



Effectiveness of Different Medical Interventions Implemented When a Change in Hearing Status is Detected During Ototoxicity Monitoring

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by

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Table of Contents

Plagiarism Declaration	1
Acknowledgements	2
List of Abbreviations	5
List of Tables	7
List of Figures.....	7
Abstract.....	8
Chapter One: INTRODUCTION	11
South African incidence and burden of Tuberculosis	11
Drug-resistant Tuberculosis and its threat to TB control	11
Treatment of Drug-Resistant Tuberculosis	12
Aminoglycoside Cochleotoxicity and Hearing Loss	13
Study Rationale	14
Chapter Two: LITERATURE REVIEW	16
Incidence of Aminoglycoside-Induced Cochleotoxicity	16
Pathophysiology of Aminoglycoside-Induced Ototoxicity.....	24
Risk Factors for Cochleotoxicity	26
Prevention of Aminoglycoside-Induced Hearing Loss.....	33
Interventions Implemented	33
Chapter Three: METHODOLOGY.....	36
Aims.....	36
Objectives.....	36
Research Design	36
Participants.....	37
Inclusion and Exclusion criteria	37
Sampling	38
Recruitment Strategy.....	39
Data Collection	40
Instrumentation.....	40
Pilot Study	41
Procedure.....	41
Test protocol (Cochleotoxicity Monitoring Protocol)	44

Classification of Hearing Loss	45
Management of participants who developed hearing loss.....	46
Data Management.....	46
Data Analysis.....	47
Reliability and Validity.....	47
Ethical Considerations.....	50
Chapter Four: RESULTS	53
Participant Description	53
Incidence of cochleotoxicity following treatment	53
Associations between participant factors and the possibility of developing aminoglycoside-induced significant threshold shift.....	55
Type of Intervention Strategy Implemented following cochleotoxicity	56
Chapter Five: DISCUSSION	60
Study Strengths and Limitations	67
Chapter Six: CONCLUSION AND RECOMMENDATIONS	69
Conclusions, Implications and Recommendations for Future Research	69
REFERENCES.....	72
APPENDICES.....	83
Appendix A1: Letter of request for assistance to medical staff	83
Appendix A2: Invitation to Participate in a Research Study: Information letter for prospective Participants.....	85
Appendix A3: Informed consent form	89
Appendix B: Advertisement for patients with Drug-Resistant Tuberculosis (DR-TB)	90
Appendix C1: Case History Questionnaire	91
Appendix C2: Case History form and Audiogram	93
Appendix D: Approval letter Human Research Ethics Committee University of Cape Town.....	95
Appendix E: Letter of request for permission to Institution	96
Appendix F: Approval letter Metro TB Hospital Centre Western Cape Government	98
Appendix G: Data collection tests, norms and participants instructions.....	99
Appendix H: Confidentiality Agreement.....	104

List of Abbreviations

AAA: American Academy of Audiology

AC: Air Conduction

ADR: Adverse Drug Reaction

AIDS: Acquired Immunodeficiency Syndrome

ASHA: American Speech-Language-Hearing Association

BC: Bone Conduction

BCH: Brooklyn Chest Hospital

CHL: Conductive Hearing Loss

CI: Confidence Interval

cPTA: Conventional Pure Tone Audiometry

dB: Decibel

dB HL: Decibel Hearing Loss

DoH: Department of Health

HAART: Highly Active Antiretroviral Therapy

HF-PTA: High-Frequency Pure Tone Average

HIV: Human Immunodeficiency Virus

HL: Hearing Loss

Hz: Hertz

kHz: Kilo Hertz

MDR: Multi-drug resistant

OHC: Outer Hair Cells

OT: Otoscopy

PTA: Pure Tone Average

RR: Rifampicin resistant

SA: South Africa

SNHL: Sensorineural Hearing Loss

STS: Significant Threshold Shift

TB: Tuberculosis

TYMP: Tympanometry

UHF: Ultra-High Frequency

WHO: World Health Organization

XDR: Extreme Drug-Resistant

List of Tables

Table 1: Incidence of Aminoglycoside-Induced Cochleotoxicity	17
Table 2: Risk Factors for Cochleotoxicity	26
Table 3: Parameters for sample size calculation.....	39
Table 4: Participants' Description (n=64)	53
Table 5: Association between Sex, HIV status and hearing thresholds changes.....	55
Table 6: Number of days on treatment and intervention by strategy.....	57
Table 7: Participant Demographics and Intervention Strategy	58

List of Figures

Figure 1: Summary of Procedure.....	43
Figure 2: Exit audiogram results for high frequency range based on PTA: 4 kHz, 6kHz and 8 kHz	55
Figure 3: Distribution of participants according to aminoglycoside treatment modification (n=58).	56
Figure 4: Proportion of participants who did not have further STS as a function of intervention	58

Abstract

Background: Fourteen thousand (14, 000) people fell ill with Multi-Drug Resistant (MDR) or Rifampicin-Resistant (RR) Tuberculosis (TB) in South Africa (SA) in 2019. Aminoglycosides, which are commonly used anti-tuberculosis drugs in the treatment for RR/MDR-TB patients, are associated with ototoxicity (cochlear or vestibular). Aminoglycoside-induced cochleotoxicity is characterised by permanent, bilateral, high-frequency (HF) sensorineural hearing loss (SNHL). The impact of hearing loss (HL) due to aminoglycoside-induced cochleotoxicity can influence a patient's communication, psychological, physical functioning and overall well-being negatively and lead to a reduced quality of life (QoL). To reduce the risk of aminoglycoside-induced cochleotoxicity, patients' hearing thresholds are monitored (i.e., cochleotoxicity monitoring) when they are being treated with cochleotoxic aminoglycosides. Cochleotoxicity monitoring is performed to detect a significant threshold shift (STS) early and prevent further deterioration of hearing thresholds and avoid hearing loss which may end up affecting frequencies that are important for speech perception. When a STS or hearing loss is detected during cochleotoxicity monitoring, there are various intervention strategies that can be implemented by the treating medical personnel to avoid further deterioration of patient's hearing thresholds. These strategies may include discontinuing the aminoglycoside, changing the aminoglycoside to a less cochleotoxic alternative in the regimen or changing the frequency of administration of the aminoglycoside. This study, therefore, aimed to determine the effectiveness of different strategies used when a STS in hearing occurred during cochleotoxicity monitoring to prevent further deterioration in hearing thresholds.

Methodology: A descriptive prospective repeated-measures design was used in this study. Patients who underwent RR/MDR-TB treatment with Kanamycin, a cochleotoxic aminoglycoside, at Brooklyn Chest Tuberculosis Hospital (BCH) between June to December 2016 were recruited to participate in the study. Only patients (n= 69) with normal hearing thresholds (i.e., pure tone average (PTA) at 500 Hz, 1 kHz and 2 kHz ≤ 25 dB HL) at baseline and age 18 – 55 years were included. Patients who were receiving two aminoglycosides, were retreatment patients or had active middle ear (ME) pathology were excluded from this study. Participants were sampled via a purposive sampling strategy. All audiological testing was performed in a sound-treated booth and participants underwent the following types of assessment; baseline, periodic monitoring, and

diagnostic assessment (when indicated). The following tests were performed at baseline: case history, otoscopy (OT), tympanometry (TYMP), conventional pure tone audiometry (cPTA) including air conduction (AC) and bone conduction (BC), and ultra-high frequency audiometry (UHFA). Follow-up monitoring assessment occurred monthly if there was no significant change in hearing thresholds, and bi-weekly if an STS was detected. The ASHA criteria were used to determine STS. The degree of hearing loss was described as mild, moderate, moderately-severe, severe or profound and the type of hearing loss was either conductive, sensorineural, or mixed. Both descriptive and inferential (Chi-squared, Mann-Whitney U and Kruskal-Wallis) statistical tests were used for data analysis.

Results: A total of sixty-nine (69) patients who were undergoing treatment for RR/MDR-TB were recruited to participate in this study. Five participants dropped out of the study due to various reasons, therefore, leaving 64 participants in the study. There was 38 males and 26 females. The median age was 31 [range; 18 - 55] years old. An aminoglycoside-induced cochleotoxicity incidence of 90.6% (58/64) was found in this study. There were no statistically significant associations between the occurrence of STS and age ($p = 0.487$), sex ($p = 0.329$) and HIV status ($p = 0.764$). Three types of intervention strategies were used when a participant experienced an STS: (i) discontinue Kanamycin (Strategy A), (ii) modify the frequency of Kanamycin administration (Strategy B), (iii) and leave the regimen unchanged, i.e., no intervention (Strategy C). A smaller proportion of participants, 12 out of 33, experienced further deterioration of hearing thresholds after intervention strategy A (discontinue Kanamycin) was used, when compared to participants who underwent intervention strategies B and C, but the difference was not statistically significant ($p = 0.056$).

Conclusion: This study found a high incidence of cochleotoxicity among patients receiving Kanamycin treatment for RR/MDR-TB. The results showed that discontinuing Kanamycin led to fewer participants developing further deterioration of hearing thresholds, although not statistically significant. There were no statistically significant associations between the occurrence of STS and age, sex, and HIV status. This study had some limitations; only cochlear hearing loss was investigated, participants were not followed up beyond six months, and genetic testing was not performed. Nonetheless, this study revealed that fewer participants had further significant

threshold shifts after discontinuing Kanamycin, and for those patients who still receive regimens containing aminoglycosides, these findings are relevant.

Keywords: Ototoxicity, Ototoxicity Monitoring, Cochleotoxicity, Aminoglycoside, Kanamycin, Multi-drug resistant, Tuberculosis, Significant Threshold Shift

Chapter One: INTRODUCTION

This chapter will provide the background to the study by presenting global and South African tuberculosis statistics. The chapter will also introduce the relationships between tuberculosis, its treatment, and its contribution to the burden of hearing loss and provide a rationale for this study.

South African incidence and burden of Tuberculosis

South Africa (SA) is one of the high tuberculosis (TB) burden countries (HTBBC) and is ranked among the top eight of the 30 HTBBC worldwide (World Health Organization [WHO], 2020). South Africa is ranked eighth worldwide in terms of absolute number of TB cases and contributing 3.6% of the world's TB cases. In 2019, there were 360, 000 people who fell ill with TB in SA (WHO, 2020). This means that about 0.6% of the South African population (59 million people) developed active TB disease. Of the 360, 000 active TB cases, 209, 000 were Human Immunodeficiency Virus (HIV) positive and about 14,000 were Multi-Drug Resistant (MDR)-TB or Rifampicin Resistant (RR)-TB cases. In South Africa, it was estimated that 58, 000 people died of TB, therefore making TB the number one cause of mortality in the country. Two-thirds (36, 000) of these deaths were HIV positive and 22, 000 were HIV negative (WHO, 2020). The Western Cape, where the current study was conducted, is among the top three provinces in South Africa with the highest incidence of TB (681 per 100, 000), after the Eastern Cape (692 per 100 000) and Kwa-Zulu Natal (685 per 100, 000) (Kanabus, 2020).

Drug-resistant Tuberculosis and its threat to TB control

The development of resistance to the anti-tuberculosis drugs is one of the biggest threats to TB control efforts globally. For the past decade, there has been an increase in the number of individuals diagnosed with Drug-Resistant (DR)-TB (Dheda et al., 2017a; Zager & McNerney, 2008) and this has put a lot of stress on resources available to fight TB. In 2019, there were 465, 000 (range, 400, 000 – 535, 000) new TB cases with resistance to rifampicin. These new cases comprised of 362, 700 cases of MDR-TB (78%), and 102, 300 cases were RR (WHO, 2020). India, China, and the Russian Federation had the largest numbers of RR/MDR-TB cases, together contributing 49% of the global total. It was estimated that 3.3% (95% Confidence Interval [CI]: 2.3–4.3%) of the new cases and 18% (95% [CI]: 9.7–27%) of previously treated cases had RR/MDR-TB globally in 2019 (WHO, 2020). About one quarter of the global TB mortality is

made up of the DR-TB cases. In 2019, about 182, 000 (range, 113, 000 – 250, 000) people died from RR/MDR-TB (WHO, 2020).

The South African National Department of Health (NDoH) TB programme has also faced the challenge of an increase in the number of patients diagnosed with DR-TB, specifically RR (Department of Health [DoH]: Republic of South Africa, 2018). Of the DR-TB cases in SA in 2019, it was estimated that 3.4% were new cases and 7.1% were retreatment cases of RR/MDR-TB (WHO, 2020). In addition, more than 50% of these patients were HIV positive. Data from the WHO shows that there were at least 13, 005 laboratory confirmed cases of RR/MDR-TB and 406 Extensively Drug-Resistant (XDR)-TB cases in South Africa during 2019 (WHO, 2020). Of these, 8, 743 RR/MDR-TB patients and 406 XDR-TB patients were started on treatment, respectively.

Treatment of Drug-Resistant Tuberculosis

Prior to 2018, the WHO's recommended treatment regimen for RR/MDR-TB involved the use of aminoglycoside antibiotics (such as Kanamycin and Streptomycin). The aminoglycoside injectable was given for a minimum of six months (WHO, 2016). Aminoglycoside antibiotics are known to be toxic to the auditory and vestibular systems, and kidneys (Duggal & Sarkar, 2007; Guthrie, 2008; Huth et al., 2011) and may lead to severe side effects (Guthrie, 2008; Pinto & Menzies, 2011). One of the common side effects of aminoglycoside treatment is permanent damage to the auditory and/ or vestibular system (American Academy of Audiology [AAA], 2009; American Speech-Language-Hearing-Association [ASHA], 1994; Rybak & Ramkumar, 2007) known as ototoxicity. The side effects from these medications give rise to sensorineural hearing loss (SNHL) and/or vestibular hypofunction (AAA, 2009; ASHA, 1994).

In South Africa, Kanamycin was one of the key drugs used to treat RR/MDR-TB patients and led to a significant number of those patients developing permanent hearing loss following treatment with it. However, with the introduction of the new WHO guidelines related to treatment of DR-TB in 2018, an option of choosing an aminoglycoside-free short or long RR/MDR-TB regimen has been made available. Bedaquiline (BDQ), an injectable-free drug is used instead of the aminoglycoside and given orally for a minimum duration of six months. Patients can be treated on a short regimen for a duration of nine to 11 months or on a long regimen for a duration of 18-20 months. Advantages of the shorter regimen are that it is shorter in duration and contains fewer drugs in its regimen compared to the long regimen (WHO, 2020). The longer regimen, taken for

18 – 20 months, has a longer duration for patients to complete their treatment and may still contain an aminoglycoside (Amikacin or Streptomycin) in the regimen for certain patients where limited treatment options are available (WHO, 2020). Therefore, even though the use of Kanamycin has been discontinued as one of the drugs that is used to treat RR/MDR-TB patients, there is still a proportion of patients on RR/MDR-TB treatment who will be treated with ototoxic aminoglycosides, which means they are at a risk of developing cochleotoxic hearing loss. Once cochleotoxic hearing loss is acquired, it may have major implications on an individual's quality of life (QoL).

Aminoglycoside Cochleotoxicity and Hearing Loss

One of the most common side effects of aminoglycoside treatment is hearing loss. Aminoglycoside-induced hearing loss resulting from RR/MDR-TB treatment can negatively impact on the individual's communication ability (AAA, 2009; ASHA, 1994), psychological functioning, emotions, physical functioning and overall well-being (Gispen et al., 2014; Midha & Malik, 2015; Petersen & Rogers, 2015), and therefore, lead to a reduced QoL (Boothroyd, 2007; Carlsson et al., 2011; Dalton et al., 2003; Nachtegaal et al., 2009).

Individual self-reported communication difficulties and hearing handicap are reported to be significantly associated with the severity of the hearing loss (Dalton et al., 2003). Another study found that more severe hearing losses were significantly associated with poor QoL (Carlsson et al., 2011). This is concerning because aminoglycoside-induced hearing losses tend to be any degree from mild to profound in the degree of hearing loss (Appana et al., 2016; Harris et al., 2012a).

Individuals with hearing loss are also more likely to experience anxiety, lack of self-confidence, depression and/or social isolation irrespective of the aetiology and type of hearing loss (Alamgir et al., 2016). Nachtegaal et al. (2009), reported higher levels of depression, anxiety, and distress in individuals with poorer hearing in the age group of 40-49 years. Similarly, Kim et al. (2017) found that the risk of depression was significantly increased in individuals with severe hearing loss irrespective of age ($p < 0.001$). However, the relationship is not always linear between decreased hearing and decreased mental health (Gopinath et al., 2009; Kim et al., 2017). Gopinath et al. (2009) found that symptoms of depression were significantly higher among individuals with mild hearing loss when compared to those with moderate or severe hearing loss, showing that hearing loss affects the psychological well-being of people differently.

Research literature related to the associations between hearing loss, cognitive decline and all-cause dementia, have increased over the past decade (Lin et al., 2011, 2013; Loughrey et al., 2018). In a study involving a large sample of adults ($n = 639$), it showed that adults with hearing loss had an increased risk of cognitive decline and risk of dementia (Lin et al., 2011). Adults with severe degree of hearing loss had a five-fold increase for the risk of cognitive decline. Three possible reasons for the relationship between hearing loss and cognitive decline have been suggested (Lin et al., 2011). Firstly, the natural aging process suggests as you get older, the natural metabolic processes of ageing causes hair cells, spiral ganglion cells and neuron loss. Because these cells do not regenerate, the impact of hearing loss on these neural connections further diminishes cognitive abilities. Secondly, poor social networks, where communication impairments caused by hearing loss can lead to social isolation. The link between social isolation and hearing loss suggests the more severe a hearing loss and impairment is, the less likely the hearing-impaired person is to engage in social activities. However, individuals who remain actively involved and participate in leisure activities despite their hearing loss have a lower risk of dementia (Lin et al., 2011). This is because individuals who regularly participate in activities such as walking, jogging or bowling keep their neural connections strong and continuously functioning. Lastly, decreased cognitive reserve suggests that, because of sensory deprivation (i.e., hearing loss), reallocation of resources occurs to compensate for the hearing loss, and therefore, processes, such as working memory, are affected. In addition, individuals with hearing impairment compared to those with normal hearing also have accelerated brain volume decline (Lin et al., 2015).

Study Rationale

South Africa has a high burden of RR/MDR-TB. Prior to 2018, aminoglycoside antibiotics (specifically, Kanamycin), were part of the treatment regimen for patients who were undergoing treatment for RR/MDR-TB in SA. Aminoglycosides, which are used to treat RR/MDR-TB, are associated with permanent hearing loss, which can negatively impact on the patient's QoL (Dalton et al., 2003; Kim et al., 2017; Lin et al., 2011). Even though SA has moved to a predominantly aminoglycoside-free regimen since 2018, there are still a small percentage of RR/MDR-TB patients who are being treated with aminoglycosides as per recommendations of the revised WHO guidelines released in 2020 (WHO, 2020).

To minimise the risk of aminoglycoside-induced hearing loss for those patients who are on treatment for RR/MDR-TB, monitoring of their hearing is recommended while receiving treatment (i.e., cochleotoxicity monitoring). The purpose of monitoring patients' hearing thresholds when they are treated with cochleotoxic aminoglycosides is to detect significant threshold shifts (STS) early and to provide treating doctors an opportunity to implement appropriate medical intervention to prevent further deterioration of patients' hearing thresholds. There are several medical interventions that can be implemented by the treating medical personnel when a STS occurs. These may include discontinuing the aminoglycoside, changing to an alternative drug with fewer cochleotoxic side effects or changing the frequency of aminoglycoside administration. All these interventions utilised are to prevent deterioration of hearing thresholds before it progresses to the frequencies that are important for speech perception.

There is currently a lack of research evidence in South Africa regarding the effectiveness of different medical interventions used when a change in hearing threshold is detected. To bridge the gap both in literature and clinical practice, a description of what interventions are implemented when a STS occurs as well as the effectiveness of these interventions are needed. This will help to establish which intervention is the most effective to prevent further deterioration of hearing thresholds. This study, therefore, sets out to answer the following research question: What intervention, when implemented for patients who are being treated with cochleotoxic aminoglycosides and experiencing a significant hearing threshold shift, is the most effective to minimise further deterioration of hearing thresholds and prevent severe degrees of hearing loss?

Chapter Two: LITERATURE REVIEW

This chapter will present literature on the incidence, the pathophysiology and risk factors for aminoglycoside-induced cochleotoxicity. It will also present a review of literature on interventions used to prevent further deterioration of hearing thresholds due to aminoglycoside-induced cochleotoxicity.

Incidence of Aminoglycoside-Induced Cochleotoxicity

Many studies have been conducted over the years to determine the incidence of aminoglycoside-induced cochleotoxicity in patients undergoing treatment for DR-TB (Appana et al., 2016; Brummett & Fox, 1989; de Vasconcelos et al., 2018; Duggal & Sarkar, 2007; Fausti et al., 1993; Ghafari et al., 2020; Guthrie, 2008; Peloquin et al., 2004; Ramma & Ibekwe, 2012; Sturdy et al., 2011). Incidence of aminoglycoside-induced cochleotoxicity in these studies varies considerably; from as low as 18% to 100% in some studies. Table 1 provides a summary of studies reviewed.

