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Hearing Function in Adults with Multiple Drug Resistant-TB: A Retrospective Review

A RESEARCH DISSERTATION ON A STUDY PROJECT PRESENTED TO

The Discipline of Speech Pathology and Audiology
School of Human and Community Development
Faculty of Humanities
University of Witwatersrand
Johannesburg

In partial fulfilment of the requirements for the degree M.A. Audiology by Dissertation

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DECLARATION

I, Angela Kavallieratos, hereby declare that this submission is my own original work and that the assistance I have is detailed in the Acknowledgments of this report. To the best of my knowledge and belief, it contains no material which has been accepted for the award of any other degree or diploma at any other university or other institute of higher learning. I am responsible for the study and conclusions reached.

_____ _____

ANGELA KAVALLIERATOS DATE

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ABSTRACT

KwaZulu-Natal has been ranked as having the fourth highest incidence of transmitted Multiple Drug Resistant-Tuberculosis (MDR-TB) in sub-Saharan Africa. Substantial literature exists indicating the permanent damage that MDR-TB medication has on hearing abilities. The purpose of this study was to describe the hearing function of adults on long term MDR-TB treatment from Murchison Hospital MDR-TB unit in the Ugu District in rural KwaZulu-Natal. The primary aim of the study was to review the possible changes in hearing function in a group of adults on long-term treatment for MDR-TB. Secondly, the study aimed to estimate the number of adults who may present with changes following MDR-TB treatment and establish if relationships exist between the audiological findings and factors such as age and gender. The design of the study was a retrospective comparative data review of 68 patient records, all of which underwent audiological investigations from the start of MDR-TB treatment over a five-month period. The study made use of descriptive and inferential statistics to analyse the data. Specific inferential statistical analysis included analysis of covariance as well as regression analysis. Results from the study showed changes in hearing function in Distortion Product Otoacoustic Emissions (DPOAEs) and Pure Tone Audiometry (PTA) results at all five audiological sessions and across a range of frequencies. 84% of the total sample presented with overall refer readings for DPOAEs and 98.53% of the group of adults presented with criteria indicative of ototoxic hearing loss, specifically a bilateral mild-profound sloping SNHL on clinical PTA results. In the total sample of patient records reviewed in this study, all 68 records showed a change in hearing function, be that changes in DPOAE function and/or changes in PTA thresholds, following long-term treatment for MDR-TB. Variations in the effects of gender and ear difference were minimal and non-significant in all results. Similar presentation, to ototoxic hearing loss, of other degenerative conditions exists; however these conditions were accounted for as exclusion criteria in this study. Therefore the only remaining cause of possible hearing deficit was that of ototoxicity. The study provided valuable data regarding hearing function in a population of adults on long-term MDR-TB treatment in South Africa. Furthermore, the study has highlighted the need for the establishment of standardised

audiological monitoring programmes sensitive to ototoxic hearing loss, within the South African context where the incidence of Tuberculosis (TB) and MDR-TB is reportedly high.

Key Words: Multiple Drug Resistant – Tuberculosis (MDR-TB), ototoxicity, aminoglycosides, Distortion Product Otoacoustic Emissions (DPOAEs), pure tone audiometry (PTA).

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LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ASHA	American Speech-Language-Hearing Association
DPOAEs	Distortion Product Otoacoustic Emissions
HFA	High-frequency Audiometry
HIV	Human Immunodeficiency Virus
MDR-TB	Multiple Drug Resistant Tuberculosis
OAEs	Otoacoustic Emissions
PTA	Pure Tone Audiometry
TB	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organisation

CHAPTER ONE
INTRODUCTION

1.1 Tuberculosis

Literature has demonstrated a relationship between anti-tuberculosis medications and hearing loss (Duggal & Sarkar, 2007; Human, Hagen, de Jong, Harris, Lombard, Christiansen, & Bardien, 2010). It has been documented that patients on anti-tuberculosis drugs present with permanent damage to the cochlea (Khoza-Shangase, Mupawose, & Mlangeni, 2009), causing a bilateral sensorineural hearing loss (Castillo & Roland, 2007). Internationally, these studies have mainly focused on patients receiving first-line drugs administration for tuberculosis (TB); however, South African studies on patients with multiple-drug-resistant tuberculosis (MDR-TB) are sparse, hence the current study.

Tuberculosis is a worldwide pandemic (World Health Organization [WHO], 2009a). The mycobacterium that causes the highly infectious disease known as TB is *Mycobacterium tuberculosis* (*M. tuberculosis*). This bacterium typically attacks the lungs, leading to what is known as pulmonary tuberculosis. This bacterium may however also attack any other part of the body, e.g. the kidneys, spine and brain (Dye, 2009), causing extra-pulmonary tuberculosis. TB is a rapidly contagious disease that is spread through the air when an individual with active TB expels these bacteria into the air through coughing, sneezing, speaking or singing. People in close proximity need only to breathe in the bacteria to possibly become infected (Centers for Disease Control and Prevention, 2010). However, not everyone infected with TB bacteria will become actively sick with the disease, as two TB-related conditions exist: latent TB and TB (Dye, 2009). In latent TB the bacteria remain dormant in the body for as long as the body is able to combat the spread of the disease and shows no signs or symptoms of the disease. Latent TB is not contagious.

However, if the bacteria become active and begin to multiply, the individual runs the risk of developing active TB. Active TB is contagious and people with this condition show signs and symptoms of TB, such as chest pain, night sweats, fever, a bad cough that

lasts three weeks or longer, chills, coughing up of blood and sputum, weight loss, fatigue and loss of appetite (Mayo Foundation for Medical Education and Research, 2011). In individuals with weak and compromised immune systems, such as patients with Human Immunodeficiency Virus (HIV), Acquired Immunodeficiency Syndrome (AIDS), the risk of developing active TB is much higher than in individuals with uncompromised immune systems (Idemyor, 2007). Both types of TB need treatment to prevent further spread of the disease (Dye, 2009). If not treated, each person with active TB can infect on average 10 to 15 people a year (WHO, 2009a) and one in every ten of those will become sick with active TB in his or her lifetime (WHO, 2009a).

Global statistics show that more than two billion people, or one third of the world's total population, are infected with the TB bacterium (WHO, 2009a; Centers for Disease Control and Prevention, 2011a). National statistics from *Statistics South Africa (2009)* stated that South Africa had a total population of 49 320 000. According to the most recent South Africa Profile WHO Report (2009c) on Global Tuberculosis Control, the incidence of TB is 461 000 new cases per year and 948 per 100 000. The prevalence of TB in South Africa is 336 000 cases and 692 per 100 000, whilst the global average is only 206 per 100 000. In 2008 alone there were 138 803 reported cases of TB in South Africa (WHO 2010a).

Along with incidence and prevalence, mortality rates regarding the TB pandemic are also high. The most recent statistics from WHO reported that a total of 1.77 million people died from TB in 2007 (including 456 000 people with HIV), equal to approximately 4800 deaths per day (WHO, 2009a). The vast majority of TB deaths occur in developing countries. It is a disease associated with poverty, with Africa having the highest estimated incidence rates (WHO, 2009c). WHO (2004) asserts that Africans are most likely to die from infectious diseases such as TB or pneumonia, with pneumonia accounting for 23% of deaths in the African population.

The natural progression of the disease process has a myriad of symptoms, complications, secondary conditions or other disorders; there exists a long list of complications which vary according to the site of the TB bacteria. The most common complication in pulmonary tuberculosis is that of respiratory infections and lung tissue damage (Mayo Foundation for Medical Education and Research, 2011). Untreated TB is

characterized by pulmonary infiltrates, formation of granulomas with caseation (the conversion of necrotic tissue to a cheese-like material), fibrosis and cavitation (Dye, 2009). Typically, the disease process is that the TB bacillus settles in the alveolar lung tissue where infection occurs, causing alveolar-capillary dilation and endothelial cell swelling. Alveolitis results and the infection replicate and spread with an influx of polymorphonuclear leukocytes. These organisms then spread through the body's lymphatic system, the circulatory system and then through the entire body (Springhouse, 2005). In the presence of a healthy, uncompromised immune system, the disease will arrest (Idemyor, 2007). However, if the infection reactivates the body's response, it may lead to caseous necrosis. The caseum may localize, undergo fibrosis, or become exposed and form cavities. These cavities consist of walls studded with TB bacilli that constantly multiply and the infected caseous debris may spread through the entire tracheobronchial tree of the lung system (Springhouse, 2005; Knechel, 2009).

1.2 Multiple-Drug-Resistant Tuberculosis

Poor TB management leads to the development of drug-resistant strains of TB (Mayo Foundation for Medical Education and Research, 2011), such as multiple-drug-resistant tuberculosis and Extensively/Extremely Drug Resistant tuberculosis. MDR-TB is resistant to anti-tuberculosis drugs (Zager & McNerney, 2008), a resistance which occurs in *M. tuberculosis* by random, spontaneous mutations of the bacterial chromosome (Knechel, 2009; Villarino, Geiter, & Simone, 1992). It occurs when there is a substantial increase in the proportion of organisms resistant to one or more anti-tuberculosis drugs. In particular, MDR-TB is resistant to at least isoniazid and rifampicin (Aziz et al., 2006; Human et al., 2010). The emergence of drug-resistant TB has been seen as a result of poor TB control, failure and/or delay in identification, poor isolation measures, delayed start of treatment, inadequate and incomplete adherence to treatment, incorrect drug dosages, unavailability of drugs and drugs of poor quality (Aziz et al., 2006; Centers for Disease Control and Prevention, 2010; Duggal & Sarkar, 2007; Easterbrook, 1996). MDR-TB is spread in the same manner as TB; however, risk factors exist for developing this disease (Centers for Disease Control and Prevention, 2010). Drug-resistant forms of the disease exacerbate the TB burden. MDR-TB represents a considerable challenge to TB control programmes, because treatment is more complex, more costly, requires more

time and is usually less successful (Aziz et al., 2006) as seen in the discussion below. As with TB, death by MDR-TB is usually due to secondary complications (Mayo Foundation for Medical Education and Research, 2011). According to the WHO (2010a), the estimated number of MDR-TB deaths globally, excluding those with HIV infection, was 97 000 in 2008. There exist little data providing direct measurement of MDR-TB case fatality, creating uncertainty about mortality estimates. Compounding this issue are the incomplete global data on drug-resistant TB. Even in ideal treatment settings, MDR-TB cure rates are generally below 50%. On average, 30% of cases are fatal within two years, while the remaining patients continue to be infectious and chronically ill, posing a continual threat to communities (Njaramba, 2005).

According to the WHO (2010b), in 2008 an estimated 390 000 to 510 000 cases of MDR-TB occurred worldwide (best estimate is 440 000 cases). The global incidence of this disease is rising (WHO, 2010a; Zignol et al., 2006), as seen in an investigation done in 2000 when estimates were only about 273, 000 of new cases worldwide (Dye, Espinal, Watt, Mbiaga & William, 2002). The estimated global incidence of MDR-TB episodes among new and relapsed TB cases in 2008 is between 310 000 and 430 000 episodes, whereas the estimated global incidence for acquired MDR-TB episodes was between 83 000 and 110 000, with the best estimate at 94 000 episodes (WHO, 2010a). This global increase is caused by the low cure rates due to inappropriate and inefficient treatment (Suchindran, Brouwer, & Van Rie, 2009). A contributing factor to low cure rates is the increased cost of treating the disease, which is up to 100 times higher than the cost of other drug susceptible diseases (WHO, 2010c). Despite the efficient Direct Observation Treatment (DOT), as recommended by the WHO (2010d), the continued spread of MDR-TB lies in poor patient compliance and is therefore a man-made problem (Duggal & Sarkar, 2007; Karim, 2008). These low compliance rates to the treatment regimen can be attributed to the lengthy regimens, development of tolerance, drug adherence and ototoxic outcomes (Duggal & Sarkar, 2007).

African countries have the highest incidence rate of TB in the world, while the latest estimates of the number of MDR-TB cases in Africa is only 69 000 (Amor, Nemser, Singh, Sankin, & Schluger, 2008; WHO, 2010a). The low proportions of cases of MDR-TB are said to be due to the limited data available from most African countries

(WHO, 2010a). Of the 46 countries in Africa, 22 (48%) have provided representative data on drug-resistant TB. The burden of TB drug resistance in Africa remains largely unmeasured; however, this is not necessarily the case in South Africa, where surveillance data on case detection, culture positivity, drug susceptibility testing coverage and accuracy is routinely collected (WHO, 2010d). Therefore, even with the high incidence of MDR-TB in South Africa, there are attempts to keep accurate records that could be used for clinical applications.

Sub-Saharan Africa has been reported to have amongst the highest proportion of MDR-TB in the world (Amor et al., 2008). South Africa is said to have a high rate of MDR-TB, as described by the summarised WHO (2010b) findings reflected in Table 1.

Table 1

Summary of MDR-TB rates in South Africa among various groups

Multiple Drug Resistant TB	Percentages and Numbers
Among new TB cases	1.8 (1.5-2.3)%
Among previously treated TB cases	6.7 (5.5-8.1)%
Among incident new and relapse TB cases	10 000 (7 500-13 000)
Incident acquired MDR-TB case	2 800 (1 900-3 900)
Among incident total TB cases	13 000 (10 000-16 000)

In a study by Zager and McNerney (2008) eight of South Africa's provinces were included in data showing the highest proportion of new MDR-TB cases globally. Their study reported that KwaZulu-Natal had an estimated population of 9 146 296 and was ranked as having the fourth highest incidence of transmitted MDR-TB in Sub-Saharan Africa with an estimated 1 286 cases, an estimated incidence of 14.06 cases per 100,000 and a ranking of 25th in the list of high prevalence MDR-TB countries.

The other form of drug-resistant TB, namely extremely drug-resistant TB, is resistant to second line drugs and the disease becomes virtually untreatable (Kliiman & Altraja, 2009). There is an on-going outbreak of extremely drug-resistant TB and related

high death rates in South Africa (Zager & McNerney, 2008). Only three countries, Rwanda, the United Republic of Tanzania and South Africa have examined the proportion of extremely drug-resistant TB cases among cases of MDR-TB. South Africa has a proportion of 10.5 %, while Rwanda and Tanzania have a proportion of 0% of such cases (WHO, 2010a).

1.3 HIV and Tuberculosis

As previously mentioned, there exists a close link between HIV and TB since the emergence of HIV due to the nature of the immunity destroying HI virus and its contribution to the increased incidence of TB (Gandhi et al., 2006; Goozé & Daley, 2003; Khoza, 2007; Lawn, Bekker, Middelkoop, Myer, & Wood, 2006). HIV/AIDS continues to be a worldwide pandemic (Khoza, 2007; WHO, 2010b). South Africa continues to be home to the world's largest population of people living with HIV (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2009). It is one of the countries most severely affected by the HIV/AIDS epidemic, with the largest number of HIV infections in the world. UNAIDS's latest report (2009) states that in 2009 the total number of persons living with HIV in South Africa was 5.7 million. There is a high prevalence and HIV transmission rate (UNAIDS, 2009). None of the studies or surveys regarding HIV/AIDS can ever provide a precise number of individuals living with, infected with, dying of HIV/AIDS, or died of it. However, the severity of the HIV/AIDS pandemic is certainly evident by the alarming statistics (Khoza, 2007).

