Community-based ototoxicity monitoring with extended high-frequency audiometry and community health workers for drug-resistant tuberculosis

By

Lucia Jane Stevenson (23051592)

A thesis submitted in partial fulfilment for the degree

PhD Audiology

Department of Speech-Language Therapy and Audiology,

Faculty of Humanities, University of Pretoria

Supervisor: Professor De Wet Swanepoel

Co-supervisor: Associate Professor Leigh Biagio-de Jager

27 June 2022

Lucia Jane Stevenson has, for the research described in this work, obtained the applicable research ethics approval.

The author declares that she has observed the ethical standards required in terms of the University of Pretoria's code of ethics for researchers and the Policy guidelines for responsible research.

Lucia Jane Stevenson

Department of Speech-Language Therapy and Audiology

University of Pretoria

Pretoria

South Africa

luciaj.stev@gmail.com

ACKNOWLEDGEMENTS

Success

From "The Ladder of St. Augustine"

By Henry Wadsworth Longfellow (1807-1882)

We have not wings, we cannot soar;
But we have feet to scale and climb
By slow degrees, by more and more,
The cloudy summits of our time.

The mighty pyramids of stone
That wedge-like cleave the desert airs,
When nearer seen, and better known,
Are but gigantic flights of stairs.

The distant mountains, that uprear
Their solid bastions to the skies,
Are crossed by pathways, that appear
As we to higher levels rise.

The heights by great men reached and kept
Were not attained by sudden flight,
But they, while their companions slept,
Were toiling upward in the night.

For my family.

I wish to thank the following people for making this research project possible and for helping me to reach the successful completion of this work:

To Prof De Wet Swanepoel, thank you for your unwavering guidance, support, expertise and belief in me and this project. I feel privileged to have you as my supervisor.

To Prof Leigh Biagio-de Jager, thank you for your attention to detail and suggestions that guided me to approach elements of this research project from a different angle.

To Prof Marien Graham, thank you for your tireless, thorough and enthusiastic approach to my research findings and your endless patience with my statistical requests.

Thank you to the primary health care audiologists, community health workers, ototoxicity monitoring programme managers and patients involved in this project, without whom this work would not have been possible.

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PUBLICATIONS AND RESEARCH OUTPUTS

The following original articles are part of this thesis:

1. **Stevenson, L. J.**, Biagio-de Jager, L., Graham, M. A., & Swanepoel, D. W. (2021). Community-based ototoxicity monitoring for drug-resistant tuberculosis in South Africa: An evaluation study. *International Journal of Environmental Research and Public Health*, *18*(21), 11342.

2. **Stevenson, L. J.**, Biagio-de Jager, L., Graham, M. A., & Swanepoel, D. W. (2022). A longitudinal community-based ototoxicity monitoring programme and treatment effects for drug-resistant tuberculosis treatment, Western Cape. *South African Journal of Communication Disorders*, 69(1), a886.

3. **Stevenson, L. J.**, Biagio-de Jager, L., Graham, M. A., & Swanepoel, D. W. (2022). Extended high frequency audiometry for ototoxicity monitoring: A longitudinal evaluation of drug-resistant tuberculosis treatment. *American Journal of Audiology*, *In review*.

ABSTRACT

Title: Community-based ototoxicity monitoring with extended high-frequency audiometry and community health workers for drug-resistant tuberculosis

Name: Lucia Jane Stevenson

Supervisor: Professor De Wet Swanepoel

Co-supervisor: Associate Professor Leigh Biagio-de Jager

Department: Speech-Language Therapy and Audiology

Degree: PhD Audiology

Ototoxicity occurs when certain life-saving drugs or ionising radiation are administered to patients for the treatment of illness such as cancers, cystic fibrosis and tuberculosis. Ototoxic drugs, including aminoglycoside antibiotics and platinum-based chemotherapies, cause damage to the cochlear or vestibular structures of the inner ear, or both, affecting sensory function. South Africa has a high burden of drug-resistant tuberculosis (DRTB) and until recently, aminoglycosides, were predominant in treatment regimens. Decentralised community-based ototoxicity monitoring programmes (OMPs) facilitated by community health workers (CHWs) have been implemented in response to the DRTB ototoxicity burden and to support early detection of hearing loss and increased patient access to services. This research project entailed a retrospective record review of longitudinal ototoxicity monitoring of 831 patients with DRTB, using data collected at 19 community-based clinics by six CHWs and two primary health care (PHC) audiologists, using portable audiological equipment in the City of Cape Town between 2013 and 2017. Three studies were conducted.

Study I evaluated the service delivery practices of a decentralised, community-based OMP facilitated by CHWs for 831 patients (age mean = 36.1; SD = 11.0) with DRTB. The service delivery practices were evaluated against the OMP protocol and national

and international recommended guidelines for ototoxicity monitoring. Approximately half (46.8%) of the patients had an initial assessment conducted in accordance with the OMP protocol recommendations. The OMP follow-up rates improved from 53.7% to 79.5% as the OMP became more established over time, higher than those of a similar DRTB treatment programme. However, the frequency and regularity of ototoxicity monitoring assessments for patients in this study did not meet the recommendations of the OMP protocol or the guidelines for ototoxicity monitoring. On average, patients were assessed 3.1 (SD = 2.31) times, with just 8% (69/831) of patients returning for the recommended six or more ototoxicity monitoring assessments. Ototoxicity monitoring was conducted on average every 58.3 (SD = 6.23) days, almost twice the 30 days recommended by the OMP protocol. Extended high-frequency (EHF) pure-tone audiometry (27.5%) was underutilised by testers and data recording was inconsistent (e.g. 37.7% of patient gender was not recorded by testers).

Study II described the observed longitudinal treatment effects for DRTB and ototoxicity monitoring conducted by CHWs using conventional audiometry (0.25–8 kHz), in a decentralised community-based model of care. Of the 831 patients included in Study I, 194 (age mean = 36.2; SD = 11.3) met the selection criteria and were included in Study II. Patients' initial assessments were conducted on average 16.8 days (SD = 86.5; range = -494 to 14 days) before treatment initiation. Follow-up rates for consecutive monitoring assessments reached as high as 80.6% for patients assessed by CHWs. However, few patients (14.2–32.6%) were assessed with the frequency (≥ 6 assessments) and regularity required for effective ototoxicity monitoring, with assessments conducted on average every 53.4 to 64.3 days. There was a significant (p = 0.019; U = 2637.0) difference between the average number of follow-up visits made by patients assessed by CHWs (average = 3.3; SD = 2.1; 148/194) and those assessed by PHC audiologists (average = 4.3; SD = 2.5; 46/194). However, the average number of days elapsing between monitoring assessments were fewer for patients assessed by CHWs (53.4 days; SD = 10.3) than for patients assessed by PHC audiologists (64.3 days; SD = 19.3). There was a high prevalence (51.5%; 100/194) of pre-existing hearing loss for patients at the time of the initial assessment. Following DRTB treatment, 51.5% (100/194) of patients presented with a significant ototoxic shift meeting one or more of the American Speech-Language-Hearing Association (ASHA)

criteria with ototoxic shifts occurring most often at the high frequencies (4–8 kHz). Deterioration in hearing thresholds was bilateral and most pronounced ($p < 0.05$) at the high frequencies (4–8 kHz) and high frequency pure tone average (PTA) (3–8 kHz). The presence of pre-existing hearing loss, HIV co-infection, and a history of noise exposure were significant predictors ($p < 0.05$) of ototoxicity in DRTB patients.

Study III investigated EHF audiometry for monitoring ototoxicity in a longitudinal treatment programme. Of the 831 patients included in Study I, 69 (age mean = 37.9; SD = 11.2) met the selection criteria and were included in Study III. Gender (27.5%; 19/69) and medication type (47.8%; 33/69) administered to patients was not recorded on the data collection forms by some testers and was therefore unavailable for inclusion in this retrospective study. Initial assessments were conducted on average 40.3 days (SD = 70.9; range = 0 to 301 days) after treatment initiation. At the initial assessment, 36.2% (25/69) of patients presented with a hearing loss in one or more frequency in the conventional range (0.25–8 kHz); compared to 65.2% (45/69) of patients when also considering EHF thresholds (0.25–16 kHz). Following treatment, the mean hearing threshold deterioration was significant ($p < 0.05$) at EHFs and the EHF PTA (9–16 kHz) of both ears. Including EHF thresholds resulted in more than half of patients (56.5%; 39/69) presenting with a significant ototoxic shift meeting one or more of the ASHA criteria, compared to 31.9% (22/69) if EHFs were not considered. Absent EHF thresholds owing to maximum equipment output limits were most pertinent at 16 kHz, with 17.4% of patient thresholds absent at the time of the initial assessment.

This research project demonstrated that community-based ototoxicity monitoring is a feasible option to improve access to services and improve follow-up rates for patients. With ongoing training and supportive supervision, CHWs can facilitate community-based ototoxicity monitoring. DRTB treatment with kanamycin resulted in a significant deterioration of hearing status longitudinally, most markedly in the high frequencies and EHFs. The findings confirm that EHF audiometry is most sensitive for the early detection of ototoxicity and should be included in OMPs. However, to improve community-based OMP outcomes, OMP managers should reassess current protocols, guidelines and data recording practices and consider novel devices for ototoxicity monitoring with shortened optimised assessment approaches that target frequencies most sensitive to ototoxicity, including EHFs.

KEYWORDS

Audiometry

Community-based services

Community health workers

Decentralised

Drug-resistant tuberculosis

Extended high-frequency audiometry

Hearing loss

Ototoxicity monitoring

South Africa

ABBREVIATIONS

AAA	American Academy of Audiology
ASHA	American Speech-Language-Hearing Association
CHW	Community health worker
COVID-19	Coronavirus disease 2019
CoCT	City of Cape Town
dB HL	Decibel hearing level
DRTB	Drug-resistant tuberculosis
EHF	Extended high frequency
HIV	Human immunodeficiency virus
HPCSA	Health Professions Council of South Africa
Hz	Hertz
kHz	Kilohertz
MDRTB	Multidrug-resistant tuberculosis
OAE	Otoacoustic emission
OMP	Ototoxicity monitoring programme
PHC	Primary health care
PTA	Pure tone average
RRTB	Rifampicin-resistant tuberculosis
TB	Tuberculosis
WHO	World Health Organisation
XDRTB	Extensive drug-resistant tuberculosis

DEFINITIONS OF KEY TERMS

COMMUNITY- BASED SERVICES	Integrated person-centred healthcare services provided to patients outside hospital settings, such as clinics, which are delivered by a broadly defined community health workforce supported and supervised by centralised facility-based personnel.
COMMUNITY HEALTH WORKERS	A variety of community health aides who are trained and working in their own communities. Community health workers are supported by a health system but not necessarily part of its organisation. Community health workers engage in task-sharing, which involves the appropriate reallocation of tasks traditionally performed by highly qualified healthcare workers to non-specialist workers, with shorter training and fewer qualifications.
DRUG-RESISTANT TUBERCULOSIS	Tuberculosis that is resistant to one or more of the most effective anti-TB drugs, rifampicin and isoniazid. Rifampicin-resistant TB (RRTB), multidrug-resistant TB (MDRTB) and extensive drug-resistant TB (XDRTB) are the main types of drug-resistant tuberculosis.

EXTENDED HIGH-FREQUENCY PURE TONE AUDIOMETRY

Pure tone air-conduction threshold audiometry is the behavioural measurement of an individual's hearing sensitivity for calibrated pure tones, using earphones. Extended high-frequency (EHF) pure tone audiometry involves the assessment of the frequencies 0.25 kHz, 0.5, 1, 2, 3, 4, 6, 8, 9, 11.2, 12.5, 14 and 16 kHz.

OTOTOXICITY MONITORING

Regular monitoring of a patient's hearing thresholds throughout the course of ototoxic treatment, by comparing hearing thresholds obtained before, during and after treatment for purposes of the early detection, prevention and treatment of changes in hearing to reduce the functional impact of drug-induced ototoxicity.

CHAPTER 1: INTRODUCTION

The aim of this chapter is to provide an overview of the literature on ototoxicity monitoring for drug-induced ototoxicity using conventional audiometry and extended frequency (EHF) audiometry, and the ototoxicity observed in drug-resistant tuberculosis (DRTB) patients.

1.1 Background

Ototoxicity occurs when certain life-saving pharmaceutical drugs or ionising radiation are administered to patients, causing damage to the cochlear or vestibular structures of the inner ear, or both, and affecting sensory function (Rizk et al., 2020; Steyger, 2021b). Between 200 to 600 drugs are known to cause ototoxic damage to hearing and/or balance (Lanvers-Kaminsky et al., 2017; Watts, 2019; World Health Organisation [WHO], 2021b). Environmental ototoxins such as certain solvents, heavy metals and chemicals are also known to be ototoxic (Steyger, 2021b; Watts, 2019). Cochleotoxicity typically results in tinnitus and/or hearing loss while vestibulotoxicity causes impairment of coordination, such as dizziness, imbalance and vertigo (Rizk et al., 2020). Ototoxic agents can also affect the vestibulocohlear nerve and/or central auditory pathways and are thus considered neurotoxic (Salvi, 2020; Steyger, 2021b; Watts, 2019). Each ototoxic agent has a particular mechanism of action that causes damage to the inner ear, resulting in a particular manifestation of the symptoms associated with ototoxicity (Rizk et al., 2020; Watts, 2019). The extent of the damage caused by ototoxic drugs to the cochlear and vestibular structures is also dependent on the characteristics of exposure, including drug dosage, duration and route of administration (Lanvers-Kaminsky et al., 2017; Steyger, 2011; WHO, 2021b). It is therefore important to consider how much, how often and for how long exposure to an ototoxic drug has occurred (Watts, 2019). Patient-specific factors such as a genetic predisposition to drug-induced ototoxicity, previous exposure to ototoxic drugs, clinical conditions/diseases, metabolic status and the presence of pre-existing hearing loss may influence the impact of drug-induced ototoxicity experienced by a patient (Watts, 2019; WHO, 2021b).

The most frequently used ototoxic drug classes are aminoglycoside antibiotics and platinum-based chemotherapies (American Academy of Audiology [AAA], 2009; Campbell & Le Prell, 2018; Kros & Steyger, 2019; Lanvers-Kaminsky et al., 2017; Steyger, 2021a). Aminoglycoside antibiotics are typically used for the treatment of bacterial and mycobacterial infections, such as tuberculosis, and in the treatment of exacerbated respiratory infections in children with cystic fibrosis (Steyger, 2021b). Platinum-based chemotherapies are used in the treatment of cancers (Campbell & Le Prell, 2018; Lanvers-Kaminsky et al., 2017). Sensory and neural damage to the auditory and vestibular systems causes functional impairment, which may range from barely noticeable to completely debilitating (Watts, 2019).

Both platinum-based chemotherapeutic agents and aminoglycosides target outer hair cells at the basal turn of the cochlea, before affecting the apical and inner hair cells (Rizk et al., 2020). Outer hair cell death can continue in the lower frequencies of the apical region of the cochlea with prolonged ototoxic drug use, leading eventually to inner hair cell death (Campbell & Le Prell, 2018; Ganesan et al., 2018; Meiyan et al., 2017; Rizk et al., 2020; Steyger, 2021a). Damage caused to the cochlear structures and sensory function of the inner ear may result in permanent ototoxic hearing loss typically progressing from the high to the low frequency range of hearing (Blankenship et al., 2021; Ganesan et al., 2018; Ghafari et al., 2020; Meiyan et al., 2017; Steyger, 2021a). Although rare, certain patients with a genetic susceptibility caused by mitochondrial DNA gene mutations (Bardien et al., 2009) may develop a sudden onset of profound sensorineural hearing loss following a single dose of an aminoglycoside (Ramma, Heinze, et al., 2019). The estimated prevalence of ototoxic hearing loss from the use of aminoglycosides is 63%, while 23% to 50% of adults, and up to 60% of children, develop hearing loss from the use of platinum-based chemotherapy (WHO, 2021b).

1.2 Ototoxicity and drug-resistant tuberculosis

Clinical research into ototoxicity explores the presence, progression and conditions under which functional impairment occurs in populations of interest (Watts, 2019). One such population of interest, which presents as an important use case for ototoxicity monitoring, is patients with DRTB, who have historically been treated using injectable

aminoglycosides (Department Health Republic of South Africa [DOH], 2013, 2018). Tuberculosis (TB), a communicable disease caused by the spread of aerobic bacteria, remains the world's most deadly infectious disease (WHO, 2020b). The World Health Organisation (WHO) has identified South Africa as one of eight countries making up two thirds of the 10 million people who developed TB in 2019 (WHO, 2020b). In addition, South Africa is classified as one of 14 countries presenting with a high burden of TB, TB and human immunodeficiency virus (HIV) co-infection and multidrug-resistant TB (MDRTB) (WHO, 2020b, 2021a). Tuberculosis resistance to one or more anti-TB drugs is known as DRTB, the main types of which are MDRTB, extensive drug-resistant TB (XDRTB) and Rifampicin-resistant TB (RRTB) (Centers for Disease Control and Prevention (CDC), 2016; DOH, 2018; Western Cape Government Health, 2018).

DRTB occurs mainly as a result of poor adherence by TB patients to treatment regimens and/or incorrect management or treatment of TB patients by health care providers (DOH, 2018; Duggal & Sarkar, 2007); however, direct transmission of drug-resistant strains is also responsible (Bardien et al., 2009). DRTB has been identified as one of the most serious threats to public health, to the control of TB and to economic growth (Horsburgh et al., 2019; WHO, 2020b). The COVID-19 pandemic has caused significant disruption of access and delivery of TB diagnostic treatment services to patients (WHO, 2020d, 2021a). Therefore, in 2021 the WHO calculated the estimated global burden of DRTB by using new methods, including consideration of pre-2020 trends (WHO, 2021b). In so doing, the WHO has estimated that half a million people developed DRTB globally in 2019, with the estimated incidence remaining stable in 2021 (WHO, 2020b, 2021a). Together with Nigeria, South Africa accounted for more than half (54%) of the global incidence of cases of DRTB in 2018 (Oga-Omenka et al., 2020), with the estimated burden of DRTB set to rise in South Africa in the future (Lange, Dheda, et al., 2019; Sharma et al., 2017). South Africa has the highest number of patients with MDRTB on the African continent (Lange, Aarnoutse, et al., 2019), with an estimated 23 out of every 100 000 people being infected with RR/MDRTB (WHO, 2020b). TB and HIV co-infection may contribute to the increase in the prevalence of drug-resistant TB (DRTB) in patients with TB (Wells et al., 2007).

Until 2018, before the release of the updated DRTB treatment regimen guidelines (DOH, 2018; WHO, 2020c), the treatment regimen for DRTB patients included the use of a combination of first and second-line anti-TB drugs, including injectable aminoglycosides, for a period of 18 months or longer (DOH, 2018). The global prevalence of ototoxic hearing loss as a result of DRTB treatment using aminoglycosides has been estimated as 50% (WHO, 2021b). In the Western Cape, between 47% and 57% of patients with DRTB develop aminoglycoside-induced hearing loss (Melchionda et al., 2013; Petersen & Rogers, 2015; Ramma, Heinze, et al., 2019). As of July 2018, the use of injectable-free non-aminoglycoside DRTB treatment regimens, which recommend the use of novel, less toxic and more efficient all-oral drugs, has been routinely phased in in South Africa (DOH, 2018; Zhao et al., 2019). The use of non-injectable DRTB treatment regimens, such as bedaquiline, protects against the high risk of hearing loss associated with injectable aminoglycosides (Khoza-Shangase & Prodromos, 2021; WHO, 2021b). The latest WHO DRTB treatment guidelines (WHO, 2020c) support the use of all-oral DRTB treatment regimens; however, access to these newer drugs is very limited in many countries (Lange, Aarnoutse, et al., 2019) and aminoglycosides are still used. Almost half (46%; 17/37) the high-burden TB countries recently surveyed reported still using injectable aminoglycosides in the treatment of DRTB (Medicins Sans Fronteires [MSF], 2020b) resulting in the continued risk of ototoxicity for these patients. Furthermore, for patients not suited to an all-oral DRTB treatment regimen, the WHO recommendations continue to include the use of amikacin, which is associated with a high prevalence (38.9%) of hearing loss (Dillard et al., 2021; Evans et al., 2015; WHO, 2020c; Wrohan et al., 2021).

1.3 Ototoxicity monitoring

Unaddressed hearing loss is detrimental to quality of life, communication, cognition, education, employment, mental health and relationships and causes considerable economic impact on society at large (WHO, 2021b). Children are especially vulnerable to the pervasive effects of hearing loss, particularly when the acquisition of speech and language are interrupted, causing long-term developmental, cognitive, social and educational delays (WHO, 2021b). In ideal circumstances, ototoxicity is a preventable

form of acquired hearing loss (Steyger, 2021b); however, the impact of the effects of ototoxicity on quality of life necessitate the implementation of otoprotective actions to preserve hearing, including ototoxicity monitoring (Steyger, 2021b; Watts, 2019). Monitoring the hearing of patients undergoing ototoxic treatment is aimed at the early detection, prevention and treatment of changes in hearing to reduce the functional impact of drug-induced ototoxicity (AAA, 2009; American Speech-Language-Hearing Association [ASHA], 1994; Campbell & Le Prell, 2018; Ganesan et al., 2018; Health Professions Council of South Africa [HPCSA], 2018; Petersen & Rogers, 2015; Prendergast et al., 2020). Ototoxic damage caused to hearing is detected by regular monitoring of a patient's hearing thresholds throughout the course of treatment (WHO, 2021b), typically by comparing hearing thresholds obtained before, during and after treatment (Campbell & Le Prell, 2018; Ganesan et al., 2018; WHO, 2021b). The detection of ototoxic shifts in hearing allows clinicians to adjust treatment regimens, or change treatment to an all-oral regimen, which is less toxic and more effective (Khoza-Shangase & Prodromos, 2021; Lange, Aarnoutse, et al., 2019; Lange, Dheda, et al., 2019; Lanvers-Kaminsky et al., 2017; Van Deun et al., 2020).

The American Academy of Audiology (AAA), the American Speech-Language-Hearing Association (ASHA) and the Health Professions Council of South Africa (HPCSA) have provided guidelines for managers and audiologists to follow when implementing an ototoxicity monitoring programme (OMP) (AAA, 2009; ASHA, 1994; HPCSA, 2018). The essential components of an OMP include the identification of patients at risk for developing ototoxic hearing loss, the timely recording of valid baseline hearing thresholds, monitoring assessments conducted at sufficiently regular intervals to detect changes in hearing and the employment of follow-up assessments to determine the post-treatment effects on hearing (AAA, 2009; ASHA, 1994; HPCSA, 2018). A variety of protocols for ototoxicity monitoring exist; however, their implementation varies (Crundwell et al., 2016). The determination of the presence or absence of ototoxicity depends on the test selected for ototoxicity monitoring and the parameters of its use (Campbell & Le Prell, 2018; Watts, 2019). The basic test battery for detecting ototoxic hearing loss includes the use of conventional pure tone audiometry, where air conduction hearing thresholds of the frequencies 0.25–8 kHz are assessed (Campbell & Le Prell, 2018). Conventional audiometry is the most commonly used assessment

procedure for ototoxicity monitoring (Ganesan et al., 2018). Ototoxicity resulting from aminoglycoside and platinum-based drug use follows a well-established pattern of outer hair cell damage, from the basal to the apical region of the cochlea, initially causing high frequency hearing loss, progressing to the lower frequency ranges of hearing (Campbell & Le Prell, 2018). As a result, extended high-frequency (EHF) audiometry, which involves the assessment of air conduction hearing thresholds of the frequencies beyond those included in conventional audiometry, 9–16 kHz, and which is considered the most sensitive behavioural method for detecting early cochlear outer hair cell damage (Campbell & Le Prell, 2018; Harris, Peer, et al., 2012), is recommended by national and international guidelines for ototoxicity monitoring (AAA, 2009; ASHA, 1994; HPCSA, 2018). However, there is considerable variation in the assessment procedures recommended for ototoxicity monitoring and their clinical implementation (Ganesan et al., 2018).

Even though the recommendation for the use of EHF audiometry is well established (AAA, 2009; ASHA, 1994; HPCSA, 2018), it is still not routinely used for ototoxicity monitoring (Blankenship et al., 2021; Ganesan et al., 2018). In South Africa, it is common practice for OMPs to use conventional audiometry predominantly when conducting ototoxicity monitoring (Govender & Paken, 2015; Khoza-Shangase & Masondo, 2021). The lack of routine EHF audiometry use has been attributed to, amongst others, time constraints and limited audiological resources (Blankenship et al., 2021; Campbell & Le Prell, 2018). A key limitation of EHF audiometry is that it may not be practical because the assessment requires more time to conduct than conventional audiometry (Ganesan et al., 2018). Patients who are administered ototoxic drugs are often ill and fatigued and completing valid behavioural testing may be difficult and time consuming for them (Ganesan et al., 2018; Rieke et al., 2017). Furthermore, several additional challenges are faced when using EHF audiometry in a clinical setting. These challenges Include the possibility of absent hearing thresholds in the EHF range of hearing, maximum output limitations of equipment and interference from artefacts when reaching the maximum output limits of the equipment, and the choice of which EHFs to include in the assessment (Prendergast et al., 2020; Wang et al.,2021). In addition, audiology clinics in the private health care sector may, in some instances, not receive medical insurance reimbursement for the inclusion of EHFs in

diagnostic audiological evaluations. The lack of reimbursement may exacerbate the clinical time-cost burden for the use of EHF audiometry, the outcome of which may not result in treatment regimen modification or mitigate further ototoxic hearing loss.

Ototoxicity monitoring using the most sensitive methods for detecting ototoxic damage is important to minimise the severity of ototoxic hearing loss (Ganesan et al., 2018). For patients to qualify for substitution of non-ototoxic drugs, such as bedaquiline, many DRTB treatment programmes require evidence of treatment-related hearing loss (Hong et al., 2018). Furthermore, the inclusion of amikacin in the latest WHO treatment guidelines (WHO, 2020c) and the continued use of aminoglycosides for the treatment of DRTB in some countries means that ototoxicity monitoring will remain an integral part of DRTB treatment (Hong et al., 2018).

1.4 Novel approaches to ototoxicity monitoring in South Africa

Challenges to the delivery of hearing health care services, including OMPs, are pervasive and include access to care, a lack of trained hearing health care workers and a lack of resources to conduct serial monitoring (Dillard et al., 2021; Khoza-Shangase & Masondo, 2021; WHO, 2021b). There is a critical global shortage of hearing health care workers, particularly in low- and middle-income countries (WHO, 2021b). In the WHO Africa region, 78% of countries have fewer than one audiologist per 1 million people (WHO, 2021b). Task-sharing has been proposed to address the gaps in the hearing health care workforce with the aim of increasing access to high-quality hearing health care services (O'Donovan et al., 2019; WHO, 2021b). Task-sharing involves the appropriate reallocation of tasks traditionally performed by highly qualified ear and hearing care workers to non-specialist workers, with shorter training and fewer qualifications, such as community health workers (CHWs) (WHO, 2021b). CHWs include a variety of community health aides who are trained and working in their own communities (WHO, 2007). The South African DOH has recognised the need to train CHW in the field of rehabilitation, and in 2012 existing CHW were given additional training to address the needs of people with disabilities, including hearing loss, in two underserved communities in the Western Cape (Gamiet & Rowe, 2019).

The challenges facing the delivery of hearing health care have been overcome in many parts of the world by adopting public health strategies (WHO, 2021b). The WHO has identified community-based services in the context of primary health care as a comprehensive framework for addressing the needs of people with hearing loss (Gamiet & Rowe, 2019; WHO, 2021b). Advances in technology allowing for boothless assessment of hearing using portable audiometers and automated EHF audiometry have enabled the assessment of patients in decentralised settings, with limited training and resources (WHO, 2021b). Concerns regarding the high incidence of ototoxicity associated with aminoglycoside DRTB treatment and the challenges facing widespread ototoxicity monitoring, have led the South African government to implement decentralised community-based ototoxicity monitoring facilitated by CHWs (Gamiet & Rowe, 2019; Leavitt et al., 2021; Ramma, Nhokwara, et al., 2019; WHO, 2021b). The use of CHWs, supported by innovative technologies, has demonstrated improved access to ear and hearing care services (Bright et al., 2019; Eksteen et al., 2019; O'Donovan et al., 2019) and, together with a public health approach can help to address the limited human resources available for ototoxicity monitoring (WHO, 2021b).

The COVID-19 pandemic has presented another major challenge to health care delivery and has had an extremely negative impact on the provision of and access to TB services for patients globally (Migliori et al., 2021; WHO, 2020d; WHO, 2021b). This has served to exacerbate the existing difficulties in treating TB and monitoring associated ototoxicity. The reallocation of human, financial and other resources from TB to the COVID-19 response has had a detrimental impact on essential TB services (WHO, 2020b). WHO guidelines promote the establishment of community-based TB services delivered primarliy by CHWs, and in the context of the COVID-19 pandemic such programmes may mitigate the addtitonal strain on health services and the delivery of essential TB services (WHO, 2020a; WHO, 2020b; WHO, 2021a).

1.5 Study Rationale

When ototoxic injectable medications are used in DRTB treatment, ototoxicity monitoring is essential to avoid long-term effects on hearing (Wrohan et al., 2021). Evaluating the effectiveness and quality of ototoxicity monitoring services is of paramount importance (HPCSA, 2018). To our knowledge, this is the first study to report on ototoxicity monitoring for DRTB conducted by CHWs in a decentralised community-based model of care for increased patient access. Therefore, this study aimed to describe the service delivery practices of a community-based OMP for DRTB, including a comparison of the facilitation of ototoxicity monitoring by CHWs and by PHC audiologists. The practices of this real-world community-based OMP were evaluated against the national and international guidelines for ototoxicity monitoring and to the OMP protocol to identify successes and pitfalls, with the objective of improving services and guiding future OMP implementations. Furthermore, this study aimed to provide important additional information on service delivery models implementing task-sharing practices in communities, as recommended by the WHO (WHO, 2021b). In addition, the study aimed to describe the ototoxicity observed in a DRTB patient population. To our knowledge, this is the first study to report on observed treatment effects for DRTB over time, with ototoxicity monitoring conducted by CHWs, in a decentralised community-based model of care for increased patient access.

Owing to the limited use of EHF audiometry and the use of different criteria to define ototoxicity, the prevalence of aminoglycoside-induced hearing loss and the value of EHF audiometry in identifying early changes in hearing remains unclear (Ganesan et al., 2018; Steyger, 2021a). Very few studies have reported on the use of EHF audiometry (Appana et al., 2016; Ghafari et al., 2020; Hong et al., 2020a) as the monitoring procedure for DRTB ototoxicity. In instances where EHF audiometry has been used for ototoxicity monitoring of DRTB patients, a high prevalence of ototoxic hearing loss (74% to 100%) has been reported (Appana et al., 2016; Ghafari et al., 2020; Hong et al., 2020a). However, additional insights into cochleotoxicity and the use of EHF audiometry can be supported by widespread ototoxicity monitoring with improved, objective data-driven measures of hearing loss using EHF audiometry (Steyger, 2021a, 2021b). Therefore, this study also aimed to describe the longitudinal

monitoring of ototoxicity with EHF audiometry in DRTB patients receiving aminoglycoside treatment in order to determine the value of EHF audiometry in identifying early changes in hearing.

1.6 Research project

This research project consisted of three original studies that focused on community-based ototoxicity monitoring with EHF audiometry and CHWs for DRTB. These three studies aimed to add to the scant body of knowledge on decentralised ototoxicity monitoring facilitated by non-specialist personnel and the treatment effects of DRTB on hearing as well as the value of EHF audiometry in ototoxicity monitoring to detect early changes in hearing.

Study I described the service delivery practices of a decentralised, community-based OMP for DRTB, including a comparison of ototoxicity monitoring facilitated by CHWs and by PHC audiologists. The service delivery practices of the OMP were evaluated against the national and international guidelines for ototoxicity monitoring and the OMP protocol.

Study II reported on the service delivery characteristics of a decentralised, community-based OMP for patients with DRTB, facilitated by CHWs and PHC audiologists using conventional audiometry (0.25–8 kHz) for ototoxicity monitoring. In addition, this study described the ototoxic hearing loss observed in DRTB patients over time.

Study III described the longitudinal monitoring of ototoxicity with EHF audiometry in patients receiving aminoglycoside treatment for DRTB to determine the value of EHF audiometry in detecting early changes in hearing.

Chapter 2 describes the methodology followed for each study. Chapters 3 to 5 are the three manuscripts either published, accepted or submitted for publication in peer-reviewed journals. Finally, Chapter 6 discusses the results, conclusions and clinical implications of the three studies making up this research project.

CHAPTER 2: METHODOLOGY

The aim of this chapter is to outline the research objectives, design, participants, equipment and materials used in this research project. The chapter highlights the research procedures, statistical analyses and data processing conducted. The ethical considerations adhered to are described.

2.1 Research objectives and design

2.1.1 Research objectives

The main aim of this research project was to describe the service delivery practices of a decentralised, community-based OMP for DRTB facilitated by CHWs in the Western Cape, and to describe the treatment effects observed in this population longitudinally. In addition, the research project investigated ototoxicity monitoring for DRTB patients with EHF audiometry to determine the value of EHF audiometry in detecting early changes in hearing. In order to achieve these aims, the research project was divided according to three research objectives, each comprising a study that was submitted as an article to a peer-reviewed journal listed in the Web of Science Master Journal List. The three studies are summarised in Table 2.1 according to the title, research objectives, journal, publication status and corresponding thesis chapter.

Table 2.1 *Summary of Studies I to III: Title, research objectives, journal, publication status and corresponding thesis chapter*

Study	I	II	III
Title	Community-based ototoxicity monitoring for drug-resistant tuberculosis in South Africa: An evaluation study	A longitudinal community-based ototoxicity monitoring programme and treatment effects for drug-resistant tuberculosis treatment, Western Cape	Extended high frequency audiometry for ototoxicity monitoring: A longitudinal evaluation of drug-resistant tuberculosis treatment
Research objectives	To describe the service delivery practices of a community-based OMP for DRTB using conventional and EHF audiometry facilitated by CHWs and PHC audiologists, in terms of: The timing and frequency of ototoxicity monitoring assessments The follow-up rates of the programme The ototoxicity monitoring assessment methods used The OMP data management procedures Comparison of data collected by CHWs and by PHC audiologists Comparison of the OMP service delivery practices with international and national recommended guidelines for ototoxicity monitoring and the OMP protocol	To describe the longitudinal DRTB treatment effects on the hearing of patients enrolled in a community-based OMP using conventional audiometry. The service delivery practices of the OMP facilitated by CHWs and PHC audiologists are described in terms of: The frequency, timing and follow-up rates of ototoxicity monitoring assessments, with comparisons between CHWs and PHC audiologists To describe the ototoxicity observed in this population according to: The prevalence of pre-existing hearing loss before the initiation of DRTB treatment Hearing threshold and pure tone average (PTA) deterioration, and the prevalence of ototoxic shifts in hearing following DRTB treatment The severity of ototoxic hearing loss following DRTB treatment The predictors of ototoxic hearing loss for DRTB treatment	To describe the longitudinal monitoring of ototoxicity in DRTB patients receiving aminoglycoside treatment with EHF audiometry, in terms of: The prevalence of pre-existing hearing loss before the initiation of DRTB treatment with comparison between conventional and EHF audiometry The ototoxicity observed, including hearing threshold and PTA deterioration and the prevalence of ototoxic shifts in hearing following DRTB treatment with comparison between conventional and EHF audiometry The occurrence of absent EHF hearing thresholds owing to maximum audiometer output limits
Journal	International Journal of Environmental Research and Public Health	South African Journal of Communication Disorders	American Journal of Audiology
Publication status	Published	Published	In review
Thesis chapter	3	4	5

2.1.2 Research design

Studies I, II and III involved a retrospective record review using a longitudinal, non-experimental, comparative, descriptive research design and quantitative data (Brink et al., 2018; Kumar, 2019; Leedy & Ormrod, 2020; Manchaiah et al., 2022). The researcher collected data without introducing changes to the setting or variables so that phenomena could be observed in order to explore and explain relationships between variables (Brink et al., 2018). Data were collected from the same sample of patients, at different points in time and in this way comparisons of changes over time could be made (Brink et al., 2018; Manchaiah et al., 2022). A descriptive design was used to gather information from a representative sample of the population, with the emphasis of data collection on structured observation to describe a phenomenon (Brink et al., 2018). Variables were compared to describe differences between two or more groups to determine if and how they differed (Brink et al., 2018).

With the aim of gathering information to guide future OMP implementations, **Study I** described the service delivery practices of a decentralised community-based OMP according to the research objectives listed in Table 2.1. Comparisons were made between patients assessed by CHWs and those assessed by PHC audiologists, and the study findings were compared to and evaluated against the OMP protocol and the international and national guideline recommendations for ototoxicity monitoring.

Study II described the service delivery practices of an OMP facilitated by CHWs, and the ototoxicity observed in DRTB patients over time when conventional audiometry was used as the assessment method, according to the research objectives indicated in Table 2.1. Comparisons were made between patients assessed by CHWs and by PHC audiologists and between hearing thresholds and PTAs at the time of the initial and the exit assessments. In addition, a correlational research design was used to identify and describe existing relationships between variables to determine the relationship between the independent and dependent variables (Brink et al., 2018) and to determine the predictors of hearing loss.

Study III described the longitudinal monitoring of ototoxicity with EHF audiometry in patients receiving aminoglycoside treatment for DRTB to determine the value of EHF

audiometry in detecting early changes in hearing. In order to describe the ototoxicity observed in DRTB patients following treatment, comparisons were made between hearing thresholds and PTAs at the time of the initial and the exit assessments, and between the ototoxicity observed when conventional and EHF ranges were considered.

2.2 Research context

All three studies were conducted in the City of Cape Town and involved a retrospective record review using data collected at 19 PHC clinics and community health centres where a community-based OMP utilising conventional and EHF audiometry has been in existence since between May and July 2013. All the studies used data collected at decentralised community-based clinics in two sub-districts of the City of Cape Town, namely the Mitchells Plain/Klipfontein and the Western/Southern sub-districts. In 2012, the Western Cape Department of Health, in collaboration with the University of Cape Town, initiated a pilot project in which 30 CHWs underwent a yearlong certificate training programme to become members of the PHC team (Clark, 2015; Gamiet & Rowe, 2019). The CHW were provided with skills and knowledge in community-based rehabilitation to support people with disabilities in two underserved communities in the Western Cape (Gamiet & Rowe, 2019). To facilitate ototoxicity monitoring for DRTB in a community-based setting, six CHWs received additional training from the PHC audiologist responsible for the Mitchells Plain/Klipfontein sub-district. The six CHWs were also trained to conduct home-based hearing screening and hearing screening of school aged children and patients attending a PHC clinic. The Mitchells Plain/Klipfontein and the Western/Southern sub-districts were selected for inclusion in this study because both the upskilled CHW and the PHC audiologists were the testers in these areas. The City of Cape Town district is administered by both local and provincial authorities, where PHC clinics are managed mostly by the City of Cape Town, and community health centres by the provincial government, the Western Cape Department of Health.

2.3 Ethical considerations

Studies I to III were conducted according to the guidelines of the Declaration of Helsinki and were approved by the Institutional Review Board (or Ethics Committee) of the University of Pretoria (GW20161128HS; 63/2017), the City of Cape Town (7788) and the Western Cape Department of Health (WC_2017RP22_896) (Appendices A to E). Owing to the retrospective nature of this study, consent to access the existing data collection forms on behalf of patients was granted by the Western Cape Department of Health and the City of Cape Town Health Department. Data collection forms contained patients' audiological data and medical history, including HIV status, DRTB medication/s, comorbidities and adverse audiological effects. Medical history information was obtained from patients' medical records in a clinic file and/or verbally reported to the CHWs and PHC audiologists during the patient interview and then recorded on data collection forms. The research project was initiated and conducted within the framework of the ethical principles set out in "Ethics in Health Research: Principles, Processes and Structures – 2015" (DOH, 2015), which was developed in accordance with a mandate by section 72 of the National Health Act 61 of 2003 (Republic of South Africa, 2004). This document contains the national policy and guidelines for conducting health research responsibly and ethically, specific to the South African context. The core ethical principles and human rights related to health research are listed and their application to the studies is discussed in Table 2.2.

Table 2.2 *Ethical principles and human rights applied to the research design, patient selection, recruitment procedures, data collection and analysis procedures for Studies I to III (Brink et al., 2018; DOH, 2015)*

Ethical Principle	Definition	Application to Studies I to III
Beneficence and non-maleficence	The researcher needs to secure the patients' well-being. The risks imposed by the research must be reasonable considering the anticipated benefits and the research should seek to improve the human condition.	• There were no medical risks associated with the procedures of these studies and no physical harm came to patients. • As the data were collected retrospectively, patients and health care workers were not unduly inconvenienced. • The findings of the research project were intended to increase knowledge of the health care practices for ototoxicity monitoring for DRTB patients. The research project intended to benefit health care delivery to the public by suggesting improvements for ototoxicity monitoring practices for patients receiving ototoxic medication.
Distributive justice (equality)	Recruitment, selection, inclusion and exclusion of patients must be based on sound scientific and ethical principles. No patient should be unfairly excluded or targeted for the research.	• All patients with DRTB enrolled in the OMP between 2013 and 2017 were included in the research project and were selected for reasons directly related to the project. • The aim of the research project was that patients with DRTB administered ototoxic medication would benefit from the findings, if not immediately then in the future. No segment of the population was denied the knowledge derived from this research as the findings were published on a public platform and made known to all the key role players involved in the research.
Dignity and autonomy	Patients must be treated with respect, be allowed to exercise self-determination, and be allowed to deliberate and act on a decision (autonomy). The researcher must respect the participants' right to	• No data collection commenced prior to approval from the Research Ethics Committee of the Faculty of Humanities of the University of Pretoria, the Western Cape Department of Health and the City of Cape Town (CoCT).

	privacy, anonymity, confidentiality, well-being and dignity. The welfare and safety of the researcher must be considered, including authorship and intellectual property interests.	• The researcher (the PhD candidate) and contributors (the PhD supervisor, co-supervisor and statistician) took measures to ensure the privacy and confidentiality of the patients throughout the research process and when disseminating the findings. All patients were given an individual number code which appeared on all data collected and stored and no other identifiable information was noted. The master copy of patient names and the allocated codes was available to the researcher and contributors only and was stored in password protected software. Data from the project could not be linked to individual patients and no unauthorised persons could gain access to the data. • There were no medical risks associated with the procedures of this project and no physical harm came to the patients. There was no financial gain for the patients, researcher or contributors. • Findings were reported in the public sphere in an open and timely fashion, allowing for public and peer review. • The contributors to the project were duly noted as co-authors. • Respect was shown for the organisational culture and reputation, and the dignity, well-being and safety of the patients, researcher and contributors was the main concern of the researcher.
Relevance and value	The research project will contain the expected contribution of knowledge and of how the findings may be translated into interventions, services and processes that will improve access to, and the quality of hearing health care.	• The aim of the findings was to determine the successes and pitfalls of a decentralised, community-based OMP facilitated by CHWs to improve service delivery and act as a guide for widespread implementation. • The treatment effects of DRTB on hearing thresholds using conventional and EHF audiometry were reported on to obtain

		epidemiological statistical data to gain further insight into aminoglycoside-induced ototoxicity. • The value of EHF audiometry in detecting early changes in hearing was reported on. • The findings of the research project were translated into suggestions to improve ototoxicity monitoring services.
Scientific integrity	Research design and methodology are vital to research integrity and are likely to result in reliable and valid data outcomes that address the research objectives. Thus, the research design must be sound, and the researcher must be competent to conduct the research.	• Ethical clearance for the research design and methodology was obtained from the Faculty of Humanities of the University of Pretoria, the Western Cape Department of Health and the CoCT prior to the commencement of this research project. • The researchers' competence is evidenced by previous academic education and qualifications, HPCSA certification, work experience and publications. Mandatory continuous professional development includes training in ethics. The researcher was accurate and honest when conducting and reporting the research, and resources were managed in an effective, efficient and economical manner. • The researcher disseminated the findings to the scientific community as well as the key role players in a timely, accessible, responsible and competent manner. • The interests of the researcher and contributors were considered, including welfare and safety interests, authorship and intellectual property interests, and collegial and professional interests.
Role player engagement	Researchers will engage the key role players throughout the process of planning and conducting the research to improve the quality of the research, to increase acceptability of the key role players and to harness expertise.	• PHC audiologists and managers engaged in the OMP were active partners in the planning and execution of the research project and were kept abreast of the research process. • The researcher disseminated the findings to the key role players in a timely, accessible, responsible and competent manner.

