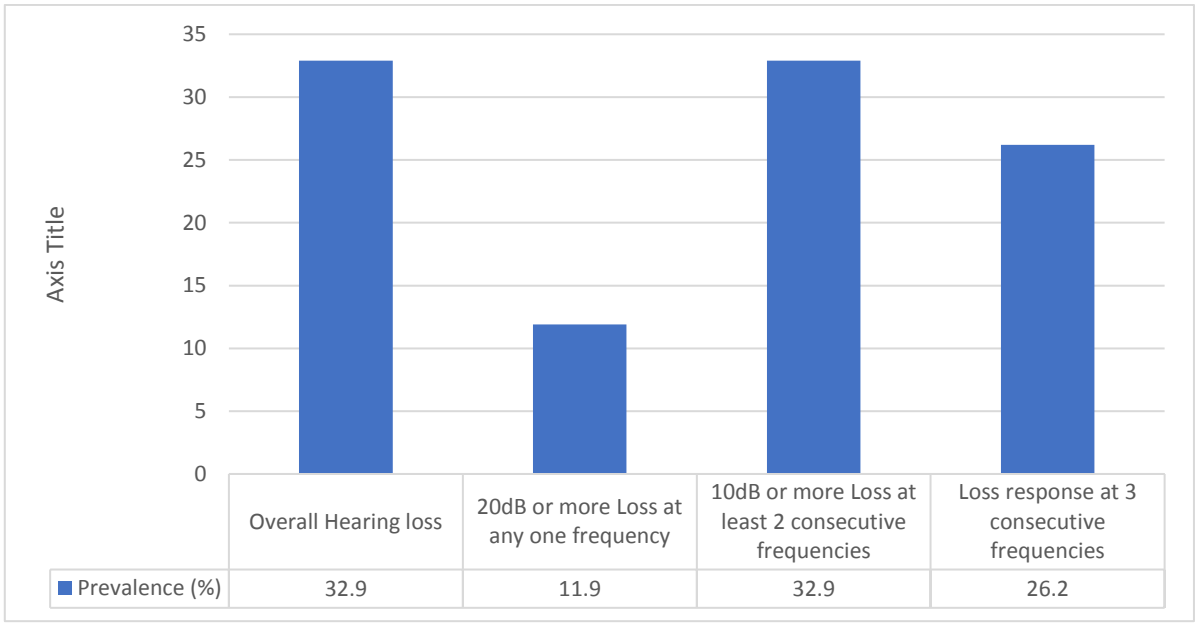

Figure 4.2: The prevalence of hearing loss per category

The overall prevalence of hearing loss was found to be 32.9% and hearing loss at 20dB or more loss at any frequency was low at 11.9% while hearing loss at 10B or more loss at any frequency was the highest at 32.9% followed by loss response at 3 consecutive frequencies at 26.2% as presented in Figure 4.2 above.

In Table 4.3 below it was revealed that hearing loss was increasing with increasing age from 8.3% in age group 18 – 24 years to 90.5% in age group 44 – 54 years in males at *p-value <0.001* and from 20% in age group 35 – 44 years to 80.% in age group 44 – 54 years in females at *p-value =0.003*. A similar trend was seen in all categories of degrees hearing loss which revealed a statistical significant difference in increasing age at *p-value <0.001* in both males and females.