Swanepoel (2006) describes the HIV pandemic as having created a unique and overwhelming burden on audiological services in South Africa. Therefore, given the context in which this study has been conducted, one cannot ignore the incidence of HIV/AIDS in South Africa. Moreover, the documented high prevalence of HIV/AIDS in the TB infected population in South Africa (UNAIDS, 2009) means that one cannot ignore the fact that Sub-Saharan Africa remains the most heavily affected area with HIV/AIDS and TB co-infection worldwide (WHO, 2010b). HIV is reported to alter the pathological make-up of TB, therefore complicating the TB infection and creating greater co-infection risks for HIV patients (Idemyor, 2007), resulting from both newly acquired infection and from reactivation of latent infections (Muma, Lyons, Borucki, & Pollard, 1997). HIV-related TB is treatable and curable, but coupled with the poor compliance to

TB treatment, gives rise to more cases of MDR-TB (Goozé & Daley, 2003; Suchindran et al., 2009).

There appears to be divergent data on a "standard" or typical type of hearing dysfunction seen in patients on HIV treatment (Khoza, 2007). Treatment success rates remain low with patients co-infected with HIV and MDR-TB, due to high mortality rates within the HIV-infected population (Muma et al., 1997). Individuals with HIV/AIDS and MDR-TB should be treated in the same manner as those patients who are not HIV-infected, except for slight adjustments to their regimen. They should not be treated with thiacetazone and should be isolated from both TB and MDR-TB infected patients (Gupta, Espinal, & Raviglione, 2008).

1.4 HIV in the Context of this Study

Given the large co-infection rates between TB and HIV (WHO, 2010b) and the large number of the South African population infected with HIV (UNAIDS, 2009), the effects of HIV on hearing cannot be ignored in this study. There appears to be a large discrepancy in data regarding the exact effects HIV has on the auditory system, so much so that no specific type or degree of hearing loss can be attributed to the manifestation of HIV in patients. Types of hearing loss include conductive, sensorineural or central hearing losses and the degree of loss ranges from mild to profound (Khoza, 2007). Therefore, the baseline audiograms and case histories that were reviewed in this study were crucial in eliminating confounding variables such as existing conductive and central hearing losses.

Currently there are no data on the incidence of hearing loss induced by aminoglycoside in South Africa, despite the common and increasing use of such drugs in this country; therefore, a study attempting to provide such data and is considered necessary, given the unique resource that this country's population offers (Human et al., 2010). Conducting a study on a South African population and reviewing the effects of the treatment of MDR-TB on hearing sensitivity will hopefully shed light on the severity and prevalence of hearing loss in such a population and prompt the development of an ototoxic monitoring programme to meet the standards of audiological service in South Africa.

1.5. Gender and Tuberculosis

Male and female TB patients have differing levels of risk for developing and contracting drug resistance based on differences in access to health care services and exposure to other risk factors (WHO, 2009b). The incidence of TB, as well as its mortality rate, has been reported to be significantly higher in males than in females (WHO, 2009b). It appears that the trend with TB is that more men are diagnosed with TB (58%) and pass away from it than women (WHO, 2010e). This is not to say that TB does not affect women; annually, approximately 700 000 women are reported to die from TB and over three million contract the disease globally. Young adults are mostly affected by TB, especially women in their economically and reproductively active years, impacting heavily on family systems (WHO, 2009b). Overall, global data collected by the WHO (2010b) show no overall association between MDR-TB and gender of the patient. In South Africa, although a higher number of male than female cases were reported with the disease (4826 versus 4615 cases, respectively), data from a total of 81 794 TB patients of known gender (95% of all patients) indicate that female TB patients have a 1.2 times higher chance of harbouring MDR-TB strains than male TB patients (WHO, 2010c).

1.6 Diagnosis and Treatment of Tuberculosis and multiple-drug-resistant TB

Diagnosis of TB includes radiographic tests such as chest X-rays, a tuberculin skin test, sputum smears and cultures to identify the *M. tuberculosis* disease (Centers for Disease Control and Prevention, 2011b). Treatment of TB depends on the type of TB with which the patient presents, i.e. pulmonary tuberculosis or extra-pulmonary tuberculosis (WHO, 2010d). First-line anti-TB drugs are administered according to body weight and the combinations of these drugs should conform to the WHO Guidelines for TB Treatment (2010d) and are based on the *WHO Model List of Essential Medicines* (2010f). The first-line TB drugs are a class of anti-bacterial substances known as anti-tubercular drugs and include isoniazid, rifampicin, pyrazinamide, Ethambutol and streptomycin. Isoniazid is a bactericidal drug against *M. tuberculosis*, but its method and pathway of action is unclear. It more than likely accumulates intra-cellularly because in the bacterium it is converted to a membrane permeable acid called isonicotinic. Rifampicin is a type of gyrase inhibitor; specifically inhibiting the resealing of opened

DNA strands and thereby acts as a bactericide against *M. tuberculosis* by inhibiting the bacterial enzyme that catalyses DNA template-directed RNA transcription. Ethambutol has anti-tubercular action and pyrazinamide exerts a bactericidal action; however, both mechanisms of action are unknown (Lüllmann, Mohr, Ziegler, & Bieger, 2000). Streptomycin falls under the umbrella term "aminoglycosides". It was introduced in the 1940's as the first successful drug to combat TB (Begg & Barclay, 1995; Konrad-Martin, Wilmington, Gordon, Reavis, & Fausti, 2005). It is administered intravenously and is ototoxic but has minor nephrotoxicity in comparison to its ototoxicity (Lüllmann et al., 2000). The audiological side effects of streptomycin include hair cell loss in the basal region of the cochlea, high-frequency hearing loss, tinnitus and vestibular symptoms (Campbell, 2007). Similar hearing loss was observed in a study conducted by De Lima, Lessa, Aguiar-Santos and Medeiros (2006) where 85% of participants on streptomycin for a minimum period of 15 days and a maximum period of eight months presented with a bilateral sensorineural high frequency hearing loss. The degree of hearing loss was not indicated in this study.

After the introduction of streptomycin in the 1940s, other semi-synthetic aminoglycosides soon followed, among them kanamycin (in 1957), gentamycin, neomycin and amikacin (in 1972) (Begg & Barclay, 1995; Konrad-Martin et al., 2005; Schacht, 1998). Well documented adverse effects of anti-TB drugs have been reported (Duggal & Sarkar, 2007) and undoubtedly the most significant limitation of the therapeutic use of aminoglycosides is their toxic and adverse effects on the auditory and nephritic systems (Konrad-Martin et al., 2005; Schacht, 1998). Nephrotoxicity, the destruction of kidney cells by toxic drugs is usually reversible (http://www.medicaldictionary.thefreedictionary.com/nephrotoxicity).

Ototoxicity was first discovered in 1945 when the first clinical trial with streptomycin was done (Begg & Barclay, 1995). Ototoxicity is the damage to the hair cells of the inner ear and vestibular end organs due to toxic drugs (Stach, 2003). The ototoxicity is permanent, because damage to the sensory hair cells and stria vascularis in the cochlea occurs (Bardien et al., 2009), often leaving the patient with a bilateral sensorineural hearing loss (Castillo & Roland, 2007). Typically, hearing within normal limits in adults is between 0 and 25 dBHL and between 0 and 15 dBHL in children

(Roeser & Clark, 2007). People receiving medication with ototoxic side effects may present with hearing that falls outside of these normal levels. The type of medication used to combat the MDR-TB is known to be highly ototoxic (Duggal & Sarkar, 2007; Easterbrook, 1996; Steyger & Karasawa, 2008), with kanamycin and amikacin reported to be exclusively cochleotoxic (De Jager & Van Altena, 2002; Duggal & Sarkar, 2007; Mudd, Edmunds, Glatz, Campbell & Rybak, 2010).

Part of TB management includes the need for proper and effective health care systems (WHO, 2009a). Direct observation treatment of TB involves assigning caregivers or health workers to observe the administration of anti-TB drugs. The goal of this method of treatment is to monitor the treatment regimen and reduce the development of resistant organisms (Centers for Disease Control and Prevention, 2011c). Direct observation treatment has a success rate of 74% nationally in South Africa (WHO, 2009c).

TB requires combined drug treatment to prevent the emergence of resistant mycobacteria (Lüllmann, et al., 2000). Resistance occurs when the plasmids in the cytoplasm produce inactivating enzymes, which provide resistance to aminoglycosides' bonding action; therefore impairing conveyance of the drugs microbes (Begg & Barclay, 1995). "Multiple-drug-resistant" implies resistance mostly to isoniazid and rifampicin; therefore these drugs are seldom used to treat MDR-TB. Drug susceptibility tests are then done to prove susceptibility on a culture, and then aminoglycosides are used rather than regular anti-TB drugs (Human et al., 2010; Lüllmann, et al., 2000). MDR-TB treatment encompasses the aminoglycoside drugs such as amikacin, streptomycin, kanamycin and gentamycin (Duggal & Sarkar, 2007) and can include some of the first-line drugs and drugs of other classes of antibiotics (Bardien et al., 2009; Gibbon, 2005). Literature strongly suggests that the initial treatment regimen should consist of at least six drugs: an aminoglycoside, a fluoroquinolone, a thioamide, pyrazinamide and as many residual first-line oral drugs as possible (Duggal & Sarkar, 2007; Gupta et al., 2008). This regimen can be chosen on the basis of a patient's history and previous susceptibility tests results or on the basis of the local community's resistance pattern. Drug administration can begin even while further susceptibility testing is being done. Once susceptibility data is available, the patient should be administered at least four drugs, of

which at least two should be bactericidal and should include an intravenously administered drug (i.e. an aminoglycoside) and a fluoroquinolone. The injectable drug should be administered for as long as possible and for a minimum of six months. Total chemotherapy should last 24 months. Monthly status monitoring should be done using sputum smear and culture testing. Ideally, drug regimen modification should be implemented when a patient does not respond to treatment based on drug-resistant pattern detected by continued susceptibility testing. Once patients complete treatment, they should be monitored for at least one year for early detection of relapses. This process of combining first-line and second-line drugs is said to produce a higher treatment success rate (Gupta et al., 2008). Literature states that patients on a four-drug regimen may show a faster negative result sputum culture and have a better chance of cure with no relapse, even if the full course is not completed, than a patient treated for the same length of time on a three-drug regimen. Villarino et al. (1992) suggest at least 18 months of drug therapy when a patient is diagnosed with MDR-TB and preferably continue for 24 months after conversion to negative in a patient's sputum culture. As with typical emergence of MDR-TB, many patients discontinue their treatment and consequently do not recover. They are then forced to resume a prolonged, more toxic drug regimen which may increase their chances of ototoxicity (De Lima et al., 2006). Some drug regimens range from 14 days (De Jager & Van Altena, 2002) up to several years (Duggal & Sarkar, 2007).

There exits great variability in the dosage strategies of aminoglycosides, which lead to individualized dosage strategies being implemented dependent on the clinical situation. Aminoglycosides are concentration-dependent in order for them to work effectively against bacteria; Begg and Barclay (1995) suggested that they are better given less frequently in larger doses. In contrast to the above dosage strategy, Lüllmann et al. (2000) suggested that smaller doses are sufficient because the antibacterial effect of the individual drug substance are additive, thereby lowering the risk of individual adverse effects. Traditionally, dosing has been on a daily or 3 times per week basis due to the slow rate at which mycobacteria replicate; however, it has been unclear which pharmacological parameter is responsible for the development of toxicity (Peloquin et al., 2004). Studies were conducted where toxicity of the cochlear, vestibular and renal

systems were compared using the 2 dosing routines mentioned above. No significant difference was found between the two routines (Begg & Barclay, 1995; Peloquin et al., 2004). As with first-line drugs, dosages of second-line drugs are also dependent on the patient's body weight (Li & Steyger, 2009).

A study conducted by Peloquin et al. (2004) compared the incidences of toxicity associated with the two most common dosing regimens: daily versus three weekly dosages including aminoglycosides, streptomycin, kanamycin and amikacin. Therapy duration ranged from one to 137 weeks. Conventional audiograms were used in order to ascertain the incidence of ototoxicity every two weeks in a sample size of 87 patients diagnosed with *M. tuberculosis*. They defined ototoxicity as a ≥ 20 decibels (dB) sensorineural hearing loss from baselines in either ear at any frequency. According to their findings ototoxicity was not associated with the size or frequency of the aminoglycoside dosage; rather, it was associated with old age, longer treatment duration and total dosage received. Of the sample, 32 out of the 87 patients had ototoxic hearing loss with onset mostly occurring after nine weeks of receiving treatment, but some participants showed audiological changes as earlier as five weeks after starting treatment. Most participants showed evidence of hearing loss in frequencies ≥ 2 000 Hertz (Hz), with five out of 36 participants showing loss in both the low and high frequencies. Streptomycin was found to be the least ototoxic substance. Patients reported on subjective hearing loss and associated symptoms, such as tinnitus, before conventional audiometry detected hearing changes. The study did not include other audiological evaluations that are more specific to ototoxic hearing changes, such as high frequency audiometry (HFA) and otoacoustic emissions (OAEs). Furthermore, they did not exclude participants with a history of hearing loss and didn't exclude participants with age related hearing losses (Peloquin et al., 2004). Therefore, it appears necessary to investigate hearing loss exclusively related to ototoxicity and to control for variables such as age and previous hearing loss which may influence the findings of such an investigation. Peloquin et al. (2004) suggested full dosages for the shortest possible period of time for the treatment of MDR-TB as opposed to lower, more prolonged dosages or maximum-capped doses. Streptomycin was found to be less ototoxic than kanamycin and amikacin. The researchers emphasised the need for clinicians to be vigilant in monitoring, even in

short dosage regimens (Peloquin et al., 2004). The study was not an audiological study, but focused on dosage regimens; however, it did highlight the need for ototoxic-specific monitoring programmes.

1.7 Pharmacology and Pharmacotoxicology

A large body of literature exists on the mechanisms, pathophysiology and pharmacology of aminoglycosides; however, the specific intra-cochlear trafficking of aminoglycosides in ototoxicity is still unknown (Begg & Barclay, 1995; Li & Steyger, 2009; Steyger & Karasawa, 2008; Mudd et al., 2010).

Aminoglycoside antibiotics consist of glycoside-linked amino sugars, i.e. two or more amino sugars connected to an aminocyclitol nucleus. The different aminoglycosides are distinguishable by their different amino sugars (Begg & Barclay, 1995; Lüllmann et al., 2000). They inhibit protein synthesis and alter the membranes of cells. They contain numerous hydroxyl groups and amino groups that can bind protons, making these compounds highly polar, poorly lipid membrane permeable; they show no enteric absorption. Therefore, for the treatment of serious infections, aminoglycosides must be administered intravenously (e.g. streptomycin, amikacin, and kanamycin) (Li & Steyger, 2009; Lüllmann et al., 2000). Aminoglycosides' mechanism of access to the bacterial interior is by the use of two bacterial carrier systems. The first transport system allows uptake across the lipid's inner membrane. The rate of crossing is limited and can be blocked by calcium and magnesium ions, low pH and anaerobic conditions. The second transport phase is energy dependent and the drug accumulation is much faster than in phase one (Lüllmann et al., 2000). Aminoglycosides are dependent on bactericidal concentration activity and intermittent doses are required to combat bacterial resistance (Peloquin et al., 2004) and aminoglycoside ototoxicity is most likely related to multiple factors (Mudd et al., 2010).