It is clear from Table 1 that these studies differed in several methodological variables, hence the variation in the range of incidences reported. Most notable were the variations in study designs (e.g., retrospective vs. prospective), monitoring protocol used (conventional pure tone audiometry (cPTA) vs. ultra-high frequency audiometry (UHFA) vs otoacoustic emissions (OAE)), type of aminoglycoside under study (Amikacin vs. Kanamycin) and classification to define hearing loss. All these variables can influence the incidence of aminoglycoside-induced cochleotoxicity reported, hence the variation in the incidences reported.

Table 1: Incidence of Aminoglycoside-Induced Cochleotoxicity

Study & Country	Year	Design	Drug	Tests used	Sample size	Incidence	Classification of HL/STS defn	Comments
Appana et al. (South Africa)	2016	Prospective Longitudinal Cohort Descriptive	Kanamycin	Conventional pure tone audiometry including Ultra-high frequencies OAEs	52	100%	25 dB for normal hearing, ASHA, (1994) criteria for STS	Monitored monthly for 6months
Chauhan et al. (India)	2011	Prospective Observational	Gentamicin Amikacin Cisplatin	Conventional pure tone audiometry including Ultra-high frequencies	105	43%	Not specified	Treatment for 18 months
De Jager & Van Altena (Netherlands)	2002	Retrospective Folder review	Amikacin Kanamycin Streptomycin	Conventional pure tone audiometry air conduction only	110	18%	30 dB normal 15 dB loss at two or more frequencies, or a minimum of 20 dB hearing loss at one frequency	Treatment for > 14 days 5year review period
De Vasconcelos et al. (Brazil)	2018	Prospective Longitudinal Cohort	Amikacin	Conventional pure tone audiometry including Ultra-high frequencies OAEs	10	70%	20 dB loss from baseline at any one test frequency or a 10 dB loss at any two adjacent test frequencies	Monitored for 6 months
Duggal & Sarkar (India)	2007	Prospective Longitudinal Observational	Amikacin Kanamycin Capreomycin	Conventional pure tone audiometry	64	25%	25 dB for normal hearing, ASHA, (1994) criteria for STS	Treatment for 18–24 months
Fausti et al. (United States of America)	1994	Prospective Cohort	Gentamicin	Conventional pure tone audiometry including Ultra-high frequencies	53	47%	ASHA, (1994) criteria for STS	Monitored for 6months
Ghafari et al. (South Africa)	2020	Prospective Observational Cohort	Kanamycin	Conventional pure tone audiometry including Ultra-high frequencies	102	82.4%	25 dB for normal hearing, ASHA, (1994) criteria for STS; University of Cape Town (UCT) cochleotoxic grading scale	Monitored baseline, 4, 8, 12 weeks

Harris et al. (South Africa)	2012	Prospective Cohort	Kanamycin, Streptomycin Capreomycin	Conventional pure tone audiometry	151	58%	25 dB for normal hearing, ASHA, (1994) criteria for STS	Monitored monthly for 3 months
Irwan et al. (Indonesia)	2017	Cross sectional Observational Descriptive	Kanamycin	Conventional pure tone audiometry OAEs	33	91% (ASHA criteria) 55% (Brock criteria)	ASHA, (1994) criteria for STS and Brock ototoxicity grading scale	Data collected monthly for 4 months
Nizamuddin et al. (India)	2015	Prospective Longitudinal Cohort	Amikacin, Kanamycin, Streptomycin	Conventional pure tone audiometry	84	58%	25 dB for normal hearing, ASHA, (1994) criteria for STS	Monitored every 3months Treatment for 18-24months
Piubello et al. (Niger)	2014	Prospective Cohort	Kanamycin	Conventional pure tone audiometry	65	20%	Not specified	Monitored for 4months
Sharma et al. (India)	2016	Prospective Observational	Kanamycin	Conventional pure tone audiometry	100	18%	25 dB for normal hearing, ASHA, (1994) criteria for STS	Treatment for 6 weeks
Sogebi et al. (Nigeria)	2016	Prospective Analytical Cohort	Kanamycin	Conventional pure tone audiometry	70	22.9%	25 dB for normal hearing, ASHA, (1994) criteria for STS	Monitored monthly for 4 months
Sogebi et al. (Nigeria)	2016	Prospective Longitudinal Cohort	Not specified	Conventional pure tone audiometry	132	78.8%	25 dB normal hearing	Monitored for 12 months
Sturdy et al. (United Kingdom)	2011	Retrospective Non-randomized Folder review Multi-centre	Amikacin, Capreomycin, Streptomycin	Conventional pure tone audiometry	50	28%	20 dB loss from baseline at any one test frequency or a 10 dB loss at any two adjacent test frequencies	Treatment > 2 weeks 5-year review period
Van der Walt et al. (South Africa)	2013	Prospective Multi-centre Cohort	Amikacin or Kanamycin	Conventional pure tone audiometry	1390	40%	No definition for hearing loss except weekly patient self-report screening	Monitored for 4months Treatment for 18-24months

Note: Conventional pure tone audiometry (cPTA) tests frequencies (250 Hertz [Hz] - 8 kiloHertz [kHz]) for air conduction and frequencies (250 Hz - 4 kHz) for bone conduction. Ultra-high frequency audiometry (UHFA) tests frequencies (9 kHz – 20 kHz) for air conduction.

Study Design: Prospective vs. Retrospective

The majority of studies reviewed were prospective in nature and occurred in developing countries. In general, most of the prospective studies reviewed tend to report high incidences of aminoglycoside-induced cochleotoxicity. For instance, a study by Sogebi et al. (2016b) reported a 78.8% incidence of hearing loss when monitoring for cochleotoxicity in patients (n = 132) receiving Kanamycin treatment for RR/MDR-TB. Whereas Nizamuddin et al. (2015) reported an incidence of 58% cochleotoxicity in their study conducted in India (n = 84). Similarly, Harris et al. (2012a) prospectively monitored RR/MDR-TB patients' (n = 151) receiving Kanamycin in Cape Town, South Africa, for three months, and reported an incidence of 58%. A study by Ghafari et al. (2020) found a higher incidence of hearing loss (82.4%) among their patient cohort (n = 102) receiving Kanamycin at a TB hospital in Cape Town, South Africa, when monitoring for three months. Likewise, Appana, Joseph and Paken (2016) monitored RR/MDR-TB patients' (n = 52) hearing for six months in a hospital in Kwa-Zulu Natal, South Africa, and found an incidence of 100%.

A possible reason why prospective studies tend to yield higher incidences than the retrospective studies reviewed could be due to the fact that in prospective studies, there is better control over the data being collected as strict protocols and guidelines are adhered to from the start and throughout the study. Thereby allowing for better quality of data to be collected. Moreover, fewer potential sources of error arise as data are collected regularly at specific time intervals.

In the retrospective studies (De Jager & Van Altena, 2002; Sturdy et al., 2011) reviewed, the incidences were lower. De Jager and Van Altena (2002) found 18% cochleotoxicity in their patients in the Netherlands when retrospectively reviewing folders for a five-year period. Comparably, Sturdy et al. (2011) did a multi-centre folder review of the centres treating RR/MDR-TB patients in the United Kingdom (UK) and found 28% cochleotoxicity. These low incidences can be attributed to the nature of retrospective studies where data are obtained historically, i.e., looking back in time at data and therefore, have missing data in the folders such as frequency of audiograms not recorded or conducted regularly, patients not attending follow-up sessions or simply, a general lack of recording certain information (as healthcare professionals were unaware of what data needed to be recorded for future reviews).

However, some prospective studies (Chauhan et al., 2011; Duggal & Sarkar, 2007; Piubello et al., 2014; Sharma et al., 2016; Sogebi et al., 2016a; Van der Walt et al., 2013) found cochleotoxicity incidences to be less than 50% even when prospective monitoring of hearing thresholds occurred. This difference could be attributed to the test protocols used to monitor the thresholds (cPTA vs. UHFA) and the classification used to determine hearing loss or the definition for STS.

Cochleotoxicity Protocol - Conventional versus Ultra-High Frequency versus Otoacoustic Emissions

The various protocols used for the monitoring of cochleotoxicity, as well as the lack of uniform criteria for defining cochleotoxic changes (i.e., STS), use of different tests to monitor cochleotoxicity (i.e., cPTA vs. UHFA) could be some of the reasons why there is a lot of variability in the incidence of cochleotoxicity reported across different studies. The majority of the studies reviewed only tested conventional frequencies (250 Hz to 8 kHz) and not an ultra-high frequency range (i.e., > 8 000 Hz). Cochleotoxicity typically starts in the higher frequencies (Guthrie, 2008; Rybak & Ramkumar, 2007) thus, cochleotoxicity monitoring protocols that include tests such as UHFA or OAEs testing should be used, as these tests are more sensitive to detecting cochlear damage sooner than cPTA (AAA, 2009; ASHA, 1994).

For instance, Chauhan, Saxena and Varshey (2011) monitored a cohort of patients (n = 105) in India to investigate the efficacy of using UHFA as a means for early detection of cochleotoxicity. They reported an incidence of 42.9% (45/105 patients) and concluded that if cPTA were solely conducted on these patients', many patients would have been missed for early cochleotoxic hearing changes, therefore, advocating for the use of UHFA. In another study by de Vasconcelos and colleagues (2018), both cPTA and UHFA testing was used to monitor hearing for early detection of cochleotoxicity in their patient cohort. They found that UHFA testing detected STS sooner than cPTA, and the incidence of cochleotoxicity was higher when using UHFA (de Vasconcelos et al., 2018). For example, when using cPTA to check thresholds for cochleotoxicity after two months of treatment, none of the patients had threshold shifts. However, when using UHFA, both the right and left ears had cochleotoxic shifts (50% and 60% of patients, respectively) at two months during treatment (de Vasconcelos et al., 2018). Furthermore, an overall incidence of cochleotoxicity of 20% for cPTA and an cochleotoxicity incidence of 70% for UHFA

was found at the end of the six-month treatment. Similarly, Fausti et al. (1994) used both cPTA and UHFA testing for monitoring hearing thresholds and reported that 37.8% of ears had cochleotoxic changes when using cPTA compared to 71.1% when using UHFA. Studies have also been conducted in South Africa using UHFA to detect early STS and determine the incidence of cochleotoxicity. For instance, Ghafari et al. (2020) prospectively monitored a cohort of patients' (n = 102) receiving Kanamycin at a TB hospital in Cape Town, South Africa with UHFA and found an incidence of 82.4%. Likewise, Appana et al. (2016) reported a high incidence of cochleotoxicity (100%) when using UHFA testing on their patients (n = 52) hearing thresholds.

In the studies reviewed where cPTA (250 Hz -8 000 Hz) was utilised to assess hearing, the incidences were lower than most studies that used UHFA (Duggal & Sarkar, 2007; Piubello et al., 2014; Sharma et al., 2016). For instance, Duggal & Sarkar (2007) reported an cochleotoxicity incidence of 25% despite monitoring their patients for one year. Similarly, Piubello et al. (2014) and Sharma et al. (2016) reported a low cochleotoxicity incidence of 20% and 18% respectively, amongst their patient cohorts.

OAEs testing is another test that can be used to assess hearing and monitor for cochleotoxicity which can also influence the reported incidence. For example, Appana et al. (2016) used OAEs testing, specifically distortion product (DP) OAEs and monitored patient hearing for six months while on the intensive phase. The frequency range 750 Hz to 8 000 Hz were assessed. On baseline testing, 27 (55%) patients had absent DPOAEs on the right ear and 22 (45%) patients on the left ear, and by the end of the first month of treatment, they found that 52% (27/52) of their patients had a STS. After six months of treatment (end of their study), they found that all patients acquired a hearing loss on both UHFA and DPOAEs when compared to baseline data. In contrast, Irwan et al. (2017) used OAEs to monitor their patients' hearing thresholds during cochleotoxicity monitoring. They found that out of the 66 ears (33 patients) assessed in their cohort, 47/66 ears passed, and 19/66 ears had a referral result at the end of the treatment. The referral result indicates that only 19 ears in their cohort experienced cochleotoxicity that was detected via OAEs. However, a high pass rate (47/66 ears) would be expected as only frequencies 1 000 Hz to 5 000 Hz were assessed, and hearing loss due to cochleotoxicity starts in the higher frequencies > 8 kHz first before progressing to the lower frequencies (ASHA, 1994). The reason why they could have obtained a high pass rate may be because the hair cells in this frequency range (i.e., 1 000 Hz to 5 000 Hz) may not have been affected yet by the aminoglycoside (Irwan et al., 2017). A similar

observation was reported by de Vasconcelos et al. (2018), where DPOAE testing did not detect any cochleotoxic shifts in their patient cohort. However, they also only assessed frequencies 1 000 Hz to 6 000 Hz, of which the frequency range tested may not have been sensitive for early detection of cochleotoxic shifts (de Vasconcelos et al., 2018). Therefore, OAE testing should include higher frequencies > 8 kHz as it is more sensitive to cochleotoxic shifts and can help with the early identification of hearing loss.

As can be seen from the studies reviewed, in general studies that include UHFA (9 000 Hz -20 000 Hz) testing as part of the monitoring tests tended to identify a greater number of patients with hearing loss and threshold shifts than cPTA (250 Hz - 8 000 Hz). Overall, these studies highlight the importance of including more sensitive tests e.g., UHFA and OAE testing in the test battery when monitoring patients for cochleotoxicity (Appana et al., 2016; Chauhan et al., 2011; Ghafari et al., 2020; Konrad-Martin et al., 2014; de Vasconcelos et al., 2018).

In addition to the study design and protocol used, which varied in the studies reviewed, there was also variation in the criteria used to define a STS. The majority of studies used the ASHA (1994) criteria to identify this shift (Appana et al., 2016; Duggal & Sarkar, 2007; Ghafari et al., 2020; Harris et al., 2012a; Nizamuddin et al., 2015; Sharma et al., 2016; Sogebi et al., 2016a). However, there were a few studies that did not use the ASHA (1994) criteria to define STS, but rather relied on patient self-reports of hearing loss or used other criteria to define cochleotoxicity. These criteria used can impact the incidence. For instance, Van der Walt et al. (2013) conducted a prospective multi-centre cohort study of 1390 RR/MDR-TB individuals from 2000 - 2004, across all nine provinces in South Africa. Weekly screening of adverse drug reactions (ADR) was conducted through passive patient self-reports or nurse observation during the clinic visit. Their study found that 40% of their RR/MDR-TB patients reported cochleotoxicity as the main adverse drug reaction despite not having formal audiometry conducted. This study should be viewed with caution because the hearing was not tested via audiometry testing, nor was objective testing such as OAEs performed to determine cochleotoxicity (Van der Walt et al., 2013). Therefore, patient self-reporting tolerance levels or patient fear of hearing loss could have contributed to the incidence found in their study.

Another study conducted in Ogun, Nigeria reported a cochleotoxicity incidence of 78.8% among RR/MDR-TB patients. The patient's hearing thresholds were tested in a quiet room and

were prospectively monitored over a one year period (Sogebi et al., 2016b). Conventional frequencies were assessed, and baseline hearing thresholds could be both normal and hearing loss. This is concerning because pure aminoglycoside-induced hearing loss may not have been the only contributing factor to threshold shifts as some baselines were not normal to start with and had conductive components which may have influenced the hearing threshold changes i.e., the presence of an ear infection could have worsened the hearing. Moreover, the ASHA (1994) criteria for STS were not used in their study to determine cochleotoxicity. Therefore, evidence from studies like these with significant methodological challenges should be viewed with caution.

Drugs – Amikacin-Kanamycin-Capreomycin

Another factor that can influence the incidence of cochleotoxicity is the type of aminoglycoside used. The level of cochleotoxicity varies among different aminoglycosides. Studies exploring the cochleotoxicity of more than one aminoglycoside or comparing the aminoglycoside report conflicting results. Some studies report Kanamycin is more cochleotoxic while others report Amikacin to be more cochleotoxic (De Jager & Van Altena, 2002; Duggal & Sarkar, 2007). Most studies reviewed used Kanamycin, and where it was used, a higher incidence of cochleotoxicity was reported compared to other aminoglycosides used in the same studies (De Jager & Van Altena, 2002; Harris et al., 2012a). For instance, in a study by Harris et al. (2012a), 145/151 patients received Kanamycin and patients in this group had a higher hearing loss than those in the other two groups. Similarly, De Jager and Van Altena (2002) found that patients who received Kanamycin had more hearing loss than those who were given Amikacin or Streptomycin. De Jager and Van Altena (2002) also reported that the most common aminoglycoside used in their patients was Kanamycin (90/110). In both studies, the number of patients in the Kanamycin group was larger than the other two groups. This is because Kanamycin was readily available to these patients and preferred in these settings and may have contributed to the large number of patients experiencing cochleotoxicity due to Kanamycin.

In other studies, however, Amikacin was found to be more cochleotoxic and have a higher incidence of hearing loss. Nizamuddin et al. (2015) found that Amikacin was more cochleotoxic than Kanamycin and Streptomycin in their patients as well as having a higher incidence of hearing loss, (33%) compared to Kanamycin (17.5%), and Streptomycin (18%). Similarly, Sturdy et al.

(2011) found that patients who were treated with Amikacin reported hearing loss more frequently than those who received Capreomycin. The use of Amikacin was also significantly associated with cochleotoxicity ($p = 0.02$). Moreover, Duggal and Sarkar (2007) found a 20.6% incidence in their Amikacin group compared to 15% in their Kanamycin group of patients.

In the studies reviewed where Capreomycin, a polypeptide antibiotic, was administered, Harris et al. (2012a) and Sturdy et al. (2011) found it to be less cochleotoxic than the other aminoglycosides. Conversely, Duggal and Sarkar (2007) found that patients who received Capreomycin had a higher incidence of cochleotoxicity (25%). However, caution should be taken with reports like these as only 4/64 patients received Capreomycin and only 1/4 had cochleotoxicity, thus, skewing the percentage, providing more weighting, and consequently displaying a higher incidence.

From the literature reviewed it is clear that the majority of the studies were conducted in developing countries and demonstrated that cochleotoxicity is a frequent adverse side-effect in this patient population. Again, if aminoglycosides remain in the treatment regimen, the number of patients acquiring a hearing loss will probably increase. The various types of drugs used, the protocol for testing hearing, as well as the different criteria to classify hearing loss and identify STS all play a role in the reported incidence of cochleotoxicity. In addition, reporting and comparing of incidences are difficult amid no universal standardised protocol used.

Pathophysiology of Aminoglycoside-Induced Ototoxicity

Aminoglycoside-induced ototoxicity is a familiar and documented challenge of the second-line aminoglycoside injectables (Selimoglu, 2007). Soon after administration, aminoglycosides enter the fluids of the cochlea in the inner ear via the bloodstream and enter the cochlear hair cells through a channel (Huth et al., 2011; Selimoglu, 2007). Acting like a one-way valve the channel traps the aminoglycoside in the hair cell where it is not metabolised. Once in the hair cells, it binds with iron to form an oxidative compound and produces free radicals in the inner ear, which in turn damage the hair cells (Huth et al., 2011; Roland, 2004). This damage was also previously seen in animal models, such as the gerbil (Abbas & Rivolta, 2015), and guinea pig (Yang et al., 2009). Long-term exposure of aminoglycosides is linked to outer hair cell (OHC) damage in the organ of

Corti in the cochlear, and type 1 sensory hair cell loss in the vestibular system, respectively (Selimoglu, 2007).

Damage usually occurs first at the basal portion of the cochlea and progresses to the apical portion affecting the outer hair cells, before affecting the inner hair cells (Duggal & Sarkar, 2007; Guthrie, 2008; Li & Steyger, 2009; Rybak & Ramkumar, 2007). This damage, therefore, affects the part that processes high frequency information before progressing to lower frequencies or frequencies needed for speech communication (Cassia et al., 2006; Rybak & Ramkumar, 2007; Selimoglu, 2007). Because hair cell damage may occur before any perceived loss of hearing by patients, an understanding of which frequencies are affected first and what effects it might have on an individual's speech communication is important for clinical management. Thereby, indicating that subjective patient reports cannot be relied on for detection of cochleotoxicity. Hence, sensitive tests such as UHFA and OAE testing are essential for the early identification of cochleotoxicity and prompt management.

Aminoglycosides may either damage the cochlea, vestibular system or the kidney (Huth et al., 2011; Selimoglu, 2007). Different aminoglycoside antibiotics vary in their ability to produce cochlear or vestibular toxicity. For instance, Amikacin, Kanamycin and Neomycin typically damage the cochlear, while Streptomycin and Gentamicin generally target the vestibular portion to cause toxicity (ASHA, 1994). The effect of aminoglycoside-induced cochleotoxicity is recognised by a specific pattern of hearing loss (Selimoglu, 2007), starting at the basal portion of the cochlea and later progressing to the apical portion. De Jager and Van Altena (2002) investigated the ototoxic effects of aminoglycosides on hearing and the kidney and found that ototoxic effects generally do not appear until five days after starting the aminoglycoside treatment. In addition, the distribution of the drug within the inner ear tissues damages the cells in the cochlear or vestibular systems (Roland, 2004).