2.4 Research participants

All patients with DRTB who were enrolled in the OMP between May 2013 and September 2017 were included as participants in Studies I to III. The research sample for these studies was representative of the population from which it was selected, as it included a large number of patients of various ages and both genders, from 19 PHC clinics and community health centres in several locations across the City of Cape Town (Brink et al., 2018). Male and female patients with normal hearing or any degree of hearing loss at the time of the initial assessment were included in Studies I to III. It was estimated that there would be 500 patients with DRTB accessing the OMP services. The sampling method used to select the patients for each of the three studies is described below:

- **Study I:** Non-probability quota sampling (Brink et al., 2018; Leedy & Ormrod, 2020) was used to select all patients with DRTB enrolled in the OMP from date of programme inception to date of data collection commencement (2013 to 2017) for inclusion in this study.

- **Study II:** Using non-probability purposive sampling (Brink et al., 2018; Leedy & Ormrod, 2020), all patients with DRTB enrolled in the OMP from date of programme inception to date of data collection commencement (2013 to 2017) and meeting certain selection criteria were considered for inclusion in this study. Study II included patients from Study I who met the following selection criteria: patients who received kanamycin; patients whose hearing was assessed using conventional audiometry (0.25–8 kHz); patients who had an initial assessment conducted before, on the same day, or within two weeks of initiation of medication; patients who had one or more follow-up monitoring assessments conducted after the initial assessment.

- **Study III:** Using non-probability purposive sampling (Brink et al., 2018; Leedy & Ormrod, 2020) all patients with DRTB enrolled in the OMP from date of programme inception to date of data collection commencement (2013 to 2017) and meeting certain selection criteria were considered for inclusion in this study. Study III included patients from Study I who met the following selection criteria:

patients whose hearing was assessed using conventional (0.25–8 kHz) and EHF (9–16 kHz) audiometry; patients who had one or more follow-up monitoring assessments conducted after the initial assessment; and conventional (0.25–8 kHz) and EHF (9–16 kHz) audiometry was used for both the initial and exit assessments.

2.5 Research equipment

The following equipment was used for the purpose of conducting ototoxicity monitoring assessments for Studies I to III of the research project:

2.5.1 Otoscopy

Otoscopy was conducted by CHWs and PHC audiologists using the Heine mini 3000 otoscope with reusable speculae (Heine, Germany). This compact pocket otoscope with direct illumination was used to visually inspect the external ear canal and the tympanic membrane.

2.5.2 Conventional and EHF audiometry

The KUDUwave audiometer (eMoyo, Johannesburg, South Africa) was used by CHWs and PHC audiologists without a soundproof booth to obtain the hearing thresholds of DRTB patients attending serial ototoxicity monitoring assessments. The KUDUwave audiometer is a portable, computer-based (Dell laptop) clinical diagnostic audiometer with integrated supra-aural ear-cup and insert earphone headset for additional attenuation (Type II clinical audiometer in accordance with EN60645-1 and ANSI S3.6). An electronic patient-response button is connected to the headset software interface that controls the KUDUwave audiometer. The audiometer consists of automated (using Hughson and Westlake methodology ISO 8253-1, automatic standard ascending and shortened and standard bracketing) and manual programs able to conduct audiometry from 0.25–16 kHz. Four built-in SPL meters monitor environmental noise via the headset (Ambi-dome^{TM}) to ensure compliant background noise levels during testing. Audiometers were calibrated in a laboratory at 23 degrees Celsius to the following standards: ANSI S3.6 1996, EN60645-, EN60645-2, SABS

0154-1 and SABS 0154-2. Otoscopic and audiometric results were recorded by CHWs and PHC audiologists on paper data collection forms (Appendix F)

2.6 Data collection procedures: Studies I to III

For Studies I to III, structured observation was used as the descriptive data collection technique (Brink et al., 2018). Structured observation entails specifying in advance the behaviours or events to be observed, as outlined in the research objectives of this research project, as well as preparing forms for record keeping (Brink et al., 2018). Retrospective data encompassing existing paper data collection forms for each patient enrolled in the OMP were collected by the researcher from the managing PHC audiologist in each sub-district for analysis, and returned upon completion of the studies. The paper data collection forms acted as the data collection instrument for this research project. Existing records offer a rich source of data, serving as an economical source of information while permitting the examination of trends over time and eliminating the need for patient co-operation (Brink et al., 2018). However, a retrospective record review may be open to many sources of errors, such as facts being omitted and erratic record-keeping, with some data not being available because of patient confidentiality (Brink et al., 2018).

At the time of data collection (2013 to 2017), the official South African ototoxicity monitoring guidelines had not yet been published, thus OMP managers relied on adaptations of the international guidelines of the ASHA (1994) and the AAA (2009) when developing the OMP protocol. An unpublished draft of the Health Professions Council of South Africa's (HPCSA) ototoxicity monitoring guidelines (HPCSA, 2018) was, however, available to the OMP developers to assist them in applying the international guidelines to the South African context.

Patient interviews and ototoxicity monitoring assessments were conducted by six CHWs and two PHC audiologists who acted as the data collectors for the research project, at 19 PHC clinics and community health centres in the two sub-districts in which the OMP was active. Patients visited a PHC clinic or community health centre daily for the first six months of DRTB treatment to receive their medication from a nurse. After the initial six-month treatment period, medication was continued for 18

months with patients visiting a clinic weekly to obtain their medication, and monthly to consult with the managing doctor. CHWs and PHC audiologists travelled to the clinics situated in each sub-district with portable audiological equipment (KUDUwave audiometer and otoscope). The clinic provided a quiet room in which patient interviews and audiological assessments took place. All patients receiving ototoxic medication for treatment of DRTB were identified and referred by their managing doctor and included in the OMP as part of the package of care. The protocol followed by the OMP at the time of data collection was as follows:

2.6.1 Patient interviews and otoscopy

At the time of a patient's initial assessment, identifying information including the patient's name, date of birth, gender and medical history pertaining to HIV status, DRTB medication/s, comorbidities and adverse audiological effects were recorded manually on a data collection form by CHWs and PHC audiologists. This information was obtained from the patient's medical records in a clinic file and/or verbally reported to the CHWs and PHC audiologists during the patient interview. A bilateral otoscopic examination was conducted as part of the initial assessment and each monitoring assessment, and the findings were recorded on the data collection form. If pathology was suspected, the patient was referred to the managing doctor or nurse for appropriate treatment in addition to audiometry, as per the OMP protocol.

2.6.2 Conventional and EHF audiometry and the determination of ototoxicity

Initial and ototoxicity monitoring assessments included bilateral conventional audiometry (0.25–8 kHz) or conventional audiometry and EHF audiometry (9–16 kHz) using the KUDUwave audiometer. The patient was seated in a safe and comfortable manner which promoted validity of testing by avoiding visual cues, but maintaining easy observation of patient responses to stimuli (ASHA, 2005). Prior to the start of the audiometric assessment, patients were given instructions in their own language as far as possible. Additional instructions may have been provided to enhance understanding, such as gestures, and demonstrations indicating that patients should press the response button every time a tone was heard. The combined supra-aural

ear-cup and insert earphone headset were placed over the patient's ears; with insert earphones comfortably deep in the ear canal in accordance with the manufacturer's recommendations, and the supra-aural ear-cups directly over the entrance of the ear canal (ASHA, 2005). The equipment required to conduct both conventional and EHF audiometry became available in November 2015 at the Southern/Western sub-district and in July 2016 at the Mitchell's Plain/Klipfontein sub-district; prior to this, only conventional audiometry was available for ototoxicity monitoring. Typically, an automatic mode of threshold determination would have been used, however, manual testing may have been selected by PHC audiologists in some instances.

Pure tone or warble tones were used. The better ear, when known, was tested first. The initial test frequency would typically have been 1 kHz, followed by 2, 3, 4, 6 and 8 kHz for conventional audiometry and 9, 11.2, 12.5, 14 and 16 kHz included for EHF audiometry, followed by a retest of 1 kHz before testing 0.5 and 0.25 kHz for conventional and EHF audiometry. A hearing threshold was recorded if the patient's response was judged to be clinically reliable for at least two responses out of three presentations at the single softest intensity at each frequency in each ear (ASHA, 2005). Manual or automatic air conduction masking was applied if the difference in the air conduction thresholds of the test and non-test ear was 40 dB HL or more (ASHA, 2005; HPCSA, 2018). Initial assessments were conducted at the clinics within two weeks of DRTB treatment initiation, while monitoring audiograms were conducted once a month during the initial six-month treatment regimen. Monitoring audiograms were then conducted at three, six and 18 months post the initial six-month treatment period.

The presence of an ototoxic shift was determined using the criteria developed by ASHA (1994), where a change in hearing thresholds was determined relative to the hearing thresholds obtained during the initial assessment. The criteria to indicate hearing decrease for ototoxicity monitoring were defined as: ≥ 20 dB HL pure tone threshold decrease at any one test frequency; ≥ 10 dB HL pure tone threshold decrease at any two adjacent test frequencies; no response at three consecutive test frequencies where pure tone threshold responses were previously obtained. Changes were confirmed by repeat testing.

When an ototoxic shift meeting the predetermined criteria (ASHA, 1994) was evident, the managing doctor was informed immediately. Monitoring audiograms were then conducted every two weeks until no change in hearing thresholds was observed. Monitoring audiograms were conducted at three, six and 18 months post the initial six-month treatment course. A nurse managing the ototoxicity monitoring appointment dates contacted patients either telephonically or at the patients' home if they did not return for scheduled ototoxicity monitoring assessments. Patients' descriptive and audiological data were recorded on a paper data collection form which was then stored in the patient's clinic file, with the CHW or the PHC audiologist and the managing PHC audiologist responsible for each sub-district. This would thus conclude the data management protocol.

2.6.3 Data collection forms

Each patient's descriptive and audiological data were recorded manually by the CHWs and PHC audiologists on paper data collection forms and stored in the patient's clinic file. A copy of each patient's data collection form was kept with the CHWs and PHC audiologists and regularly made available to the managing PHC audiologist responsible for each sub-district for review. Upon completion of a patient's DRTB treatment and ototoxicity monitoring, the form was stored permanently with the PHC audiologist responsible for each sub-district. The paper data collection forms for each patient enrolled in the OMP were collected by the researcher from the managing PHC audiologist in each sub-district for analysis and returned upon completion of the studies.

2.7 Data processing and analysis procedures

The research project was divided into three separate studies, each with their own data processing and analysis procedures. For Studies I to III anonymised quantitative data from paper data collection forms were processed and manually recorded by the researcher into Excel spreadsheets to organise the data. Data were then imported from Excel into Statistical Package for Social Sciences (SPSS, IBM Corp. Armonk, NY, USA) software (version 27) by a qualified statistician who assisted with statistical analysis. Data cleaning was performed where data, such as dates, which had been

captured incorrectly by the data collectors (the CHWs and PHC audiologists) and/or the researcher were corrected so that they were uniform in format. In cases where data were accidentally not captured by the researcher, the data collection forms were re-examined to supplement any missing data.

Descriptive statistics were used to present, summarise and interpret the data so that they were meaningful (Brink et al., 2018). Descriptive statistics used in Studies I to III included the following: frequency distributions indicating the number of times a result occurred; weighted arithmetic mean; measures of central tendency indicating the most typical or average result in a distribution; measures of variability indicating the amount of dispersion in the dataset; and measures of relationships indicating the correlation between variables (Brink et al., 2018; Leedy & Ormrod, 2020). To describe the patient sample, frequencies and cross-tabulations were compiled to visually display nominal data and the relationships between data.

Inferential statistics were used in Studies I to III to make inferences about the study population from a smaller sample, and assisted the researcher in determining whether a difference between two groups was genuine or by chance (Brink et al., 2018). P-values, indicating the probability that the outcome was due to chance, were used to communicate the significance, or non-significance of differences (Brink et al., 2018). The inferential statistical parametric procedures used for Studies I to III included the following: the two proportions z-test, regression models and the Nagelkerke R^2 test. In Studies II and III, the data differed significantly from normality (Shapiro-Wilk p-values <0.05) and therefore, nonparametric statistical procedures, where no assumptions were made regarding the normal distribution of the targeted population, were used (Brink et al., 2018; Field, 2018). The nonparametric statistical procedures used were the Mann-Whitney U and the Wilcoxon signed-rank (W) tests. For inferential statistics, a 5% level of significance was used throughout the research project.

2.7.1 Study I: Community-based ototoxicity monitoring for drug-resistant tuberculosis in South Africa: An evaluation study

Descriptive statistics were used to determine the following:

- The number of patients included in the OMP.

- The number of patients assessed by CHWs and PHC audiologists and the number of patients assessed using conventional and EHF audiometry.
- Patient variables, including age, gender, treatment regimen, treatment duration, risk factors for ototoxicity, audiological symptoms and the presence of wax impaction.
- Mean and standard deviation for patient age, treatment duration, the timing of the initial ototoxicity monitoring assessments in relation to treatment initiation, the number of monitoring assessments attended by patients and days elapsing between assessments.
- The timing and frequency of ototoxicity monitoring assessments attended by patients including follow-up rates, number of assessments attended by patients and days elapsing between assessments.

The following inferential statistical procedures were applied:

- The two proportions z-test was used to determine whether two proportions of two groups (patients who were assigned a follow-up return date and those who were not) differed significantly on one characteristic, the follow-up return rate.
- A multivariate logistic regression model is an equation where two or more independent variables are used to predict the dependent variable. A multivariate logistic regression model was built to determine the effect of gender, age, HIV status and treatment duration on whether patients would follow-up after the initial assessment or not, a dichotomous dependent variable (Leedy & Ormrod, 2020).
- The Nagelkerke R^2 was used to determine the percentage of variation of the dependent variable which was explained by the predictors (age, gender, treatment duration and HIV status).

2.7.2 Study II: A longitudinal community-based ototoxicity monitoring programme and treatment effects for drug-resistant tuberculosis treatment, Western Cape

Descriptive statistics were used to determine the following:

- The number of patients who met the participant selection criteria for inclusion in the study.
- The number of patients assessed by CHWs and PHC audiologists.
- Patient variables, including age, gender, treatment regimen, treatment duration, risk factors for ototoxicity and audiological symptoms.
- Mean and standard deviation for patient age, treatment duration, the timing of the initial ototoxicity monitoring assessments in relation to treatment initiation, the number of monitoring assessments attended by patients and days elapsing between assessments.
- The timing and frequency of ototoxicity monitoring assessments attended by patients including follow-up rates, number of assessments attended by patients and days elapsing between assessments.
- The number of patients presenting with a pre-existing hearing loss (ASHA, 2021, 2022; Stach & Ramachandran, 2017).
- The number of patients presenting with hearing loss meeting any category of hearing loss severity (Olusanya et al., 2019; WHO, 2021b) and the number of patients presenting with an ototoxic shift meeting one or more of the ASHA criteria (ASHA, 1994).

The following inferential statistical procedures were applied:

- The Wilcoxon signed-rank (*W*) test, an alternative to the dependent form of the t-test, is used to compare the medians of two correlated variables when the data are ordinal rather than interval in nature (Leedy & Ormrod, 2020). This test was used to compare significant differences between dependent groups (hearing thresholds and PTAs at the time of the initial and exit assessments).
- The Wilcoxon signed-rank (*W*) test was also used to determine whether there were significant differences in hearing threshold and PTA deteriorations and the presence of ototoxic shift meeting the ASHA (1994) criteria between the left and right ears.
- The Mann-Whitney U test, an alternative to the independent form of the t-test, is used to compare the median of two groups when the data are ordinal rather than interval in nature (Leedy & Ormrod, 2020). This test was used to determine

whether there was a difference in the variables (timing of initial assessments and the number of monitoring assessments attended by patients) for independent groups (patients assessed by CHWs and patients assessed by PHC audiologists).

- Regression models examine how accurately one or more variables enable prediction regarding the values of another dependent variable (Leedy & Ormrod, 2020). In order to determine significant predictors for hearing deterioration, quantile regression models, robust to outliers and not requiring the assumptions of normally distributed error terms, were used.

2.7.3 Study III: Extended high frequency audiometry for ototoxicity monitoring: A longitudinal evaluation of drug-resistant tuberculosis treatment

Descriptive statistics were used to determine the following:

- The number of patients who met the participant selection criteria for inclusion in the study.
- Patient variables, including age, gender, treatment regimen, treatment duration, risk factors for ototoxicity, the number of patients assessed by CHWs and PHC audiologists and audiological symptoms.
- Mean and standard deviation for patient age, treatment duration, the timing of the initial ototoxicity monitoring assessments in relation to treatment initiation and the time between initial and exit assessments.
- The number of absent hearing thresholds for pure tone audiometry owing to maximum audiometer output limits across frequencies.
- The number of patients presenting with a hearing loss at the time of the initial and exit assessments (ASHA, 2021; Stach & Ramachandran, 2017).
- The number of patients presenting with an ototoxic shift meeting one or more of the ASHA criteria (ASHA, 1994).

The following inferential statistical procedures were applied:

- The Wilcoxon signed-rank (*W*) test was used to compare significant differences between dependent groups (hearing thresholds and PTAs at the time of the initial and exit assessments).
- The Wilcoxon signed-rank (*W*) test was also used to determine if there were significant differences in hearing threshold and PTA deteriorations and the presence of ototoxic shift meeting the ASHA (1994) criteria between the left and right ears.

CHAPTER 3: COMMUNITY-BASED OTOTOXICITY MONITORING FOR DRUG-RESISTANT TUBERCULOSIS IN SOUTH AFRICA: AN EVALUATION STUDY

Authors: Stevenson, L. J.; Biagio-de Jager, L.; Graham, M. A.; Swanepoel, D.

Journal: International Journal of Environmental Research and Public Health

Accepted: 24 October 2021 (Appendix G)

Publication: 2021, *18*(21), 11342

Note: This chapter was referenced and edited according to the style of this document and may differ from the style of the published study.

3.1 Abstract

In response to the drug-resistant tuberculosis (DRTB) ototoxicity burden in South Africa, ototoxicity monitoring has been decentralised, with community health workers (CHWs) acting as facilitators. This study describes a community-based ototoxicity monitoring programme (OMP) for patients with DRTB. Findings are compared to the recommended guidelines for ototoxicity monitoring, the OMP protocol and published studies. This was a retrospective study of longitudinal ototoxicity monitoring of 831 patients with DRTB, using data collected at community-based clinics in the City of Cape Town between 2013 and 2017. Approximately half (46.8%) of the patients had an initial assessment conducted in accordance with the OMP protocol recommendations, and follow-up rates (79.5%) were higher than those of a similar DRTB programme. However, patients in this study were not monitored within the timeframes or with the regularity recommended by the guidelines or the OMP protocol. Extended high-frequency pure-tone audiometry (27.5%) was underutilised by testers and data recording was inconsistent (e.g. 37.7% of patient gender was not recorded by testers). Community-based OMP using CHWs to facilitate monitoring showed improvement over previous hospital-based reports, with more accessible services and

higher follow-up rates. However, to improve OMP outcomes, OMP managers should reassess current protocols and data recording practices.

Keywords: community-based services; community health workers; decentralised services; drug-resistant tuberculosis; tuberculosis; hearing loss; ototoxicity monitoring; audiometry; South Africa

3.2 Introduction

An estimated 10 million people globally fell ill with tuberculosis (TB) in 2019 and South Africa has been identified as one of the eight countries that make up two-thirds of these cases (World Health Organisation [WHO], 2020a). With an estimated 615 people per 100,000 presenting with TB, compared to the global estimate of 130 cases per 100,000 (WHO, 2020a), South Africa is recognised as one of 30 countries with a high burden of TB (WHO, 2020a). Despite advances in the effective diagnosis and treatment of TB, it is the leading cause of death in the country (WHO, 2015). South Africa is furthermore afflicted by a high incidence of TB/human immunodeficiency virus (HIV) coinfection, with more than half (58%) of new and relapsed patients with TB being reported as HIV positive in 2019 (WHO, 2019; WHO, 2020a).

Tuberculosis that is resistant to first-line anti-TB drugs is known as drug-resistant TB (DRTB), the main types of which are multi-drug-resistant TB (MDRTB), extensive drug-resistant TB (XDRTB) and Rifampicin-resistant TB (RRTB) (Centers for Disease Control and Prevention (CDC), 2012; Western Cape Government Health, 2018). In 2019, half a million people globally developed MDRTB/RRTB, with an estimated 14,000 cases in South Africa (WHO, 2020a). The emergence of drug-resistant strains has complicated TB control; never before have more people globally been affected by MDRTB (Lange, Aarnoutse, et al., 2019), with numbers set to rise in high-burden countries in the coming decades (Lange, Dheda, et al., 2019; Sharma et al., 2017).

Treatment of DRTB is complex and challenging for the patient, health care providers and for the health system (Lange, Aarnoutse, et al., 2019). Historically, patients with DRTB have required prolonged treatment, lasting two years or more (Lange, Dheda, et al., 2019), with the use of toxic second-line aminoglycosides, including Kanamycin

(Bardien et al., 2009; Department Health Republic of South Africa [DOH],2013). Aminoglycosides are often used in developing countries for the treatment of DRTB because they have advantages over other classes of antibiotics and are inexpensive to produce (Meiyan et al., 2017; Xie et al., 2011). Aminoglycosides are known to be toxic to both the vestibular and cochlear structures of the ear and to divisions of the eighth cranial nerve and the connections within the central nervous system (de Jager & van Altena, 2002; Rogers & Petersen, 2011). The effects of cochleotoxicity result in permanent hearing loss (Duggal & Sarkar, 2007; Huth et al., 2011) and/or tinnitus caused by the death of cochlear outer hair cells (Bardien et al., 2009; de Jager & van Altena, 2002; Schacht et al., 2012). Encouragingly, injectable-free, non-aminoglycoside treatment regimens comprising shorter treatment durations with novel and repurposed drugs such as Bedaquiline, are being routinely phased in in South Africa for patients meeting specific eligibility criteria (2018; WHO, 2020b). However, more than half the high-burden TB countries surveyed in 2020 were still using toxic injectable medicines, with 46% of countries reporting the use of Kanamycin and/or Capreomycin in the treatment of DRTB, counter to the most recent World Health Organisation (WHO, Geneva, Switzerland) recommendations (Medicins Sans Frontieres [MSF], 2020). As a result, a significant portion of the TB population may still be affected by aminoglycoside-induced hearing loss (Huth et al., 2011).

Ototoxic hearing loss has a negative impact on an individual's social participation, emotional and behavioural well-being, quality of life, activities of daily living and employment status (Bardien et al., 2009; Rogers & Petersen, 2011). As a result, the monitoring of hearing during DRTB treatment is recommended (American Academy of Audiology [AAA], 2009; American Speech-Language-Hearing Association [ASHA], 1994; Health Professions Council of South Africa [HPCSA], 2018) to ensure that hearing loss is detected early and that appropriate medical and rehabilitative intervention is implemented to mitigate the potential loss and negative effects (Petersen & Rogers, 2015; Ramma, Heinze, et al., 2019). Through the implementation of an audiological ototoxicity monitoring programme (OMP), ototoxicity is determined by comparing pure tone hearing thresholds, ideally obtained prior to the initiation of treatment and known as a baseline assessment, to subsequent hearing threshold monitoring measurements (Duggal & Sarkar, 2007). Weekly to monthly (AAA, 2009;

ASHA, 1994; HPCSA, 2018) monitoring is recommended following the baseline evaluation. A change in hearing thresholds that meets predetermined criteria for the presence of an ototoxic shift may offer medical personnel the opportunity to alter the treatment regimen (Lange, Aarnoutse, et al., 2019; Melchionda et al., 2013). Management strategies can be implemented as soon as a hearing loss is identified to eliminate its negative consequences and to ensure improved outcomes for patients (Lange, Aarnoutse, et al., 2019). Avoiding or minimising ototoxic hearing loss in patients with DRTB requires a combined approach of serial audiological monitoring and a tailored treatment regimen, which remains a significant challenge globally (Melchionda et al., 2013).

The significant burden of DRTB in South Africa has necessitated careful consideration of appropriate strategies for effective ototoxicity monitoring. Strategies that have been implemented include, amongst others, the introduction of new drugs and treatment regimens, the decentralisation of TB and ototoxicity monitoring services, the inclusion of community health workers (CHWs) in the model of care and the supply of audiological ototoxicity monitoring equipment and training. A decentralised model of care has been included as part of national policy for DRTB management to complement the capacity of centralised TB hospitals, to increase access to care and to improve treatment outcomes for patients with DRTB (DOH, 2013; Ndjeka et al., 2020; The South African National Aids Council, 2017). Decentralisation of services allows patients to access DRTB treatment on an outpatient basis at a facility nearest to them, such as a primary healthcare (PHC) or community health clinic, instead of at a centralised TB hospital. Outpatient units have been tasked with initiating and administering treatment, including offering audiological ototoxicity monitoring (DOH, 2013), and monitoring any adverse side effects of the treatment.

With advances in portable audiometric technology, hearing assessments can be conducted at PHC and community level with limited training and resources (WHO, 2021). In response to the high incidence of ototoxic hearing loss in patients with DRTB, South Africa implemented a national ototoxicity prevention programme to improve access to audiological monitoring and to reduce ototoxic hearing loss (WHO, 2021). As part of this programme, training and portable automated audiometers were provided

to selected health facilities, including PHC and community health clinics. This has reduced the waiting time for patients wanting to be assessed and linked to rehabilitative audiological services (WHO, 2021). In order to address the shortage and poor distribution of healthcare workers in resource-constrained settings, the employment of CHWs has been proposed (WHO, 2018). The South African department of health has recognised the need to expand the PHC system by integrating 50,000 CHWs into the public health system between 2019 and 2024 to improve access to services (DOH, 2020). CHW include a variety of community health aides who are trained and working in their own communities (WHO, 2007). CHWs engage in task-sharing that involves the appropriate reallocation of tasks to nonspecialists, such as hearing assessments that are traditionally performed by ear and hearing specialists (WHO, 2021). The use of CHWs, supported by innovative technologies has demonstrated improved access to ear and hearing care services (Duggal & Sarkar, 2007; O'Donovan et al., 2019; Swanepoel, 2020) and, together with a public health approach can offer a solution to the limited human resources available (WHO, 2021).

Despite South African DRTB treatment guidelines recommending that all patients receiving treatment should undergo ototoxicity monitoring (DOH, 2013), historically a lack of OMPs has seen very few patients being monitored (Khoza-Shangase, 2010; Khoza-Shangase & Stirk, 2016). The development of OMPs in South Africa has been hindered by a number of obstacles including a lack of human and material resources necessary for ototoxicity monitoring (Harris et al., 2012; Khoza-Shangase, 2010), poor collaboration amongst healthcare professionals treating patients, and patient-related barriers such as a lack of awareness of treatment side effects and difficulties travelling to ototoxicity monitoring service locations (Khoza-Shangase & Masondo, 2021). Up until 2018, when the official South African guidelines for ototoxicity monitoring were introduced (HPCSA, 2018), international guidelines (AAA, 2009; ASHA, 1994) were modified by health care providers to suit the South African context, leading to considerable variation in their application (Govender & Paken, 2015). Recent reports indicate, however, that where OMPs do exist, the assessment and management practices of audiologists of patients on ototoxic medication do not align with guideline recommendations (Khoza-Shangase & Masondo, 2020) and that outpatient-based ototoxicity monitoring services are underused by patients (Ramma, Nhokwara, et al.,

2019). The COVID-19 pandemic has exacerbated the challenges of treating TB and the monitoring of associated ototoxicity because of the extra burden on health care services, care seeking behaviour and the reallocation of human, financial and other resources from TB to COVID-19 care (WHO, 2020a).

Monitoring the effectiveness of ototoxicity monitoring services and reporting on the practices of existing OMPs is essential to support evidenced-based health care (HPCSA, 2018) and to optimise and improve care (Khoza-Shangase & Stirk, 2016). This study aimed to describe the service delivery practices of a decentralised, community-based OMP for DRTB, including a comparison between CHWs and PHC audiologists facilitating the ototoxicity monitoring. The practices of this real-world community-based OMP were compared to the national and international guidelines for ototoxicity monitoring and to the OMP protocol to identify successes and pitfalls with the aim of improving services and guiding future OMP implementations. To our knowledge, this is the first study to report on ototoxicity monitoring for DRTB conducted by CHWs in a decentralised community-based model of care for increased patient access.

3.3 Materials and Methods

This was a longitudinal retrospective study of ototoxicity monitoring of patients with DRTB between 2013 and 2017. The study aimed to describe the practices of community-based OMP for patients with DRTB, focusing on the following aspects: the timing and frequency of ototoxicity monitoring assessments, the follow-up rates of the program, the ototoxicity monitoring assessment methods used and the OMP data management procedures. The findings of the OMP practices were compared to the most widely used recommended guidelines for ototoxicity monitoring and management (AAA, 2009; ASHA, 1994; HPCSA, 2018), to the OMP protocol and to other comparable published studies. Data collected by CHWs were compared to data collected by audiologists in PHC.

3.3.1 Participants

This study used data collected at outpatient community-based clinics in two subdistricts of the City of Cape Town, namely the Mitchells Plain/Klipfontein and the Western/Southern subdistricts. In 2012, a pilot project to upgrade the skills of 30 existing CHWs in the field of rehabilitation was implemented in the Western Cape in order to improve PHC and community-based rehabilitation for people with disabilities (Gamiet & Rowe, 2019). This new category of CHWs was trained to conduct ototoxicity monitoring, amongst other tasks, and is known as rehabilitation care workers. The Mitchells Plain/Klipfontein and the Western/Southern subdistricts were selected for inclusion in this study because both the upskilled CHW and PHC audiologists were the active testers in these areas. They used conventional pure-tone audiometry and/or extended high-frequency pure-tone audiometry for ototoxicity monitoring associated with DRTB. Nonprobability purposive sampling was used to select all patients with DRTB, regardless of age or gender, who were enrolled in the OMP between May 2013 and September 2017. The patient interviews and ototoxicity monitoring assessments were conducted by testers at 19 PHC and community health clinics in the two subdistricts.

3.3.2 Procedures

The OMP protocol that was implemented at the time of data collection is outlined in Figure 3.1. All patients who received ototoxic medication for treatment of DRTB were identified and referred by their managing doctor and included in the OMP as part of the package of care. Patients visited a PHC or community health clinic daily for the first six months of treatment to receive their medication from a nurse. After the initial six-month treatment period, medication was continued for 18 months with patients visiting a clinic weekly to obtain their medication, and monthly to consult with their managing doctor.

Testers travelled to the clinics in each subdistrict with portable audiological equipment. The KUDUwave audiometer (eMoyo, Johannesburg, South Africa) was used by testers in this study. It is a portable, PC (Dell laptop, Dell Inc., Round Rock, Texas, USA)-controlled clinical diagnostic audiometer and integrated supra-aural ear cup and insert earphone headset and electronic response button for use without a soundproof booth.

Automated and manual programs conduct audiometry up to 16,000 Hz. Results are stored electronically and store-and-forward for printing. PHC audiologists and CHW were testers in the Michell's Plain/Klipfontein subdistrict whereas only PHC audiologists were testers in the western/southern subdistrict. At the time of a patient's initial assessment, identifying data including the patient's name, date of birth, gender and medical history pertaining to HIV status, DRTB medication/s, comorbidities and adverse effects were recorded manually on a paper data collection form by the tester. This information was obtained from the patient's medical records in a clinic file and/or verbally reported to the tester during the patient interview. A bilateral otoscopic examination was conducted and the findings recorded on the data collection form. If pathology was suspected, the patient was referred to the managing doctor or nurse for appropriate treatment, in addition to audiometry, as per the OMP protocol.

At the time of data collection, the official South African ototoxicity monitoring guidelines had not yet been published, thus health care providers relied on adaptations of the international guidelines of the American Speech-Language-Hearing Association (ASHA, Rockville, MD, USA) (ASHA, 1994) and the American Academy of Audiology (AAA, Reston, VA, USA) (AAA, 2009) when developing the OMP procedure protocol. An unpublished draft of the Health Professions Council of South Africa's (HPCSA) ototoxicity monitoring guidelines (HPCSA, 2018) was, however, available to the OMP developers to assist them in applying the international guidelines to the South African context.

The protocol followed by the OMP at the time of data collection is outlined in Figure 3.1. Initial assessments were conducted at the clinics within two weeks of the DRTB treatment initiation. Monitoring assessments were conducted once a month during the initial six-month treatment regimen and then at three, six and 18 months thereafter. The timing of the initial and monitoring assessments was determined by the OMP managers to best suit the community-based nature of the OMP where testers had to travel to numerous clinics on a rotational basis. Where an ototoxic shift meeting predetermined criteria (ASHA, 1994) was evident, the managing doctor was informed immediately and monitoring assessments were then conducted every two weeks until no change in hearing thresholds was detected. Assessments were conducted in a quiet

environment and included bilateral pure-tone audiometry (250–8 kHz), or pure-tone audiometry and extended high-frequency pure-tone audiometry (250–16 kHz) if available. The equipment required to conduct both pure-tone audiometry and extended high-frequency pure-tone audiometry became available in November 2015 at the southern/western subdistrict and in July 2016 at the Mitchell's Plain/Klipfontein subdistrict; prior to this, only pure-tone audiometry was available for ototoxicity monitoring. Typically, manual testing would have been done; however, an automatic mode of threshold determination may also have been used in some instances.

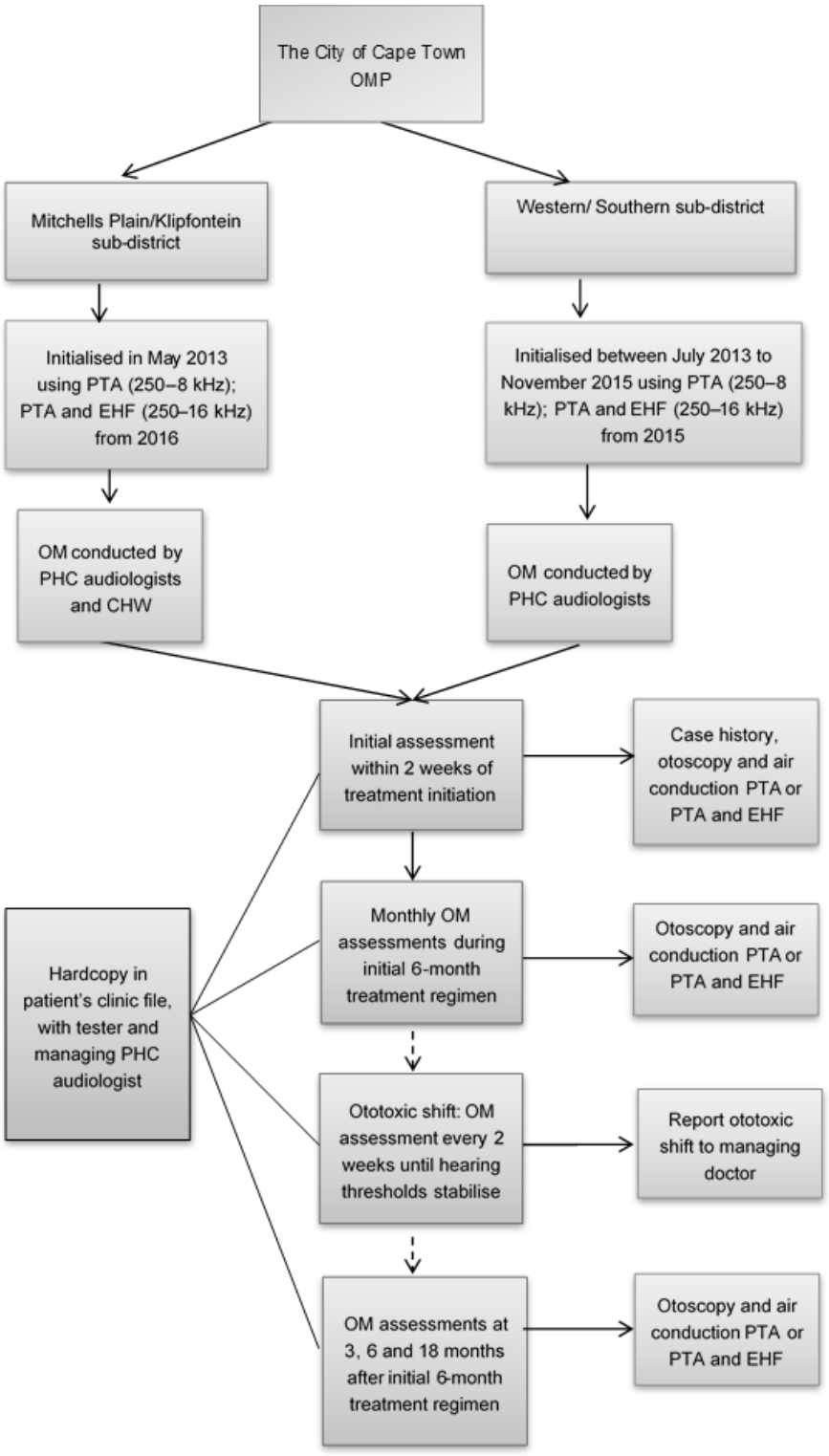


Figure 3.1 *The City of Cape Town ototoxicity monitoring programme (OMP) protocol.*

PTA, pure-tone audiometry; EHF, extended high-frequency pure-tone audiometry; OM, ototoxicity monitoring; PHC, primary healthcare; CHW, community health worker.

Each patient's descriptive and audiological data were recorded manually by the testers on paper-based data collection forms and stored in the patient's clinic file. A copy of each patient's data collection form was kept with the tester and regularly made available to the managing PHC audiologist responsible for each subdistrict for review. Upon completion of a patient's DRTB treatment and ototoxicity monitoring, the data collection form was stored permanently with the PHC audiologist responsible for each subdistrict. The researchers collected the hard copies of the patients' data collection forms from the managing PHC audiologists in each subdistrict for analysis and these were returned upon completion of this study.

3.3.3 Data analysis

Data were imported from Excel into Statistical Package for Social Sciences (SPSS, IBM Corp. Armonk, NY, USA) software (version 27), after which descriptive statistics such as frequency distributions, weighted arithmetic mean, measures of central tendency, variability and relationships (correlations) were used to present and interpret the data in a meaningful way. Frequencies and cross-tabulations were compiled to describe the patient sample. The two proportions z-test was used to determine whether two proportions of two groups (patients who were assigned a follow up return date and those who were not) differed significantly on one characteristic, the follow up return rate. A multivariate logistic regression model was built, with the dependent variable being dichotomous (whether a patient would follow-up after the initial test or not). The Nagelkerke R^2 was used to determine the percentage of variation of the dependent variable which was explained by the predictors (age, gender, treatment duration and HIV status).

The OMP used paper-based data collection forms that were manually completed by the tester for each patient. However, the collection of data by testers describing the patients and their treatment regimens was sporadic. Where important data were missing, this was because it was not recorded on the data collection forms by the testers and was therefore unavailable to the researchers for inclusion in this retrospective study. Many of the patients (37.7%; *n* = 313) did not have their gender recorded on their data collection forms and for almost a fifth of patients (18.7%; *n* = 155) no DRTB medication type and/or date indicating when their treatment was

initiated was recorded (27.6%; *n* = 229). Thus, treatment duration could only be determined for a minority of patients (14.2%; *n* = 118) for whom both treatment initiation and end dates had been recorded on their data collection forms.

3.4 Results

3.4.1 Participants

A total of 831 DRTB patients who attended ototoxicity monitoring services between 2013 and 2017 was included as patients in this study. The patients' ages (798/831 (this format denotes *n*/group total)) ranged from 12.3 to 68 years with a mean of 36.1 years (standard deviation (SD) = 11.00). CHWs assessed 60.3% of patients (501/831), whereas the remaining 39.7% patients (330/831) were assessed by PHC audiologists. Of the 676 patients whose medication had been recorded, 99.4% (672/676) were administered Kanamycin. Only 2.2% of patients (15/676) had more than one medication recorded, therefore only the primary medication administered was used to determine the duration of treatment and to report on the timing of ototoxicity monitoring assessments in relation to treatment initiation. At the time of the initial assessment, 29.1% of patients (242/831) reported having TB/HIV coinfection and 24.1% (200/831) had the use of antiretroviral medication recorded on their data collection forms (Table 3.1). Where treatment initiation and end dates were recorded, treatment duration ranged from six to 596 days with a mean of 160.5 days (SD = 106.84).

Table 3.1 *Patient description at the time of the initial assessment (n = 831).*

Variable	%	*n*/group total
Gender		
Not recorded	37.7	313/831
Male	57.3	297/518
Female	42.7	221/518
Treatment regimen		
Not recorded	18.7	155/831
Kanamycin	99.4	672/676
Capreomycin, Azithromycin or Amikacin	0.6	4/676
More than one medication	2.2	15/676
Treatment duration		
Treatment initiation date not recorded	27.6	229/831
Treatment initiation date recorded	72.4	602/831
Risk factor for ototoxicity		
Tuberculosis/Human immunodeficiency virus coinfection	29.1	242/831
Antiretroviral treatment	24.1	200/831
Noise exposure	14.9	124/831
Audiological symptoms		
Tinnitus	18.2	151/831
Hearing loss	10.2	85/831
Aural fullness	8.5	71/831
Wax impaction		
Left ear	11.1	92/831
Right ear	11.7	97/831
Tester		
Primary healthcare audiologist	39.7	330/831
Community health worker	60.3	501/831

3.4.2 Timing and frequency of ototoxicity assessments

A total of 72.4% of the patients (602/831) had a treatment initiation date recorded by the tester on their data collection form (Table 3.1). Almost half (46.8%; 282/602) of the patients had had an initial assessment conducted prior to or within two weeks of treatment initiation, in accordance with the OMP protocol recommendation (Table 3.2); 89.9% of patients (541/602) had an initial assessment conducted after starting their treatment and had been receiving their medication for more than two months (70.3 days; SD = 131.50) before undergoing an initial assessment (Table 3.2).

Table 3.2 *Timing of initial assessment in relation to treatment initiation (n = 602).*

Timing of initial assessment	Prior to treatment initiation		Post treatment initiation			
	≥4 weeks prior to treatment initiation	Same day as treatment initiation	1–3 days post treatment initiation	4–14 days post treatment initiation	2–4 weeks post treatment initiation	≥4 weeks post treatment initiation
Patients % (n)	4.5 (27)	5.6 (34)	9.0 (54)	27.7 (167)	18.6 (112)	34.6 (208)
Days from treatment initiation and initial assessment Average (SD)	163.6 (166.41)	0 (0)	70.3 (131.50)			

SD, standard deviation.

Follow-up default rates ranged from 27.6 to 31.9% across consecutive monitoring assessments (Table 3.3). Follow-up rates improved from 53.7 to 79.5% from 2013 to 2017 (Figure 3.2). On average, patients were assessed 3.1 (SD = 2.31) times but 31.6% (263/831) attended an initial assessment only and just 8% (69/831) returned for the recommended (AAA, 2009; ASHA, 1994; HPCSA, 2018) six or more ototoxicity monitoring assessments (Figure 3.3).

