HEARING LOSS AMONGST DR-TB PATIENTS THAT RECEIVED EXTENDED HIGH FREQUENCY PURE TONE AUDIOMETRY MONITORING (KUDUwave) AT THREE DR-TB DECENTRALIZED SITES IN KWAZULU-NATAL

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KEY WORDS

Ototoxicity

Drug-resistant TB

Sensorineural hearing loss

Aminoglycosides

Extended high frequency audiometry

ABBREVIATIONS

ART – Antiretroviral therapy

ABR - Auditory Brainstem Response

BDQ – Bedaquiline

CRF – Chronic renal failure

dB – Decibels (unit of intensity of sound)

dB HL – Decibels hearing level dBA – A-weighted decibels

DR DR-TB – Drug- resistant tuberculosis

ETO - Ethionamide

HIV – Human Immuno Deficiency virus

Hz – Hertz (unit of frequency) INH – Isoniazid

kHz – Kilohertz (= 1 000 Hz) KM – Kanamycin

MDR MDR-TB – Multi Drug Resistant Tuberculosis

MFX – Moxifloxacin

NDoH – National Department of Health

OAE -Outo Acoustic emissions

OR – Odds ratio

PTA – Pure tone audiometry

RIF – Rifampicin

RR-TB – Rifampicin- Resistant Tuberculosis or RIF-resistant tuberculosis

SNHL – Sensory Neural Hearing Loss

TB – Tuberculosis

TRD – Terizidone

WHO – World Health Organization

XDR-TB – Extensively drug-resistant tuberculosis

OPERATIONAL DEFINITIONS

Hearing loss is a reduction in the ability to hear sounds, It can range in severity from mild to profound as stipulated in table 1 below. 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.

Table 1: Common ways to classify hearing loss

Degree of hearing loss	**Hearing loss range (dB HL)**
Normal	–10 to 15
Slight	16 to 25
Mild	26 to 40
Moderate	41 to 55
Moderately severe	56 to 70
Severe	71 to 90
Profound	91+
Source: Clark, J. G. (1981). Uses and abuses of hearing loss classification. *Asha, 23*, 493–500.	

Figure (i): Audiogram produced by Conventional audiometry and showing the degrees of hearing loss

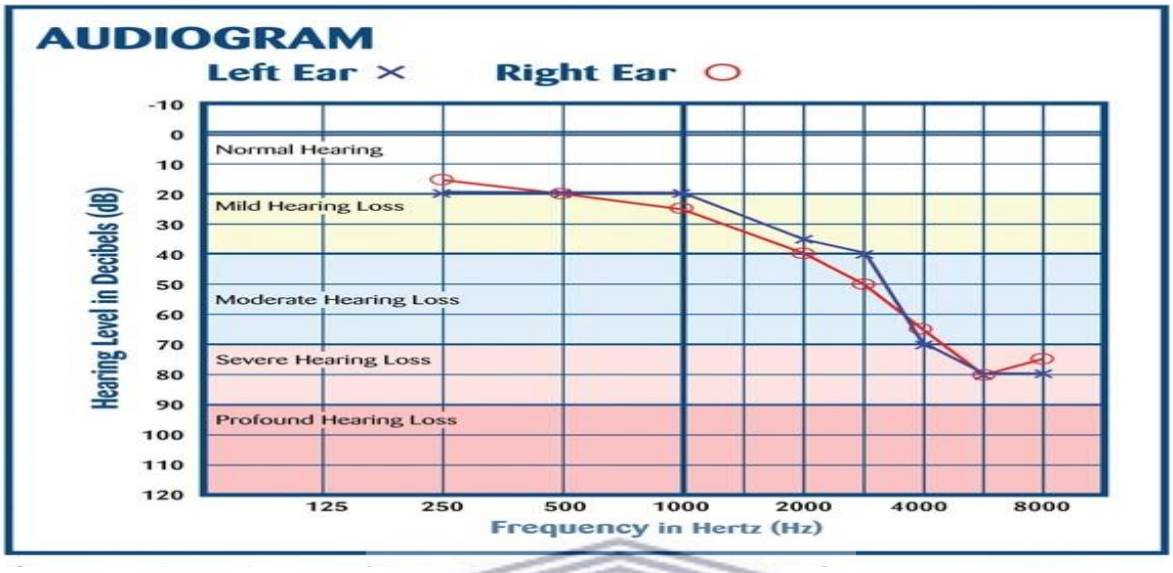


Figure (ii): An audiogram produced by an extended high frequency audiometer

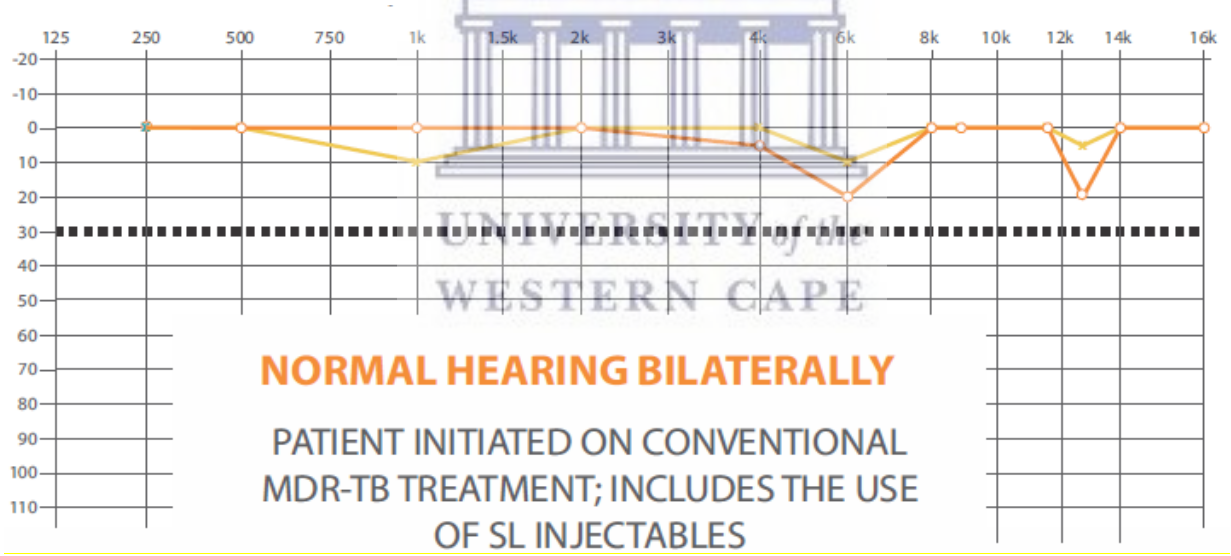
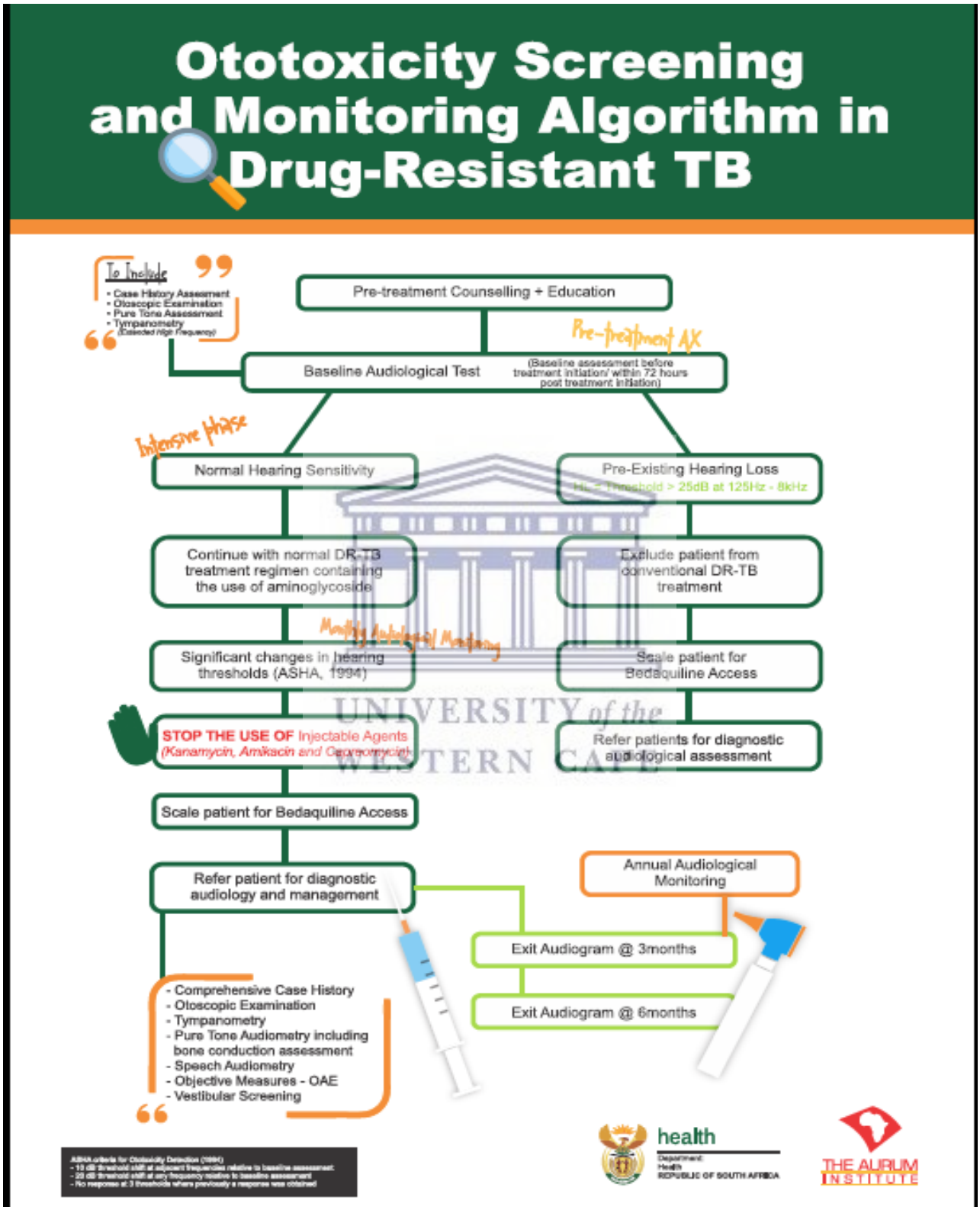


Figure (iii): National Department of Health, Ototoxicity management algorithm



ABSTRACT

Ototoxic induced hearing loss is a common adverse event related to aminoglycosides used in Multi Drug Resistant -Tuberculosis treatment. Exposure to ototoxic drugs damages the structures of the inner ear. Symptomatic hearing loss presents as tinnitus, decreased hearing, a blocked sensation, difficulty understanding speech, and perception of fluctuating hearing, dizziness and hyperacusis/recruitment. The World Health Organization (1995) indicated that most cases of ototoxic hearing loss globally could be attributed to treatment with aminoglycosides.

The aim of the study was to determine the proportion of DR-TB patients initiated on treatment at three decentralized sites during a defined period (1st October to 31st December 2015) who developed ototoxic induced hearing loss and the corresponding risk factors, whilst receiving audiological monitoring with an extended high frequency audiometer (KUDUwave).

A retrospective cross-sectional study was conducted. Cumulatively across the three decentralized sites, 69 patient records were reviewed that met the inclusion criteria of the study. The mean age of the patients was 36.1, with a standard deviation (SD) of 10.7 years; more than half (37) were female. Ototoxicity , a threshold shift, placing patients at risk of developing a hearing loss was detected in 56.5% (n=39)of patients and not detected in 30.4%(n=21).The remaining 13,1% (n=9)is missing data. As a result, the regimen was adjusted in 36.2% of patients. .

From the 53 patients who were tested for hearing loss post completion of the injectable phase of treatment, 22.6% (n=12) had normal hearing, 17.0 % (n=9) had unilateral hearing loss, and 60.4% (n=32) had bilateral hearing loss. Therefore, a total of 41 patients had a degree of hearing loss: over 30% (n=22)had mild to moderate hearing loss, and only about 15% (n=11)had severe to profound hearing loss. Analysis of risk factors showed that having ototoxicity detected and not adjusting regimen significantly increases the risk of patients developing a hearing loss.

The key findings of the study have shown that a significant proportion of DR-TB patients receiving an aminoglycoside based regimen are at risk of developing ototoxic induced hearing loss, despite receiving audiological monitoring with an extended high frequency audiometer that allows for early detection of ototoxicity (threshold shift).

DECLARATION

I declare that **PREVENTING HEARING LOSS IN DRUG-RESISTANT TUBERCULOSIS PATIENTS RECEIVING AMINOGLYCOSIDES:** THE INTRODUCTION OF HIGH FREQUENCY MOBILE AUDIOMETRY IN THE MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS is my own work, that it has not been submitted for any degree or examination at any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Full name .....

Date .....

Signed .....