Due to the longer half-life of the aminoglycoside, it takes >30days for it to be cleared out of the hair cells, thus, resulting in an accumulation of the injectable medication. Furthermore, the drug may remain in the inner ear tissues for six months or longer after cessation of aminoglycoside treatment. Hence, this is the reason why individuals with a history of previous aminoglycoside use are more susceptible to ototoxicity than those who have not received aminoglycoside therapy before (Rybak & Ramkumar, 2007).

Risk Factors for Cochleotoxicity

There are several factors that have been reported to increase patients' susceptibility to cochleotoxicity during treatment with cochleotoxic aminoglycoside antibiotics. Available literature mainly report two categories of these risk factors; inherent or external in nature (ASHA, 1994; Petersen & Rogers, 2015; Schellack & Naude, 2013; WHO, 2020). Risk factors that belong to the individual or part of the individual are called inherent, and factors that are outside of the individuals' control but have an influence are called external (AAA, 2009; Health Professionals Council of South Africa (HPCSA), 2018) (Table 2).

Table 2: Risk Factors for Cochleotoxicity

Inherent Risk Factors	External Risk Factors
Age	Type of drug
Sex	Dose, Frequency and Duration of Treatment
HIV/AIDS	Noise exposure
Renal impairment	
Genetics	

Inherent risk factors

Age

Age is an important consideration as a risk factor for cochleotoxicity. Park et al. (2016) conducted a study on a South Korean population and found a difference at the hearing thresholds of 3 kHz, 4 kHz, and 6 kHz for people older than 30 years old. As age increased, the hearing thresholds at all of the tested frequencies worsened (Park et al., 2016). Similarly, Sogebi et al. (2016a) found that being older ($p = 0.018$) was associated with an increased risk of developing cochleotoxicity in their patient's receiving treatment for RR/MDR-TB. Sturdy et al. (2011), also found a significant association between cochleotoxicity and increased age ($p = 0.02$).

Children and older adults are at a greater risk for cochleotoxicity than younger and middle-aged adults (Duggal & Sarkar, 2007), specifically, children younger than five years old and the elderly (Li et al., 2004). The negative impact of cochleotoxicity in children can, thus, have detrimental consequences on a child's development such as speech and language, social-emotional and academics (McKay et al., 2008). Therefore, cochleotoxicity management for children younger than five years old must be prioritised.

Limited published literature exists on cochleotoxicity in children treated for RR/MDR-TB (Garcia-Prats et al., 2016). Pure tone audiometry testing is sometimes difficult in young children and alternative methods of testing such as OAEs and/or auditory brainstem response (ABR) testing can be used instead (ASHA, 1994). A study conducted at a TB hospital reported that 48% of children treated for RR/MDR-TB had a hearing loss confirmed by cPTA (Ghafari et al., 2015). Seddon et al. (2013) conducted a retrospective folder review of children treated for RR/MDR-TB at a TB hospital in Cape Town, South Africa, and found that 24% of children had hearing loss. Hearing loss was also confirmed using cPTA testing and OAE testing (Seddon et al., 2013). Seddon et al. (2014) later performed a prospective follow-up in the same setting and found that 25/142 (17.6%) children had hearing loss (Seddon et al., 2014). However, only children (n = 94) with severe RR/MDR-TB disease was treated with an aminoglycoside, and hearing was only monitored for four months. Therefore, it is possible that under-estimating hearing loss in this cohort was due to only severe RR/MDR-TB disease receiving an aminoglycoside and the monitoring duration being short. The elderly and very young patients are of interest because drugs are less likely to be studied comprehensively in these extreme age populations, drug absorption and metabolism are also less predictable and more variable (Alomar, 2014). Children are also at high risk for developing ADRs due to having an immature renal tubular function, low body fat, hypotension, or hypoalbuminemia.

Sex

The effect of many drugs in the body is affected by the inherent biological differences between males and females (Alomar, 2014). These biological differences are body weight, body composition, liver and renal function and gastrointestinal tract factors. Women have lower body weight, organ size, more body fat and lower rate of excreting urine compared to men. Drug absorption, distribution, metabolism, and elimination are all affected by these differences. In a multi-country study of nine countries in West Africa and Central Africa conducted by Trebucq et al. (2018), RR/MDR-TB patients with a lower body mass index were found to be at an increased risk for adverse drug reactions. In this study, the most common ADR was hearing loss (11.4%) with deterioration occurring after four months (Trebucq et al., 2018). Similarly, a study conducted

by Sharma et al. (2016), found that hearing loss was more common in males (66.67%) than females (33.3%).

Contrary to the above studies, Harris et al. (2012a) found no associations between sex and the risk of developing hearing loss in their cohort. De Jager and Van Altena (2002) also found that hearing loss was not significantly associated with sex, age, duration of treatment or total aminoglycoside doses. The lack of significant associations with hearing loss in the De Jager and Van Altena (2002) study could be due to a retrospective folder review being performed; many baseline audiograms were missing, there was variability in the frequency of audiogram tests performed and many prescribed medications were not noted.

HIV/AIDS

It has been reported that people who are HIV positive, have TB or malaria and are receiving simultaneous treatment for it, have a higher risk of cochleotoxicity (Olusanya et al., 2014; WHO, 2020). In South Africa, the TB/HIV burden is high and the prevalence of DR-TB is also high among the HIV positive population (Dheda et al., 2017b; Harris et al., 2012a). Often RR/MDR-TB treatment and treatment for HIV, such as highly active antiretroviral therapy (HAART) are given simultaneously to the patient (Harris et al., 2012b). Giving these drugs together has the potential to act synergistically to increase the risk of cochleotoxicity (Harris et al., 2012b; Jacobs & Ross, 2012). The risk of contracting opportunistic central nervous system infections are also higher in HIV positive individuals, as it is believed HAART drugs are cochleotoxic (Harris et al., 2012b; Khoza-Shangase, 2010). Several studies have been conducted in South Africa to determine the prevalence of cochleotoxicity in patients on RR/MDR-TB treatment who are co-infected with HIV. A study conducted by Jacobs and Ross (2012) in Durban, South Africa, found that hearing loss (28.7%) was the most common side effect experienced among their patients. Adverse drug reactions were also significantly more common in patients who had HIV than in patients who did not.

Harris et al. (2012a) reported that individuals who were HIV positive had a three times greater risk of developing hearing loss than those who did not have HIV. This increased risk may be due to individuals with more severe disease or slow response to treatment; therefore, they must take the aminoglycoside injectable treatment longer. In a retrospective study conducted in

Namibia, it was reported that patients who were co-infected with HIV (odds ratio [OR] = 3.4, 95 % CI: 1.1–10.6) were more at risk of developing hearing loss than those who were not (Sagwa et al., 2015). In another study, Sogebi et al. (2016a) reported an increased risk of developing cochleotoxicity in their HIV positive patients. In addition, RR/MDR-TB patients who are co-infected with HIV had a 22% higher risk of developing cochleotoxicity than HIV negative patients during RR/MDR-TB treatment (Hong et al., 2018). Contrary to these studies, Ghafari et al. (2020) found no association between HIV and cochleotoxicity.

Renal impairment

Although renal damage and electrolyte abnormalities are common and can be reversible through appropriate management, it is still life-threatening and a risk factor for ototoxicity. The function of the kidneys is to excrete drugs, and any change in renal function may increase toxicity in the kidney or decrease a therapeutic effect of the drug. If the renal system is compromised and the kidneys are unable to excrete harmful drugs from the body, the individual is left vulnerable to the potential increase of adverse drug reactions (Alomar, 2014). Sturdy et al. (2011), found that decreased renal function was significantly associated with ototoxicity in RR/MDR-TB patients ($p = 0.01$).

Genetics

There have been a few studies that investigated the relationship between genetics and a predisposition for cochleotoxic hearing loss (Bardien et al., 2009b; Foster & Tekin, 2015; Gardner et al., 1997; Human et al., 2010; Huth et al., 2011; Xie et al., 2011). Several mutations have been described to influence cochleotoxicity such as the A1555G, T1095C, C1494T, A827G, 961delT and T1291C. The A1555G mutation has been identified as a risk factor for aminoglycoside-induced hearing loss in the Chinese, Spanish, Arab-Israeli, and South African populations (Bardien et al., 2009a). Among other less common genetic mutations, the studies found individuals with the genetic mutation, A1555G to be more susceptible to cochleotoxicity (Xie et al., 2011). Moreover, for the A1555G mutation, a frequency of 0.9% was also found by Bardien et al. (2009b) among black South Africans and the 961delT+C(n) variant in 6.6% of their black control group and 2% in the mixed ancestry control group. Given the high incidence of RR/MDR-TB in the black ethnic

group, the frequency of this mutation is of concern. The incidence of aminoglycoside-induced hearing loss also increases to 17% – 33% when genetic variations are involved (Huth et al., 2011). Therefore, having the necessary means to identify these mutations prior to treatment, allows for high-risk individuals who potentially could develop hearing loss to be identified before the start of aminoglycoside treatment. However, genetic testing is expensive to conduct and not routinely available for patients on RR/MDR-TB treatment. Contrary to the above studies, a study by Harris et al. (2012a) found that none of the RR/MDR-TB patients (n = 151) who developed cochleotoxicity in their cohort had any of these known mutations.

External risk factors

Type of drug

The proportion of patients who develop cochleotoxic hearing loss vary according to the type of aminoglycoside used (ASHA, 1994). This is because the aminoglycoside itself varies in its level of ototoxicity and different aminoglycosides affect different parts of the audiovestibular system (Huth et al., 2011). For example, Kanamycin is more cochleotoxic, while Gentamicin is more vestibulotoxic. Therefore, depending on the drug used, different parts of the inner ear can be affected. However, the risk for ototoxicity between the different aminoglycoside drugs has not been well categorised and compared. Peloquin et al. (2004) found that patients who received Streptomycin had less cochleotoxicity (19%) than the other two groups, Kanamycin and Amikacin, 42% and 55% respectively. Similarly, Nizamuddin et al. (2015) found that Amikacin was more cochleotoxic than Kanamycin and Streptomycin in their patients as well as having a higher incidence of hearing loss (33%), compared to Kanamycin (17.5%), and Streptomycin (18%). Furthermore, a retrospective review of patients treated with RR/MDR-TB, patients who received Amikacin had a greater risk of developing more severe forms of hearing loss than patients who received Kanamycin (Sagwa et al., 2015). However, Sagwa et al. (2015) did not report on or control for treatment duration and total dose in this study. Nonetheless, a higher risk of cochleotoxicity is suggested in their study with the use of Amikacin.

In contrast to the studies reviewed where Amikacin was reported to have higher cochleotoxicity, in the studies where Kanamycin was used, Kanamycin cochleotoxicity was reported to be higher. For example, both Harris et al. (2012a) and De Jager et al. (2002), reported

that patients' who received Kanamycin had a higher incidence of cochleotoxicity when compared to the other aminoglycosides used. However, in both Harris et al. (2012a) and De Jager et al. (2002), the number of patients who received Kanamycin, 145/151 (Harris et al., 2012a) and 90/110 (De Jager & Van Altena, 2002) were larger. It could be that Kanamycin was preferred in their settings as an aminoglycoside of choice because it was readily accessible thus contributing to the number of patients experiencing cochleotoxicity due to Kanamycin because many patients were receiving it in their treatment regimen. From the studies reviewed (De Jager & Van Altena, 2002; Harris et al., 2012a; Nizamuddin et al., 2015; Peloquin et al., 2004; Sagwa et al., 2015) it can be seen that irrespective of the type of aminoglycoside drug used, they all produced cochleotoxicity and, therefore, the need to monitor hearing is essential.

Dose, Frequency and Duration of Treatment

Previous studies have reported that cumulative dosage over time contributes to cochleotoxicity rather than peak and trough levels of drugs (Bardien et al., 2009a; Modongo et al., 2015; Rybak & Ramkumar, 2007). Cochleotoxicity still occurs even if the recommended therapeutic range of aminoglycoside blood concentrations is utilised. However, even a single dose of the aminoglycoside injection may cause a hearing loss, but this occurrence is uncommon (Guthrie, 2008). In a large cohort of patients in Botswana treated for RR/MDR-TB with Amikacin (15–25 milligram (mg)/kilogram (kg) daily, maximum 1000 mg), 270/437 (62%) reported hearing loss. Of these patients, 147 (54%) were confirmed by audiological testing, and hearing loss was associated with dose and duration of treatment (Modongo et al., 2014). In another study conducted in Botswana, 11/28 (39%) adults with RR/MDR-TB treated with Amikacin 750–1000 mg/day, had hearing loss; the main predictors for cochleotoxicity were cumulative days of treatment and cumulative Amikacin area under the concentration time curve (AUC). In addition, peak and trough concentrations of Amikacin were not associated with hearing loss (Modongo et al., 2015).

Pavlidis et al. (2010) found that a higher dosage of Amikacin, when administered less frequently, was associated with less risk of cochleotoxicity. A similar study by, De Jager and Van Altena (2002) found that the frequency of administration of the aminoglycosides (Kanamycin, Amikacin and Streptomycin) were reduced from the initial six days per week, to three times a week and it was effective in reducing the risk of hearing loss. Therefore, changing the frequency

of the aminoglycoside administration should be considered as a strategy to prevent further deterioration of hearing loss when treating RR/MDR-TB patients (Pavlidis et al., 2010). However, this strategy is only viable if the aminoglycoside retains its effectiveness in killing the bacteria.

In contrast to Pavlidis et al. (2010) and De Jager & Van Altena (2002) studies, Peloquin et al. (2004), found that changing the frequency or dosage or both does not minimise the risk of hearing loss amongst patients that are being treated with aminoglycosides. Peloquin et al. (2004) further demonstrated that the risk of cochleotoxicity was not correlated with the size of the dosage or the frequency of drug administration and reported that giving the aminoglycoside once daily or thrice weekly does not matter, but the cumulative dosage does. Similarly, Piubello et al. (2014) reduced the frequency of the aminoglycoside injectable from daily to three times weekly. However, changing the frequency was ineffective as cumulative dose contributed to hearing loss in their cohort.

Studies have shown that the duration of treatment (i.e., how long an aminoglycoside is used for) leads to an increased risk of developing cochleotoxicity. This is due to the accumulation of the aminoglycoside drug inside the hair cells over time (Huth et al., 2011; Sturdy et al., 2011). Therefore, healthcare professionals should be cognisant when prescribing (i.e., the type of aminoglycoside drug and treatment start and completion period) potentially ototoxic drugs (Alomar, 2014; Hong et al., 2018; Peloquin et al., 2004; WHO, 2020).

Noise exposure

In a retrospective review conducted by Khoza-Shangase (2019) on the hearing levels of gold miners exposed to noise in the mines', hearing loss was worse for gold miners with a history of TB treatment compared to gold miners without a history of TB treatment, indicating an increased risk for noise-induced hearing loss when on TB treatment, but more so when noise and ototoxic medication is given simultaneously (Khoza-Shangase, 2019). However, Li and Steyger (2009) found that the synergistic effect of ototoxicity does not always occur when aminoglycoside treatment and noise exposure occur simultaneously. Aminoglycoside-induced cochleotoxicity can occur in individuals who had previous noise exposure or acoustic insult (Li & Steyger, 2009). Even if aminoglycosides are given weeks later, prior noise exposure potentiates cochleotoxicity. In addition, noise-induced cochlear damage still occurs even if the prescribed dosage of the

aminoglycoside drug is lowered (i.e., given at a sub-damaging dosage). This suggests that noise exposure damages the antioxidant capacity of the hair cells even if initially auditory function was not damaged.

Prevention of Aminoglycoside-Induced Hearing Loss

A common practice for individuals receiving aminoglycoside treatment for RR/MDR-TB is to monitor their hearing thresholds regularly during treatment (i.e., cochleotoxicity monitoring) so that modifications to the regimen can be made to prevent hearing loss. The purpose of cochleotoxic monitoring is two-fold; (1) to detect cochleotoxicity early so that appropriate interventions can be made to the patient's treatment before hearing loss progresses to a point where the patient's communication abilities are negatively affected and, (2) to intervene early with rehabilitation when and where necessary (ASHA, 1994). A typical cochleotoxicity monitoring programme consists of the following components: counselling before treatment initiation regarding the risk of cochleotoxicity from the treatment, baseline audiometric assessments prior to treatment initiation of aminoglycosides to identify a patient's risk of developing cochleotoxicity, monitoring and follow-up evaluations during treatment, and criteria for determining STS and a system to grade adverse effects on hearing due to cochleotoxicity which should be pre-selected. For an cochleotoxicity monitoring programme to function smoothly and ensure that hearing loss is identified early, and timely intervention occurs, various components of the monitoring programme need to be in place. It is generally accepted that effective cochleotoxic monitoring requires testing hearing thresholds in the ultra-high frequencies, (i.e., beyond 8000 Hz) (ASHA, 1994; DoH, 2018; HPCSA, 2018). In addition to UHFA testing, the use of electrophysiologic tests such as OAEs can be used to identify hearing changes earlier and, hence, adjustments to treatment could be made earlier. Thus, potentially reducing the likelihood of hearing loss before it reaches conventional speech frequencies (HPCSA, 2018).

Interventions Implemented

Treating doctors have several options regarding intervention that they can implement when an STS is detected during treatment with aminoglycosides. These include a) changing the frequency of the aminoglycoside administration, or b) changing the aminoglycoside to a non-

cochleotoxic alternative (DoH, 2015). In other words, for patients who are experiencing STS following treatment initiation, the frequency of drug administration could be changed to three times per week as opposed to six times per week and the aminoglycoside could be changed to an alternative drug with less cochleotoxic side effects. There has, however, been a debate about whether these various strategies have any effect on cochleotoxicity, and different studies have yielded different results with the various treatment modifications implemented. Available research evidence seems to suggest that these treatment modifications appear to be ineffective in minimising further deterioration of patients' hearing thresholds. For instance, a higher dose of the aminoglycoside at a less frequent occurrence is reported to be beneficial (Pavlidis et al., 2010), while another study reports that dose and frequency do not contribute to a risk of cochleotoxicity, instead cumulative dosage over time is a risk factor (Peloquin et al., 2004). In studies where the frequency of drug administration was adjusted from six times per week to three times per week, the hearing loss continued to worsen in their patients, irrespective of the change (Piubello et al., 2014; Sturdy et al., 2011). Similarly, for studies where the aminoglycoside was replaced with an alternative drug of lesser cochleotoxic side effects, hearing continued to deteriorate (Duggal & Sakar, 2007; Sharma et al., 2016).

In similar studies involving other patient populations e.g., cancer patients, it was shown that treatment modifications did not prevent deterioration of patient thresholds. For instance, a study by Chakara and Ramma (2019) involving a retrospective folder review of cancer patients receiving cochleotoxicity monitoring at a tertiary hospital in Cape Town, South Africa, found that despite treatment modifications, most patients still experienced cisplatin-induced cochleotoxicity (Chakara & Ramma, 2019).

Prior to 2018, DR-TB patients in South Africa received an aminoglycoside injectable (Kanamycin) as part of their regimen in their treatment (DoH, 2018; WHO, 2016). If a STS was detected during monitoring of hearing thresholds, the common practice was to change the dosage of Kanamycin or reduce the frequency. With the introduction of new drug options to the treatment management of DR-TB patients in SA (DoH, 2018), the recommended protocol used in SA when a patient received an aminoglycoside injectable and had STS occur due to cochleotoxicity, was to discontinue the use of the cochleotoxic drug and replace it with a less toxic or non-cochleotoxic alternative (DoH, 2018).

Since July 2018, all patients who are to receive treatment for RR/MDR-TB are now initiated on an aminoglycoside/injection-free regimen containing Bedaquiline (BDQ). Bedaquiline is a repurposed drug used in the treatment of patients with DR-TB. It is a non-cochleotoxic drug (WHO, 2020; DoH, 2018) and has no or minimal reported cochleotoxic effects on hearing compared to aminoglycosides (Diacon et al., 2012; WHO, 2020). However, because of the antibiotic benefits of Kanamycin and Amikacin in TB patients especially in dire circumstances, for example, patients whose sputum culture does not convert and their sputum culture remains positive (i.e., bacteria in a sputum culture continues to grow) despite receiving many months of treatment and/or where the disease is so advanced that the patient does not qualify for surgery; some patients may still receive it in the initial phase of treatment if their baseline hearing thresholds are normal. Currently, the South African DoH recommends that whether the patient receives a treatment regimen containing a cochleotoxic drug or an injectable-free regimen, their hearing thresholds should be monitored (cochleotoxicity monitoring) using UHFA so that early identification and intervention can occur (DoH, 2018; HPCSA, 2018).

Chapter Three: METHODOLOGY

This chapter will outline the aims and objectives of this study. Study design, methods, study tools, procedures and justification for their selection will be presented. Finally, ethical considerations for this study will also be discussed.

Aims

The study aimed to determine the effectiveness of different medical interventions used to prevent further deterioration of hearing thresholds when a significant change in hearing threshold is detected in RR/MDR-TB patients treated with aminoglycoside antibiotics.

Objectives

1. To determine the incidence of STS among patients receiving treatment for rifampicin resistant/ multi-drug resistant TB at Brooklyn Chest Tuberculosis Hospital (BCH).