Males (n=112)						
	18 – 24 years	25 – 34 years	35 – 44 years	45 – 54 years	≥55 years	*P-value*
	(n=218)	(n= 226)	(n= 216)	(n= 218)	(n= 218)	
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	
Overall Hearing loss	8.3 (1.3 – 41.9)	-	25.0 (12.3 – 44.2)	53.8 (34.9 – 71.7)	90.5 (68.5 – 97.6)	<0.001
20dB or more Loss at any one frequency	-	-	3.5 (0.4 – 21.8)	19.2 (8.2 – 38.9)	47.6 (27.7 – 68.4)	<0.001
10dB or more Loss at least 2 consecutive frequencies	8.3 (1.1 – 41.9)	-	25.0 (12.3 – 44.2)	53.8 (34.9 – 71.8)	90.5 (68.5 – 97.6)	<0.001
Loss response at 3 consecutive frequencies	8.3 (1.3 – 41.9)	-	14.3 (5.4 – 32.7)	46.2 (28.2 – 64.1)	85.7 (63.6 – 95.4)	<0.001
Females (n=82)						
	(18 – 24 years)	(25 – 34 years)	(35 – 44 years)	(45 – 54 years)	(45 – 54 years)	*P-value*
	(n=218)	(n= 226)	(n= 216)	(n= 218)	(n= 218)	
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)		
Overall Hearing loss	-	-	20.0 (6.5 – 47.5)	75.0 (48.7 – 90.4)	80.0 (45.3 – 95.1)	0.003

20dB or more Loss at any one frequency	-	-	-	6.3 (0.85 – 34.2)	60.0 (29.3 – 84.4)	<0.001
10dB or more Loss at least 2 consecutive frequencies	-	-	20.0 (6.5 – 47.5)	75.0 (48.7 – 90.4)	80.0 (45.3 – 95.1)	<0.001
Loss response at 3 consecutive frequencies	-	-	20.0 (6.5 – 47.5)	37.5 (17.7 – 62.6)	70.0 (37.2 – 90.2)	<0.001

Table 4.3: The prevalence of hearing loss per category stratified by age group and gender

4.5 The association between selected demographics with hearing loss in MDR-TB patients with Bedaquiline at Zithulele Hospital

Variables	**20dB or more Loss at any one frequency**	**10dB or more Loss at least 2 consecutive frequencies**	**Loss response at 3 consecutive frequencies**	**Overall Hearing loss**
Age				
18 – 44 years	Reference (1)	Reference (1)	Reference (1)	Reference (1)
≥45 years	2.2 (0.2 – 23.3)***	4.4 (1.4 – 14.2)*	1.9 (0.5 – 7.3)	4.4 (1.4 – 14.1)*
Gender				
Female	Reference (1)	Reference (1)	Reference (1)	Reference (1)
Male	1.6 (0.5 – 5.3)	1.5 (0.5 – 4.8)	2.6 (0.9 – 8.3)	1.4 (0.5 – 4.8)
Employment status				
Not working	Reference (1)	Reference (1)	Reference (1)	Reference (1)
Working	1.7 (2.3 – 3.2)	0.7 (0.2 – 2.3)	0.4 (0.1 – 1.2)	0.7 (0.2 – 2.3)
Previous drug history				
new on BDQ	Reference (1)	Reference (1)	Reference (1)	Reference (1)
prev user of injectables	-	11.5 (3.1 – 26.4)***	5.6 (0.9 – 11.8)***	11.3 (3.1 – 24.4)***

Table 4.4: Logistic regression to determine predictors of hearing loss

Values are reported as odds ratios (95%CI); * significant *at p<0.05; ** *significant *at p<0.005; *** *significant *at p<0.001*

Table 4.4 reveals that age was significantly associated with hearing loss as older patients were 2.2 times more likely to have a hearing loss at a degree of 20dB and 4.4 times more likely to have a hearing loss at a degree of 10dB. Previous use of injectables was also significantly associated with hearing loss as patients who used injectables previously were 11.5 times more likely to have a hearing loss at degree of 10dB, 5.6 and 11.3 times more likely to have a hearing loss at loss response at 3 consecutive frequencies and overall hearing loss respectively as presented in Table 4.4 above.