Contents

KEY WORDS ii
ABBREVIATIONS iii
OPERATIONAL DEFINITIONS v
ABSTRACT viii
DECLARATION ix
CHAPTER 1: INTRODUCTION 13
1.1 A GLOBAL OVERVIEW OF DRUG RESISTANT TUBERCULOSIS (DR-TB) AND PATIENT CLASSIFICATION 13
1.2 OVERVIEW OF DR-TB MANAGEMENT IN SOUTH AFRICA 14
1.3 STANDARD MDR-TB REGIMEN AND DR TB PATIENT CATEGORY IN SOUTH AFRICA 14
1.4 OTOTOXICITY AS AN ADVERSE EVENT ASSOCIATED WITH AMINOGLYCOSIDE ADMINISTRATION 15
1.5 MDR-TB MODEL OF CARE AND OTOTOXICITY MANAGEMENT IN SOUTH AFRICA 17
1.6 INTRODUCTION OF THE MOBILE AUDIOMETER TO IMPROVE OTOTOXICITY MANAGEMENT OF MDR-TB PATIENTS 19
1.9 AIM 21
1.10 OBJECTIVES 21
1.11 THE STRUCTURE OF THE MINI-THESIS 21
CHAPTER 2: LITERATURE REVIEW 23
2.1 INTRODUCTION 23
2.2 EPIDEMIOLOGY AND SURVEILLANCE OF OTOTOXICITY AND HEARING LOSS 23
2.3 FACTORS ASSOCIATED WITH OTOTOXICITY 25
2.4 EARLY SCREENING AND MONITORING FOR OTOTOXICITY 28
2.5 HEALTH/AUTOMATED INTERPRETATION 29
2.6 SUMMARY 30
CHAPTER 3 METHODOLOGY 32
3.1 INTRODUCTION 32
3.2 STUDY DESIGN 32
3 .3 STUDY SETTING 32
3.4 STUDY POPULATION AND SAMPLING 33
3.5 JUSTIFICATION OF DATA SOURCE 34
3.6 PRE-TEST OF DATA ABSTRACTION TOOL 35
3.7 DATA COLLECTION 35

3.8 ANALYSIS 36
3.9 VALIDITY AND RELIABILITY 36
3.12 GENERALISABILITY 37
3.13 ETHICAL CONSIDERATIONS 37
CHAPTER 4: RESULTS 39
4.1 INTRODUCTION 39
4.2 DESCRIPTION OF THE STUDY POPULATION'S BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS 39
4.3 HEARING STATUS AFTER SIX MONTHS OF INJECTABLE ADMINISTRATION 42
4.4 SUMMARY 47
CHAPTER 5: DISCUSSION 48
5.1 DISCUSSION OF THE STUDY POPULATION'S BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS 48
5.2 PATIENTS THAT PRESENTED WITH A HEARING LOSS 49
5.3 HEARING STATUS AFTER SIX MONTHS OF INJECTABLE ADMINISTRATION 49
5.4 THE RISK FACTORS ASSOCIATED WITH DR-TB PATIENTS DEVELOPING OTOTOXICITY RESULTING IN HEARING LOSS 51
5.5 STUDY LIMITATIONS 52
CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS 54
6.1 CONCLUSIONS 54
6.2 RECOMMENDATIONS 55
REFERENCES 57
APPENDICES: DATA ABSTRACTION TOOL 65

LIST OF TABLES

TABLE 1 POPULATION DATA PER DISTRICT 35
TABLE 2. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF MDR-TB PATIENTS INITIATED ON DR-TB 45
TABLE 3. DEGREE OF HEARING LOSS POST THE INJECTABLE PHASE 50
TABLE 4. HEARING LOSS POST THE INJECTABLE PHASE 50
TABLE 5. RISK FACTORS ASSOCIATED WITH HEARING LOSS 51

LIST OF FIGURES

FIGURE (iv) MDR TB PATIENTS STARTED ON TREATMENT 44

FIGURE 1: AGE AND GENDER DISTRIBUTION…… ……. 45

FIGURE 2: DURATION ON INJECTABLE…… …… 46

FIGURE 3: DR- TB DIAGNOSIS TO TREATMENT INITIATION …… ……..47

FIGURE 4: NUMBER OF FOLLOW UP HEARING TESTS……..48

FIGURE 5: HEARING LOSS POST THE INJECTABLE PHASE…….49

CHAPTER 1: INTRODUCTION

1.1 A GLOBAL OVERVIEW OF DRUG RESISTANT TUBERCULOSIS (DR-TB) AND PATIENT CLASSIFICATION

Despite the strides that have been made globally to combat Tuberculosis (TB), it remains an area of concern for global health. This is reflected in the data reported to the World Health Organization (WHO) in 2013 which showed that globally, nine million people developed TB and approximately one and a half million people died because of the disease (WHO, 2014). Furthermore, 360 000 were also diagnosed as HIV positive. The annual increase of diagnosed Rifampicin-resistant tuberculosis (RR-TB) cases in South Africa has been noted with concern by the health authorities (WHO, 2014). RR-TB is defined as, resistance to rifampicin, multidrug-resistant tuberculosis (MDR-TB) is defined as resistance to the first-line drugs, isoniazid (INH) and rifampicin (RIF). RR-TB at present is being utilized as the proxy for MDR-TB at both an international and national level (WHO, 2014).

The WHO (2014) indicated that 123 000 RR-TB cases, eligible for treatment with MDR-TB regimens, were notified worldwide of which, India, the Russian Federation and South Africa accounted for almost half of these notifications. The number of extensively drug-resistant tuberculosis (XDR- TB) cases also showed a significant increase in comparison to the previous years. XDR-TB is defined as a patient with bacteriologically proven TB whose disease is due to bacilli showing in vitro MDR-TB together with resistance to any fluoroquinolone plus resistance to one or more of the following injectable anti-TB drugs: kanamycin, amikacin and capreomycin (South African National Department of Health, 2013). Globally in 2014, 4 044 XDR-TB patients were enrolled on treatment as compared to 3 284 in 2013 (WHO, 2014).

The management of drug-resistant TB (DR-TB) is often clinically complex and in addition to various social challenges, may result in poor treatment outcomes. The 2011 global MDR-TB treatment outcomes showed that only 48% of the patients were successfully treated, 16% died, 24% did not have their treatment outcome documented or interrupted treatment, and 12% failed treatment. The treatment success rate for XDR-TB patients in the 2011 cohort was only 22% (WHO, 2012).

1.2 OVERVIEW OF DR-TB MANAGEMENT IN SOUTH AFRICA

TB continues to be a leading cause of mortality in South Africa. In a population of 52 776 000, 328 896 TB cases were reported in 2013, of which 89 000 patients have died (WHO, 2014). South Africa has the third highest incidence of TB globally and the fifth highest number of MDR-TB cases in the world (WHO, 2011). Harris et al. (2012) concluded that HIV is a major health issue in developing countries. They further support this with statistical evidence showing, that the number of patients living with HIV in South Africa increased from 4.2 million in 2001 to 5.4 million in 2011. The TB epidemic is fuelled by the HIV epidemic that reached a prevalence of 12.2% in 2012 (Shisana et al. 2014). The TB-HIV co-infection rate in South Africa is very high, which necessitates the administration of anti-retroviral therapy (ART) and TB treatment simultaneously.

While evidence suggests that both TB incidence and prevalence are declining due to improvements in its detection and treatment in South Africa, MDR-TB remains a public health crisis (South African Government, 2013). MDR-TB presents with more complex challenges in terms of increased treatment cost, an extended treatment period and a variety of side effects associated with drug toxicities, resulting in higher defaulter rates and lower rates of treatment success. In 2011, of those people diagnosed with MDR-TB in South Africa, 20% defaulted from treatment, 18% died, and treatment failed for a further 5% (WHO, 2013). The mortality rate amongst XDR-TB patients is high due to a very low treatment success rate. Approximately 50% of people with XDR-TB in South Africa died in 2010 (Ndjeka, 2014).

1.3 STANDARD MDR-TB REGIMEN AND DR TB PATIENT CATEGORY IN SOUTH AFRICA

A study by Petersen et al. (2015), showed that patients who had previous exposure to aminoglycosides are more likely to present with ototoxicity than a new patient that has never received aminoglycosides. For the study, these patient categories assigned to patients at the start of treatment are defined as: A **new** patient has not received anti-tuberculosis medicines or who has received anti- tuberculosis medicines for less than one month. A **Relapsed (R)** patient whose most recent treatment outcome was "cured" or "treatment completed", and who is subsequently diagnosed with bacteriologically positive TB by sputum smear microscopy, culture or GeneXpert. **Treatment after loss to follow up (TAL):** A patient who returns to treatment following

interruption of treatment for two or more consecutive months. **Treatment after failure of Category I (TF1)** patient who has received Category I also known as regimen 1 for TB and in whom treatment has failed. Failure is defined as sputum smear positive at five months or later during treatment. **Treatment after failure of Category II (TF2):** A patient who has received Category II also known as regimen 2 for TB and in whom treatment has failed. Failure is defined as sputum smear positive at seven months or later during treatment. The **Other** category refers to patients who may not fit into any of the above categories. Examples include: sputum smear positive patients who received treatment other than Category I or II (possibly in the private sector); patients who have received several unsuccessful treatments (South African National Department of Health, 2013).

The standard regimen for the management of MDR-TB in South Africa in 2015 at the time this study was conducted, consisted of, Moxifloxacin, Ethionamide, Pyrazinamide, Terizidone and Kanamycin as per the national guidelines on the management of drug resistant TB cases in South Africa (South African National Department of Health, 2013). The guidelines recommend that MDR-TB patients receive the kanamycin or amikacin injectable drugs (aminoglycoside) daily, seven days a week, for the duration of the intensive phase treatment period that is approximately six months. After patients, have completed the intensive phase they continue the oral medication for an additional 18 months. The total duration of MDR-TB treatment, on average, is twenty-four months (South African National Department of Health, 2013).

1.4 OTOTOXICITY AS AN ADVERSE EVENT ASSOCIATED WITH AMINOGLYCOSIDE ADMINISTRATION

There are many side effects associated with the MDR-TB drugs. Zhang et al. (2017:2348) stated that: "Adverse events are under appreciated negative consequences that are significant clinical problems for patients undergoing anti - MDR-TB treatment due to longer duration treatment and the need for concurrent use of multiple second line drugs". Their study further showed that 90,7% of the patients enrolled experienced at least one type of adverse event and 55,2% of them required a change to their MDR-TB treatment.

It is believed that the most debilitating side-effect experienced by DR-TB patients with permanent repercussions for the patient's quality of life is ototoxicity that results in a permanent hearing loss (AAA, 2009; Duggal and Sarkar, 2007) due to aminoglycoside administration.

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(Ndjeka et al. 2015). This provides the prospect for early detection of ototoxicity at the higher frequencies and a predictor of ototoxic hearing loss.

The WHO (1995:2) stated that "ototoxicity signifies the harmful effect of a drug on the cochlea ". The human ear possesses the ability to hear an auditory range up to 20 000Hz and the involvement of extended high frequency pathology is usually linked to age-related hearing loss, acoustic trauma or ototoxicity. Exposure to ototoxic drugs damages the structures of the inner ear. Symptomatic hearing loss presents as tinnitus, decreased hearing, a blocked sensation, difficulty understanding speech, and perception of fluctuating hearing, dizziness and hyperacusis.

The major components evaluated in hearing loss for MDR-TB patients receiving aminoglycoside therapy are the frequency and the intensity of the sound. The frequency refers to the pitch or tone at which the patient hears a sound. Human hearing is typically in the range of 20Hz (a low pitch sound) to 20 000Hz (a high pitch sound). The intensity refers to the loudness of the sound (expressed in decibels) required to be heard (AAA, 2009). Aminoglycosides have been known to affect hearing initially in the extended high frequencies (9000 – 20 000 Hz) prior to presentation of hearing loss in lower frequencies (Dreschler et al. 1985; Fausti et al. 1999). Therefore, studies that report hearing loss based on patient complaints or testing across the conventional frequency range (250–8 000 Hz) may underestimate the ototoxic effects of these drugs.

Early ototoxic sensory neural hearing loss (SNHL)may go unrecognized by the patient and initially manifests as an increase in the threshold of the higher frequencies (>8 000 Hz) (AAA, 2009). With progression, lower speech frequencies are affected, with the patient becoming profoundly hearing impaired. This may occur even if the offending drug is discontinued (AAA, 2009). 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).

A review conducted by Seddon et al. (2012) describing the American Speech-Language-Hearing Association (ASHA) guidelines for ototoxicity detection and monitoring further recommended that

Pure Tone (PT) Audiometry should be carried out for frequencies 250 Hz to 8 000 Hz, and where possible 12 000 Hz. Additionally, octave and inter-octave intervals (1 500, 3 000 and 6 000 Hz) need to be tested as well. This should be done at baseline and, for ototoxic drugs testing, should be conducted weekly. Ideally extended -high frequency audiometry greater than 8 000 Hz, i.e. 12 000 Hz to 20 000 Hz should be assessed as well, as this allows for changes to be recorded and documented, before frequencies in the speech spectrum become affected.