1.1 Characterise hearing loss in terms of type, degree, laterality, and configuration.

1.2 To determine the associations between the development of aminoglycoside-induced hearing loss and patient factors such as: age, sex and HIV status.

2. To describe the intervention used when a change in patient's hearing status is detected during cochleotoxicity monitoring.

3. To compare the effectiveness of different intervention strategies to minimise or prevent aminoglycoside-induced cochleotoxicity.

Research Design

A descriptive prospective cohort within-subject repeated measures design was used in this study (Brink et al., 2006; Burkett, 1990). The descriptive aspect of this study design is used to describe what happens to the participants' hearing thresholds while on the medication, rather than the how, when, or why it happened, and because it is prospective, it allows the researcher to monitor what happens to the hearing over time (Brink et al., 2006). The advantages of using a prospective time frame are that it allows the researcher to follow the group of individuals forward in time to determine the progression of hearing loss and allows for high quality data to be collected and provided evidence with regards to the effects the drug has on hearing deterioration (Burkett, 1990). The study also had strong validity because the individual was monitored from exposure of the drug, to the occurrence of STS (Mann, 2003).

Another advantage of this design is that it can be used in studies where experimental study designs may lead to ethical concerns. In addition, this study assessed participants' hearing thresholds repeatedly, i.e., participants' hearing thresholds were documented at treatment initiation and during the course of treatment with cochleotoxic medications (Maxwell & Satake, 2006). The participants, therefore, acted as their own controls, hence increasing internal validity. Moreover, test-retest reliability was evaluated over time through this mechanism.

However, the drawbacks of this study design are that it can be expensive to conduct, time consuming and demanding on both the researcher and participants due to the longitudinal period. It is also not possible to determine cause and effect using this study design (Mann, 2003). However, it was not intended that this study would infer any causal relationships. Lastly, a disadvantage of repeated measures is that individuals may become better with the test over time, and this is known as practice effects (Maxwell & Satake, 2006). Or conversely, individuals become bored and fatigued due to the test. However, to reduce the practice effects in this study, the researcher varied the presentation stimuli of the tones and took necessary breaks to avoid fatigue between testing sessions.

Participants

All patients diagnosed with RR/MDR-TB, receiving a treatment that included Kanamycin and monitored for cochleotoxicity, at BCH, were invited to participate in this study.

Inclusion and Exclusion criteria

Inclusion criteria (Patients who met the following criteria were recruited and invited to participate in the study):

- a. Newly diagnosed RR/MDR-TB patients receiving an aminoglycoside for the very first time.
- b. Baseline testing within 72 hours of first aminoglycoside administration.
- c. Age range of 18-55 years.
- d. Normal hearing thresholds (i.e., PTA; 0.5, 1, and 2 kHz $\leq$ 25 dB HL) at the time of treatment initiation.

Exclusion criteria (Patients who were excluded from the study):

1. Previously received any ototoxic drug (i.e., retreatment patients)
2. Receiving two ototoxic drugs in the regimen
3. Active middle ear (ME) pathology

Sampling

Sampling Frame

The set of source materials from which a sample is selected, is called a sampling frame (Gross et al., 2002). For this study, it was any new adult rifampicin resistant/multi-drug resistant TB patient receiving an aminoglycoside for the very first time, seen within 72 hours of first aminoglycoside administration and between the age of 18-55 years old. There were 71 participants in the sampling frame, and two did not consent to participate. A total of 69 participants met the inclusion criteria and consented to take part in the study. Participants underwent treatment for RR/MDR-TB and audiological monitoring at BCH, Cape Town, South Africa between June to December 2016.

Sampling Strategy

This study had two stages to the sampling strategy. The study site was selected by convenience sampling and the participants by purposive sampling. These are non-probability techniques used to select participants for a study where the participants are conveniently accessible and within immediacy of the researcher to conduct the study (i.e., convenient) and the participants were selected according to pre-determined criteria that are specific to the purpose of this study (i.e., purposive) (Maxwell & Satake, 2006). These sampling strategies were used in this study because it is easy, cost effective and readily available (Maxwell & Satake, 2006), and this was the best option due to the researcher being based at BCH. A disadvantage of convenience and purposive sampling is that generalisability is limited and it is highly vulnerable to selection bias (Farrokhi & Mahmoudi-Hamidabad, 2012).

Sample size calculation with power analysis

According to Burns & Grove (2001), a sample size of at least 30 participants should be used for quantitative study designs. Clinical Calculator (ClinCalc), an online calculator, was used

to determine the sample size needed in the study. The study group design selected on ClinCalc was selected as one study and the primary end point was selected as dichotomous. The statistical parameters are shown in Table 3. The following parameters below were used to determine the required sample size (Table 3):

Table 3: Parameters for sample size calculation

Study Parameters	
Anticipated Incidence	Type 1 or 2 error rate
Known population: 50%	Alpha: 0.05
Study group: 70%	Power: 90%
	Beta: 0.1

Based on these parameters, the required sample size for the study was 61 participants (i.e., 122 ears). A total of 69 participants met the inclusion criteria and consented to take part in the study. Therefore, the sample size was adequate for the study.

Recruitment Strategy

Recruitment of the participants started after ethics approval and permission to conduct the study was received from relevant authorities. Thereafter, the researcher requested the assistance of members of the medical staff (doctors and nurses) who work directly with RR/MDR-TB patients. The medical staff were informed about the study (Appendix A1) and asked to invite the patients to participate in this study. All medical doctors and RR/MDR-TB nurses at the facility were asked to assist in identifying and inviting patients to participate in this study (Appendix A2) and were furnished with the study information and the study consent form (Appendix A3). The study information forms, and consent forms were available in English, Afrikaans, and isiXhosa.

The RR/MDR-TB nursing sister was asked to give the study information letter (in the patient's preferred language) to all the patients who indicated willingness to be part of this study. The medical staff approached all potential participants, explained the purpose of the study, and obtained informed consent. The participants were subsequently referred to the Audiology department for testing as per treatment protocol. A notice inviting patients to be part of this study was also displayed at the entrance of the Audiology department for all individuals attending the out-patient clinic to view (Appendix B).

Data Collection

Instrumentation

- *Case History Form:* The standard case history form used at BCH was used in this study to obtain the following information from the participant: biographical information, medical history and diagnosis, auditory and vestibular concerns (Appendix C1 and C2).
- *Audiometric Booth:* All Audiological tests were conducted in a sound-treated booth in the Audiology department at BCH. The booth was compliant with the South African National Standards (SANS) standards (SANS 10182: 2006) and Standards of Practice for Audiology in the Health Professionals Council of South Africa (HPCSA) document of 2002. Hence, there was no need to test ambient noise levels as the tests were conducted in a sound treated booth.
- *Otoscope:* A Welch Allyn wall mounted electrical otoscope was used to perform an otoscopic examination. Otoscopy (OT) was conducted to assess the outer and middle ear status to see if any foreign bodies (wax or perforations) existed.
- *Tympanometry:* A Greyson-Stadler (GSI) Tymptstar Version 2 tympanometer was used to perform tympanometry (TYMP). Tympanometry was performed to assess the middle ear status and the mobility of the eardrum (tympanic membrane) as a function of varying air pressure in the ear canal to see if any ear infection exists or middle ear dysfunction.
- *Pure tone audiometry:* An Interacoustics AC40 clinical dual channel Audiometer with TDH 39 headphones was used to assess cPTA and KOSS R/80 headphones were used to assess UHFA testing. cPTA testing was conducted to assess the hearing levels of the participants. Both air conduction (AC) and bone conduction (BC) tests were conducted to assess the degree, type and configuration of the hearing levels, and to determine the nature of the hearing loss. The frequencies 250 Hz – 8 000 Hz were assessed for conventional AC and 10 000 Hz – 16 000 Hz for UHFA. The frequencies, 250 Hz – 4 000 Hz, were assessed for BC testing.

All the equipment were calibrated according to the SANS (SANS 10154-1: 2012 and SANS 10154-2: 2012) prior to testing and data collection. A biological check of all the equipment was performed daily (in the morning) prior to testing any participant.

Pilot Study

A pilot study was conducted (after ethics approval) and prior to the start of data collection for the main study. A pilot study is a mini-preliminary study used to test the sampling strategies, data collection tools and protocols before the main study is conducted. It helps to identify any potential threats or concerns that might arise during the main study. Hence, it assists in refining the study aims and objectives. A pilot study aids in assessing whether the data collection tools and procedures were feasible and appropriate for the main study (Maxwell & Satake, 2006). It also helps to estimate the amount of time and resources needed for the main study. Specific to the current study, a pilot study was conducted:

- (a) To establish the average time, it will take to complete the test battery.
- (b) To establish what is the most convenient and efficient time of day to test the participants.
- (c) To determine if the tests selected in the test battery were suitable for the main study outcomes.

Ten (10) participants were recruited to be part of the pilot study and the outcome of the pilot study showed that:

- (a) The average time taken to do the first and follow-up assessments were 45 and 25 minutes per participant, respectively.
- (b) Participants preferred hearing testing to be performed in the mornings (i.e., 9am – 12pm).
- (c) All tests were deemed suitable in the test battery for the main study.

Therefore, there were no major adjustments to the data collection procedures, except the time when participants came for testing at the Audiology department. The time of testing was amended due to outcomes from the pilot study where participants indicated their preferred time for testing was in the morning sessions, rather than the late afternoons, as indicated that their concentrations levels were much higher as opposed to late afternoons.

Procedure

Ethical approval was sought and received from the Faculty of Health Sciences Human Research Ethics Committee (HREC REF: #204/2016) (Appendix D), at the University of Cape Town. Permission was requested (Appendix E) and obtained from the Provincial Department of

Health in the Western Cape (WC_2016RP2_318) (Appendix F) and the Medical Superintendent at BCH to conduct the study. Data collection began after all relevant approvals were obtained.

Written informed consent was obtained from the participants before commencement of the study. The information sheets as well as the informed consent forms were available in English, Afrikaans, and isiXhosa. The RR/MDR-TB nursing sisters or doctors managed the process of informing the patient about the study and obtaining consent from the patient. They subsequently referred the patient to the Audiology department for assessment. All assessments were conducted by the researcher who is a qualified Audiologist and has over 10 years' experience in Clinical Audiology and was assisted by a fellow Audiologist colleague working in the same department who has more than five years' experience in Clinical Audiology.

All the assessments that were conducted on the participants are assessments that are usually performed as part of the standard of care for this group of patients at this facility. All hearing test results were recorded manually on the Audiology department audiogram stationery forms. A summary of the procedure for assessment and monitoring is provided in a flow diagram shown in Figure 1.

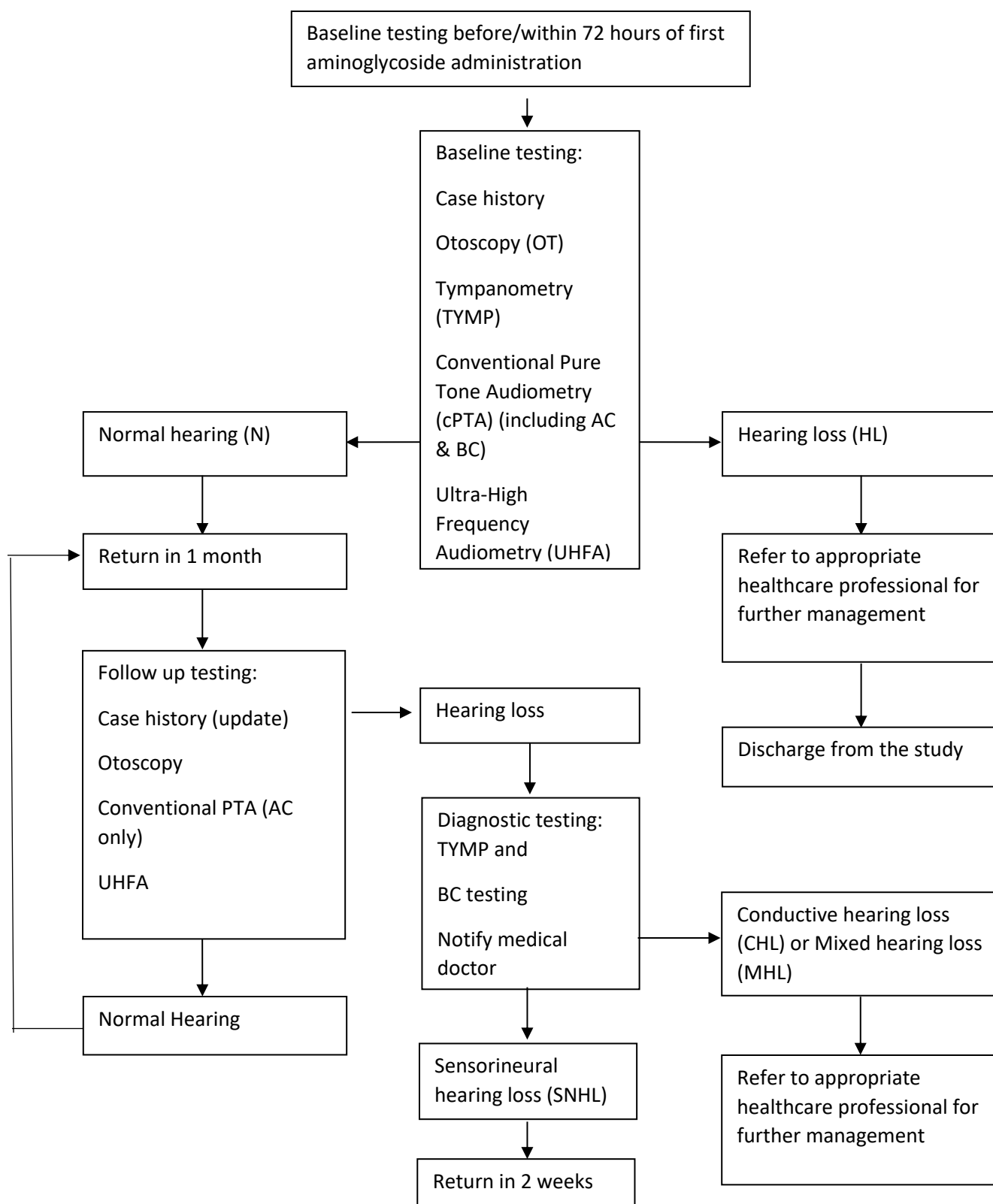


Figure 1: Summary of Procedure

Test protocol (Cochleotoxicity Monitoring Protocol)

The auditory system mechanism is complex in nature and requires a test battery approach. Therefore, multiple tests were employed in this study, and the battery approach allowed the researcher to reach a more confident diagnosis for clinical practice (ASHA, 2004). The researcher selected the most cost-effective tests for which validity and reliability are the highest. All participants in this study underwent the following assessments: baseline assessment, periodic audiometric monitoring/screening, and diagnostic assessment (when indicated).

Infection Control:

Before the participant entered the Audiology department, all participants had to ensure that they wore a N95 mask inside the clinical room and sound treated booth for infection, prevention, and control purposes. All equipment was sanitised and disinfected in the mornings before any participant arrived for testing. Equipment was also disinfected between participants during testing sessions to ensure no cross contamination of equipment and participants occurred. The following is a brief description of assessments that participants in this study underwent (Appendix G has further information about data collection tests, and procedures).

Baseline Evaluation

Each ear was tested separately and the ear that the participant considered their better ear was tested first in all test procedures. The following tests were conducted at baseline: case history, OT, TYMP, cPTA [including AC and BC] and UHFA with AC only. The modified Hughson-Westlake technique was used for both cPTA and UHFA pure tone testing at baseline and follow-up sessions. The frequency range of 250 Hz to 8 000 Hz for cPTA testing and the frequency range of 10 kHz to 16 kHz for the UHFA testing were assessed, respectively. The frequency range of 250 Hz to 4 000 Hz were assessed for BC testing.

Participants who had normal hearing was given a follow-up date to return in one month for testing. Participants who displayed hearing loss on baseline testing were discharged from the study and referred to the appropriate healthcare professional (audiologist or doctor) at the hospital for further management.

Monitoring Evaluation

Audiological monitoring of participants' hearing thresholds proceeded as per BCH protocol. Participants were monitored monthly (if no STS/hearing loss was detected during monitoring assessments) or bi-weekly (if STS/hearing loss was detected during monitoring assessments). There were no additional hearing test appointments that were scheduled exclusively for the purpose of this study. The following tests were conducted at follow-up for normal hearing thresholds: case history (update), OT, cPTA and UHFA with AC. However, if STS /hearing loss was detected, a diagnostic assessment was conducted.

Diagnostic Evaluation

Diagnostic testing of participants' hearing thresholds was conducted when a STS/hearing loss was detected and proceeded as per BCH protocol. The following tests were included when a STS/hearing loss occurred: TYMP and BC and the treating doctor was notified about the change in hearing threshold.

Significant Threshold Shift

Significant Threshold Shift (STS) was described according to the ASHA (1994) criteria where a significant shift in hearing threshold is defined as a 10 dB HL change in two consecutive frequencies, a change of greater than 20 dB HL in any one frequency, or an absence of response at three consecutive test frequencies in which responses were previously present across the 250 Hz to 8 000 Hz frequency range (ASHA, 1994).

Classification of Hearing Loss

Normal hearing was classified by pure tone average (PTA) of 500 Hz, 1 kHz and 2 kHz $\leq$ 25 dB HL and a hearing loss was defined as any threshold $\geq$ 26 dB HL (Clark, 1981). The degree of hearing loss was described as follows: (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 (Clark, 1981). To determine a high frequency hearing loss, the PTA for frequencies 4 kHz – 8 kHz $\geq$ 26 dB HL was used. For UHFA, the participants' hearing thresholds at baseline served as their norm. The configuration of hearing loss was classified according to the pure tone results as flat, irregular, rising (low frequency), sloping (high frequency) configuration (Katz et al., 2014). The researcher also examined the laterality and

symmetry of hearing loss and described whether the hearing loss was unilateral or bilateral, and whether it was symmetrical or asymmetrical (Katz et al., 2014).

Disabling Hearing Loss

The PTA at 500 Hz, 1 kHz, 2 kHz and 4 kHz was used to determine a disabling hearing loss. When the PTA of the hearing loss was > 40 dB HL, it was considered disabling (WHO, 2008). The best ear is used to determine disabling hearing loss. This is because the better ear compensates for the loss of function of the worst ear (Valete-Rosalino & Rozenfeld, 2005).

Type of Hearing Loss

The type of hearing loss was according to a classification by Margolis & Saly (2007): **Conductive** hearing loss was defined as a 10 dB air-bone gap at three or more frequencies or 15 dB at any one frequency. **Sensorineural** hearing loss refers to any hearing loss related to damages or loss in the sensory or neural portion of the inner ear and was defined as an air-bone gap equal or less than 10 dB. **Mixed** hearing loss refers to both conductive and sensorineural components involved and was described as an air-bone gap of greater than 20 dB.

Management of participants who developed hearing loss

When the participant experienced an STS at any of the frequencies, the researcher explained the results to the participant and provided counselling. The relevant medical doctor was also informed about the changes in hearing and the participant was informed to return in two weeks' time for a follow-up session. If further counselling or management of the hearing loss was needed, the participant was referred to the appropriate healthcare professional (e.g., Psychologist/counsellor or Ear/Nose/Throat specialist). Participants who acquired disabling hearing loss were referred for an appropriate audiological intervention to manage their hearing loss and minimise hearing disability, i.e., assistive devices.

Data Management

Paper-based information was transferred into a password-protected Microsoft Excel (2016) spreadsheet and stored on a password protected computer. All hard copies of the data were kept confidential and locked away in a lockable cupboard. All participants were assigned a research number sequentially as they enrolled into the study and this number was used on all documentation related to the study. Only the researcher had access to the data. However, a fellow audiology

colleague working at the same Audiology department at BCH checked 10% of the data to ensure that it was imported correctly. This individual signed a confidentiality agreement (Appendix H) not to disclose any information related to the study.

Data Analysis

For each step of the procedure, real-time analysis and interpretation of the results were provided, as this had a significant impact on decision making for the next step to follow in the procedure. The data were then entered, cleaned, and analysed using Statistica (Version 13) and IBM SPSS (Version 24). Data were analysed using descriptive and inferential statistics. Descriptive statistics were generated for the sample in the form of percentages for categorical variables and means and standard deviations for continuous variables. The appropriate non-parametric tests were used to analyse data that were not normally distributed.

Chi-squared tests of contingency were used to assess whether HIV status, sex, and intervention strategy were associated with development of aminoglycoside-induced hearing loss. A Mann-Whitney U test was used to determine whether there was a difference in median age between the two groups (i.e., yes, or no for hearing threshold shifts), and if age had an influence as a risk factor for the development of aminoglycoside-induced hearing loss.

A series of Kruskal-Wallis tests were used to determine if a significant difference existed between the means of the strategies and the progression of hearing thresholds to determine which strategy was the best when treating patients on RR/MDR-TB. An alpha level of $p < .05$ was used.

Reliability and Validity

Reliability

Reliability refers to the consistency of results obtained when an instrument is used repeatedly over time by a researcher or two different researchers on the same person (Brink et al., 2006) In order to reduce the possible sources of error or threats to the reliability of the data collected, there is a need to consider the tester, participant, environment and the instrument.