5. CHAPTER FIVE: DISCUSSIONS, CONCLUSION AND RECOMMENDATIONS

5.1 Introduction

In the previous chapter, the findings of the current study were presented and interpreted. In this chapter, the results of this study are discussed and compared to the relevant literature to address the study objectives which are:

- To determine the type and onset of hearing loss in MDR-TB patients treated with Bedaquiline at Zithulele Hospital
- To determine the prevalence of hearing loss in MDR-TB patients treated with bedaquiline at Zithulele Hospital
- To determine association between selected demographics with hearing loss in MDR-TB patients with Bedaquiline at Zithulele Hospital

Therefore, this chapter will be divided into the following sub-sections:

- Introduction
- Socio-demographic characteristics of MDR-TB patients treated with bedaquiline at Zithulele Hospital
- Types of hearing loss amongst MDR-TB patients treated with bedaquiline at Zithulele Hospital
- Prevalence of hearing loss amongst MDR-TB patients treated with bedaquiline at Zithulele Hospital
- Association between selected socio-demographics and hearing amongst MDR-TB patients treated with bedaquiline at Zithulele Hospital

- Study limitations,
- Conclusion and recommendation.

5.2 Socio-demographics of MDR-TB patients treated with bedaquiline

The current study reported a similar gender distribution with a double blinded randomized trial conducted in South Africa as majority of study participants were males (Diacon, Donald, Pym, Grobusch, Patientia & Mahanyele., et al 2012) and also similar to a study conducted in the UK (Sturdy, Goodman, José, Loyse, O'Donoghue & Kon et al., 2011). Males were also found to be dominating in a prospective multicountry study conducted in Democratic People's Republic of KoreaHowever (Franke, Khan, Hewison, Khan, Huerga & Seung et al., 2021). In the current study reported a higher mean age for the participants as compared to a double blinded randomized trial conducted in South Africa by Diacon et al., (2012) and another study conducted in Eswatini by Vambe, Kay, Furin, Howard, Dlamini & Dlamini et al (2020).

5.3 The type and onset of hearing loss in MDR-TB patients treated with Bedaquiline

Normal hearing is critical to the quality of life, and any impairment undermines it considerably (Van Deun, Decroo, Tahseen, Trébucq, Schwoebel & Ortuno-Gutierrez et al., 2020). Hearing loss is characteristically permanent or irreparable, bilateral and high frequency, progressing to the lower frequencies in some patients, and is often conveyed by tinnitus (Sturdy et al., 2011). Hearing loss is a reduction in the ability to hear sounds, It can range in severity from mild to profound. Ototoxicity is defined as a threshold shift with either a 20dB decrease at any one frequency, a 10dB decrease at any two adjacent frequencies or a loss of response at three consecutive test frequencies where responses were previously obtained (Rudolph-Claasen, 2017). Hearing loss, or ototoxicity, is one of the most debilitating side effects of injectable drugs and occurs in up to 61% of patients treated for DR-TB (Almeida, Adjuntsov, Bushura, Delgado, Drasher & Fernando-Pancho et al., 2021).

Majority of the MDR-TB patients on bedaquiline at Zithulele Hospital in Eastern Cape Province did not have hearing loss which concurs with a study conducted in multicenter, prospective, observational study in 16 countries (Hewison, Khan, Bastard, Lachenal, Coutisson & Osso et al., 2022). The current study revealed that there are patients who had gradual to sudden hearig loss which also concurs with the study findings by Khoza-Shangase and Prodromos (2021) in South Africa which reported the mean threshold shifts between all treatment sessions, gradually becoming worse, particularly at higher frequencies, therefore, indicating that there had been a steady decline in hearing function, which occurred over time. Some individuals may develop sudden profound sensorineural hearing loss following a single dose of aminoglycoside (Harris, Bardien, Schaaf, Petersen, De Jong & Fagan, 2012) which is a similar case in the current study findings as 6.2% of the participants developed sudden hearing loss while on bedaquiline. A study conducted in Uganda (Lodiong, Amos, Lumori & Nuwagira, 2021) also revealed that gradual hearing loss was a problem which concurs with findings of the current study. Again a study conducted in Ethiopia revealed that hearing loss was usually gradual and a high proportion develop permanent hearing loss, which negatively impacts the quality of life due to an inability to communicate (Teferra, Teklemariam, Wares, Negeri & Bedru, 2022) which supports the findings of the current study.