The second phase transport system results in protein synthesis inhibition and alteration of the cell membranes (Lüllmann et al., 2000). More specifically, aminoglycosides bind to the 30S ribosome and inhibit bacterial protein synthesis. They act on gram-negative bacilli. They disrupt mitochondrial protein synthesis, interact with transitional metals such as iron and copper and aid in the formation of oxidation compounds that can contribute to the formation of undesirable oxygen and nitrogen free

radicals. These free radicals interact with protein and DNA in the nucleus and consequently cells self-destruct due to the oxidative stress. Hair cell destruction follows as the body's antioxidant defence system fails to neutralize these free radicals (Konrad-Martin et al., 2005). With the formation of nitric oxide the concentration of this oxide will increase and form peroxynitrite radicals that also induce cell damage and death. A cascade effect follows with cell contents leaking out (apoptosis), which is the primary mechanism of cell death (Begg & Barclay, 1995; Mudd et al., 2010).

The particular mechanisms by which aminoglycosides cause ototoxic damage are still largely unknown; however, what is known is that ototoxicity is said to possibly be the result of aminoglycoside and phosphoinositol binding, which leads directly to cell membrane alteration (Begg & Barclay, 1995). This process of cochlear hair cell damage occurs when the aminoglycosides cross the blood-labyrinth barrier and enter the fluids contained in the cochlear organs. The aminoglycosides enter the cochlear hair cells via their apical membranes that are immersed in endolymph fluid in the scala media of the cochlea, implying filtration from the endolymphatic scale media. Once they penetrate this fluid, they permeate non-selective cation channels of the hair cells and generate toxic reactive oxygen agents and interfere with other cellular pathways. Once the aminoglycoside drug has been taken up in the cell, it can induce increased calcium levels and alter intracellular conditions (Li & Steyger, 2009) which lead to hair cell death and permanent hearing loss (Li & Steyger, 2009; Steyger & Karasawa, 2008). Aminoglycosides have also been found present in the perilymphatic fluid (Li & Steyger, 2009). Tubercular cells, such as those found in the kidney and sensory cells of the vestibular system are susceptible to permanent damage (Lüllmann et al., 2000). Vestibular damage is also evident and occurs in the crista ampullaris, resulting in ataxia and nystagmus. These ampulla cells, along with cochlear cells cannot regenerate after being damaged (De Jager & Van Altena, 2002). Therefore, studies investigating the effects of ototoxic hearing loss are needed in order to advocate for ototoxic monitoring whereby permanent cell damage related to ototoxic hearing loss may be supervised and appropriate measures may be taken (Duggal & Sarkar, 2007; Campbell, 2007; Rappaport & Provencal, 2002; Vasquez & Mattucci, 2003). It appears necessary to study the

audiological consequences of ototoxicity in MDR-TB so that ototoxic-specific monitoring programmes can be implemented.

The above ototoxic process results in typically progressive, bilateral, symmetric and sensorineural hearing loss and may include symptoms such as tinnitus and difficulty with hearing in noise (Konrad-Martin et al., 2005; Steyger & Karasawa, 2008). Hearing loss is typically in the high frequencies (Duggal & Sarkar, 2007), although it may not always remain so. Hair cell damage is systematic and in the early stages the damage starts within the lower turns in the cochlea which are responsible for the higher frequencies; it then gradually moves up towards the apex of the cochlea that is responsible for the lower frequencies (De Jager & Van Altena, 2002; Schacht, 1998). The damage tends to progress from outer hair cells to inner hair cells, to supporting cells to central neural structures; this pattern of progression explains the high frequency hearing loss first seen with ototoxic treatments (Duggal & Sarkar, 2007). In addition to the above, research supports the notion that sufficiently high doses of and continued exposure to such ototoxic drugs lead to damage of progressively lower frequencies (Duggal & Sarkar, 2007; Li & Steyger, 2009). Furthermore, because cochlear sensory hair cells take a long time to clear aminoglycosides (as opposed to other organ cells that clear aminoglycosides at a normal rate), they retain the drugs, which results in the progressive hearing loss associated with ototoxic damage (Li & Steyger, 2009; Mudd et al., 2010).

Despite the typical type of hearing loss associated with ototoxic drug regimens, inter-patient variations do exist and ototoxicity can be unpredictable (Begg & Barclay, 1995; Mudd et al., 2010). Variations in degree and range of hearing loss, susceptibility to ototoxic hearing loss and onset of hearing loss are individualistic, but contributory factors include dosage, genes, physiology and biochemistry. Some studies have also suggested that the severity of the hearing loss is related to age and/or the degree of previous hearing loss (Konrad-Martin et al., 2005). Other studies evidenced that ototoxicity is more common in adults than in neonates and children (Mudd et al., 2010). Risk factors for ototoxicity include larger doses, higher blood levels, longer duration of treatment, advanced age, genetic factors, compromised renal systems, pre-existing hearing

difficulties, history of ototoxic related hearing loss and toxic medications (Konrad-Martin et al., 2005).

1.8 Side Effects of Hearing Loss

In light of the negative side effects on the auditory system highlighted earlier, there are also the side effects of post-lingual hearing loss. The side effects of post-lingual hearing loss have been reported to include psychosocial effects such as depression, irritability, fatigue, paranoia, withdrawal and isolation. In addition to these effects, if the hearing loss occurs in adulthood, these adults need to cope with social changes in their work, social and family lives (Ross & Deverell, 2004). Hearing impairment is not generally considered to be a life-threatening condition but it does impact severely on quality of life (Khoza-Shangase et al., 2009). Psychosocial, cognitive-linguistic, vocational and interpersonal aspects of a patient's life are detrimentally affected (Swanepoel, 2006). High death rates associated with MDR-TB (Amor et al., 2008; WHO, 2010b) labelled MDR-TB as life threatening and therefore treatment warrants the use of ototoxic medication. Medical professionals have to make the judgment call that the risk of toxicity from the MDR-TB regimen is outweighed by the possible life-saving benefit of the regimen (WHO, 2010a). Although preserving life is paramount, preserving the quality of life for the patient should also be a treatment goal (Fausti, Wilmington, Helt, P.V., Helt, W.J & Konrad-Martin, 2005). According to the *WHO Guidelines for the Treatment of TB* (2010d), patients should be monitored for the known adverse side effects of drug-regimens and major adverse reactions in patients with MDR-TB, such as hearing loss, which should be promptly managed in hospital.

Hearing loss can develop soon after commencement of drug therapy and will continue in a progressive manner after the ototoxic treatment has been discontinued. Continued audiological management is therefore necessary to confirm stable hearing thresholds and to evaluate rehabilitation measures. Literature affirms that these changes and effects of the aminoglycoside drugs can be seen after five days following the commencement of aminoglycoside therapy (De Jager & Van Altena, 2002) and that it may continue for up to four weeks after drug administration has been terminated (Li & Steyger, 2009). The time of onset of hearing loss is unpredictable. It may be evident after a single dose of treatment, or several weeks after treatment has ended. Regardless

of onset, the hearing loss is permanent and has severe communication and social consequences. Monitoring and management programmes therefore need to be established in order to minimize the adverse effects of these life-saving treatments. Due to the latency effect that aminoglycosides have on hearing function, monitoring should ideally continue for at least six months after the cessation of treatment (Mudd et al., 2010). A study on the treatment of MDR-TB by Gupta et al. (2008) suggested that specific management strategies should be implemented as soon as adverse reactions to drug administration such as ototoxicity, nephrotoxicity and other medical conditions occur. Gupta et al. (2008) went on to say that adverse reaction management should include the following steps in the order provided: divide dose, use ancillary drugs, reduce the dosage or replace/exclude drug. Better patient management for individuals with MDR-TB is therefore necessary (Villarino et al., 1992).

Numerous literature sources highlighted the need for any patient who is in poor medical health and is receiving large or prolonged doses of ototoxic medications to be incorporated into an audiological monitoring programme (Konrad-Martin et al., 2005). Furthermore, the use of aminoglycosides is unavoidable, but largely unregulated in developing countries such as those in Africa. The emergence of drug resistant TB has caused an increase in the use of aminoglycosides (Konrad-Martin et al., 2005; Schacht, 1998). Due to this increase an attempt needs to be made to slow down and monitor ototoxic hearing loss (Campbell, 2007). Studies have been conducted on the development of a protective therapeutic mechanism in the form of antioxidants (Schacht, 1998; Steyger & Karasawa, 2008), but this does not always appear feasible or available due to its complex and expensive nature, especially in developing countries (Schacht, 1998). A combination of anti-oxidant agents, iron chelators and aminoglycoside absorption inhibitors are required to prevent ototoxic damage (Li & Steyger, 2009; Mudd et al., 2010).

1.9 Research Rationale

Previous studies that investigated hearing function in TB revealed ototoxic irreversible hearing loss, with permanent damage to auditory and vestibular systems (Khoza-Shangase et al., 2009; Konrad-Martin et al., 2005; Li & Steyger, 2009; Peloquin et al., 2004; Schact, 1998). These studies only investigated the effects of first-line anti-

TB drugs, but not the effects of second-line anti-TB drugs (i.e., anti-multiple-drug-resistant TB drugs). A study by Duggal and Sarkar (2007) investigated the prolonged re-administration of ototoxic drugs on hearing. These authors study stated, "Initial ototoxic drug exposure typically affects cochlear regions coding the high frequencies. Continued exposure (to ototoxic drugs) results in spread of damage to progressively lower frequencies" (Duggal & Sarkar, 2007, p. 1473). This finding has implications for the stage at which a patient may actually report ototoxic symptoms to health care providers, because the symptoms may not affect their speech frequencies for some time (Khoza-Shangase et al., 2009) and therefore they may only realize much later that there has been a change in their hearing abilities. Inclusion of audiological monitoring programmes would be crucial in detecting early changes in auditory functioning (Duggal & Sarkar, 2007; Khoza-Shangase et al., 2009; Konrad-Martin et al., 2005). It is therefore critical that the audiological effects of second-line drugs, such as those used in MDR-TB, be investigated (Khoza-Shangase et al., 2009). This study focuses on hearing function in adults on long-term treatment for MDR-TB.

MDR-TB and TB have been – and continue to be – world wide epidemics (Amor et al., 2008; WHO, 2010b; Zignol et al., 2006) and the effects of TB treatment are known to cause irreversible hearing loss (Bardien et al., 2009; Duggal & Sarkar, 2007; Easterbrook, 1996; Schacht, 1998; Steyger & Karasawa, 2008). However, there appears to be no standardised guideline for monitoring ototoxicity in patients on ototoxic drugs yet (Duggal & Sarkar, 2007; Vasquez & Mattucci, 2003; WHO, 2010d).

The WHO's most recent *Guidelines on the Treatment of TB (2010d)* endorsed a symptom-based approach to the side effects of anti-TB drugs and stated that treatment and management of TB included addressing all the patient's needs. These guidelines acknowledged that a most effective regime for isoniazid resistant TB is unknown and that no evidence based research has been conducted with ethambutol (an anti-TB drug) and ototoxicity. Often the use of ototoxic treatment is unavoidable for preserving human life; however, investigating the long-term effects of such medication and instituting a monitoring programme will provide better care for an improved quality of life for such patients (De Lima et al., 2006). In a study by Bardien et al. (2009) no data were found on the incidence of hearing loss induced by aminoglycoside in South Africa. The study

went on to highlight the need for regular audiological monitoring throughout the treatment of MDR-TB (Bardien et al., 2009).

American Speech-Language-Hearing Association (ASHA) Guidelines on ototoxicity (1994) stated that the responsibility of designing and implementing an auditory monitoring programme for ototoxicity rests with the audiologist. According to ASHA (2004), the scope of practice of an audiologist includes the provision of services that optimize and enhance the ability of an individual to hear and to communicate in his/her everyday environment, while the overall goal of audiological services is to improve the quality of life for all of these individuals. The ototoxic effects of MDR-TB medication emphasise the need for early hearing loss identification, for appropriate management in the form of rehabilitative audiology, hearing amplification, education and counselling (Khoza-Shangase et al., 2009). In the case of this research, the psychological effects are greater, because the patients have a chronic life threatening illness and are facing permanent hearing loss. The need for audiologists to become involved in the intervention and management of patients with MDR-TB derives from the multidisciplinary approach of comprehensive care for complex conditions. There is no conventional structure for a multidisciplinary team in the monitoring and management of MDR-TB and the structure of such a team will be dependent on the specific needs of the community to be served. In South Africa, the audiologist is considered a paramedical care provider (Ross & Deverell, 2004) and may not be one of the health care professionals with whom patients first come into contact with at their first diagnosis with TB.

According to Duggal and Sarkar (2007) early identification of ototoxicity would allow drug regimens to be adjusted in order to curtail and/or prevent permanent hearing loss. Furthermore, appropriate planning for audiological rehabilitation and counselling should be implemented. Despite research attempts to create a milder, less toxic drug concentrate, ototoxicity can occur through even a single dose, highlighting the need for ototoxic monitoring programmes when such drugs are used (Campbell, 2007; Rappaport & Provencal, 2002; Vasquez & Mattucci, 2003). Currently, there is no programme in South Africa to monitor ototoxic effects of HIV and TB medications. In a study conducted by Khoza-Shangase et al. (2009), they highlight the need for the development

and implementation of an ototoxic monitoring programme as part of standard TB patient care. Furthermore, the inclusion of audiologists in the team management of TB has also been highlighted (ASHA, 2010; Campbell, 2007; Martin & Clark, 2003; Ross & Deverell, 2004). Zignol et al. (2006) called for an expansion in appropriate diagnostic and treatment services for patients with MDR-TB in low resource settings such as South Africa.

Some studies investigated the effects of second-line drug treatments and ototoxicity on the hearing status of patients on long-term MDR-TB treatment (Duggal & Sarkar, 2007; Jager & Van Altena, 2002). Few studies, if any, have considered gender differences, age limits (presbyacusis), or included HFA or OAEs as part of the audiological follow-up. HFA and OAEs have been shown to be very sensitive and appropriate in ototoxic monitoring (Khoza, 2007; Khoza-Shangase et al., 2009). Anti-TB drugs are known to be toxic to cochlear hair cells (Bardien et al., 2009; Duggal & Sarkar, 2007) and OAEs measure hair cell function in the cochlea (Campbell, 2007). Ototoxic drugs typically cause high-frequency hearing loss and HFA has been found to be suitable for testing the basal region of the cochlea which is responsible for the high frequencies (Beiter & Talley, 1976; Campbell, 2007; Wolfgang, Schönfeld, Mansmann, Fischer, & Gross, 1998). There exists data showing gender differences with regards to TB and MDR-TB epidemiology that cannot be overlooked in this study (WHO, 2009b; WHO, 2010a). This project will therefore report on gender differences (if any) and on HFA and OAEs in the audiological monitoring of ototoxic drug regimens.

In a retrospective study by De Jager and Van Altena (2002) on the ototoxicity of aminoglycosides in patients on long term second-line TB treatment, they found that hearing is greatly affected by long-term use of aminoglycosides. In their study, long term treatment was defined as a period of 14 days, although the treatment regimen may carry on for longer periods (Bardien et al., 2009). There was no audiological monitoring during the treatment in this study, because the audiological information was limited to a baseline and/or exit audiogram only. Some of the cases had no baseline audiogram to compare hearing function before and after the commencement of treatment. The study by De Jager and Van Altena (2002) did not have a uniform time interval between measures. Similarly, no HFA or OAEs were conducted as part of the audiological follow-up, despite their

sensitivity to ototoxic monitoring (Khoza, 2007; Khoza-Shangase et al., 2009). They did however take into account factors such as age and gender, but not previous, existing or conductive hearing loss.