Table 3.3 *Follow-up rates and days elapsing between the first three monitoring assessments.*

Assessments	Initial to 1st monitoring assessment	1st to 2nd monitoring assessment	2nd to 3rd monitoring assessment
Follow-up rate % (n)	68.1 (566/831)	68.4 (387/566)	72.4 (280/387)
Average number of days between assessments Average (SD)	58.8 (79.03)	56.1 (81.23)	53.5 (62.55)

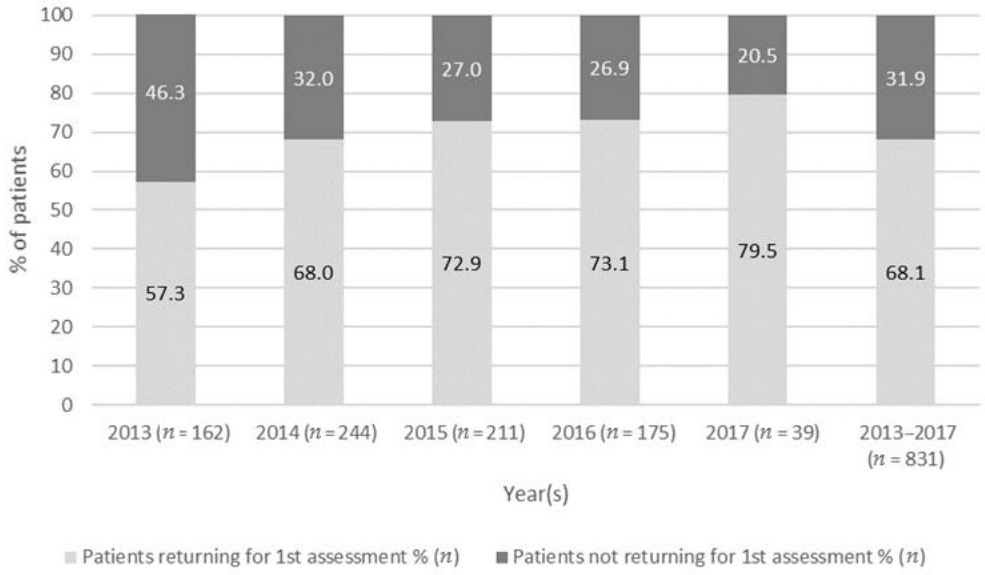


Figure 3.2 *Follow-up rates of the first monitoring assessment between years 2013–2017 (n = 831).*

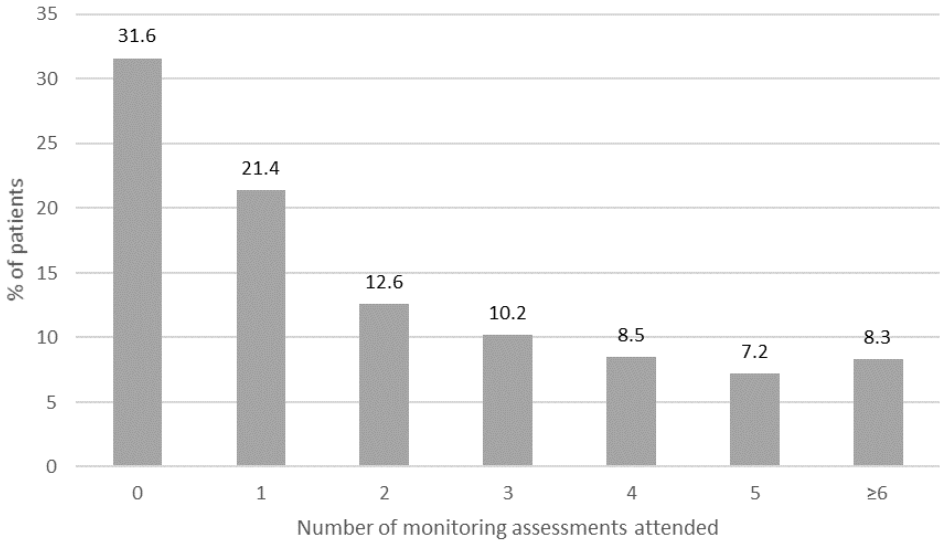


Figure 3.3 *Distribution of the number of monitoring assessments attended by patients (n = 831).*

Multivariate logistic regression models showed that gender, age, HIV status, and the duration of administration of medication did not have a significant effect on follow-up rates ($p > 0.05$). Patients who were given a specific date (25.0%; 208/831) on which to return for an ototoxicity monitoring assessment did not have a significantly better follow-up return rate (two-proportions z-test; $p = 0.052$) either. Once extended high-frequency pure-tone audiometry was introduced to the OMP in 2015, 27.5% of patients (117/425) making OMP visits had their hearing assessed using extended high-frequency pure-tone audiometry as well as pure-tone audiometry.

A comparison of patients assessed by CHWs and PHC audiologists is presented in Table 3.4. The timing and frequency of ototoxicity monitoring was similar for the two groups of testers. PHC audiologists were more likely to use both pure-tone audiometry and extended high-frequency pure-tone audiometry for the initial assessment of patients, however. The findings of this study were compared to the OMP protocol and national and international guideline recommendations, as reflected in Table 3.5.

Table 3.4 *Comparison of the audiometric protocol used, the timing and frequency of ototoxicity monitoring of patients assessed by CHWs and by PHC audiologists.*

Variable	CHWs	PHC audiologists
Patients assessed % (*n*)	60.3 (501/831)	39.7 (330/831)
Initial assessment conducted before, or 1–14 days of treatment initiation % (*n*)	45.6 (209/458)	50.7 (73/144)
Audiometric protocol for initial assessments % (*n*)	Years 2013–2017: PTA: 95.8 (480/501) Years 2015–2017: PTA and EHF: 8.3 (21/252)	Years 2013–2017: PTA: 70.9 (234/330) Years 2015–2017: PTA and EHF: 55.5 (96/173)
Follow-up rate for 1st monitoring assessment % (*n*)	68.5 (343/501)	67.6 (223/330)
Days between monitoring assessments Average (SD)	56.6 (5.62)	60.7 (9.45)
Average number of times a patient was assessed (SD)	3.0 (2.20)	3.1 (2.46)
Patients attending ≥6 monitoring assessments (%)	7.6	9.3

CHWs, community health workers; PHC, primary healthcare; PTA, pure-tone audiometry; EHF, extended high-frequency pure-tone audiometry.

Table 3.5 *Current findings compared to the OMP protocol and guideline recommendations (AAA, 2009; ASHA, 1994; HPCSA, 2018).*

Principle	OMP/guideline recommendation				Current findings % (*n*)
	ASHA	AAA	HPCSA	OMP	
Timing of initial assessment in relation to treatment initiation	Before treatment initiation or within 3 days of initiation	Before treatment initiation or within 3 days of initiation (Kanamycin)	Before treatment initiation or within 3 days of initiation	Before treatment initiation or 1–14 days after initiation	Before or within 3 days of treatment initiation: 19.1 (115/602) Before or 1–14 days after treatment initiation: 46.8 (282/602) ≥15 days after treatment initiation: 53.2 (320/602)
Audiometric protocol for initial assessments	PTA and EHF	PTA and EHF	PTA and EHF	Years 2015–2017: PTA and EHF	Years 2013–2017: PTA: 85.9 (714/831) Years 2015–2017: PTA and EHF: 27.5 (117/425)
Frequency of monitoring assessments during 2-year treatment period	Weekly, if possible, then monthly after treatment stops until hearing stabilises then at 3 and 6 months.	Weekly or biweekly. Cessation of monitoring is unspecified.	Biweekly then monthly after treatment ends until hearing stabilises then at 3 and 6 months.	Monthly for initial 6 months then at 3, 6 and 18 months post initial 6-month treatment period. This equates to at least 9 assessments.	Patients were assessed 3.1 times on average
Timing between monitoring assessments	7 days	7–14 days	14 days	30 days	58.3 (SD = 6.23) days on average
Monitoring assessment follow-up return rate	Not specified	Not specified	Not specified	Not specified	68.1–72.4% for the 1st – 3rd monitoring assessments

OMP, ototoxicity monitoring programme; ASHA, American Speech-Language-Hearing Association; AAA, American Academy of Audiologists; HPCSA; Health Professions Council of South Africa; PTA, pure-tone audiometry; EHF, extended high-frequency pure-tone audiometry; SD, standard deviation.

3.5 Discussion

Almost half (46.8%) of DRTB patients had an initial assessment conducted in accordance with the OMP protocol recommendation, before or within 14 days of treatment initiation. This is more positive compared to a previous South African hospital-based study that reported that only 10% of patients could be tested within two weeks of treatment initiation (Khoza-Shangase & Stirk, 2016). The follow-up rates for the first three assessments ranged from 68.1 to 72.4%. Encouragingly, the follow-up rates between the initial assessment and first monitoring assessment improved to 79.5% as the OMP became more established from 2013 to 2017. The follow-up rates of this study are higher than those of a community-based DRTB treatment program that included ototoxicity monitoring, where the loss to follow-up was reported as being as high as 38% (Moyo et al., 2015). This demonstrates the potential of a community-based model of care for ototoxicity monitoring to establish itself over time as a robust, widely used service. Similar timing and frequency of ototoxicity monitoring was found in patients assessed by CHW and those assessed by PHC audiologists. Therefore, the findings of the current study support the use of CHW to facilitate community-based ototoxicity monitoring of patients with DRTB.

Despite improvements in ototoxicity monitoring service delivery using community-based care and CHWs to facilitate monitoring, the OMP still falls short in several areas. The findings indicate that the OMP was unable to meet the outcomes set out by the guidelines (AAA, 2009; ASHA, 1994; HPCSA, 2018) and OMP protocol, supporting existing reports (Ramma, Nhokwara, et al., 2019). One of the indicators of quality and effectiveness of an OMP is the timely assessment and monitoring of patients who may develop ototoxic hearing loss (AAA, 2009; HPCSA, 2018). The timing of initial assessments in the current study did not meet the guideline or OMP protocol recommendations for more than half (53.2%) of the patients. Most patients (89.9%) received their medication more than two months (Average = 70.3 days; SD = 131.50) before undergoing an initial assessment. This far exceeds the guideline and OMP recommendations (AAA, 2009; ASHA, 1994; HPCSA, 2018), which state that an initial assessment should be conducted prior to, or within three to 14 days of treatment initiation. Timely initial assessments are vital to effective ototoxicity monitoring.

Subsequent monitoring measures are compared to those obtained during the initial assessment and any decisions regarding counselling, the adjustment of treatment regimens or substitution with less ototoxic drugs are based on these comparisons (Konrad-Martin et al., 2005). Historically, the recording of timeous initial assessments has been inconsistent, as reported by South African OMPs (Govender & Paken, 2015; Hong et al., 2020; Khoza-Shangase & Masondo, 2020; Khoza-Shangase & Stirk, 2016) and evidenced in the current study.

Patients in this study were not monitored with the regularity recommended by the guidelines and the OMP protocol. More than 90% did not attend the recommended six or more monthly monitoring assessments (AAA, 2009; ASHA, 1994; HPCSA, 2018). Throughout the course of DRTB treatment, lasting up to 18 months and in some cases even longer, patients were assessed on average only 3.07 (SD = 2.31) times. Ototoxicity monitoring was conducted on average every 58.3 (SD = 6.23) days, almost twice the 30 days recommended by the OMP protocol. This undermines the purpose of ototoxicity monitoring and results in a missed opportunity for early detection and management of ototoxic hearing loss. Previous reports have also indicated that audiologists conducting ototoxicity monitoring in South Africa do not conduct monitoring assessments with the frequency recommended by the national guidelines, that is, every two weeks (Khoza-Shangase & Masondo, 2020). These poorly met indicators raise questions about the effectiveness of OMPs and suggest that careful review and reconsideration of approaches, technologies and human resources used is required.

When extended high-frequency pure-tone audiometry was made available to the testers in this study it was underutilised, with less than a third of patients (27.5%) assessed undergoing using extended high-frequency pure-tone audiometry. Extended high-frequency pure-tone audiometry has been recommended for ototoxicity monitoring as a method to detect hearing damage earlier than conventional pure-tone audiometry (AAA, 2009; ASHA, 1994; HPCSA, 2018). Historically, most audiologists in South Africa have not used extended high-frequency pure-tone audiometry when conducting ototoxicity monitoring because the specialised equipment was unavailable to them (Govender & Paken, 2015). Even when available, extended high-frequency

pure-tone audiometry is often used inconsistently throughout a patient's course of treatment, making reliable comparisons of hearing thresholds difficult or impossible (Khoza-Shangase & Masondo, 2020).

It is unclear why testers in this study did not use the extended high-frequency pure-tone audiometry for ototoxicity monitoring when it was available. One reason may relate to the additional time required and the difficulty in performing consecutive tests for chronically ill patients (Ganesan et al., 2018). It is vital to conduct a quick and efficient hearing assessment on patients with DRTB as reliable behavioural responses are needed to make accurate comparisons for ototoxicity detection (Ganesan et al., 2018). Assessment procedures may need to be adapted for patients unable to cope with a comprehensive assessment (HPCSA, 2018). A sensible recommendation (AAA, 2009; HPCSA, 2018) has been to implement individualised, shortened, serial monitoring protocols that target the highest frequencies most sensitive to ototoxicity (Fausti et al., 1999), or to reduce the number of frequencies assessed to include the high frequencies only (HPCSA, 2018). The use of a sensitive range for ototoxicity has been shown to decrease test time to one third that of a comprehensive test of all frequencies (Fausti et al., 1999). The use objective, noninvasive distortion product otoacoustic emission testing could be considered as an ototoxicity monitoring assessment tool, particularly for difficult-to-test patients (Ganesan et al., 2018). Distortion product otoacoustic emission testing offers a quick, reliable, cost-effective method to detect initial cochlear ototoxic changes before they are able to be detected by conventional pure-tone audiometry (Ganesan et al., 2018). The application of such protocols and adaptions could alleviate the strain on time and human resources synonymous with ototoxicity monitoring (Fausti et al., 1999), leading to more successful OMP outcomes. In addition, the use of an automated test protocol together with a smartphone based mobile technology may further support time effective assessments (Swanepoel, 2020). These findings highlight the importance of ongoing quality control measures and supportive supervision strategies (WHO, 2018) for OMP as well as the continuous training of testers (Eksteen et al., 2019), including task-shifting, to facilitate assessments.

In this study, the data recorded by testers on paper-based data collection forms were inconsistent. The descriptive data for more than a third (37.7%) of the patients were unavailable to the researchers for retrospective analysis. In South Africa, where a systematic national electronic health data management system for ototoxicity monitoring does not exist, it is common practice for audiologists conducting ototoxicity monitoring services to rely solely on paper-based data management procedures (Khoza-Shangase & Masondo, 2021). This can lead to errors in collecting and analysing data (Khoza-Shangase & Masondo, 2021), as evidenced in this study. Thorough data collection and management in the field are necessary for auditing and research purposes, and are of particular importance when comparing repeated measures such as those of an OMP (Khoza-Shangase & Masondo, 2021). The ongoing training and monitoring of testers is important to maintaining a high standard of data collection and management for OMPs (Eksteen et al., 2019). The use of smartphone technology and cloud-based data management has been shown to offer effective data management for large scale screening purposes (Eksteen et al., 2019). Integrating secure data sharing with national health repositories should be considered to improve data management procedures of OMPs in South Africa (Swanepoel, 2020).

Limitations of this study included a high rate of data that were unavailable for analysis and the lack of quantitative measures of the quality of testing by CHWs and PHC audiologists. Furthermore, patient interviews were conducted at the initial assessment only, and not at subsequent monitoring and exit assessments; after prolonged treatment with Kanamycin, the incidence of self-reported adverse audiological symptoms may have been higher.

3.6 Conclusions

Community-based OMP using CHWs to facilitate monitoring showed improvement over previous hospital-based reports with higher follow-up rates and more accessible services. CHWs may also support OMP services by alleviating the strain on hospital-based services, particularly during the COVID-19 pandemic. However, to improve OMP outcomes and to encourage timely ototoxicity assessment, current protocols may require reassessment to optimise limited resources. The poor utilisation of extended pure-tone audiometry by testers suggests that a more targeted approach to ototoxicity

monitoring is required, where only frequencies most sensitive to ototoxicity are prioritised. Mobile smartphone audiometry solutions with paperless cloud-based data management may further support decentralised monitoring facilitated by CHWs.

Author Contributions: Conceptualisation, L.J.S. and D.S.; methodology, L.J.S. and D.W.S.; validation, L.J.S., D.W.S. and M.A.G; formal analysis, M.A.G.; investigation, L.J.S.; resources, Western Cape Department of Health and City of Cape Town Health Department.; data curation, L.J.S and M.A.G.; writing—original draft preparation, L.J.S., D.W.S. and M.A.G.; writing—review and editing, L.J.S., D.W.S., L.B.-d.J. and M.A.G.; visualization, L.J.S., D.W.S. and M.A.G.; supervision, D.W.S, L.B.-d.J. and M.A.G.; project administration, L.J.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board (or Ethics Committee) of the University of Pretoria (GW20161128HS; 63/2017), the City of Cape Town (7788) and the Western Cape Department of Health (WC_2017RP22_896).

Informed Consent Statement: Owing to the retrospective nature of this study, consent to access the existing data collection forms on behalf of the patients was granted by the Western Cape Department of Health and the City of Cape Town Health Department.

Data Availability Statement: Data supporting reported results are stored at the University of Pretoria's Department of Speech-language Pathology and Audiology and are available on request from the corresponding author. The data are not available publicly for ethical reasons pertaining to privacy, anonymity and confidentiality of the patients.

Acknowledgments: We acknowledge and thank the management and administrative members of the ototoxicity monitoring programme (OMP), the primary healthcare (PHC) audiologists and the community health workers (CHWs) who conducted the

ototoxicity monitoring assessments, and the Western Cape Department of Health and the City of Cape Town Health Department for their support of this study.

Conflicts of Interest: The authors declare no conflict of interest.

3.7 References

American Academy of Audiology. (2009). *American Academy of Audiology position statement and clinical practice guidelines ototoxicity monitoring*. Retrieved Feb 16 from https://audiology-web.s3.amazonaws.com/migrated/OtoMonGuidelines.pdf_539974c40999c1.58842217.pdf

American Speech-Language-Hearing Association. (1994). Audiologic management of individuals receiving cochleotoxic drug therapy. https://www.asha.org/policy/GL1994-00003/

Bardien, S., Fagan, J., Harris, T., Jong, G. D., Petersen, L., & Schaaf, H. S. (2009). Aminoglycoside-induced hearing Loss: South Africans at risk. *SAMJ: South African Medical Journal, 99*(6), 440-441.

Centers for Disease Control and Prevention (CDC). (2012). *TB Elimination. Multidrug-Resistant tuberculosis (MDR TB)*. Retrieved March 24 from https://www.cdc.gov/tb/publications/factsheets/drtb/MDRTB.pdf

de Jager, P., & van Altena, R. (2002). Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis. *The International Journal of Tuberculosis and Lung Disease, 6*(7), 622-627.

Duggal, P., & Sarkar, M. (2007). Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. *BMC Ear, Nose, and Throat Disorders, 7*, 5.

Eksteen, S., Launer, S., Kuper, H., Eikelboom, R. H., Bastawrous, A., & Swanepoel, D. W. (2019). Hearing and vision screening for preschool children using mobile technology, South Africa. *Bulletin of the World Health Organization, 97*(10), 672-680. https://doi.org/10.2471/BLT.18.227876

Fausti, S. A., Henry, J. A., Helt, W. J., Phillips, D. S., Frey, R. H., Noffsinger, D., Larson, V. D., & Fowler, C. G. (1999). An individualized, sensitive frequency range for early detection of ototoxicity. *Ear and Hearing, 20*(6), 497-505.

Gamiet, S., & Rowe, M. (2019). The role of rehabilitation care workers in South African healthcare: A Q-methodological study. *African Journal of Disability, 8*, 537. https://doi.org/10.4102/ajod.v8i0.537

Ganesan, P., Schmiedge, J., Manchaiah, V., Swapna, S., Dhandayutham, S., & Kothandaraman, P. P. (2018). Ototoxicity: A challenge in diagnosis and treatment. *Journal of Audiology & Otology, 22*(2), 59-68. https://doi.org/10.7874/jao.2017.00360

Govender, M., & Paken, J. (2015). Practices employed by audiologists in the management of adult patients with multidrug-resistant tuberculosis in South Africa. *South African Family Practice, 57*(6), 363-372. https://doi.org/10.1080/20786190.2015.1085222

Harris, T., Peer, S., & Fagan, J. J. (2012). Audiological monitoring for ototoxic tuberculosis, human immunodeficiency virus and cancer therapies in a developing world setting. *Journal of Laryngology and Otology, 126*(6), 548-551. https://doi.org/10.1017/S0022215112000357

Health Professions Council of South Africa. (2018). *Audiological management of patients on treatment that includes ototoxic medications. Guidelines*. Retrieved Feb 16 from https://www.hpcsa.co.za/Uploads/SLH/Guidelines%20for%20Audiological%20Management%20of%20Patients%20on%20Treatment%20that%20includes%20Ototoxic%20Medications.pdf

Hong, H., Dowdy, D. W., Dooley, K. E., Francis, H. W., Budhathoki, C., Han, H. R., & Farley, J. E. (2020). Prevalence of pre-Existing hearing loss among patients with drug-resistant tuberculosis in South Africa. *American Journal of Audiology, 29*(2), 199-205. https://doi.org/10.1044/2020_AJA-19-00103

Huth, M. E., Ricci, A. J., Cheng, A. G., & Pearson, J. P. (2011). Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection. *International Journal of Otolaryngology.*(2011).

Khoza-Shangase, K. (2010). Is there a need for ototoxicity monitoring in patients with HIV/AIDS? *African Journal of Pharmacy and Pharmacology, 4*(9), 574-579.

Khoza-Shangase, K., & Masondo, N. (2020). What are the current audiological practices for ototoxicity assessment and management in the South African healthcare context? *International Journal of Environmental Research and Public Health, 17*(7), 2613. https://doi.org/10.3390/ijerph17072613

Khoza-Shangase, K., & Masondo, N. (2021). In pursuit of preventive audiology in South Africa: Scoping the context for ototoxicity assessment and management. *Journal of Pharmacy & Bioallied Sciences, 13*(1).

Khoza-Shangase, K., & Stirk, M. (2016). Audiological testing for ototoxicity monitoring in adults with tuberculosis in state hospitals in Gauteng, South Africa. *Southern African Journal of Infectious Diseases, 31*(2), 44-49. https://doi.org/10.1080/23120053.2016.1128143

Konrad-Martin, D., Wilmington, D. J., Gordon, J. S., Reavis, K. M., & Fausti, S. A. (2005). Audiological management of patients receiving aminoglycoside antibiotics. *Volta Review, 105*(3), 229-250.

Lange, C., Aarnoutse, R. E., Alffenaar, J. W. C., Bothamley, G., Brinkmann, F., Costa, J., Chesov, D., van Crevel, R., Dedicoat, M., Dominguez, J., Duarte, R., Grobbel, H. P., Guenther, G., Guglielmetti, L., Heyckendorf, J., Kay, A. W., Kirakosyan, O., Kirk, O., Koczulla, R. A., Kudriashov, G. G., Kuksa, L., van Leth, F., Magis-Escurra, C., Mandalakas, A. M., Molina-Moya, B., Peloquin, C. A., Reimann, M., Rumetshofer, R., Schaaf, H. S., Schon, T., Tiberi, S., Valda, J., Yablonskii, P. K., & Dheda, K. (2019). Management of patients with multidrug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Disease, 23*(6), 645-662.

Lange, C., Dheda, K., Chesov, D., Mandalakas, A. M., Udwadia, Z., & Horsburgh, C. R., Jr. (2019). Management of drug-resistant tuberculosis. *Lancet (London,*

England), *394*(10202), 953-966. https://doi.org/10.1016/S0140-6736(19)31882-3

Medicins Sans Frontieres. (2020). *Step Up for TB: TB policies in 37 countries, 4th Ed*. Retrieved May 2020 from https://msfaccess.org/step-tb-tb-policies-37-countries-4th-ed

Meiyan, J., Takatoshi, K., & Peter, S. S. (2017). Aminoglycoside-induced cochleotoxicity: A review. *Frontiers in Cellular Neuroscience*.

Melchionda, V., Wyatt, H., Capocci, S., Garcia Medina, R., Solamalai, A., Katiri, S., Hopkins, S., Cropley, I., & Lipman, M. (2013). Amikacin treatment for multidrug resistant tuberculosis: How much monitoring is required? *The European Respiratory Journal,* *42*(4), 1148-1150. https://doi.org/10.1183/09031936.00184312

Moyo, S., Cox, H. S., Hughes, J., Daniels, J., Synman, L., De Azevedo, V., Shroufi, A., Cox, V., van Cutsem, G., & Via, L. E. (2015). Loss from treatment for drug resistant tuberculosis: Risk factors and patient outcomes in a community-based program in Khayelitsha, South Africa. *PloS One,* *10*(3), e0118919. https://doi.org/10.1371/journal.pone.0118919

Ndjeka, N., Hughes, J., Reuter, A., Conradie, F., Enwerem, M., Ferreira, H., Ismail, N., Kock, Y., Master, I., Meintjes, G., Padanilam, X., Romero, R., Schaaf, H. S., Riele, J. T., & Maartens, G. (2020). Implementing novel regimens for drug-resistant TB in South Africa: What can the world learn? *The International Journal of Tuberculosis and Lung Disease,* *24*(10), 1073-1080. https://doi.org/10.5588/ijtld.20.0174

O'Donovan, J., Verkerk, M., Winters, N., Chadha, S., & Bhutta, M. F. (2019). The role of community health workers in addressing the global burden of ear disease and hearing loss: A systematic scoping review of the literature. *BMJ Global Health,* *4*(2), e001141. https://doi.org/10.1136/bmjgh-2018-001141

Petersen, L., & Rogers, C. (2015). Aminoglycoside-induced hearing deficits - a review of cochlear ototoxicity. *South African Family Practice,* *57*(2), 77-82. https://doi.org/10.1080/20786190.2014.1002220

Ramma, L., Heinze, B., & Schellack, N. (2019). Prevention of treatment-induced ototoxicity : An update for clinicians. *South African Medical Journal, 109*(3), 145-149. https://doi.org/10.7196/SAMJ.2019.v109i3.13903

Ramma, L., Nhokwara, P. T., & Rogers, C. (2019). Statistical factors associated with utilisation of ototoxicity monitoring services for multi-drug-resistant tuberculosis patients in the Western Cape. *The South African Journal of Communication Disorders = Die Suid-Afrikaanse Tydskrif vir Kommunikasieafwykings, 66*(1), e1-e6. https://doi.org/10.4102/sajcd.v66i1.596

Rogers, C., & Petersen, L. (2011). Aminoglycoside-induced balance deficits: A review of vestibulotoxicity. *South African Family Practice, 53*(5), 419-424.

Schacht, J., Talaska, A. E., & Rybak, L. P. (2012). Cisplatin and aminoglycoside antibiotics: Hearing loss and its prevention. *The Anatomical Record: Advances in Integrative Anatomy and Evolutionary Biology, 295*(11), 1837-1850. https://doi.org/10.1002/ar.22578

Sharma, A., Hill, A., Kurbatova, E., van der Walt, M., Kvasnovsky, C., Tupasi, T. E., Caoili, J. C., Gler, M. T., Volchenkov, G. V., Kazennyy, B. Y., Demikhova, O. V., Bayona, J., Contreras, C., Yagui, M., Leimane, V., Cho, S. N., Kim, H. J., Kliiman, K., Akksilp, S., Jou, R., Ershova, J., Dalton, T., & Cegielski, P. T. C. F. D. C. T. T. (2017). Estimating the future burden of multidrug-resistant and extensively drug-resistant tuberculosis in India, the Philippines, Russia, and South Africa: A mathematical modelling study. *The Lancet Infectious Diseases, 17*(7), 707-715. https://doi.org/10.1016/S1473-3099(17)30247-5

Swanepoel, W. (2020). eHealth technologies enable more accessible hearing care. *Seminars in Hearing, 41*(2), 133-140. https://doi.org/10.1055/s-0040-1708510

The South African National Aids Council. (2017). *Monitoring and evaluation plan for the national strategic plan on HIV, TB and STI (2017 – 2022)*. Retrieved Feb 16 from https://sanac.org.za/wp-content/uploads/2020/01/114725-ME-Plan-3rd-Proof-5-Aug.pdf

Western Cape Government Health. (2018). *Clinical guidelines & standard operating procedure for the implementation of the short & long DR-TB regimens for adults,*

adolescents and children. Retrieved Feb 16 from https://www.westerncape.gov.za/assets/departments/health/tuberculosis_-_dr-tb_clinical_guidelines_2018.pdf

World Health Organisation. (2007). *Community health workers: What do we know about them? The state of the evidence on programmes, activities, costs and impact on health outcomes of using community health workers.* Retrieved 31 August from https://www.who.int/hrh/documents/community_health_workers.pdf

World Health Organisation. (2015). *Brochure: The WHO End TB strategy*. Retrieved Feb 16 from https://www.who.int/tb/End_TB_brochure.pdf

World Health Organisation. (2018). *WHO guideline on health policy and system support to optimize community health worker programmes.* Retrieved 06/29/2021 from http://apps.who.int/iris/bitstream/handle/10665/275474/9789241550369-eng.pdf

World Health Organisation. (2019). *TB profile: South Africa*. Retrieved March 17 from https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type=%22country%22&lan=%22EN%22&iso2=%22ZA%22

World Health Organisation. (2020a). *Global tuberculosis report 2020* (ISBN 978-92-4-001313-1). https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf

World Health Organisation. (2020b). *WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment*. Retrieved 07/09/2021 from https://www.who.int/publications/i/item/9789240007048

World Health Organisation. (2021). *World report on hearing*. World Health Organization. Retrieved August 1 from https://www.who.int/publications/i/item/world-report-on-hearing

Xie, J., Talaska, A. E., & Schacht, J. (2011). New developments in aminoglycoside therapy and ototoxicity. *Hearing Research, 281*(1-2), 28-37. https://doi.org/10.1016/j.heares.2011.05.008

CHAPTER 4: A LONGITUDINAL COMMUNITY-BASED OTOTOXICITY MONITORING PROGRAMME AND TREATMENT EFFECTS FOR DRUG-RESISTANT TUBERCULOSIS TREATMENT, WESTERN CAPE

Authors: Stevenson, L. J.; Biagio-de Jager, L.; Graham, M. A.; Swanepoel, D.

Journal: South African Journal of Communication Disorders

Accepted: 6 February 2022 (Appendix H)

Publication: 2022; *69*(1), a886

Note: This chapter was referenced and edited according to the style of this document and may differ from the style of the published study.

4.1 Abstract

Background: South Africa has a high burden of drug-resistant tuberculosis (DRTB) and until recently, ototoxic aminoglycosides were predominant in treatment regimens. Community-based ototoxicity monitoring programmes (OMPs) have been implemented for early detection of hearing loss and increased patient access.

Objective: A longitudinal study was conducted to describe the service delivery characteristics of a community-based OMP for DRTB patients facilitated by CHWs as well as observed ototoxic hearing loss in this population.

Method: A descriptive retrospective record review of longitudinal ototoxicity monitoring of 194 DRTB patients undergoing treatment at community-based clinics in the City of Cape Town between 2013 and 2017.

Results: Follow-up rates between consecutive monitoring assessments reached as high as 80.6% for patients assessed by CHWs. Few patients (14.2–32.6%) were assessed with the regularity (≥ 6 assessments) and frequency required for effective

ototoxicity monitoring, with assessments conducted on average every 53.4 –64.3 days. Following DRTB treatment, 51.5% of patients presented with a significant ototoxic shift meeting one or more of the American Speech-Language-Hearing Association (ASHA) criteria. Deterioration in hearing thresholds was bilateral and most pronounced at the high frequencies (4 kHz–8 kHz). The presence of pre-existing hearing loss, HIV co-infection, and a history of noise exposure were significant predictors of ototoxicity in DRTB patients.

Conclusion: DRTB treatment with kanamycin resulted in a significant deterioration of hearing status longitudinally, predominantly at high frequencies. With ongoing training and supportive supervision, CHWs can facilitate community-based ototoxicity monitoring of DRTB patients. Current protocols and guidelines may require reassessment for appropriate community-based ototoxicity monitoring.

Keywords: Community-based services; community health workers; decentralised services; tuberculosis; drug-resistant tuberculosis; hearing loss; ototoxicity monitoring; audiometry; South Africa.

4.2 Introduction

Tuberculosis (TB) is a communicable disease spread when people who are sick expel the TB-causing bacteria into the air (World Health Organisation [WHO], 2020a). Although TB can be successfully prevented and treated (Cox et al., 2019), it is the leading infectious disease and one of the top 10 causes of death globally (WHO, 2020a). Africa accounted for 25% of the 10 million people globally who developed TB in 2019, with South Africa being identified by the WHO as a high-burden TB country (WHO, 2020a). Furthermore, South Africa has a high prevalence rate (19.5%) of human immunodeficiency virus (HIV) infection for adults aged 15–49 years (Republic of South Africa Statistics Department, 2021; Wells et al., 2007). In 2019, 209 000 people in the country were afflicted with TB and HIV (WHO, 2020a). Tuberculosis may accelerate the course of HIV infection, which may contribute to the increase in the prevalence of drug-resistant TB (DRTB) in patients with TB (Wells et al., 2007).

Tuberculosis that is resistant to at least two of the most effective anti-TB drugs, rifampicin and isoniazid, is known as DRTB (Centers for Disease Control and Prevention [CDC], 2016). Rifampicin-resistant TB (RRTB) and multidrug-resistant TB (MDRTB), which are different types of DRTB, continue to be a public health threat (WHO, 2020a) that jeopardises the control of TB (Horsburgh, Mitnick, & Lange, 2019). Close to half a million people developed RRTB globally in 2019, 78% of whom had MDRTB (WHO, 2020a). South Africa has the highest number of patients with MDRTB on the African continent (Lange et al., 2019), with an estimated 23 out of every 100 000 people being infected with RR/MDRTB (WHO, 2020a).

Treatment of DRTB takes longer and requires drugs that are more expensive and more toxic than those used for the treatment of TB (WHO, 2020a). Before 2018, the WHO and the South African Department of Health (Department Health Republic of South Africa [DOH], 2013) included the use of a second-line injectable antibiotic (either an aminoglycoside such as kanamycin, or a polypeptide) in the DRTB treatment regimen (Wrohan, Redwood, Ho, Velen, & Fox, 2021). Aminoglycoside antibiotics are known to affect hearing and balance, or both, through ototoxicity in the cochleovestibular organ (Campbell & Le Prell, 2018). Outer hair cell damage starts at the basal coil and progresses to the apex of the cochlea, resulting in a permanent high-frequency hearing loss, progressing to the lower frequencies (De Jager & Van Altena, 2002). Damage to the outer hair cells is followed by progressive loss of the inner hair cells in more severe cases (Xie, Talaska, & Schacht, 2011). The prevalence rate of aminoglycoside-induced ototoxicity in DRTB patients, which is estimated as 63% of patients (WHO, 2021b), is dependent on the drug, drug dosage, treatment duration (Huth, Ricci, Cheng, & Pearson, 2011; Schacht, Talaska, & Rybak, 2012; Xie et al., 2011) and patients' demographic profile (Ramma, Heinze, & Schellack, 2019). In the Western Cape, it has been reported that around 47% – 57% of DRTB patients have developed aminoglycoside-induced hearing loss (Melchionda et al., 2013; Petersen & Rogers, 2015; Ramma et al., 2019).

Concerns regarding the ototoxic nature of injectable antibiotics and the availability of novel, less toxic, more effective drugs led to an update of the South African Department of Health (DOH, 2018) and WHO DRTB treatment guidelines in 2018 and 2019,

respectively (WHO, 2020b; Wrohan et al., 2021). The latest DRTB treatment guidelines recommend a shorter, all-oral regimen containing bedaquiline for the treatment of RR/MDRTB (DOH, 2018; WHO, 2020b). Bedaquiline has fewer side effects than the other drugs used to treat DRTB (Medicins Sans Frontieres [MSF], 2020) and does not appear to be associated with hearing loss, unlike kanamycin (Khoza-Shangase & Prodromos, 2021). However, an all-oral regimen may not be suitable for all patients, and therefore the guidelines continue to include the use of amikacin, which is associated with an estimated hearing loss prevalence of 38.9% (Dillard et al., 2021; Evans et al., 2015; WHO, 2020b; Wrohan et al., 2021). Furthermore, access to novel drugs has remained limited (MSF, 2020). Between 2015 and 2019, only one in nine people across 36 countries who could benefit from bedaquiline received the medication (Cox et al., 2018; MSF, 2020). Despite their adverse effects, aminoglycoside antibiotics are used in high-burden TB countries because they are easily accessible and inexpensive, leading to an increased burden of aminoglycoside induced hearing loss (Bardien et al., 2009; Campbell & Le Prell, 2018). Almost half (46%; 17/37) of the countries whose national policies and practices were surveyed in 2019 (MSF, 2020) reported still using kanamycin or capreomycin in the treatment of DRTB, contrary to the latest recommendations (WHO, 2020a). In addition, the coronavirus disease 2019 (COVID-19) pandemic threatens to undo the progress made in TB control as it causes major disruptions to essential TB services and threatens to increase the burden of TB disease (WHO, 2020a). As a result, a substantial number of patients may develop ototoxic hearing loss and require hearing loss prevention strategies, including audiological ototoxicity monitoring (Dillard et al., 2021).

When the use of injectable ototoxic medications is unavoidable, audiological ototoxicity monitoring is essential to optimise hearing-related outcomes (WHO, 2021b; Wrohan et al., 2021). Audiological ototoxicity monitoring encompasses the regular assessment of patients' hearing thresholds during treatment to detect early changes in hearing, so that treatment regimens can be adjusted and disabling hearing loss can be avoided (WHO, 2021b). In response to the high prevalence of ototoxic hearing loss associated with DRTB treatment, the South African National TB Control Programme implemented the National Ototoxicity Prevention Programme to improve the access to audiological monitoring and reduce the prevalence of ototoxic hearing loss (WHO, 2021b). As part

of this programme, portable audiometers and training were offered to selected decentralised health facilities, including primary healthcare (PHC) facilities (WHO, 2021b). Patients with DRTB were able to access ototoxicity monitoring services outside centralised TB hospitals, increasing access to care (DOH, 2013; Ndjeka et al., 2020; The South African National Aids Council, 2017).

The South African Department of Health has committed to addressing the disparity in human resources for health by prioritising the integration of 50 000 community health workers (CHWs) into the PHC system by 2024 (DOH, 2020). Community health workers are individuals working in the community in which they reside who are selected and trained to broaden the access and coverage of health care services in remote areas (WHO, 2007). Community health workers engage in task-sharing, which involves the shifting of health care tasks from highly skilled professionals such as audiologists to workers with shorter training, such as CHWs (Dillard et al., 2021; DOH, 2020). Task shifting (Mulwafu, Ensink, Kuper, & Fagan, 2017) and incorporating ototoxicity monitoring into existing service delivery models, such as community-based health care services, have been proposed to address the barriers to ototoxicity monitoring (Dillard et al., 2021).

To improve the efficacy and efficiency for early detection of hearing changes, existing ototoxicity monitoring programmes (OMPs) and treatment effects should be evaluated so that ototoxicity monitoring guidelines can be adapted to specific settings (Dillard et al., 2021; Health Professions Council of South Africa [HPCSA], 2018). The current study, therefore, aimed to describe the service delivery characteristics of a community-based OMP for patients with DRTB, facilitated by CHWs and PHC audiologists using conventional audiometry (0.25 kHz – 8 kHz) for ototoxicity monitoring according to the timing, frequency and follow-up rates of ototoxicity monitoring assessments. In addition, this study aimed to describe the ototoxic hearing loss observed in DRTB patients over time. To our knowledge, this is the first study to report on observed longitudinal treatment effects for DRTB and ototoxicity monitoring conducted by CHWs in a decentralised community-based model of care for increased patient access.

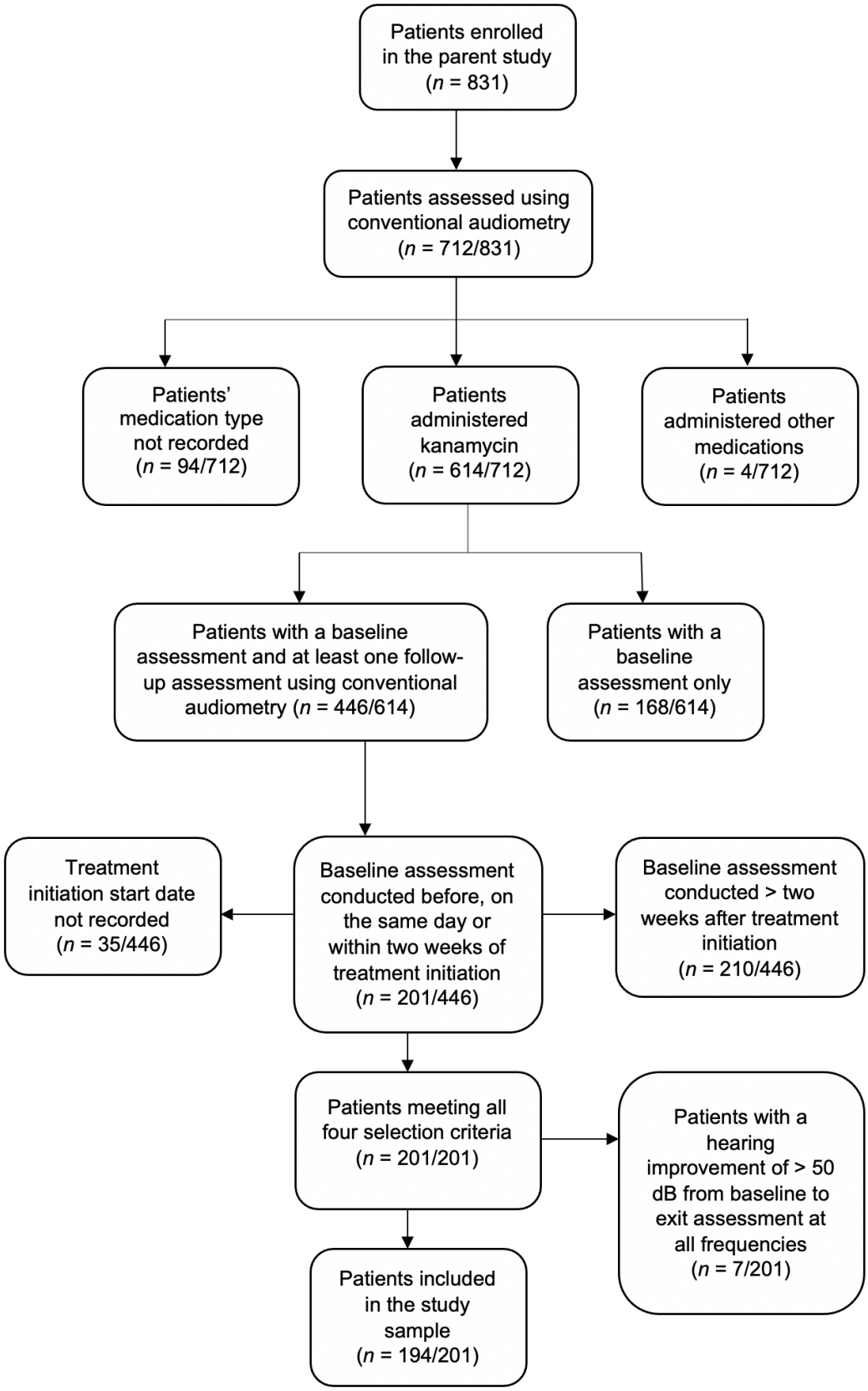
4.3 Materials and Method

This study was part of a larger, longitudinal descriptive retrospective record review of a decentralised community-based OMP for patients with DRTB facilitated by CHWs between 2013 and 2017. This specific OMP was selected for investigation as it offers a novel approach to ototoxicity monitoring for DRTB patients with a timeframe allowing for as many study participants as possible. The data were collected at community health centres and PHC clinics in two sub-districts of the city of Cape Town (CoCT), namely the [location masked for blind review] and [location masked for blind review] sub-districts. At the time of data collection, the sub-districts were characterised by a predominantly coloured (30% – 50%) and black African (19% – 46%) population who mostly resided in formal dwellings (68% – 87%) (CoCT, 2013a, 2013b, 2013c, 2013d). Most people living in the sub-districts included in this study were employed (68% – 87%), with 32% – 60% of people having completed high school education (Grade 12) (CoCT, 2013a, 2013b, 2013c, 2013d). This study aimed to supplement the findings of a larger study by describing the service delivery characteristics of a community-based OMP for DRTB patients facilitated by CHWs and PHC audiologists and the ototoxic hearing loss observed in this population over time.