The current study findings revealed that patients treated with bedaquiline had bilateral hearing loss which concurs with several studies (Diacon, Donald, Pym, Grobusch, Patientia & Mahanyele et al., 2012; Kakkar & Dahiya, 2014; Lodiong et al., 2021; Teferra, 2022). The right ear results appeared to be slightly worse than the left ear results in the current study which concurs with study conducted by Khoza-Shangase and Prodromos (2021) in South Africa. In the current study, hearing loss was reported more in elderly people as those in age group 45 and above years had high frequency hearing loss in both ears. This is supported by the findings from a study conducted in among patients with drug-resistant TB in South Africa which reported that permanent hearing loss due to the ototoxic effect is common among DR-TB patients (Hong, Dowdy, Dooley, Francis, Budhathoki & Han et al., 2020). Such irreversible sensorineural damage leads to permanent hearing loss, starting from high frequencies, which may also be accompanied by tinnitus. In a study conducted in Cape Town, South Africa, Bedaquiline was found

to be having fewer side effects than the other drugs used to treat DRTB and did not appear to be associated with hearing loss, unlike kanamycin (Stevenson, de Jager, Graham & Swanepoel, 2022). However, a case study from the introduction of bedaquiline in South Africa National TB Programme reported that 1 in every 3 persons who survives treatments experiences permanent, profound hearing loss (Bistline, 2018).

5.4 The prevalence of hearing loss in MDR-TB patients treated with bedaquiline

The overall prevalence of hearing loss in the current study was found to be high which is supported by Hong, Budhathoki, and Farley, (2018) as who reported that the high burden of HIV coinfection in sub-Saharan Africa may be the reason for the staggeringly high prevalence of AG-induced hearing loss compared with less burdened countries, such as the United States, the Netherlands, the United Kingdom and India. However, the effect of HIV was not investigated in the current study. In a study conducted in Kinshasa, Democratic Republic of the Congo on the use of Bedaquiline as replacement for aminoglycosides in the shorter regimen for multidrug-resistant tuberculosis patients (Kashongwe, Anshambi, Maingowa, Aloni, Kaswa & Marie et al., 2020), the prevalence of hearing loss was found to be much lower than the findings in the current study however the affected most age group was similar. A study conducted in pharmacy waiting areas of a medical centre in a rural area of Limpopo province, South Africa (Naude, Joubert & Millar, 2020) reported a very low hearing loss prevalence as compared to the current study.

5.5 The association between selected demographics with hearing loss in MDR-TB patients with Bedaquiline at Zithulele Hospital

The current study findings revealed that age and previous use of injectables were the only variables significantly associated with hearing loss. This is supported by studies from Almeida et al., (2021) and Stevenson et al., (2022). In these studies it was reported that age and use of injectable TB drugs were significantly assocated with hearing loss while gender, duration of administration of medication, history of tinnitus and tester (CHW or PHC audiologist) were not significant predictors of hearing

deterioration ($p > 0.05$) (Almeida et al., 2021; Stevenson et al., 2022). In another study, pre-existing hearing loss and age were also associated with an increased risk of hearing loss (Hong, Dowdy, Dooley, Francis, Budhathoki & Han et al., 2020).

South Africa is also one of the first countries to use BDQ as a therapeutic option for managing toxicity, most notably the hearing loss that occurs with injectables (Guglielmetti, Hewison, Avaliani, Hughes, Kiria & Lomtadze et al., 2017) therefore, the continued use of the injectable agent, could mean that South Africa is potentially facing the risk of a significant proportion of the DR-TB population acquiring an irreversible ototoxic induced hearing loss (Bardien et al. 2009).Second-line injectable agents (IAs) have been the cornerstone of treatment for MDR-TB for decades although evidence on the efficacy of IAs is limited, there is an expanding body of evidence on the serious adverse events caused by these drugs (Reuter, Tisile, Von Delft, Cox, Cox & Ditiu et al., 2017)

5.6 Conclusion

South Africa has a high burden of drug-resistant tuberculosis (DRTB) and until recently, ototoxic aminoglycosides were predominant in treatment regimens. Drug-resistant TB treatment with bedaquilines caused clinically and statistically significant deterioration of hearing loss in patients, most prominently at high frequencies. Although public health interventions to prevent hearing loss have been deemed cost-effective and have meaningful individual and economic implications, hearing loss and its prevention consistently receive inadequate attention as a global public health priority. Despite the serious impacts of hearing loss, little is known regarding prevalence of ototoxic hearing loss after treatment for DR-TB.