Tester. In order to reduce any error during the data collection process, procedures such as how to test, which data to collect and record on the case history form and audiogram, were kept standardised by using the Audiology department cochleotoxicity monitoring protocol and audiogram recording sheet. A potential threat to reliability in this study for data collection was the

recording of information into the Microsoft Excel spreadsheet. To minimise a potential threat to reliability due to data recording, the researcher was the only one entering data onto the spreadsheet.

In order to minimise intra-tester variability and maximise inter-tester reliability, the same way of collecting data for each participant was standardised. The researcher used the current protocol being utilised by the Audiology department at BCH, which employs the cochleotoxicity monitoring guidelines stipulated by ASHA (1994) for audiometry testing. In addition, the measurements used took place in the same manner across participants and test intervals, therefore, reducing the error variance (Maxwell & Satake, 2006).

Moreover, at the end of each testing day, the researcher went through all testing results to ensure that the data collected were correct and in accordance with the ASHA (1994) guidelines and also looked at the degree to which consistency between results and testing intervals existed. To ensure the reliability of audiometric test results, a colleague with more than 5 years of experience in audiology at the same facility re-tested 2 kHz, 8 kHz, and 12 kHz (any one ear) of every 10th participant. If the participants hearing threshold differed by more than 10 dB in any 2/3 of these frequencies, the entire test result was considered unreliable.

Participant. In order to reduce the effects of participant variability, the researcher kept the testing time as short as possible and performed data collection at the same time during the day as much as possible. When the participant's responses during pure tone audiometry testing were deemed unreliable, the results were not used. Unreliable results refer to when a participant was non-responsive or gave inconsistent responses during the test and/or unable to continue with the testing. Inconsistent refers to pressing the response button when a tone was not presented. The researcher then requested the participant to return within 24 hours to re-test. None of the participants displayed unreliable results.

Practice effects are when individuals may become better with the test over time (Maxwell & Satake, 2006) or conversely, individuals become bored and fatigued due to the test. That was mitigated by having the researcher vary stimulus presentation of the tones and including necessary breaks during pure tone testing.

Environment. In order to lessen the environmental effects on reliability, all testing took place in a sound-treated booth. The booth was compliant with SANS 10182: 2006 and Standards of Practice

in Audiology (HPCSA, 2002) recommendations for testing. By testing in a sound-treated booth, it helped reduce the effects of ambient noise levels.

Instrument. All testing equipment were calibrated for the years 2016-2017 and compliant with the SANS 10154-1: 2012 and SANS 10154-2: 2012 to ensure reliable and valid results. The researcher also performed the necessary system and biological check daily to ensure the equipment was in working condition before testing or data collection occurred. This was to ensure that all equipment was in working order so that no unwanted noise or recordings occurred, i.e., there was no feedback or artefact in the cables if the headphones are placed on a participant's ear. When a problem was detected, then the equipment was sent away for an appropriate evaluation and repairs before any further testing occurred.

Validity

Validity refers to the magnitude to which the instrument measures what it is planned to measure (Portney & Watkins, 2009). As such, validity is related to the accuracy of the conclusions or inferences that can be made on the basis of scientific research (Maxwell & Satake, 2006). In this study, concerns related to internal validity, external validity, construct, and face validity were considered. All these were appropriate for this study.

This study used a repeated measures design on a subject; therefore, the internal validity was increased with a within-subject design, as a comparison was made within the same individual, therefore, the participant acted as his/her own control. Moreover, validity was strengthened through the individual being monitored from exposure of the drug to the occurrence of the hearing loss, and therefore, provided the best information of the individuals' hearing thresholds (Mann, 2003). Furthermore, the "cross-check principle" (Turner, 2003) was utilised to cover all sections of the auditory system to confirm that the true nature of the hearing loss (i.e., sensorineural and not conductive). All tests that were used are routine clinical audiology tests with established validity. For example, tympanometry was used to assess the middle ear status and rule out any fluid behind the tympanic membrane and bone conduction testing was performed to confirm the true nature of the hearing loss. To increase internal validity with regards to the tester, the researcher was the person conducting the tests and used the current ASHA (1994) cochleotoxicity monitoring

guidelines when assessing the participant. Hence a standardised protocol was used for all participants.

External validity refers to the degree to which the results of a particular sample can be generalised to a population (Maxwell & Satake, 2006). The target population for this study was individuals receiving treatment for TB, specifically rifampicin resistant/multi-drug resistant TB and contracting the disease for the first time. The inclusion and exclusion criteria were clearly defined to include only the participants for which the study results wanted to be compared to or extrapolated, thereby increasing the external validity.

Face validity represents that an instrument appears to measure what it is supposed to and that it is a trustworthy method for doing so, while construct validity refers to the extent a tool measures an underlying construct (Portney & Watkins, 2009). In order to mitigate against any face and construct validity issues, the current Audiology department hospital stationery (data collection form) was used. Moreover, the techniques and protocol used for cochleotoxicity monitoring at BCH, involving UHFA > 8 kHz are validated with best practice standards (AAA, 2009; ASHA, 1994; Duggal & Sarkar, 2007).

Ethical Considerations

Ethical approval for this study was sought and obtained from the Faculty of Health Sciences Human Research Ethics Committee (HREC REF: #204/2016) (Appendix D), at the University of Cape Town before the start of data collection. The ethical principles set out by the Declaration of Helsinki (2013) were adhered to in this study to ensure transparency, integrity of data and respect for participants' dignity and physical well-being throughout this study (World Medical Association [WMA], 2013). Furthermore, the ethical principles of Autonomy, Beneficence, Non-maleficence, Confidentiality and Justice were adhered to in this study.

Autonomy. Refers to the self-governance of an individual and “expresses respect for the unconditional worth of an individual and for the individuals thoughts and actions” (Pera & Van Tonder, 2011, p. 53). Respect means allowing individuals to make their own decisions and providing the relevant information to make informed decisions. Each participant was informed both verbally and in writing about the aims, nature of the study and what was expected of them. To help facilitate the understanding and comprehension of the study, the information was provided in the participant's preferred language; English, Afrikaans, or isiXhosa before providing informed

consent to participate in the study (Appendix A2 & A3). Participants were also provided with an opportunity to ask questions and obtain clarity prior to signing the informed consent form and at any time during the study. In addition, it was explained to all participants verbally and in writing that participation was voluntary, and they may withdraw at any point during the study and refusal to participate in or withdrawal from the study would not affect their treatment negatively. Participants were also given an option to have both the information sheet and consent form read out to them (verbally) before they signed the consent form.

Beneficence. This principle refers to the obligation of the researcher to do no harm or prevent evil and promote only good. This means that the actions of the researcher are directed at improving the participant's well-being (Pera & Van Tonder, 2011). There were no immediate direct benefits for the participants in the study except for early detection of hearing loss, damage to the auditory system, early intervention and/or referral to relevant professionals for further management. Participants were not compensated in any form (monetary or other) when participating in the study.

Non-maleficence. The principle of non-maleficence refers to "one ought not to inflict evil or harm" on the participant (Pera & Van Tonder, 2011, p. 55). This may include physical, emotional, psychological, spiritual, moral or any other harm to the dignity of the participant. All procedures and tests that were used were non-invasive and did not cause any harm to the participant. Strict infection, prevention and control measures were adhered to. An N95 respirator was always worn by the researcher when collecting data from participants, and a N95/surgical mask was worn by the participants to protect both parties from spreading of potential bacteria or cross infection. The researcher washed hands with an antiseptic agent in order not to spread any germs from one participant to another and wore gloves when assessing participants. All necessary equipment was cleaned with alcohol swabs and disinfected according to departmental policy to ensure no spreading of germs or bacteria occurred.

Justice. The ethical principle of justice refers to fairness. In this study, it meant that equal opportunity for all patients to participate in the study was given, and provided they met the inclusion criteria and signed consent, they were included to participate in the study (Pera & Van Tonder, 2011). The sampling method used allowed for all participants to freely and fairly join in to participate in this study. In addition, the results obtained from this study were distributed for local and internal utilisation. Furthermore, the principles of distributive justice were adhered to by

identifying the possible risks and gains in the study and it was equally applied to all participants and the gains of this study were used to enhance service delivery for RR/MDR-TB patients.

Confidentiality. This principle was respected at all times throughout this study, and all participant details and results were kept confidential and anonymous throughout the study by assigning a research number to each participant. A number was assigned sequentially to participants as enrolment into the study happened. This number was used on all documentation related to the study, and data were recorded and analysed using this number, and not participant names. Identifying information was only known to the researcher, and all data collection information was kept in an electronic password-protected file and Microsoft Excel spreadsheet. Data will be stored for a period of five years in case the data need to be re-checked or audited. The researcher also guaranteed the participants both verbally and in writing (information letter) that no identifying information from any participant in this study would appear in any publication or presentation in the future.

Professional Competence. The researcher is a qualified Audiologist and has sufficient theoretical and clinical experience (10 years) to conduct the study. The researcher always acted in an accountable and responsible manner and upheld professional standards. The researcher was always aware of her health status as she was working with an exposed population and if at any point during the research felt compromised, followed the necessary reporting procedures to notify all parties involved. Moreover, the researcher made all necessary referrals to the relevant professional for herself or participant if any of the ethical considerations were breached. None of the ethical principles were breached in this study.

Research in vulnerable populations. The researcher was aware that this study population falls within the category of ‘vulnerable population’ (National Institutes of Health [NIH], 2016; WMA, 2013). To protect the rights and welfare of the study participants, the necessary safeguards were included in this study, such as: the researcher was only informed at the end of the week, on the number of individuals who consented to the study. This was to avoid undue inducement of patients to take part in this study.

Chapter Four: RESULTS

This chapter will present the findings of the current study according to its aims and objectives. Incidence of Aminoglycoside-induced cochleotoxicity, types and effectiveness of different treatment modifications implemented to minimise progression of aminoglycoside-induced hearing loss will be presented.

Participant Description

A total of sixty-nine (69) participants met the criteria for inclusion in this study. Of the 69 participants who were monitored, five did not complete the study for various reasons, e.g., defaulting on treatment, deceased and/or absconding from hospital. Table 4 below presents a description of participants included in the study.

Table 4: Participants' Description (n=64)

Participant Characteristics	n (%)
Age (median, range)	31 (18 - 55)
Sex	
Male	38 (59%)
Female	26 (41%)
HIV status	
Positive	33 (52%)
Negative	31 (48%)
Duration on injectable treatment (days)	
0 – 30 (1month)	10 (16%)
31 – 90 (1month - < 3months)	26 (41%)
91 – 193 (3months – 6months)	28 (43%)

Incidence of cochleotoxicity following treatment

All participants had normal hearing thresholds and type A tympanograms at the time of initiating RR/MDR-TB treatment. Using the ASHA (1994) criteria, 58 out of 64 participants had STS, therefore, demonstrating an incidence of 90.6% cochleotoxicity at exit pure tone hearing results.

Characterisation of hearing loss (*type, degree, laterality, and configuration*)

All 58 participants had a bilateral STS most likely due to aminoglycoside cochleotoxicity at the end of the RR/MDR-TB treatment. The true nature of the hearing loss (i.e., sensorineural) was confirmed by type A tympanograms and bone conduction testing throughout monitoring.

Degree and symmetry of hearing loss

Out of the 58 participants with STS, only 18 participants (31%) had a high frequency sensorineural hearing loss (i.e., PTA for 4 kHz – 8 kHz $\geq$ 26 dB HL). The remaining 40 participants had STS limited to 10 kHz – 16 kHz frequency range. All 58 participants' hearing thresholds were normal in the low-mid frequency range 250 Hz to 2 kHz on the exit audiogram. Of the 18 participants who had hearing loss in the high frequency range 4 kHz to 8 kHz, ten (56%) participants had bilateral hearing loss and eight (44%) participants had unilateral hearing loss. These 18 participants had sensorineural type hearing loss and presented with the typical pattern of sloping/high frequency hearing loss.

In order to determine the degree of hearing loss for these 18 participants, the PTA was calculated for each ear separately and then described according to Clark (1981) classification of hearing loss. For the 10 participants who had bilateral hearing loss, there were 20 ears that needed to be classified (Figure 2). The degree of hearing losses was as follows: six ears had mild hearing losses, one ear had moderate hearing loss, five ears had moderately-severe hearing loss, seven ears had severe hearing loss and only one ear had a profound hearing loss. All participants with bilateral hearing losses had symmetrical hearing loss. Of the eight participants who had unilateral hearing loss (with only eight ears to be classified according to the classification of hearing loss by Clark (1981)), the degree of hearing loss was as follows: six ears had a mild hearing loss, and two ears had moderate hearing loss (Figure 2).

Based on the classification of degree of hearing loss (Clark, 1981) used, it is evident that hearing loss can occur in any degree of severity as displayed in Figure 2. The most prevalent degree of hearing loss in the ears was mild (12/28), followed by severe (7/28).

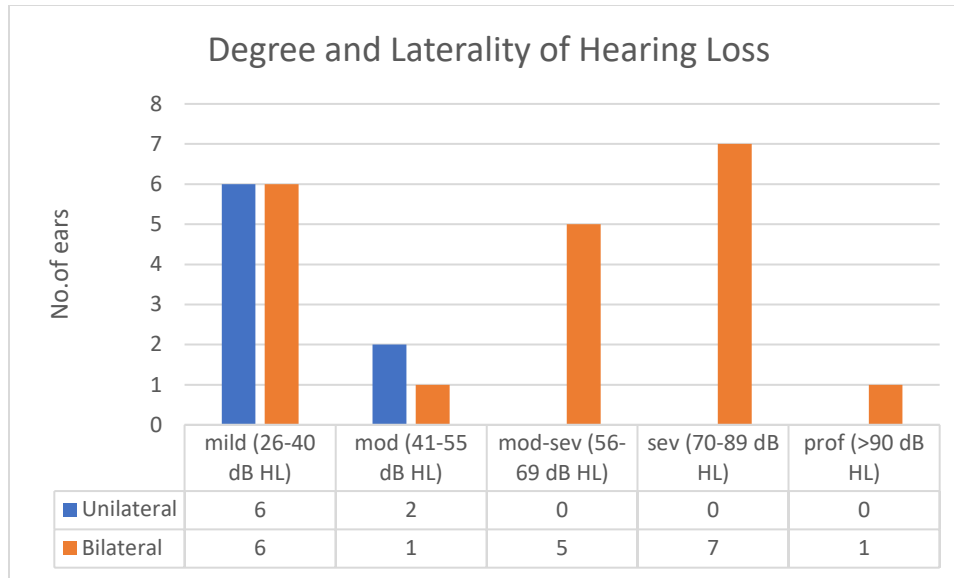


Figure 2: Exit audiogram results for high frequency range based on PTA: 4 kHz, 6kHz and 8 kHz

Associations between participant factors and the possibility of developing aminoglycoside-induced significant threshold shift

Chi-squared tests of contingency were used to determine whether HIV status and sex were associated with hearing threshold shifts. The outcome of this analysis showed that the STS was not associated with sex ($p = .329$, $p < 0.05$) or HIV status ($p = .764$, $p < 0.05$) (Table 5).

A Mann-Whitney U test was used to determine whether there was a difference in median age between the two groups (i.e., yes, or no for hearing threshold shifts). The outcome of this analysis showed there was no difference in age ($U = 374$, $p = .487$).

Table 5: Association between Sex, HIV status and hearing thresholds changes

	Hearing Threshold Progression		Statistics		
	Yes	No	X^2	P	V
Sex			0.95	.329	.128
Female	13 (48.1%)	11 (35.5%)			
Male	14 (51.9%)	20 (64.5%)			
HIV Status			0.09	.764	.039
Negative	12 (44.4%)	15 (48.4%)			
Positive	15 (55.6%)	16 (51.6%)			

Note. Data presented are number of participants with proportions in parentheses.

X^2 = Chi squared; P = probability value; V = Cramer's V

Type of Intervention Strategy Implemented following cochleotoxicity

Three different strategies were used when the participant experienced an STS during treatment; discontinue Kanamycin administration (33 patients) (Strategy A), modify the frequency of Kanamycin administration (18 patients) (Strategy B) and keep regimen unchanged (i.e., no intervention) (7 patients) (Figure 3).

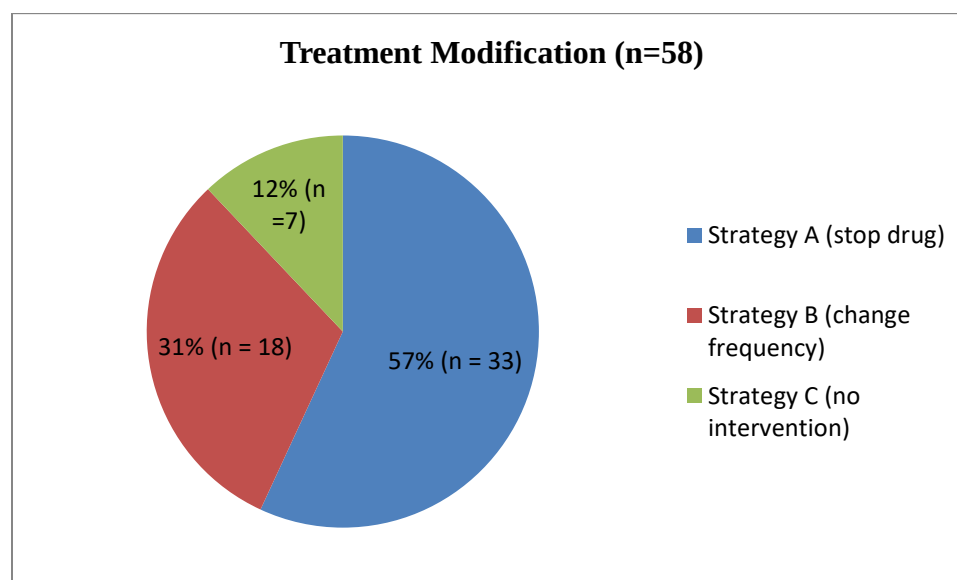


Figure 3: Distribution of participants according to aminoglycoside treatment modification (n= 58).

It was also found in this study that participants whose Kanamycin was stopped (Strategy A) immediately on presentation of a STS, received a shorter duration of treatment compared to the other two strategies. Intervention for participants who received Strategy A also occurred 19 days sooner compared to Strategy B participants (Table 6).

Table 6: Number of days on treatment and intervention by strategy

	Strategy A	Strategy B	Strategy C
Duration (days)	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Total no. of days on injectable	47 $\pm$ 37	130 $\pm$ 44	145 $\pm$ 27
No. of days between baseline and treatment initiation	10.8 $\pm$ 12	11.6 $\pm$ 16	17 $\pm$ 24
No. of days between treatment initiation and STS detected	45 $\pm$ 30	50 $\pm$ 28	62 $\pm$ 33
No. of days between STS detected and intervention	7 $\pm$ 13	26 $\pm$ 28	NA

No. = number; SD = standard deviation

Table 7 below shows a comparison of sex and HIV status between the three intervention groups ($n = 58$). All p -values for the chi-square tests are > 0.05 which means that the percentage of participants who are HIV positive vs. negative or male/female ratio are similar in the three intervention groups (A, B and C). Hence, there was no statistically significant differences in the proportion of male/female and HIV positive/negative participants across the different intervention strategies (Table 7). Table 7 also indicates that participants in the intervention groups A, B and C do not differ in terms of having hearing threshold progression. Meaning, there was no association between intervention strategy group and hearing threshold progression (i.e., it did not matter what intervention group you were in, hearing progression was similar).

In addition, there was no significant difference in age across the different intervention strategies ($H = 0.27$, $p = .875$). Meaning, participants in intervention groups A, B and C did not differ in terms of age (i.e., they were not statistically different in terms of age).

Table 7: Participant Demographics and Intervention Strategy

	Intervention Strategy				Statistics		
	A	B	C	All groups	χ^2	<i>p</i>	<i>V</i>
Sex					2.99	.224	.227
Female	12 (36.4%)	7 (38.9%)	5 (71.4%)	24 (41.4%)			
Male	21 (63.6%)	11 (61.6%)	2 (28.6%)	34 (58.6%)			
HIV Status					1.27	.530	.148
Negative	17 (51.5%)	8 (44.4%)	2 (28.6%)	27 (46.6%)			
Positive	16 (48.5%)	10 (55.6%)	5 (71.4%)	31 (53.4%)			
Hearing Threshold Progressions					5.78	.056	.316
No	21 (63.6%)	9 (50%)	1 (14.3%)	31 (53.4%)			
Yes	12 (44.4%)	9 (50%)	6 (85.7%)	27 (46.6%)			

Note. Data presented are number of participants with proportions in parentheses.

χ^2 = Chi squared; *p* = probability value; *V* = Cramer's *V*

Hearing Changes and Intervention Strategy

A Kruskal-Wallis test [non-parametric of one-way Analysis of Variance (ANOVA)] was used to compare the effect of the three intervention types on further changes (i.e., deterioration) of hearing thresholds after the intervention. A smaller proportion of participants in strategy A, experienced further deterioration of hearing thresholds after intervention when compared to participants who were managed using intervention strategies B and C. However, the difference was not statistically significant ($p = 0.056$) (Figure 4).