4.3.1 Participants

This study included patients from a larger study who met the following selection criteria: patients who (1) received kanamycin, (2) were tested using conventional audiometry (0.25 kHz – 8 kHz), (3) had a baseline assessment conducted before, on the same day, or within 2 weeks of initiation of medication, and (4) had one or more follow-up monitoring assessments using conventional audiometry thereafter. The selection criteria were based on the OMP protocol and guidelines for ototoxicity monitoring (HPCSA, 2018) to allow for comparability. Non-probability purposive sampling was used to select all patients with DRTB, regardless of age, gender or hearing status. Of the 831 patients included in the parent study, 194 patients met all the selection criteria and were eligible for inclusion in this study (Figure 4.1). The patient interviews and ototoxicity monitoring assessments were conducted by six CHWs and two PHC audiologists at 19 of the sub-districts' PHC clinics and community health centres. In 2012, the Western Cape Department of Health, in collaboration with the University of

Cape Town, initiated a pilot project in which 30 CHWs underwent a year-long certificate training programme to become members of the PHC team (Clark, 2015; Gamiet & Rowe, 2019). The CHWs were provided with skills and knowledge in community-based rehabilitation to support people with disabilities in two underserved communities in the Western Cape (Gamiet & Rowe, 2019). To facilitate ototoxicity monitoring for DRTB in a community-based setting, six CHWs received additional training from the PHC audiologist responsible for the Mitchells Plain/Klipfontein sub-district. The six CHWs were also trained to conduct home-based hearing screening and hearing screening of school-aged children and patients attending a PHC clinic.



dB, decibel.

Figure 4.1 *Patient selection procedure*

4.3.2 Data Collection Procedure

The data collection procedure for this study was the same as for the larger study (Stevenson et al., 2021). The OMP protocol implemented at the time of data collection was as follows: all patients who received ototoxic medication for treatment of DRTB were identified and referred by their managing doctor and included in the OMP as part of the package of care. Patients visited a clinic or centre daily for the first 6 months of treatment to receive their medication from a nurse. After the initial 6-month treatment period, medication was continued for 18 months, with patients visiting a clinic weekly to obtain their medication, and monthly to consult with their managing doctor. At the time of data collection, the official South African ototoxicity monitoring guidelines had not yet been published, thus the OMP developers relied on adapting the international guidelines of the American Speech-Language-Hearing Association (ASHA) (ASHA, 1994) and the American Academy of Audiology (AAA) (AAA, 2009) when developing the OMP protocol. An unpublished draft of the HPCSA ototoxicity monitoring guideline was, however, available to the OMP developers to assist them in applying the international guidelines to the South African context.

Community health workers and PHC audiologists travelled to the clinics in each sub-district with portable audiological equipment. Community health workers and PHC audiologists were testers in the Mitchells Plain/Klipfontein sub-district, whereas only PHC audiologists were testers in the Western or Southern sub-district. At the time of a patient's baseline assessment, identifying information including the patient's name, date of birth, gender and medical history pertaining to HIV status, DRTB medication/s, comorbidities and adverse effects were recorded manually on a paper data collection form by CHWs and PHC audiologists. This information was obtained from the patient's medical records in a clinic file and/or verbally reported to the CHWs and PHC audiologists during the patient interview. The KUDUwave portable audiometer (eMoyo, South Africa) was used by CHWs and PHC audiologists in this study. The KUDU wave is a PC (Dell laptop) controlled clinical diagnostic audiometer, and integrated supra-aural ear-cup and insert earphone headset, with an electronic response button for use without a soundproof booth. Automated and manual programmes conduct audiometry up to 16 kHz. Results are stored electronically and store-and-forward for printing.

The protocol for baseline and monitoring audiological ototoxicity monitoring assessments followed by the OMP at the time of data collection was as follows: a bilateral otoscopic examination was conducted followed by air-conduction pure-tone audiometry, and the findings recorded on the data collection form. If outer or middle ear pathology was suspected following otoscopy, the patient was referred to the managing doctor or nurse for appropriate treatment and referred for audiometry, according to the OMP protocol. Baseline assessments were conducted at the clinics prior to, on the same day or within 2 weeks of DRTB treatment initiation. Monitoring assessments were conducted once a month during the initial 6-month treatment regimen and then at 3, 6 and 18 months thereafter. Where an ototoxic shift meeting predetermined criteria (ASHA, 1994) was evident, the managing doctor was informed, and monitoring assessments were then conducted every 2 weeks until no change in hearing thresholds was detected. Assessments were conducted in a quiet environment using conventional audiometry (0.25 kHz – 8 kHz). Typically, manual testing would have been done; however, an automatic mode of threshold determination may also have been used in some instances. The equipment required to conduct both conventional audiometry and extended high-frequency (EHF) audiometry became available in November 2015 for use in the [location masked for blind review], and in July 2016 for use in the [location masked for blind review] sub-district. Before this, only conventional audiometry was available for ototoxicity monitoring.

Each patient's descriptive and audiological data were recorded manually by the CHWs and PHC audiologists on paper data collection forms and stored in the patient's clinic file. A copy of each patient's data collection form was kept with the CHWs and PHC audiologists and regularly made available for review to the managing PHC audiologist responsible for each sub-district. Upon completion of a patient's DRTB treatment and ototoxicity monitoring, the form was stored permanently with the PHC audiologist responsible for each sub-district. The researchers collected the hardcopies of the patients' data collection forms from the managing PHC audiologists in each sub-district for analysis, and these were returned upon completion of this study.

4.3.3 Data analysis

Data were imported from Excel into Statistical Package for Social Sciences (SPSS) software (version 27), after which descriptive statistics such as frequency distributions, measures of central tendency and measures of variability were used to present and interpret the data in a meaningful way. Data cleaning was performed where data erroneously captured by the CHWs, PHC audiologists and/or the researcher, such as dates, were corrected to be in a uniform format. In cases where data was accidentally not captured by the researcher, the data collection forms were re-examined to supplement any missing data. Because the data differed significantly from normality (Shapiro–Wilk $p < 0.05$), nonparametric tests were used (Field, 2018). The Wilcoxon signed-rank (W) test was used to compare significant differences between dependent groups (baseline assessment and exit assessment). The Mann–Whitney U (U) test was used to determine whether there was a difference in the variables (timing of baseline assessments and the number of monitoring assessments attended by patients) for independent groups (patients assessed by CHWs and patients assessed by PHC audiologists). In order to determine significant predictors for hearing deterioration, multiple linear regression models with many assumptions were run initially; one of these assumptions is that the error terms must be normally distributed. The error terms in this study were not normally distributed. Therefore, quantile regression models, which are robust to outliers and do not require the assumptions of normally distributed error terms, were used instead. For inferential statistics, a 5% level of significance was used throughout.

The OMP used paper data collection forms, which were manually completed by the CHWs and PHC audiologists for each patient. Where important data were missing, this was because data were not recorded on the data collection forms by the testers, and were therefore unavailable for inclusion in this retrospective study.

4.3.4 Ethical Considerations

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board (or Ethics Committee) of the University of Pretoria (GW20161128HS; 63/2017), the CoCT (7788) and the Western Cape

Department of Health (WC_2017RP22_896). Owing to the retrospective nature of this study, consent to access the existing data collection forms on behalf of the patients was granted by the Western Cape Department of Health and the CoCT Health Department. All patient identifying information was kept confidential as patient records were given a numerical code in order to ensure anonymity during data collection and analysis. Data from the data collection forms were recorded on a password-protected Excel spreadsheet for later analysis by the researchers.

4.4 Results

4.4.1 Participants

Of the 831 patients included in the parent study, 201 met the participant selection criteria and were eligible for inclusion in this study. Seven patients with results indicating technical or procedural issues related to their baseline and exit assessment audiograms (i.e. improved thresholds [> 50 dB HL] across all frequencies) were excluded. A final sample of 194 patients (Figure 4.1) was included, as presented in Table 4.1. The mean age of patients was 36.2 years (standard deviation [SD] = 11.3; range = 15.0 – 65.1 years). The gender of 33.0% (64/194) of the patients was not recorded by CHWs and PHC audiologists on the data collection forms and was thus unavailable for inclusion in this retrospective study. At the time of the baseline assessment, 24.7% (48/194) of patients reported having DRTB and HIV co-infection, 20.6% (40/194) reported a history of excessive noise exposure and 18.0% (35/194) reported experiencing tinnitus. Patients' baseline assessments were conducted, on average, 16.8 days (SD = 86.5; range = –494 to 14 days) before treatment initiation.

Table 4.1 *Participant description at the time of the baseline assessment (n = 194)*

	%	n
Gender		
Not recorded	33.0	64
Male	35.6	69
Female	31.4	61
Risk factor for ototoxicity		
DRTB and HIV co-infection	24.7	48
Noise exposure	20.6	40
Audiological symptoms		
Tinnitus	18.0	35
Otalgia	6.2	12
Hearing loss	5.2	10
Tester		
CHW	76.3	148
PHC audiologist	23.7	46

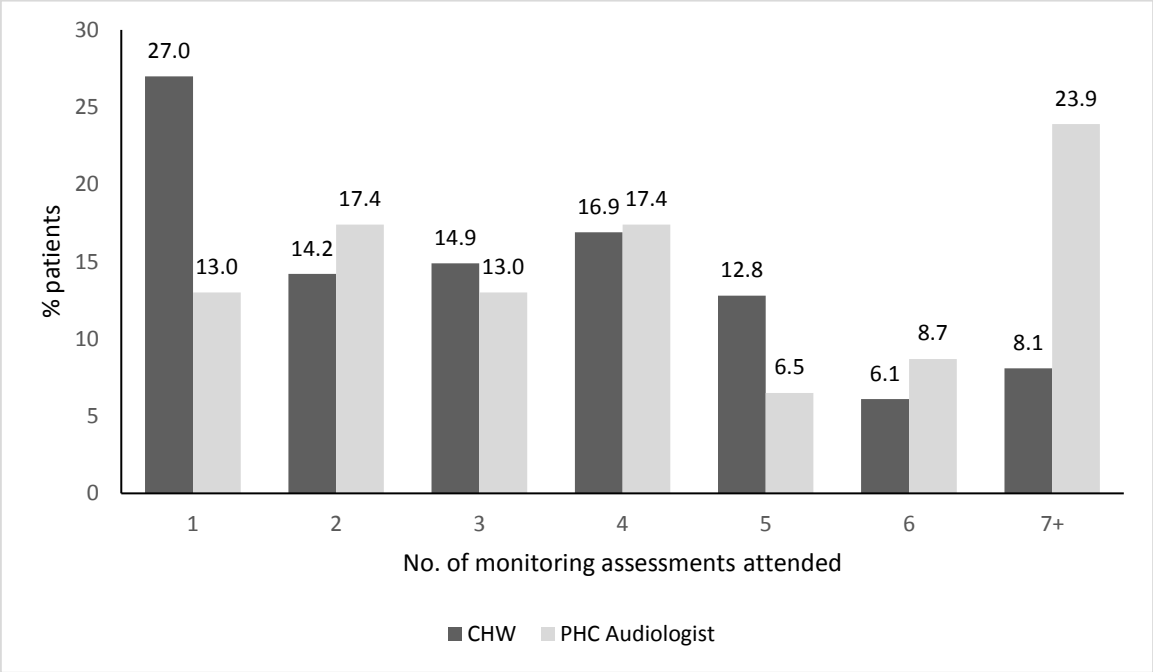
DRTB, drug-resistant tuberculosis; HIV, human immunodeficiency virus; CHW, community health worker; PHC, primary health care.

4.4.2 Ototoxicity monitoring programme characteristics

4.4.2.1 Timing and frequency of ototoxicity monitoring assessments

Community health workers tested 76.3% (148/194) of the patients in the study. There was a statistically significant difference (p = 0.003; U = 2406.5) between the timing of baseline assessments by CHWs and by PHC audiologists. Patients assessed by PHC audiologists had a baseline assessment conducted on average 52.0 days (SD = 134.9) before treatment initiation, while the patients assessed by CHWs had a baseline assessment conducted on average 5.9 days (SD = 61.2) before treatment initiation. There was a statistically significant (p = 0.019; U = 2637.0) difference between the average number of follow-up visits made by patients between CHWs and PHC audiologists; excluding the baseline assessment, patients assessed by PHC audiologists attended, on average, 4.3 (SD = 2.5; 46/194) monitoring assessments, while patients assessed by CHWs attended, on average, 3.3 (SD = 2.1; 148/194) monitoring assessments. Only 14.2% (21/148) of patients assessed by CHWs

attended six or more monitoring assessments as recommended by the HPCSA (HPCSA, 2018) and the OMP protocol (Figure 4.2), compared with 32.6% (15/46) of patients assessed by PHC audiologists.



No., number; CHW, community health worker; PHC, primary health care.

Figure 4.2 *Percentage of patients attending assessments following the baseline assessment according to tester*

4.4.2.2 Ototoxicity monitoring programme follow-up rates

The follow-up rates of the first six monitoring assessments for patients assessed by PHC audiologists (69.2% – 87.0%) were higher than for those assessed by CHWs (51.2% – 80.6%) (Table 4.2). The average days elapsed between monitoring assessments were fewer for patients assessed by CHWs (53.4 days; SD = 10.3) than for patients assessed by PHC audiologists (64.3 days; SD = 19.3) (Table 4.2). Both groups exceeded the 14–30 days between monitoring assessments recommended by the HPCSA (HPCSA, 2018) and the OMP protocol.

Table 4.2 *Follow-up return rates and average days between consecutive pure tone audiometry assessments according to tester type*

Tester/Monitoring assessments	CHWs				PHC audiologists			
	Follow-up rate %	*n*/group total	Ave no. of days between assessments	SD	Follow-up rate %	*n*/group total	Ave no. of days between assessments	SD
1st–2nd	73.0	108/148	47.8	37.8	87.0	40/46	68.1	83.9
2nd–3rd	80.6	87/108	53.2	62.1	80.0	32/40	55.2	52.6
3rd–4th	74.7	65/87	63.4	75.4	81.3	26/32	48.4	45.4
4th–5th	63.1	41/65	52.3	44.3	69.2	18/26	87.8	107.3
5th–6th	51.2	21/41	49.7	42.1	83.3	15/18	65.7	37.8

SD, standard deviation; CHW, community health worker; PHC, primary healthcare; Ave no., average number.

4.4.3 Ototoxicity characteristics

4.4.3.1 Treatment effects on hearing

More than half (51.5%; 100/194) of the patients presented with a pre-existing hearing loss at the time of the baseline assessment, where a hearing loss was defined as one or more hearing threshold > 25dB HL in one or both ears across all frequencies (ASHA, 2022; Stach & Ramachandran, 2017), increasing to 66.5% (129/194) at the time of the exit assessment. On average, a decline in hearing thresholds from the baseline to exit assessment was evident across all frequencies bilaterally, with the deterioration most pronounced at the high frequencies (Figure 4.3 and Table 4.3). The mean hearing threshold deterioration was statistically significant at the high frequencies 4 kHz (p = 0.006; W = −2.744), 6 kHz (p < 0.001; W = −3.897) and 8 kHz (p < 0.001; W = −4.371) of the left ear, and at the frequencies 500 Hz (p = 0.021; W = −2.309), 1 kHz (p = 0.029; W = −2.178), 2 kHz (p = 0.005; W = −2.248), 4 kHz (p < 0.001; W = −3.573), 6 kHz (p < 0.001; W = −4.456) and 8 kHz (p < 0.001, W = −5.322) in the right ear (Table 4.3).

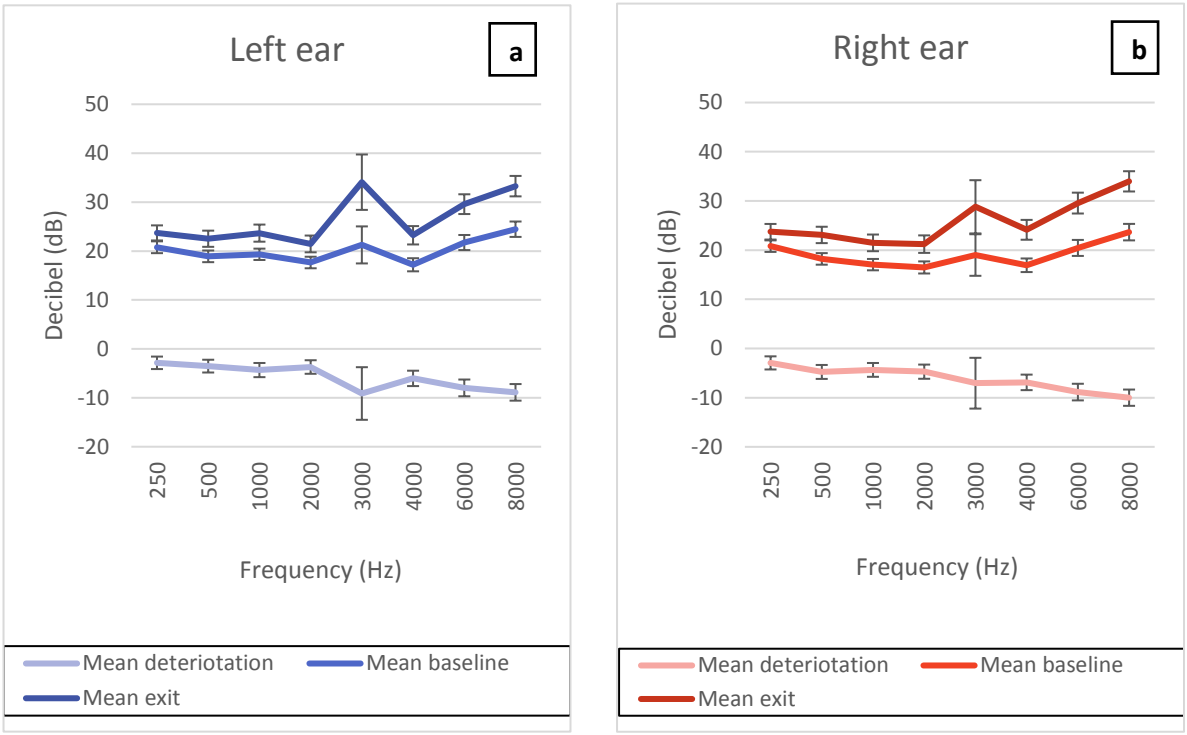


Figure 4.3 *Mean hearing thresholds and deterioration of the left (a) and right (b) ears from baseline to exit assessment (n = 194) (error bars = standard error)*

Table 4.3 *Mean baseline and exit assessment hearing threshold values and hearing deterioration for the left and right ears (n = 194)*

Frequency (Hz)	Mean baseline dB	SD	*n*	Mean exit dB	SD	*n*	Mean deterioration dB	SD	*n*
Left ear									
250	20.8	16.8	194	23.7	21.4	193	-2.8	17.8	193
500	18.9	16.6	194	22.5	23.0	193	-3.5	18.2	193
1000	19.3	16.2	194	23.7	24.3	194	-4.3	20.1	194
2000	17.7	16.4	194	21.5	23.8	193	-3.7	19.3	193
3000	21.3	16.9	20	34.1	29.4	27	-9.1	22.2	17
4000	17.2	18.6	194	23.2	26.1	194	-6.0	21.9*	194
6000	21.7	20.1	170	29.6	27.0	179	-8.0	22.2*	168
8000	24.5	21.9	194	33.3	29.0	193	-8.9	23.5*	193
Right ear									
250	20.8	16.2	192	23.7	22.1	193	-2.9	18.4	191
500	18.2	16.3	193	23.1	23.1	193	-4.8	19.7*	192
1000	17.0	16.1	193	21.5	23.6	194	-4.4	19.5*	193
2000	16.5	17.1	193	21.2	24.8	194	-4.7	20.0*	193
3000	19.0	18.9	20	28.8	27.1	25	-7.1	21.3	17
4000	16.9	19.2	193	24.1	28.1	194	-6.9	21.9*	193
6000	20.4	21.1	169	29.6	28.6	182	-8.9	21.8*	167
8000	23.7	23.3	193	34.0	28.7	194	-10.0	23.0*	193

Hz, Hertz; dB, decibel; SD, standard deviation.

*, statistical significance of $p < 0.05$.

The patients' hearing thresholds were compared according to various pure tone averages (PTAs) in Table 4.4 as follows: overall PTA (0.5 kHz – 4 kHz), low-frequency PTA (0.25 and 0.5 kHz), mid frequency PTA (1 and 2 kHz) and high frequency PTA (3 kHz – 8 kHz). Hearing deterioration was evident across all PTA groups bilaterally; however, deterioration was most pronounced at high frequencies (Table 4.4 and Figure 4.4). The results indicated statistically significant deterioration in the mean high-frequency PTA for the left ($p < 0.001$; $W = -4.125$) and right ($p < 0.001$; $W = -5.247$)

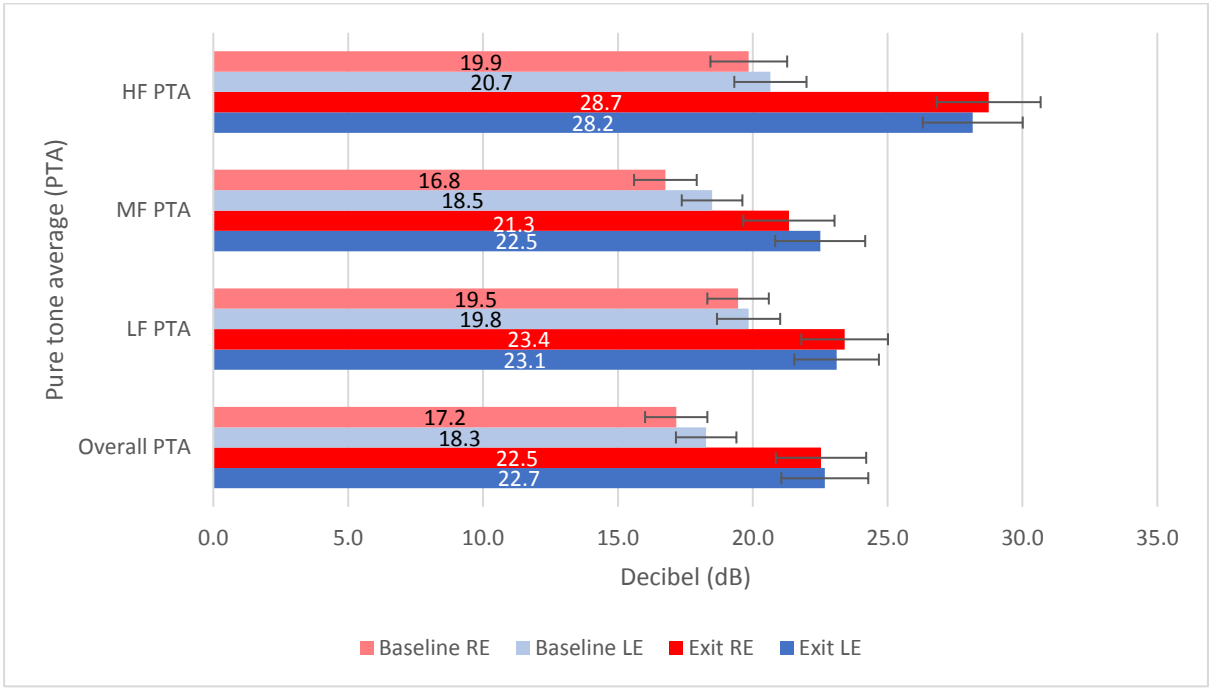
ears. The mean overall PTA deterioration (p = 0.001; W = −3.426) and the mid-frequency PTA deterioration (p = 0.017; W = −2.381) of the right ear from baseline to exit assessment was statistically significant (Table 4.4). There was no statistically significant difference in the mean hearing threshold deterioration at each frequency (p > 0.05; W = −1.499 – 0.240) or mean PTA deterioration between the left and right ears (p > 0.05; W = –1.675–0.637).

Table 4.4 *Mean pure tone average values and hearing deterioration for the left and right ears (n = 194)*

PTA frequency range (Hz)	Mean baseline dB	SD	*n*	Mean exit dB	SD	*n*	Mean deterioration dB	SD	*n*
Left ear									
Overall PTA (500–4000)	18.3	15.6	194	22.7	22.5	194	-4.4	17.6	194
LF PTA (250–500)	19.8	16.3	194	23.1	21.8	193	-3.2	17.2	193
MF PTA (1000–2000)	18.5	15.7	194	22.5	23.3	194	-4.0	18.6	194
HF PTA (3000–8000)	20.7	18.6	194	28.2	25.8	194	-7.6	20.6*	194
Right ear									
Overall PTA (500–4000)	17.2	16.0	193	22.5	23.3	194	-5.3	18.6*	193
LF PTA (250–500)	19.5	15.9	193	23.4	22.3	193	-3.9	18.4	192
MF PTA (1000–2000)	16.8	16.1	193	21.3	23.6	194	-4.5	19.0*	193
HF PTA (3000–8000)	19.9	19.8	193	28.7	26.8	194	-8.5	20.3*	193

PTA, pure tone average; Hz, Hertz; LF PTA, low-frequency pure tone average; MF PTA, mid-frequency pure tone average; HF PTA, high-frequency pure tone average; dB, decibel; SD, standard deviation.

*, statistical significance of p < 0.05.



HF, high frequency; MF, mid frequency; LF, low frequency; LE, left ear; RE, right ear.

Figure 4.4 *Mean baseline and exit assessment pure tone averages of the left and right ears (n = 194) (error bars = standard error)*

4.4.3.2 Description of ototoxic hearing loss

The presence of an ototoxic shift was determined according to the three criteria developed by ASHA (1994), the most widely used and validated criteria (AAA, 2009), as indicated in Table 4.5. Following DRTB treatment, more than half of the patients (51.5%; 100/194) presented with a significant ototoxic shift meeting one or more of the ASHA criteria. Ototoxic shifts occurred most often at high frequencies (4 kHz – 8 kHz). There was no statistically significant difference (p = 0.114; W = −1.581) in ototoxic shifts (meeting one or more of the ASHA criteria) between the left and the right ears.

Table 4.5 *Distribution of patients presenting with an ototoxic shift at the time of exit assessment*

ASHA ototoxic shift criteria	**No ototoxic shift evident %**	***n*/194**	**Group 1† %**	***n*/194**	**Group 2† %**	***n*/194**	**Group 3† %**	***n*/194**
Patients	48.5	94	42.3	82	43.3	84	4.1	8
Left ear	62.9	122	32.5	63	29.4	57	2.1	4
Right ear	55.2	107	33.0	64	36.1	70	4.1	8
Bilateral (left and right)	70.6	137	23.2	45	22.2	43	2.1	4

Source: American Speech-Language-Hearing Association (ASHA). (1994). Audiologic management of individuals receiving cochleotoxic drug therapy. Retrieved from https://www.asha.org/policy/ GL1994-00003/

ASHA, American Speech-Language-Hearing Association.

Group 1 shift of ≥ 20 dB at a single frequency; Group 2, shift of ≥10 dB at 2 adjacent frequencies; Group 3, shift to 'no response' at three consecutive frequencies.

†, 100/194 patients presented with an ototoxic shift that may have met one or more ASHA criteria: 16.0% (31) met one ASHA criterion, 33.0% (64) met two ASHA criteria and 2.6% (5) met three ASHA criteria.

The prevalence of hearing loss severity according to the revised WHO grades of hearing impairment is presented in Table 4.6. From the baseline to the exit assessment, the prevalence of patients presenting with hearing loss meeting any category of hearing loss severity increased from 22.2% (39/194) to 25.8% (50/194). For the left and right ears, from the baseline to the exit assessment, the prevalence of patients presenting with hearing loss meeting any category of hearing loss severity increased from 32% (62/194) to 39.7% (77/194), and from 27.3% (52/193) to 33.5% (66/193), respectively. Following DRTB treatment with kanamycin, there was an increase in patients presenting with a hearing loss meeting each category of hearing loss, excepting mild hearing loss, most notably for the moderate (4.9%; 9/194), total (1.5%; 3/194) and unilateral (9.8%; 19/194) categories of hearing loss severity.

Table 4.6 *Prevalence of hearing loss severity for the left (n = 194) and right (n = 193) ears at the baseline and the exit assessment according to the revised WHO grades of hearing loss*

Category	Patients†ˈ‡				Left Ear				Right Ear			
	Baseline		Exit		Baseline		Exit		Baseline		Exit	
	%	*n*/194	%	*n*/194	%	*n*/194	%	*n*/194	%	*n*/194	%	*n*/194
Normal hearing (-10 dB HL – 19.9 dB HL)	77.8	151	74.2	144	68	132	60.3	117	72.7	141	66.5	127
Mild hearing loss (20.0 dB HL – 34.9 dB HL)	19.1	37	15.5	30	23.7	46	23.2	45	17.5	34	16.5	32
Moderate hearing loss (35.0 dB HL – 49.9 dB HL)	1.5	3	4.6	9	4.1	8	5.7	11	3.6	7	8.2	16
Moderately severe hearing loss (50.0 dB HL – 64.9 dB HL)	1.0	2	2.1	4	1.5	3	5.2	10	2.1	4	1.5	3
Severe hearing loss (65.0 dB HL – 79.9 dB HL)	0.5	1	1.0	2	1.0	2	0.5	1	1.6	3	2.6	5
Profound hearing loss (80.0 dB HL – 94.9 dB HL)	0.0	0	1.0	2	0.5	1	2.1	4	2.1	4	2.6	5
Total hearing loss (≥ 95.0 dB HL)	0.0	0	1.5	3	1.0	2	3.1	6	0.0	0	3.1	6
Unilateral hearing loss (< 20.0 dB HL in the better ear, ≥ 35. 0 dB HL in the worse ear)	3.1	6	9.8	19	-	-	-	-	-	-	-	-

Source: Olusanya, B.O., Davis, A.C., & Hoffman, H.J. (2019). Hearing loss grades and the international classification of functioning, disability and health. *Bulletin of the World Health Organisation*, *97*(10), 725–728. https://doi.org/10.2471/BLT.19.230367

db HL, decibel hearing level.

†, In the better ear.

‡, Pure tone average of 500, 1000, 2000 and 4000 Hz.

4.4.3.3 Predictors of hearing loss

The presence of a pre-existing hearing loss at the time of the baseline assessment was a significant predictor of the deterioration of the overall PTA (0.5 kHz – 4 kHz) of the left (β = −8.750; 95% confidence interval [CI] [−14.953; −2.547]; p = 0.006) and right (β = −13.750; 95% CI [−19.063; −8.437]; p < 0.001) ears over time. Patients presenting with a pre-existing hearing loss had an increase in deterioration of 8.75 and 13.75 times more for the left and right ear, respectively, than those with no pre-existing hearing loss. A history of noise exposure was a second significant predictor of the deterioration for overall PTA (0.5 kHz – 4 kHz) of the right ear (β = −3.750; 95% CI [−6.682; −0.818]; p = 0.012), with patients who indicated exposure to noise having an increase in deterioration of 3.75 times more than those with no history of exposure to noise. Significant predictors of the deterioration of the high frequency PTA (3 kHz – 8 kHz) of the right ear, where hearing deterioration was most prominent, included DRTB and HIV co-infection (β = −5.833; 95% CI [−10.711; −0.956]; p = 0.019) and the presence of a pre-existing hearing loss (β = −26.667; 95% CI [−35.521; −17.812]; p < 0.001). Quantile regression models showed that gender, age, duration of administration of medication, history of tinnitus and tester (CHW or PHC audiologist) were not significant predictors of hearing deterioration (p > 0.05).

4.5 Discussion

4.5.1 Ototoxicity monitoring programme characteristics

4.5.1.1 CHWs as facilitators of decentralised community-based ototoxicity monitoring

The majority (76.3%) of patients in this study were assessed by CHWs, possibly because there were more CHWs (six) acting as testers than PHC audiologists (two). The follow-up rates between consecutive monitoring assessments for patients assessed by CHWs reached as high as 80.6%. In addition, the average number of days between assessments was lower for patients assessed by CHWs (53.4 days) than for those assessed by PHC audiologists (64.3 days). The follow-up rate of patients assessed by CHWs is better than the rate of a community-based DRTB treatment

programme that included ototoxicity monitoring, where the loss to follow-up was reported as being high as 38% (Moyo et al., 2015). Increased usage of ototoxicity monitoring and DRTB treatment services has been associated with older age (> 26 years) (Moyo et al., 2015), timing of baseline assessments (within 1 month of treatment initiation), the presence of pre-existing hearing loss and the development of ototoxic hearing loss following treatment (Ramma, Nhokwara, & Rogers, 2019). The high follow-up rate (80.6%) and the shorter timing between monitoring assessments (53.4 days) for patients assessed by CHWs in the present study may therefore be attributed to the average age of patients (36.2 years), the timing of baseline assessments (5.9 days before treatment duration), the high prevalence (51.5%) of pre-existing hearing loss and the development of ototoxic hearing loss in patients (51.5%) according to one or more of the ASHA criteria following DRTB treatment. In addition, the decentralised community-based nature of the OMP, offered in a PHC framework of care and integrated into DRTB treatments services for increased patient access to care may have attributed to the higher follow-up rates and timing between ototoxicity monitoring assessments for patients assessed by CHWs evident in this study.

Numerous challenges to the implementation of ototoxicity monitoring exist, including a shortage of trained health care professionals and a lack of resources to conduct serial monitoring (Dillard et al., 2021; Khoza-Shangase & Masondo, 2021). Sub-Saharan Africa has an extremely low coverage of ear, nose and throat, audiology and speech therapy services, and the availability of equipment remains poor (Mulwafu et al., 2017). The COVID-19 pandemic has had a severely negative impact on the provision and access to TB services for patients in many countries (Migliori et al., 2021; WHO, 2020c, 2021a, 2021b) exacerbating the existing challenges in treating TB and monitoring associated with ototoxicity. World Health Organization guidelines promote the establishment of community-based TB services primarily delivered by CHWs, and in the context of the COVID-19 pandemic such programmes may mitigate the additional strain on healthcare services and the delivery of essential TB services (WHO, 2020a), including ototoxicity monitoring. The employment of CHW for community-based hearing screening has been shown to provide increased access to hearing services (Bright et al., 2019; Eksteen et al., 2019; Mulwafu et al., 2017) and may offer a solution to the shortage of human resources synonymous with ototoxicity monitoring in South

Africa (O'Donovan, Verkerk, Winters, Chadha, & Bhutta, 2019). In addition, integrating ototoxicity monitoring into existing community-based DRTB treatment services in PHC allows for a patient-centred approach that can increase patients' access to services (Cox et al., 2014). The findings of the current study indicating high follow-up rates and shorter number of days between assessments for patients assessed by CHWs, support the feasibility of a community-based model of care for ototoxicity monitoring facilitated by CHWs as a widely used service.

4.5.1.2 Frequency and timing of ototoxicity monitoring assessments and OMP data management procedures

Although there were positive outcomes for community-based ototoxicity monitoring facilitated by CHWs, the OMP failed to meet some quality benchmarks pertaining to the frequency and timing of ototoxicity monitoring assessments, as stated in the guidelines (HPCSA, 2018) and the OMP protocol. A few patients (14.2% – 32.6%) were assessed with the regularity required by the OMP protocol and the HPCSA. Ideally, ototoxicity monitoring should be conducted every 14 (HPCSA, 2018) to 30 days (OMP protocol); however, the OMP was unable to assess patients with the frequency recommended, with assessments being conducted, on average every 2 months or more (53.4–64.3 days). This demonstrates a missed opportunity for the early detection of hearing loss that could support preventative actions through a change in treatment regimens (Crundwell, Gomersall, & Baguley, 2016). A previous report has also indicated that audiologists conducting ototoxicity monitoring in South Africa do not conduct monitoring assessments with the frequency recommended by the national guidelines (Khoza- Shangase & Masondo, 2020).

Significant differences in the frequency of ototoxicity monitoring by CHWs and by PHC audiologists were identified in this study. The number of monitoring assessments attended by patients assessed by PHC audiologists (mean 4.3) was higher than for those assessed by CHWs (mean 3.3). In addition, almost a third (32.6%) of patients assessed by PHC audiologists attended the recommended six follow-up assessments, compared to 14.2% of patients assessed by CHWs. The reasons for patients assessed by PHC audiologists attending monitoring assessments with more frequency than those assessed by CHWs could not be established in this study. However, a possible

reason may be the supervision and quality control provided by OMP managers of ototoxicity monitoring conducted by CHWs. For CHWs to fulfil their role successfully, regular training and supervision are required (WHO, 2007). Reports from sub-Saharan Africa indicate that the current provision of training for CHWs is not sufficient to improve the quality of care in this region (O'Donovan, O'Donovan, Kuhn, Sachs, & Winters, 2018). Possible suggestions to facilitate ongoing training and supervision for CHWs include the use of tools such as smartphone technology and applications like WhatsApp (O'Donovan et al., 2018). In addition to ototoxicity monitoring for DRTB, CHWs were tasked with conducting home-based, school-based and PHC clinic-based hearing screening services at various locations across the Mitchells Plain/Klipfontein sub-district. This may have affected the ability of CHWs to visit PHC and community health clinics with the frequency required to conduct regular ototoxicity monitoring assessments. Furthermore, patient retention to services during the long and arduous DRTB treatment regimen is known to be difficult, even in a well-resourced programme (Moyo et al., 2015; Ramma et al., 2019); however, the patient variables influencing the frequency of ototoxicity monitoring assessments could not be determined because of the retrospective nature of this study.

The current OMP used paper data collection forms that were manually completed by CHWs and PHC audiologists. However, important demographic information, such as patient gender (33%), was not recorded by CHWs and PHC audiologists, and was, therefore, unavailable for analysis owing to the retrospective nature of this study. An effective OMP data management system enables the comparison of serial monitoring through reliable data recording; this is more efficiently achieved using an electronic data management system (Khoza-Shangase & Masondo, 2021). The use of smartphone technology and cloud-based data management has been shown to offer effective data management for large-scale screening purposes (Eksteen et al., 2019) and is recommended for South African OMPs. Integrating secure data sharing with national health repositories should be considered in an effort to improve the data management procedures of OMPs in South Africa (Swanepoel, 2020).

4.5.2 Ototoxicity characteristics

4.5.2.1 Treatment effects on hearing and predictors of hearing loss

In resource-limited countries such as South Africa, baseline audiometric assessments are often not conducted within the recommended timeframe, before ototoxic damage is likely to occur (Ganesan et al., 2018; Govender & Paken, 2015; Khoza- Shangase & Masondo, 2020) and pre-existing hearing loss is consequently underdiagnosed (Hong et al., 2020). As a result, there are limited data on the prevalence of pre-existing hearing loss in DRTB patients, apart from a recent study by Hong et al. (2020). In the current study, where patients had a baseline assessment conducted on average 16.8 days before treatment initiation, more than half (51.5%) presented with a pre-existing hearing loss. The findings of this study support recently published reports that found that pre-existing hearing loss is prevalent in South African DRTB patients, with 60% of patients assessed using conventional audiometry presenting with a pre-existing hearing loss prior to treatment (Hong et al., 2020). The prevalence of pre-existing hearing loss is an important consideration for South African OMPs, as patients presenting with a pre-existing hearing loss prior to DRTB treatment initiation are at particular risk of developing further hearing loss following the use of aminoglycoside (Hong et al., 2020; Petersen & Rogers, 2015). The increased risk of aminoglycoside-induced hearing loss in DRTB patients with a pre-existing hearing loss is confirmed by the results of the current study, which indicated that patients presenting with a pre-existing hearing loss at the time of the baseline assessment had an increase in hearing deterioration up to 13.75 times higher than those with no pre-existing hearing loss.

A history of noise exposure was a significant predictor of hearing deterioration in the current study, with patients who reported previous exposure to noise presenting with 3.75 times the deterioration in hearing sensitivity compared with those with no history of noise exposure. A previous report concurred, indicating that patients with a history of noise exposure and aminoglycoside treatment had poorer high-frequency hearing thresholds than those exposed to noise without a history of aminoglycoside treatment (Khoza-Shangase, 2020). The findings of this study emphasise the importance of counselling for DRTB patients so that they avoid excessive noise exposure during and after aminoglycoside treatment (Campbell & Le Prell, 2018). In addition, where hearing

deterioration was most prominent at the high frequencies (3 kHz–8 kHz), a significant predictor of hearing loss was DRTB and HIV co-infection. The current study supports previous findings that HIV-infected DRTB patients are more likely to develop an aminoglycoside-induced hearing loss than their non-infected peers (Harris et al., 2012; Hong, Budhathoki, & Farley, 2018). Several significant predictors of hearing loss in DRTB patients were observed, including the presence of a pre-existing hearing loss, HIV co-infection, and a history of exposure to noise. The findings of the current study have important implications for OMPs as they highlight the need for OMPs to identify and prioritise DRTB patients presenting with pre-existing hearing loss, HIV co-infection, and noise exposure for all-oral treatment regimens, together with more vigilant audiological ototoxicity monitoring for early management of hearing deterioration. Patients presenting with these conditions should be identified by OMPs for closer supervision of attendance of ototoxicity monitoring assessments, through direct communication with patients using, for example, smartphone technology and applications like WhatsApp.

4.5.2.2 Description of hearing loss

The reported prevalence of ototoxicity varies widely and depends on various factors, including drug type and dosage, and patients' demographic profile, such as age (> 60 years), the presence of mitochondrial mutations and exposure to loud noises (Ramma et al., 2019). In addition, a lack of standardised research methodology and the use of different criteria to grade and classify hearing loss has influenced the estimates of hearing loss prevalence (Campbell & Le Prell, 2018; Dillard et al., 2021; Ganesan et al., 2018). In the current study, it was found that following DRTB treatment with kanamycin, more than half of the patients (51.5%) presented with a significant ototoxic shift meeting one or more of the ASHA criteria, with ototoxic shifts most often occurring at high frequencies. The finding of this study concurs with a recent hearing loss prevalence estimation, using ASHA criteria, of 49.7% following kanamycin use (Dillard et al., 2021). At the time of the baseline assessment, 51.5% of patients in the current study presented with one of more elevated hearing thresholds (> 25dB HL) in one or both ears across all frequencies; this increased to 66.5% (129/194) at the time of the exit assessment. In order to report on the severity of hearing loss following DRTB

treatment among the patients in this study, and to describe the functional consequences for communication associated with each category of severity, the prevalence of hearing loss severity was presented according to the revised WHO grades of hearing impairment. In the current study, following DRTB treatment with kanamycin, there was a notable increase in patients presenting with hearing loss meeting the moderate (4.9%), total (1.5%) and unilateral (9.8%) categories of hearing loss severity (Olusanya et al., 2019; WHO, 2021b). Patients with untreated moderate or unilateral hearing loss following DRTB treatment may experience difficulties hearing speech in the presence of background noise, while patients presenting with total hearing loss will be profoundly deaf, resulting in a devastating impact on the quality of life (WHO, 2021b).