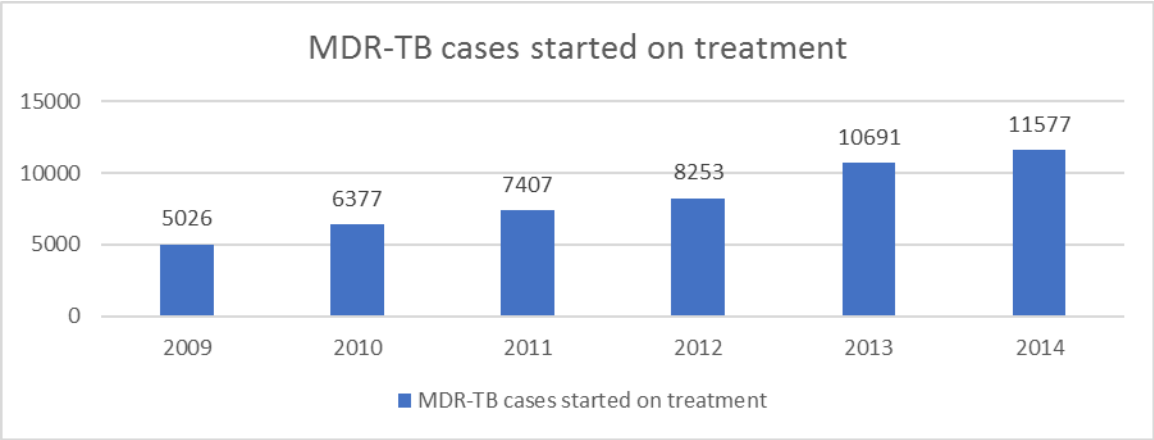
1.5 MDR-TB MODEL OF CARE AND OTOTOXICITY MANAGEMENT IN SOUTH AFRICA

In 2011, the National Department of Health (NDoH) released the "Multi-Drug Resistant Tuberculosis Policy Framework on Decentralized and Deinstitutionalized Management for South Africa", and in 2013, the "Management of Drug-Resistant Tuberculosis Policy Guidelines" were updated (South African National Department of Health, 2013). These documents emphasize the need for decentralization of MDR-TB treatment as a more effective means of addressing the disease burden in South Africa than centralized care requiring hospitalization. Specifically, the previous requirement of lengthy hospitalization for MDR-TB patients had resulted in delayed initiation of treatment, inadequate bed capacity, poor infection control, poor treatment adherence and poor treatment outcomes, ultimately contributing towards increasing rates of MDR-TB (Loveday et al. 2015). Decentralized care allows for patients to be managed on an ambulatory basis that requires no hospitalization and improves access to care.

For a health care facility to be operationalized as a decentralized site they need to meet the essential requirements that is: (1) Access to laboratory services, to diagnose and monitor DR-TB patients, (2) The availability and access to DR-TB drugs, at the appropriate levels of care, (3) A doctor or nurse to initiate care and (4) access to audiology services (to prevent hearing loss due to ototoxicity), prior to starting treatment and follow up at regular intervals (South African National Department of Health, 2015).

The figure below shows the significant increase of MDR-TB cases started on treatment annually in South Africa.

Figure (iv): MDR-TB cases started on treatment, source: EDRWeb (Ndjeka, 2015)



National Electronic Drug Resistant Tuberculosis Register (EDRWeb)

Implementation of the decentralized MDR-TB model of care has increased the number of treatment sites from 11 centralized treatment sites to 674 decentralized treatment initiation sites (South African National Department of Health,2015). The South African National DR-TB Guidelines (2013:22), state "all newly diagnosed patients should commence DR-TB treatment within five days of diagnosis". The guidelines also recommend that prior to commencing DR-TB treatment every patient should receive a baseline hearing screening (South African National Department of Health, 2013).

During the intensive phase of DR-TB treatment there should be monthly follow-up visits to monitor for potential ototoxicity (South African National Department of Health, 2013). Should a patient be identified as high risk, there should be more frequent follow-ups.

However, having more sites providing MDR-TB care that are mostly at primary health care level creates a challenge with regards to audiology capacity because these services are mostly based at a tertiary level. This impacts on the performance of the DR-TB ototoxicity prevention programme. There are currently 577 audiologists in the South African public sector (Health Professions Council of South Africa, 2015). The aforesaid in relation to the number of DR-TB patients diagnosed annually and started on DR-TB treatment , an increased number of decentralized DR-TB sites and lack of equipment to monitor ototoxicity resulted in limited access to audiology services .

1.6 INTRODUCTION OF THE MOBILE AUDIOMETER TO IMPROVE OTOTOXICITY MANAGEMENT OF MDR-TB PATIENTS

Textbook monitoring requirements for ototoxicity in DR-TB patients receiving aminoglycoside therapy requires a test battery approach that includes: a comprehensive case history, high frequency Pure Tone Audiometry (hfPTA) (250–20 000hz, with both air and bone conduction), outo acoustic emissions (OAE), as well as auditory brainstem reflex testing (ABR'S). However, the most essential of the aforementioned is access to the extended high frequency audiometer, with a soundproof testing booth that is not readily available within the South African context, due to limited resources. This limitation results in most treatment sites only having access to conventional Pure Tone Audiometry (cPTA) with a frequency ranging between 250 and 8000 Hz. Any shifts in the previously mentioned range is considered a late response to ototoxicity management.

The audiological services in South African state facilities are not designed to meet the required demand because of a lack of necessary and sufficient resources as well as the limited number of staff (Khoza-Shangase & Stirk, 2016). A consequence of this is limited ototoxicity monitoring, which negatively impacts on the provision of appropriate aural rehabilitation services.

Peer (2013) cited that screening programmes are the best mechanisms to detect early hearing loss. The strategy of the previously mentioned is intended to reduce the morbidity of the disease process being tested. It is designed to identify the auditory pathology due to ototoxicity (threshold shift) in the early stages (extended high frequencies) when treatment is most likely to be successful. However, it does not replace the gold standard that is pure tone Audiometry and the referral of patients to an Audiologist for further diagnostics.

Therefore, to address the challenges relating to ototoxicity management of MDR-TB patients and South Africa's failure to adequately respond to the need, the KUDUwave™ was developed by Dr Dirk Koekemoer in 2006. The KUDUwave™ is an extended high frequency mobile audiometer based on telemedicine principles, that allows for tele-audiometry with a web-based programme (Swanepoel & James, 2010; Bexelius et al. 2008). The purpose of the KUDUwave™ was to implement a national ototoxicity screening programme with the focus on early identification and regular follow up to prevent the onset of ototoxicity that leads to an irreversible hearing loss.

It is a computer-software-controlled audiometer connected to a laptop via a USB port that is equipped with earphones that surround the pinna (external ear). The KUDUwave™ has been shown

to provide accurate diagnostic audiometric results (Swanepoel et al. 2010). The device is portable and compact, affording the opportunity to take the service closer to patients. Midlevel workers can be trained to screen patients. The foam insert earphones are placed inside the ear canal; noise-cancelling headphones are placed over the top of the ear. The KUDUwave™ monitors background noise with an external microphone (on the outside of the circumaural earphone cup) and internal microphone (on the inside of the enclosing earphone cup) to ensure test compliance, meaning that the environment is conducive because there is no booth. The specifications state that the KUDUwave™ can test accurately up to 10 dBHL (decibels hearing level) in 50 dBA (relative loudness of sounds in air perceived by the human ear). The KUDUwave™ has the facility to test air and bone conduction and can be used for manual or automated testing. The headphone is positioned on the patient's head and the automated programs guide the examination from start to finish. There is no booth required, therefore addressing the infrastructure challenges within the South African public health sector. A report interpreting the results is generated and sent to the person who conducted the test via short message service (SMS) or email. This practice ensures early identification, as well as the measures the severity of ototoxic induced hearing loss (Swanepoel et al. 2008).

1.7 PROBLEM STATEMENT

Aminoglycosides, which can cause irreparable hearing loss, were until recently, included in most DR-TB regimens (South African National Department of Health, 2013). Regular monitoring of patient's response to treatment and quickly addressing side effects increases the chance of treatment success. If hearing with the focus on ototoxicity management could be routinely monitored in all facilities where patients with DR-TB were being managed, treatment regimens could be modified to limit hearing loss. Effective monitoring of ototoxic induced hearing loss requires extended high frequency audiometry (8000 - 20 000HZ). Most health facilities have access to conventional audiometry (250 - 8000HZ), that allows for very little or no opportunity to intervene and reduce the risk of a hearing loss, as the damage is only noted when the lower frequencies are already involved and has progressed to the advanced stages. In 2015, KUDUwave™ machines were distributed nationally to selected decentralized health facilities, which included government run district hospitals, TB hospitals, community health centres and primary health care facilities to enhance the decentralized management of DR-TB patients (Claasen, 2014). It was hoped that this practise

would improve access to audiological monitoring, with the intent of conserving the hearing of DR-TB patients by allowing for early detection of ototoxicity that would afford sufficient opportunity for the DR-TB regimen to be adjusted to prevent a hearing loss from occurring.

1.8 PURPOSE

The purpose of the study is to inform decision makers responsible for planning and policy development about the risks associated with hearing loss amongst DR -TB patients that receive aminoglycosides.

1.9 AIM

The aim of the study was to determine the proportion of DR-TB patients initiated on treatment at three decentralized sites (Madadeni, Montebello and Estcourt Hospitals) during a defined period (1st October to 31st December 2015) who developed an ototoxic induced hearing loss whilst receiving audiological monitoring with an extended high frequency audiometer (KUDUwave) and assess the associated risk factors.

1.10 OBJECTIVES

1. To determine the number of DR-TB patients that presented with ototoxicity (threshold shifts at the extended high frequency: 9000 -20 000Hz)
2. To determine how many of the DR-TB patients that presented with ototoxicity (threshold shifts at the extended high frequency: 9000 -20 000Hz) progressed to develop a degree of hearing loss (mild-moderate; moderate-severe: profound)
3. To identify the possible risk factors associated with hearing loss amongst DR-TB patients
4. To determine the number of audiological, follow up visits received by DR-TB patients
5. To determine the numbers of patients that had their regimens adjusted post ototoxicity (threshold shifts at the extended high frequency: 9000 -20 000Hz) detection.

1.11 THE STRUCTURE OF THE MINI-THESIS

The research will be presented in five chapters. The following chapter will focus on the literature review exploring both quantitative and qualitative studies. The literature review will discuss the epidemiology and surveillance of ototoxicity, the risk factors associated with ototoxic induced

hearing loss, the effects of HIV management on hearing, early screening and monitoring for ototoxicity and the role of e-health/automated interpretation.

Chapter Three will explore the methodology utilized to conduct the study, focusing on the study setting, the study population as well as the data collection methods and analyses.

Chapter Four is the results chapter that considered the findings in relation to the study objectives. Chapter Five focuses on the discussion /interpretation of the findings and Chapter Six speaks to the conclusion and the recommendations.

CHAPTER 2: LITERATURE REVIEW

2.1 INTRODUCTION

This chapter will reflect on, the epidemiology and the surveillance of ototoxic induced hearing loss at an international as well as a national level within the literature. It will explore the risk factors associated with ototoxic induced hearing loss. The standard for audiological monitoring and screening of ototoxicity will be discussed. There is significant information about the effects of HIV on hearing and how it contributes to the loss of hearing. There will be further discussion concerning the role of E-Health/Telemedicine in the management of ototoxicity.

The standardized Multi Drug Resistant Tuberculosis (MDR-TB) treatment regimen in 2015, when the study was conducted included toxic medications with numerous side-effects. A study in 2006 demonstrated that 95% of their study population experienced side-effects during their treatment (Gülbay et al. 2006). The major side effects included; ototoxicity (1.7%), hepatotoxicity (0.8%), neuropsychiatric manifestations (0.7%) and hyperuricemia (0.6%). Ototoxicity(threshold shift) experienced due to the administration of aminoglycosides, (kanamycin or amikacin) is debilitating, irreversible and negatively impedes on the quality of life of DR-TB patients. Streptomycin and gentamicin are known for their vestibulotoxic effects associated with dizziness, ataxia and/or nystagmus whereas kanamycin and amikacin are cochleotoxic and responsible for permanent hearing loss (Semiglou, 2007).

2.2 EPIDEMIOLOGY AND SURVEILLANCE OF OTOTOXICITY AND HEARING LOSS

There are different types of hearing loss namely conductive, sensory neural as well as mixed hearing loss (ASHA, 2009). For the study we focussed on sensory neural hearing loss (SNHL).