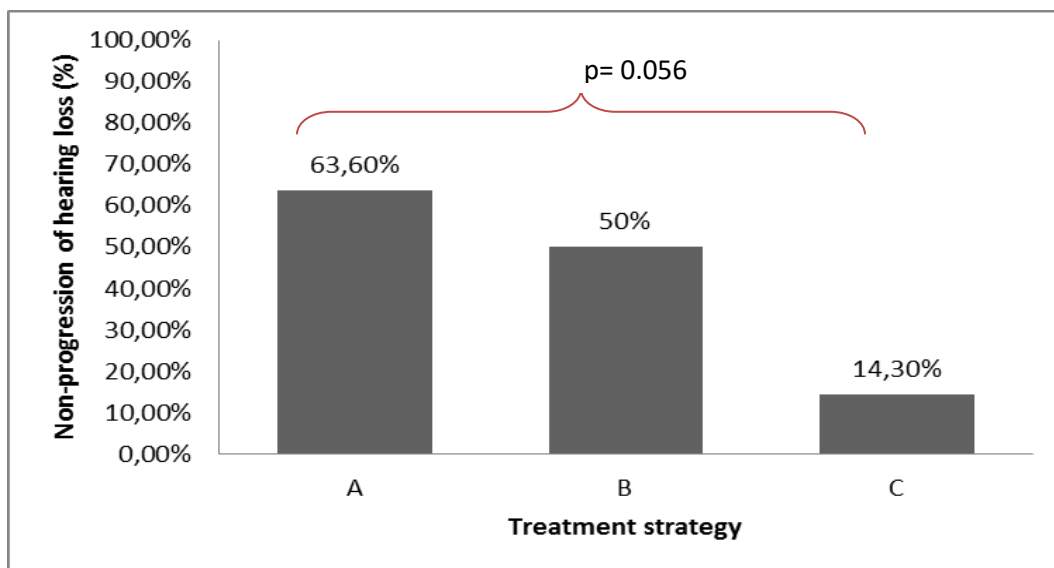


Figure 4: Proportion of participants who did not have further STS as a function of intervention

In summary, the results indicate that an aminoglycoside-induced cochleotoxicity incidence of 90.6% (58/64) was found in this study. There were no statistically significant associations between the occurrence of STS and age ($p = 0.487$), sex ($p = 0.329$) and HIV status ($p = 0.764$). Of the three types of intervention strategies used when a participant experienced an STS, a smaller proportion of participants, 12 out of 33, experienced further deterioration of hearing thresholds after intervention strategy A (discontinue Kanamycin) was used, when compared to participants who underwent intervention strategies B and C, but the difference was not statistically significant ($p = 0.056$).

Chapter Five: DISCUSSION

This chapter will discuss the study findings in relation to existing research literature on the topic. The chapter will also present the strengths and limitations of this study.

The present study aimed to determine the effectiveness of different intervention strategies used to prevent or minimise further deterioration of hearing thresholds when an STS is detected during cochleotoxicity monitoring of RR/MDR-TB patients treated with Kanamycin. Overall, the findings of this study showed that a high proportion (58/64) of the participants experienced a significant hearing threshold shift following treatment with Kanamycin. Three strategies were implemented when a participant experienced an STS during cochleotoxicity monitoring: discontinuing treatment with Kanamycin, change the frequency of Kanamycin administration and continue with Kanamycin treatment. Of the three strategies implemented, discontinuing the treatment with Kanamycin led to a lower proportion of participants experiencing further deterioration in hearing thresholds post intervention than the other two strategies, however it was not statistically significant ($p = 0.056$). The present study also found no significant associations between the occurrence of STS or further deterioration of hearing thresholds and participants' age, sex and HIV status.

Incidence of cochleotoxicity following treatment

A high proportion (90.6%) of participants in this study experienced an STS after treatment with Kanamycin. This incidence of cochleotoxicity was much higher than previously reported by most studies reviewed (De Jager & Van Altena, 2002; Duggal & Sarkar, 2007; Ghafari et al., 2020; Harris et al., 2012a; Nizamuddin et al., 2015; Piubello et al., 2014; Sharma et al., 2016; Sogebi et al., 2016b; de Vasconcelos et al., 2018). While it is acknowledged that there is generally a wide variation in incidences of aminoglycoside-induced cochleotoxicity reported in previous studies; ranged from 18% (Sharma et al., 2016) to 100% (Appana et al., 2016), the incidence reported in this study still ranks amongst some of the highest reported to date.

In general, studies that included monitoring of UHF 9000 Hz -16 000 Hz tended to report a high incidence of aminoglycoside-induced cochleotoxicity (Appana et al., 2016; Ghafari et al., 2020) when compared to those that monitor hearing thresholds in the conventional frequency range 250 Hz - 8 000 Hz (De Jager & Van Altena, 2002; Duggal & Sarkar, 2007; Piubello et al., 2014; Sharma et al., 2016; Sturdy et al., 2011). For instance, Ghafari et al. (2020) reported a high

incidence of cochleotoxicity (82.4%) amongst RR/MDR-TB patients treated with Kanamycin when utilising UHFA to monitor their hearing thresholds. Likewise, Appana et al. (2016) also reported a high incidence of cochleotoxicity (100%) in their patients when UHFA. Ultra-high frequency audiometry is more sensitive to changes in the cochlear, and therefore, can detect changes in patients' hearing thresholds earlier than cPTA. Conventional audiometry testing is only sensitive to cochleotoxic changes in frequencies ≤ 8 kHz (Chauhan et al., 2011). It is, therefore, possible, that in studies that used cPTA, early changes in patients' hearing thresholds were missed and were only detected once it manifested in the conventional frequency range 250 Hz – 8 000 Hz.

It is important to note that out of the 58 participants in this study who experienced STS, 69% (40/58) had STS in the ultra-high frequency range and not in the conventional frequency range. As a result, if only cPTA were used to monitor their hearing thresholds, changes in the hearing threshold of these 40 participants would not have been detected. A similar observation was reported by Fausti et al. (1994) who showed in their study that when using UHFA, 71.1% of ears had cochleotoxic changes compared to when using cPTA, only 37.8% of ears would have been identified as having cochleotoxic change. Similarly, de Vasconcelos et al. (2018) used cPTA and UHFA to monitor hearing thresholds for early detection of cochleotoxic changes and found UHFA testing detected cochleotoxic shifts sooner than conventional testing. For example, none of their patients had cochleotoxicity at two months follow-up when using cPTA. But, when using UHFA, 50% and 60% of their patients, respectively, in their right and left ears had cochleotoxic shifts at two months during treatment (de Vasconcelos et al., 2018).

Characterisation of hearing loss (type, degree, laterality, and configuration)

Of all the participants who experienced STS, 31% (18/58) had abnormal >25 dB HL high frequency hearing thresholds in the conventional frequency range 4 kHz – 8 kHz, and 69% (40/58) had STS limited to the UHF range 10 kHz – 16 kHz. All participants in this study who showed a significant change in their hearing thresholds experienced bilateral STS. For those participants who had an STS (31%) in the conventional frequency range 4 kHz – 8 kHz, all of them had SNHL. These findings are similar to those reported by Sogebi et al. (2016b) in Nigeria in which 78.8% of patients were reported to have developed SNHL following treatment with aminoglycosides, with 87.1% of those who developed hearing losses being bilateral hearing losses (Sogebi et al., 2016b). In the present study, participants who developed abnormal hearing thresholds had degrees of

hearing loss that ranged from mild ≥ 26 dB HL to profound ≥ 90 dB HL high frequency SNHL. Similar findings were reported by Appana et al. (2016) who also found degrees of hearing loss that ranged from mild to profound in their patient cohort.

While several studies have reported that a majority of patients who developed STS following treatment with aminoglycosides develop bilateral hearing loss, some studies had previously reported unilateral/asymmetrical hearing losses in these patients (Chauhan et al., 2011; Harris et al., 2012a; Sharma et al., 2016). It was also found in this study that eight out of 18 (44%) participants developed unilateral hearing loss, which is consistent with the findings of these previous studies. Chauhan et al. (2011) hypothesised that the reason for unilateral hearing loss may be due to serial monitoring of hearing thresholds with ultra-high frequency detecting cochleotoxicity before it becomes bilateral, but this is yet to be confirmed.

Intervention Strategy Implemented following cochleotoxicity

When a STS was identified in the present study, one of the following three interventions were implemented; (1) discontinue treatment with Kanamycin (Strategy A), (2) change the frequency of Kanamycin administration (Strategy B), or (3) no intervention (i.e., keep regimen unchanged) (Strategy C). It was found that a lower proportion of participants had further deterioration of hearing thresholds when discontinuing Kanamycin, when a STS was detected compared to when using the other two strategies. Thirty-three (57%) of the participants in this study received Strategy A, and 21/33 (64%) of them had no further deterioration of hearing thresholds post intervention. Similar findings were reported by Ghafari et al. (2020) in a study involving patients on treatment for RR/MDR-TB who also reported that when Kanamycin treatment was discontinued, fewer patients had further deterioration of hearing thresholds. Only 20% of their (Ghafari et al., 2020) patients developed moderate to severe degree of hearing loss post intervention. Most of their patients had normal hearing or mild degrees of hearing loss and the speech frequencies were not affected.

Several reasons could potentially explain why discontinuing the Kanamycin (Strategy A) may have worked better than the other two interventions implemented. First, STS generally occurred sooner among patients in this group which may have prompted early intervention to occur. The first appearance of STS in Strategy A participants occurred on average 45 days into treatment when compared to 50 days into treatment for participants in Strategy B and on average,

62 ± 33 (days ± SD) into treatment for participants in Strategy C. Secondly, the intervention was implemented sooner among patients whose Kanamycin was discontinued (Strategy A) (on average, 7 ± 13 days ± SD) when compared to an intervention that implemented about 26 ± 28 (days ± SD) for participants in Strategy B. Therefore, timeous intervention may have reduced the proportion of participants getting STS. This is because the total duration of the Kanamycin injectable treatment (i.e., cumulative dose) in days was different between these three groups of participants. Participants whose Kanamycin was discontinued, received on average a total duration of 47 days treatment while participants whose frequency was changed, received a duration of 130 days in total. Hence, intervention time took three times longer in the group whose frequency was changed. For the participants who received no intervention, the total average duration of the Kanamycin injectable was 145 days. Cumulative dose of aminoglycoside treatment has previously been reported as a significant risk factor for cochleotoxicity (Modongo et al., 2015; Peloquin et al., 2004). Participants whose Kanamycin was discontinued, therefore received a shorter duration of treatment and ultimately reducing the overall cumulative dose which may have contributed to a why a smaller proportion of participants in Strategy A had further hearing threshold deterioration compared to the other interventions implemented.

While Strategy A was found to yield a smaller proportion of participants to have further hearing threshold deterioration after intervention in this study and Ghafari et al. (2020), other studies reported that this modification did not prevent or minimise further deterioration of STS (Sharma et al., 2016; Sogebi et al., 2016a; Van der Walt., 2013). For instance, Sharma et al. (2016) reported that hearing loss continued to worsen into the speech frequencies even though the aminoglycoside was discontinued. Similarly, Sogebi et al. (2016a) discontinued Kanamycin and changed to a different drug, but hearing continued to worsen. Possible reasons why this modification was found to be ineffective in these studies was due to the fact that UHFA was not used for testing and the aminoglycoside even, though discontinued, was replaced with another cochleotoxic drug. Therefore, it missed early STS in frequencies beyond 8 kHz that UHFA testing would have detected sooner. Secondly, the aminoglycoside was discontinued but replaced with another less cochleotoxic drug. For instance, Sogebi et al. (2016a) changed from Kanamycin to Capreomycin. It is known that aminoglycosides' longer half-life nature takes more than 30 days to disappear out of the hair cell (Rybak & Ramkumar, 2007). Therefore, replacing the drug with another cochleotoxic drug possibly contributed to the accumulation of the injectable medication

in the hair cell, which worsened the hearing thresholds in these studies, thereby making this modification ineffective.

Another strategy that was used in this study was changing the administration frequency of Kanamycin from six times per week to three times per week. Eighteen participants received this intervention strategy, and nine out of 18 participants (50%) continued to show deterioration of hearing thresholds despite the intervention. Previous studies that used this strategy also reported that despite this treatment modifications being implemented, patients continued to experience deterioration in hearing (Piubello et al., 2014; Sturdy et al., 2011; Modongo et al., 2014). For instance, Piubello et al. (2014), Sturdy et al. (2011) and Modongo et al. (2014) all reported that irrespective of changing the frequency of administration of the aminoglycoside from seven/ six times per week to three times a week, patients' hearing continued to deteriorate, and hearing loss was permanent. Continued deterioration of participants' hearing thresholds is consistent with what was reported in previous studies in which cumulative dose or total duration of treatment was reported to be a significant determinant of the risk of cochleotoxicity (Modongo et al., 2015).

However, the proportion of participants in the current study who experienced further deterioration of hearing thresholds 9/18 (50%), despite implementing this treatment modification was unexpected, as previous studies (Modongo et al., 2014; Peloquin et al., 2004) reported less than 50% of patients had further deterioration of hearing thresholds when changing the frequency of administration of the aminoglycoside. However, those studies used cPTA to monitor hearing whereas the current study used UHFA therefore, 50% is understandable because UHFA identifies hearing changes sooner than cPTA. This high proportion reported in this study could be due to the small number of participants who received this modification when compared to both studies by Modongo et al. (2014) and Peloquin et al. (2004), which involved larger samples of 437 and 87 participants, respectively.

The third strategy used in the current study was to leave the regimen unchanged (referred to, in this study, as strategy C or no intervention). In seven (12%) of the participants, no intervention was made in their RR/MDR-TB treatment despite experiencing STS. For those participants for who Strategy C was implemented, it was found to be the least effective strategy in this study, as six out of seven (86%) participants continued to have further deterioration of thresholds. This was an expected finding because these participants will end up receiving a higher

cumulative dose of Kanamycin and that is known to be a risk factor for developing cochleotoxicity. This finding was also consistent with the findings of previous studies using the same approach. For example, Nizamuddin et al. (2015) who also did not implement any treatment modification in their patients when an STS was detected reported that 58% of their patients experienced hearing loss. Similarly, Appana et al. (2016) reported 100% of patients had hearing loss.

This study did not involve asking treating doctors how they made decisions about patients who received specific interventions. However, it is possible that these patients were not good candidates for any treatment modification given their RR/MDR-TB stage. Another possible reason why this treatment approach was used in this study could be that participants did not complain of any hearing loss or initially had better tolerance to their treatment than other participants. It is also worth noting that this was a very small proportion of the participants.

This progression of hearing loss is part of the commonly observed pattern of deterioration in aminoglycoside-induced cochleotoxicity patients and has been reported on by several studies (Appana et al., 2016; Nizamuddin et al., 2015; Selimoglu, 2007; Rybak & Ramkumar, 2007; de Vasconcelos et al., 2018). Moreover, literature shows that aminoglycosides may remain for six months or longer in the hair cells post cessation of the injectable (Huth et al., 2011; Sturdy et al., 2011). Therefore, for these participants who had reduction in frequency administration and no intervention or no change in the regimen, the impact of the aminoglycoside on hearing is expected to be greater because the aminoglycoside injectable was used for a longer duration and cumulative dose would have been greater (Ghafari et al., 2020; Modongo et al., 2015).

Irrespective of the Strategy used to prevent further STS, treating personnel should take into consideration the anti-bacterial efficacy of the intervention chosen. This is because, discontinuing the aminoglycoside or changing the frequency should be considered only if it is a viable option in retaining its effectiveness in killing the bacteria. However, if it is not effective then implementing the Strategy will not be beneficial to the patient. i.e., it will not be a positive outcome for the patient.

Risk factors for cochleotoxicity

The present study found no statistically significant association between development of aminoglycoside-induced hearing loss and the following factors: age, sex and HIV status. Age has previously been reported to be a risk factor for developing cochleotoxicity (Chauhan et al., 2011;

Sogebi et al., 2016a; Sturdy et al., 2011). However, the present study found no statistically significant ($U = 374$, $p = .487$) association between age and cochleotoxicity. This concurs with other studies who also found no association (De Jager & Van Altena, 2002; Sharma et al., 2016). However, Sogebi et al. (2016a) found that with every yearly increase in age, cochleotoxicity increases by about 6%. Similarly, Sturdy et al. (2011) found a significant association with cochleotoxicity ($p = 0.02$) in their patient cohort. The reason for the association in Sturdy et al. (2011) may be due to the mean age in the group with cochleotoxicity (41.3 ± 14.5) which was higher than the group who had no cochleotoxicity (31.9 ± 11.2) in their study. Previous studies have reported that the elderly and very young children are more susceptible to cochleotoxicity at the start of treatment with aminoglycosides (Duggal & Sarkar, 2007). However, individuals falling in these age extremes were excluded from the current study (33.3 ± 8.5) and therefore probably decreased the likelihood of finding an association.

Sex of the patient is also known to be a risk factor (Sharma et al., 2016; Sogebi et al., 2016b; Trebucq et al., 2018). However, in this study there was no statistically significant association between sex and hearing threshold shifts ($p = .329$, $p < 0.05$). This is consistent with several studies (Chauhan et al., 2011; De Jager & Van Altena, 2002; Harris et al., 2012a) that also found no association between sex and developing cochleotoxicity. However, Sogebi et al. (2016b) found male gender to be associated with developing cochleotoxicity. A possible reason could be that their sample size ($n = 132$) was bigger whereas this study had a small sample size ($n = 58$) and could have reduced the likelihood of finding an association.

Another risk factor for cochleotoxicity is patients receiving simultaneous treatment for RR/MDR-TB and HIV (Harris et al., 2012a; Hong et al., 2018; Olusanya et al., 2014; Sagwa et al., 2015; Sogebi et al., 2016a; WHO, 2020). In the present study hearing threshold shifts were not associated with HIV status ($p = .764$, $p < 0.05$). This finding is consistent with those of Ghafari et al. (2020) who also found HIV status not to be associated with cochleotoxicity ($p = 0.813$). However, Harris et al. (2012a) found HIV to be associated with cochleotoxicity. The reason for the association in Harris et al. (2012a) may be because 85% of their sample population had received an aminoglycoside (Streptomycin) previously in the preceding six months of RR/MDR-TB treatment, which could have contributed to cochleotoxicity due to cumulative dose being a risk. Moreover, all of the HIV positive patients (86/151) in their study were on combination antiretroviral therapy. The potential of a synergistic effect to cause cochleotoxicity is increased

when giving these drugs simultaneously (Harris et al., 2012b; Jacobs & Ross, 2012). Therefore, due to South Africa having a high burden of TB/HIV and high prevalence of DR-TB among HIV positive population (Dheda et al., 2017b; Harris et al., 2012a), HIV should be considered a risk factor for cochleotoxicity.

Study Strengths and Limitations

This study was one of the few studies conducted among patients receiving RR/MDR-TB treatment in the South African population whose hearing thresholds were monitored prospectively during cochleotoxic treatment. The prospective nature of the study was one of its strengths because that allowed for more control over the quality of data collected. This study also utilised UHFA testing which is more sensitive to significant changes in thresholds above 8 kHz than cPTA. Therefore, allowing more detection of STS sooner and encouraging treatment modification to occur earlier. Also, cochleotoxicity monitoring was performed monthly if hearing thresholds were normal and bi-weekly every time if STS occurred until the completion of therapy for each participant. Bi-weekly monitoring is considered a strength in the study because changes in thresholds could still be monitored closely and, identified early to implement appropriate interventions when STS occurred. Another strength of this study was that the patient population was diverse, both from in-patient hospital and out-patient facilities, and therefore, allowed the sample to be representative of all patients who receive RR/MDR-TB treatment.

This study also had some limitations that must be considered when interpreting its findings: participants hearing thresholds were only monitored for six months. Nizamuddin et al. (2015) reported that incidence increased over time from 22.7% to 58% post one-year follow-up. Similarly, Fausti et al. (2005) found with subsequent long-term follow-up sessions, incidence and progression of hearing loss increased. Patients whose dose was reduced initially experienced 25% incidence but as time progressed it increased to 76% (Fausti et al., 2005). Hence, in the present study the researcher did not perform long term follow-up of hearing thresholds post cessation of Kanamycin and therefore, cumulative dose could not be assessed as a risk factor. The sample size was also too small to find associations between sex, age and HIV status. In addition, patient self-report was not used as a measure for incidence of hearing loss in this study, however, it may be useful to use as a criterion if the goal is to identify patients who will pursue and benefit from amplification intervention.

Another limitation of this study was the fact that it did not explore genetic factors and their effect in determining individual's risk of cochleotoxicity. Existing literature shows that genetic factors play an important role in determining susceptibility to aminoglycoside cochleotoxicity. For instance, individuals with the genetic mutation A1555G have been reported to have increased susceptibility to cochleotoxicity (Bardien et al., 2009b; Huth et al., 2011; Xie et al., 2011). Because genetic tests were not conducted among participants of this study to determine those who had predisposing genetic mutations, that cannot be ruled out as a mitigating factor why some participants' hearing thresholds progressed while others did not. It may have been that those participants whose hearing worsened, may have underlying genetic contributions. However, despite these limitations, this study yielded some valuable findings that can influence further management of patients on treatment for RR/MDR-TB who are treated with aminoglycosides in the future.