In a cohort study by Duggal and Sarkar (2007), audiological assessments began at base-line level and follow-up was conducted every two months until completion of drug therapy (mean length of therapy was 20.3 months). All patients with previous or current hearing loss of any type as well as those with a history of previous ototoxic drug regimens were excluded from the study. Pure tone audiometry ranged from 125Hz to 8kHz and included air and bone conduction thresholds. This study included baseline and renal function tests and excluded patients with abnormal renal and/or liver results. The patients' age ranged from 17 to 65 years and they were on a drug regime that included anamycin, kanamycin and capreomycin (similar toxicity to aminoglycosides). Those on two ototoxic drugs were excluded from the study. The study found that a number of patients presented with sensorineural hearing loss on either ototoxic drug.

The current study investigated the hearing function in adults on long term MDR-TB treatment and includes HFA and OAEs, explores gender differences and presbyacusis, and was conducted in South Africa. It was felt that such a study would contribute to the field of MDR-TB in this context.

CHAPTER TWO
METHODOLOGY

2.1 Main Aim of the Study

The main aim of the study was to describe the hearing function in adults on long-term treatment for MDR-TB.

2.2 Sub Aims of the Study

The sub aims of the study were:

1. To review for possible audiological changes in adults receiving MDR-TB treatment from the commencement of MDR-TB treatment over a five month period
2. To estimate the number of adults who may present with changes in hearing following long-term MDR-TB treatment at a district hospital in KwaZulu-Natal.
3. To look for possible relationships between the audiological findings and factors such as age and gender in a group of adults receiving long-term MDR-TB treatment.

2.3 Hypotheses of the Study

The null hypothesis for the study was that there are audiological changes in adults receiving long-term MDR-TB treatment.

The alternate hypothesis stated that there are no audiological changes in adults receiving long-term MDR-TB treatment.

2.4 Research Design

The design of the study was that of a retrospective comparative data review of hospital records from an MDR-TB unit. The research project was based on data that already existed before the research aim was formulated. The investigator was, therefore, dependent on participant classification and criterion-variable measurements performed at a different time to that of the data collection. A disadvantage of utilizing this retrospective research design was that a different person conducted the investigations at a different time, leaving room for biases and inaccuracies, thus raising questions about

reliability and validity of the existing data (McBurney & White, 2007; Schiavetti & Metz, 2002). However, in order to address these concerns about reliability and validity, the researcher made use of the research site's well-documented patient records, equipment calibration records and measurement methods, and the site's audiology department made use of an audiological assessment protocol based on international standards and research (ASHA, 1994; 2004; Campbell, 2007; Fausti et al., 1999). Comparative research was therefore also employed to allow the investigator to control participation selection during the data collection (Schiavetti & Metz, 2002). A record review study was useful in this instance, where it was prospectively and logistically unfeasible to conduct an experiment relating the variables of interest (McBurney & White, 2007) due to the long-term nature of the study and high mortality rates of such patients in interest. A retrospective comparative record review was therefore useful (McBurney & White, 2007) and was deemed appropriate for this study.

2.5 Description of the Sample

The demographic information has been included as part of the sample description rather so that the sample composition is established from the outset and will be referred to later in the results and discussion.

Table 2

The age demographic profile of the sample reviewed in the study (N = 68)

Factor	N	Range	Minimum	Maximum	Mean	Percentage	Std. Deviation
Age	68	31	18.00	49.11	33.40	N/A	8.412
Male	33	31	18.00	49.11	35.64	48.53%	N/A
Female	35	26	18.00	44.11	31.29	51.47%	N/A

As seen in Table 2, 68 patient records were reviewed and included in this study; patient records included both male and female records. The age ranged from 18.00 years to 49.11 years with a mean age of 33.4 years.

2.5.1 Sample Selection Criteria - Sample inclusion criteria:

- All the patient records from the sample had to be adults, between 18.00 years and 49.11 years of age because the study was focused on adults with MDR-TB and its effects. As stated in Section 28 of the Bill of Rights (2009/1996), the legal age of the start of adulthood is age 18 and a child is any person who is under the age of 18 years. Children were excluded from the current study as normative data pertaining to children regarding hearing function differs to that of the normative data pertaining to adult findings on hearing loss (Roeser & Clark, 2007). Studies have highlighted that there is a much higher incidence of middle ear pathologies (an exclusion variable in this study) in the paediatric population and furthermore, audiological test sensitivity and results differ in paediatric and adult populations (Khoza, 2007).
- Only records including a baseline audiogram (including otoscopic examination, screening DPOAEs and HFA) and consistent audiological monitoring over a five-month period from the start of MDR-TB treatment and including an exit audiogram were considered. In general, the adherence to drug treatment for MDR-TB is poor in all populations (WHO, 2010a); given this fact many patients may abort full-term drug regimens. Therefore five months of consistent audiological monitoring was used to gain a large enough sample size.

2.5.2 Sample Selection Criteria - Sample exclusion criteria:

- Patient records that indicated older than 50 years during their time at Murchison Hospital were excluded from the study as an attempt to rule out the additional risk of ototoxicity, which is higher in the elderly (Peloquin et al., 2004) and hearing loss as age related phenomenon (presbyacusis). Presbyacusis can be described as the sensory, neural, vascular, mechanical and synaptic changes that the auditory systems undergo with age. It is hearing loss caused by the physiological process of aging. As these components change, hearing acuity decreases over time but varies amongst individuals (Jordan & Roland, 2000). Literature suggests that the increased risk of ototoxicity is associated with older age (Begg & Barclay, 1995;

Mudd et al., 2010; Peloquin et al., 2004). Therefore the records of persons older than 50 years were excluded from the data for analysis so as not to introduce the confounding variable of presbyacusis.

- Furthermore, records with any history of any hearing loss prior to starting the MDR-TB treatment were excluded from the study by reviewing the case files and past case histories, thereby not including their results in the data analysis so as to control for pre-existing hearing loss which could confound the research findings. Also, records that indicated middle ear pathologies, for example, any other tympanogram besides a Type A tympanogram or if there was a complete blockage of the ear canal due to cerumen, were excluded from the record review because conditions such as middle ear pathologies obstruct the transmission of sound through the outer and/or middle ear systems, resulting in a conductive hearing loss (Martin & Clark, 2003) and influence OAE findings (Castillo & Roland, 2007). Many studies investigating hearing sensitivity in patients having MDR-TB have not found MDR-TB drug regimens to cause typical conductive hearing loss (Duggal & Sarkar, 2007; Peloquin et al., 2004).
- Records that showed inconsistent monthly monitoring, i.e. patients who had regularly missed hearing assessments, were excluded from the sample to ensure consistent, long term data.

2.6 Sampling Procedure

A non-probability convenience sampling technique was used in this study as this technique is useful when descriptive statistical methods are being used (Grove, 2005). Patients at the MDR-TB unit at Murchison Hospital were referred to the audiology department within a week of admission and start of MDR-TB treatment. The sample was limited to the accessibility of patient records which were part of the MDR-TB audiological-monitoring programme and adhered to the inclusion criteria set out for this study. Many patient records did not include at least five monthly audiological assessments because of the poor adherence to MDR-TB treatment (CDC, 2010) and high mortality rates common in MDR-TB patients (WHO, 2008). Random sampling may have been inappropriate and problematic to achieve (Trochim, 2006) given the specific inclusion criteria required for this study. Purposive sampling was used for the sample and

research site, as purposive sampling is utilized when the researcher targets a particular group with information that is specific to the central themes being researched (Kemper, Stringfield & Teddlie, 2003). The research site was purposefully selected, as this site has the appropriate patient records with the information required by the researcher and is representative of the population of interest in the study.

2.7 The sample – Sample Size and Distribution

The sample consisted of 68 past patient files, of both male and female patients that met the strict sample inclusion criteria, which were available and these were reviewed from Murchison Hospital MDR-TB unit in the Ugu District in rural KwaZulu-Natal. The Murchison Hospital Audiology Department started the MDR-TB audiological monitoring programme in April 2008, and it is still running presently. Since the start of the audiological monitoring programme until June 2010, 270 MDR-TB patients had been seen; only patients from this time period were considered as patients after June had not been seen for at least five consecutive sessions. Ethical clearance was granted in September 2010 for the study, so the review date and data collection took place in September 2010. The sample size of 68 patient records may appear small in relation to the total number of MDR-TB patients seen at Murchison Hospital, but this smaller sample size was because of the exclusion of patients who presented with middle ear pathologies, did not attend for four consistent follow-up sessions due to acute illness, those who defaulted treatment and hospital care, or those who passed away. Murchison Hospital provides a district level of care services for a large rural area of KwaZulu-Natal with 260 beds, with only a small portion available for the MDR-TB unit. It also has eight referring satellite clinics. The hospital serves a population of approximately 200 000 people. The hospital has a well-established rehabilitation unit with an audiology department, which keeps monthly audiological records on the MDR-TB patients. KwaZulu-Natal has one of the highest incidences of transmitted MDR-TB in sub-Saharan Africa (Zager & McNerney, 2008) and therefore appeared to be well suited to study hearing levels in persons with MDR-TB. At Murchison Hospital, the dosing for MDR-TB treatment is dependent on patients' body weight, for example, a patient weighing approximately 50kg receives a 2 millilitre dosage (Li & Steyger, 2009). The medical staff administer this medication uniformly, i.e. all patients with MDR-TB receive a 6 month

injectable course of kanamycin. Thereafter a tablet-form medication is administered for two years. The tablets contain ofloxacin, terizidone, ethambutol, pyrazinamide (PZA) and ethionamide. The regimen is dependent on the patient's condition; they will either receive a once a day dosage for five consecutive days or a twice a day dosage for three consecutive days (Begg & Barclay, 1995; Peloquin et al., 2004).

KwaZulu-Natal province has the second-largest population in South Africa, estimated at 10 449 300 million people in 2009, with approximately 105 people per square kilometre. With a total area of 94 361 square kilometres, KwaZulu-Natal is South Africa's third-smallest province, taking up 7.7% of South Africa's land area. It has a 21.2% population share of the total South African population (Statistics South Africa, 2009). Ugu District is considered an area affected by poverty and makes up 8.2% of KwaZulu-Natal's total population, making it a good representation of the South Africa's general rural population (Provincial Decision-Making Enabling, 2005). The above mentioned factors, namely good hospital records, high MDR-TB rates and good representative population of South Africa, highlight the accessibility and importance of conducting the research in this area.

2.9 Materials and Procedures

2.9.1. Data capturing

The researcher was responsible for collecting and reviewing the patient records. Prior to data collection taking place, the researcher had to ensure approval for the study was obtained from the relevant supervisory authority at the hospital and from the University of Witwatersrand Ethical Committee (Medical). A spreadsheet was then used to organize the data from the relevant patient files. The following information was collected and inserted onto the spread sheet (See Appendix A):

- Sample code number
- Age
- Gender
- Admission and discharge dates
- History of hearing loss due to noise exposure, middle ear pathologies or other causes for exclusion purposes

- Audiological results, including otoscopic examination, tympanograms, Distortion Product OAEs and Pure Tone Audiometry (from 250-12 500 Hz)
- Audiological management, including recommendations, hearing aid evaluation and/or fitting of hearing aids

2.10 Testing Protocol

The principle behind testing hearing is "to aid in the process of making decisions regarding the type and extent of a patient's hearing loss" (Martin & Clark, 2003, p. 67). Therefore, several audiological assessments are needed to achieve the above as no single test can provide a clear picture of a patient's hearing status (Sweetow & Sabes, 2008). At the Audiology Department at Murchison Hospital, a standardized audiological protocol was used for the monitoring programme. Listed below is the protocol and equipment used for initial and monthly follow-up assessments:

- Case history (case history form)
- Otoscopic examination (Heine Mini Otoscope and its accessories)
- Acoustic Immittance (GSI 38 Auto Tymp and its accessories)
- DPOAEs (Bio-Logic AuDX device and its accessories)
- Pure Tone audiometry up to 12 500 Hz (Madsen Orbiter 922 clinical audiometer)

The case history is the beginning of any audiological evaluation. It contains pertinent information including medical problems and previous hearing loss (Bess & Humes, 2008; Martin & Clark, 2003). In this part of the audiological evaluation, the researcher was able review the case histories notes and exclude those patients records presenting with any of the exclusion criteria (i.e. history of hearing loss, middle ear pathologies and age range) and include those records deemed appropriate by the inclusion criteria for the study.

The otoscopic examination, conducted using a Heine mini otoscope, allowed for the audiologist to examine the pinna, outer ear canal and tympanic membrane for any foreign bodies or obstructions as well as infection and ear canal collapse (Wall, 1995). Occlusion in the outer ear canal may be the cause of a conductive hearing component, which was an exclusion criterion in this research project. It also allowed the audiologists to choose the correct tympanometer nub size. Selecting the correct nub size allows a

hermetic seal to be made with the external auditory meatus, which leads to more accurate tympanometry readings being recorded (Jordan & Roland, 2000; Gelfand, 2001).

At the time of testing, all audiological testing took place in a sound-attenuating booth, ensuring valid and reliable results (Gordon, Phillips, Helt, Konrad-Martin, & Fausti, 2005). Static acoustic immittance is described as the immittance of the middle ear at some "representative" air pressure (Gelfand, 2001). Acoustic immittance is a sensitive and objective diagnostic tool that is used to identify the presence of fluid in the middle ear, to evaluate Eustachian tube and facial nerve function, to predict audiometric findings, to determine the nature of hearing loss, and to assist in diagnosing the site of auditory lesion (Bess & Humes, 2008). The GSI 38 Auto Tymp, is a tympanometer that was used for this part of the assessment and was particularly useful in determining middle ear status of the patients (Margolis & Hunter, 2000), therefore excluding those patient records that indicated middle ear pathologies from the study. Immittance audiometry includes tympanometry and acoustic reflexes. Standard single frequency tympanometry was employed using an 85.5dB SPL tone test set at 226 Hz, by default of the GSI Auto Tymp. Tympanometry measures the mobility and compliance of the tympanic membrane by pressurizing the air in the external ear canal. This measurement gives invaluable information regarding the condition of the middle-ear structures (Martin & Clarke, 2003; Fire, 1995). Basic acoustic reflex testing involves presenting a sufficiently intense sound to activate the middle-ear muscles reflex and observing any resulting change in immittance, which is usually seen as a decrease in the ear's static admittance (Gelfand, 2001). If the reflex is elevated or absent, a conductive hearing loss exists (Gelfand, 2001), and thus patient records that presented with these results were excluded from the study. The Jerger system (1970) was used to analyse tympanometry results. This system is the most common system of classification of tympanograms, and it is a qualitative method based on the tympanograms height and peaks (Fowler & Shanks, 2002). Only patient records that presented with Type A tympanograms during their monthly audiological follow-ups were considered for this study. A Type A tympanogram indicates normal or a sensorineural hearing loss, where all other types indicate other abnormal findings (Margolis & Hunter, 2000).