SNHL is caused by damage to the sensory hair cells and the stria vascularis in the cochlea. It is also referred to as chemotoxicity. The damage to the cochlear due to aminoglycoside administration is permanent and very debilitating and occurs in two stages. During stage one there is biochemical damage and during the final stage there is cell death (WHO, 1995). The sustained or excessive peak serum concentrations are thought to be a risk factor for developing ototoxicity. The cumulative dose plays an important role in the onset and severity of SNHL (WHO, 1995).

Hearing is considered normal between -10 and 15 dB. The degree of hearing loss is classified as follow: Mild 26 to 40 dB, Moderate 41 to 55 dB, moderately severe 56 to 70B, Severe 71 to 90 dB and Profound 91+ dB (Clark, 1981).

In 2012, the World Health Organization (WHO) released the new estimates on the magnitude of disabling hearing loss greater than 40 dB in adults. It was estimated that there were 360 million persons living with disabling hearing loss, which is over 5% of the world's population. In sub–Saharan Africa the prevalence for disabling hearing loss is estimated to be 9% (WHO, 2012). It is unknown what proportion of the reported hearing loss is attributed to ototoxicity globally. Gülbay et al. (2006) noted that the incidence may be as low as 3.2% during the initial phase of therapy. However, the standard management of DR–TB required a six-month administration of the injectable which could possibly account for most, if not all patients experiencing some degree of hearing loss (Duggal & Sarkar, 2007). There is currently no epidemiological data that is routinely collected with regards to ototoxic deafness and hearing impairment in either developed or developing countries (WHO, 1995). The literature pertaining to this topic appears outdated or is not necessarily relevant to the context of this study. Findings from a national survey in China, conducted in 30 provinces and municipalities showed that 1.7% of those surveyed had hearing impairment and among these 3.7% was due to ototoxic damage. If this was extended to the whole population in China the study estimates that there would be 744 000 cases of hearing impairment caused by ototoxic damage (Yuan et al. 2010).

Wide variability exists in the reported incidence of aminoglycoside ototoxicity. According to the American Speech-Language-Hearing Association (ASHA), the actual frequency of ototoxicity associated with aminoglycosides is unclear due to the inconsistent reporting of results (AAA, 2009; Petersen & Rogers, 2015). Incidence rates appear variable and controversial due to differences in study design and methodologies. Studies have used different criteria to define ototoxicity as well as various means to monitor hearing. The variability can also be ascribed to a lack of standardized guidelines for the monitoring of cochleotoxicity, as well as the lack of universal criteria for ototoxic changes (ASHA, 2009).

A study conducted in 2005, indicated that 69% of MDR-TB patients presented with an adverse event, of which the most frequently observed was ototoxicity at 48% (Torun et al. 2005).

In South Africa, currently, there is no routine data for monitoring of DR-TB associated ototoxicity. However, evidence both locally and internationally, indicated that the incidence of ototoxicity due to amikacin or kanamycin varies between 18 to 57% (De Jager et al. 2002; Duggal & Sarkar, 2007; Almaky et al.2011; Surdy et al. 2011; Ramma et al. 2012; Harris et al. 2012). This is further supported by Harris and Fagan (2012) that showed, 57% of the DR-TB patients in receipt of three months of aminoglycoside therapy, presented with a SNHL and of those that received treatment for HIV, there was a 70% SNHL that occurred.

2.3 FACTORS ASSOCIATED WITH OTOTOXICITY

There have been very limited investigations with regards to aminoglycoside induced ototoxic hearing loss in DR-TB patients and the risk factors associated with it. Petersen et al. (2011) documented the intrinsic risk factors for cochlea ototoxicity as follows: Previous treatment with ototoxic medication, prolonged exposure, renal impairment, genetic susceptibility, poor nutrition, advanced age, excessive noise exposure, pre-existing hearing loss and vestibular dysfunction and HIV/AIDS. The extrinsic risk factors are concomitant treatment with other ototoxic or nephrotoxic drugs, dosage in relation to weight, health practitioner's knowledge of cochleotoxicity, attitude of staff when symptoms are reported and the availability of diagnostic/monitoring services.

2.3.1 Renal impairment

Chronic kidney disease is a common phenomenon amongst MDR-TB patients. This is as result of anti-TB drugs excreted by the kidney accumulateto toxic levels in patients with renal dysfunction. Thodi et al. (2006:3) state that "hearing loss among patients with chronic renal failure (CRF) has been a common finding in studies investigating the effects of renal failure on auditory function. Despite differences in methodologies and indices of auditory function, existence of hearing loss has been a common thread".

Mimi et al. (2011) showed that patients with chronic renal failure have a higher incidence of TB, estimated at 10 to 15 times higher than the general population. Aminoglycosides are predominantly excreted by the kidneys and therefore patients with renal failure have an increased risk for ototoxic induced hearing loss as the serum concentrations remain higher for longer.

Bergstrom and Johnson (1983) described hearing loss in 40% of CRF patients on hemodialysis. A study by Kusakari et al. (1981) on the inner ear function of 229 patients on chronic hemodialysis,

found that 60% had hearing loss, 36% had vestibular dysfunction and 26% had a combination of both. Johnson and Mathog (1976) reported high frequency hearing loss in 61 adults early during hemodialysis. Zeigelboim, Mangabeira-Albernaz and Fukuda (2001) measured thresholds between 9000 and 18 000 Hz in 37 patients with CRF undergoing conservative treatment and a control group with normal hearing function. More severe high-frequency hearing loss was found in those with CRF and it is therefore recommended that kidney functions be assessed prior to the commencement of aminoglycoside administration.

2.3.2 Cumulative dose of aminoglycosides and higher serum aminoglycoside concentrations

DR-TB patients in managed in South Africa in 2015 received aminoglycoside therapy once a day, every day of the week, for a duration of six months (South African National Department of Health, 2013). Rybak et al. (1999) noted that the cumulative doses of aminoglycosides increased the risk of patients developing ototoxicity and nephrotoxicity. Kokotas et al. (2007) and Petersen et al. (2009), also stated that aminoglycoside therapy lasting for more than seven days as well as prior exposure, high daily doses and elevated serum levels increases and accelerate the development of ototoxic induced hearing loss.

Douglas et al. (1992) demonstrated that ototoxic induced hearing loss was significantly related to high peak concentration of the aminoglycoside. Patients that received higher doses were more likely to present with ototoxic induced hearing loss. This is supported by a trial conducted by Peloquin et al. (2004) that looked at the incidence of toxicities associated with two recommended dosing regimens (daily vs. three times per week of intravenous streptomycin, kanamycin, or amikacin). It was noted that ototoxic induced hearing loss was associated with a larger cumulative dose and older age. This suggests that ototoxic induced hearing loss due to aminoglycoside administration is linked to the total dose administered and the dosing frequency. However genetic susceptibility also has an influence (Steyger, 2011; Huth et al.2011).

2.3.3 Advanced age and concomitant ototoxic drugs

While the ageing process itself is associated with degeneration of the auditory system, other abuse to the cochlea from noise or ototoxic drugs can accumulate over a lifetime and contribute to the decline in hearing experienced by older people. Presbycusis or age-related hearing loss is prevalent

in the older population and often goes unnoticed by both the patient and health care professionals in the early stages and is therefore under treated (Yueh et al. 2003; Pacalla et al. 2011). Ahmed and Quraishi (2006) suggests that age was a primary predictor for deterioration of hearing thresholds in the high frequency range (10-18 kHz) and this is exacerbated, among patients exposed to aminoglycosides who are likely to present with hearing loss.

2.3.4 Genetic predisposition

Genetic predisposition is one of the most documented risk factors associated with ototoxic induced hearing loss. Bardien et al. (2009) argues that the mitochondrial mutation A1555 G increases aminoglycoside-induced ototoxicity. Ototoxicity (threshold shift) can be induced after a single dose of aminoglycoside administration in those patients that are genetically susceptible. Guan (2006) stated that at least five different homoplasmic mutations in the mitochondrial gene encoding 125 rRNA (MT-RNR1) have been found to pre-dispose individuals to irreversible hearing loss if they are treated with aminoglycoside antibiotics (Prezant et al.,1993). The A1555G mutation is the most common variant and has been reported in diverse populations worldwide and individuals harbouring the gene can develop hearing loss in the absence of aminoglycoside therapy (Guan, 2006). A study by Bardien et al. (2009) showed a frequency of 0.9% for the A1555G mutation in the black population in South Africa which is also the population group with the highest incidence of MDR-TB.

Human et al. (2010) noted that to date there are six known mitochondrial mutations which have been linked to aminoglycoside induced hearing loss: A1555G, C1494T, T1095C, T1291C, 961delT+C(n) and A827G, with A1555G being the most common. Human et al. (2010) therefore noted that individuals should be screened before commencing aminoglycosides to detect those who are more susceptible to hearing loss, and this will allow for genetic counselling and informed consent.

2.3.5 The effects of HIV treatment on hearing

"In developing countries, TB and human immunodeficiency virus (HIV) co-exist, therefore highly active antiretroviral therapy (HAART) and ototoxic TB drugs are often given simultaneously, thereby increasing the potential for ototoxicity" (Harris et al. 2012:7). The incidence of hearing impairment in persons living with HIV varies between 20-40% (Prasad, Bhojwani, Shenoy & Prasad,

2006). HIV affects the sensory-neural auditory system either directly or indirectly (Stearn & Swanepoel, 2010). Indirect causes may also be associated with other opportunistic infections that affect the sensory and neural structures of the inner ear causing a sensory neural hearing loss (SNHL). Direct causes refer to the primary infection of HIV to the peripheral or central nervous system (Stearn & Swanepoel, 2010).

Harris et al. (2012) reported that HIV positive MDR-TB patients on ART were more likely to develop ototoxic hearing loss than HIV negative patients. In his study 70% of the HIV-positive patients developed hearing loss compared to 42% of the HIV- negative patients. Van der Westhuizen, Swanepoel, Heinze and Hofmeyr (2013) reported similar results.

2.4 EARLY SCREENING AND MONITORING FOR OTOTOXICITY

Konrad-Martin et al. (2005) noted that a there are number of studies indicating that ototoxicity can occur as early as 72 hours after aminoglycoside administration. This led them to recommend that baseline evaluations should take place within 72 hours of aminoglycoside administration and there should be a follow-up evaluation within 24 hours of the initial baseline.

The literature indicates that there is a dire need for more research to understand how to conserve the hearing of DR-TB patients receiving aminoglycosides (Seddon et al. 2012; Harris & Heinz, 2013). The review conducted by Seddon et al. (2012), showed that different methodologies have been used to monitor DR-TB patients in South Africa and that a more systematic approach to hearing screening in patients with DR-TB is required. Furthermore, ototoxic injury and associated hearing loss may progress for weeks following the cessation of treatment. Wang et al. (1999) demonstrated that ototoxicity (threshold shift) may persist for up to one year even after stopping the offending drug.

The availability of extended high frequency auditory monitoring of patients on aminoglycosides will allow for early detection of ototoxicity (threshold shift), before hearing loss progresses to the frequencies needed for speech communication (Seddon et al.2012; AAA, 2009). Olusanya (2008) asserts that early identification through screening programmes can effectively reduce the burden of ototoxic deafness by 50%; however, this is restricted by the availability of resources and socio-economic factors. It is recommended by the WHO that the surveillance of ototoxicity include

monitoring of the proper dose, duration of treatment as well as the assessment of symptoms and audiometry should be executed as indicated in high risk groups (WHO, 1995).

Campbell (2004) stated that there are two main purposes for monitoring ototoxicity. The first purpose is to detect changes in hearing within the frequencies that affect speech to minimize the negative effect on communication. Early detection will allow the physician to consider alternative medication. The second purpose is to assist the patient and their family with the consequences of hearing loss. This may include counselling, maintaining communication, introducing communication strategies and possibly providing amplification post-treatment. To monitor cochleotoxicity effectively it is recommended that; other causes for auditory dysfunction should be excluded, such as middle ear problems (Petersen & Rogers, 2014). This will assist the clinician with ensuring that the impaired hearing function is indeed sensory neural in nature. It is essential to have a test battery approach that is inclusive of case history, conventional pure tone audiometry, high frequency pure tone audiometry, oto-acoustic emissions (OAE) and auditory brainstem response (ABR).

2.5 HEALTH/AUTOMATED INTERPRETATION

"Tele-audiology holds the promise of bridging the gap by delivering services through an expanding reach of global connectivity" (Paglialonga, Tognola & Pinciroli, 2015:3).

Swanepoel and Hall (2010), during a systematic review demonstrated the feasibility and reliability of telehealth using both synchronous ("real time," through video conferencing, face-to face contact) and asynchronous ("anytime," through store-and-forward technology that transmits digital information for later response) models. The procedures reported included audiometry, video–otoscopy, oto-acoustic emissions and auditory brainstem response that confirmed the clinical equivalent results for both enabled tests (remote) and conventional face-to-face versions. The KUDUwave^{TM}'s focus is pure tone audiometry.