It is worth mentioning at this point that this study took place during the early phase of introduction of Bedaquiline as a non-cochleotoxic alternative to aminoglycoside-based RR/MDR-TB treatment regimen. At that time, doctors could discontinue treating the patient with Kanamycin and use BDQ instead, especially among patients who show adverse reactions (e.g., hearing loss during treatment). Bedaquiline an alternative to the aminoglycosides can be administered easily without having the patient to endure painful injection sites or suffer irreversible hearing loss (DoH, 2018; Schnippel et al., 2016; WHO, 2016). While BDQ was not yet adopted as part of a standard RR/MDR-TB regimen in South Africa, doctors could use it among a limited number of patients. This had an impact on this study because it significantly limited the number of participants who could be enrolled into the study, hence the small sample size of the current study.

Chapter Six: CONCLUSION AND RECOMMENDATIONS

This chapter will present a conclusion drawn directly from the study findings, clinical implications of its findings as well as recommendations for future research.

Conclusions, Implications and Recommendations for Future Research

This study found that a high incidence of cochleotoxicity (90.6%) among patients on RR/MDR-TB treatment that is being treated with Kanamycin. The findings of this study also revealed that discontinuing treatment with Kanamycin led to a smaller proportion of participants having further deterioration of hearing thresholds when implemented timeously as soon as a STS was detected, however it was not statistically significant. Using UHFA (testing frequencies above 8 kHz) was critical to the effectiveness of this intervention strategy because it is a more sensitive audiometric test. Due to this test being used, STS was identified sooner in the high frequencies before progressing to lower frequencies, which then prompted the need for swift intervention to occur and henceforth impacting positively on the outcome of the treatment modifications that were implemented. Moreover, because of timeous intervention, only 31% had hearing loss and only two participants needed further management such as hearing aids for disabling hearing loss following Kanamycin treatment. These two participants were from the group of participants whose Kanamycin was discontinued.

Participant factors such as age, sex and HIV status, which have been reported previously as risk factors for cochleotoxicity in other studies, were found not to be associated with cochleotoxicity in the present study. A multitude of other risk factors were not examined in the present study such as cumulative dose, genetics, various toxicity of aminoglycoside drug type and noise exposure which are all risk factors for developing aminoglycoside-induced hearing loss. Therefore, it is recommended that future studies include these.

It is important to point out that the treatment guidelines for the management of RR/MDR-TB in South Africa has been revised and currently does not include Kanamycin as a standard first-line drug in the treatment regimen for RR/MDR-TB patients (DoH, 2019). South Africa was one of the first countries in the world to discontinue the use of Kanamycin as a first-line drug for treatment of RR/MDR-TB. Current treatment guidelines recommend the use of BDQ instead of Kanamycin, which is not cochleotoxic and does not require painful daily injections. This has

significantly improved the management and treatment outcomes of patients who are on treatment for RR/MDR-TB (Ndjeka et al., 2018).

However, despite availability of non-cochleotoxic drugs such as BDQ, aminoglycosides remain part of a recommended treatment regimen for RR/MDR-TB among some patients. Current WHO guidelines (the *WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment – Drug-Resistant Tuberculosis*) released in 2020, recommends aminoglycosides such as Amikacin and Streptomycin for the treatment of RR/MDR-TB. The findings of this study are, therefore, still relevant and contribute to the growing body of evidence that supports the use of an injection-free regimen for treatment of RR/MDR-TB (Honeyborne et al., 2019). However, there are some patients (that are treated with BDQ) who are contraindicated due to possible side effects. These may include cardiac toxicity, renal toxicity, hepatotoxicity, and less severe problems such as rash, headaches, nausea and vomiting (Borisov et al., 2017; DoH, 2019; Nguyen et al., 2016; Pym et al., 2016). The most concerning is cardiac issues or even cardiac arrest (Borisov et al., 2017). Hence, the need for and importance of treating doctors to know which strategy is more useful to minimise hearing loss, if BDQ cannot be used in the regimen.

Future research should prospectively monitor patients' hearing using UHFA and document the intervention strategy used when a significant change occurs, so that the effectiveness of the specific intervention can be investigated. Furthermore, considering the treatment modification of discontinuing the Kanamycin injectable used in this study led to a smaller proportion of patients further developing hearing loss, this strategy should be considered when treating patients with cochleotoxic medication to minimise hearing loss. There is a need for both audiologists and treating doctors to change their clinical practice management and provide evidence-based intervention strategies when treating patients on RR/MDR-TB. In addition, it is important to note there are other ways to reduce cochleotoxic effects of aminoglycosides, such as otoprotectors. Although not used in this study, antioxidants such as D-methionine, glutathione, and N-acetylcysteine (NAC) have shown reduced cochleotoxicity in animal models (Huth et al., 2011). For the prevention of cochleotoxicity in humans, the use of these agents has shown to be beneficial in some studies (Feldman et al., 2012). For example, among adults with acute infections receiving short courses of gentamycin in a randomised controlled trial, cochleotoxicity was 13% for those receiving the placebo and 3% for those receiving aspirin (Chen et al., 2007). The efficacy and safety and potential of NAC treatment as an otoprotective strategy in RR/MDR-TB patients in

preventing aminoglycoside-induced cochleotoxicity has been demonstrated in a systematic review and meta-analysis (Kranzer et al., 2015). Moreover, the increase in clinical trials related to otoprotectors as an effective means to reduce or prevent ototoxicity is ongoing (Jiang et al., 2017). With all the various ways to help prevent or reduce ototoxicity, it is important that a multi-disciplinary and multi-modal approach to hearing loss prevention during aminoglycoside RR/MDR-TB treatment be considered.

Lastly, genetics testing was not conducted in the present study, and therefore, the association between genetics and progression of hearing thresholds cannot be ruled out for the various interventions implemented. Nonetheless, given the high incidence of RR/MDR-TB in South Africa, it is recommended that future research consider other factors such as genetic predisposition and cumulative drug concentration among RR/MDR-TB patients treated with aminoglycosides. Moreover, more prospective, and randomised controlled studies to investigate the risk factors for cochleotoxicity in the South African population is recommended for future research.

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APPENDICES

Appendix A1: Letter of request for assistance to medical staff



School of Health and Rehabilitation Sciences

Faculty of Health Sciences

Divisions of Communications Sciences and Disorders,
Nursing and Midwifery, Occupational Therapy,
Physiotherapy

F45 Old Main Building, Groote Schuur Hospital,
Observatory 7925

Tel: +27 (0) 21 406 6401 Fax: +27 (0) 21 406 6323

Dear Doctor

Good day,

Please note a research study is currently being conducted at your institution. My name is Kayleen Gangerdine. I am a researcher from the University of Cape Town. I am currently conducting a research study as part of my master's Audiology project. I am investigating the effects of drug resistant (DR) tuberculosis (TB) treatment on hearing. I therefore request your assistance recruiting potential participants at your institution.

The aim of this study is to evaluate the effectiveness of different medical interventions used when a change in hearing status is detected to prevent further deterioration of hearing thresholds in DR-TB patients treated with aminoglycoside antibiotics.

The first part of the study is to determine the proportion of patients seen at the audiology department who develops a change in hearing thresholds. Another is to describe the medical intervention used when a change in patient's hearing status is detected and to evaluate the effectiveness of different medical interventions used when a change in hearing thresholds is detected.

I therefore plan to test patients' hearing throughout their treatment phase while receiving an aminoglycoside injectable drug. The testing will not interfere with any daily patient care that will

be conducted at the audiology department. I plan to test patients hearing for the time period 2016. All participants must:

Inclusion criteria:

- be new drug resistant tuberculosis patients receiving an aminoglycoside for the very first time
- seen within 72 hours of first aminoglycoside administration
- be between the age of 18-55 years

Exclusion criteria:

- any participant who previously received any ototoxic drug due to a previous regimen
- any participant receiving two ototoxic drugs in the regimen
- no active middle ear pathology

If you have any queries or concerns regarding this study, please feel free to contact myself or my supervisors at the numbers provided below:

Yours faithfully,

1. Kayleen Gangerdine - Student (078-366-8900)
2. Associate Professor Lebogang Ramma - Supervisor (021) 406-6954 and (073 153 3803)
3. Mrs Lucretia Petersen – Co- Supervisor (021) 406-6993

Appendix A2: Invitation to Participate in a Research Study: Information letter for prospective Participants



School of Health and Rehabilitation Sciences

Faculty of Health Sciences

Divisions of Communications Sciences and Disorders,
Nursing and Midwifery, Occupational Therapy,
Physiotherapy

F45 Old Main Building, Groote Schuur Hospital,
Observatory 7925

Tel: +27 (0) 21 406 6401 Fax: +27 (0) 21 406 6323

Study Title: Effectiveness of Different Medical Interventions Implemented When a Change in Hearing Status is Detected During Ototoxicity Monitoring

Researcher: Kayleen Morea Gangerdine

Dear Sir/Madam

I would like to invite you to participate in a researcher study that is currently being conducted at this hospital. The study is conducted by my colleague Ms Kayleen Gangerdine as part of the requirements for a Masters' Degree at the University of Cape Town (UCT). The aim of the study is to investigate how effective are the different changes made by doctors to the patients' Rifampicin resistant (RR)/ Multi-drug resistant (MDR) – Tuberculosis (TB) treatment when their treatment is found to affect their hearing.

This information sheet explains the study. You are free to decide if you want to take part or not. Please ask me if there is anything which is not clear. If you decide to take part, I will ask you to sign a consent form to show that you understand the study and agree to take part. It is your right to withdraw from the study at any time. Your decision to take part or not will not affect your RR/MDR-TB treatment in any way. You will be doing us a favour if you decide to participate in this study.

Ethical approval: *This has been submitted to the University of Cape Town, Faculty of Health Sciences Human Research Ethics Committee (FHS HREC) and written ethical approval (HREC # 204/2016) has been granted by that committee.*

Why are we doing this study?

Medications that are used to treat drug resistant (DR) tuberculosis (TB) have side effects that may affect your hearing system and sometimes your balance system. Some patients get a hearing loss and some patients do not. It is currently not possible to tell beforehand whether the medications will affect your hearing or not. If a patient gets a hearing loss due to the medication, the hearing loss is usually permanent. Even if you complete your treatment and you are cured from the tuberculosis, the hearing loss can remain. By us doing this study, we hope to determine how many people get a hearing loss, what changes doctors make to treatment when a hearing loss is detected on your hearing test result and which of those changes made by doctors are more effective to prevent further progression of hearing damage.

If I decide to take part in this study, what will happen?

As part of your treatment for DR-TB, we need to closely monitor your hearing, and this means you will need to attend the audiology department on a regular basis while you are on medications that poses risk to hearing. The researcher basically asks for permission to use your hearing test results for the purpose of this research. As part of your treatment, you will first need to attend the audiology department for a first-time hearing test (baseline) before you start your drug resistant tuberculosis treatment. Thereafter, you will need to come to have your hearing tested either on a monthly basis (if the medications are not affecting your hearing) or every two weeks (if medications are affecting your hearing). **The first test session (baseline) will take about 45 – 60 minutes and the follow up sessions may take 25 - 30 minutes each.**

The following is a list of assessments that you will undergo:

1. Case History taking- Before the start of the test you will be asked some questions about yourself and whether you have had problems with your hearing before.
2. Otoscopy- The researcher will use a small light instrument to look at the outside of your ears to check whether it is clear for a hearing assessment.
3. Tympanometry- The researcher will place an ear plug, probe tip into your ear canal to test how well your ear drum is moving and rule out any ear infections that may affect the test results.
4. Hearing test- The purpose of this test is to see what the softest sound is you can hear and at what level.

What are the risks of taking part in this study and what happens if I get hurt taking part in this study?

There is no risk of harm to your health associated with participation in this study. None of the hearing tests that are used in this study are dangerous or uncomfortable and we have never heard of any reports of any injury or harm due to a hearing test. However, if you do get hurt or injured as a result of participating in this study (which is highly unlikely), you may claim compensation from the University of Cape Town No faults Compensation Insurance Policy for Clinical Trials. This policy covers you, if you suffer a bodily injury because you are taking part in this study. The insurer will pay for all reasonable medical costs required to treat your bodily injury, according to the South African Good Clinical Practice Guidelines 2006, which are based on the Association of the British Pharmaceutical Industry (ABPI) Guidelines. The ABPI guidelines recommend that the insurer pay you without you having to prove that the research was responsible for your bodily injury. However, the insurer will not pay you for harm during this study, if you:

- Use medicines or other substances that are not allowed
- Do not follow the researcher's instructions
- Do not take reasonable care of yourself during the study

If you are harmed and the insurer compensates you for the necessary medical costs, usually you will be asked to accept that insurance payment as full settlement of the claim for medical costs. However, accepting this offer of insurance cover does not mean you give up your right to make a separate claim for other losses based on negligence, in a South African court.

Therefore, it is important to follow the researchers' instructions and to report straightaway if you have a concern about the study.

What are the benefits of taking part in this study?

Taking part in this study will not benefit you directly. However, the results of the study will help us know which of the changes made to the patient's treatment are more useful to prevent further hearing loss.

What happens if I do not agree to take part in this study?

You do not have to take part in this study: You can choose not to take part in this study and there will be no negative consequences to you as a result of your decision. If you decide to take part in

this study and then later change your mind, please know that you can stop taking part in the study at any time, without giving a reason.

How will information collected during this study be kept confidential?

All the results of your hearing test will be kept as per hospital policy. Also, all the information that the researcher gets from your medical folder (hearing test results) will be stored electronically on a password protected document and in a lockable cupboard in an office and the researcher will be the only person who has access to that information. However, information collected in this study may be reviewed by the Ethics Committee (and co-investigators in this research study), to check that the study procedures were performed correctly. Reports about the study and results that may also be published in scientific journals but those will not include any information which allows you to be identified.

Who can I contact if I have questions about this study?

If you have any questions about this study, please feel free to ask me now. Otherwise more specific details about the study can be given by Ms Kayleen Gangerdine (the researcher) and her number is 0215087429 (office) or 0783668900 (mobile)

The research ethics committee reviewing this study is the University of Cape Town Faculty of Health Sciences Research Ethics Committee. If you have any questions or concerns about your rights and welfare as a person taking part in a research study, or if you wish to make a complaint about the study, you may contact Prof. Marc Blockman, Chairperson of the University of Cape Town, Faculty of Health Sciences Human Research Ethics Committee, an independent committee established to help protect the rights of research participants, at **021-406-6338**.

We will give you a copy of this sheet which explains the study to take away with you. If you would like a copy of a report on this study, and you give us an email or postal address, we will send you a report. The results may not be available until 9 - 12 months from now.

Appendix A3: Informed consent form



School of Health and Rehabilitation Sciences

Faculty of Health Sciences

Divisions of Communications Sciences and Disorders,
Nursing and Midwifery, Occupational Therapy,
Physiotherapy

F45 Old Main Building, Groote Schuur Hospital,
Observatory 7925

Tel: +27 (0) 21 406 6401 Fax: +27 (0) 21 406 6323

Title of Study: 'Effectiveness of Different Medical Interventions Implemented When a Change in Hearing Status is Detected During Ototoxicity Monitoring'

PRINCIPAL INVESTIGATOR: A/Prof Lebogang Ramma

Co-investigators: Mrs Lucretia Petersen

MSc Student: Kayleen Morea Gangerdine

INSTITUTION: University of Cape Town, Divisions of Communications Sciences and Disorders, School of Health and Rehabilitation Sciences, Audiology

I, the undersigned hereby acknowledge that the purpose and procedures of the study has been fully explained to me. I also understand what is expected of me. I understand that I can withdraw from the study at any stage without being affected in any way. I have the contact details of the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee if I have any queries about participating in this study. There was an opportunity for me to ask questions and there will be during the study.

Please tick the appropriate box below:

☐ I hereby give my consent to participate in the study

☐ I do not give my consent to participate in the study

Signed: _____ (Participant)

_____ (Researcher)

_____ (Witness)

Date: _____

Appendix B: Advertisement for patients with Drug-Resistant Tuberculosis (DR-TB)

Be part of this new and exciting research!

You are needed for a study to determine when hearing threshold changes occurs in patients with drug resistant TB

Study outline

I am a master's student at the University of Cape Town, I am investigating how soon hearing threshold changes occur in patients with drug resistant tuberculosis. If I can determine when hearing thresholds changes occur and to see which management is the best, then it can potentially help assist in prevention of hearing loss in patients receiving medication for drug resistant tuberculosis. I will be monitoring your hearing regularly while you are on treatment for drug resistant tuberculosis.

You will be required to attend your hearing test appointments regularly at this audiology department. On your first visit I will use various tests to assess your hearing and be able to tell you how well you can hear. I will use special headphones called ultra-high frequency headphones to test very high-pitched sounds. The first testing session will take about 45 – 60 minutes. You will be required to either come on a monthly basis or in two weeks' time for a follow-up test. You will need to participate in this study for duration of six months. During the hearing test you will be required to press a button every time you have heard the sound. **None of the tests are painful or damaging to your hearing.**

If you are interested in participating in this study, you should:

- a. be new drug resistant tuberculosis patients receiving an aminoglycoside for the very first time and seen within 72 hours of first aminoglycoside administration
- b. be between the age of 18-55 years
- c. no active middle ear pathology

A benefit in taking part in this study is that you will know how well you can hear as well as be part of the group of patients who helped in the early identification of hearing loss. If you want to sign up for the study, you can enquire by your doctor or nurse in the ward or you may contact the researcher below for further information.

Researcher name: Kayleen Gangerdine Email: kayleen.jacobs@westerncape.gov.za; Cell: 078-366-8900

Appendix C1: Case History Questionnaire

BROOKLYN CHEST HOSPITAL AUDIOLOGY DEPARTMENT TEL: 021-508-7429		
Affix patient sticker	Audio#	
Ward:		

1. Do you know why you are here today at this department?	Yes	No
2. Can you explain to me why you think you are here today?	Yes	No
3. Do you know why it is important that you test your hearing?	Yes	No
4. Do you have any problems with your hearing/ ears?	Yes	No
5. When did your hearing/ ears problem start?		
6. Did it start before/ after or during your TB treatment?		
7. Do you know what type/ kind of TB you have?	Yes	No
8. What type/ kind of TB do you have?		
9. Do you get tablets every day?	Yes	No
10. Do you get injections every day?	Yes	No
11. How often do you get injections? Example: 3 times a week/ 5 times a week		
12. Is this the first time you get TB?	Yes	No
13. When was the first time you got TB?		
14. Did you have normal/ sensitive TB or drug resistant TB before?		
15. How long did you take that treatment? Example: 2 months/ 6months/ 1year or more		
16. Do you take any other medication besides TB? What are you taking?	Yes	No
17. Do you have any ringing/ buzzing/ noises in your ears?	Yes	No
18. Please explain the ringing/ buzzing/ noises in your ears		
19. Do you have any current ear infection or previous ear infection?	Yes	No
20. Do you have any pain in your ears?	Yes	No
21. Were you ever exposed to a noisy environment before? Example: work in a factory/ boiler room/ kitchen/ airport etc.	Yes	No

22. Did you wear personal protective equipment? Example: earmuffs/ ear plugs etc.	Yes ☐	No ☐
23. How long did you work at that place? Example: 6months/ 1year/ 5years or more		
24. Is there anyone in your family that has a hearing loss or hearing problem?	Yes ☐	No ☐
25. Who has a hearing problem? When did it start? Example: born deaf/ accident/ assault etc.		
26. Do you feel dizzy or have any complaints about dizziness?	Yes ☐	No ☐
27. Please explain to me when you feel dizzy		
28. Did your dizziness start before or after you started with TB treatment?		
29. Is this the first time you are having a hearing test?	Yes ☐	No ☐
30. Where did you test your hearing/ ears?		
31. What was your result? Normal or hearing loss?		