OAEs are inaudible, acoustic energy produced by the healthy cochlea and recorded in the external auditory canal by a sensitive microphone (Bhagat, 2009). They reflect pre-neural activity and are a result of outer hair cell (OHC) motility. OAE testing is a measurement of function, (i.e. OHC function) not of hearing. DPOAEs are responses generated when the cochlea is stimulated simultaneously by two closely paced pure tone frequencies. Therefore DPOAEs occur as a result of the interaction between the two primary tones. DPOAEs are good clinical tools because the frequency at which the response occurs is predicted exactly by the frequency of the primary tones (Hall, 2000). DPOAE amplitude is not influenced by gender, race, body temperature and/or position or sedatives/anaesthetics (Schmuziger, Lodwig & Probst, 2006). The Bio-Logic AuDX device was used in the Murchison Hospital to perform DPOAE screening measures. The OAE audiometer is an automatic device that can be used for diagnostic and screening purposes and provides objective evaluation but subjective interpretation of its data and test results (Schmuziger et al., 2006). The AuDX is the first hand-held automated OAE system and it does not require a connection to a computer. The user can customize test protocols and programme the device to perform a desired function i.e. ototoxic hearing-loss screening. The device was programmed as a diagnostic screener, as per the manufacturer's protocol, as it indicates a pass/refer criteria for each frequency tested. Though this may still be a screening protocol and not a full diagnostic measure, the display of pass/refer ensures consistent interpretation of results between different testers and from patient to patient and reduces user error in applying the pass/refer criteria (Hall, 2000). This was particularly useful in the clinical setting at Murchison Hospital, as testing was performed monthly on each patient and by several audiologists. For statistical purposes, an overall pass/refer criterion was set for each DPOAE repeated measure done at each frequency. This was based on a pass for more than 50% of the high frequencies (4000-8000 Hz), as literature supports (Campbell, 2007; Duggal & Sarkar, 2007; Konrad-Martin et al., 2005) that ototoxic hearing loss is characterized by high-frequency hearing loss. Furthermore, literature suggested that DPOAE readings should be present for at least half of the tested frequencies in order for a pass criterion to be granted (Schmuziger et al., 2006).

Some of the AuDX features that made it an appropriate measurement include that one ear probe with multiple nub sizes can be used for performing DPOAE, it is portable, and has compact hardware. The AuDX also has a measurement-based stopping rule. This rule is based on the set of criteria that determines the duration of averaging during OAE testing (Hall, 2000). This is a far superior method than the fixed averaging time method, as it helps to obtain an optimal response measurement in the shortest amount of time possible for a test. The device automatically stops averaging once an online assessment of the OAE and noise floor amplitude is complete and sufficient information is obtained according to the devices' algorithm. The AuDX has an automatic, unique, proprietary method for reducing effects of noise on DPOAE readings, therefore improving testing performance in noisy environments. The method by which the noise floor is measured is: by calculating the noise floor amplitude by averaging the signal amplitude present in four 50 Hz frequency bins surrounding the DP frequency bin. The AuDX also has an in-the-ear-calibration process that automatically adjusts the stimulus to its target level according to the ear canal size. The AuDX also displays if a probe fit was not achieved and will not continue testing unless a fit is achieved, ensuring reliable test results are obtained (Hall, 2000). All these features and methods are designed to optimize testing protocols and result in accurate and reliable DPOAE readings.

OAEs are valuable for ototoxic monitoring as they are site- and frequency-specific for cochlear dysfunction and ototoxic agents exert their effect on OHC's. The recording is electrophysiological and objective and results can be obtained from patients who are medically unable to perform behavioural audiometry (Hall, 2000). OAEs provide valuable and sensitive information on cochlear auditory function and can make an important and unique contribution to early detection of cochlear impairment, as ototoxic drugs affect the outer hair cells of the cochlea (Hall, 2000).

Research suggests that OAEs are sensitive to pre-clinical changes in OHC functioning, therefore detecting high-frequency changes earlier than conventional behavioural audiometry (Konrad-Martin et al., 2005). An advantage of using DPOAEs in this study was because DPOAEs are said to have higher sensitivity to ototoxic damage than Transient Evoked OAEs (Konrad-Martin et al., 2005). The limitation with OAEs is their unreliability to predict pure-tone thresholds and when calibrating the OAE

equipment errors are often made above 3000 Hz. Also, DPOAE levels only correlate with pure-tone thresholds up to about 55dB SPL (Konrad-Martin et al., 2005). The limitation in this study was that OAE testing was not conducted at frequencies over 8000 Hz; but at 250, 750, 1000, 2000, 3000, 4000, 6000 and 8000 Hz i.e. Eight frequencies for both left and right ears at each audiological session. There have been studies to show that DPOAEs can detect changes before conventional audiometry following ototoxic exposure; however some other studies suggest that no DPOAE changes occur in early exposure (Bhagat, 2009), thus raising the importance of using a combination of audiological investigations (Sweetow & Sabes 2008), as was observed in this record review.

Pure tone audiometry had been conducted on each patient at each monthly interval of monitoring. Its clinical use was to determine the degree, type and configuration of hearing loss (Roeser & Clark, 2007). However in this study it was also used to monitor any audiological changes seen over time, especially as the higher frequencies appear to be more susceptible to external factors such as the effects of medication (Harrell, 2002). It is a behavioural assessment that involves the central and peripheral auditory systems (Stach, 2003) and is dependent on the integrity of inner hair cells and the auditory nervous system (Bhagat, 2009). Pure tone thresholds specify the softest audible sound to a patient (i.e. hearing sensitivity) at least 50% of the time (Bess & Humes, 2008) across a range of frequencies. These usually include 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz (Martin & Clarke, 2003). However, as mentioned previously, HFA is a suggested method for monitoring the effects of ototoxic medication (Harrell, 2002).

A Madsen Orbiter 922 clinical audiometer that could conduct high frequency testing was used to obtain behavioural thresholds in the right and left ear of each patient. The modified Hughson-Westlake technique (Carhart & Jerger, 1959) was used, in conjunction with the use of Welch Allan standard TDH-39 circumaural headphones, to determined pure tone air conduction thresholds. The Hughson-Westlake technique was established to decrease the influences of perseveration, adaption and inhibition. The tone is presented in a pulse-type manner; if a response is obtained then the intensity is decreased by 10dB and then increased by 5dB until a response is made again (Roeser,

Buckley & Stickney, 2000). If there is a loss in hearing sensitivity, pure tone air conduction audiometry specifies the degree of loss (Martin & Clarke, 2003). Ototoxic hearing loss is characterized by significant drop in the high frequencies, following considerable doses of ototoxic medication. Inter-octave frequency testing was only performed when a difference of 20dB or more was evident in the thresholds at adjacent octaves (Harrell, 2002) but was not included in the statistical analysis, as the need to conduct inter-octave testing was only performed on a few patients. According to Stach (2003) 'high frequencies' is a non-specific term referring to frequencies above approximately 2000 Hz; a high-frequency audiometer is described as an audiometer with a frequency range extending beyond 8000 Hz. It is further said that HFA has a larger deviation than standard audiometry ranges and this variability is more evident in older age groups. Research conducted by Hallmo, Sundby and Mair (1994) found that over the age of 50 years, few participants were able to detect the higher-frequency tones which suggests that as age increases the sensitivity for higher-frequency tones appears to decrease (Harrell, 2002). In another study by Wiley, Cruickshanks, Nondahl, Tweed, Klein and Klein (1998), adults aged 48-92 years old were investigated using ultra HFA. They found that hearing sensitivity, for ultra-high frequencies increased with advancing age and that males presented with higher thresholds in the frequencies 8000-14 000 Hz than females at those frequencies. For the higher frequencies (14 000-20 000 Hz), no gender differences were observed in their threshold sensitivity. Regardless of the HFA not extending up to 20 000 Hz in this study due to the audiometer limitations, there is research that suggests that low frequency distortion occurs when tones at 16 000 Hz are presented at high levels (Schmuziger, Patscheke & Probst, 2007). More research indicates that intra-participant threshold variability exists for frequencies ranging from 14 000-16 000 Hz, with 16 000 Hz having the highest variability in repeated thresholds (Schmuziger, Probst & Smurzynski, 2004). Therefore had higher frequencies (14 000-20 00 Hz) been included in the audiological assessment of the patients', the reliability of these thresholds would have been questionable.

HFA is said to have good test-re-test reliability and low false-positive rates (Konrad-Martin et al., 2005; Frank, 2001; Gordon et al., 2005), thus making it ideal for reliable and sensitive ototoxic evaluation. Serial monitoring with intra-subject reliability

is said to be the most reliable method for detecting ototoxic hearing loss. Test-retest HF thresholds need to be within ± 10dB range in order for serial ototoxic monitoring to be an effective and reliable tool (Gordon et al., 2005). This study achieves this reliability by containing test-retest thresholds, especially for the HF, that are within ± 10dB range of each other; and test-retest thresholds for frequencies below 8k, that are within ± 5dB range of each other. Furthermore, testing was completed in a sound-attenuated booth, ensuring reliability across the frequencies (Gordon et al., 2005). It is highly recommended that HFA not be done in isolation, due to the lack of hearing threshold shift normative data. Therefore, as recommended by research (Schmuziger et al., 2004; Sweetow & Sabes, 2008), HFA rather be done in conjunction with other audiological investigations and with conventional PTA, as done in this study.

According to ASHA's 1994 guidelines, specific criteria exist for defining ototoxic hearing loss. The change in hearing sensitivity must always relate to baseline measures and must always be confirmed by repeated testing. The specific criteria are defined as (1) a 20dB decrease at any one test frequency, (2) a 10 dB decrease at any two adjacent test frequencies, or (3) a loss of response at three consecutive test frequencies where responses were previously obtained. This last criterion refers specifically to the highest frequencies tested, where earlier responses are measured close to the limits of audiometer and later responses cannot be obtained at the limits of the audiometer. It is highly recommended that change be confirmed with repeat testing. Specific criteria for defining ototoxic hearing loss have been controversial and varied (Simpson, Schwan, & Rintelmann, 1992); therefore the ASHA criteria were used as they have been well-researched and ASHA strives for uniformity in audiological practices (ASHA, 1994; Schmuziger et al., 2004). The criteria are conservative as "the occasional false-positive identification is preferable to methods that may delay detection of the ototoxic process" (ASHA, 1994, pp. 5). Shifts seen at adjacent test frequencies and decreases seen on repeated measures reflect valid changes in threshold sensitivity (ASHA, 1994). A shift in threshold, relative to baseline measures, seen at least twice indicates a true shift. Consequently, the three criteria set by ASHA (1994), were used to indicate ototoxic hearing loss for each participant record, at each baseline and the four follow-up audiometry evaluations.

The hospital where the data was reviewed operates under strict infection-control procedures. During all patient contact for hearing testing and subsequent treatment, the audiologist employed effective infection control procedures, specifically as these patients were already very ill and contagious and harmful organisms could be easily passed from person to person (Martin & Clarke, 2003). All patients who were found to have abnormal conductive hearing impairments were referred for appropriate medical treatment.

The purpose of audiological monitoring is for early identification of ototoxic hearing loss. This allows professionals and patients to make informed decisions about treatment options, drug regimens can be adjusted, patients can be counseled and be prepared for living with a hearing loss and rehabilitation can be planned and implemented (Konrad-Martin et al., 2005). There are published guidelines about the audiological management of patients treated with ototoxic medications (ASHA, 1994; 2004; Campbell, 2007; Fausti et al., 1999) but none are published for the South African population. These previously mentioned guidelines suggest that basic audiological evaluation be conducted with the inclusion of ototoxic-specific measures such as HFA (>8000 Hz) and OAEs. The inclusion of objective measures such as OAEs and/or central auditory monitoring is useful given the medical condition of such patients undergoing this treatment. Furthermore, such measures that can detect changes in the high frequencies, before speech related frequencies are affected, should be incorporated in the audiological monitoring given the nature of the hearing loss caused by ototoxic agents (Konrad-Martin et al., 2005). Bhagat (2009) strongly suggests that the inclusion and refinement of DPOAE test protocols in detecting cochlear damage can enhance hearing conservation of patients exposed to ototoxic medications, as DPOAE's accurately reflect cochlear status, even at early exposure instances. ASHA (1994) has highlighted the need for baseline audiological evaluations before the commencement of treatment and consecutive, periodic monitoring thereafter.

2.11 Data Analysis and Statistical Procedures

The study made use of descriptive and inferential statistics. The total sample consists of 68 patient records, with each patient being seen over five sessions (i.e. 340 result readings) and each ear yielding individual results (i.e. 680 result readings). Descriptive statistics form the basis of quantitative analysis, as they provide simple

summaries about the sample and the measures and allow the researcher to provide basic features of these data (Trochim, 2006). Furthermore, the researcher could develop trends or relationships among variables and allowed possible group differences to be observed (Schiavetti & Metz, 2002). "Research of this type provides an empirical picture of what was observed at one time or of observed changes over a period of time, without the manipulation of independent variables by the researcher" (Schiavetti & Metz, 2002, p. 46). The independent variables in the current study that were reviewed by the researcher were as follows: age, gender, ear performance and audiological testing results over time.

Descriptive statistics were used to describe the demographics of the sample and the possible audiological changes in the total sample including otoscopic examination, tympanograms, DPOAEs and PTA thresholds. For DPOAEs results, the total patient records indicated that DPOAE readings were taken for both ears at all five audiological sessions across eight frequencies; therefore for DPOAEs n=1088. DPOAEs were analysed descriptively as left ear, then right ear, then both ears together for better comparison to the remaining audiological tests used. Whereas, for PTA results, mean thresholds were used to clinically describe the results for left ear, then right ear, then both ears at all five audiological sessions across nine frequencies; therefore n=68. Clinical reference to the classification system of hearing loss (Table 3) by Silman and Silverman (1991) is used in the descriptive analysis of PTA thresholds, to show significant PTA threshold changes in this group of adults on MDR-TB treatment.

Table 3

Classification of hearing loss

Classification of Hearing Loss (Silman & Silverman, 1991)	
Decibels (dB)	**Hearing severity**
26	Normal
26-40	Mild
41-55	Moderate
56-70	Moderate-Severe
71-90	Severe
90	Profound

The use of inferential statistics is a more mathematical method that allows for inferences to be made beyond the immediate data. Research outcomes can be easily generalized (Trochim, 2006) using probability theory and assists the researcher to test a particular hypothesis. It is also concerned with the precision and reliability of the inferences it helps depict (Fife-Shaw, 2002). For this reason descriptive and inferential statistics were used in this study.

Specific inferential statistical analysis methods included a mixed model analysis of covariance (ANCOVA) and logistical regressions were used to test the relationship between audiological findings (PTA and DPOAE) and the independent variables: age, gender, ear and time, respectively. According to Schiavetti and Metz (2002, p. 342), this "allows the researcher to test (the) main effect of each independent variable" and the interaction between the variables. That is, the study would like to investigate whether age, gender, ear and time have a significant impact on DPOAE and PTA results in adults on long-term MDR-TB medication. Hence, age, gender, ear and time are predictors or independent variables, and DPOAE and PTA are predicted or response variables. To examine the relationship between DPOAE and the four factors, a logistic regression was carried out. Logistical regression is a multiple regression where the response variable is

dichotomous (nominal variable with two categories), like DPOAE, with refer and pass. As PTA results are in interval scale, and factors are in continuous scale (age) and nominal scale (gender, ear and time), analysis of covariance (ANCOVA) was carried out to examine the relationship between pure tone results and the four factors. ANCOVA uses categorical and continuous predictor variables; it is a joining of the regression model with the analysis of variance. The objective of an analysis of covariance is to compare the means of the response variable in the different levels of categorical predictor variables, after adjusting for differences due to the covariate (continuous predictor variable) (Armitage, Berry & Matthews, 2009). The null hypothesis stated that there are audiological changes in adults receiving long-term MDR-TB treatment. The alternate hypothesis stated that there are no audiological changes in adults receiving long-term MDR-TB treatment. To statistically test this hypothesis, calculated *p*-values were considered statistically significant at or above an alpha value of 0.05. This meant that there would be a 95% confidence level that results were not due to chance (Howell, 2008) and all the hypotheses were tested at 5% significant level. Thus, null hypotheses are rejected if *p*-values are less than 0.05. Statistical procedures were performed by a statistician.