5.7 Recommendations

When the use of injectable ototoxic medications is unavoidable, audiological ototoxicity monitoring is essential to optimise hearing-related outcomes

Audiological ototoxicity monitoring encompasses the regular assessment of patients' hearing thresholds during treatment to detect early changes in hearing, so that treatment regimens can be adjusted and disabling hearing loss can be avoided (WHO, 2021b). In response to the high prevalence of ototoxic hearing loss associated with

DRTB treatment, the South African National TB Control Programme implemented the National Ototoxicity Prevention Programme to improve the access to audiological monitoring and reduce the prevalence of ototoxic hearing loss

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APPENDIX A: DATA COLLECTION TOOL

ID | | | |

SECTION A: SOCIO-DEMOGRAPHICS

Gender ☐ Male ☐ Female

Age ☐ years

Previous drug treatment history

☐ Newly diagnosed
☐ Relapse
☐ Prev. user of injectable
☐ New on BDQ

Employment status

☐ Employed
☐ Unemployed

Type of hearing loss

☐ Unilateral
☐ Bilateral

Hearing loss onset

☐ Sudden
☐ Gradual
☐ No change

SECTION B: BASELINE ASSESSMENT

		PURE TONE AUDIOMETRY											
		.25	**.5**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**
Right ear	AC												
	BC												
Left ear	AC												
	BC												

SECTION C: FOLLOW-UP ASSESSMENT

		Classification system for ototoxic hearing loss: ASHA, 1994	Is the hearing loss a new

		20dB or more Loss at any one frequency		10dB or more Loss atleast 2 consecutive frequencies		Loss response at 3 consecutive frequencies		change when compared to the baseline or previous audiograms	
Treatment Phase		YES	NO	YES	NO	YES	NO	YES	NO
Month 1									
Month 2									
Month 3									
Month 4									
Month 5									
Month 6/ Exit Audiogram									

APPENDIX B: PERMISSION LETTER TO CONDUCT THE STUDY

Zitulele Hospital Private Bag X 504 Mqanduli 5080

For queries
Name: Sibulele Matikinca
Cel: 083 6738023
Tel: 047 573 8935
Fax: 047 573 8942
sibulelematikinca@gmail.com

REQUEST FOR PERMISSION TO CONDUCT RESEARCH ZITHULELE HOSPITAL

Dear Mrs Matebese

I am Sibulele Matikinca, a Speech therapist and Audiologist at Zithulele Hospital. I'm a master's student at the University of Limpopo. One of the requirements for the program is to conduct a mini dissertation. The title of my research topic is "The effects of bedaquiline on hearing loss amonst multi-drug resistant-tubertolosis (MDR-TB) patients at Zithulele Hospital, Eastern Cape Province". This project will be conducted under the supervision of Dr Ntuli and co-supervisor Dr maimela both working at the University of Limpopo. I am asking for consent to access and analyse audiograms of MDR-TB patients at Zithulele Hospital. I have included a copy of my research proposal, assessment tool and consent forms. Upon completion of the study, I will provide the hospital and the Department of Health with a copy of the research report. Thank you for considering my request.