Swanepoel and Biaggio (2011) assert that computer based audiometry allows for remote testing and automation which may improve the accessibility and efficiency of hearing assessments in various clinical settings. Swanepoel et al. (2010) further demonstrated that the air and bone thresholds of the KUDUwave^{TM} correspond to those of the standard audiometer within typical test–retest reliability limits. Goulios and Patuzzi (2008) concluded that automation provides a solution to

address the Audiology service-delivery shortage. Important benefits of automated pure-tone testing have been highlighted by Margolis and Morgan (2008), stating that the utilization of pure tone automated audiometry increases the access for a larger proportion of the population to much needed hearing evaluations in a limited resource setting. In addition, to increased efficiency due to automating test procedures provides the audiologist the opportunity to focus on providing core services. A recent study by Paglialongaa et al. (2010) further demonstrated that the air and bone thresholds of the KUDUwave™ correspond to those of the standard audiometer within typical test–retest reliability limits. Goulios and Patuzzi (2008) concluded that automation provides a solution to address the Audiology service-delivery shortage. In addition, to increased efficiency due to automating test procedures provides the audiologist the opportunity to focus on providing core services. A recent study by Paglialongaa et al. (2015) indicated that, in hearing health care, there is a distribution of available apps in five major categories: i) education and information (23%), ii) hearing testing (18%), iii) rehabilitation (24%), iv) sound enhancement (28%), and visual assistive tools (7%).

2.6 SUMMARY

In summary ototoxicity is an underestimated cause of hearing loss, that is completely avoidable through monitoring the use of ototoxic drugs (WHO, 1995). There is no evidence of routine monitoring systems or standardization in the literature and therefore quantifying ototoxic induced hearing loss remains a challenge. Despite the limited literature with regards to quantifying ototoxic induced hearing loss and routine monitoring systems, the evidence suggests that there is an overwhelming need for this. According to the literature the most common risk factors for ototoxicity is exposure to aminoglycosides. The studies reviewed showed that patients with renal failure or HIV have an increased risk of developing ototoxicity when exposed to aminoglycosides. The evidence further showed that the older the patient the greater the risk.

Paglialonga et al. (2015) suggests that mobile applications for screening have gained much interest of the past few years. However, as a field in its infancy much work remains to be done to develop and validate the technology available as a means of delivering and improving audiology screening services. Limited hearing healthcare as is the case in South Africa for most people with hearing loss raises a moral obligation to pursue ways of providing the much-needed Audiological service to underserved communities. Therefore, Swanepoel & Hall (2010) concluded that tele-audiology

holds significant promise in extending services to underserved communities; however, it requires considerable empirical research to inform future implementation.

CHAPTER 3 METHODOLOGY

3.1 INTRODUCTION

The following chapter describes the process that was followed to achieve the study objectives.

3.2 STUDY DESIGN

This was a retrospective cross-sectional study consisting of both descriptive and analytical components (Ehrlich & Joubert, 2008). Hence, it allowed for the quantification of the outcome as well as being able to calculate the measure of association. Data was collected utilizing a data extraction sheet (Appendix 1) from 69 patient folders of DR-TB patients started on DR-TB treatment during the defined period at the three selected decentralized sites in KZN. Utilization of the retrospective study design allowed for the outcome of interest: ***hearing loss***, to have already occurred. The exposure was ototoxicity (threshold shifts of 20 dB at one frequency or 2 of 10dB at 2 consecutive frequencies within the extended high frequency: 9000 -20 000Hz).

3 .3 STUDY SETTING

The study was conducted at, Montebello, Estcourt and Madadeni Hospital, all newly decentralized DR-TB sites in KZN. These facilities initiate Drug Resistant Tuberculosis (DR-TB) treatment for patients that are diagnosed within the following districts, namely Amajuba, ILembe and UThukela. Table 1 reflects the respective district population per race.

Table 1: District population table per race group

District Population	uThukela		Amajuba		iLembe	
Black	636 394	95.15	465 142	93.06	550 758	90.76
White	11 437	1.7	17 030	3.45	14 713	2.42
Asian/Indian	16 023	2.4	13 167	2.68	35 911	5.92
Coloured	3 923	0.59	3 449	0.69	3 222	0.53
Other	1 070	0.16	1 052	0.21	2 205	0.36
Total	668 847		499 840		606 809	

These sites provided both in-patient and ambulatory care for DR-TB patients, except for Montebello hospital that only provided ambulatory care. In August 2015, the KUDUwave™ (mobile extended high frequency audiometer) was introduced at Estcourt, Madadeni and Montebello Hospitals respectively. Prior to this, these facilities only had access to conventional audiometry (250-8000Hz), except for Montebello that had no equipment. Both Madadeni and Estcourt Hospital had the audiological equipment to provide further diagnostics and aural rehabilitation for patients that require the service. Montebello Hospital must refer patients for further diagnostics if any abnormalities are detected during the screening process. These facilities are district hospitals that provide general care and only manage uncomplicated DR-TB cases, that include RR-TB and MDR-TB cases.

All Pre-XDR and XDR-TB patients are managed at the centres of excellence. These facilities followed the National guidelines with regards to the introduction of new drugs framework that stipulated (Ndjeka et al., 2015), high frequency audiometry should be utilized for the monitoring of ototoxicity to prevent or reduce the possibility of an irreversible hearing loss occurring. The framework also recommended that when ototoxicity (threshold shift) is identified in the absence of a hearing loss, the frequency of the aminoglycoside should be reduced or replaced with new drugs, like Bedaquiline (BDQ).

3.4 STUDY POPULATION AND SAMPLING

The study population included all the DR-TB patients that were referred to Madadeni, Montebello and Estcourt Hospitals and started on DR–TB treatment between 1st October and 31st December 2015 that met the inclusion criteria. This included both standardized and individualized regimens. The national electronic DR-TB register (EDRWeb) was utilized to identify patients at all three sites. The defined period was selected because the patients included in this study would have received the injectable for a minimum of six months and is aligned with the average duration of aminoglycoside administration as stipulated in the National Drug Resistant Tuberculosis guideline (South African National Department of Health 2013).

The study population were patients, nine years and older, with co-morbidities as well as pregnant women referred to Madadeni, Estcourt and Montebello hospital for DR-TB treatment initiation between the 1st October and the 31st December 2015. The version of the KUDUwave™ available

when the study was conducted could not condition children younger than nine years of age and therefore children below nine were excluded. The patients all had exposure to aminoglycosides during their intensive phase of treatment. The patients enrolled in the study all had a baseline or initial screening with the KUDUwave^{TM}. Imperatively the KUDUwave^{TM} test, was the only mode for audio screening of DR-TB patients at the three decentralized sites, for infection control purposes.

Patients that presented with a hearing loss at baseline or during the initial screening were excluded from the study. All Pre-XDR TB and XDR TB patients were excluded because they were initiated and managed at the centres of excellence.

3.5 JUSTIFICATION OF DATA SOURCE

The EDRWeb (electronic drug resistant TB register) is the National reporting system that captured the clinical as well as surveillance data for all DR-TB patients in South Africa that have commenced treatment. All patients that were started on DR-TB treatment between 1st October and 31st December 2015 that reflected on the EDRWeb at the three decentralized sites were enrolled in study. The EDRWeb which showed the number of DR-TB patients that were registered at Montebello (41), Madadeni (34) and Estcourt hospital (27) from the 1st October to the 31st December 2015.

The eMoyo database captured the information of the DR-TB patients that were screened with the KUDUwave for ototoxicity during the defined period. This database also provided the information pertaining to the hearing status of the patients that were screened. The numbers reflected on the database were as follows, Montebello hospital (4), at Madadeni Hospital (54) and at Estcourt hospital (109) adding to a total of (167) patients.

The data captured on EDRWeb showed that for the defined period, 101 DR-TB patients were registered collectively at these three sites. All the eligible DR-TB patients registered at these three sites, with a normal hearing test at baseline/initially and screened using the KUDUwave^{TM} would have been used as the basis for enrolment into the study.

The number of patients that were eligible to be enrolled in the study based on the selection criteria was as follow: Madadeni hospital displayed (37) patients, Estcourt Hospital (72) patients and at Montebello Hospital (0) patients.

There was a concerning variance with regards to the number of patients registered on the EDRWeb and the number of patients screened on the eMoyo database. Ideally the number of DR-TB patients captured on the EDRWeb and the number of DR-TB patients screened reflecting on the eMoyo database should be the same. It was and still is a national directive that all newly diagnosed DR-TB patients that are started on treatment should be registered on the EDRWeb and be in receipt of a baseline hearing screening, prior to commencing DR-TB treatment. However, the variance between the two data sources showed that at Montebello Hospital there were thirty-seven more DR-TB patients captured on the EDRWeb than on the eMoyo database. This could possibly be attributed to offline testing with the KUDUwave™, resulting in these records not being uploaded on the eMoyo server and therefore not reflecting. Therefore, it was decided that the most reliable data source for the study was the patient clinical folder. The folders at the three decentralized sites were selected based on the inclusion criteria of the study.

3.6 PRE-TEST OF DATA ABSTRACTION TOOL

The tool was piloted at Tshwane district hospital during March 2016. Ten DR-TB patient folders were reviewed that provided an opportunity to assess whether the data was attainable from the clinical record. This allowed for revisions that excluded information that was not relevant for the study, to avoid the tool becoming too cumbersome. Additions were made based on the information that was available within the patient folder.

3.7 DATA COLLECTION

The data was collected the last week of July 2016. The investigator developed a data extraction tool that recorded the information of all the DR-TB patients enrolled in the study individually. The data was then collated on an excel summary sheet. The four persons that assisted with the data collection were health care professionals that have expertise of Audiology management and monitoring. The patient clinical folder, prescription chart as well as the electronic database were perused to complete all the data fields comprehensively. Fields that had missing data were completed by capturing, zero (0).

The variables that were collected referred to patient and clinical information. The patient variables were as follows: age, gender and race. Clinical variables were: the type of DR-TB, patient category,

medication, co-morbidities, HIV status, duration of the injectable, hearing status at baseline or initial test, ototoxicity (threshold shift) detected, degree of hearing loss, hearing status after the injectable phase, regimen adjustment and the number of follow up visits.

3.8 ANALYSIS

Stata 15/SE software was used for the analysis. A univariate analysis was performed using chi-square tests for categorical data and t-test for continuous data. Data frequencies were utilized during the analysis for categorical data (sex, patient category, degree of hearing loss, co-morbidities (HIV, hypertension, diabetes,), other drugs (ART, loop diuretics), regimen adjustment, further diagnostics required). Categorical data was also displayed using bar charts and pie charts. For numerical data, the median was calculated to determine the number of days from diagnosis to treatment initiation since the data were not symmetrically distributed. The median and the interquartile range was calculated for the treatment start date to baseline/initial hearing assessment and the duration of aminoglycosides (injectable) use. The mean age was calculated, together with the corresponding standard deviation, since the data was symmetrically distributed. A multivariate logistical regression analysis to determine the risk factors associated with DR-TB patients developing hearing loss was not performed because there were only two factors that were significant in the bivariate analysis. P-values from Chi-square tests were calculated to show the statistically significant variables, where p-values of less than 0.05 was considered significant.

3.9 VALIDITY AND RELIABILITY

Validity refers to the accuracy or the extent to which the tool measures what it is meant to measure (Sarantakos, 1998). The staff screening the patients, also referred to as operators, with the KUDUwave™ have been trained to use of the software and the KUDUwave™ tone threshold audiometry test. The software had Macros which are the test protocols that ensure a baseline test is conducted between (250 Hz-16 000Hz), screening (100 Hz–16 000 Hz) and an exit test between (250Hz-16 000 Hz). Prior to the operator conducting the test, the software had a conditioning page to ensure that the patient knew what is expected of them during the procedure. This was repeated until the operator was confident that the patient fully understood how they should respond during the test.

Pure tone audiometry measures were utilized in the KUDUwave™ and are well suited for automation as it is based on pre-determined sequenced steps. These steps were based on reliable algorithms that have been transferred to a computer capable of reproducing them. This ensured consistent test procedures and improved standardization of test procedures overall.

The algorithm for the software measured the ototoxic threshold shift from the initial baseline audiogram as: (1) >20 decibel (dB) decrease at any one test frequency, (2) >10 dB decrease at any 2 adjacent frequencies, or (3) loss of response at three consecutive frequencies where responses had previously been obtained. The severity of hearing loss was graded as: (1) mild: PTA 26 - 40 dB hearing level (HL), (2) moderate: PTA 41 - 55 dB HL, (3) moderately severe: PTA 56 - 70 dB HL, (4) severe: PTA 71 - 90 dB HL, and (5) profound: PTA>90 dB HL (Swanepoel et al., 2010).

The data capturers were trained health care professionals that recorded the information from the patient folder to the data abstraction tool and then on to the excel spreadsheet. They have been trained and were familiar with all the fields that required completion.

The data extraction tool was pre-tested at a district hospital, utilizing 10 folders, to ensure its reliability and validity. Selection bias was addressed by using the list of patients as reflected on the EDRWeb and using the records of all study eligible patients as the study sample. The sample size was smaller than anticipated and possibly affected the precision and the power of the study.