Logistical regression is used for prediction of occurrence of an event (Armitage, et al., 2009). The logistical regression expresses the relationship between the logarithm of Odds of an event (pass or refer) and the predictors (age, gender, ear and time) in the following model:

$$\text{Log (Odds)} = \beta_0+\beta_1*x_1+\beta_2*x_2+\beta_3*x_3+\beta_4*x_4 \text{ or}$$

$$\text{Odds} = \text{Exponential } (\beta_0+\beta_1*x_1+\beta_2*x_2+\beta_3*x_3+\beta_4*x_4)$$

Odds are defined as the ratios of probability of pass over the probability of refer. β_0 is the intercept, the value of the log (Odds) without any predictor variables; β_1, β_2, β_3 and β_4 are parameter estimates of predictors x_1, x_2, x_3 and x_4 respectively (x_1, x_2, x_3 and x_4 represent age, gender, ear and time respectively).

Table 4

Creation of dummy variables

Categorical Variables Codings					
		Parameter coding			
		(1)	(2)	(3)	(4)
Time	First month	1	0	0	0
	Second month	0	1	0	0
	Third month	0	0	1	0
	Fourth month	0	0	0	1
	Fifth month	0	0	0	0
Ear	Left	1			
	Right	0			
Gender	Female	1			
	Male	0			
Dependent variable coding					
DPOAE	Refer	0			
	Pass	1			

Table 4 indicates the creation of dummy variables or indicator variables. From variable time, four dummy variables (1), (2), (3) and (4) are created; dummy variables are binary variables with the value of 0 or 1. The last category, i.e. the fifth month, is considered as a reference category; that is, the absence of the first four implies the presence of the fifth month. From ear and gender, only one binary variable is created, respectively. A binary variable with a value of 0 will cause that variable's coefficient to disappear and a binary with a value of 1 will cause the coefficient to operate as an additional intercept in a regression model (Sharma & Garavaglia, 1998). Thus each time the dummy variable occurs as the substitute variable, it assumes the value of 1 in the regression (Gelman & Hill, 2007). Dummy variable or indicator variables were assigned to certain qualitative variables such as gender and ear, as seen in table 4 i.e. left ears has been assigned the value of 1 and right ears the value of 0; males has been assigned 0 and females has been assigned the value of 1. These binary variables are assigned the value of 0 or 1 to indicate the absence or presence of a categorical effect (i.e. time) that may be

expected to shift the outcome effects (Draper & Smith, 1998). The dummy variables act as substitute variables for qualitative variables in regression models such as this one, where dependant variables can be influenced by qualitative variables such as ear and gender and quantitative variables such as time. Dummy variables have been used as they are often used in regression models and in time analyses such as this study (Gelman & Hill, 2007).

Table 5

Test of Model Signification

Hosmer and Lemeshow Test			
Step	Chi-square	df	*P*-value
1	25.111	8	.046

The Hosmer–Lemeshow test was also used, as it is a statistical test of the effectiveness and beneficial match for a logistic regression model. The test assesses whether or not the observed event rates match expected event rates in sub-samples of the total sample. The Hosmer–Lemeshow test specifically identifies sub-samples as the deciles of matched risk values; that is, one of the values of the variable divided the distribution of the variable into sub-samples of equal occurrences. Models for which expected and observed event rates in sub-samples are similar and are referred to as well-calibrated (Allan, 2002). Table 5 indicates the results of the signification of the model. That is, it is important to investigate whether the model with the independent variables included, is significantly better than a model with just intercept variables. So, the null hypothesis states:

H0: $\beta_1 = \beta_2 = \beta_3 = \beta_4 = 0$

and the alternative hypothesis states:

H1: at least one of the betas (β) is different from zero.

The *p*-value is < 0.046; hence the conclusion is the rejection of the null hypothesis. That is, the model with independent variables is significant.

Graphical and tabular representation were also used, as graphs and tables are a valuable and organized manner in which to present data and results, as they show the overall contour of the distribution (Schiavetti & Metz, 2002, p. 163.).

2.12 Reliability and Validity

In order to increase the reliability and validity of the study, certain conditions were considered when utilizing the data available for the study. Conditions included well-documented patient records, calibration records (See Appendices G-K) and measurement methods (Schiavetti & Metz, 2002). The researcher reviewed and collected the files personally to ensure constancy in the study.

The files, which were reviewed, were from an established audiology department at Murchison District Hospital. When the data were collected, the audiological team consisted of a qualified senior audiologist and two community service speech therapists and audiologists. The protocols in the department used existing and established protocols and followed the recommended programme in order to effectively monitor patients on MDR-TB treatment monthly. These tests were selected based on their appropriateness and validity in testing for ototoxicity (Khoza-Shangase et al., 2009). HFA (>8000 Hz) has been suggested as a method for monitoring the effects of ototoxic medication, as the higher frequencies appear to be more susceptible to external factors such as the effects of medication (Harrell, 2002). In accordance with Murchison Hospital's regimen protocol, the patients were on uniform drug regimens where either dosing routines were used depending on the patient's condition. This in turn attempts to reduce the variability and improves the reliability of the current study. Previous literature confirmed that the use of two different weekly dosing routines made no difference in the development of ototoxic hearing loss (Begg & Barclay, 1995; Peloquin et al., 2004). Duggal and Sarkar (2007), suggested drug treatment start immediately due to the high infection rate of MDR-TB. Therefore, patients admitted to the MDR-TB unit began drug treatment immediately and were referred to the audiology department within one week of admission or on admission. ASHA (1994) suggests that audiological testing should occur prior to or within 72 hours of drug commencement. Despite not having baseline measures prior to drug

commencement, the inclusion criteria were set as a means of controlling for previous hearing loss of any kind. The audiological investigations used in this study were repeated measures that the patients routinely underwent. Due to this routine testing, false-positives were reduced, thus improving the reliability of the study. Repeated measurements are a useful feature to have when it is unfeasible for the investigator to select a random or large sample (Schiavetti & Metz, 2002). Furthermore, the patient record information was considered to be reliable since the information was obtained from medical and audiological records and not from patient-self reports. Self-reports run the risk of dishonesty, misunderstanding of the research protocols and false-positives by the participants (Turkkan, 2000). External validity relates to the ability of the outcomes of the study to be generalized to a larger population or other studies (Trochim, 2006). Generalization is improved with direct replication, in this case availability of repeated measurements on the same participants. In this study, the sample was representative of the population in the area, therefore strengthening external validity (Trochim, 2006).

2.13 Ethical Considerations

According to the Health Professionals Council of South Africa (HPCSA) Professional Guidelines (2008), in some instances research projects may depend on using samples and it is not always possible to contact patients to seek their consent. Furthermore, many of the MDR-TB patients had passed away given the seriousness of the illness. Permission was granted from the supervisory authorities of Murchison Hospital, namely the medical manager, the rehabilitation supervisor and the senior audiologist of the audiology department, for use of record data and any additional information that may be needed. Data were collected under the following conditions:

1. Ethical approval for the study was obtained from the relevant supervisory authority and from the University of Witwatersrand Ethical Committee (Medical).
2. Hospital approval from the medical manager of Murchison Hospital.
3. Departmental approval from the supervisor of the audiology department at Murchison Hospital.
4. If the research proposal had been altered, prior approval would have been obtained from management.
5. The results of the proposed research will be made accessible to the hospital.

(See Appendix B and C)

According to Chabon and Morris (2005), ethics is a set of moral principles that govern or influence decisions and conduct on a coherent and consistent basis; in this case research conducted by an audiologist. Ethical responsibilities described by professional medical bodies include "continuing education, research, and scientific advancements so that the quality of care available and the efficacy and efficiency with which resources are used in that care can be improved over time" (Chabon & Morris, 2005, p. 6.). Therefore, the following ethical considerations were considered during the proposed research.

- Beneficence and Non-maleficence: acting in the best interest of the patients and doing no harm to them (ASHA, 2010). This principle was upheld as no harm or risk came to pass for patients whose files were reviewed.
- Confidentiality: was maintained as the names of those patient records used were not published while anonymising data further ensures confidentiality (Irwin, Pannbacker, Powell & Vekovious, 2007; Trochim, 2006) by supplying the patient records that were reviewed with numbers as a research coding system.
- Justice: all participant data were treated in an "impartial, fair and just manner" (HPCSA, 2008, p. 3.).
- Professional competence and the Community: the researcher attempted to maintain a high level of professionalism during the collection and revision of the data. Furthermore, the research will be made available to the community at hand, so as to contribute to the improvement of society (HPCSA, 2008, p. 9.) and the researcher has considered the long-term implications of the study (Wisker, 2001)

CHAPTER THREE
RESULTS

3.1 Introduction

The outcomes of the investigation into the hearing function of adults on long-term MDR-TB treatment from a hospital in KwaZulu-Natal are presented in this chapter in accordance with the primary and secondary aims of the study. To achieve the study's aims and test the hypotheses, statistical analyses were carried out using the Statistical Packages for Social Sciences (SPSS) version 16 (2012). The main aim, sub aims and the hypothesis were answered using both descriptive statistics (means and standard deviations) and inferential statistics. Regression analysis and ANCOVA was used to test the relationships between audiological findings on HFPTA and DPOAEs, and age, gender, ear and time. The data will be summarised and presented before the discussion of the results. In this analysis, calculated *p*-values were considered statistically significant at or above an alpha value of 0.05. This meant that there would be a 95% confidence level that results were not due to chance (Howell, 2008).

3.2 Descriptive statistics

3.2.1 Demographics

The study comprised of 68 patient records, of which all records indicated that patients were between the ages of 18.00 and 49.11 years of age. The sample records included 33 males (49%) and 35 females (51%), with a mean age of 33.4 years. All patients were admitted to Murchison Hospital's MDR-TB unit and seen monthly at the hospital's audiology department.

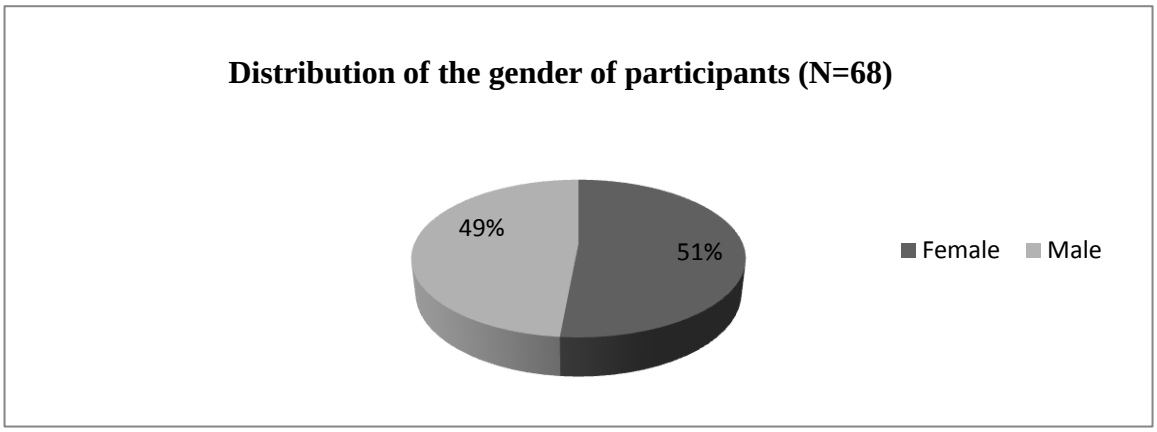


Figure 1

Distribution of the gender of the sample

Figure 1 shows the percentages of males and females used in the study. It can be seen from the above figure that the male: female distribution is fairly balanced i.e. 49% vs. 51%. The researcher used a non-probability convenience sampling technique, and so was limited to the availability of patient files, be that male or female files.

3.2.2 Results of the audiological changes reviewed in the total sample

The primary aim of investigating for possible audiological changes from commencement of MDR-TB treatment over a five-month period is explained in accordance with the audiological test protocol used at Murchison Hospital from initial assessment through to the final assessment. This information was gathered by reviewing all audiological investigations that the patients underwent from initial audiological assessment until the fifth audiological assessment. All information pertinent to this study was obtained from patient files.

i. Otoscopic Examination and Tympanograms

In accordance with the inclusion and exclusion criteria set out for this study, only patient records with obstruction-free ear canals and Type A tympanograms at each audiological investigation, were considered for this study. Other patient files were considered, but found to be unsuitable as the records revealed obstructed ear canals and therefore incomplete tympanograms. According to the records used in this study, all 68

patient records revealed obstruction-free ear canals and Type A tympanograms at all five audiological sessions, including the baseline audiological investigation. The results for otoscopic examination and tympanograms will be examined further in the discussion chapter.

ii. DPOAEs

DPOAEs were conducted on all patients (N=68) at initial audiological assessment and at each follow-up session. Each patient had readings taken for their left and right ear i.e. 136 readings per patient; and at each frequency (250-8000 Hz). Therefore, within the total sample, 1088 DPOAE readings were collected from the records, with 544 readings per ear in the total sample. The results for DPOAEs at each audiological session will be descriptively discussed in this section and related to statistical analysis, beginning with initial DPOAE readings at session one, followed by DPOAE readings at sessions two-four, and lastly the fifth and final DPOAE reading at session five. The researcher was concerned with the number of 'refer' readings, as this indicates a dysfunction with hearing function. The results will be discussed in the subsequent chapter.