Patients in this study presented with a bilateral decline in hearing thresholds in all PTA groups, with the most pronounced deterioration at high frequencies at the time of the exit assessment. Drug-resistant TB treatment using kanamycin therefore had a negative effect on the hearing status of the patients in this study, with clinically and statistically significant deterioration of hearing thresholds, most markedly in the high frequencies. The findings of the current study, therefore, support the implementation of OMPs for DRTB patients who are administered aminoglycosides, particularly as the latest WHO DRTB treatment guidelines (WHO, 2020b) continue to include amikacin, which is known to be ototoxic. The occurrence of high-frequency hearing deterioration measured in this study further supports the recommendation (HPCSA, 2018) of the use of EHF audiometry for ototoxicity monitoring in DRTB patients, particularly for those most at risk for developing ototoxic hearing loss. Extended high-frequency audiometry, which assesses air conduction hearing thresholds above 8 kHz, is considered to be the most sensitive behavioural method for detecting early cochlear outer hair cell damage (Campbell & Le Prell, 2018; Harris, Peer, & Fagan, 2012; Petersen & Rogers, 2015) before it affects hearing functionality, and is therefore recommended for the monitoring of ototoxicity (HPCSA, 2018). There have been significant advances in point of care testing and mobile health technologies in hearing assessment (Garinis et al., 2021), which should be considered for ototoxicity monitoring in South Africa. In particular, the use of smartphone technology with automated EHF audiometry hearing assessment applications and cloud-based

capabilities for integrated data management should be considered for community-based ototoxicity monitoring (Bornman, Swanepoel, De Jager, & Eikelboom, 2019; Eksteen et al., 2019; WHO, 2021b; Yousuf Hussein, Swanepoel, Mahomed, & Biagio de Jager, 2018).

The limitations of this study included the absence of quality indicators for audiometry conducted by CHWs and PHC audiologists. In addition, the prevalence of adverse side effects experienced by patients was not established by testers at the time of exit assessment. Immittance measures were not included as part of OMP protocol, and therefore, the prevalence of ototoxic hearing loss may have been influenced by the inclusion of patients presenting with middle-ear disorders. Important data pertaining to patient description and treatment were at times not recorded by testers and were, therefore, unavailable for inclusion in this retrospective study, and thus, may have caused research bias. Researcher and analysis triangulation were applied to reduce the effects of research bias. The use of a non-probability sampling method may limit the generalisability of the results of this study.

4.6 Conclusion

The findings of this study support the employment of CHWs to facilitate community-based ototoxicity monitoring of patients with DRTB. However, the findings reveal that over time, community-based OMPs for DRTB show gaps in service delivery practices, most notably in the frequency and timing of ototoxicity monitoring assessments. The possible reasons for this may highlight the need for ongoing training and supervision of CHWs using novel tools, such as smartphone technology and applications like WhatsApp. Drug-resistant TB treatment with kanamycin caused clinically and statistically significant deterioration of hearing thresholds in patients, most prominently at high frequencies. In this study, the patients co-infected with HIV, those with a pre-existing hearing loss and those exposed to excessive noise were at higher risk for developing ototoxicity-induced hearing deterioration. Patients presenting with these conditions should be identified and prioritised by OMPs for more vigilant ototoxicity monitoring and all-oral treatment regimens. South African OMPs need support and novel approaches for community-based ototoxicity monitoring, with revision of the current recommendations to best suit the South African context. These may include

the widespread integration of ototoxicity monitoring services facilitated by CHWs into the existing decentralised, community-based PHC service delivery frameworks using a portable, automated technology with integrated data-sharing capabilities.

Acknowledgements

The authors acknowledge and thank the key role players who made this study possible through their support and participation.

Competing interests

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

Authors' contributions

L.J.S. and D.S. were responsible for conceptualisation and contributed towards the methodology. L.J.S., D.S. and M.A.G contributed towards the validation and visualisation. M.A.G conducted the formal analysis. L.J.S. was responsible for the investigation. Resources were provided by the Western Cape Department of Health and City of Cape Town Health Department.

L.J.S., D.S. and M.A.G. prepared and wrote the original draft and L.B.d.J assisted with reviewing and editing the manuscript. L.J.S. was responsible for project administration, while D.S, L.B.d.J. and M.A.G. provided supervision for the study. All authors have read and agreed to the published version of the manuscript.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Data availability

The data that support the findings of this study are available on request from the corresponding author, L.J.S., for ethical reasons. The data are not publicly available as they contain information that could compromise the privacy of research participants.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

4.7 References

American Academy of Audiology (AAA). (2009). *American academy of audiology position statement and clinical practice guidelines ototoxicity monitoring.* Retrieved from https://audiology-web.s3.amazonaws.com/migrated/OtoMonGuidelines.pdf_539974c40999c1.58842217.pdf.

American Speech-Language-Hearing Association (ASHA). (1994). Audiologic management of individuals receiving cochleotoxic drug therapy. Retrieved from https://www.asha.org/policy/GL1994-00003/

American Speech-Language-Hearing Association (ASHA). (2022). *Hearing loss in adults*. https://www.asha.org/practice-portal/clinical-topics/hearing-loss/

Bardien, S., Fagan, J., Harris, T., Jong, G.D., Petersen, L., & Schaaf, H.S. (2009). Aminoglycoside-induced hearing loss: South Africans at risk. *SAMJ: South African Medical Journal, 99*(6), 440–441

Bornman, M., Swanepoel, D.W., De Jager, L.B., & Eikelboom, R.H. (2019). Extended high-frequency smartphone audiometry: Validity and reliability. *Journal of the American Academy of Audiology, 30*(03), 217–226. https://doi.org/10.3766/jaaa.17111

Bright, T., Mulwafu, W., Phiri, M., Ensink, R.J.H., Smith, A., Yip, J. … Polack, S. (2019). Diagnostic accuracy of non-specialist versus specialist health workers in diagnosing hearing loss and ear disease in Malawi. *Tropical Medicine and International Health, 24*(7), 817–828. https://doi.org/10.1111/tmi.13238

Campbell, K.C.M., & Le Prell, C.G. (2018). Drug-induced ototoxicity: Diagnosis and monitoring. *Drug Safety, 41*(5), 451–464. https://doi.org/10.1007/s40264-017-0629-8

Centers for Disease Control and Prevention (CDC). (2016). *TB elimination multidrugresistant tuberculosis (MDRTB)*. Retrieved from https://www.cdc.gov/tb/ publications/factsheets/drtb/MDRTB.pdf

City of Cape Town (CoCT). (2013a). *City of Cape Town – Census 2011 – Klipfontein health district*. Retrieved from https://resource.capetown.gov.za/documentcentre/Documents/Maps%20and%20statistics/Klipfontein%20Health%20District.pdf

City of Cape Town (CoCT). (2013b). *City of Cape Town – Census 2011 – Mitchells Plain health district*. Retrieved from https://resource.capetown.gov.za/documentcentre/Documents/Maps%20and%20statistics/Mitchells%20Plain%20Health%20District.pdf

City of Cape Town (CoCT). (2013c). *City of Cape Town – Census 2011 – Southern health district*. Retrieved from https://resource.capetown.gov.za/documentcentre/Documents/Maps%20and%20statistics/Southern%20Health%20District.pdf

City of Cape Town (CoCT). (2013d). *City of Cape Town – Census 2011 – Western health district*. Retrieved from https://resource.capetown.gov.za/documentcentre/Documents/Maps%20and%20statistics/Western%20Health%20District.pdf

Clark, G. (2015). *Rehabilitation care workers' perceptions of the outcomes of a pilot training program*. University of Cape Town. Retreived from https://open.uct.ac.za/bitstream/handle/11427/15488/thesis_hsf_2015_clrgra011-thesis%20%281%29.pdf?sequence=1&isAllowed=y

Cox, H., Hughes, J., Daniels, J., Azevedo, V., McDermid, C., Poolman, M., … Van Cutsem, G. (2014). Community-based treatment of drug-resistant tuberculosis in Khayelitsha, South Africa. *The International Journal of Tuberculosis and Lung Disease, 18*(4), 441–448. https://doi.org/10.5588/ijtld.13.0742

Cox, V., Brigden, G., Crespo, R.H., Lessem, E., Lynch, S., Rich, M.L., … Furin, J. (2018). Global programmatic use of bedaquiline and delamanid for the treatment of

multidrug-resistant tuberculosis. *The International Journal of Tuberculosis and Lung Disease, 22*(4), 407–412. https://doi.org/10.5588/ijtld.17.0706

Cox, V., Cox, H., Pai, M., Stillo, J., Citro, B., & Brigden, G. (2019). Health care gaps in the global burden of drug-resistant tuberculosis. *The International Journal of Tuberculosis and Lung Disease, 23*(2), 125–135. https://doi.org/10.5588/ijtld.18.0866

Crundwell, G., Gomersall, P., & Baguley, D.M. (2016). Ototoxicity (cochleotoxicity) classifications: A review. *International Journal of Audiology, 55*(2), 65–74. https://doi.org/10.3109/14992027.2015.1094188

De Jager, P., & Van Altena, R. (2002). Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis. *The International Journal of Tuberculosis and Lung Disease, 6*(7), 622–627.

Department of Health Republic of South Africa (DOH). (2020). *National department of health stategic plan 2020/21 – 2024/25*. Retrieved from https://www.health.gov.za/wcontent/uploads/2020/11/depthealthstrategicplanfinal2020-21to2024-25-1.pdf

Dillard, L.K., Martinez, R.X., Perez, L.L., Fullerton, A.M., Chadha, S., & McMahon, C.M. (2021). Prevalence of aminoglycoside-induced hearing loss in drug-resistant tuberculosis patients: A systematic review. *Journal of Infection, 83*(1), 27–36. https://doi.org/10.1016/j.jinf.2021.05.010

Eksteen, S., Launer, S., Kuper, H., Eikelboom, R.H., Bastawrous, A., & Swanepoel, D.W. (2019). Hearing and vision screening for preschool children using mobile technology, South Africa. *Bulletin of the World Health Organisation, 97*(10), 672–680. https://doi.org/10.2471/BLT.18.227876

Evans, L.S., Nunurai, R., Farai, M., Timothy, R., Hubert, G.M.L., & Aukje, K.M.-T. (2015). Comparing amikacin and kanamycin-induced hearing loss in multidrug-resistant tuberculosis treatment under programmatic conditions in a Namibian retrospective cohort. *BMC Pharmacology and Toxicology, 16*(1), 36. https://doi.org/10.1186/s40360-015-0036-7

Field, A.P. (2018). *Discovering statistics using IBM SPSS statistics* (5th ed.). Thousand Oaks, CA: Sage.

Gamiet, S., & Rowe, M. (2019). The role of rehabilitation care workers in South African healthcare: A q-methodological study. *African Journal of Disability, 8*, 537. https://doi.org/10.4102/ajod.v8i0.537

Ganesan, P., Schmiedge, J., Manchaiah, V., Swapna, S., Dhandayutham, S., & Kothandaraman, P.P. (2018). Ototoxicity: A challenge in diagnosis and treatment. *Journal of Audiology & Otology, 22*(2), 59–68. https://doi.org/10.7874/jao.2017.00360

Garinis, A.C., Poling, G.L., Rubenstein, R.C., Konrad-Martin, D., Hullar, T.E., Baguley, D.M., … Brewer, C.C. (2021). Clinical considerations for routine auditory and vestibular monitoring in patients with cystic fibrosis. American Journal of Audiology, 30(3S), 1–10. https://doi.org/10.1044/2021_AJA-21-00031 Govender, M., & Paken, J. (2015). Practices employed by audiologists in the management of adult patients with multidrug-resistant tuberculosis in South Africa. *South African Family Practice, 57*(6), 363–372. https://doi.org/10.1080/20786190.2015.1085222

Harris, T., De Jong, G., Bardien, S., Schaaf, H.S., Fagan, J.J., & Petersen, L. (2012). Aminoglycoside-induced hearing loss in HIV-positive and HIV-negative multidrugresistant tuberculosis patients: Research. *South African Medical Journal, 102*(6), 363–366. https://doi.org/10.7196/SAMJ.4964

Harris, T., Peer, S., & Fagan, J.J. (2012). Audiological monitoring for ototoxic tuberculosis, human immunodeficiency virus and cancer therapies in a developing world setting. *Journal of Laryngology and Otology, 126*(6), 548–551. https://doi.org/10.1017/S0022215112000357

Health Professions Council of South Africa (HPCSA). (2018). *Audiological management of patients on treatment that includes ototoxic medications: Guidelines*. Retrieved from https://www.hpcsa.co.za/Uploads/SLH/Guidelines%20for%20Audiological%20

Management%20of%20Patients%20on%20Treatment%20that%20includes%20Ototoxic%20Medications.pdf

Hong, H., Budhathoki, C., & Farley, J.E. (2018). Increased risk of aminoglycosideinduced hearing loss in MDR-TB patients with HIV coinfection. *The International Journal of Tuberculosis and Lung Disease, 22*(6), 667–674. https://doi.org/10.5588/ijtld.17.0830

Hong, H., Dowdy, D.W., Dooley, K.E., Francis, H.W., Budhathoki, C., Han, H.R., & Farley, J.E. (2020). Prevalence of pre-existing hearing loss among patients with drug-resistant tuberculosis in South Africa. *American Journal of Audiology, 29*(2), 199–205. https://doi.org/10.1044/2020_AJA-19-00103

Horsburgh, C.R., Mitnick, C.D., & Lange, C. (2019). The MDR-TB epidemic – A statusreport. *The International Journal of Tuberculosis and Lung Disease, 23*(2), 121–122. https://doi.org/10.5588/ijtld.18.0000

Huth, M.E., Ricci, A.J., Cheng, A.G., & Pearson, J.P. (2011). Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection. *International Journal of Otolaryngology*, 2011, 937861. https://doi.org/10.1155/2011/937861

Khoza-Shangase, K. (2020). Hearing function of gold miners with and without a history of tuberculosis treatment: A retrospective data review. *Brazilian Journal of Otorhinolaryngology, 86*(3), 294–299. https://doi.org/10.1016/j.bjorl.2018.12.003

Khoza-Shangase, K., & Masondo, N. (2020). What are the current audiological practices for ototoxicity assessment and management in the South African healthcare context? *International Journal of Environmental Research and Public Health, 17*(7), 2613. https://doi.org/10.3390/ijerph17072613

Khoza-Shangase, K., & Masondo, N. (2021). In pursuit of preventive audiology in South Africa: Scoping the context for ototoxicity assessment and management. *Journal of Pharmacy & Bioallied Sciences, 13*(1), 46–60. https://doi.org/10.4103/jpbs.JPBS_334_19

Khoza-Shangase, K., & Prodromos, M. (2021). Impact of drug-resistant tuberculosis treatment on hearing function in South African adults: Bedaquiline versus

kanamycin. *The South African Journal of Communication Disorders = Die Suid-Afrikaanse Tydskrif vir Kommunikasieafwykings, 68*(1), e1–e8. https://doi.org/10.4102/sajcd.v68i1.784

Lange, C., Aarnoutse, R.E., Alffenaar, J.W.C., Bothamley, G., Brinkmann, F., Costa, J., …Dheda, K. (2019). Management of patients with multidrug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Disease, 23*(6), 645–662. https://doi.org/10.5588/ijtld.18.0622

Medicins Sans Frontieres (MSF). (2020). *Step up for TB: TB policies in 37 countries (4th ed.)*. Medicins Sans Frontieres. Retrieved from https://msfaccess.org/step-tb-tbpolicies-37-countries-4th-ed

Melchionda, V., Wyatt, H., Capocci, S., Garcia Medina, R., Solamalai, A., Katiri, S., … Lipman, M. (2013). Amikacin treatment for multidrug resistant tuberculosis: How much monitoring is required? *The European Respiratory Journal, 42*(4), 1148–1150. https://doi.org/10.1183/09031936.00184312

Migliori, G.B., Thong, P.M., Alffenaar, J.W., Denholm, J., Tadolini, M., Alyaquobi, F., … Ong, C.W.M. (2021). Gauging the impact of the COVID-19 pandemic on tuberculosis services: A global study. *The European Respiratory Journal, 58*(5).https://doi.org/10.1183/13993003.01786-2021

Moyo, S., Cox, H.S., Hughes, J., Daniels, J., Synman, L., De Azevedo, V., … Via, L.E. (2015). Loss from treatment for drug resistant tuberculosis: Risk factors and patient outcomes in a community-based program in Khayelitsha, South Africa. *PLoS One, 10*(3), e0118919. https://doi.org/10.1371/journal.pone.0118919

Mulwafu, W., Ensink, R., Kuper, H., & Fagan, J. (2017). Survey of ENT services in sub-Saharan Africa: Little progress between 2009 and 2015. *Global Health Action,10*(1), 1289736. https://doi.org/10.1080/16549716.2017.1289736

Ndjeka, N., Hughes, J., Reuter, A., Conradie, F., Enwerem, M., Ferreira, H., … Maartens, G. (2020). Implementing novel regimens for drug-resistant TB in South Africa: What can the world learn? *International Journal of Tuberculosis and Lung Disease, 24*(10), 1073–1080. https://doi.org/10.5588/ijtld.20.0174

O'Donovan, J., O'Donovan, C., Kuhn, I., Sachs, S.E., & Winters, N. (2018). Ongoing training of community health workers in low-income andmiddle-income countries: A systematic scoping review of the literature. *BMJ Open, 8*(4), e021467. https://doi.org/10.1136/bmjopen-2017-021467

O'Donovan, J., Verkerk, M., Winters, N., Chadha, S., & Bhutta, M.F. (2019). The role of community health workers in addressing the global burden of ear disease and hearing loss: A systematic scoping review of the literature. *BMJ Global Health, 4*(2), e001141. https://doi.org/10.1136/bmjgh-2018-001141

Olusanya, B.O., Davis, A.C., & Hoffman, H.J. (2019). Hearing loss grades and the international classification of functioning, disability and health. *Bulletin of the World Health Organisation, 97*(10), 725–728. https://doi.org/10.2471/BLT.19.230367

Petersen, L., & Rogers, C. (2015). Aminoglycoside-induced hearing deficits – A review of cochlear ototoxicity. *South African Family Practice, 57*(2), 77–82. https://doi.org/10.1080/20786190.2014.1002220

Ramma, L., Heinze, B., & Schellack, N. (2019). Prevention of treatment-induced ototoxicity: An update for clinicians. *South African Medical Journal, 109*(3), 145–149. https://doi.org/10.7196/SAMJ.2019.v109i3.13903

Ramma, L., Nhokwara, P.T., & Rogers, C. (2019). Statistical factors associated withutilisation of ototoxicity monitoring services for multi-drug-resistant tuberculosis patients in the Western Cape. *The South African Journal of Communication Disorders = Die Suid-Afrikaanse Tydskrif vir Kommunikasieafwykings, 66*(1), e1–e6. https://doi.org/10.4102/sajcd.v66i1.596

Republic of South Africa Statistics Department. (2021). *Statistical release p0302: Midyear population estimates 2021 embargoed*. Retrieved from http://www.statssa.gov.za/publications/P0302/P03022021.pdf

Schacht, J., Talaska, A.E., & Rybak, L.P. (2012). Cisplatin and aminoglycoside antibiotics: Hearing loss and its prevention. *The Anatomical Record: Advances in Integrative Anatomy and Evolutionary Biology, 295*(11), 1837–1850. https://doi.org/10.1002/ar.22578

Stach, B. A., & Ramachandran, V. (2017). *Clinical audiology an introduction* (3rd ed. ed.). Plural Publishing, Incorporated. http://public.eblib.com/choice/PublicFullRecord.aspx?p=6499978

Stevenson, L.J., Biagio-de Jager, L., Graham, M.A., & Swanepoel, D.W. (2021). Community-based ototoxicity monitoring for drug-resistant tuberculosis in South Africa: An evaluation study. *International Journal of Environmental Research and Public Health, 18*(21), 11342. https://www.mdpi.com/1660-4601/18/21/11342

Swanepoel, W. (2020). Ehealth technologies enable more accessible hearing care. *Seminars in Hearing, 41*(2), 133–140. https://doi.org/10.1055/s-0040-1708510

The South African National Aids Council. (2017). *Monitoring and evaluation plan for the national strategic plan on HIV, TB and STI (2017–2022)*. Retrieved from https://sanac.org.za/wp-content/uploads/2020/01/114725-ME-Plan-3rd-Proof-5-Aug.pdf

Wells, C.D., Cegielski, J.P., Nelson, L.J., Laserson, K.F., Holtz, T.H., Finlay, A., … Weyer, K. (2007). HIV infection and multidrug-resistant tuberculosis: The perfect storm. *The Journal of Infectious Diseases, 196*(Suppl 1), 86–107. https://doi.org/10.1086/518665

World Health Organisation. (2007). *Community health workers: What do we know about them? The state of the evidence on programmes, activities, costs and impact on health outcomes of using community health workers*. Retrieved from https://www.who.int/hrh/documents/community_health_workers.pdf

World Health Organisation. (2020a). *Global tuberculosis report 2020*. World Health Organisation. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf

World Health Organisation. (2020b). *WHO consolidated guidelines on tuberculosis. Module 4: Treatment – Drug-resistant tuberculosis treatment.* World Health Organisation. Retrieved from https://www.who.int/publications/i/item/9789240007048

World Health Organisation. (2020c). *World health organisation (WHO) information note tuberculosis and COVID-19.* World Health Organisation. Retrieved from https://www.who.int/docs/default-source/documents/tuberculosis/infonote-tbcovid-19.pdf

World Health Organisation. (2021a). *Global tuberculosis report 2021.* World Health Organisation. Retrieved from https://www.who.int/publications/i/item/9789240037021

World Health Organisation. (2021b). *World report on hearing*. World Health Organisation. Retrieved from https://www.who.int/publications/i/item/worldreport-on-hearing

Wrohan, I., Redwood, L., Ho, J., Velen, K., & Fox, G.J. (2021). Ototoxicity among multidrug-resistant TB patients: A systematic review and meta-analysis. *The International Journal of Tuberculosis and Lung Disease, 25*(1), 23–30. https://doi.org/10.5588/ijtld.20.0217

Xie, J., Talaska, A.E., & Schacht, J. (2011). New developments in aminoglycosidetherapy and ototoxicity. *Hearing Research, 281*(1–2), 28–37. https://doi.org/10.1016/j.heares.2011.05.008

Yousuf Hussein, S., Swanepoel, W., Mahomed, F., & Biagio de Jager, L. (2018).Community-based hearing screening for young children using an mhealth servicedelivery model. *Global Health Action, 11*(1), 1467077. https://doi.org/10.1080/16549716.2018.1467077

CHAPTER 5: EXTENDED HIGH-FREQUENCY AUDIOMETRY FOR OTOTOXICITY MONITORING: A LONGITUDINAL EVALUATION OF DRUG-RESISTANCE TUBERCULOSIS TREATMENT

Authors: Stevenson, L. J.; Biagio-de Jager, L.; Graham, M. A.; Swanepoel, D.

Journal: American Journal of Audiology

Review submission confirmation: 27 May 2022 (Appendix I)

Publication: To be confirmed

5.1 Abstract

Purpose: To describe extended high-frequency (EHF) pure tone audiometry monitoring of ototoxicity in a longitudinal treatment program for drug-resistant tuberculosis (DRTB).

Method: This was a retrospective record review of longitudinal conventional (0.25–8 kHz) and EHF (9–16 kHz) audiometry for ototoxicity monitoring of DRTB patients undergoing treatment at community-based clinics between 2013 and 2017. Data from 69 patients with an average age of 37.9 years (SD = 11.2; range = 16.0 to 63.8 years) were included. Patients were assessed by primary health care (PHC) audiologists (87%) or community health care workers (CHWs) (13%) using portable audiological equipment. The average length of time between initial and exit assessments was 84.6 days (SD = 74.2; range = 2 to 335 days).

Results: EHF ototoxicity of a mild or greater degree of hearing loss (> 25 dB HL in one or both ears across frequencies) was evident in 85.5% of patients' post-treatment, compared to 47.8% of patients across conventional frequencies. EHF audiometry

demonstrated an ototoxic shift (ASHA criteria) in 56.5% of cases compared to 31.9% when only conventional audiometry was considered. Mean hearing deterioration for patients was significant across EHFs (9–16 kHz) bilaterally ($p < 0.05$). Absent EHF thresholds at the initial assessment, owing to maximum output limits, was a limitation that occurred most frequently at 16 kHz (17.4%; 24/138).

Conclusion: EHF audiometry is most sensitive for the early detection of ototoxicity and should be included in monitoring programs. Clinical ototoxicity monitoring protocols should consider shortened assessment approaches that target frequencies most sensitive to ototoxicity, including EHF.

5.2 Introduction

A plethora of drugs are known to cause ototoxicity (Lanvers-Kaminsky et al., 2017; Watts, 2019), resulting in damage to the cochlear or vestibular system of the inner ear, or both (Rizk et al., 2020), depending on their dosage, duration and route of administration (Lanvers-Kaminsky et al., 2017; Steyger, 2011). Cochleotoxicity typically results in tinnitus and/or hearing loss, while vestibulotoxicity causes impairment of coordination, such as dizziness, balance and vertigo (Rizk et al., 2020). The drug classes commonly associated with ototoxicity include aminoglycoside antibiotics, typically used in the treatment of bacterial and mycobacterial infections (Kros & Steyger, 2019; Lanvers-Kaminsky et al., 2017; Steyger, 2021a), and platinum-based chemotherapies, used in the treatment of cancers (Campbell & Le Prell, 2018; Lanvers-Kaminsky et al., 2017).

Ototoxic medications can cause vestibular and cochlear damage via several mechanisms (Rizk et al., 2020). Damage caused to the cochlea (Meiyan et al., 2017; Steyger, 2021a), resulting in permanent ototoxic hearing loss, typically progresses from the high to low frequency ranges of hearing sensitivity (Blankenship et al., 2021; Ganesan et al., 2018; Ghafari et al., 2020; Steyger, 2021a). Both platinum-based chemotherapeutic agents and aminoglycosides initially affect outer hair cells at the basal, high frequency region of the cochlea, resulting in high frequency hearing loss (Campbell & Le Prell, 2018; Ganesan et al., 2018; Meiyan et al., 2017; Rizk et al., 2020; Steyger, 2021a). Outer hair cell damage progresses to the lower frequencies of

the apical region of the cochlea with continued ototoxic drug exposure, eventually leading to inner hair cell death (Campbell & Le Prell, 2018; Ganesan et al., 2018; Meiyan et al., 2017; Rizk et al., 2020; Steyger, 2021a).

Monitoring the hearing of patients undergoing ototoxic treatment is a necessary precaution to preserve hearing and to mitigate the negative impact of hearing loss (Campbell & Le Prell, 2018; Ganesan et al., 2018; Prendergast et al., 2020; Watts, 2019). Serial ototoxicity monitoring detects changes in hearing for the purpose of early identification, prevention and treatment of hearing loss (American Academy of Audiology [AAA], 2009; American Speech-Language-Hearing Association [ASHA], 1994; Health Professions Council of South Africa [HPCSA], 2018). The detection of ototoxic shifts in hearing allows clinicians to adjust treatment regimens, or substitute treatment with an all-oral regimen, which is less toxic and more effective (Khoza-Shangase & Prodromos, 2021; Lange, Aarnoutse, et al., 2019; Lange, Dheda, et al., 2019; Lanvers-Kaminsky et al., 2017; Van Deun et al., 2020; Watts, 2019). The basic test battery for detecting ototoxic hearing loss includes the use of conventional behavioural pure tone audiometry where air conduction hearing thresholds of the frequencies 0.25–8 kHz are assessed (Campbell & Le Prell, 2018; Ganesan et al., 2018).

Extended high-frequency (EHF) pure tone audiometry, assessing hearing above 8 kHz, is a sensitive behavioural method for detecting early cochlear outer hair cell damage (Campbell & Le Prell, 2018; Ganesan et al., 2018; Harris, Peer, et al., 2012). EHF audiometry has been recommended for ototoxicity monitoring in patients receiving potentially ototoxic drugs, such as aminoglycosides and platinum-based chemotherapy, for the treatment of illnesses such as tuberculosis, cancer and cystic fibrosis (AAA, 2009; ASHA, 1994; Caumo et al., 2017; HPCSA, 2018). Despite recommendations for using EHF audiometry, it is still not routinely employed for ototoxicity monitoring (Blankenship et al., 2021; Ganesan et al., 2018). The lack of routine EHF audiometry use has been attributed to, amongst others, time constraints and limited audiological equipment resources (Blankenship et al., 2021; Campbell & Le Prell, 2018). A key limitation of EHF audiometry is that it may be impractical because of the additional time needed for an assessment (Ganesan et al., 2018). Patients in

need of ototoxic medications are often ill and fatigued, and completing valid behavioural testing may be challenging and time consuming for them (Rieke et al., 2017). In addition, the possibility of absent hearing thresholds in the EHF range of hearing, equipment output limitations, and the choice of which EHFs to assess are challenges faced by testers when using EHF audiometry in clinical settings (Prendergast et al., 2020; Wang et al., 2021).

Drug-resistant tuberculosis (DRTB), which occurs when tuberculosis-causing bacteria become resistant to the drugs used to treat tuberculosis, is a widespread condition with ototoxic treatment regimens (Centres for Disease Control and Prevention (CDC) [CDC], 2016). Half a million people developed DRTB globally in 2019, with the incidence remaining stable in 2021 (World Health Organisation [WHO], 2020b, 2021a). China, India and the Russian Federation account for approximately half the global burden of DRTB (WHO, 2020b). Up to 2018, before the release of the updated DRTB treatment regimen guidelines (Department Health Republic of South Africa [DOH], 2018; WHO, 2020c), the treatment regimen for DRTB patients included the use of aminoglycosides (DOH, 2018). The latest WHO DRTB treatment guidelines (WHO, 2020c) have now recommended the use of less toxic, more efficient all-oral DRTB treatment regimens. Access to these newer drugs is, however, very limited in some countries (Lange, Aarnoutse, et al., 2019). Almost half (46%; 17/37) of the high-burden TB countries recently surveyed reported still using injectable aminoglycosides in the treatment of DRTB (MSF, 2020b), resulting in the continued risk of ototoxicity and the need for ototoxicity monitoring for these patients.

Limited studies have reported using EHF audiometry for DRTB ototoxicity monitoring (Appana et al., 2016; Ghafari et al., 2020; Hong et al., 2020a). In instances where ototoxicity monitoring of DRTB patients employed EHF audiometry, a high prevalence of ototoxic hearing loss (74 to 100%) was reported (Appana et al., 2016; Ghafari et al., 2020; Hong et al., 2020a). Owing to the limited use of EHF audiometry and the application of various criteria to define ototoxicity, the prevalence of aminoglycoside-induced EHF hearing loss, and the subsequent value of EHF audiometry to identify early changes in hearing remains unclear (Ganesan et al., 2018; Steyger, 2021a). Additional insights into cochleotoxicity can be garnered from widespread ototoxicity

monitoring with improved, data-driven measures of hearing loss, including EHF audiometry (Steyger, 2021a, 2021b). This study therefore aimed to describe longitudinal monitoring of ototoxicity with EHF audiometry in patients receiving aminoglycoside treatment for DRTB.

5.3 Method

This retrospective record review aimed to describe EHF audiometry monitoring of ototoxicity for DRTB treatment with EHF audiometry, and the prevalence of ototoxic hearing loss observed in this population. The study was part of a larger longitudinal, retrospective descriptive study of a decentralised community-based ototoxicity monitoring program (OMP) for patients with DRTB, using conventional and EHF audiometry facilitated by community health workers (CHWs) and primary health care (PHC) audiologists between 2013 and 2017 (Stevenson et al., 2021). The objective of the larger study was to compare the OMP service delivery practices with the international (AAA, 2009; ASHA, 1994) and national (HPCSA, 2018) recommended guidelines for ototoxicity monitoring to improve services and to guide future OMP implementations. Quantitative data was collected at community-based community health centres and primary health care (PHC) clinics in two sub-districts of the City of Cape Town, South Africa, namely the Mitchells Plain/Klipfontein and the Western/Southern sub-districts and made available to the authors of this study only.

The study was approved by the Institutional Review Board (or Ethics Committee) of the University of Pretoria (GW20161128HS; 63/2017), the City of Cape Town (7788) and the Western Cape Department of Health (WC_2017RP22_896).

5.3.1 Participants

This study included patients from the larger study who met the following selection criteria: 1) tested using both conventional (0.25, 0.5, 1, 2, 4, 6 and 8 kHz) and EHF (9, 11.2, 12.5, 14, and 16 kHz) behavioural pure tone audiometry; 2) had an initial assessment conducted, and one or more follow-up monitoring assessments conducted thereafter; 3) EHF audiometry was used for both the initial and exit assessments. Non-probability purposive sampling was used to select all patients with DRTB, regardless

of age, gender or hearing status. Of the 831 patients included in the parent study, 69 patients met the selection criteria and were eligible for inclusion in this study (Figure 5.1). The patient interviews and ototoxicity monitoring assessments were conducted by six CHWs and two PHC audiologists who were the testers at 19 PHC clinics and community health centres. In 2012, the Western Cape Department of Health initiated a pilot project where 30 CHWs underwent upskill training to become members of the PHC team (Gamiet & Rowe, 2019). The CHWs were trained for community-based rehabilitation to support people with disabilities in two underserved communities of the Western Cape (DOH, 2018; Gamiet & Rowe, 2019). These CHWs were also trained to facilitate ototoxicity monitoring for DRTB in community-based settings.

5.3.2 Data Collection Procedures

The data collection procedure for this study was the same as that of the larger study (Stevenson et al., 2021) from which the patient sample was obtained. At the time of data collection, patients receiving the standardised DRTB treatment regimen stipulated by the South African Department of Health would have been administered second-line drugs, including injectable aminoglycosides (DOH, 2013). Patients undergoing DRTB treatment visited a PHC clinic or community health centre daily for the first six months of treatment to receive their medication from a nurse. After the initial six-month treatment period, medication was continued for 18 months with patients visiting a clinic/centre weekly to obtain their medication, and monthly to consult with their managing doctor. All patients who received ototoxic medication for treatment of DRTB were referred by their managing doctor and included in the OMP as part of the package of care.

At the time of data collection OMP developers relied on the international guidelines of the American Speech-Language-Hearing Association (ASHA) (ASHA, 1994) and the American Academy of Audiology (AAA) (AAA, 2009) when developing the OMP procedure protocol. An unpublished draft of the Health Professions Council of South Africa's (HPCSA) national ototoxicity monitoring guideline was, however, available to the OMP developers. OMP developers made adaptions to the recommendations of the international and national guidelines for the timing and frequency of ototoxicity monitoring assessments, to suit the context and resources available to the OMP.

Testers travelled with portable audiological equipment to the clinics/centres in each sub-district to conduct ototoxicity monitoring assessments. PHC audiologists and CHWs were testers in the Michell's Plain/Klipfontein sub-district whereas only PHC audiologists were testers in the Western/Southern sub-district. The protocol followed by the OMP for audiological ototoxicity monitoring assessments at the time of data collection was as follows: At the time of a patient's initial assessment a case history intake interview was conducted by the CHW or PHC audiologist who manually recorded patient information on a paper-based data collection form. During the interview, information was obtained from the patient's medical records in a clinic file and/or verbally reported by the patient to the CHW or PHC audiologist. Identifying information including the patient's name, date of birth and gender was recorded on the data collection form. CHWs and PHC audiologists also completed a checklist on the data collection form indicating patients' HIV status, DRTB medication/s and risk factors for ototoxic hearing loss, such as exposure to excessive noise and pre-existing hearing loss. Excessive noise exposure was defined by the OMP as exposure to noise with an intensity of ≥ 85 dBA (A-weighted decibels) for a duration of eight hours or longer (DOH, 2001). Initial and monitoring assessments included bilateral otoscopy, conventional behavioural pure tone audiometry and EHF audiometry (0.25, 0.5, 1, 2, 4, 6, 8, 9, 11.2, 12.5, 14 and 16 kHz). If pathology was suspected following otoscopy, the patient was referred to the managing doctor or nurse for appropriate treatment, and referred for audiometry, according to the OMP protocol. Initial assessments were conducted prior to, on the same day, or within two weeks of the DRTB treatment initiation, while monitoring assessments were conducted once a month during the initial six-month treatment regimen, and then at three, six, and 18 month intervals thereafter. The presence of an ototoxic shift was determined according to the three criteria developed by ASHA (1994), the most widely used and validated criteria (AAA, 2009), where a change in hearing thresholds was determined relative to the hearing thresholds obtained during the initial assessment. The criteria to indicate hearing decrease for ototoxicity monitoring were defined as: ≥ 20 dB HL pure tone threshold decrease at any one test frequency; ≥ 10 dB HL pure tone threshold decrease at any two adjacent test frequencies; no response at three consecutive test frequencies where pure tone threshold responses were previously obtained. Changes were confirmed by repeat testing. Where an ototoxic shift meeting the criteria (ASHA, 1994)

was evident, the managing doctor was informed, and monitoring assessments were then conducted every two weeks until no change in hearing thresholds was detected. Assessments were conducted in a quiet environment using the KUDUwave audiometer (eMoyo, Johannesburg, South Africa) employing insert earphones covered by noise-reducing circumaural earcups. Typically, automated testing would have been done applying the Hughson-Westlake procedure (ISO 8253-1), automatic standard ascending and shortened and standard bracketing; however, a manual mode of threshold determination, using the modified method of limits test paradigm (Stach & Ramachandran, 2017), may also have been selected by PHC audiologists in some instances. The maximum audiometer output limits across EHFs were 90 dB at 6 kHz; 80 dB at 8, 9 and 12.5 kHz; 75 dB at 11.2 kHz; 65 dB at 14 kHz and 45 dB at 16 kHz.

Each patient's descriptive (gender, audiological symptoms, treatment regimen), audiological data and risk factors for ototoxicity (history of exposure to excessive noise, pre-existing hearing loss and DRTB and HIV coinfection) were recorded manually by the testers on data collection forms and stored in the patient's clinic file. A copy of each patient's data collection form was kept with the tester and regularly made available to the managing PHC audiologist responsible for each sub-district for review. Upon completion of a patient's DRTB treatment and ototoxicity monitoring, the data collection form was stored permanently with the PHC audiologist responsible for each sub-district. The researchers requested the hardcopies of the patients' data collection forms from the managing PHC audiologists in each sub-district for anonymised data capturing and analysis.

5.3.3 Data analysis

This study aimed to describe longitudinal monitoring of ototoxicity with EHF audiometry in patients receiving aminoglycosides for DRTB treatment by determining the sensitivity of EHF audiometry for the early detection of ototoxicity. Therefore, a statistical analysis plan was defined prior to data analysis describing which variables, outcomes and statistical analysis methods would be included in the study to achieve the aim (Yuan et al., 2019) and how missing data would be handled. Statistical analysis models used a within subject comparison of longitudinal hearing deterioration (dependant variables) when considering conventional and EHFs (independent

variables). Data were imported from Excel into Statistical Package for Social Sciences (SPSS) software (version 27) after which descriptive statistics such as frequency distributions, measures of central tendency, and measures of variability were used to present and interpret the data in a meaningful way. Since all the continuous scale data differed significantly from normal distribution (Shapiro-Wilk p-values < 0.05), nonparametric tests were used (Field, 2018). The Wilcoxon signed-rank (Z) test was used to determine whether there were significant differences between dependent groups (initial and exit audiometric assessment and left and right ears).

Some hearing thresholds could not be obtained for initial and exit assessments owing to the maximum equipment output limits being reached. In these cases, analysis included only instances where thresholds were present at initial assessment. Where exit assessment thresholds were unobtainable because of the maximum output limits being reached, corrections were made by replacing absent values with the maximum output limit plus one intensity increment (viz. 5 dB).

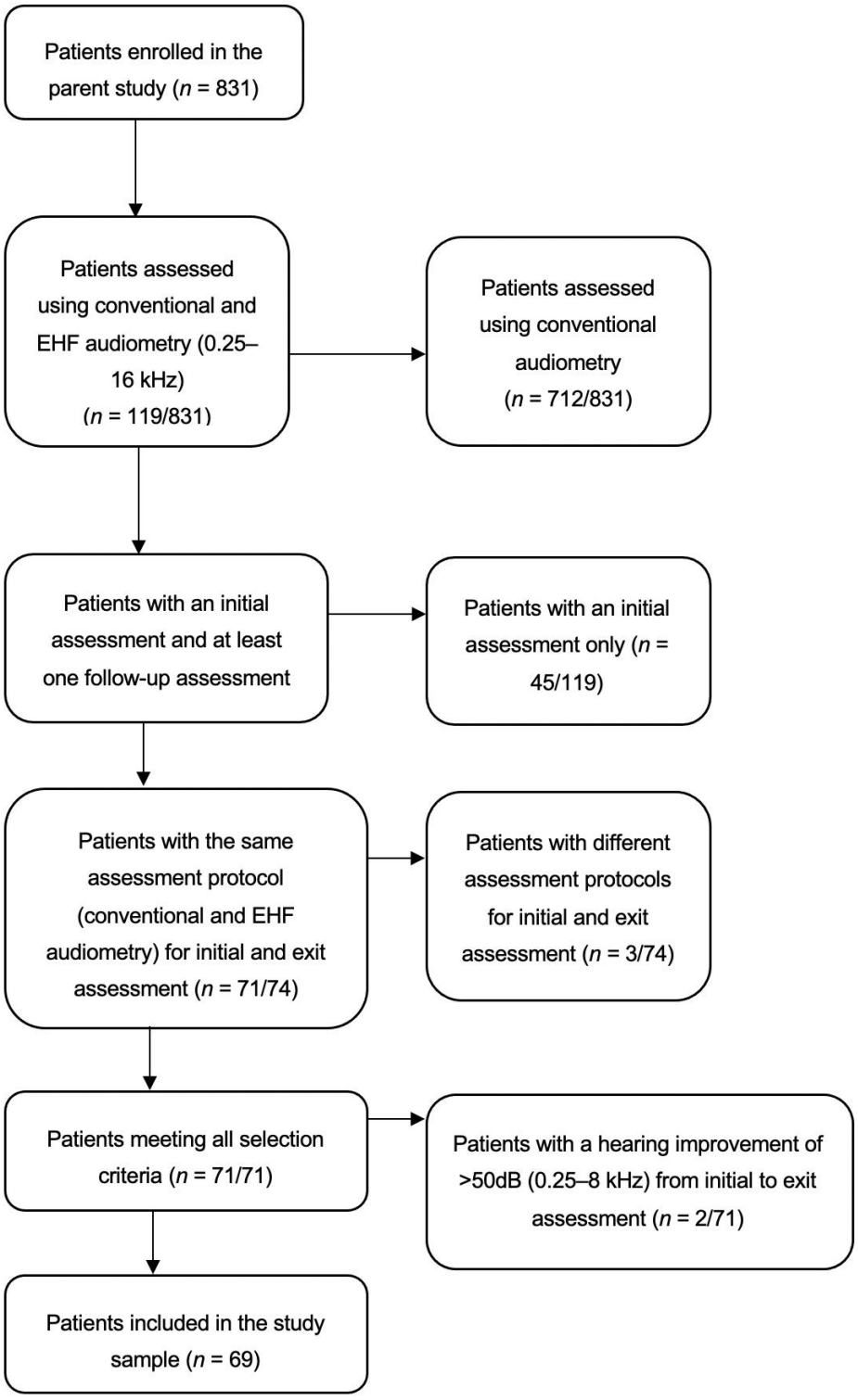
Some descriptive data (gender and medication type) were missing as this was not recorded on the data collection forms by the CHWs and PHC audiologists and was therefore unavailable to the researchers for inclusion in this retrospective study. For some patients, hearing thresholds were not measured by the CHWs and PHC audiologists, most frequently occurring at the low frequencies (0.25 and 0.5 kHz) of the exit assessments. The pairwise deletion method for handling missing data was used instead of the listwise deletion method because the latter leads to a smaller sample size and lower statistical power, as the entire record is excluded from analysis if a single value is missing (Raaijmakers, 1999).