Appendix C2: Case History form and Audiogram

BROOKLYN CHEST HOSPITAL
 AUDIOLOGY DEPARTMENT
 TEL: 021-508-7429

Affix patient sticker

Audio#

Ward:

Case History: (tick if applicable)

- | | | |
|---|---|-----------|
| ☐ Hearing loss noted | ☐ Noise exposure | |
| ☐ Ear infection history | ☐ MDR TB-start date: | end date: |
| ☐ Tinnitus | ☐ XDR TB-start date: | end date: |
| ☐ Pain | ☐ PRE XDR TB-start date | end date: |
| ☐ Family history of hearing loss | ☐ Amikacin-start date: | end date: |
| ☐ Dizziness | ☐ Kanamycin-start date: | end date: |
| ☐ HIV | ☐ Capreomycin-start date: | end date: |
| ☐ Other medication | ☐ Streptomycin-start date: | end date: |

Comments: _____

Date

Assessment Results and Management

Otoscopy: R- Tymps: R-
 L- L-

Audiogram: _____ TCA: _____

Otoscopy: R- Tymps: R-
 L- L-

Audiogram: _____ TCA: _____

Otoscopy: R- Tymps: R-
 L- L-

Audiogram: _____ TCA: _____

Otoscopy: R- Tymps: R-
 L- L-

Audiogram: _____ TCA: _____

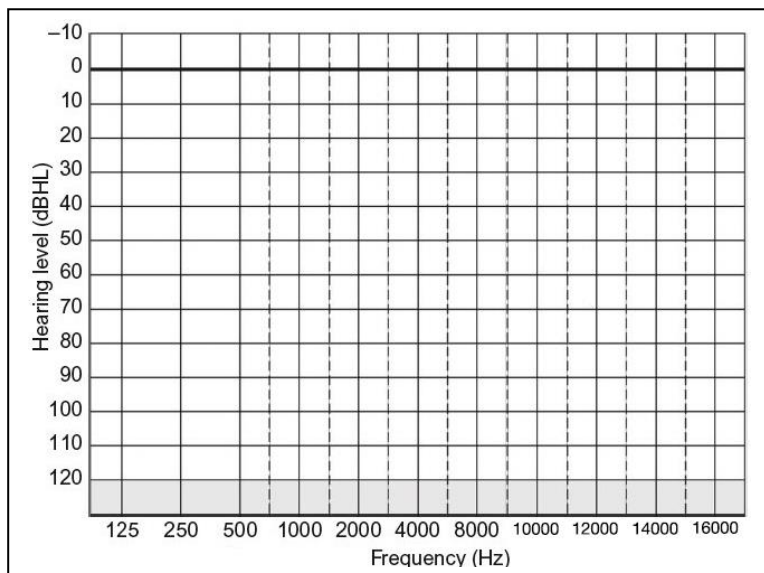
Otoscopy: R- Tymps: R-
 L- L-

Audiogram: _____ TCA: _____

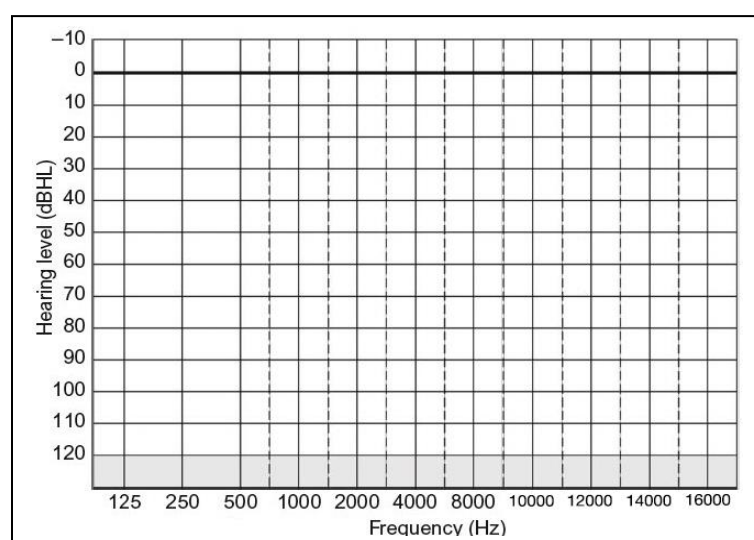
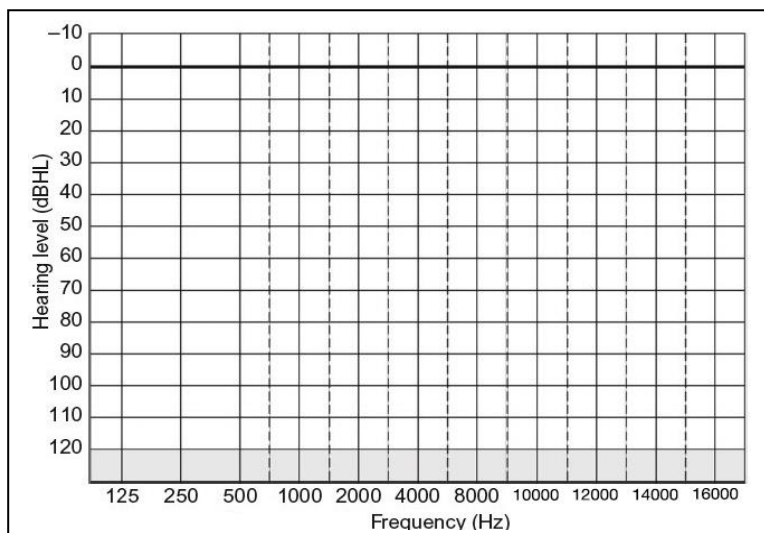
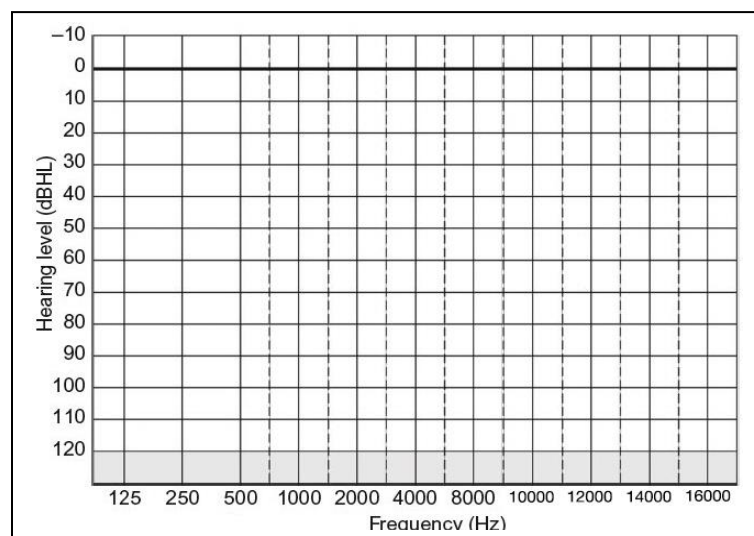
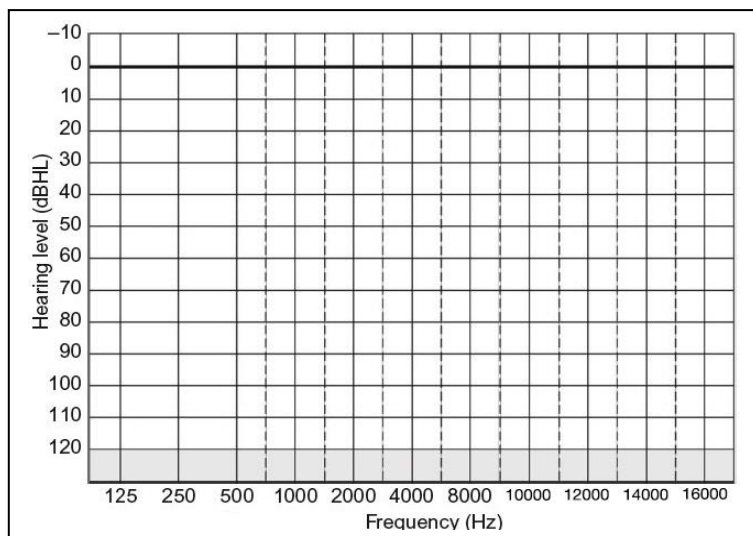
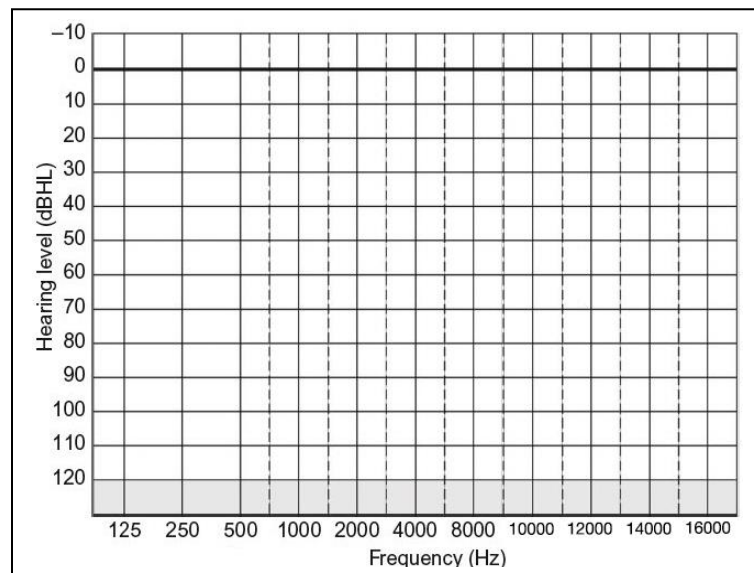
Otoscopy: R- Tymps: R-
 L- L-

Audiogram: _____ TCA: _____

PURE TONE AUDIOGRAM



PURE TONE AUDIOGRAM



Appendix D: Approval letter Human Research Ethics Committee University of Cape Town



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E53-46 Old Main Building
 Groote Schuur Hospital
 Observatory 7925
 Telephone [021] 406 6626
 Email: shirlette.thomas@uct.ac.za
 Website: www.health.uct.ac.za/fhs/research/humanethics/forms

17 June 2016

HREC REF: 204/2016

A/Prof L Ramma
 Communication Science and Disorders
 Health & Rehab
 F-floor, OMB

Dear A/Prof Ramma

PROJECT TITLE: EFFECTIVENESS OF DIFFERENT MEDICAL INTERVENTIONS IMPLEMENTED WHEN A CHANGE IN HEARING STATUS IS DETECTED DURING OTOTOXICITY MONITORING (MASTERS CANDIDATE - MS K JACOBS)

Thank you for your letter to the Faculty of Health Sciences Human Research Ethics Committee received on 14 June 2016.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th June 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

The HREC acknowledge that the student, Kayleen Jacobs will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

HREC 204/2016

Appendix E: Letter of request for permission to Institution



School of Health and Rehabilitation Sciences

Faculty of Health Sciences

Divisions of Communications Sciences and Disorders,
Nursing and Midwifery, Occupational Therapy,
Physiotherapy

F45 Old Main Building, Groote Schuur Hospital,
Observatory 7925

Tel: +27 (0) 21 406 6401 Fax: +27 (0) 21 406 6323

Dear _____

Good day,

My name is Kayleen Gangerdine. I am a researcher from the University of Cape Town. I am currently conducting a research study as part of my master's Audiology project. I am investigating the effects of drug resistant (DR) tuberculosis (TB) treatment on hearing. I therefore request permission to conduct this research at your institution.

The aim of this study is to evaluate the effectiveness of different medical interventions used when a change in hearing status is detected to prevent further deterioration of hearing thresholds in DR-TB patients treated with aminoglycoside antibiotics. The first part of the study is to determine the proportion of patients seen at the audiology department who develops a change in hearing thresholds. Another is to describe the medical intervention used when a change in patient's hearing thresholds is detected and to evaluate the effectiveness of different medical interventions used when a change in hearing thresholds is detected.

I therefore plan to test patients' hearing throughout their treatment phase while receiving an aminoglycoside injectable drug. The testing will not interfere with any daily patient care that will be conducted at the audiology department. I plan to test patients' hearing for the time period 2016. I therefore request permission to conduct my research at your institution and permission to approach the medical staff (doctors and nurse) to help recruit patients for this study and patients at your hospital to invite them to be part of this study.

If you have any queries or concerns regarding this study, please feel free to contact myself or my supervisors at the numbers provided below:

Yours faithfully,

1. Kayleen Gangerdine - Student (078-366-8900)
2. Associate Professor Lebogang Ramma - Supervisor (021) 406-6954 and (073 153 3803)
3. Mrs Lucretia Petersen – Co- Supervisor (021) 406-6993

Appendix F: Approval letter Metro TB Hospital Centre Western Cape Government



METRO DISTRICT HEALTH SERVICES
 Metro TB Hospital Centre
 Dr P Spiller
 Manager: Medical Services
 E-Mail: Paul.Spiller@westerncape.gov.za
 Stanberry street, Ysterplaat 7425
 Tel: 021-500 7403
 Fax: 0865236549 Cell: 072-115-2289

Josh Lee Kroukamp
 Intern: Health Research
 Directorate: Health Impact Assessment
 Western Cape Government: Health

Your Ref: WC_2016RP2_318

Principal investigator: Kayleen Morea Jacobs Address: University of Cape Town Department of Health and Rehabilitation Sciences	Research Title: Effectiveness of Different Medical Interventions Implemented When a Change in Hearing Status is detected during Ototoxicity Monitoring
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Dear Ms Jacobs

Thank you for your request. Permission is hereby granted for you to conduct the research at Brooklyn Chest Hospital and DP Marais Hospital.

Kindly note the following:

1. All individual patient information obtained must be kept confidential.
2. Access to the hospital must be arranged with the Manager so that normal activities are not disrupted
3. No original documents or files must leave the hospital premises.
4. A copy of the final report must be sent to the Manager: Medical Services, Metro TB Hospital Complex, within 3 months of its completion.
5. Feedback must be given to the role players at the respective hospitals.

We would value any research recommendations which would help to improve our services.
 Thank you for your co-operation and please feel free to contact me should you require further information or assistance.

Yours

Dr P Spiller
 Manager: Medical Services
 Metro TB Hospital Complex
 Date: 30 June 2016

Appendix G: Data collection tests, norms and participants instructions

Test	Definition	Participant Procedure
Baseline evaluation		
Case History	The recording of biographical information (date of birth, age, sex and medical history) occurred, and the aim was to identify any medical or audiological issues which may guide the researcher for the next step of the testing procedure. For example, if the participant had any perceived subjective hearing loss or if the participant reported childhood ear infection, then it would guide the researcher on what potential scarring could appear on the eardrum when conducting the otoscopic examination or which ear to be tested first in the process.	On arrival at the audiology department the participant was asked to enter a quiet room and was seated on a comfortable chair. The case history form was then verbally researcher-administered to the participant.
Otoscopic examination (OT)	A visual examination of the outer ear, middle ear and tympanic membrane was performed to see if any wax or foreign objects or perforations were present. Participants who displayed any visible dermatological signs of the pinna, impacted wax in the ear canal, tympanic membrane perforations or active middle ear infections were recorded on the results sheet and were referred to the appropriate healthcare professional for further management.	An otoscopic examination was conducted after case history taking. The researcher asked the participant to remain quiet and stare directly to the front and not move while the researcher conducted an otoscopic examination. The researcher explained to the participant that it would not hurt or be harmful and the participant should remain relaxed.
Tympanometry (TYMP) examination)	A Type A tympanogram was considered normal when peak pressure was between -150 and +100 daPa, ear canal volume	The participant was instructed to keep quiet, not talk, swallow, or chew during the examination. The test was performed by

	between 0.2 and 2.0 cm³ and compliance/peak pressure between 0.2 and 2.0cm³. This indicated that there was a normal pressure in the middle ear with natural movement of the eardrum and the ossicular chain. A Type B tympanogram was considered when no peak value existed i.e., straight flat line, which is associated with ear infection, impacted wax or foreign objects obstructing the ear canal. A Type C tympanogram was indicated when peak compliance values were in a negative range compared with normal. i.e. < 0.2 cm³. This was associated with recovery of fluid in the middle ear or a sign of Eustachian tube (ET) dysfunction. If abnormal results (type B or C tympanograms) were obtained, the test was immediately performed again to confirm the result obtained. All probe tips were cleaned and removed after the tympanometry testing.	inserting a clean rubber probe tip with suitable size and shape into the participants' ear canal and sending various pressures from +200 to -400 daPa and a pure tone of 226Hz into the ear canal to see if any ear infection existed or middle ear dysfunction. The results were shown in a tympanogram, which was displayed on the tympanometry equipment unit screen (Clark et al, 2007).
Audiometric examination- Conventional Pure Tone Audiometry (cPTA) (including air (AC) and bone (BC) conduction)	A 1000 Hz tone at a 30 dB HL intensity level was used as the initial test frequency. When the participant responded to the presence of the sound, the sound intensity was decreased by 10 dB HL increments until the participant failed to respond to the sound. The intensity of the sound was then increased by 5 dB HL increments until a response was heard again. This is called the modified Hughson-Westlake technique. This procedure was repeated until two consecutive responses were obtained at a	Participants were asked to listen to various sounds and press a button or raise their hand each time a sound was heard. Once seated inside the booth on a comfortable chair, the researcher placed a headphone (TDH-39 supra-aural headphones) over the participants' ear canals sealing off the ear canals for the testing to begin.

	certain intensity level for that specific frequency. When two consecutive responses were obtained the threshold was then recorded as the response to the lowest audible tone at each frequency. The pure tone thresholds for each ear were obtained, in order of 1000, 2000, 3000, 4000, 6000, 8000, 1000 (recheck), 500 and 250 Hz (ASHA, 1994; HPCSA, 2018). Whenever there was a difference of 20 dB or more between two adjacent octave frequencies, then the inter-octave frequencies were assessed (AAA, 2009; HPCSA, 2018). To determine the bone conduction thresholds, the same procedure was used as above except the bone conductor was placed on the mastoid process and not over the ear canals. The frequency range of 250 to 4000 Hz was used to obtain the bone conduction thresholds (Diefendorf, 2009). Masking was performed for both air and bone conduction when indicated and appropriate to do so (AAA, 2009).	
Audiometric examination- Ultra-High Frequency Audiometry (UHFA)	Same procedure described above as in conventional audiometry was conducted to determine the air conduction thresholds of the participants, with the exception that frequencies 10000 Hz – 16000 Hz were tested, and no bone conduction was performed. In addition, for ultra-high frequency audiometry the participants' baselines served as their norm. After the	Before conducting UHFA, the headphones were changed, and specialized headphones (KOSS/ R80) were used to test the frequency range 10 kHz to 16 kHz was placed on the participant's ears. Participants lifted their hand or pressed a button when a sound was heard.

	audiometric examination was performed, the researcher removed the headphones and the participant remained in the sound treated booth for the next step in the procedure.	
Monitoring evaluation	Participants hearing thresholds were tested before, during, and post-treatment to determine any threshold shifts following treatment with aminoglycosides. Significant threshold shifts were determined using the ASHA (1994) criteria.	
Case History (update)	To determine if any information has changed to the previous session.	The participant was invited to enter the room and be seated on a comfortable chair. The researcher enquired if the personal details remained the same, if any changes, this data was amended and recorded. After the case history was updated, the researcher proceeded to the next step in the procedure.
Otoscopic examination (OT)	The researcher performed a visual inspection of the outer and middle ear and tympanic membrane using an otoscope and noted any changes from the previous OT examination result.	Again, the participant was seated on a chair and informed not to cough, swallow, chew or move when the examination was being conducted. This session result was recorded and compared to the previous result to confirm any changes. The researcher then proceeded to the next step.
Tympanometry (TYMP) examination	The researcher performed tympanometric examination when indicated. Dependent on the types obtained, tymp A, B or C, the relevant procedure followed. i.e., if type A	The participant was instructed as before to remain quiet, sit still and be calm. And follow instructions when given by the researcher.

	continued with testing, and if type B referred for middle ear management	
Audiometric examination- Conventional Pure Tone Audiometry (cPTA): only air conduction	Frequencies 250 Hz – 8 kHz were tested and compared to previous results. For normal hearing at the follow-up session, the participant was asked to return in 1month time for a follow-up. For hearing loss or STS, then bone conduction testing was included in this step. The bone conduction testing was included to ascertain what type of hearing loss existed. i.e., sensorineural or conductive or mixed. If it was a conductive or mixed hearing loss, then the participant was referred to the appropriate healthcare professional for management. i.e., medical doctor or ear nose and throat specialist	Again, the participant was seated in the sound treated booth. Instructions were given as before. The results were recorded on the audiogram sheet and allowed for comparison of the threshold results of the previous session and current session to occur.
Audiometric examination- Ultra-High Frequency Audiometry (UHFA)	The results were recorded on the audiogram sheet for easy comparison of the threshold results from the previous session and follow-up session. If the participant had no significant change of thresholds at the follow-up session, then the participant was asked to return in 1month time for a follow-up. When a significant change occurred, participants returned in 2 weeks' time, and it was recorded and reported to the relevant healthcare professionals.	The same instructions as above were given to the participant. After the conventional frequency audiometry range was tested, the researcher swopped the headphones from TDH-39 supra-aural headphones to KOSS R/80 ultra-high frequency headphones and proceeded to test the frequency range 10 kHz – 16 kHz.

Appendix H: Confidentiality Agreement

Study title: Effectiveness of Different Medical Interventions Implemented When a Change in Hearing Status is Detected During Ototoxicity Monitoring

Regarding my access to your confidential information, I hereby agree to:

- access and only use patient information as needed for the study
- only access information I need to know
- keep all information confidential and not disclose it
- not misuse confidential information obtained
- safeguard confidential information obtained by storing it in an electronic file that is password protected and ensure that no other person beside the researcher has access to this information

I understand and agree that if I violate any of the duties and responsibilities explained in this agreement, I will be subjected to a disciplinary process and possible termination of the research project and/or a legal liability. I understand and agree that my privileges to access confidential patient information may be revoked any time.

I further understand and agree that my obligations to keep such information confidential will remain in effect even after conclusion of the research project.

Signature Researcher

Date and Place

Signature Institutional Head

Date and place

Signature Witness

Date and place