3.12 GENERALISABILITY

The participants were not randomly selected into the study and therefore findings may not be applied to the broader DR-TB patient population in South Africa. However, the clinical findings might give weight in a way that demands consideration of the results.

3.13 ETHICAL CONSIDERATIONS

Ethics approval was received from the University of the Western Cape as well as the KwaZulu-Natal Provincial Ethics committee. A letter of permission to interrogate and use the data on the EDRWeb.net and the eMoyo KUDUwave™ data as well as the review of the folders was obtained from the National Department of Health DR-TB Directorate. A letter of support was also received from the KZN Provincial TB Director. To ensure the confidentiality of the patients the EDRWeb

is a password controlled system. The investigator received excel exports from the EDRWeb for the respective sites and defined period upon request.

There was no direct contact with the study population for data collection. The study presented no risk for the patients that were enrolled in the study. All records were treated with confidentiality. Once the data was abstracted from the folder only the investigator had access. The data was collected on site and records were returned immediately to the records division at the end of each day. No patient records left the hospital premises. The hard copies of the data abstracted was filed in a locked filing cabinet. All the electronic data was password protected. No patient names were collected, a unique identifier was provided. The EDRWeb number was blinded by assigning the unique identifier (first 3 letters of the facility and then the chronological number). Facility staff were provided with an information sheet to ensure that they are informed with regards to the process. There was no harm inflicted during the process. The data collectors on site ensured that patient records were returned as received.

The study sites as well as the selection criteria ensured that there was equal opportunity for the identified group to be selected. There was no exploitation of vulnerable groups.

CHAPTER 4: RESULTS

4.1 INTRODUCTION

A description of the study population, their baseline demographics and their clinical characteristics will be provided. The demographics include age, gender, and racial group. The clinical characteristics will include patient category, ototoxicity, and type of regimen that they were receiving. The number and proportion of patients who developed hearing loss will be given, including details regarding whether it was unilateral or bilateral. The degree of hearing loss will also be described. This will be followed by an analysis of the risk factors for DR-TB patients developing hearing loss.

4.2 DESCRIPTION OF THE STUDY POPULATION'S BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

A total of 69 patient folders collected at the three decentralized DR-TB sites in KwaZulu-Natal, namely Montebello, Madadeni and Estcourt hospitals, were analysed. The demographic and clinical characteristics are summarized in Table 2.

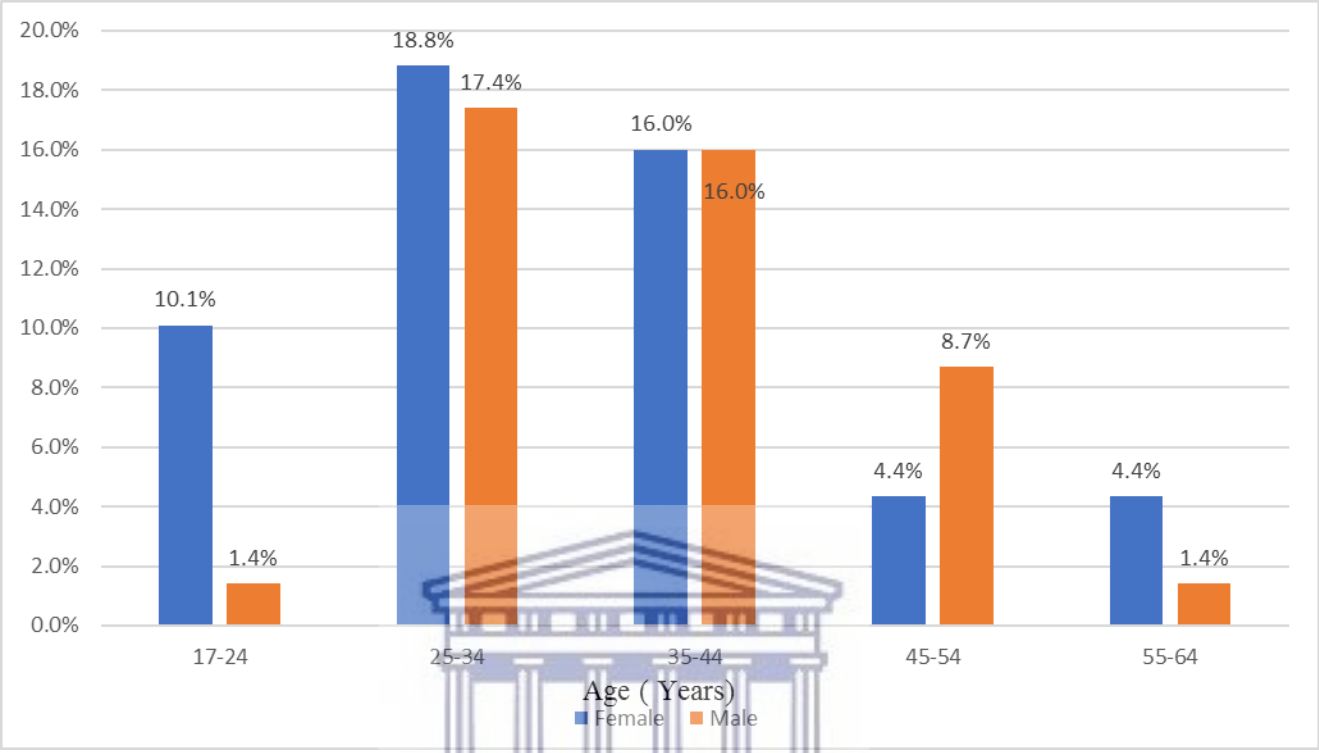
Most of the patients were from Estcourt Hospital (n=33, 47.8%), followed by Montobello (n=25, 36.2%), and Madadeni (n=11, 15.9%) Hospitals. The sex distribution of the patients enrolled in the study indicated that, 53.6% (n=37) were female. The mean age of the patients was 36.1, with standard deviation (SD) of 10.7 years. The ages of patients ranged from 17–63 years, with more than two-thirds of the patients (n=47, 68.1%) aged 25-44 years. The age and gender distribution is displayed in Figure 1.

The patient category, showed that the majority were new patients (n=54, 80.6%) and 11.9% (n=8) were relapse patients and 7.5% (n=5) were transfer-in patients. More than half of the patients (n=40, 58.0%) were on standard regimen and the remaining 42.0% (n=29) were on an individualized regimen. The majority of the patients enrolled in the study (n=56, 81.2%) were co-infected with HIV and the other comorbidities included diabetes (8.7%, n=6) and hypertension (2.9%, n=2).

Table 2. Demographic and clinical characteristics of DR-TB patients initiated on DR-TB treatment at three decentralized sites in KZN (1 October 2015 -31 December 2015)

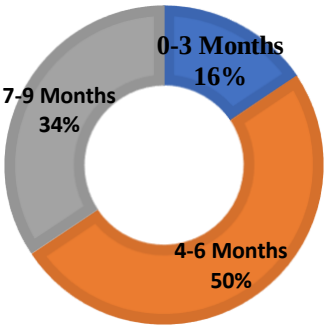
Characteristic	N = 69	%
Site		
Estcourt	33	47.8
Madadeni	11	15.9
Montebello	25	36.2
Sex		
Female	37	53.6
Male	32	46.4
Patient category		
New	54	80.6
Relapse	8	11.9
Transfer in	5	7.5
Age in years		
17-24	8	11.6
25-34	25	36.2
35-44	22	31.9
45-54	9	13.0
55-64	5	7.2
TB Regimen		
Standard regimen	40	58.0
Individualized regimen	29	42.0
HIV Status		
Positive	56	81.2
Negative	11	15.9
Unknown	2	2.9
Diabetes		
Yes	6	8.7
No	63	91.3
Hypertension		
Yes	2	2.9
No	67	97.1
Duration of injectable		
0-3 Months	10	14.5
4-6 Months	32	46.4
7-9 Months	22	31.9
Missing	5	7.2
Ototoxicity detected		
Detected	39	56.5
Not detected	21	30.4
Missing	9	13.1
Regimen adjusted		
Yes	25	36.2
No	20	29.0
Not applicable	24	34.8
Number of days between DR-TB diagnosis and treatment		
0 - 7 days	23	38.3
8-14 days	16	26.7
15 - 30 days	14	23.3
More than 30 days	7	11.7
Missing	9	13.0

Figure 1. Age and gender distribution of DR-TB patients (n=69) from Estcourt, Montebello and Madadeni Hospitals, KwaZulu-Natal, South Africa, 2015



A larger number of patients received the injectable for 4-6 months (n=32, 46.4%) and 7-9 months (n=22, 31.9%), with the remaining 14.5% (n=10) for 0-3 months (Figure 2).

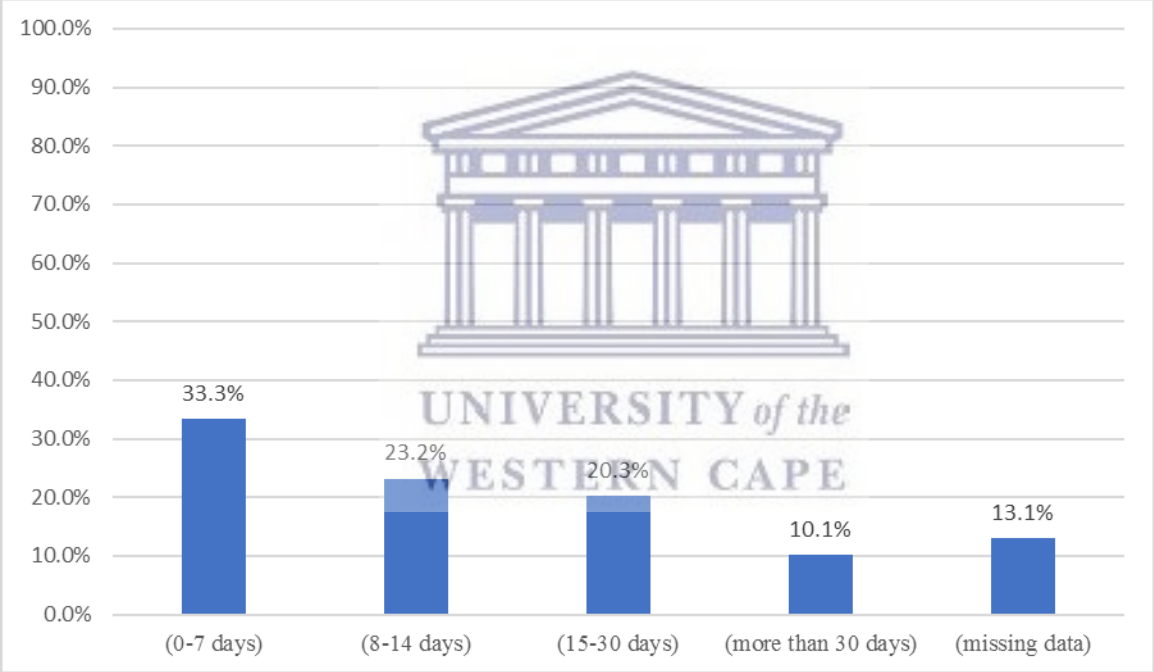
Figure 2. Duration on injectable for DR-TB patients (n=69) from Estcourt, Montebello and Madadeni Hospitals, KwaZulu-Natal, South Africa, 2015



Ototoxicity was detected in 56.5% (n=39) of patients and not detected in 30.4% (n=21). As a result, of those that presented with ototoxicity, 64%(n=25) of the patients had their the regimen was adjusted.

The number of days between DR-TB diagnosis and treatment initiation had a median of 9 days (ranging from 0 to 80 days); the majority (n=23, 38.3%) within a week, 26.7% (n=16) within the second week, and 23.3% (n=14) between two weeks and a month, and only 11.7% (n=7) were more than a month (Figure 3).