5.4 Results

5.4.1 Participants

Of the 831 patients included in the parent study, 71 met the selection criteria and were eligible for inclusion. Two patients with results indicating technical or procedural issues related to their initial assessments were excluded. The final analytic sample included

69 patients (Figure 5.1) with a mean age of 37.9 years (SD = 11.2; range = 16.0 to 63.8 years) (Table 5.1).



EHF, extended high-frequency; kHz, kilohertz

Figure 5.1 *The ototoxicity monitoring program's application of EHF audiometry and the study patient selection procedure*

Table 5.1 *Patient description at the time of the initial assessment (n = 69)*

	%	*n*
Gender		
Not recorded	27.5	19
Male	43.5	30
Female	29.0	20
Risk factor for ototoxicity		
DRTB and HIV coinfection	17.4	12
Noise exposure	10.1	7
Audiological self-reported symptoms		
Tinnitus	13.0	9
Otalgia	2.9	2
Hearing loss	5.8	4
Tester		
CHW	13.0	9
PHC audiologist	87.0	60

DRTB, drug-resistant tuberculosis; HIV, human immunodeficiency; CHW, community health worker; PHC, primary health care.

At the time of the initial assessment, 17.4% (12/69) of patients reported DRTB and HIV co-infection, 10.1% (7/69) reported a history of excessive noise exposure, and 13.0% (9/69) reported experiencing tinnitus. Gender (27.5%; 19/69) and medication type (47.8%; 33/69) administered were not recorded on the data collection forms by some testers. Of the 36 patients with a medication type recorded on their data collection form, 100%were administered kanamycin. Of the 36/69 patients who had a medication type recorded, 30/36 also had a treatment initiation date and initial assessment date recorded, allowing the determination of treatment duration at the time of the initial assessment. Initial assessments were conducted on average 40.3 days (SD = 70.9; range = 0 to 301 days) after treatment initiation, with just one patient having an initial assessment conducted on the same day as treatment initiation. The average length of time between initial and exit assessments was 84.6 days (SD = 74.2; range = 2 to 335 days).

5.4.2 Ototoxicity characteristics

In the current study, hearing loss was defined as one or more hearing threshold > 25 dB HL in one or both ears across conventional frequencies (0.25–8 kHz) and EHFs (0.25–16 kHz) (ASHA, 2022; Stach & Ramachandran, 2017). At the initial assessment, 36.2% (25/69) of patients presented with a hearing loss in one or more frequency in the conventional range (0.25–8 kHz) compared to 65.2% (45/69) of patients when also considering EHF thresholds (0.25–16 kHz). Hearing loss in patients at the time of the exit assessment increased to 47.8% (33/69) considering only conventional frequencies compared to 85.5% (59/69) when EHFs were also considered. Some hearing thresholds could not be determined for initial and exit assessments because of the maximum equipment output limits reached (Table 5.2).

Table 5.2 *Absent hearing thresholds for pure tone audiometry owing to maximum audiometer output limits across frequencies (left and right ears combined; n = 138)*

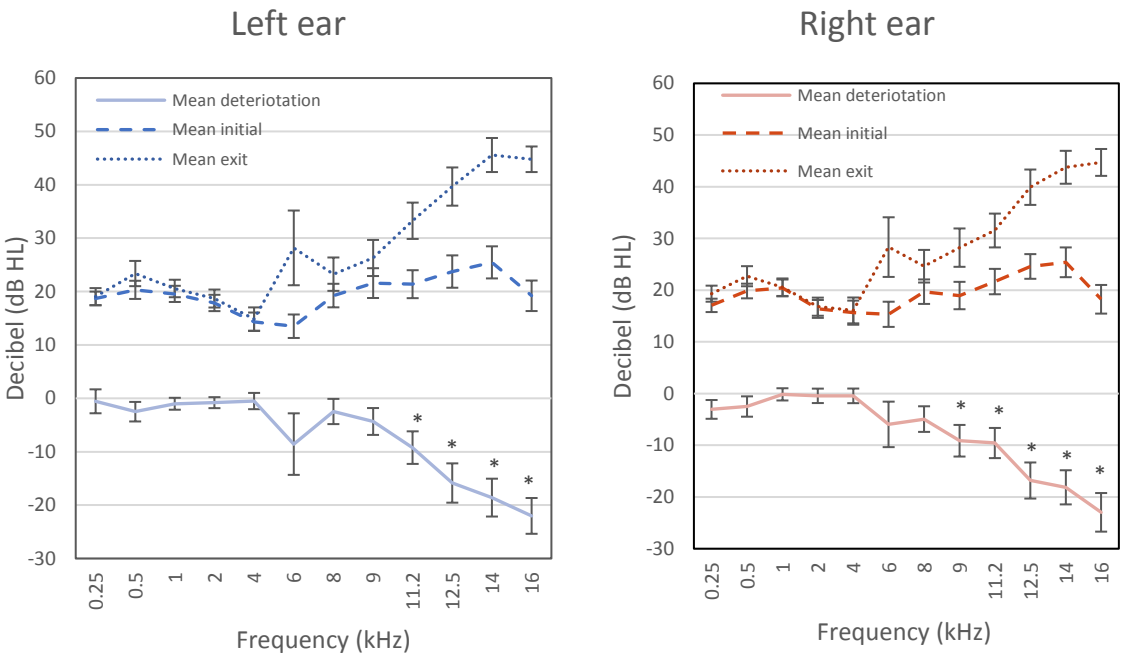
Frequency kHz* and maximum output (dB)	6 (90)	8 (80)	9 (80)	11.2 (75)	12.5 (80)	14 (65)	16 (45)
Initial test % (n)	0.7 (1)	1.4 (2)	0.7 (1)	2.2 (3)	3.6 (5)	3.6 (5)	17.4 (24)
Exit test % (n)	0.7 (1)	1.4 (2)	7.2 (10)	3.6 (5)	7.2 (10)	10.1 (14)	23.2 (32)

**Absent thresholds owing to the maximum output limits only recorded for frequencies above 4 kHz.*

kHz, Kilohertz; dB, decibel.

The distribution of initial and exit assessment hearing thresholds and longitudinal changes in hearing for the patients are presented in Figure 5.2 (Table 5.5 of supplementary material). On average, a decline in hearing thresholds from the initial to exit assessment was evident across all frequencies in both ears, with the deterioration most pronounced in the EHF range (Figure 5.2). The mean deterioration was statistically significant at EHF thresholds of the left (11.2, 12.5, 14 and 16; p = 0.000 to 0.005; Z = -4.947 to -2.801) and the right ears (9, 11.2, 12.5, 14 and 16 kHz; p = 0.000 to 0.007; Z = -4.705 to -2.711). Patients' mean hearing thresholds at the initial assessment were compared to the mean hearing thresholds at the exit assessment according to various pure tone averages (PTA) (Table 5.3). Hearing deterioration was evident across all PTA groups in both ears; however, deterioration

was most pronounced in the EHF PTA group in both ears (Table 5.3 and Figure 5.3). Results indicated significant deterioration in the mean EHF PTA for the left (p = 0.000; Z = -4.160) and right (p = 0.000; Z = -4.546) ears.



** statistical significance of p < 0.05*

Figure 5.2 *Mean hearing thresholds and deterioration (error bars = standard error) of the left (panel A) and right (panel B) ears from initial to exit assessment (n = 69)*

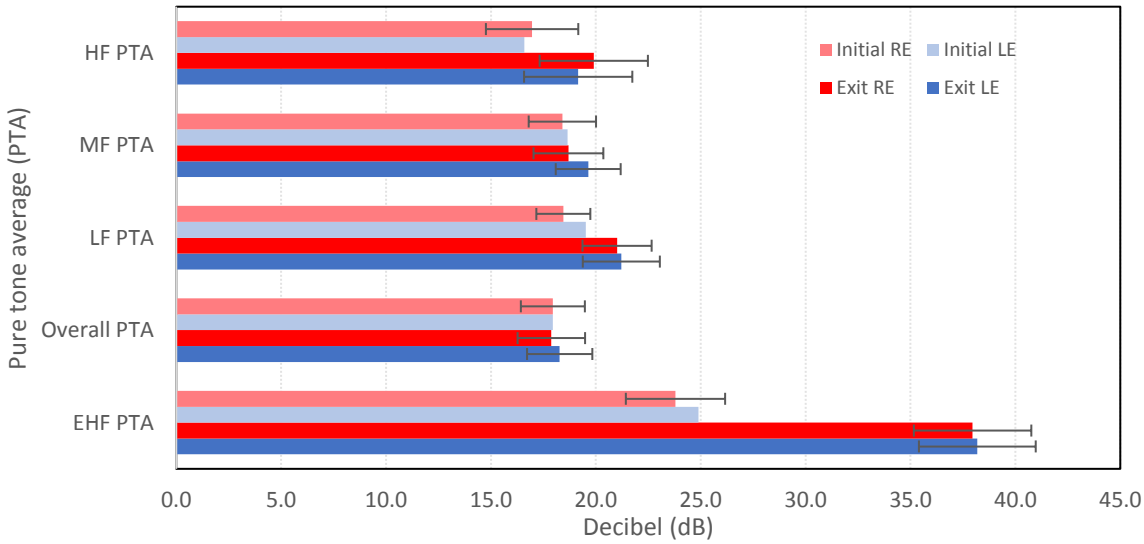
There was no significant deterioration in hearing thresholds for frequencies below 9 kHz in the right ear (p = 0.153 to 0.913; Z = -0.077 to -1.54), or for frequencies below 11.2 kHz in the left ear (p = 0.124 to 0.939; Z = -1.918 to -0.049). In addition, there was no significant deterioration in the mean PTA of the overall low frequency, mid frequency, or high frequency PTA groups for the left (p = 0.305 to 0.832; Z = -0.212 to -1.025) or right ears (p = 0.120 to 0.623; Z = -0.491 to -1.556). No statistically significant difference in the mean hearing threshold deterioration (p = 0.055 to 0.961; Z = -1.918 to -0.049) or mean PTA deterioration (p = 0.209 to 0.534; Z = -1.256 to 0.622) was found between the left and right ears.

Table 5.3 *Mean pure tone averages and hearing deterioration across ears (n = 69)*

Frequency (kHz)	Overall PTA (0.5 – 4)	LF PTA (0.25 – 0.5)	MF PTA (1 – 2)	HF PTA (3 – 8)	EHF PTA (9 – 16)
Left ear					
Mean initial dB (SD)	18.0 (11.6)	19.5 (11.0)	18.7 (12.0)	16.6 (15.5)	24.9 (21.7)
n	69	62	69	69	68
Mean exit dB (SD)	18.3 (12.9)	21.2 (11.2)	19.6 (12.9)	19.2 (21.4)	38.2 (23.1)
n	69	37	69	69	69
Mean deterioration dB (SD)	-0.7 (7.9)	-1.5 (11.7)	-1.0 (8.1)	-1.6 (15.0)	-11.9 (22.9) *
n	69	36	69	69	67
Right ear					
Mean initial dB (SD)	18.0 (12.7)	18.5 (10.2)	18.4 (13.3)	17.0 (18.3)	23.8 (19.7)
n	69	63	69	69	69
Mean exit dB (SD)	17.9 (13.4)	21.0 (10.0)	18.7 (13.8)	19.9 (21.4)	38.0 (23.3)
n	69	37	69	69	69
Mean deterioration dB (SD)	-0.3 (9.2)	-2.8 (10.4)	-0.3 (10.1)	-2.6 (14.7)	-13.0 (23.0) *
n	69	36	69	69	69

kHz, kilohertz; PTA, pure tone average; LF PTA, low frequency pure tone average; MF PTA, mid frequency pure tone average; HF PTA, high frequency pure tone average; EHF PTA, extended high-frequency pure tone average; dB, decibel; SD, standard deviation.

** statistical significance of $p < 0.05$*



HF, high frequency; MF, mid frequency; LF, low frequency; EHF, extended high-frequency; LE, left ear; RE, right ear.

Figure 5.3 *Mean initial and exit assessment pure tone averages of the left and right ears (n = 69) (error bars = standard error)*

The presence of an ototoxic shift was determined according to the three criteria developed by ASHA (1994), as indicated in Table 5.4. Including EHF thresholds resulted in more than half the patients (56.5%; 39/69) presenting with a significant ototoxic shift meeting one or more of the ASHA criteria, compared to 31.9% (22/69) if EHFs were not considered (Table 5.4). There was no significant difference in ototoxic shifts (meeting one or more of the ASHA criteria) between the left and right ears (conventional audiometry: p = 0.237, Z = -1.182; EHF audiometry: p = 0.785, Z = -0.272).

Table 5.4 *Distribution of patients presenting with an ototoxic shift according to ASHA criteria when considering conventional and EHF pure tone audiometry at the exit assessment (ASHA, 1994) (n = 69)*

ASHA ototoxic shift criteria	No ototoxic shift evident	ASHA Group 1	ASHA Group 2	ASHA Group 3
Conventional audiometry (0.25–8 kHz) *				
Patients % (n/69)	68.1 (47)	29.0 (20)	21.7 (15)	0.0 (0)
Left ear % (*n*/69)	75.4 (52)	23.2 (16)	18.8 (13)	1.4 (1)
Right ear % (*n*/69)	78.3 (54)	20.3 (14)	14.5 (10)	0.0 (0)
Bilateral (Left and right) % (*n*/69)	84.1 (58)	14.5 (10)	11.6 (8)	0.0 (0)
EHF audiometry (0.25–16 kHz) **				
Patients % (n/69)	43.5 (30)	52.2 (36)	52.2 (36)	15.9 (11)
Left ear % (*n*/69)	47.8 (33)	47.8 (33)	47.8 (33)	11.6 (8)
Right ear % (*n*/69)	50.7 (35)	49.3 (34)	49.3 (34)	5.8 (4)
Bilateral (Left and right) % (*n*/69)	55.1 (38)	44.9 (31)	44.9 (31)	1.4 (1)

ASHA, American Speech-Language-Hearing Association; ASHA Group 1, shift of ≥20 dB at a single frequency; ASHA Group 2, shift of ≥10 dB at two adjacent frequencies; ASHA Group 3, shift to 'no response' at three consecutive frequencies; kHz, kilohertz; EHF, extended high-frequency.

** 22/69 (31.9%) patients presented with an ototoxic shift which may have met one or more ASHA criteria: 11.6% (8) met one ASHA criterion, 20.3% (14) met two ASHA criteria and 0.0% (0) met three ASHA criteria.*

*** 39/69 (56.5%) patients presented with an ototoxic shift which may have met one or more ASHA criteria: 5.8% (4) met one ASHA criterion, 37.7% (26) met two ASHA criteria and 13.0% (9) met three ASHA criteria.*

5.5 Discussion

When EHFs were included in data analysis in the present study, the prevalence of patients (56.5%) presenting with an ototoxic shift meeting one or more of the ASHA criteria was almost twice as high as when EHF were not considered (31.9%). The mean hearing threshold deterioration from initial to exit assessment in the present study was significant only at EHFs from 9-16 kHz for the right and 11.2-16 kHz for the left ears. Furthermore, following treatment, mean PTA deterioration was significant only in the EHF PTA range (9-16 kHz) for the right and left ears. This suggests that EHF audiometry may be more sensitive for early detection of aminoglycoside induced deterioration than conventional audiometry. The early detection of ototoxic hearing loss through the use of EHF audiometry may offer medical professionals the opportunity to adjust treatment regimens, or to substitute ototoxic drugs with non-ototoxic drugs where suitable, before hearing loss becomes disabling to the patient (Konrad-Martin et al., 2018). In cases where alteration of treatment regimens is not possible, early detection of ototoxic hearing loss using EHFs allows proactive counselling of patients on the expected impact of progressive hearing loss on activities of daily living, and timeous referral for aural rehabilitation (Konrad-Martin et al., 2018).

In this study, the occurrence of ototoxic shifts according to ASHA criteria (56.5%) after aminoglycoside treatment was lower than that of previous reports, where 82.4 to 100% (Appana et al., 2016; Ghafari et al., 2020) of DRTB patients assessed using EHF audiometry developed an ototoxic shift according to ASHA criteria following kanamycin treatment. A possible reason for the higher occurrence of ototoxic shifts reported by Appana et al. (2016) and Ghafari et al. (2020) is that 94% and 63.7% of their patients presented with DRTB and HIV co-infection respectively, compared to the 17.4% of patients in the current study. DRTB with HIV co-infection is an additive risk factor for the development of an aminoglycoside-induced hearing loss for patients with DRTB (Harris, De Jong, et al., 2012; Hong et al., 2018; Stevenson et al., 2021).

There was a high prevalence of pre-existing hearing loss (one or more hearing threshold > 25 dB in one or both ears across all frequencies [0.25-16 kHz]) in this study with more than half (65.2%) of patients presenting with a pre-existing hearing loss at the time of the initial assessment. These results are consistent with previous findings

(Hong et al., 2020b; Stevenson et al., 2021) indicating some degree of pre-existing hearing loss prior to treatment in DRTB patients in South Africa. The pre-existing hearing loss prevalence in the current study may also have been exacerbated by the timing of initial assessments, where patients were assessed for the first time on average 40.3 days after treatment initiation, which was a limitation of the study. This is contrary to the ototoxicity monitoring guidelines recommending that initial assessments should be conducted prior to, or within three days of treatment initiation (AAA, 2009; ASHA, 1994; HPCSA, 2018). Kanamycin-induced hearing deterioration can occur as soon as one week after treatment initiation (Sogebi et al., 2021) and some patients who are more susceptible to ototoxicity can present with ototoxic damage after a single aminoglycoside injection (Huth et al., 2011). Therefore, it is possible that ototoxic shifts meeting one or more of the ASHA criteria may well have been present in more than 56.5% of patients reported in the current study, had initial assessments been completed at or prior to treatment initiation.

Recommendations (AAA, 2009; ASHA, 1994; HPCSA, 2018) for the inclusion of EHFs in ototoxicity monitoring are supported by the study findings but important considerations must be taken in to account. The limitation of test intensity ranges for EHF audiometry can restrict its usefulness in ototoxicity monitoring (Prendergast et al., 2020). When assessing individuals above the age of 30 to 40 years, the likelihood of observing no measurable hearing at 16 kHz and above increases dramatically and so the value of EHF audiometry to monitor hearing becomes reduced (Prendergast et al., 2020; Wang et al., 2021). In addition, any history of pre-existing hearing loss may limit the value of EHF audiometry (AAA, 2009). In the current study, where patients had an average age of 37.9 years and the prevalence of possible pre-existing hearing loss was high (65.2%), absent EHF thresholds owing to maximum intensity constraints were most pertinent at 16 kHz, with 17.4% of patient thresholds absent at the time of the initial assessment. However, missing data points were much less prevalent (0.7 to 3.6%) in frequencies below 16 kHz. The use of EHF audiometry will also significantly increase the time required to conduct an assessment, which may be impractical for patients who are likely to be ill and who are easily fatigued (Konrad-Martin et al., 2005). One way to reduce test time when EHF audiometry is included is to consider an optimized approach by testing only a selected group of frequencies that are most likely

to be sensitive to ototoxicity (Rieke et al., 2017). Results of the current study indicate that hearing deterioration was most prevalent at 6, 8, 9, 11.2, 12.5, 14 and 16 kHz, which suggests that these frequencies may be most sensitive to identifying deterioration. Since 16 kHz had the highest prevalence of absent thresholds at initial assessment, this frequency may need to be excluded from an optimised protocol. A shortened method of assessing EHF hearing, such as the sensitive range for ototoxicity (Fausti et al., 1992, 1999; Ganesan et al., 2018), or the fixed-level frequency threshold method by Rieke et al. (2017) should also be evaluated for their potential efficiency and efficacy (Prendergast et al., 2020; Rieke et al., 2017). Distortion product otoacoustic emission testing could be considered as an ototoxicity monitoring assessment tool, as it offers a quick, reliable, cost-effective method to detect initial cochlear ototoxic changes before they are able to be detected by conventional audiometry (Ganesan et al., 2018).

There have been significant advances in point-of-care testing and mobile health technologies in hearing assessment (Garinis et al., 2021), which could also serve to improve the accessibility and efficiency of EHF ototoxicity monitoring. The use of mobile smartphone-based EHF audiometry with calibrated headphones has recently been demonstrated to be a reliable method for accurate measurement of EHF hearing thresholds (Bornman et al., 2019). In addition, decentralised community-based DRTB ototoxicity monitoring, using portable technology facilitated by nonprofessional hearing health care providers (e.g. CHWs) has been demonstrated to be a promising service model at infectious disease clinics and PHC settings (Brittz et al., 2019; Stevenson et al., 2021).

Limitations of this study included a limited number of patients from the larger study cohort and the absence of measured noise levels in the test environments to confirm the reliability of testing. Ototoxicity monitoring outside a soundproof booth requires attenuation and monitoring of ambient noise levels to ensure the accurate measurement of hearing thresholds (Swanepoel et al., 2013). An additional limitation of this study was the timing of initial assessments after medication initiation. Timing of initial assessments exceeded recommended guidelines (AAA, 2009; ASHA, 1994; HPCSA, 2018) and may have contributed to the prevalence of pre-existing hearing

loss, the mean hearing threshold deterioration values and ototoxic shifts meeting ASHA (1994) criteria which were reported in this study. Future research utilising a prospective study design would address these limitations.

5.6 Conclusion

Findings of this study suggest that EHF audiometry may be more sensitive for early detection of aminoglycoside induced hearing deterioration than conventional audiometry. In cases of ototoxicity monitoring, such as in DRTB treatment, assessment of EHFs should be considered to ensure the best sensitivity to early changes in hearing. Clinical ototoxicity monitoring protocols must consider shortened assessment approaches that target frequencies most sensitive to ototoxicity, including EHF, to optimise time-efficiency in patient groups who are often sick.

Acknowledgements

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article. The authors received no financial support for the research, authorship, and/or publication of this article. The data that support the findings of this study are available on request from the corresponding author [L.J.S.] for ethical reasons. The data are not publicly available as they contain information that could compromise the privacy of research participants.

5.7 References

American Academy of Audiology. (2009). *American Academy of Audiology position statement and clinical practice guidelines ototoxicity monitoring*. Retrieved Feb 16 from https://audiology-web.s3.amazonaws.com/migrated/OtoMonGuidelines.pdf_539974c40999c1.58842217.pdf

American Speech-Language-Hearing Association. (1994). Audiologic management of individuals receiving cochleotoxic drug therapy. https://www.asha.org/policy/GL1994-00003/

American Speech-Language-Hearing Association. (2022). *Hearing loss in adults*. https://www.asha.org/practice-portal/clinical-topics/hearing-loss/

Appana, D., Joseph, L., & Paken, J. (2016). An audiological profile of patients infected with multi-drug resistant tuberculosis at a district hospital in Kwazulu-Natal. *The South African Journal of Communication Disorders = Die Suid-Afrikaanse Tydskrif vir Kommunikasieafwykings*, *63*(1), e1-e12. https://doi.org/10.4102/sajcd.v63i1.154

Blankenship, C. M., Hunter, L. L., Feeney, M. P., Cox, M., Bittinger, L., Garinis, A. C., Lin, L., McPhail, G., & Clancy, J. P. (2021). Functional impacts of aminoglycoside treatment on speech perception and extended high-frequency hearing loss in a pediatric cystic fibrosis cohort. *American Journal of Audiology*, 1-20. https://doi.org/10.1044/2020_AJA-20-00059

Bornman, M., Swanepoel, D. W., De Jager, L. B., & Eikelboom, R. H. (2019). Extended high-frequency smartphone audiometry: Validity and reliability. *Journal of the American Academy of Audiology*, *30*(03), 217-226. https://doi.org/10.3766/jaaa.17111

Brittz, M., Heinze, B., Mahomed-Asmail, F., Swanepoel, D. W., & Stoltz, A. (2019). Monitoring hearing in an infectious disease clinic with mhealth technologies. *Journal of the American Academy of Audiology*, *30*(06), 482-492. https://doi.org/10.3766/jaaa.17120

Campbell, K. C. M., & Le Prell, C. G. (2018). Drug-induced ototoxicity: Diagnosis and monitoring. *Drug Safety*, *41*(5), 451-464. https://doi.org/10.1007/s40264-017-0629-8

Caumo, D. T. M., Geyer, L. B., Teixeira, A. R., & Barreto, S. S. M. (2017). Hearing thresholds at high frequency in patients with cystic fibrosis: A systematic review. *Brazilian Journal of Otorhinolaryngology*, *83*(4), 464-474. https://doi.org/10.1016/j.bjorl.2016.10.006

Centers for Disease Control and Prevention (CDC). (2016). *TB elimination multidrug-resistant tuberculosis (MDR TB)*. Retrieved 29 September from https://www.cdc.gov/tb/publications/factsheets/drtb/MDRTB.pdf

Department Health Republic of South Africa. (2013). *Management of drug-resistant tuberculosis policy guidelines (updated)*. Department Health Republic of South Africa Retrieved from https://health-e.org.za/wp-content/uploads/2014/06/MDR-TB-Clinical-Guidelines-Updated-Jan-2013.pdf

Department Health Republic of South Africa. (2018). *Interim clinical guidance for the implementation of injectable-free regimens for rifampicin-resistant tuberculosis in adults, adolescents and children*. Department Health Republic of South Africa Retrieved from https://tbsouthafrica.org.za/resources/interim-clinical-guidance-implementation-injectable-free-regimens-rifampicin-resistant

Department Labour Republic of South Africa. (2001). *Occupational health and safety act 1993. Draft noise induced hearing loss regulations*. Department Labour Republic of South Africa Retrieved from https://www.gov.za/sites/default/files/gcis_document/201409/224990.pdf

Fausti, S. A., Henry, J. A., Helt, W. J., Phillips, D. S., Frey, R. H., Noffsinger, D., Larson, V. D., & Fowler, C. G. (1999). An individualized, sensitive frequency range for early detection of ototoxicity. *Ear and Hearing*, *20*(6), 497-505.

Fausti, S. A., Henry, J. A., Schaffer, H. I., Olson, D. J., Frey, R. H., & McDonald, W. J. (1992). High-frequency audiometric monitoring for early detection of aminoglycoside ototoxicity. *The Journal of Infectious Diseases*, *165*(6), 1026-1032.

Field, A. P. (2018). *Discovering statistics using IBM SPSS statistics* (5th edition. ed.). SAGE Publications.

Gamiet, S., & Rowe, M. (2019). The role of rehabilitation care workers in South African healthcare: A q-methodological study. *African Journal of Disability*, *8*, 537. https://doi.org/10.4102/ajod.v8i0.537

Ganesan, P., Schmiedge, J., Manchaiah, V., Swapna, S., Dhandayutham, S., & Kothandaraman, P. P. (2018). Ototoxicity: A challenge in diagnosis and treatment. *Journal of Audiology & Otology*, *22*(2), 59-68. https://doi.org/10.7874/jao.2017.00360

Garinis, A. C., Poling, G. L., Rubenstein, R. C., Konrad-Martin, D., Hullar, T. E., Baguley, D. M., Burrows, H. L., Chisholm, J. A., Custer, A., Hawe, L. D., Hunter, L. L., Marras, T. K., Ortiz, C. E., Petersen, L., Steyger, P. S., Winthrop, K., Zettner, E. M., Clark, K., Hungerford, M., Vachhani, J. J., & Brewer, C. C. (2021). Clinical considerations for routine auditory and vestibular monitoring in patients with cystic fibrosis. *American Journal of Audiology*, 1-10. https://doi.org/10.1044/2021_AJA-21-00031

Ghafari, N., Court, R., Chirehwa, M. T., Wiesner, L., Petersen, L., Maartens, G., Gumbo, T., McIlleron, H., & Ramma, L. (2020). Pharmacokinetics and other risk factors for kanamycin-induced hearing loss in patients with multi-drug resistant tuberculosis. *International Journal of Audiology*, *59*(3), 219-223. https://doi.org/10.1080/14992027.2019.1690170

Harris, T., De Jong, G., Bardien, S., Schaaf, H. S., Fagan, J. J., & Petersen, L. (2012). Aminoglycoside-induced hearing loss in HIV-positive and HIV-negative multidrug-resistant tuberculosis patients: Research. *South African Medical Journal*, *102*(6), 363-366.

Harris, T., Peer, S., & Fagan, J. J. (2012). Audiological monitoring for ototoxic tuberculosis, human immunodeficiency virus and cancer therapies in a developing world setting. *Journal of Laryngology and Otology*, *126*(6), 548-551. https://doi.org/10.1017/S0022215112000357

Health Professions Council of South Africa. (2018). *Audiological management of patients on treatment that includes ototoxic medications. Guidelines*. Retrieved Feb 16 from https://www.hpcsa.co.za/Uploads/SLH/Guidelines%20for%20Audiological%20Management%20of%20Patients%20on%20Treatment%20that%20includes%20Ototoxic%20Medications.pdf

Hong, H., Budhathoki, C., & Farley, J. E. (2018). Increased risk of aminoglycoside-induced hearing loss in MDR-TB patients with HIV coinfection. *The International Journal of Tuberculosis and Lung Disease*, *22*(6), 667-674. https://doi.org/10.5588/ijtld.17.0830

Hong, H., Dowdy, D. W., Dooley, K. E., Francis, H. W., Budhathoki, C., Han, H.-R., & Farley, J. E. (2020a). Aminoglycoside-induced hearing loss among patients being treated for drug-resistant tuberculosis in South Africa: A prediction model. *Clinical Infectious Diseases*, *70*(5).

Hong, H., Dowdy, D. W., Dooley, K. E., Francis, H. W., Budhathoki, C., Han, H. R., & Farley, J. E. (2020b). Prevalence of pre-existing hearing loss among patients with drug-resistant tuberculosis in South Africa. *American Journal of Audiology*, *29*(2), 199-205. https://doi.org/10.1044/2020_AJA-19-00103

Huth, M. E., Ricci, A. J., Cheng, A. G., & Pearson, J. P. (2011). Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection. *International Journal of Otolaryngology.*(2011).

Khoza-Shangase, K., & Prodromos, M. (2021). Impact of drug-resistant tuberculosis treatment on hearing function in south african adults: Bedaquiline versus kanamycin. *The South African Journal of Communication Disorders = Die Suid-Afrikaanse Tydskrif vir Kommunikasieafwykings*, *68*(1), e1-e8. https://doi.org/10.4102/sajcd.v68i1.784

Konrad-Martin, D., Poling, G. L., Garinis, A. C., Ortiz, C. E., Hopper, J., O'Connell Bennett, K., & Dille, M. F. (2018). Applying U.S. national guidelines for ototoxicity monitoring in adult patients: perspectives on patient populations, service gaps, barriers and solutions. *International Journal of Audiology, 57*(sup4), S3-S18. https://doi.org/10.1080/14992027.2017.1398421

Konrad-Martin, D., Wilmington, D. J., Gordon, J. S., Reavis, K. M., & Fausti, S. A. (2005). Audiological management of patients receiving aminoglycoside antibiotics. *Volta Review*, *105*(3), 229-250.

Kros, C. J., & Steyger, P. S. (2019). Aminoglycoside- and cisplatin-induced ototoxicity: Mechanisms and otoprotective strategies. *Cold Spring Harbor Perspectives in Medicine*, *9*(11). https://doi.org/10.1101/cshperspect.a033548

Lange, C., Aarnoutse, R. E., Alffenaar, J. W. C., Bothamley, G., Brinkmann, F., Costa, J., Chesov, D., van Crevel, R., Dedicoat, M., Dominguez, J., Duarte, R.,

Grobbel, H. P., Guenther, G., Guglielmetti, L., Heyckendorf, J., Kay, A. W., Kirakosyan, O., Kirk, O., Koczulla, R. A., Kudriashov, G. G., Kuksa, L., van Leth, F., Magis-Escurra, C., Mandalakas, A. M., Molina-Moya, B., Peloquin, C. A., Reimann, M., Rumetshofer, R., Schaaf, H. S., Schon, T., Tiberi, S., Valda, J., Yablonskii, P. K., & Dheda, K. (2019). Management of patients with multidrug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Disease*, *23*(6), 645-662.

Lange, C., Dheda, K., Chesov, D., Mandalakas, A. M., Udwadia, Z., & Horsburgh, C. R., Jr. (2019). Management of drug-resistant tuberculosis. *Lancet (London, England)*, *394*(10202), 953-966. https://doi.org/10.1016/S0140-6736(19)31882-3

Lanvers-Kaminsky, C., Zehnhoff-Dinnesen, A. A., Parfitt, R., & Ciarimboli, G. (2017). Drug-induced ototoxicity: Mechanisms, pharmacogenetics, and protective strategies. *Clinical Pharmacology and Therapeutics*, *101*(4), 491-500. https://doi.org/10.1002/cpt.603

Medicins Sans Frontieres. (2020). *Step up for TB: TB policies in 37 countries, 4th ed*. Medicins Sans Frontieres. Retrieved 29 September from https://msfaccess.org/step-tb-tb-policies-37-countries-4th-ed

Meiyan, J., Takatoshi, K., & Peter, S. S. (2017). Aminoglycoside-induced cochleotoxicity: A review. *Frontiers in Cellular Neuroscience*.

Prendergast, G., Hymers, M., & Lee, A. (2020). A quick and reliable estimate of extended high-frequency hearing. *International Journal of Audiology*, *59*(11), 823-827. https://doi.org/10.1080/14992027.2020.1767810

Raaijmakers, Q. A. W. (1999). Effectiveness of different missing data treatments in surveys with likert-type data: Introducing the relative mean substitution approach. *Educational and Psychological Measurement, 59*(5), 725-748.

Rieke, C. C., Clavier, O. H., Allen, L. V., Anderson, A. P., Brooks, C. A., Fellows, A. M., Brungart, D. S., & Buckey, J. C. (2017). Fixed-level frequency threshold testing for ototoxicity monitoring. *Ear and Hearing*, *38*(6), e369-e375. https://doi.org/10.1097/AUD.0000000000000433

Rizk, H. G., Lee, J. A., Liu, Y. F., Endriukaitis, L., Isaac, J. L., & Bullington, W. M. (2020). Drug-induced ototoxicity: A comprehensive review and reference guide. *Pharmacotherapy*, *40*(12), 1265-1275. https://doi.org/10.1002/phar.2478

Sogebi, O. A., Adefuye, B. O., & Ajayi, E. A. (2021). Early hearing threshold changes and peculiarities of audiometric assessments among patients in a drug-resistant tuberculosis treatment center. *African Health Sciences*, *21*(1), 230-237. https://doi.org/10.4314/ahs.v21i1.30

Stach, B. A., & Ramachandran, V. (2017). *Clinical audiology an introduction* (3rd ed. ed.). Plural Publishing, Incorporated. http://public.eblib.com/choice/PublicFullRecord.aspx?p=6499978

Stevenson, L. J., Biagio-de Jager, L., Graham, M. A., & Swanepoel, D. W. (2021). Community-based ototoxicity monitoring for drug-resistant tuberculosis in South Africa: An evaluation study. *International Journal of Environmental Research and Public Health*, *18*(21), 11342. https://www.mdpi.com/1660-4601/18/21/11342

Steyger, P. S. (2011). Mechanisms involved in ototoxicity. *Seminars in Hearing*, *32*(03), 217-228. https://doi.org/10.1055/s-0031-1286616

Steyger, P. S. (2021a). Mechanisms of aminoglycoside- and cisplatin-induced ototoxicity. *American Journal of Audiology*, *30*(3S), 887-900. https://doi.org/10.1044/2021_AJA-21-00006

Steyger, P. S. (2021b). Mechanisms of ototoxicity and otoprotection. *Otolaryngologic Clinics of North America*, *54*(6), 1101-1115.

Swanepoel, D. W., Maclennan-Smith, F., & Hall, J. W. (2013). Diagnostic pure-tone audiometry in schools: Mobile testing without a sound-treated environment. *Journal of the American Academy of Audiology*, *24*(10), 992-1000. https://doi.org/10.3766/jaaa.24.10.10

Van Deun, A., Decroo, T., Tahseen, S., Trébucq, A., Schwoebel, V., Ortuno-Gutierrez, N., de Jong, B. C., Rieder, H. L., Piubello, A., & Chiang, C. Y. (2020). World health organization 2018 treatment guidelines for rifampicin-resistant tuberculosis: Uncertainty, potential risks and the way forward. *International*

Journal of Antimicrobial Agents, *55*(1), 105822. https://doi.org/10.1016/j.ijantimicag.2019.10.003

Wang, M., Ai, Y., Han, Y., Fan, Z., Shi, P., & Wang, H. (2021). Extended high-frequency audiometry in healthy adults with different age groups. *Journal of Otolaryngology - Head & Neck Surgery*, *50*(1). https://doi.org/10.1186/s40463-021-00534-w

Watts, K. L. A. D. (2019). Ototoxicity: Visualized in concept maps. *Seminars in Hearing*, *40*(02), 177-187. https://doi.org/10.1055/s-0039-1684046

World Health Organisation. (2020a). *Global tuberculosis report 2020* (ISBN 978-92-4-001313-1). https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf

World Health Organisation. (2020b). *Who consolidated guidelines on tuberculosis. Module 4: Treatment - drug-resistant tuberculosis treatment*. Retrieved 07/09/2021 from https://www.who.int/publications/i/item/9789240007048

World Health Organisation. (2021). *Global tuberculosis report 2021*. https://www.who.int/publications/i/item/9789240037021

Yuan, I., Topjian, A. A., Kurth, C. D., Kirschen, M. P., Ward, C. G., Zhang, B., & Mensinger, J. L. (2019). Guide to the statistical analysis plan. *Paediatric Anaesthesia, 29*(3), 237-242. https://doi.org/10.1111/pan.13576

5.8 Supplementary material

Table 5.5 *Mean hearing thresholds for initial and exit assessment with hearing deterioration across ears (n = 69)*

Frequency (kHz)	0.25	0.5	1	2	4	6	8	9	11.2	12.5	14	16
Left ear												
Mean initial dB (SD)	18.7 (10.1)	20.3 (13.4)	19.6 (12.6)	17.9 (12.6)	14.4 (14.3)	13.5 (16.6)	19.3 (18.1)	21.6 (22.2)	21.4 (21.1)	23.8 (23.5)	25.5 (24.0)	19.2 (21.6)
n	62	62	69	68	69	57	67	63	65	60	64	57
Mean exit dB (SD)	19.1 (9.7)	23.4 (14.4)	20.6 (13.6)	18.7 (14.0)	14.9 (18.1)	28.2 (32.8)	23.3 (26.0)	26.3 (26.6)	33.3 (28.3)	39.7 (28.0)	45.6 (26.5)	44.8 (19.9)
n	37	37	69	69	69	22	69	62	69	61	69	69
Mean deterioration dB (SD)	-0.6 (13.5)	-2.5 (11.0)	-1.0 (9.3)	-0.8 (8.5)	-0.5 (12.7)	-8.6 (26.4)	-2.5 (19.3)	-4.3 (19.5)	-9.2 (24.6) *	-15.9 (28 0) *	-18.6 (28.4) *	-22.0 (25.3) *
Right ear												
Mean initial dB (SD)	17.1 (10.3)	19.8 (11.3)	20.4 (13.6)	16.4 (14.4)	15.7 (19.4)	15.3 (18.7)	19.7 (19.7)	19.0 (21.0)	21.7 (20.4)	24.6 (18.6)	25.4 (23.0)	18.2 (20.4)
n	63	63	69	69	69	59	69	63	69	61	64	54
Mean exit dB (SD)	19.3 (9.4)	22.7 (11.8)	20.6 (14.1)	16.8 (14.6)	16.1 (20.8)	28.3 (26.4)	24.6 (26.2)	28.2 (29.0)	31.5 (27.0)	39.9 (26.7)	43.8 (26.4)	44.7 (21.6)
n	37	37	69	69	69	21	69	61	68	61	69	69
Mean deterioration dB (SD)	-3.1 (10.9)	-2.5 (11.8)	-0.1 (9.8)	-0.4 (11.6)	-0.4 (11.7)	-6.0 (20.2)	-4.9 (20.6)	-9.1 (23.7) *	-9.6 (24.0) *	-16.8 (26.6) *	-18.1 (26.4) *	-23.0 (27.4) *

kHz, kilohertz; dB, decibel; SD, standard deviation

** significant hearing deterioration (p < 0.05)*

CHAPTER 6: DISCUSSION, CLINICAL IMPLICATIONS AND CONCLUSION

This chapter provides a discussion of the results of this research project and their implications for clinical practice. The research conducted is critically evaluated in terms of its contributions, strengths and limitations. Recommendations for future research are presented and conclusions drawn from the findings.

This research project comprised three studies incorporating a retrospective record review and aimed to describe the service delivery practices of a community-based ototoxicity monitoring programme (OMP) for drug-resistant tuberculosis (DRTB) facilitated by community health workers (CHWs), and the ototoxicity observed in a DRTB patient population. In addition, this research project investigated the monitoring of ototoxicity in DRTB patients receiving aminoglycoside treatment with extended high-frequency (EHF) audiometry in order to determine the value of EHF audiometry in identifying early changes in hearing.

6.1 Summary of findings

Study I reported on the service delivery practices of a decentralised, community-based OMP for 831 patients with DRTB served by CHWs and primary health care (PHC) audiologists between 2013 and 2017. The service delivery practices were compared to and evaluated against the OMP protocol and the national and international recommended guidelines for ototoxicity monitoring (AAA, 2009; ASHA, 1994; HPCSA, 2018). CHWs assessed 60.3% of patients (501/831), while the remaining 39.7% patients (330/831) were assessed by PHC audiologists. The timing and frequency of ototoxicity monitoring assessments for patients in this study did not meet the recommendations of the OMP protocol or the guidelines for ototoxicity monitoring (AAA, 2009; ASHA, 1994; HPCSA, 2018). The initial assessment conducted for more than half the patients (53.2%; 320/602) exceeded the timeframes recommended by the OMP protocol and the guidelines (AAA, 2009; ASHA, 1994; HPCSA, 2018), that is prior to or within two weeks of treatment initiation. On average, patients were assessed

3.1 (SD = 2.31) times, but 31.6% (263/831) attended an initial assessment only and just 8% (69/831) returned for the recommended six or more ototoxicity monitoring assessments. Ototoxicity monitoring was conducted on average every 58.3 (SD = 6.23) days, almost twice the 30 days recommended by the OMP protocol. The OMP follow-up default rates ranged from 27.6% to 31.9% across consecutive monitoring assessments and improved from 53.7% to 79.5% as the OMP became more established over time between 2013 and 2017.

EHF audiometry (0.25-16 kHz) was underutilised by testers in this study. Once EHF audiometry was introduced to the OMP, only 27.5% of patients (117/425) had their hearing assessed using EHF audiometry. However, PHC audiologists (55.5%; 96/173) were more likely than CHWs to use EHF audiometry for the initial assessment of patients. In addition, data recording of patients' descriptive information was inconsistent; for instance, 37.7% of patient gender was not recorded by testers in this study.

Study II reported on the observed longitudinal treatment effects for DRTB and ototoxicity monitoring conducted by CHWs, in a decentralised community-based model of care. Of the 831 patients included in Study I, 194 met the selection criteria and were eligible for inclusion in Study II. At the time of the initial assessment, 24.7% (48/194) of patients reported having DRTB and HIV co-infection and 20.6% (40/194) reported a history of excessive noise exposure. Patients' initial assessments were conducted on average 16.8 days (SD = 86.5; range = -494 to 14 days) before treatment initiation. CHWs tested 76.3% (148/194) of the patients in the study, while PHC audiologists tested the remaining 23.7% (46/194).