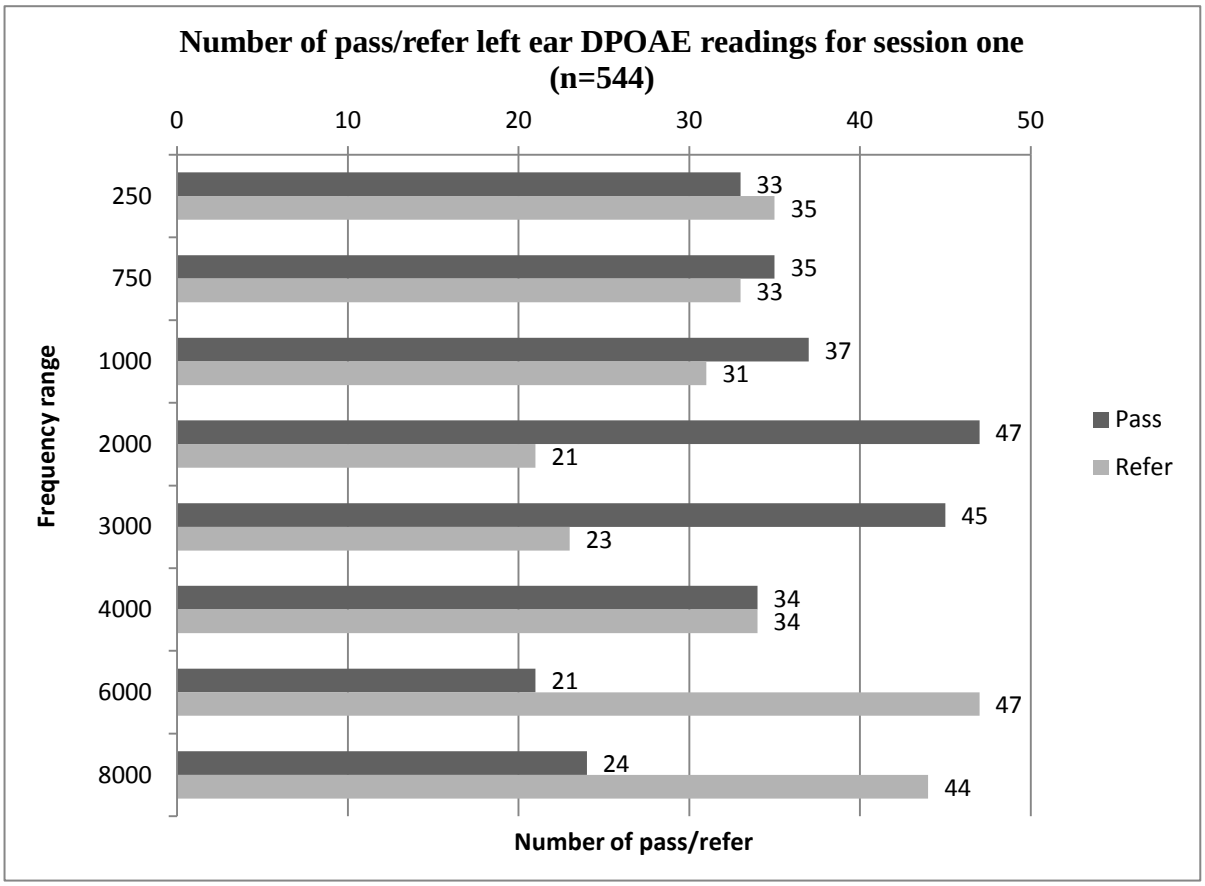


Figure 2

Number of pass/refer left ear DPOAE readings at session one

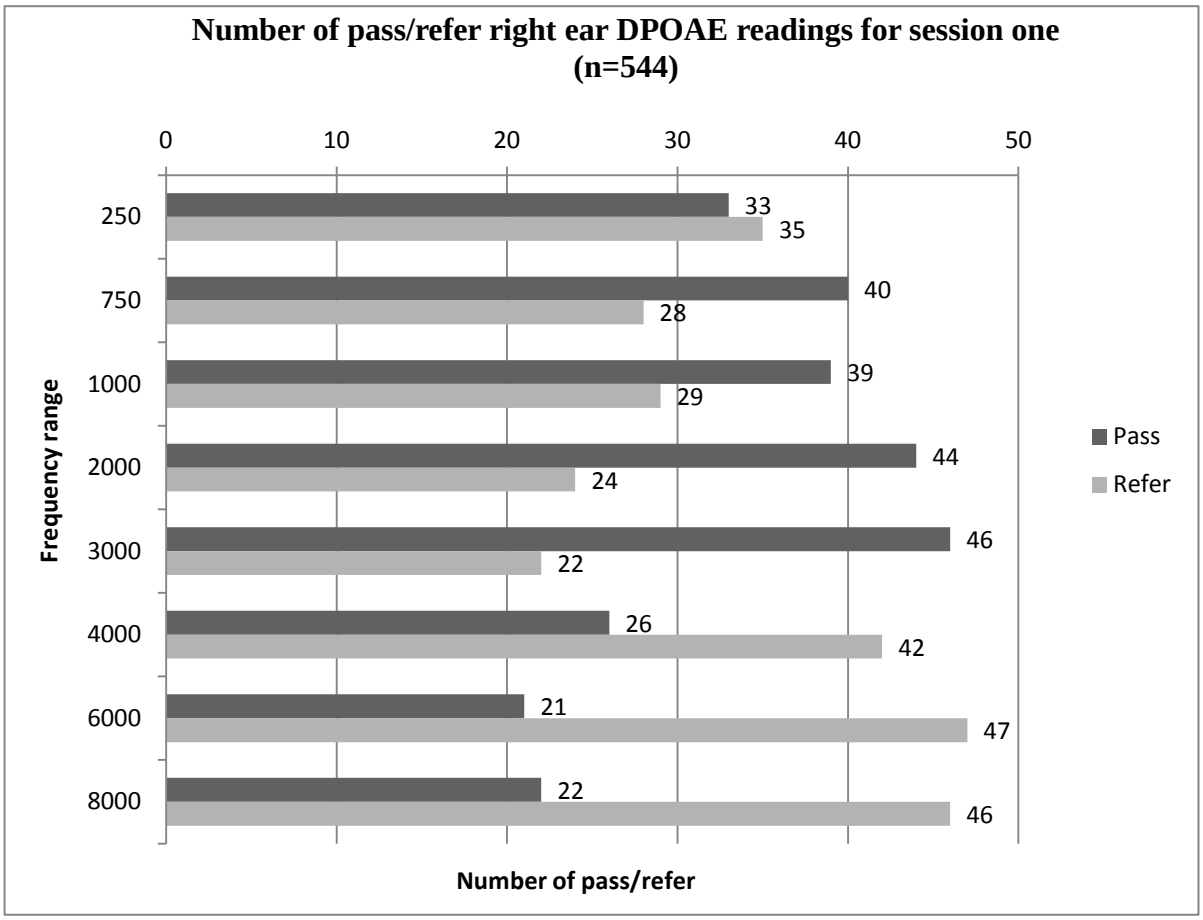


Figure 3

Number of pass/refer right ear DPOAE readings at session one

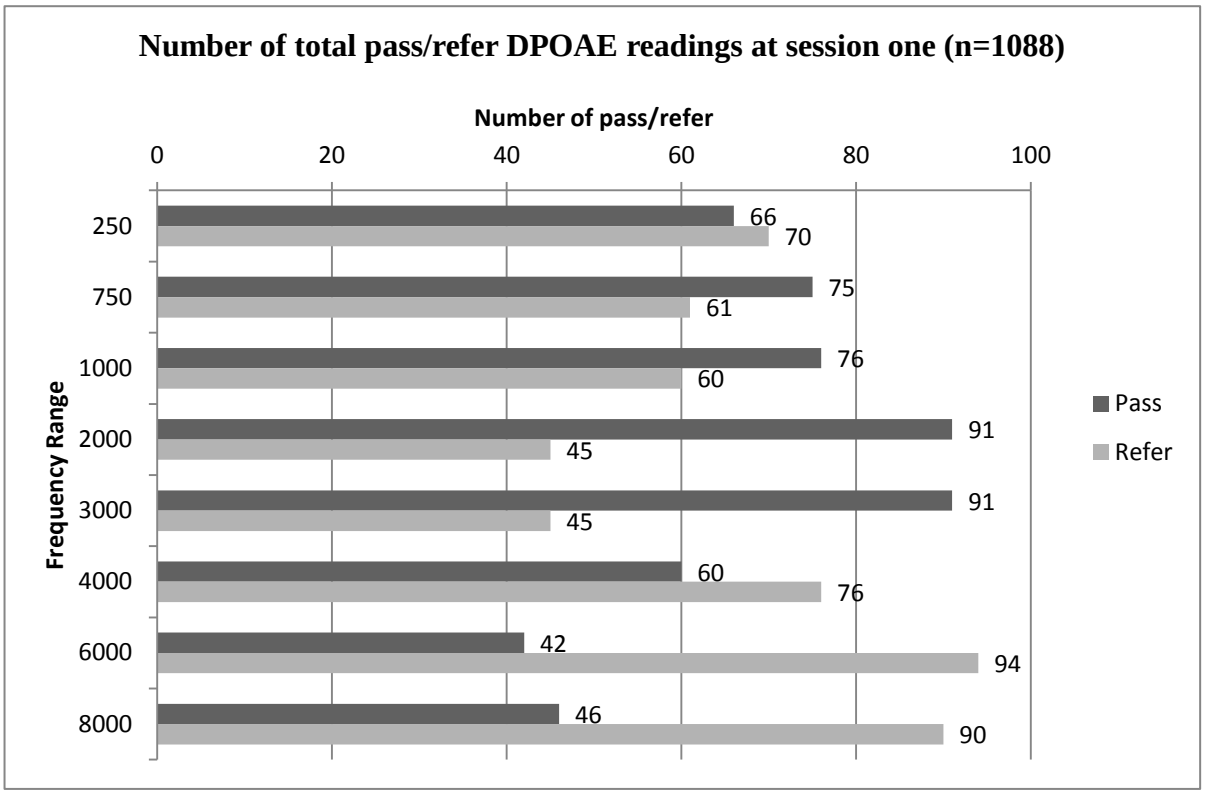


Figure 4

Number of total pass/refer DPOAE readings at session one

Figures 2, 3 and 4 depict the number of pass/refer readings for DPOAEs at the initial audiological investigation. Figure 2 depicts the number of pass/refer readings for all the left ears across the DPOAE frequency ranges that were reviewed from the total sample (n=544); and Figure 3 depicts the number of pass/refer readings for all the right ears across the DPOAE frequency ranges that were reviewed from the total sample (n=544). Whereas, Figure 4 depicts both left and right ear DPOAE readings for the total sample (n=1088). The number of pass/refer for the left ear compared to the right ear are very similar across the DPOAE frequency range. At 4000 Hz; the number of left ear refer readings are 34 (50%) and the number of right ear refer readings are 42 (61.76%) respectively. For the combined ears and total DPOAE readings at the initial session; at the lower and mid frequency range i.e. 250–3000 Hz, the number of pass readings is higher than the refer readings for the total sample reviewed; nevertheless the numbers

indicate that the sample does show a considerable number of refer readings at the lower frequencies. From frequency 4000-8000 Hz, the number of pass readings decreases and there is a much higher number of refer readings at session one. On average, at session one, the mean average of the total number of pass readings was 33.88 compared to the total number of refer readings, at 34.13

Sessions two, three and four, took place whilst the participants were midway in their treatment for MDR-TB whilst at Murchison Hospital.