Figure 3. Number of days from DR-TB diagnosis (69) to treatment initiation for study patients from Estcourt, Montebello and Madadeni Hospitals, KwaZulu-Natal, South Africa, 2015

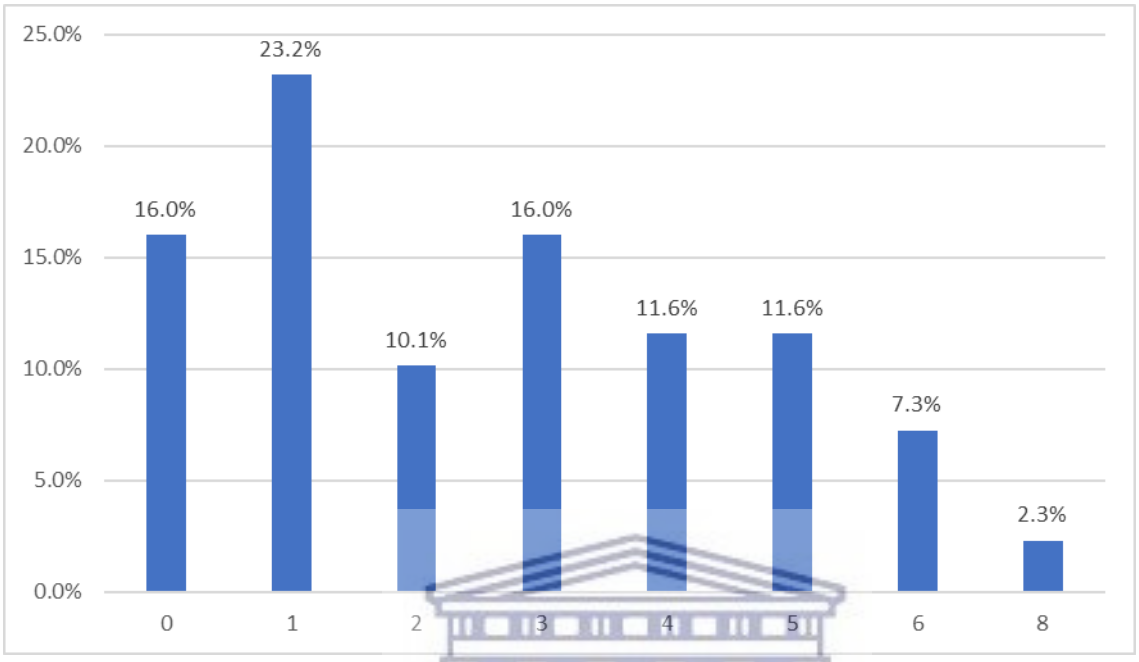


4.3 HEARING STATUS AFTER SIX MONTHS OF INJECTABLE ADMINISTRATION

4.3.1 Number of follow-up hearing tests

The patients underwent a number of follow-up hearing tests however there were 16.2 % (n=11) who did not have a follow up hearing test. The larger part (23.5%, n=16) had one hearing test, 10.3% (n=7) had two hearing tests, 16.2% (n=11) had three hearing tests, 31% (21) had four to six hearing tests, and 2.9% (n=2) had up to eight follow-up hearing tests (Figure 4).

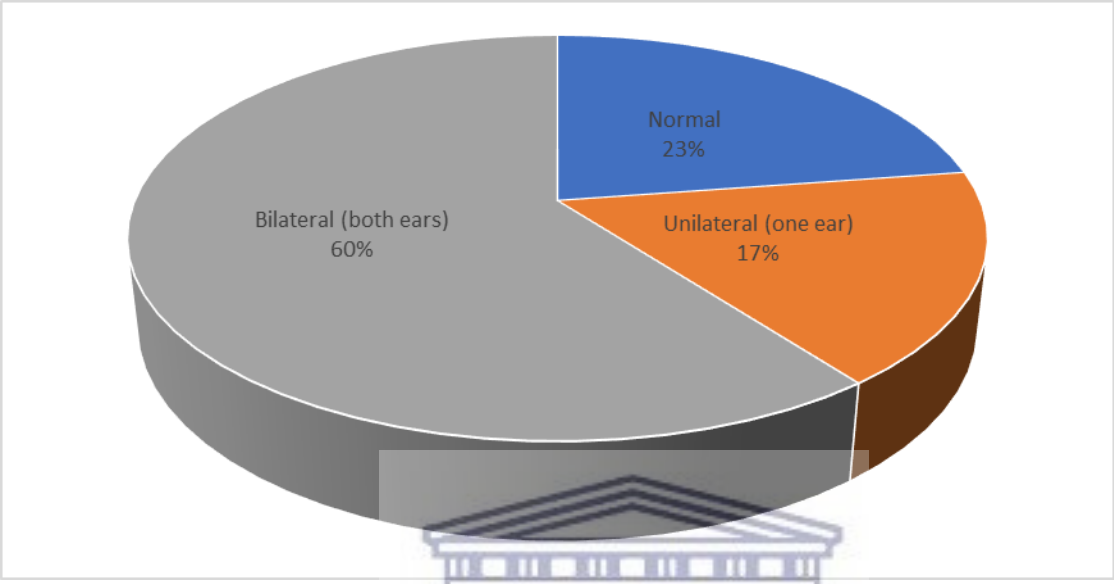
Figure 4. Number of follow-up hearing tests for MDR-TB study patients (n=69) from Estcourt, Montebello and Madadeni Hospitals, KwaZulu-Natal, South Africa, 2015



4.3.2 Hearing Loss

From the 53 patients who were tested for hearing loss post completion of the injectable phase of treatment, 22.6% (n=12) had normal hearing, 17.0 % (n=9) had unilateral (one ear) hearing loss, and the majority (60.4%, n=32) had bilateral (both ears) hearing loss (Figure 5). Therefore, a total of 41 (77,3) patients had a degree of hearing loss.

Figure 5. Hearing loss post completion of the injectable phase of treatment for MDR-TB study patients (n=53) from Estcourt, Montebello and Madadeni Hospitals, KwaZulu-Natal, South Africa, 2015



4.3.2 Degree of hearing Loss

The degree on hearing loss was recorded per ear (Table 3). More than 20%(n=15) of the patients had normal hearing, and over 30% (n=22)had mild to moderate hearing loss, and approximately 15%(n=11) had severe to profound hearing loss.

Table 3. Degree of hearing loss post the injectable phase of patients initiated between 1 October and 31 December 2015 at Estcourt, Madadeni and Montebello hospitals in KZN

	Total N=69	Total %
Right ear		
Normal (0–25 dB)	15	21.7
Mild (26–40 dB)	8	11.6
Moderate (41–55 dB)	14	20.3
Moderate–severe (56–70 dB)	4	5.8
Severe (71–90 dB)	9	13
Profound (90+ dB)	2	2.9
Inconclusive	1	1.4
Missing data	16	23.2
Left Ear		
Normal (0–25 dB)	16	23.2
Mild (26–40 dB)	13	18.8
Moderate (41–55 dB)	12	17.4
Moderate–severe (56–70 dB)	10	14.5
Severe (71–90 dB)	9	13
Profound (90+ dB)	1	1.4
Inconclusive	1	1.4
Missing data	7	10.1

4.3.3 Risk Factors for hearing loss

Risk factors associated with any hearing loss (right ear only, left ear only, or both ears) was determined using Chi-square tests and the results are summarized in Table 4.

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Table 4. Risk factors for hearing loss among DR-TB patients from Estcourt, Montebello and Madadeni Hospitals, KwaZulu-Natal, South Africa, 2015

	Hearing loss						
	No N	**No %**	**Yes N**	**Yes %**	**Total N = 53**	**Total %**	**P-value**
Site							0.379
Estcourt	5	41.7	26	63.4	31	58.5	
Madadeni	1	8.3	3	7.3	4	7.5	
Montebello	6	50	12	29.3	18	34	
Sex							0.664
Female	7	58.3	21	51.2	28	52.8	
Male	5	41.7	20	48.8	25	47.2	
Patient category							0.153
New	10	83.3	30	76.9	40	78.4	
Relapse	0	0	7	17.9	7	13.7	
Transfer in	2	16.7	2	5.1	4	7.8	
Age in years							0.106
17-24	3	25	3	7.3	6	11.3	
25-34	7	58.3	14	34.1	21	39.6	
35-44	2	16.7	16	39	18	34	
45-54	0	0	5	12.2	5	9.4	
55-64	0	0	3	7.3	3	5.7	
TB Regimen							0.403
Standard regimen	6	50	26	63.4	32	60.4	
Individualized regimen	6	50	15	36.6	21	39.6	
HIV Status							0.859
Positive	10	83.3	33	80.5	43	81.1	
Negative	2	16.7	7	17.1	9	17	
Unknown	0	0	1	2.4	1	1.9	
Diabetes							0.335
Yes	0	0	3	7.3	3	5.7	
No	12	100	38	92.7	50	94.3	
Hypertension							0.346
Yes	1	8.3	1	2.4	2	3.8	
No	11	91.7	40	97.6	51	96.2	
Duration of injectable							0.377
0-3 Months	0	0	6	15	6	12	
4-6 Months	7	70	21	52.5	28	56	
7-9 Months	3	30	13	32.5	16	32	
Ototoxicity detected							**<0.001**
Detected	2	16.7	32	78	34	64.2	
Not detected	8	66.7	9	22	17	32.1	
Missing	2	16.7	0	0	2	3.8	
Regimen adjusted							**<0.001**
Yes	2	16.7	20	48.8	22	41.5	
No	0	0	16	39	16	30.2	
Not applicable	10	83.3	5	12.2	15	28.3	
Number of days between DR-TB diagnosis and treatment							0.62
0 - 7 days	5	41.7	14	40	19	40.4	
8-14 days	2	16.7	12	34.3	14	29.8	
15 - 30 days	3	25	6	17.1	9	19.1	
More than 30 days	2	16.7	3	8.6	5	10.6	

Only ototoxicity detected and regimen adjustment were significant risk factors for hearing loss. The site, sex, patient category, age, TB regimen, HIV status, diabetes, hypertension, duration of injectable, and number of days between TB diagnosis and treatment, were not significantly associated with hearing loss.

4.4 SUMMARY

The bivariate analysis showed that the following variables, (1) ototoxicity detected and (2) regimen adjusted was statistically significant for risk factors associated with hearing loss. Ototoxicity was detected in the larger part of the study population. The regimen was adjusted for two thirds of those that presented with ototoxicity.

From the 53 patients who were tested for hearing loss post completion of the injectable phase of treatment, 22.6% (n=12) had normal hearing, 17.0 % (n=9) had unilateral hearing loss, and 60.4% (n=32) had bilateral hearing loss. Therefore, a total of 41 patients had a degree of hearing loss: over 30% (n=22)had mild to moderate hearing loss, and only about 15%(n=11) had severe to profound hearing loss

CHAPTER 5: DISCUSSION

This chapter begins with a discussion on the clinical characteristics of the study population, followed by a discussion on the study objectives.

The study is the first of its kind to describe and quantify ototoxic induced hearing loss amongst DR-TB patients that have received audiological monitoring with an extended high frequency audiometer. It will also provide further insights with regards to the possible risk factors associated with this type of hearing loss amongst DR-TB patients. The findings could be of interest to the National programmes that are responsible for the development of DR-TB guidelines as well as rehabilitation services, with regards to improving ototoxicity monitoring, which will conserve the hearing of these patients.

5.1 DISCUSSION OF THE STUDY POPULATION'S BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The study included more female than male DR-TB patients. The study by O'Donell et al. (2011) showed that in industrialised countries more male than female patients are diagnosed with DR-TB; however, in KwaZulu-Natal the female sex is significantly associated with DR-TB and diagnosed in higher volumes. A WHO report (2015) stated that the diagnosis of DR-TB is more prevalent among the age range 35 to 40 years of age, as reflected in this study. In contrast to the WHO report (2015), most of the patients who were enrolled in the study were categorised as "new" (primary infections) patients, which is suggestive of high transmission within the community. Shisana et al. (2014) note that TB is fuelled by the HIV epidemic, which has a high co-infection rate in South Africa. Similarly, most of the patients enrolled in this study were co-infected with HIV and were on antiretroviral therapy (ART). Qianqian et al. (2017) discovered that between 10% and 23% of DR-TB patients in South Africa had diabetes. The study showed that 2.9% the DR-TB patients enrolled had diabetes. There was no data on the prevalence of hypertension among DR-TB patients, and very few patients presented with this condition. Most of the DR-TB patients received the injectable for the period proposed in the national DR-TB guideline (South African National Department of Health, 2013).

Based on the literature, it is suggested that patients who have been exposed to aminoglycosides previously are more at risk of developing ototoxicity. However, this study demonstrated that in relation to patient category, most of the patients across the three included sites were new. However, there is the probability that patients that have been previously treated with a DR-TB regimen might have presented with a hearing loss at baseline and were therefore excluded from the study. However, the category of the patient was not statistical significant with regards to the risk factors associated with developing a hearing loss.

Even though there was no genetic testing during the study, all the patients enrolled in the study were black. A study by Bardien et al. (2009) showed a frequency of 0.9% for the A1555G mutation in the black population in South Africa which is also the population group with the highest incidence of MDR-TB. This mutation increases the risk of patients developing ototoxic induced hearing loss due to aminoglycoside exposure. The study demonstrated that most of the patients presented with a degree of hearing loss post the injectable phase.

5.2 PATIENTS THAT PRESENTED WITH A HEARING LOSS

Petersen and Rogers (2015) found that there is wide variability in the incidence of aminoglycoside-induced ototoxicity in South Africa. This makes quantifying the incidence at a national level challenging. Of the 69 patients enrolled in the study, more than half presented with ototoxicity. The literature reviewed estimated the incidence of aminoglycoside-induced ototoxicity to range between 7 and 90% (ASHA, 1999).