Follow-up rates for consecutive monitoring assessments reached as high as 80.6% for patients assessed by CHWs and up to 87.0% for patients assessed by PHC audiologists. However, few patients were assessed with the frequency required for effective ototoxicity monitoring as recommended by the national guidelines and the OMP protocol. Only 14.2% (21/148) of patients assessed by CHWs attended the recommended six or more monitoring assessments compared to 32.6% (15/46) of patients assessed by PHC audiologists. There was a significant (p = 0.019; U = 2637.0) difference between the average number of follow-up visits by patients

assessed by CHWs (average = 3.3; SD = 2.1; 148/194) and those assessed by PHC audiologists (average = 4.3; SD = 2.5; 46/194). Furthermore, patients in this study did not undergo ototoxicity monitoring with the regularity recommended by the OMP protocol or the guidelines (every seven to 30 days). However, the average number of days elapsing between monitoring assessments were fewer for patients assessed by CHWs (53.4 days; SD = 10.3) than for patients assessed by PHC audiologists (64.3 days; SD = 19.3).

The study findings revealed a high prevalence (51.5%; 100/194) of pre-existing hearing loss for patients at the time of the initial assessment, where a hearing loss was defined as one or more hearing threshold > 25 dB HL in one or both ears at one or more frequencies. Following DRTB treatment using kanamycin, patients presented with clinically and statistically significant deterioration of hearing thresholds, most markedly in the high frequencies. The mean hearing threshold deterioration was significant ($p < 0.05$) at the high frequencies of the left ear (4–8 kHz) and in the majority of frequencies in the right ear (0.5, 1, 2, 4, 6, 8 kHz) ear. Results indicated significant deterioration in the mean high frequency PTA (3–8 kHz) of the left ($p < 0.05$; $W = -4.125$) and right ($p < 0.05$; $W = -5.247$) ear. Following DRTB treatment, more than half the patients (51.5%; 100/194) presented with a significant ototoxic shift meeting one or more of the American Speech-Language-Hearing Association (ASHA) criteria, with ototoxic shifts occurring most often at the high frequencies (4–8 kHz). From the initial to the exit assessment, the prevalence of patients presenting with hearing loss meeting any category of hearing loss severity increased from 22.2% (39/194) to 25.8% (50/194). The presence of pre-existing hearing loss, HIV co-infection, and a history of noise exposure were significant predictors ($p < 0.05$) of ototoxicity in DRTB patients.

Study III described EHF audiometry monitoring of ototoxicity in a longitudinal treatment programme. Of the 831 patients included in Study I, 69 met the selection criteria and were eligible for inclusion in Study III. The mean age of patients at the time of the initial assessment was 37.9 years (SD = 11.2; range = 16.0 to 63.8 years). Gender (27.5%; 19/69) and medication type (47.8%; 33/69) administered to patients was not recorded on the data collection forms by some testers and was therefore unavailable for

inclusion in this retrospective study. Initial assessments were conducted on average 40.3 days (SD = 70.9; range = 0 to 301 days) after treatment initiation.

There was a high prevalence of patients presenting with a pre-existing hearing loss at the time of the initial assessment, where hearing loss was defined as one or more hearing threshold > 25 dB HL in one or both ears at one or more frequencies. At the initial assessment, 36.2% (25/69) of patients presented with a hearing loss in one or more frequency in the conventional range (0.25–8 kHz); compared to 65.2% (45/69) of patients when also considering EHF thresholds (0.25–16 kHz). From initial to exit assessment, the number of patients with hearing loss increased to 47.8% (33/69) when EHFs were not considered (0.25–8 kHz), and to 85.5% (59/69) when EHFs were considered (0.25–16 kHz). Following treatment, the mean hearing threshold deterioration was significant at EHFs of the left (11.2, 12.5, 14 and 16 kHz; $p < 0.05$; $W = -4.947$ to -2.801) and of the right ear (9, 11.2, 12.5, 14 and 16 kHz; $p < 0.05$; $W = -4.705$ to -2.711). Following treatment, results indicated significant deterioration in the mean EHF PTA for the left ($p < 0.05$; $W = -4.160$) and right ($p < 0.05$; $W = -4.546$) ear.

Including EHF thresholds resulted in more than half of patients (56.5%; 39/69) presenting with a significant ototoxic shift meeting one or more of the ASHA criteria, compared to 31.9% (22/69) if EHFs were not considered. Absent EHF thresholds owing to maximum equipment output limits occurred most frequently at 16 kHz, with 17.4% of patient thresholds absent at the time of the initial assessment. However, missing data points were uncommon (0.7 to 3.6%) in frequencies below 16 kHz. The study findings therefore confirmed that EHF audiometry was significantly more sensitive for early detection of aminoglycoside-induced deterioration in hearing than conventional audiometry.

6.2 Clinical implications

The findings of this research project gave rise to six main clinical implications.

Firstly, decentralised, community-based ototoxicity monitoring for DRTB offered in a PHC framework of care was a feasible service delivery model. The OMP follow-up

default rates ranged from 27.6% to 31.9% across consecutive monitoring assessments, and improved from 53.7% to 79.5% as the OMP became more established over time, between 2013 and 2017. The OMP follow-up default rates were lower than a similar DRTB treatment programme offering ototoxicity monitoring (Moyo et al., 2015). This demonstrates the potential of a community-based model of care for ototoxicity monitoring to establish itself over time as a robust, widely used service.

Secondly, the findings of Studies I and II demonstrated that CHWs were able to conduct ototoxicity monitoring assessments with similar timing and frequency as PHC audiologists. Study II showed a shorter number of days between assessments for patients assessed by CHWs than for patients assessed by PHC audiologists. Therefore, the findings of this research project support the feasibility of a community-based model of care for ototoxicity monitoring facilitated by CHWs as a recognised service. For this reason, the inclusion of CHWs as facilitators of ototoxicity monitoring within a community setting for increased patient access to services is supported and encouraged by the researcher.

Thirdly, the findings of this research project highlight the challenges encountered by OMPs, with particular reference to the South African context. The findings demonstrated that the OMP was unable to assess patients within the timeframes or with the regularity and frequency recommended by national and international guidelines (AAA, 2009; ASHA, 1994; HPCSA, 2018). In addition, the data management of the OMP was inconsistent, with important patient descriptive data (such as gender) not consistently recorded by testers. Furthermore, the findings of Studies I and II were able to support existing reports that EHF audiometry is underutilised by testers for the purpose of ototoxicity monitoring. The OMP shortfalls identified in this research project call for a reconsideration of current ototoxicity monitoring guidelines and protocols; novel approaches to ototoxicity monitoring, including decentralised, community-based ototoxicity monitoring by non-specialised personnel using the latest technology, including digital technology and applications with automated EHF audiometry applications, and cloud-based integrated data sharing capabilities should be included. Furthermore, these findings, suggest the importance of ongoing training and

supervision of non-specialised personnel undertaking task-sharing to optimise OMP service delivery practices.

Fourthly, the findings of Study III confirm that EHF audiometry (0.25–16 kHz) is significantly more sensitive for early detection of aminoglycoside-induced hearing deterioration than conventional test frequencies. EHF audiometry should therefore be included in ototoxicity monitoring for patients receiving ototoxic drugs. Consequently, in an effort to encourage the use of EHF audiometry for ototoxicity monitoring, the researcher recommends a novel optimised shortened protocol for EHF audiometry, where the frequencies most sensitive to ototoxicity are assessed. An optimised shortened protocol for EHF audiometry would entail the exclusion of the assessment of the low and mid- to high frequency ranges (0.25–4 kHz) with the inclusion of the assessment of the frequencies 6, 8, 9, 11.2, 12.5, 14 and 16 kHz only. In the event of severe time constraints due to for example, a fatigued patient, the frequencies 9–16 kHz can be prioritised for assessment. The option to exclude 16 kHz from the test protocol is suggested as 16 kHz had the highest prevalence of absent hearing thresholds at the time of the initial assessment owing to maximum equipment output limits.

Fifthly, the findings of Studies II and III confirm that DRTB treatment using kanamycin had a negative effect on the hearing status of the patients in this research project, with clinically and statistically significant deterioration of hearing thresholds, most markedly in the high frequency and EHF ranges. These findings provide further evidence to support the implementation of all-oral treatment regimens for DRTB patients and highlight the continuing need for OMPs to monitor the hearing of patients receiving ototoxic drugs

Finally, the findings of Study II demonstrated that the prevalence of pre-existing hearing loss was high for DRTB patients. In addition, the presence of pre-existing hearing loss, HIV co-infection, and a history of noise exposure were found to be significant predictors of ototoxicity in DRTB patients in this study. This has clinical implications for OMPs as patients presenting with these conditions can be identified and prioritised for vigilant ototoxicity monitoring and closer supervision of attendance of monitoring assessments through direct communication with patients using, for

example, smartphone technology and applications like WhatsApp. By prioritising these patients, the limited resources synonymous with OMPs in South Africa may be optimised.

6.3 A recommended service delivery model for community-based ototoxicity monitoring

The results of Studies I to III were used to inform the development of a proposed service delivery model for community-based ototoxicity monitoring facilitated by CHWs using digital technology (Figure 6.1).

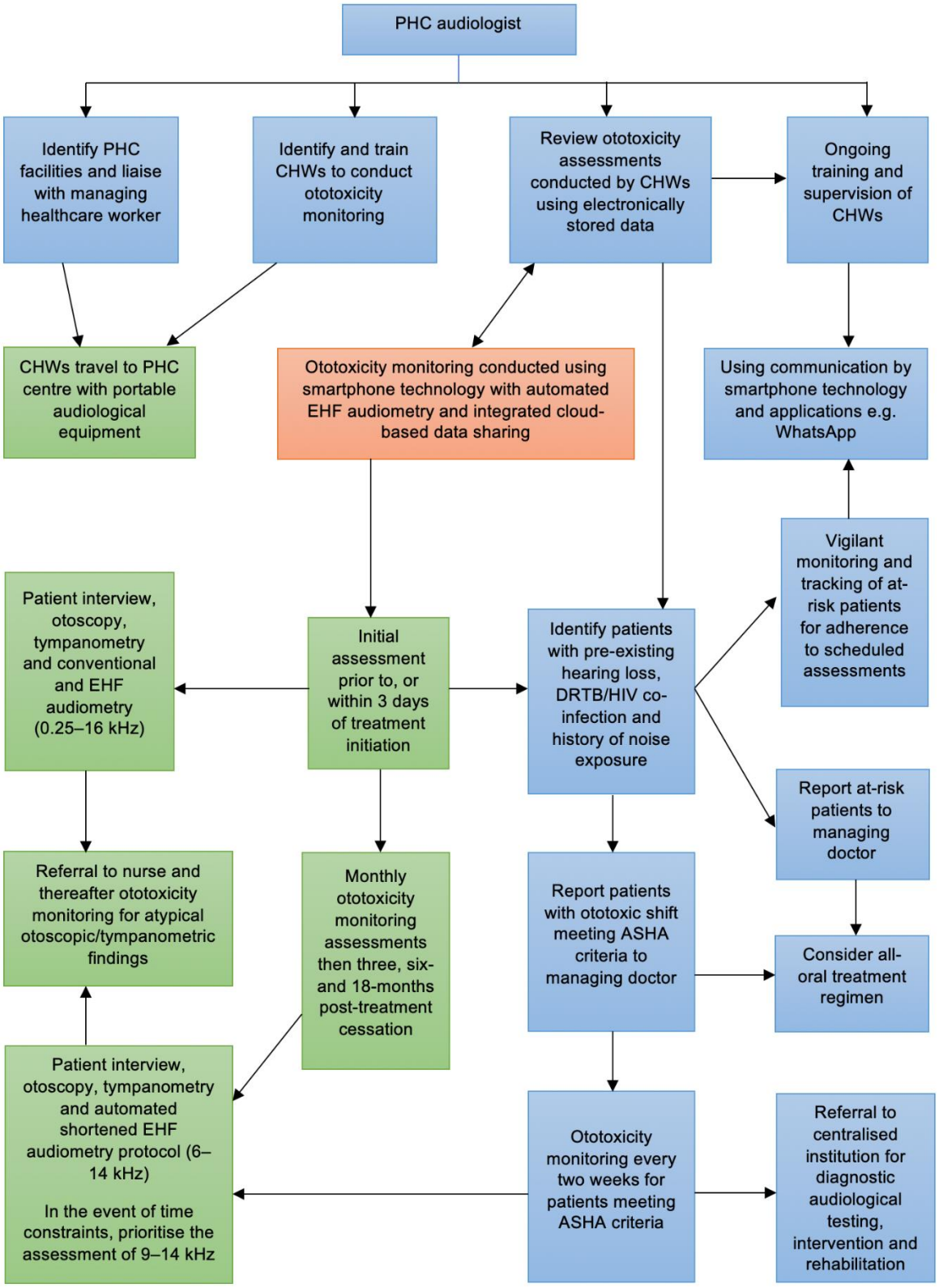


Figure 6.1 *Flowchart of proposed community-based ototoxicity monitoring facilitated by CHWs*

In light of the research project findings, the following suggestions are to improve patient access to OMPs, and the service delivery practices of OMPs. A multidisciplinary team approach should be taken for the development and implementation of an OMP, including involvement of key role players in the treatment and management of patients receiving ototoxic drugs in decentralised PHC settings, such as PHC clinics and/or community health clinics. Role players may include PHC doctors, nurses, audiologists, CHWs, provincial/local government OMP managers and administrative staff. However, the PHC audiologist should assume the leading role for the management of the OMP. The PHC audiologist and provincial/local government administrative staff would be responsible for selecting suitable PHC facilities and CHWs for inclusion in the OMP. To facilitate access to care, ototoxicity monitoring services should be made available to patients at the PHC facilities where they currently receive intervention and management services related to ototoxic drug treatment. This is feasible using low-cost portable audiological equipment for ototoxicity monitoring, such as smartphone technology with automated EHF audiometry and integrated cloud-based data sharing, facilitated by CHWs.

The PHC audiologist should be responsible for the initial and ongoing training of the CHWs who will be conducting the ototoxicity monitoring assessments. The WHO Primary Ear Care Training Resources (basic and intermediate levels) (WHO, 2006a, 2006b) can be used as educational resources for the training of CHWs, while practical training on conducting patient interviews, otoscopy, tympanometry, ototoxic monitoring assessments and data capturing should be included in the training. This training should furthermore inform the CHWs about ototoxicity monitoring conducted using smartphone technology with automated EHF audiometry.

The ongoing supervision of CHWs by PHC audiologists is recommended to ensure a high standard of care: this can be achieved by remotely reviewing the ototoxicity assessments conducted by CHWs and using the electronically stored cloud-based data. PHC audiologists should provide CHWs with regular support and performance feedback using smartphone technology and applications such as WhatsApp for text and video call communication.

The CHWs should travel to the PHC facilities with an otoscope, tympanometer and mobile technology with automated EHF audiometry and integrated cloud-based data sharing. The technology should be customisable for ototoxicity monitoring in a PHC context using conventional and EHF audiometry. Furthermore, an optimised, shortened, automated protocol should be available for use by the CHWs, where only the frequencies most sensitive to ototoxicity, and least sensitive to maximum equipment output limits, are assessed. The novel protocol for EHF audiometry should entail the exclusion of the assessment of the low and mid- to high frequency ranges (0.25–4 kHz) with the inclusion of the assessment of the frequencies 6, 8, 9, 11.2, 12.5, and 14 kHz only. In the event of severe time constraints, the frequencies 9–14 kHz should be prioritised for assessment. The recommendation to include the frequencies 9–14 kHz is based on the findings of Study III, where over time, statistically significant deteriorations in hearing thresholds were measured for the frequencies 9 kHz and higher only. Equipment should be regularly calibrated, as scheduled by the managing PHC audiologist.

Patients receiving ototoxic drugs should be identified by their managing doctor and referred for inclusion in the OMP as part of the package of care. In line with the guideline recommendations (AAA, 2009; ASHA, 1994; HPCSA, 2018), initial assessments should be conducted prior to, or within three days of drug treatment initiation. The comprehensive initial assessment should include a patient interview, otoscopy, tympanometry and conventional and EHF audiometry (0.25–16 kHz). If otoscopic and/or tympanometric findings indicate possible outer and/or middle ear pathology, patients should be referred to the managing doctor or nurse for appropriate treatment, followed by audiometry upon the resolution of the treatment addressing any outer and/or middle ear pathology. Patients presenting with risk factors for the development of ototoxicity (*viz*. pre-existing hearing loss, DRTB and HIV co-infection and/or a history of noise exposure) should be identified. The managing doctor and the PHC audiologist should be informed of these patients and they should be considered for all-oral treatment regimens and for vigilant ototoxicity monitoring and adherence to scheduled monitoring assessments. The PHC audiologist may identify the at-risk patients as part of the review of CHW-conducted initial ototoxicity assessments, and

thereafter communicate with the identified patients using smartphone technology and applications such as WhatsApp, using texts or video calls.

Ototoxicity monitoring assessments should be conducted monthly and then at three, six- and 18-month intervals following treatment completion. As well as patient interviews, otoscopy and tympanometry, monitoring assessments should include the use of an optimised, shortened protocol for EHF audiometry (6–14 kHz; or 9–14 kHz in the event of time constraints) by CHWs. Patients presenting with an ototoxic shift meeting one of the ASHA criteria should be referred by the PHC audiologist to the managing doctor for consideration for all-oral treatment regimens. In addition, patients presenting with ototoxic shifts meeting the ASHA criteria should attend ototoxicity monitoring assessments every two weeks, with smartphone and application-based communication by PHC audiologists to ensure patient adherence to scheduled assessments. Patients presenting with ototoxic hearing loss following treatment should be referred by the PHC audiologist to a centralised institution for diagnostic audiological assessment, intervention and rehabilitation.

6.4 Research contributions, strengths and limitations

This section critically evaluates the contributions, strengths and limitations of this research project.

6.4.1 Research contributions

This research project has made several contributions to research. Firstly, this research project was the first to report longitudinally on, and to describe the service delivery practices of a novel approach to ototoxicity monitoring for DRTB patients using a decentralised, community-based model of care facilitated by non-specialist personnel. The service delivery practices of the OMP were compared to similar hospital-based and decentralised OMPs, to national and international guidelines for ototoxicity monitoring and to the OMP protocol. The findings demonstrated that a community-based OMP using CHWs to facilitate monitoring showed improvement over previous hospital-based reports, with more accessible services and higher follow-up rates.

Therefore, the findings support and encourage the implementation of community-based OMP offered within the a PHC framework of care.

Secondly, this research project was the first to include longitudinal comparisons of OMP assessments by PHC audiologists and by CHWs for DRTB patients. Comparisons of the audiometric protocol used for ototoxicity monitoring (conventional audiometry versus conventional and EHF audiometry), and the timing and frequency of ototoxicity monitoring assessments were made. Similar timing and frequency of ototoxicity monitoring was found in patients assessed by CHW and those assessed by PHC audiologists (Study I), with a shorter number of days between assessments for patients assessed by CHWs than for patients assessed by PHC audiologists (Study III). This research project demonstrated that non-specialist personnel (CHWs) were able to conduct ototoxicity monitoring assessments for DRTB patients using portable audiological equipment in a decentralised, community-based setting.

Thirdly, in addition to the research findings demonstrating the improvement in ototoxicity monitoring service delivery using community-based care and CHWs to facilitate monitoring, the OMP service delivery practices in need of improvement were also identified. The findings indicated that the OMP was unable to meet the outcomes set out in the ototoxicity monitoring guidelines and the OMP protocol. These included the timing and frequency of ototoxicity monitoring assessments and data management practices. These poorly met indicators suggest that a careful review and reconsideration of ototoxicity monitoring approaches, technologies and human resources used is required.

Fourthly, several significant predictors of hearing loss in DRTB patients were observed, including the presence of a pre-existing hearing loss, HIV co-infection, and a history of exposure to noise. The findings of the research project, therefore, have important implications for OMPs as they highlight the need for these programmes to identify and prioritise DRTB patients presenting with pre-existing hearing loss, HIV co-infection, and noise exposure for all-oral treatment regimens, together with more vigilant audiological ototoxicity monitoring and adherence to scheduled assessments for early management of hearing deterioration.

Fifthly, this study provided additional statistical information on the prevalence and severity of aminoglycoside-induced ototoxic hearing loss in DRTB patients. The research project was able to demonstrate that DRTB treatment using kanamycin had a negative effect on the hearing status of patients (Studies II and III), with clinically and statistically significant deterioration of hearing thresholds, most markedly in the high frequency and EHF ranges. These findings therefore support the implementation of OMPs for DRTB patients who are administered aminoglycosides, particularly as the latest WHO DRTB treatment guidelines continue to include amikacin, which is known to be ototoxic.

Lastly, the findings of this research project confirmed that EHF audiometry was significantly more sensitive for early detection of aminoglycoside induced deterioration in hearing than conventional audiometry. The occurrence of high frequency hearing deterioration measured in Study III further supports the recommendation of the use of EHF audiometry for ototoxicity monitoring in DRTB patients, particularly for those most at risk for developing ototoxic hearing loss. The research project found, however, that EHF audiometry was underutilised by the testers (Studies I and III). To encourage the widespread use of EHF audiometry for ototoxicity monitoring, a novel shortened optimised testing protocol was suggested by the researcher. An optimised shortened protocol for EHF audiometry would entail the exclusion of the assessment of the low and mid- to high frequency ranges (0.25–4 kHz) with the inclusion of the assessment of the frequencies 6, 8, 9, 11.2, 12.5, 14 and 16 kHz only. In the event of severe time constraints, the EHFs of 9–16 kHz could be prioritised for assessment. Since 16 kHz had the highest occurrence of absent thresholds at the initial assessment (Study III) this frequency could be excluded from an optimised protocol.

6.4.2 Research strengths

There were six main strengths identified across Studies I to III. Firstly, ototoxicity monitoring assessments were conducted on a large sample of patients for Studies I and II, allowing for more precise analysis and generalisation of the results. Findings based on larger samples have more evidential certainty than those based on smaller ones; in most cases the larger the sample, the more accurate the findings (Kumar,

2019). Although the sample size for Study III was smaller than for Studies I and III, the sample size was comparable to that of a similar published study (Appana et al., 2016).

Secondly, the longitudinal nature of this research project allowed the researcher to explore patterns of change and the potential reasons for changes in variables in order to make recommendations for clinical practice for ototoxicity monitoring (Brink et al., 2018). Long-term service delivery analysis allowed the researcher to assess improvements in areas such as the OMP follow-up rates, which has seldom been reported on. The researcher was able to determine specific tendencies with greater certainty, thereby enabling the researcher to make predictions (Brink et al., 2018), such as the predictors of hearing loss. As part of this research project, identical, factual information was gathered continuously over an extended period of time, thereby enhancing the accuracy of the research findings (Kumar, 2019), such as the prevalence of ototoxic hearing loss in patients following DRTB treatment

Thirdly, this research project evaluated the OMP service delivery practices of an existing service delivery model, enhancing the ecological validity of the findings. Therefore, the results of this project can be generalised to clinical practice in a real-world setting (Andrade, 2018). The research findings provided evidence of the strengths and weaknesses of decentralised community-based ototoxicity monitoring facilitated by CHWs in the field, and changes can therefore be implemented directly to OMP protocols and guidelines for the purposes of health care improvements (Brink et al., 2018).

Fourthly, although the assessment of conventional and EHF ranges (0.25–16 kHz) is recommended by national and international guidelines for ototoxicity monitoring, it is not routinely implemented by OMPs. The inclusion of both conventional and EHF audiometry in this research project allowed comprehensive reporting on the prevalence of ototoxic hearing loss following DRTB treatment. The inclusion of EHFs in data analysis in Study III resulted in the early identification of ototoxic hearing loss for almost twice as many patients (56.5%) as when EHF were not considered (31.9%). Therefore, the findings of this research project provided a scientifically justifiable reason for the inclusion of EHF audiometry as part of ototoxicity monitoring (Brink et al., 2018).

Fifthly, the researcher was rigorous in striving for attention to detail and accuracy throughout the research process. Data were collected systematically, thoroughly and objectively and were analysed in a manner that minimised contamination and enhanced accuracy (Brink et al., 2018).

Lastly, translational research allowed the researcher to make specific recommendations and provide implications for clinical practice for ototoxicity monitoring, immediately after the research findings were obtained, to directly benefit patients receiving ototoxic drug treatment. To promote evidence-based practice, the findings and recommendations of the research project were presented in a coherent manner for any persons using and implementing the findings (Brink et al., 2018).

6.4.3 Research limitations

Several limitations across the three studies were identified. Firstly, the prevalence of adverse audiological symptoms experienced by patients, for example tinnitus, was recorded by testers at the time of the initial assessment only, and not at subsequent monitoring and exit assessments. After prolonged treatment with kanamycin, which causes cochleotoxicity and typically results in tinnitus and/or hearing loss, the incidence of self-reported adverse audiological symptoms for patients in this research project may have been higher (Rizk et al., 2020; Sagwa et al., 2012). Therefore, the prevalence of adverse audiological symptoms following DRTB treatment could not be established in this research project. Furthermore, as a result of patient loss to follow-up, the prevalence of ototoxic hearing loss at three, six and 18 months post treatment could not be determined for all the patients reported on in this research project. In addition, this research project evaluated ototoxicity monitoring assessment data only and did not determine diagnostic, intervention and rehabilitation outcomes for patients who presented with ototoxic hearing loss and who were not lost to follow-up.

Secondly, the lack of quantitative measures of the quality of testing by CHWs and PHC audiologists is a research limitation of this project. Within-subject repeated-measures evaluation using the test-retest method of determining reliability of behavioural pure tone testing would have been valuable. Intrasession reliability could have been established by retesting frequencies in addition to 1 kHz, for example, 2, 8 and 12 kHz (ASHA, 1994). Quantitative measures of inter-rater reliability could have been

assessed by comparing the behavioural pure tone test results between the same patients when assessed by CHWs and PHC audiologists, to better quantify the differences between the two groups of testers (Shojaeemend & Ayatollahi, 2018). A 5 to 10 dB difference between thresholds of assessments conducted by different testers could be considered reliable (ASHA, 1994; Sandström et al., 2016).

A third limitation is the use of portable audiometric equipment in conditions where ambient noise was not controlled. However, in order to offer ototoxicity monitoring in a community-based setting for increased patient access to care, this was mitigated in the following ways: the portable audiometer (KUDUwave) used in this project was equipped with insert and circumaural earphones, providing attenuation of ambient noise, and was able to continuously monitor noise levels and pause the assessment when background noise exceeded maximum permissible limits (Brennan-Jones et al., 2016). In addition, testers were provided with a quiet room within which to conduct ototoxicity monitoring assessments.

Fourthly, immittance measures were not included as part of ototoxicity monitoring assessments. Therefore, the prevalence of ototoxic hearing loss demonstrated in this research project may have been influenced by the inclusion of patients presenting with middle ear conductive pathology, which typically affects low frequency hearing thresholds (Stach & Ramachandran, 2017). However, for Study II, significant low frequency hearing threshold deterioration was evident at 500 Hz in the right ear only, while there was no significant low frequency hearing deterioration evident in either ear for the patients in Study III.

Due to the nature of the research project which involved evaluation of an OMP in the field, a fifth limitation was that Study III included a relatively small subset of patients. A sample size that is too small may not be able to detect clinically important effects and may lead to sampling error, causing a failure of the sample to provide an accurate representation of the population (Brink et al., 2018; Kumar, 2019). In addition, the use of a non-probability sampling method used for the three studies may have limited the generalisability of the results of this research project (Brink et al., 2018; Kumar, 2019).

Lastly, limitations due to the retrospective nature of this research project are as follows. The OMP and patient variables influencing the frequency, timing, and regularity of ototoxicity monitoring assessments could not be determined. In addition, the OMP service delivery practices identified by this research project in need of improvement, and the subsequent recommnedations made by the researcher to improve ototoxicity monitoring, could not be addressed. Lastly, important data pertaining to patient description (e.g. gender), and treatment type and duration were at times not recorded by testers and could therefore not be included in this retrospective study. While the unavailability of important data may have caused research bias, researcher and analysis triangulation were applied to reduce the effects of any such bias. Research triangulation encompassed the use of more than one researcher, from more than one discipline, each making a valuable contribution to this research project, to achieve intersubjective agreement. Analysis triangulation involved the use of more than one analytical technique to analyse the data of this research project (Brink et al., 2018).

6.5 Recommendations for future research and clinical guidelines

The following suggestions for future research can be made based on the research project results and conclusions.

An investigation of the OMP service delivery characteristics and prevalence of ototoxic hearing loss when using the model proposed in Figure 6.1 would be valuable. The OMP service delivery practices when using the proposed model could be compared to the findings of this research project to determine whether the recommendations made by this researcher are feasible and effective and result in improvements in service delivery for ototoxicity monitoring. The service delivery characteristics which could be evaluated when using the proposed model could include the timing of initial assessments, follow-up rates between consecutive assessments, regularity of assessments, the use of EHF audiometry and the prevalence of ototoxic hearing loss following ototoxic drug treatment, particularly in the EHF range for the purposes of the early detection of ototoxicity.

Ototoxicity monitoring is not routinely practiced across public health oncology units in South Africa (Ehlert et al., 2022). An investigation into the feasibility of decentralised, community-based ototoxicity monitoring conducted by CHWs for patients receiving ototoxic drug treatment for diseases other than DRTB, such as cancers and cystic fibrosis, is recommended. It is possible that an ototoxicity monitoring protocol like that presented in Figure 6.1 could be feasible for these populations and should be investigated.

An investigation into decentralised, community-based ototoxicity monitoring for patients receiving ototoxic drugs facilitated by CHW using novel devices and technology, including smartphone and automated EHF audiometry applications with integrated cloud-based data sharing capabilities, is recommended. The use of novel devices and technology may encourage the application of EHF audiometry by testers for ototoxicity monitoring by decreasing the time and expertise needed to conduct an assessment. The effect of integrated cloud-based data sharing on the data management practices of OMPs, and on the ongoing supervision of testers, should be determined with the aim of assisting OMPs in adhering to the guideline recommendations for service delivery practices. An investigation into the effect of ongoing training and monitoring of CHWs using smartphone technology and applications such as WhatsApp on OMP service delivery practice outcomes would be valuable.

An investigation into the feasibility and efficacy of ototoxicity monitoring for patients receiving ototoxic drugs using a novel shortened testing protocol that assesses the EHFs most sensitive to ototoxicity, is also recommended. An optimised shortened protocol for EHF audiometry could entail the exclusion of the assessment of the low and mid- to high frequency ranges (0.25–4 kHz) with the inclusion of the assessment of the frequencies 6, 8, 9, 11.2, 12.5, 14 and 16 kHz only. In the event of severe time constraints, the EHFs of 9–14 kHz could be prioritised for assessment. An optimised ototoxicity monitoring protocol assessing the frequencies most sensitive to ototoxicity may serve to increase testers' use of EHF audiometry for the purpose of early detection of ototoxicity for patients receiving ototoxic drugs.

This research project (Study II) found a significant difference between the average number of follow-up visits made by patients assessed by CHWs and those assessed by PHC audiologists. Due to the retrospective nature of this study, the reason for patients assessed by PHC audiologists attending more follow-up assessments could not be determined. However, the researcher speculates that a possible reason may be due to patient counselling by CHWs of the importance of adherence to scheduled ototoxicity monitoring assessments, for the purpose of early detection of ototoxicity. This in turn, points to the ongoing training and supervision of CHWs by PHC audiologists, and the need for the emphasis of patient counselling in the training of CHWs. To optimise patient adherence to scheduled ototoxicity monitoring assessements, an investigation into the patient and OMP variables influencing the timing, frequency and regularity of ototoxicity monitoring assessments of community-based ototoxicity monitoring services would be valuable. This might assist OMPs in prioritsing resources to optimise service delivery practices and follow-up rates for the purposes of serial ototoxicity monitoring.

Investigation of the experiences of CHWs and PHC audiologists' as facilitators of ototoxicity monitoring could be valuable and is recommended. This research project found that data management by CHWs and PHC audiologists was at times sporadic, leading to the absence of important data for inclusion in the project. Interviews aimed at gathering information from CHWs and PHCs audiologists on their experiences as part of the OMP and the possible reasons for sporadic data management could be conducted. Interviews could gather information on ways to improve ototoxicity monitoring services, particularly with regards to the timing and frequency of assessments, suggested by CHWs and PHCs audiologists. CHWs perspectives on facilitating audiological ototoxicity monitoring would be novel and could be a valuable contribution to the field. Information gathered from CHWs and PHC audiologists active in the field could assist OMPs develop practical data management procedures and improve service delivery practices.

6.6 Conclusion

This research project demonstrated that decentralised community-based ototoxicity monitoring for DRTB patients using CHWs to facilitate monitoring is a feasible solution to increasing patient access to care and to addressing the limited resources synonymous with ototoxicity monitoring in South Africa. The findings of this project support and encourage the employment of CHWs to facilitate community-based ototoxicity monitoring of patients with DRTB. However, the findings revealed that over time, community-based OMPs for DRTB show gaps in service delivery practices, most notably in the frequency and timing of ototoxicity monitoring assessments, data management practices and the use of EHF audiometry by testers.

The research project demonstrated that patients co-infected with HIV, those with a pre-existing hearing loss and those exposed to excessive noise were at higher risk for developing ototoxicity-induced hearing deterioration. It is therefore recommended that OMPs identify and prioritise patients with these risk factors for more vigilant ototoxicity monitoring and for all-oral treatment regimens. The research project demonstrated that DRTB treatment using kanamycin caused clinically and statistically significant deterioration of hearing thresholds in patients, most prominently at the high frequency and EHF ranges, and that EHF audiometry is more sensitive for the early detection of aminoglycoside-induced ototoxic hearing loss than conventional audiometry. Therefore, the recommendation for the use of EHF audiometry for ototoxicity monitoring is supported by the findings of this project. However, the poor utilisation of EHF audiometry by testers in this research project suggests that a shorter, more targeted approach to ototoxicity monitoring may be required where only those frequencies most sensitive to ototoxicity are prioritised. The findings of the current research project suggest that the frequencies most sensitive to ototoxicity and least affected by maximum equipment output limits should be included in an optimised, shortened protocol for EHF audiometry for ototoxicity monitoring.

In order to improve OMP service delivery outcomes and to encourage timely and regular ototoxicity assessment, current protocols and guidelines for ototoxicity monitoring should be reassessed to optimise limited resources and increase patient access to care. Reconsideration of the protocols and guidelines should include novel

approaches to ototoxicity monitoring, comprising decentralised community-based OMP facilitated by CHWs using novel devices and technology, such as mobile smartphone audiometry solutions and automated EHF audiometry with paperless cloud-based data management. Smartphone technology and applications, for instance WhatsApp, should be used for the ongoing supervision and training of testers and for communication with patients to improve adherence to scheduled ototoxicity monitoring assessments for the early detection of hearing loss.

REFERENCES

American Academy of Audiology. (2009). *American Academy of Audiology position statement and clinical practice guidelines ototoxicity monitoring*. Retrieved Feb 16 from https://audiology-web.s3.amazonaws.com/migrated/OtoMonGuidelines.pdf_539974c40999c1.58842217.pdf

American Speech-Language-Hearing Association. (1994). Audiologic management of individuals receiving cochleotoxic drug therapy. https://www.asha.org/policy/GL1994-00003/

American Speech-Language-Hearing Association. (2005). *Guidelines for manual pure-tone threshold audiometry*. American Speech-Language-Hearing Association. Retrieved November 28 from https://www.asha.org/policy/gl2005-00014/

American Speech-Language-Hearing Association. (2021). Degree of hearing loss. https://www.asha.org/public/hearing/degree-of-hearing-loss/

American Speech-Language-Hearing Association. (2022). *Hearing loss in adults*. American Speech-Language-Hearing Association. https://www.asha.org/practice-portal/clinical-topics/hearing-loss/

Andrade, C. (2018). Internal, external, and ecological validity in research design, conduct, and evaluation. *Indian Journal of Psychological Medicine*, *40*(5), 498-499. https://doi.org/10.4103/IJPSYM.IJPSYM_334_18

Appana, D., Joseph, L., & Paken, J. (2016). An audiological profile of patients infected with multi-drug resistant tuberculosis at a district hospital in Kwazulu-Natal. *The South African Journal of Communication Disorders = Die Suid-Afrikaanse Tydskrif vir Kommunikasieafwykings*, *63*(1), e1-e12. https://doi.org/10.4102/sajcd.v63i1.154

Bardien, S., Fagan, J., Harris, T., Jong, G. D., Petersen, L., & Schaaf, H. S. (2009). Aminoglycoside-induced hearing loss: South africans at risk. *SAMJ: South African Medical Journal*, *99*(6), 440-441.

Blankenship, C. M., Hunter, L. L., Feeney, M. P., Cox, M., Bittinger, L., Garinis, A. C., Lin, L., McPhail, G., & Clancy, J. P. (2021). Functional impacts of aminoglycoside treatment on speech perception and extended high-frequency hearing loss in a pediatric cystic fibrosis cohort. *American Journal of Audiology*, 1-20. https://doi.org/10.1044/2020_AJA-20-00059

Bornman, M., Swanepoel, D. W., De Jager, L. B., & Eikelboom, R. H. (2019). Extended high-frequency smartphone audiometry: Validity and reliability. *Journal of the American Academy of Audiology*, *30*(03), 217-226. https://doi.org/10.3766/jaaa.17111

Brennan-Jones, C. G., Eikelboom, R. H., Swanepoel, D. W., Friedland, P. L., & Atlas, M. D. (2016). Clinical validation of automated audiometry with continuous noise-monitoring in a clinically heterogeneous population outside a sound-treated environment. *International Journal of Audiology*, *55*(9), 507-513. https://doi.org/10.1080/14992027.2016.1178858

Bright, T., Mulwafu, W., Phiri, M., Ensink, R. J. H., Smith, A., Yip, J., Mactaggart, I., & Polack, S. (2019). Diagnostic accuracy of non-specialist versus specialist health workers in diagnosing hearing loss and ear disease in Malawi. *Tropical Medicine and International Health*, *24*(7), 817-828. https://doi.org/10.1111/tmi.13238

Brink, H., Van der Walt, C., & Van Rensburg, G. H. (2018). *Fundamentals of research methodology for healthcare professionals* (Fourth edition. ed.). Juta. http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&AN=1647445

Brittz, M., Heinze, B., Mahomed-Asmail, F., Swanepoel, D. W., & Stoltz, A. (2019). Monitoring hearing in an infectious disease clinic with mhealth technologies. *Journal of the American Academy of Audiology*, *30*(06), 482-492. https://doi.org/10.3766/jaaa.17120

Campbell, K. C. M., & Le Prell, C. G. (2018). Drug-induced ototoxicity: Diagnosis and monitoring. *Drug Safety*, *41*(5), 451-464. https://doi.org/10.1007/s40264-017-0629-8

Caumo, D. T. M., Geyer, L. B., Teixeira, A. R., & Barreto, S. S. M. (2017). Hearing thresholds at high frequency in patients with cystic fibrosis: A systematic review. *Brazilian Journal of Otorhinolaryngology*, *83*(4), 464-474. https://doi.org/10.1016/j.bjorl.2016.10.006

Centers for Disease Control and Prevention (CDC). (2012). *TB elimination. Multidrug-resistant tuberculosis (MDR TB)*. Retrieved March 24 from https://www.cdc.gov/tb/publications/factsheets/drtb/MDRTB.pdf

Centers for Disease Control and Prevention (CDC). (2016). *TB elimination multidrug-resistant tuberculosis (MDR TB)*. Retrieved 29 September from https://www.cdc.gov/tb/publications/factsheets/drtb/MDRTB.pdf

City of Cape Town. (2013a). *City of Cape Town - census 2011 - Klipfontein health district*. Retrieved from https://resource.capetown.gov.za/documentcentre/Documents/Maps%20and%20statistics/Klipfontein%20Health%20District.pdf

City of Cape Town. (2013b). *City of Cape Town - census 2011 - Mitchells Plain health district*. Retrieved from https://resource.capetown.gov.za/documentcentre/Documents/Maps%20and%20statistics/Mitchells%20Plain%20Health%20District.pdf

City of Cape Town. (2013c). *City of Cape Town - census 2011 - Southern health district*. Retrieved from https://resource.capetown.gov.za/documentcentre/Documents/Maps%20and%20statistics/Southern%20Health%20District.pdf

City of Cape Town. (2013d). *City of Cape Town - census 2011 - Western health district*. Retrieved from https://resource.capetown.gov.za/documentcentre/Documents/Maps%20and%20statistics/Western%20Health%20District.pdf

Clark, G. (2015). *Rehabilitation care workers' perceptions of the outcomes of a pilot training program.* University of Cape Town. https://open.uct.ac.za/bitstream/handle/11427/15488/thesis_hsf_2015_clrgra011-thesis%20%281%29.pdf?sequence=1&isAllowed=y

Cox, H., Hughes, J., Daniels, J., Azevedo, V., McDermid, C., Poolman, M., Boulle, A., Goemaere, E., & van Cutsem, G. (2014). Community-based treatment of drug-resistant tuberculosis in Khayelitsha, South Africa. *The International Journal of Tuberculosis and Lung Disease*, *18*(4), 441-448. https://doi.org/10.5588/ijtld.13.0742

Cox, V., Brigden, G., Crespo, R. H., Lessem, E., Lynch, S., Rich, M. L., Waning, B., & Furin, J. (2018). Global programmatic use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. *The International Journal of Tuberculosis and Lung Disease*, *22*(4), 407-412. https://doi.org/10.5588/ijtld.17.0706

Cox, V., Cox, H., Pai, M., Stillo, J., Citro, B., & Brigden, G. (2019). Health care gaps in the global burden of drug-resistant tuberculosis. *The International Journal of Tuberculosis and Lung Disease*, *23*(2), 125-135. https://doi.org/10.5588/ijtld.18.0866

Crundwell, G., Gomersall, P., & Baguley, D. M. (2016). Ototoxicity (cochleotoxicity) classifications: A review. *International Journal of Audiology*, *55*(2), 65-74. https://doi.org/10.3109/14992027.2015.1094188

de Jager, P., & van Altena, R. (2002). Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis. *The International Journal of Tuberculosis and Lung Disease*, *6*(7), 622-627.

Department Health Republic of South Africa. (2013). *Management of drug-resistant tuberculosis policy guidelines (updated)*. Department Health Republic of South Africa. Retrieved from https://health-e.org.za/wp-content/uploads/2014/06/MDR-TB-Clinical-Guidelines-Updated-Jan-2013.pdf

Department Health Republic of South Africa. (2015). *Ethics in health research: Principles, processes and structures (2nd ed.)*. Retrieved from https://www.sun.ac.za/english/research-innovation/Research-Development/Documents/Integrity%20and%20Ethics/DoH%202015%20Ethics%20in%20Health%20Research%20-%20Principles,%20Processes%20and%20Structures%202nd%20Ed.pdf

Department Health Republic of South Africa. (2018). *Interim clinical guidance for the implementation of injectable-free regimens for rifampicin-resistant tuberculosis in adults, adolescents and children*. Department Health Republic of South Africa. Retrieved from https://tbsouthafrica.org.za/resources/interim-clinical-guidance-implementation-injectable-free-regimens-rifampicin-resistant

Department of Health Republic of South Africa. (2020). *National department of health stategic plan 2020/21 - 2024/25*. Retrieved from https://www.health.gov.za/wp-content/uploads/2020/11/depthealthstrategicplanfinal2020-21to2024-25-1.pdf

Department Labour Republic of South Africa. (2001). *Occupational health and safety act 1993. Draft noise induced hearing loss regulations*. Department Labour Republic of South Africa Retrieved from https://www.gov.za/sites/default/files/gcis_document/201409/224990.pdf

Dillard, L. K., Martinez, R. X., Perez, L. L., Fullerton, A. M., Chadha, S., & McMahon, C. M. (2021). Prevalence of aminoglycoside-induced hearing loss in drug-resistant tuberculosis patients: A systematic review. *Journal of Infection*, *83*(1), 27-36. https://doi.org/10.1016/j.jinf.2021.05.010

Duggal, P., & Sarkar, M. (2007). Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. *BMC Ear, Nose, and Throat Disorders*, *7*, 5.