Yours sincerely

Sibulele Matikinca

APPENDIX C: Approval from Turfloop Research Ethics Committee (TREC)

University of Limpopo
Department of Research Administration and Development
Private Bag X1106, Sovenga, 0727, South Africa
Tel: (015) 268 3935, Fax: (015) 268 2306, Email: anastasia.ngobe@ul.ac.za

TURFLOOP RESEARCH ETHICS COMMITTEE

ETHICS CLEARANCE CERTIFICATE

MEETING: 24 February 2022

PROJECT NUMBER: TREC/24/2022: PG

PROJECT:

Title:	The Burden of Hearing Loss amongst Multi-Drug Resistant-Tuberculosis Patients on Bedaquiline at Zithulele Hospital, Eastern Cape Province
Researcher:	S Matikinca
Supervisor:	Dr E Maimela
Co-Supervisor/s:	N/A
School:	Health Care Science
Degree:	Master's in Public Health

PROF P MASOKO
CHAIRPERSON: TURFLOOP RESEARCH ETHICS COMMITTEE

The Turfloop Research Ethics Committee (TREC) is registered with the National Health Research Ethics Council, Registration Number: **REC-0310111-031**

Note:

i) **This Ethics Clearance Certificate will be valid for one (1) year, as from the abovementioned date. Application for annual renewal (or annual review) need to be received by TREC one month before lapse of this period.**

ii) **Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee, together with the Application for Amendment form.**

iii) **PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.**

Finding solutions for Africa

APPENDIX D: Permission from Eastern Cape Department of Health Research Committee, Eastern Cape Province

Province of the
EASTERN CAPE
HEALTH

Enquiries: Yvonne Sixolo Tel no: 079 074 3859

Email: Yvonne.Sixolo@echealth.gov.za / yvsixolo@gmail.com

Date: 17 March 2022

THE BURDEN OF HEARING LOSS AMONGST MULTI-DRUG RESISTANT-TUBERCULOSIS PATIENTS ON BEDAQUILINE AT ZITHULELE HOSPITAL, EASTERN CAPE PROVINCE. (EC_202203_001)

Dear Ms. S. Matikinca

The department would like to inform you that your application for the abovementioned 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 Department of Health in writing.

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 COMMITTE

2030 NDP

TOGETHER, MOVING THE HEALTH SYSTEM FORWARD

APPENDIX E: Permission from Zithulele Hospital, Eastern Cape Province

ZITHULELE HOSPITAL

Province of the Eastern Cape • Iphondo leMpuma-Koloni
Department of Health • Isebe leZempilo

Enquiries: Dr CB Gaunt

Ref: Matikinca S – support for study

Date: 9 January 2019

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www.zithulele.org

To Whom it May Concern

REGISTRATION FOR MPH: SIBULELELE MATIKINCA

This letter serves to acknowledge that I am aware that Ms Sibulelele Matikinca, who works at Zithulele Hospital as a Speech Therapist and Audiologist: Grade 1, is registering for a Masters in Public Health and will require time away from work at certain periods in order to fulfil the requirements of her course.

I fully support this course of study and look forward to the growth that will accompany it.

Please contact me should you require any further details regarding this.

Yours faithfully

Dr Benjamin Gaunt
Clinical Manager
Zithulele Hospital

APPENDIX F: Evidence of language edit

Tiyiselani & Rapetsoa scientific services

Article Publishing • Proof-reading • Editing

85 Compensatie Street,
Duplex Park No 5,
Polokwane, 0699
Postnet Suite 179 • Private Bag X9307 • Polokwane •
0700 Tel: 074 866 6914 • Fax: 0864154022

Date: 22 July 2022

To Whom it May Concern

I hereby confirm that I have proof-read the Master of Public Health mini-dissertation titled: **"THE BURDEN OF HEARING LOSS AMONGST MULTI-DRUG RESISTANT-TUBERCULOSIS PATIENTS ON BEDAQUILINE AT ZITHULELE HOSPITAL, EASTERN CAPE PROVINCE"** authored by Ms S Matikinca with student number **201306326**. The document has been edited and proofread for grammar, spelling, punctuation, overall style and logical flow. Considering the suggested changes that the author may or may not accept, at her discretion, each of us has our own unique voice as far as both spoken and written language is concerned. In my role as proof-reader, I try not to let my own "written voice" overshadow the voice of the author, while at the same time attempting to ensure a readable document. Please refer any queries to me.

Malatji MS