5.3 HEARING STATUS AFTER SIX MONTHS OF INJECTABLE ADMINISTRATION

The average length of the injectable (aminoglycoside) administration stipulated in the national DR-TB guideline is six months (South African National Department of Health, 2013). Cumulatively across the three sites, most of the patients received the injectable for a duration of between four and six months, with a smaller number receiving it for a duration of between seven and nine months. More than half of the patients presented with ototoxicity. According to Rogers and Peter (2015) higher and a more frequent dosage increases the likelihood of developing ototoxic induced hearing loss. However, the findings of this study showed that the duration of the injection did not increase the risk of developing an ototoxic hearing loss.

The introduction of the new the drugs policy framework by the National Department of Health in 2014 (Ndjeka et al., 2015) stated that patients presenting with ototoxicity should have their regimen adjusted over and beyond the reduction in the kanamycin from five to three days per week. These patients should receive an alternate drug known as Bedaquiline (BDQ).

Of the patients who presented with ototoxicity, a larger part had their regimen adjusted, that meant a reduction in the frequency of kanamycin administration. Across the three sites, none of the patients who presented with ototoxicity received BDQ to replace the aminoglycoside as recommended in the national framework (Ndjeka et al., 2015).

After the injectable phase, a fifth of the patients had normal hearing, with the majority having experienced a degree of hearing loss. The most prevalent hearing loss experienced by a third of the patients was a moderate hearing loss that ranged between 41 dB and 45 dB. Moderate hearing loss will result in a patient having difficulty understanding speech, especially in the presence of background noise. High volume levels are needed to hear a television or radio (ASHA, 2009). Bilaterally, a quarter of the participants presented with mild hearing loss (26–40 dB). Mild hearing loss will affect the patient to the extent that they have difficulty hearing soft speech and conversations in noisy, more reverberant situations. However, they will be able to hear with comprehension in a quieter environment (ASHA, 2009). Bilaterally, a tenth of patients presented with moderate to severe hearing loss (56 –70 dB). This implies that the patient's clarity of speech is significantly affected. Speech must be louder than usual and difficulties in group conversations will occur (AAA, 2009). Possibly, administering the new drug (Bedaquiline) and frequent monitoring could have prevented this.

As per the national ototoxicity protocol (Ndjeka, 2015), DR-TB patients should on average receive a minimum of five follow-ups for the duration of the injectable administration, as proposed in ASHA's (2009) guideline for monitoring ototoxicity. Monthly follow-ups for patients who are receiving aminoglycoside therapy, as well as a six month post the injectable phase, are recommended. In the event where patients were classified as high risk for ototoxicity, more frequent follow-ups were recommended. However, the data reflect that a larger part of the patients only received one follow-up test post their initial hearing screening test. No exit audio screening was conducted as per the guideline despite the fact there is sufficient evidence that ototoxic induced hearing loss can develop one year post the last dose of aminoglycosides (Wang et al., 1997).

The literature clearly supports that if hearing loss is identified early, the recommendation may include changing the medication to one that is less ototoxic, stopping treatment with the ototoxic agent, or altering the medication dosage (Fausti et al., 2006). This study supported these findings.

5.4 THE RISK FACTORS ASSOCIATED WITH DR-TB PATIENTS DEVELOPING OTOTOXICITY RESULTING IN HEARING LOSS

5.4.1 HIV and other co-morbidities

Harris et al. (2012) reported that HIV-positive MDR-TB patients on highly active ART were more likely to develop ototoxic hearing loss than HIV-negative patients. The results of the study showed that most of the patients enrolled in the study were HIV positive, however they had no greater risk of developing an ototoxic induced hearing loss.

It is suggested that other co-morbidities such as diabetes also increases the risk of a patient developing an ototoxic induced hearing loss when exposed to aminoglycosides (Moore et al. 1984). The findings in this study however showed that DR-TB patients with hypertension and diabetes did not have an increased risk for developing ototoxicity that will result in a hearing loss.

5.4.2 Sex

Javadi et al. (2011) demonstrated that males were more likely than females to develop ototoxicity. The data showed that gender did not increase the risk of developing ototoxic induced hearing loss in this study.

5.4.3 Age

Ahmed and Quraishi (2006) suggested that age was a primary predictor for deterioration of hearing thresholds in the high-frequency range (10–18 kHz). The bivariate analysis showed that age was not statistical significant as a risk factor for DR-TB to develop a hearing loss, however the number of patients enrolled 45 years and older was very snall and there were no patients older than 64 years of agee.

5.4.4 Cumulative dose and Patient category

Rybak et al. (1999) noted that the cumulative doses of aminoglycosides increased the risk of patients developing ototoxicity and nephrotoxicity. Kokotas et al. (2007) and Petersen et al. (2009) also

found that aminoglycoside therapy lasting for more than seven days – as well as prior exposure, high daily doses and elevated serum levels – increased and accelerated the development of ototoxic hearing loss. This is supported by the study that showed that once ototoxicity was detected and the regimen was adjusted from every day, seven days a week aminoglycosides administration to three times a week, can reduce the risk of acquiring a hearing loss and the progression thereof. In the event where the regimen was not adjusted patients were at risk of developing an ototoxic induced hearing loss. Patient category was not significant as a risk factor to develop ototoxic induced hearing loss.

5.4.5 Ototoxicity (threshold shift)

The findings of this study showed that developing ototoxicity (a threshold shift) is a significant risk factor for hearing loss, ranging from mild to severe. A study by Sharmi et al. (2016) described the incidence of ototoxicity amongst their study subjects as 2% after 1 week of aminoglycoside administration and 12% after week 6. Of these presenting with ototoxicity, 13 % developed a degree of hearing loss bilaterally and 5% unilaterally. Their study further showed that ototoxicity was more prevalent among males. In this study the majority of the study population presented with ototoxicity and further developed a degree of hearing loss.

5.5 STUDY LIMITATIONS

Differences in loss to follow-up of the exposed group could have led to bias as the people who were lost to follow-up may have been more (or less) likely to have developed the outcome of interest. There was the risk that the absence of data on potential confounding factors, especially in instances where data have been collected in the past. This could have translated to the resulting estimate of the effect being less accurate. It is a common phenomenon that DR-TB patients often present with more than one TB episode. This, of course, means that they have had previous exposure to aminoglycosides that might have caused hearing loss. Therefore, a significant number of patients presented with a hearing loss at baseline and were excluded from the sample. This reduced the sample size that might have affected the precision and power of the study.

It was intended to use the eMoyo database to quantify the proportion of patients that presented with a degree of hearing loss at a national level. The variance in the data sources clearly showed the challenge in capturing the data and its effects on the reporting system. Even though the two

electronic systems (EDRWeb and eMoyo database) are interoperable, there was no unique identifier across the two systems to link the patient records or data. This resulted in the duplication of patients, that could have translated to an increase number of patients that would have inflated the number of patients that presented with a hearing loss. Due to these factors, the eMoyo database was deemed to be an unreliable data source for quantifying hearing loss amongst DR-TB patients.

Taking the above limitations into consideration, the patient folders were reviewed instead due to it being the most reliable data source; however, that decreased the sample size may have affected the power and precision.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 CONCLUSIONS

The study is the first of its kind in South Africa that quantified the ototoxic induced hearing loss amongst DR-TB patients that received audiological monitoring with an extended high frequency mobile audiometer with telemedicine principles.

Most of the DR-TB patients at these three hospitals received baseline hearing screening within eight days and less post their DR-TB diagnosis.

This study showed that the DR-TB patients that were enrolled, who presented with ototoxicity were detected early enough to reduce their risk or prevent the development of a hearing loss. However, the results of the study showed that the audiological monitoring was not adequate and therefore did not meet the standard as proposed in the introduction of new drugs framework (Ndjeka et al. 2015). Most of the patients had less than the required follow up that could possibly have contributed to why a larger part of the patients experienced a degree of hearing loss, despite having their regimen adjusted. This can be attributed to the absence of a comprehensive standardized test battery for the management of ototoxicity within the South African DR-TB programme.

Most of the patients post the injectable phase presented with a permanent degree of hearing loss that would require communication assistive devices that will impede on their quality of life. These findings indicate that though it was hoped that the introduction of extended high frequency audiometry (KUDUwave) in the DR-TB programme will prevent or reduce the risk of DR-TB patients developing a hearing loss, it was not achieved. It was suggestive that in the absence of a comprehensive Audiological test battery approach that is inclusive of case history, conventional pure tone audiometry, high frequency pure tone audiometry, oto-acoustic emissions (OAE) and auditory brainstem response (ABR), as well as an appropriate referral pathway, conserving the hearing of DR-TB patients receiving aminoglycosides will not be attained.

It was evident that aminoglycoside administration poses a risk for DR-TB patients to lose their hearing. Now that new drugs are available perhaps the option of an injectable free regimen should be explored as it will be less debilitating to the patient and preserve their quality of life.

6.2 RECOMMENDATIONS

The recommendations are as follows:

6.2.1 Improving the eMoyo database

- The implementation of a unique identifier at a National level for DR-TB patients, applicable to all recording and reporting systems, as well as the interoperability between the KUDUwave and the EDRWeb to allow for data imports between the two systems.
- This will also reduce the risk of non-DR-TB patients being tested and reflecting on the eMoyo database and make the database a more reliable source to collect routine programmatic data fpr Audiology.
- Enforcing the principle of on line testing will provide real time data. To assist with reducing the inconclusive results. eMoyo should amend the software that will make it compulsory for screeners to include the 500 Hz frequency in the test macro.

6.2.2 Integrated Audio Monitoring with an established referral pathway

- The National and Provincial Departments of Health should include the Audio service in the DR-TB clinical and programme audit that will provide an opportunity to monitor and identify quality improvement initiatives that will enhance the quality of the Audio services utilizing the KUDUwave.
- Include audiology services in the standard DR-TB clinical audit to ensure adequate monitoring and accountability. As well as including the audiology fields in the standard DR-TB patient record will reinforce accountability.
- Expand the access of new drugs such as Bedaquiline to ensure that patients that are considered high risk for developing ototoxic induced hearing loss, have access to these in the hope of preventing hearing loss. The results of the study suggest that an intervention such as the administering the new drug, Bedaquiline and frequent monitoring could have prevented the extent of the hearing loss, with more of their hearing being conserved and less debilitation.
- Improving the referral pathway /continuum of care across the health system to ensure that patients that have been screened and are presenting with ototoxicity or a hearing loss should be referred to the appropriate service for further diagnostics and aural rehabilitation.
- Fausti et al. (2006) suggest that early identification of hearing loss allows medical practitioners

to minimize further damage as well as to prevent a hearing loss progressing to a stage when aural rehabilitation or alternative communication is warranted.

- The literature asserts that if a hearing loss is identified early, the recommendation may include changing the medication to one that is less ototoxic, stopping treatment with the ototoxic agent or altering the medication dosage. It emphasizes that the communication between professionals should form an integral part of an ototoxicity monitoring programme (Fausti et al. 2006).
- It is proposed to monitor cochleotoxicity effectively; other causes for auditory dysfunction should be excluded, such as middle ear problems (Petersen & Rogers, 2014). This will assist the clinician with ensuring that the impaired hearing function is indeed sensory neural in nature. It is essential to have a test battery approach that is inclusive of case history, conventional pure tone audiometry, high frequency pure tone audiometry, oto-acoustic emissions (OAE) and auditory brainstem response (ABR).

6.2.3 Further Research Proposed

- A cost benefit analysis /health economic study should be conducted to determine the cost for the Department of Health due to managing debilitating hearing losses caused by aminoglycoside induced ototoxicity and the loss of income for households versus an injectable free regimen with new drugs such as Bedaquiline.

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APPENDICES: DATA ABSTRACTION TOOL

NAME OF SITE		**STUDY NO:**	
PATIENT CATEGORY			
DR-TB REGISTRATION NUMBER:		**AGE**	
MALE		**FEMALE**	
DR-TB TREATMENT START DATE			
DR-TB REGIMEN			
OTTHER MEDICATION			
CO -MORBIDITIES			
HIV STATUS	**POS**	**NEG**	**UNKNOWN**
DIABETES	**YES**	**NO**	
HYPERTENSION	**YES**	**NO**	
OTHER CONDITIONS			

DATE OF BASELINE OF HEARING TEST			
DATE OF INITIAL HEARING TEST			
HEARING AT BASELINE			
NUMBER OF FOLLOW UP HEARING TEST:			
OTOTOXICTY DETECTED:	YES	NO	
IF YES WAS THE REGIMEN ADJUSTED	YES	NO	
IF YES SPECIFY HOW	KANAMYCIN STOPPED	KANAMYCIN REDUCED	REFERRED FOR BDQ
DURATION OF INJECTABLE (kanamycin)			
HEARING STATUS AFTER 6 MONTHS ON TREATMENT	NORMALHEARING		
	MILD HEARING LOSS		
	MODERATE HEARING LOSS		
	SEVERE HEARING LOSS		
	PROFOUND HEARING LOSS		
	NO RESULT		

DATE OF LAST HEARING TEST	
REFERRED FOR A COMMUNICATION ASSISTIVE DEVICE	YES NO N/A