Ehlert, K., Heinze, B., & Swanepoel, D. W. (2022). Ototoxicity monitoring in south african cancer facilities: A national survey. *South African Journal of Communication Disorders*, *69*(1). https://doi.org/10.4102/sajcd.v69i1.846

Eksteen, S., Launer, S., Kuper, H., Eikelboom, R. H., Bastawrous, A., & Swanepoel, D. W. (2019). Hearing and vision screening for preschool children using mobile technology, South Africa. *Bulletin of the World Health Organization*, *97*(10), 672-680. https://doi.org/10.2471/BLT.18.227876

Evans, L. S., Nunurai, R., Farai, M., Timothy, R., Hubert, G. M. L., & Aukje, K. M.-T. (2015). Comparing amikacin and kanamycin-induced hearing loss in multidrug-

resistant tuberculosis treatment under programmatic conditions in a Namibian retrospective cohort. *BMC Pharmacology and Toxicology*, *16*(1), 36.

Fausti, S. A., Henry, J. A., Helt, W. J., Phillips, D. S., Frey, R. H., Noffsinger, D., Larson, V. D., & Fowler, C. G. (1999). An individualized, sensitive frequency range for early detection of ototoxicity. *Ear and Hearing*, *20*(6), 497-505.

Fausti, S. A., Henry, J. A., Schaffer, H. I., Olson, D. J., Frey, R. H., & McDonald, W. J. (1992). High-frequency audiometric monitoring for early detection of aminoglycoside ototoxicity. *The Journal of Infectious Diseases*, *165*(6), 1026-1032.

Field, A. P. (2018). *Discovering statistics using IBM SPSS statistics* (5th edition. ed.). SAGE Publications.

Gamiet, S., & Rowe, M. (2019). The role of rehabilitation care workers in South African healthcare: A q-methodological study. *African Journal of Disability*, *8*, 537. https://doi.org/10.4102/ajod.v8i0.537

Ganesan, P., Schmiedge, J., Manchaiah, V., Swapna, S., Dhandayutham, S., & Kothandaraman, P. P. (2018). Ototoxicity: A challenge in diagnosis and treatment. *Journal of Audiology & Otology*, *22*(2), 59-68. https://doi.org/10.7874/jao.2017.00360

Garinis, A. C., Poling, G. L., Rubenstein, R. C., Konrad-Martin, D., Hullar, T. E., Baguley, D. M., Burrows, H. L., Chisholm, J. A., Custer, A., Hawe, L. D., Hunter, L. L., Marras, T. K., Ortiz, C. E., Petersen, L., Steyger, P. S., Winthrop, K., Zettner, E. M., Clark, K., Hungerford, M., Vachhani, J. J., & Brewer, C. C. (2021). Clinical considerations for routine auditory and vestibular monitoring in patients with cystic fibrosis. *American Journal of Audiology*, 1-10. https://doi.org/10.1044/2021_AJA-21-00031

Ghafari, N., Court, R., Chirehwa, M. T., Wiesner, L., Petersen, L., Maartens, G., Gumbo, T., McIlleron, H., & Ramma, L. (2020). Pharmacokinetics and other risk factors for kanamycin-induced hearing loss in patients with multi-drug resistant tuberculosis. *International Journal of Audiology*, *59*(3), 219-223. https://doi.org/10.1080/14992027.2019.1690170

Govender, M., & Paken, J. (2015). Practices employed by audiologists in the management of adult patients with multidrug-resistant tuberculosis in south africa. *South African Family Practice*, *57*(6), 363-372. https://doi.org/10.1080/20786190.2015.1085222

Harris, T., De Jong, G., Bardien, S., Schaaf, H. S., Fagan, J. J., & Petersen, L. (2012). Aminoglycoside-induced hearing loss in HIV-positive and HIV-negative multidrug-resistant tuberculosis patients: Research. *South African Medical Journal*, *102*(6), 363-366.

Harris, T., Peer, S., & Fagan, J. J. (2012). Audiological monitoring for ototoxic tuberculosis, human immunodeficiency virus and cancer therapies in a developing world setting. *Journal of Laryngology and Otology*, *126*(6), 548-551. https://doi.org/10.1017/S0022215112000357

Health Professions Council of South Africa. (2018). *Audiological management of patients on treatment that includes ototoxic medications. Guidelines*. Retrieved Feb 16 from https://www.hpcsa.co.za/Uploads/SLH/Guidelines%20for%20Audiological%20Management%20of%20Patients%20on%20Treatment%20that%20includes%20Ototoxic%20Medications.pdf

Hong, H., Budhathoki, C., & Farley, J. E. (2018). Increased risk of aminoglycoside-induced hearing loss in MDR-TB patients with HIV coinfection. *The International Journal of Tuberculosis and Lung Disease*, *22*(6), 667-674. https://doi.org/10.5588/ijtld.17.0830

Hong, H., Dowdy, D. W., Dooley, K. E., Francis, H. W., Budhathoki, C., Han, H.-R., & Farley, J. E. (2020a). Aminoglycoside-induced hearing loss among patients being treated for drug-resistant tuberculosis in South Africa: A prediction model. *Clinical Infectious Diseases*, *70*(5).

Hong, H., Dowdy, D. W., Dooley, K. E., Francis, H. W., Budhathoki, C., Han, H. R., & Farley, J. E. (2020b). Prevalence of pre-existing hearing loss among patients with drug-resistant tuberculosis in South Africa. *American Journal of Audiology*, *29*(2), 199-205. https://doi.org/10.1044/2020_AJA-19-00103

Horsburgh, C. R., Mitnick, C. D., & Lange, C. (2019). The MDR-TB epidemic—a status report. *The International Journal of Tuberculosis and Lung Disease*, *23*(2), 121-122. https://doi.org/10.5588/ijtld.18.0000

Huth, M. E., Ricci, A. J., Cheng, A. G., & Pearson, J. P. (2011). Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection. *International Journal of Otolaryngology.*(2011).

Khoza-Shangase, K. (2010). Is there a need for ototoxicity monitoring in patients with HIV/aids? *African Journal of Pharmacy and Pharmacology*, *4*(9), 574-579.

Khoza-Shangase, K. (2020). Hearing function of gold miners with and without a history of tuberculosis treatment: A retrospective data review. *Brazilian Journal of Otorhinolaryngology*, *86*(3), 294-299. https://doi.org/10.1016/j.bjorl.2018.12.003

Khoza-Shangase, K., & Masondo, N. (2020). What are the current audiological practices for ototoxicity assessment and management in the South African healthcare context? *International Journal of Environmental Research and Public Health*, *17*(7), 2613. https://doi.org/10.3390/ijerph17072613

Khoza-Shangase, K., & Masondo, N. (2021). In pursuit of preventive audiology in South Africa: Scoping the context for ototoxicity assessment and management. *Journal of Pharmacy & Bioallied Sciences*, *13*(1).

Khoza-Shangase, K., & Prodromos, M. (2021). Impact of drug-resistant tuberculosis treatment on hearing function in South African adults: Bedaquiline versus kanamycin. *The South African Journal of Communication Disorders = Die Suid-Afrikaanse Tydskrif vir Kommunikasieafwykings*, *68*(1), e1-e8. https://doi.org/10.4102/sajcd.v68i1.784

Khoza-Shangase, K., & Stirk, M. (2016). Audiological testing for ototoxicity monitoring in adults with tuberculosis in state hospitals in Gauteng, South Africa. *Southern African Journal of Infectious Diseases*, *31*(2), 44-49. https://doi.org/10.1080/23120053.2016.1128143

Konrad-Martin, D., Poling, G. L., Garinis, A. C., Ortiz, C. E., Hopper, J., O'Connell Bennett, K., & Dille, M. F. (2018). Applying U.S. national guidelines for

ototoxicity monitoring in adult patients: perspectives on patient populations, service gaps, barriers and solutions. *International Journal of Audiology, 57*(sup4), S3-S18. https://doi.org/10.1080/14992027.2017.1398421

Konrad-Martin, D., Wilmington, D. J., Gordon, J. S., Reavis, K. M., & Fausti, S. A. (2005). Audiological management of patients receiving aminoglycoside antibiotics. *Volta Review*, *105*(3), 229-250.

Kros, C. J., & Steyger, P. S. (2019). Aminoglycoside- and cisplatin-induced ototoxicity: Mechanisms and otoprotective strategies. *Cold Spring Harbor Perspectives in Medicine*, *9*(11). https://doi.org/10.1101/cshperspect.a033548

Kumar, R. (2019). *Research methodology : A step-by-step guide for beginners* (Fifth edition. ed.). SAGE.

Lange, C., Aarnoutse, R. E., Alffenaar, J. W. C., Bothamley, G., Brinkmann, F., Costa, J., Chesov, D., van Crevel, R., Dedicoat, M., Dominguez, J., Duarte, R., Grobbel, H. P., Guenther, G., Guglielmetti, L., Heyckendorf, J., Kay, A. W., Kirakosyan, O., Kirk, O., Koczulla, R. A., Kudriashov, G. G., Kuksa, L., van Leth, F., Magis-Escurra, C., Mandalakas, A. M., Molina-Moya, B., Peloquin, C. A., Reimann, M., Rumetshofer, R., Schaaf, H. S., Schon, T., Tiberi, S., Valda, J., Yablonskii, P. K., & Dheda, K. (2019). Management of patients with multidrug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Disease*, *23*(6), 645-662.

Lange, C., Dheda, K., Chesov, D., Mandalakas, A. M., Udwadia, Z., & Horsburgh, C. R., Jr. (2019). Management of drug-resistant tuberculosis. *Lancet (London, England)*, *394*(10202), 953-966. https://doi.org/10.1016/S0140-6736(19)31882-3

Lanvers-Kaminsky, C., Zehnhoff-Dinnesen, A. A., Parfitt, R., & Ciarimboli, G. (2017). Drug-induced ototoxicity: Mechanisms, pharmacogenetics, and protective strategies. *Clinical Pharmacology and Therapeutics*, *101*(4), 491-500. https://doi.org/10.1002/cpt.603

Leavitt, S. V., Jacobson, K. R., Ragan, E. J., Bor, J., Hughes, J., Bouton, T. C., Dolby, T., Warren, R. M., & Jenkins, H. E. (2021). Decentralized care for rifampin-resistant tuberculosis, Western Cape, South Africa. *Emerging Infectious Diseases*, *27*(3), 728-739. https://doi.org/10.3201/eid2703.203204

Leedy, P. D., & Ormrod, J. E. (2020). *Practical research* (12th ed. ed.). Pearson Education Limited. https://public.ebookcentral.proquest.com/choice/publicfullrecord.aspx?p=6142159

https://public.ebookcentral.proquest.com/choice/publicfullrecord.aspx?p=6142162

https://public.ebookcentral.proquest.com/choice/publicfullrecord.aspx?p=6142569

Manchaiah, V., Beukes, E. W., & Roeser, R. J. (2022). *Evaluating and conducting research in audiology*. Plural Publishing, Inc. https://public.ebookcentral.proquest.com/choice/publicfullrecord.aspx?p=6499979

Medicins Sans Frontieres. (2020a). *Step up for TB: TB policies in 37 countries, 4th ed*. Retrieved May 2020 from https://msfaccess.org/step-tb-tb-policies-37-countries-4th-ed

Medicins Sans Frontieres. (2020b). *Step up for TB: TB policies in 37 countries, 4th ed*. Medicins Sans Frontieres. Retrieved 29 September from https://msfaccess.org/step-tb-tb-policies-37-countries-4th-ed

Meiyan, J., Takatoshi, K., & Peter, S. S. (2017). Aminoglycoside-induced cochleotoxicity: A review. *Frontiers in Cellular Neuroscience*.

Melchionda, V., Wyatt, H., Capocci, S., Garcia Medina, R., Solamalai, A., Katiri, S., Hopkins, S., Cropley, I., & Lipman, M. (2013). Amikacin treatment for multidrug resistant tuberculosis: How much monitoring is required? *The European Respiratory Journal*, *42*(4), 1148-1150. https://doi.org/10.1183/09031936.00184312

Migliori, G. B., Thong, P. M., Alffenaar, J. W., Denholm, J., Tadolini, M., Alyaquobi, F., Blanc, F. X., Buonsenso, D., Cho, J. G., Codecasa, L. R., Danila, E., Duarte,

R., García-García, J. M., Gualano, G., Rendon, A., Silva, D. R., Souleymane, M. B., Tham, S. M., Thomas, T. A., Tiberi, S., Udwadia, Z. F., Goletti, D., Centis, R., D'Ambrosio, L., Sotgiu, G., & Ong, C. W. M. (2021). Gauging the impact of the COVID-19 pandemic on tuberculosis services: A global study. *The European Respiratory Journal*, *58*(5). https://doi.org/10.1183/13993003.01786-2021

Moyo, S., Cox, H. S., Hughes, J., Daniels, J., Synman, L., De Azevedo, V., Shroufi, A., Cox, V., van Cutsem, G., & Via, L. E. (2015). Loss from treatment for drug resistant tuberculosis: Risk factors and patient outcomes in a community-based program in Khayelitsha, South Africa. *PloS One*, *10*(3), e0118919. https://doi.org/10.1371/journal.pone.0118919

Mulwafu, W., Ensink, R., Kuper, H., & Fagan, J. (2017). Survey of ENT services in sub-Saharan Africa: Little progress between 2009 and 2015. *Global Health Action*, *10*(1), 1289736. https://doi.org/10.1080/16549716.2017.1289736

Ndjeka, N., Hughes, J., Reuter, A., Conradie, F., Enwerem, M., Ferreira, H., Ismail, N., Kock, Y., Master, I., Meintjes, G., Padanilam, X., Romero, R., Schaaf, H. S., Riele, J. T., & Maartens, G. (2020). Implementing novel regimens for drug-resistant TB in South Africa: What can the world learn? *The International Journal of Tuberculosis and Lung Disease*, *24*(10), 1073-1080. https://doi.org/10.5588/ijtld.20.0174

O'Donovan, J., O'Donovan, C., Kuhn, I., Sachs, S. E., & Winters, N. (2018). Ongoing training of community health workers in low-income and middle-income countries: A systematic scoping review of the literature. *BMJ Open*, *8*(4), e021467. https://doi.org/10.1136/bmjopen-2017-021467

O'Donovan, J., Verkerk, M., Winters, N., Chadha, S., & Bhutta, M. F. (2019). The role of community health workers in addressing the global burden of ear disease and hearing loss: A systematic scoping review of the literature. *BMJ Global Health*, *4*(2), e001141. https://doi.org/10.1136/bmjgh-2018-001141

Oga-Omenka, C., Tseja-Akinrin, A., Sen, P., Mac-Seing, M., Agbaje, A., Menzies, D., & Zarowsky, C. (2020). Factors influencing diagnosis and treatment initiation for

multidrug-resistant/rifampicin-resistant tuberculosis in six sub-Saharan African countries: A mixed-methods systematic review. *BMJ Global Health*, *5*(7).

Olusanya, B. O., Davis, A. C., & Hoffman, H. J. (2019). Hearing loss grades and the international classification of functioning, disability and health. *Bulletin of the World Health Organization*, *97*(10), 725-728. https://doi.org/10.2471/BLT.19.230367

Petersen, L., & Rogers, C. (2015). Aminoglycoside-induced hearing deficits - a review of cochlear ototoxicity. *South African Family Practice*, *57*(2), 77-82. https://doi.org/10.1080/20786190.2014.1002220

Prendergast, G., Hymers, M., & Lee, A. (2020). A quick and reliable estimate of extended high-frequency hearing. *International Journal of Audiology*, *59*(11), 823-827. https://doi.org/10.1080/14992027.2020.1767810

Raaijmakers, Q. A. W. (1999). Effectiveness of different missing data treatments in surveys with likert-type data: Introducing the relative mean substitution approach. *Educational and Psychological Measurement, 59*(5), 725-748.

Ramma, L., Heinze, B., & Schellack, N. (2019). Prevention of treatment-induced ototoxicity: An update for clinicians. *South African Medical Journal*, *109*(3), 145-149. https://doi.org/10.7196/SAMJ.2019.v109i3.13903

Ramma, L., Nhokwara, P. T., & Rogers, C. (2019). Statistical factors associated with utilisation of ototoxicity monitoring services for multi-drug-resistant tuberculosis patients in the Western Cape. *The South African Journal of Communication Disorders = Die Suid-Afrikaanse Tydskrif vir Kommunikasieafwykings*, *66*(1), e1-e6. https://doi.org/10.4102/sajcd.v66i1.596

Republic of South Africa. (2004). *Government gazette no. 61 of 2003: National health act, 2004*. Retrieved 3 June from https://www.gov.za/sites/default/files/gcis_document/201409/a61-03.pdf

Republic of South Africa Statistics Department. (2021). *Statistical release p0302. Mid-year population estimates 2021 embargoed*. Retrieved 29 September from http://www.statssa.gov.za/publications/P0302/P03022021.pdf

Rieke, C. C., Clavier, O. H., Allen, L. V., Anderson, A. P., Brooks, C. A., Fellows, A. M., Brungart, D. S., & Buckey, J. C. (2017). Fixed-level frequency threshold testing for ototoxicity monitoring. *Ear and Hearing*, *38*(6), e369-e375. https://doi.org/10.1097/AUD.0000000000000433

Rizk, H. G., Lee, J. A., Liu, Y. F., Endriukaitis, L., Isaac, J. L., & Bullington, W. M. (2020). Drug-induced ototoxicity: A comprehensive review and reference guide. *Pharmacotherapy*, *40*(12), 1265-1275. https://doi.org/10.1002/phar.2478

Rogers, C., & Petersen, L. (2011). Aminoglycoside-induced balance deficits: A review of vestibulotoxicity. *South African Family Practice*, *53*(5), 419-424.

Sagwa, E., Mantel-Teeuwisse, A. K., Ruswa, N., Musasa, J. P., Pal, S., Dhliwayo, P., & van Wyk, B. (2012). The burden of adverse events during treatment of drug-resistant tuberculosis in Namibia. *Southern Med Review*, *5*(1), 6-13.

Salvi, R. (2020). Hidden hearing loss and brain changes from ototoxic drugs. *The Hearing Journal*, *73*(2), 32,34,35. https://doi.org/10.1097/01.HJ.0000654936.64301.56

Sandström, J., Swanepoel, D. W., Carel Myburgh, H., & Laurent, C. (2016). Smartphone threshold audiometry in underserved primary health-care contexts. *International Journal of Audiology*, *55*(4), 232-238. https://doi.org/10.3109/14992027.2015.1124294

Schacht, J., Talaska, A. E., & Rybak, L. P. (2012). Cisplatin and aminoglycoside antibiotics: Hearing loss and its prevention. *The Anatomical Record: Advances in Integrative Anatomy and Evolutionary Biology*, *295*(11), 1837-1850. https://doi.org/10.1002/ar.22578

Sharma, A., Hill, A., Kurbatova, E., van der Walt, M., Kvasnovsky, C., Tupasi, T. E., Caoili, J. C., Gler, M. T., Volchenkov, G. V., Kazennyy, B. Y., Demikhova, O. V., Bayona, J., Contreras, C., Yagui, M., Leimane, V., Cho, S. N., Kim, H. J., Kliiman, K., Akksilp, S., Jou, R., Ershova, J., Dalton, T., & Cegielski, P. T. C. F. D. C. T. T. (2017). Estimating the future burden of multidrug-resistant and extensively drug-resistant tuberculosis in India, the Philippines, Russia, and

South Africa: A mathematical modelling study. *The Lancet Infectious Diseases*, *17*(7), 707-715. https://doi.org/10.1016/S1473-3099(17)30247-5

Shojaeemend, H., & Ayatollahi, H. (2018). Automated audiometry: A review of the implementation and evaluation methods. *Healthcare Informatics Research*, *24*(4), 263-275. https://doi.org/10.4258/hir.2018.24.4.263

Sogebi, O. A., Adefuye, B. O., & Ajayi, E. A. (2021). Early hearing threshold changes and peculiarities of audiometric assessments among patients in a drug-resistant tuberculosis treatment center. *African Health Sciences*, *21*(1), 230-237. https://doi.org/10.4314/ahs.v21i1.30

Stach, B. A., & Ramachandran, V. (2017). *Clinical audiology an introduction* (3rd ed. ed.). Plural Publishing, Incorporated. http://public.eblib.com/choice/PublicFullRecord.aspx?p=6499978

Stevenson, L. J., Biagio-de Jager, L., Graham, M. A., & Swanepoel, D. W. (2021). Community-based ototoxicity monitoring for drug-resistant tuberculosis in South Africa: An evaluation study. *International Journal of Environmental Research and Public Health*, *18*(21), 11342. https://www.mdpi.com/1660-4601/18/21/11342

Steyger, P. S. (2011). Mechanisms involved in ototoxicity. *Seminars in hearing*, *32*(03), 217-228. https://doi.org/10.1055/s-0031-1286616

Steyger, P. S. (2021a). Mechanisms of aminoglycoside- and cisplatin-induced ototoxicity. *American Journal of Audiology*, *30*(3S), 887-900. https://doi.org/10.1044/2021_AJA-21-00006

Steyger, P. S. (2021b). Mechanisms of ototoxicity and otoprotection. *Otolaryngologic Clinics of North America*, *54*(6), 1101-1115.

Swanepoel, D. W., Maclennan-Smith, F., & Hall, J. W. (2013). Diagnostic pure-tone audiometry in schools: Mobile testing without a sound-treated environment. *Journal of the American Academy of Audiology*, *24*(10), 992-1000. https://doi.org/10.3766/jaaa.24.10.10

Swanepoel, W. (2020). eHealth technologies enable more accessible hearing care. *Seminars in Hearing*, *41*(2), 133-140. https://doi.org/10.1055/s-0040-1708510

The South African National Aids Council. (2017). *Monitoring and evaluation plan for the national strategic plan on HIV, TB and STI (2017 – 2022)*. Retrieved Feb 16 from https://sanac.org.za/wp-content/uploads/2020/01/114725-ME-Plan-3rd-Proof-5-Aug.pdf

Van Deun, A., Decroo, T., Tahseen, S., Trébucq, A., Schwoebel, V., Ortuno-Gutierrez, N., de Jong, B. C., Rieder, H. L., Piubello, A., & Chiang, C. Y. (2020). World health organization 2018 treatment guidelines for rifampicin-resistant tuberculosis: Uncertainty, potential risks and the way forward. *International Journal of Antimicrobial Agents*, *55*(1), 105822. https://doi.org/10.1016/j.ijantimicag.2019.10.003

Wang, M., Ai, Y., Han, Y., Fan, Z., Shi, P., & Wang, H. (2021). Extended high-frequency audiometry in healthy adults with different age groups. *Journal of Otolaryngology - Head & Neck Surgery*, *50*(1). https://doi.org/10.1186/s40463-021-00534-w

Watts, K. L. A. D. (2019). Ototoxicity: Visualized in concept maps. *Seminars in Hearing*, *40*(02), 177-187. https://doi.org/10.1055/s-0039-1684046

Wells, C. D., Cegielski, J. P., Nelson, L. J., Laserson, K. F., Holtz, T. H., Finlay, A., Castro, K. G., & Weyer, K. (2007). HIV infection and multidrug-resistant tuberculosis: The perfect storm. *The Journal of Infectious Diseases*, *196*(Suppl 1), 86-107.

Western Cape Government Health. (2018). *Clinical guidelines & standard operating procedure for the implementation of the short & long DR-TB regimens for adults, adolescents and children*. Retrieved Feb 16 from https://www.westerncape.gov.za/assets/departments/health/tuberculosis_-_dr-tb_clinical_guidelines_2018.pdf

World Health Organisation. (2006a). *Primary ear and hearing care training resource basic level*. Retrieved from https://www.who.int/pbd/deafness/activities/hearing_care/basic.pdf?ua=1

World Health Organisation. (2006b). *Primary ear and hearing care training resource trainer's manual intermediate level*. Retrieved from https://www.who.int/pbd/deafness/activities/hearing_care/trainer.pdf?ua=1

World Health Organisation. (2007). *Community health workers: What do we know about them? The state of the evidence on programmes, activities, costs and impact on health outcomes of using community health workers.* Retrieved 31 August from https://www.who.int/hrh/documents/community_health_workers.pdf

World Health Organisation. (2015). *Brochure: The WHO end TB strategy*. Retrieved Feb 16 from https://www.who.int/tb/End_TB_brochure.pdf

World Health Organisation. (2018). *Who guideline on health policy and system support to optimize community health worker programmes.* Retrieved 06/29/2021 from http://apps.who.int/iris/bitstream/handle/10665/275474/9789241550369-eng.pdf

World Health Organisation. (2019). *TB profile: South Africa*. Retrieved March 17 from https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type=%22country%22&lan=%22EN%22&iso2=%22ZA%22

World Health Organisation. (2020a). *Community-based health care, including outreach and campaigns, in the context of the COVID-19 pandemic.* World Health Organisation. https://www.who.int/publications/i/item/WHO-2019-nCoV-Comm_health_care-2020.1

World Health Organisation. (2020b). *Global tuberculosis report 2020*. World Health Organisation. https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf

World Health Organisation. (2020c). *WHO consolidated guidelines on tuberculosis. Module 4: Treatment - drug-resistant tuberculosis treatment*. Retrieved 07/09/2021 from https://www.who.int/publications/i/item/9789240007048

World Health Organisation. (2020d). *World health organisation (WHO) information note tuberculosis and COVID-19*. World Health Organisation.

https://www.who.int/docs/default-source/documents/tuberculosis/infonote-tb-covid-19.pdf

World Health Organisation. (2021a). *Global tuberculosis report 2021*. https://www.who.int/publications/i/item/9789240037021

World Health Organisation. (2021b). *World report on hearing*. World Health Organization. Retrieved August 1 from https://www.who.int/publications/i/item/world-report-on-hearing

Wrohan, I., Redwood, L., Ho, J., Velen, K., & Fox, G. J. (2021). Ototoxicity among multidrug-resistant TB patients: A systematic review and meta-analysis. *The International Journal of Tuberculosis and Lung Disease*, *25*(1), 23-30. https://doi.org/10.5588/ijtld.20.0217

Xie, J., Talaska, A. E., & Schacht, J. (2011). New developments in aminoglycoside therapy and ototoxicity. *Hearing Research*, *281*(1-2), 28-37. https://doi.org/10.1016/j.heares.2011.05.008

Yousuf Hussein, S., Swanepoel, W., Mahomed, F., & Biagio de Jager, L. (2018). Community-based hearing screening for young children using an mhealth service-delivery model. *Global Health Action*, *11*(1), 1467077. https://doi.org/10.1080/16549716.2018.1467077

Yuan, I., Topjian, A. A., Kurth, C. D., Kirschen, M. P., Ward, C. G., Zhang, B., & Mensinger, J. L. (2019). Guide to the statistical analysis plan. *Paediatric Anaesthesia, 29*(3), 237-242. https://doi.org/10.1111/pan.13576

Zhao, Y., Fox, T., Manning, K., Stewart, A., Tiffin, N., Khomo, N., Leslie, J., Boulle, A., Mudaly, V., Kock, Y., Meintjes, G., & Wasserman, S. (2019). Improved treatment outcomes with bedaquiline when substituted for second-line injectable agents in multidrug-resistant tuberculosis: A retrospective cohort study. *Clinical Infectious Diseases*, *68*(9), 1522-1529. https://doi.org/10.1093/cid/ciy727

APPENDICES

APPENDIX A

Ethical Clearance Letter: Faculty of Humanities (A)

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Research Ethics Committee

15 December 2016

Dear Prof Vinck

Project:	**Ototoxicity monitoring for drug-resistant tuberculosis (DRTB) using automated and mobile health technology**
Researcher:	**L Scheepers**
Supervisor:	**Prof DCD Swanepoel**
Department:	**Speech-Language Audiology and Pathology**
Reference:	**23051592 (GW20161128HS)**

Thank you for the response to the Committee's correspondence of 2 December 2016.

I am pleased to inform you that the above application was **conditionally approved** by the **Research Ethics Committee** on 14 December 2016 as written permission is requested by:

- The Department of Health and the healthcare facilities in the Western Cape.

Please note that data collection may not commence prior to the above institutions giving written permission and subject to final approval by this committee. To facilitate the administrative process, please respond to Ms Tracey Andrew at tracey.andrew@up.ac.za or Room HB 7-27, at your earliest possible convenience.

Sincerely

Prof Karen Harris
Acting Chair: Research Ethics Committee
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail: tracey.andrew@up.ac.za

Research Ethics Committee Members: Prof MME Schoeman (Deputy Dean); Prof KL Harris; Dr L Blokland; Dr R Fasselt; Ms KT Govinder; Dr E Johnson; Dr C Panebianco; Dr C Puttergill; Dr D Reyburn; Prof GM Spies; Prof E Taljard; Ms B Tsebe; Dr E van der Klashorst; Mr V Sithole

APPENDIX B

Ethical Clearance Letter: Faculty of Humanities (B)

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Research Ethics Committee

22 November 2017

Dear Ms Scheepers Stevenson

Project:	**Ototoxicity monitoring for drug-resistant tuberculosis (DRTB) using automated and mobile health technology**
Researcher:	**L Scheepers Stevenson**
Supervisor:	**Prof DCD Swanepoel**
Department:	**Speech-Language Audiology and Pathology**
Reference:	**23051592 (GW20161128HS)**

Thank you for your response to the Committee's letter of 15 December 2016.

The Committee notes that approvals from the Western Cape City Health and Strategic & Health Support departments as well from the Faculty of Health Science's Research Ethics Committee.

I have pleasure in informing you that your application was **approved** by the **Research Ethics Committee** on 14 November 2017. Data collection may therefore commence.

Please note that this approval is based on the assumption that the research will be carried out along the lines laid out in the proposal. Should the actual research depart significantly from the proposed research, it will be necessary to apply for a new research approval and ethical clearance.

We wish you success with the project.

Sincerely

Prof Maxi Schoeman
Deputy Dean: Postgraduate Studies and Ethics
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail: tracey.andrew@up.ac.za

cc: Prof DCD Swanepoel (Supervisor)

Research Ethics Committee Members: Prof MME Schoeman (Deputy Dean); Prof KL Harris; Mr A Bless; Dr L Blokland; Ms A dos Santos; Dr R Fasselt; Ms KT Govender; Dr E Johnson; Dr C Panebianco; Dr C Puttergill; Dr D Reyburn; Dr M Taub; Prof GM Spies; Prof E Taljard; Dr M Soer; Dr V Thebe; Ms B Tsebe; Ms D Mokalapa

APPENDIX C

Ethical Clearance Letter: Faculty of Health Sciences

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 28 August 2018.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 22/04/2017.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

15/03/2017

Approval Certificate
New Application

Ethics Reference No.: 63/2017

Title: Ototoxicity monitoring for drug-resistant tuberculosis using automated and mobile health technology

Dear Ms Lucia Scheepers

The **New Application** as supported by documents specified in your cover letter dated **28/02/2017** for your research received on the 1/03/2017, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 15/03/2017.

Please note the following about your ethics approval:
- Ethics Approval is valid for 4 years
- Please remember to use your protocol number (**63/2017**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
- The ethics approval is conditional on the receipt of **6 monthly written Progress Reports**, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

*** Kindly collect your original signed approval certificate from our offices, Faculty of Health Sciences, Research Ethics Committee, Tswelopele Building, Level 4-60*

Dr R Sommers; MBChB; MMed (Int); MPharMed,PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health).

☎ 012 356 3084 deepeka.behari@up.ac.za / fhsethics@up.ac.za http://www.up.ac.za/healthethics
Private Bag X323, Arcadia, 0007 - Tswelopele Building, Level 4, Room 60, Gezina, Pretoria

APPENDIX D

Letter of Research Request Approval: City of Cape Town

CITY OF CAPE TOWN
ISIXEKO SASEKAPA
STAD KAAPSTAD

CITY HEALTH

Dr Hélène Visser
Manager: Specialised Health

T: 021 400 3981 F: 021 421 4894 M: 083 298 8718
E: Helene.Visser@capetown.gov.za

2017-01-27

Re: Research Request: Ototoxicity Monitoring for Drug-Resistant Tuberculosis using automated and Mobile Health Technology (ID NO: 7788)

Dear Dr Scheepers,

Your research has been approved as per your request in the facilities mentioned below:

Eastern & Khayelitsha:	Phumlani, Rocklands, Eastridge, Mzamomhle, Ikwezi, Somerset West, Sir Lowry Pass, Gordons Bay, Eersteriver, Wesbank, Dr Ivan Toms, Kuilsriver, Sarepta and Blue Downs Clinics
Contact Person	Dr V de Azevedo (Area Manager) virginia.deAzevedo@capetown.gov.za Tel/Cell: (021) 360-1258/ 083 629 3344
Mitchells Plain & Southern:	Ocean View, Masiphumelele, Westlake, Seawinds, Lavender Hill, Klip Road, Philippi, Strandfontein, Wynberg, Silvertown, Phumlani, Rocklands, Eastridge and Mzamomhle Clinics
Contact Person	Mrs S Elloker (Area Manager) Tel/Cell: (021) 391-5012/ 084 222 1478 Soraya.Elloker@capetowngov.za
Klipfontein & Tygerberg:	Elsies River, Kasselsvlei CHC, Delft South, Hanover Park, Bishop Lavis and St Vincent Clinics
Contact Person	Mrs M Alexander (Area Manager) Merle.Alexander@capetown.gov.za Tel/Cell: (021) 938-8279 / 084 222 1471
Northern & Western:	Fisantekraal Wallacedene, Bloekombos, Durbanville, Hout Bay Main Road, Brackenfell, Langa, Protea Park, Factreton and Chapel Street Clinics
Contact Person	Dr A Zimba (Acting: Area Manager) Mandile.Zimba@capetown.gov.za Tel/Cell: (021) 980-1230 / 084 627 2425

Please note the following:

1. All individual patient information obtained must be kept confidential.
2. Access to the clinics and clients must be arranged with the relevant Managers such that normal activities are not disrupted.
3. A copy of the final report must be sent to the City Health Head Office, P O Box 2815 Cape Town 8001, within 6 months of its completion and feedback must also be given to the clinics involved.
4. Your project has been given an ID Number (7788) Please use this in any future correspondence with us.
5. No monetary incentives to be paid to clients on the City Health premises.

Thank you for your co-operation and please contact me if you require any further information or assistance.

Yours sincerely

H Visser.

DR G H VISSER
MANAGER: SPECIALISED HEALTH

cc. Dr A Zimba
Dr V de Azevedo
Mrs S Elloker
Ms M Alexander
Dr K Jennings KarenAnn.Jennings@capetown.gov.za
Ms J Caldwell Judy.Caldwell@capetown.gov.za

APPENDIX E

Letters of Research Request Approval: Western Cape Government, Health

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 6857; fax: +27 21 483 9895
5th Floor, Norton Rose House, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za

REFERENCE: WC_2017RP22_896
ENQUIRIES: Ms Charlene Roderick

University of Pretoria

Elandspoort 357-JR

Pretoria

0002

For attention: Ms Lucia Stevenson

Re: Ototoxicity monitoring for drug-resistant tuberculosis using automated and mobile health technology.

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.

Please contact following people to assist you with any further enquiries in accessing the following sites:

Delft CHC	**Sheron T Forgus**	**021 954 2237**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

APPENDIX F

OMP Data Collection Form

Western Cape Government
Health

OTOTOXICITY MONITORING

Southern/Western Substructure

[redacted]

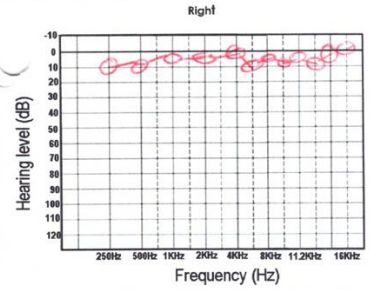
Patient name: [redacted]
Patient File/ID nr: [redacted]
DOB: [redacted] Affix Patient Sticker

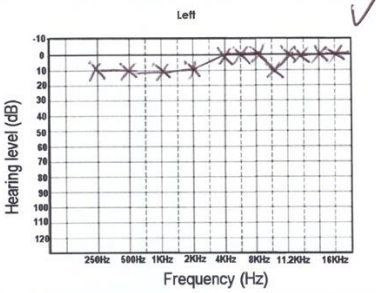
Assessed at: [redacted]
Referred from: _____
DR TB Reg No.: _____
Seen within 2 weeks of start date: (Yes) / No

☐	Hearing loss noted	☐	Family history of hearing loss	☑	MDR TB
☐	Ear infection history	☑	Noise exposure	☑	Kanamycin (Started) 4/12/15 (Stopped) _____
☐	Tinnitus	☐	HIV	☐	Amikacin (started) _____ (Stopped) _____
☐	Pain	☐	Other medication	☐	Capreomycin (started) _____ (Stopped) _____

Other:

Pure Tone Audiogram Screener: [redacted] Date: 14/12/15





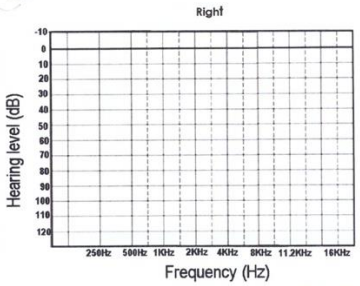
Otoscopy		
	L	NAD
	R	NAD

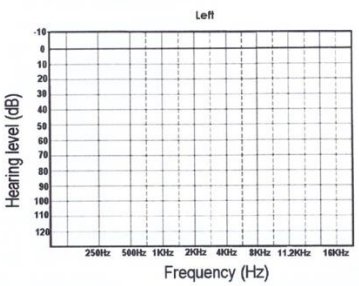
Tymps		Right	Left
	Type		
	Vol		DNE
	dPa		
	Compl		

OAE	Right	Left
Reliability	Good	Poor
TCB	11/1/16	

Findings				
	☐ Yes	☐ No	Ear Canal obstructed with _____
	☐ Yes	☐ No	Abnormal eardrum (describe) _____
	☐ Yes	☐ No	Abnormal audiogram
	☐ Yes	☐ No	Significant change in hearing levels from baseline/audiogram tested on _____(Date)
	☐ Yes	☐ No	Patient referred to Doctor & Audiologist urgently
Comments / management (Audiologist only)	(N) hearing bl Ototoxicity explained.		Signature: [redacted]

e Tone Audiogram Screener: _____ Date: _____





Otoscopy		
	L	
	R	

		Right	Left
	Type		
	Vol		
	dPa		
	Compl		

OAE	Right	Left
Reliability	Good	Poor
TCB		

Findings			
	☐ Yes	☐ No	Ear Canal obstructed with _____
	☐ Yes	☐ No	Abnormal eardrum (describe) _____
	☐ Yes	☐ No	Abnormal audiogram
	☐ Yes	☐ No	Significant change in hearing levels from baseline/audiogram tested on _____(Date)
	☐ Yes	☐ No	Patient referred to Doctor & Audiologist urgently
Comments / management (Audiologist only)			Signature: _____

Key	Response	No-Response
Right:	O	
Left:	X	

APPENDIX G

Publication Certificate (Study I)

International Journal of
Environmental Research and Public Health

Indexed in: PubMed | CITESCORE 3.4 SCOPUS | IMPACT FACTOR 3.390

an Open Access Journal by MDPI

CERTIFICATE OF PUBLICATION

Certificate of publication for the article titled:

Community-Based Ototoxicity Monitoring for Drug-Resistant Tuberculosis in South Africa: An Evaluation Study

Authored by:

Lucia Jane Stevenson; Leigh Biagio-de Jager; Marien Alet Graham; De Wet Swanepoel

Published in:

Int. J. Environ. Res. Public Health **2021**, Volume 18, Issue 21, 11342

MDPI Academic Open Access Publishing since 1996

Basel, October 2021

APPENDIX H

Proof of Publication Acceptance (Study II)

Date: 6 February 2022

To: Mrs Lucia Jane Stevenson <luciaj.stev@gmail.com>

Cc: Leigh Biagio-de Jager <leigh.biagio@up.ac.za>,
Marien A. Graham <marien.graham@up.ac.za>,
De Wet Swanepoel <dewet.swanepoel@up.ac.za>

From: aosis@sajcd.org.za

Reply to: sajcdeditor@saslha.co.za

Subject: SAJCD External Review Decision 886 - Accepted for publication

Ref. No.: 886
Manuscript title: Longitudinal community-based ototoxicity monitoring and treatment effects for drug-resistant tuberculosis treatment, Western Cape Journal: South African Journal of Communication Disorders ISSN: 0379-8046, E-ISSN: 2225-4765

Dear Authors,

The journal has a double-blinded peer review process and your manuscript was assessed by two expert independent reviewers. Read our peer review process https://aosis.co.za/policies#peer_review.

Thank you for your revised manuscript. We have reached a decision regarding your submission. I am pleased to inform you that your manuscript has now been accepted for publication.

The Editorial Office will contact you by 13 February 2022 to finalise your manuscript

for the Finalisation and Publication Office. If you need any assistance, kindly contact the Editorial Office at submissions@sajcd.org.zawith any questions or concerns.

We remind our authors that our publisher is a member of CrossChecks plagiarism detection initiative and endorses and applies the standards of the Committee on Publication Ethics which promotes integrity in peer-reviewed research publications. This journal also conforms to the accreditation requirements by both the Department of Higher Education and Training of South Africa and Scielo SA. Be assured that upon publication, your manuscript will be indexed in various international research repositories for further dissemination and reach in readership.

****

Please help us to improve your experience as an author by taking a few minutes to tell us about the service that you have received. We appreciate your participation and want to make sure we met your expectations, which will give us the opportunity to better serve the community.

Feedback:
https://forms.office.com/Pages/ResponsePage.aspx?id=mXfgHQ3TR0ix-TiElOAkzi4e5bmbrRhDux1_hEph7SZUQVZUWDNTR0tLQTVQODVUNlJTT001SzhHSC4u

Thank you for submitting your interesting and important work to the South African Journal of Communication Disorders. We value your contribution to the journal and for the active involvement in the development of the discipline. Your manuscript will soon form part of this open access publication and your content will be licensed under the Creative Commons Attribution License. We look forward to your future contributions.

Kind regards,
Dr Anita Edwards
SAJCD Editor-in-chief

APPENDIX I

Proof of Revised Submission Confirmation (Study III)

Date: 27 May 2022

To: Mrs Lucia Jane Stevenson <luciaj.stev@gmail.com>

From: AJA <em@editorialmanager.com>

Reply to: AJA <em@editorialmanager.com>

Subject: Submission Confirmation for AJA-22-00039R1

Dear Mrs Stevenson,

American Journal of Audiology has received your revised submission.

You may check the status of your manuscript by logging onto Editorial Manager at (https://www.editorialmanager.com/aja/).

IMPORTANT NOTE REGARDING COVID-19:
ASHA Journals strives to complete peer review as expeditiously as possible. However, we may experience a slowdown in completing peer reviews over the next few weeks as many regular reviewers have already indicated they are unable to volunteer their time or will likely request extensions to enable them to complete their peer reviews. We will inform you if we experience a delay in posting a decision for your revised submission. We appreciate your patience and understanding during this difficult time.

Kind regards,

American Journal of Audiology

NIH-funded authors