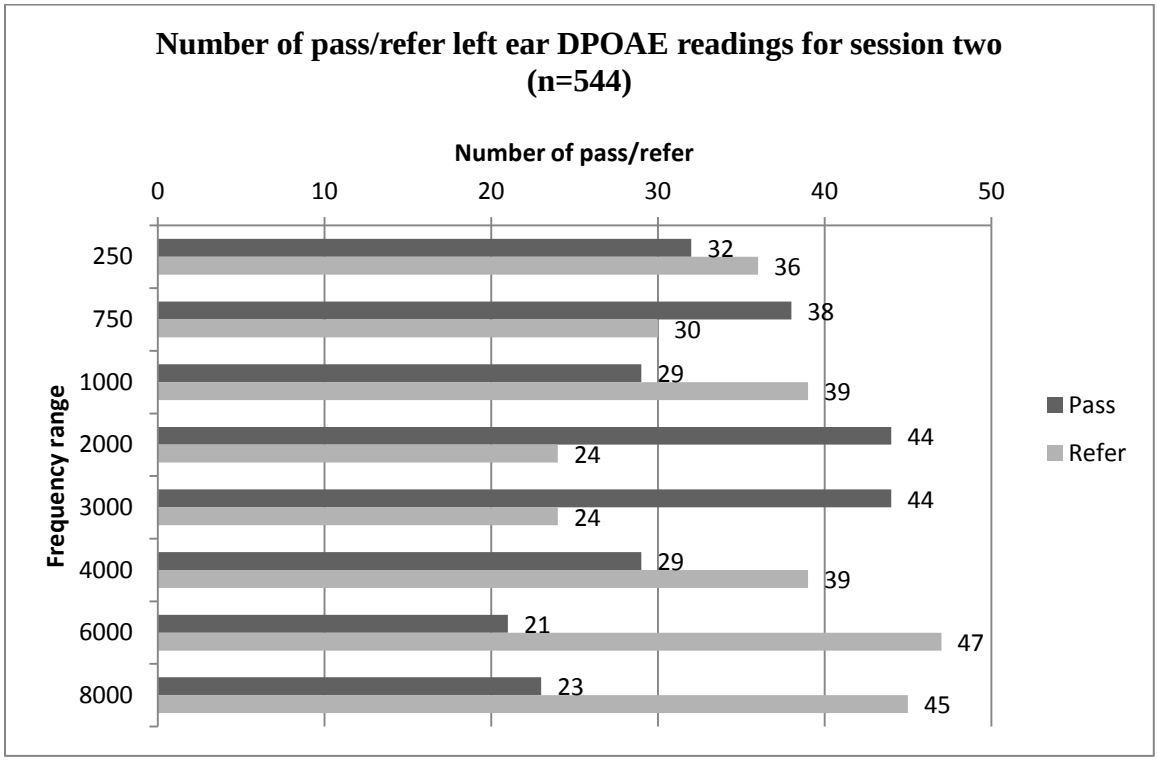


Figure 5

Number of pass/refer left ear DPOAE readings at session two

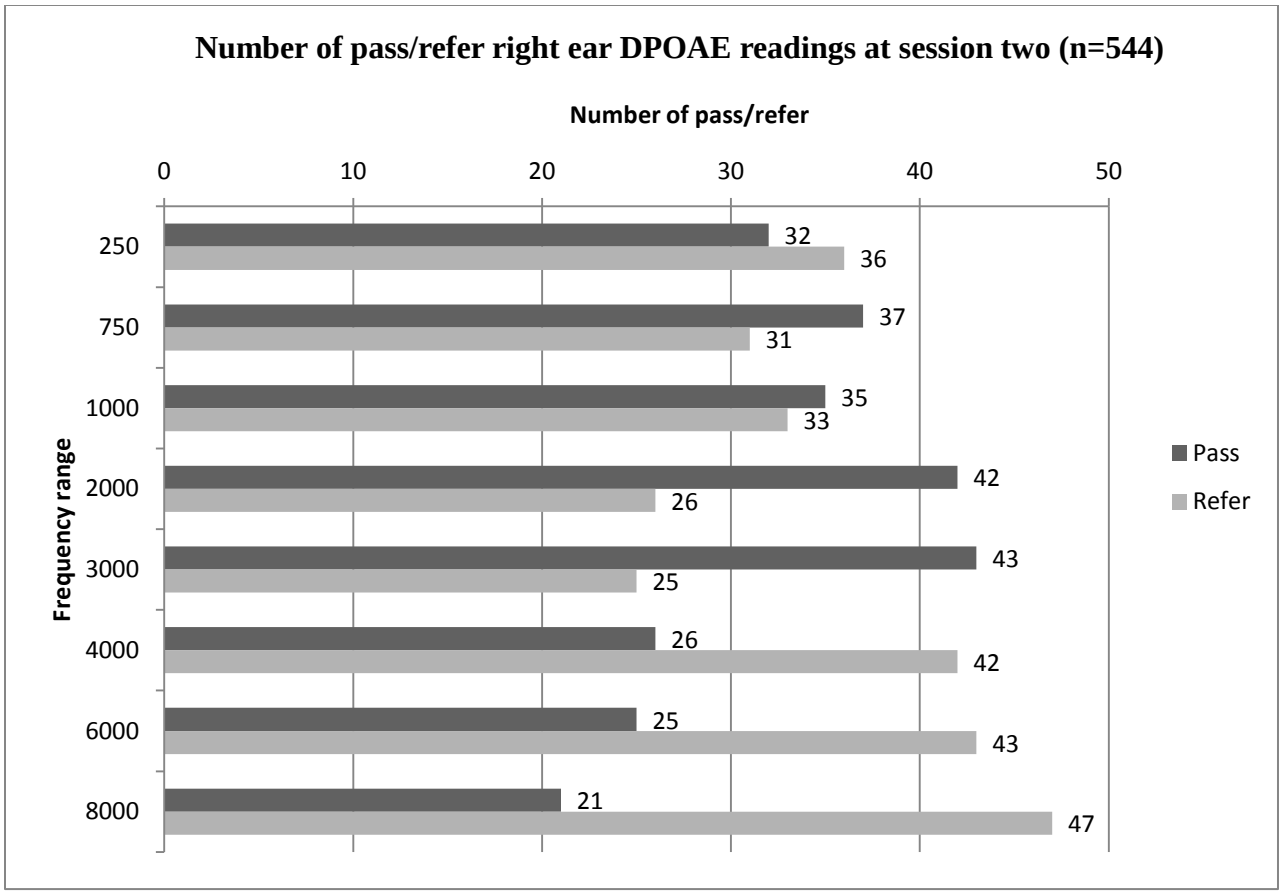


Figure 6

Number of pass/refer right ear DPOAE readings at session two

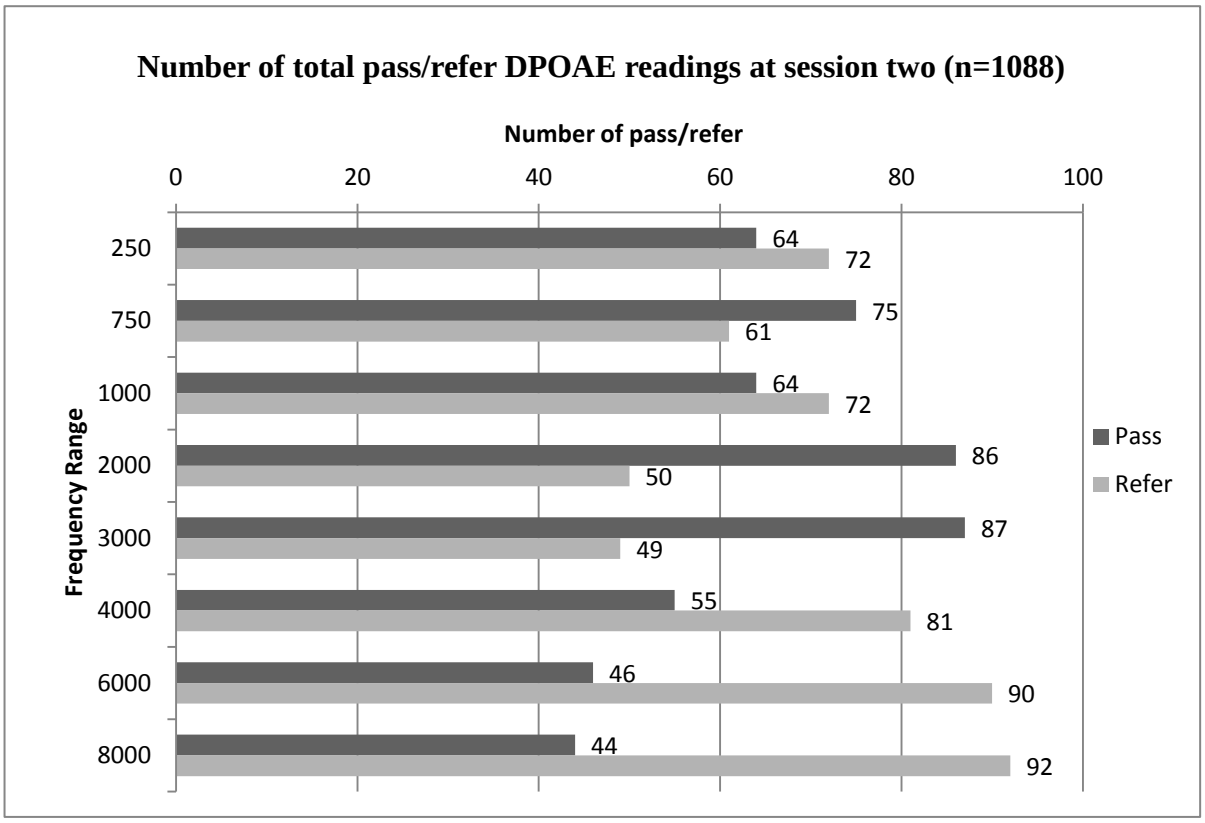


Figure 7

Number of total pass/refer DPOAE readings at session two

At session two, the DPOAE readings for left and right ears are comparably the same across the frequency range, as seen in Figure 5 and 6. On average, at session two, the mean average of the number of pass readings was 32.63 compared to the number of refer readings, at 35.38. Therefore, at session two, the overall number of refer readings exceeds the number of pass readings (Figure 7).

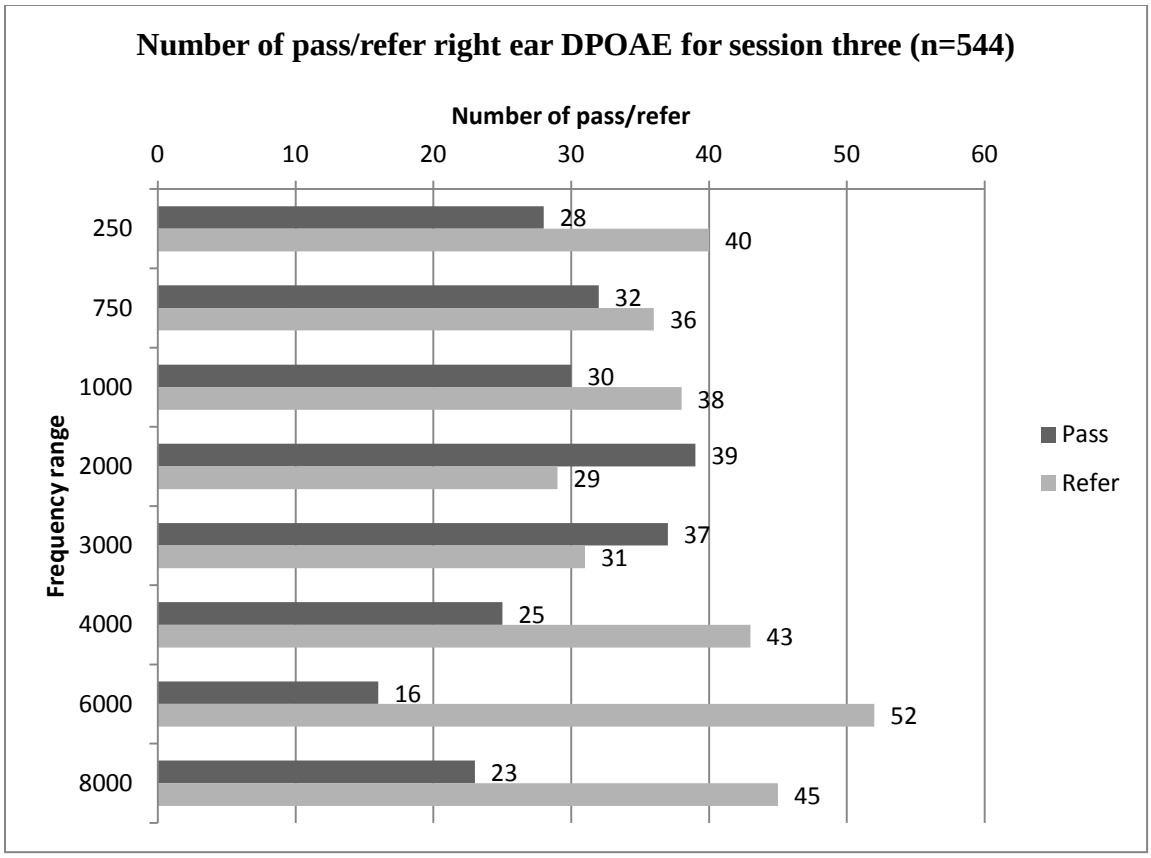


Figure 8

Number of pass/refer left ear DPOAE readings at session three

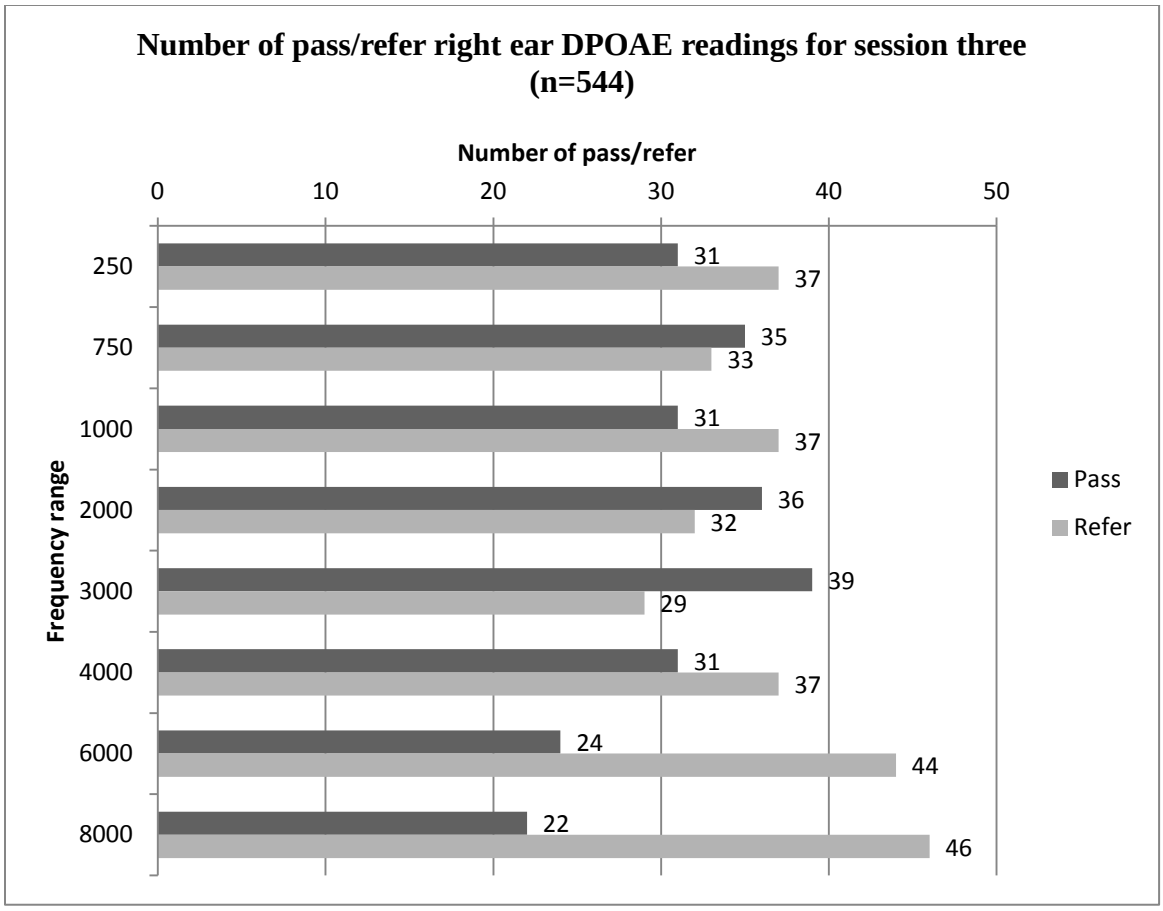


Figure 9

Number of pass/refer right ear DPOAE readings at session three

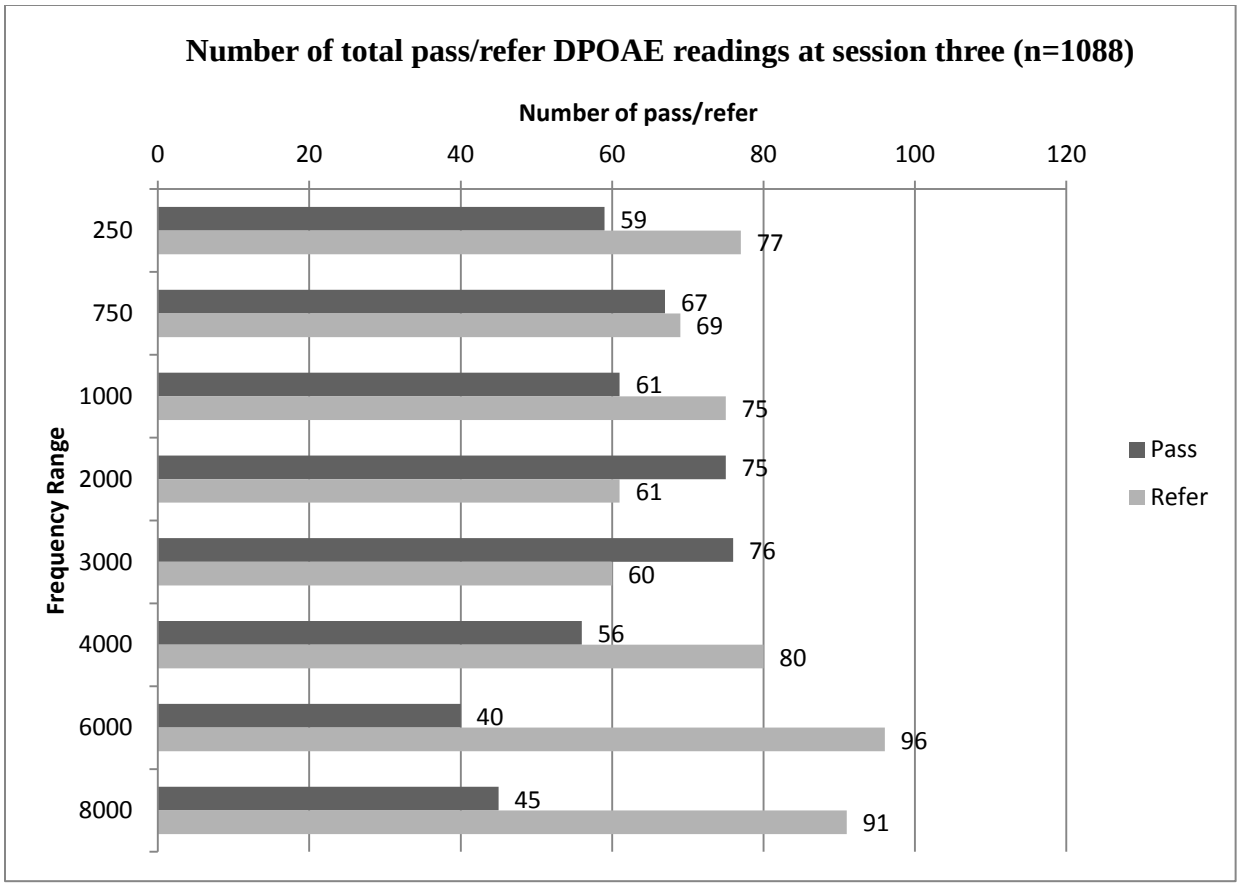


Figure 10

Number of total pass/refer DPOAE readings at session three

Differences between the numbers of pass/refer readings for the left and right ear readings are visible in Figure 8 and 9 respectively at 4000 and 6000 Hz. The number of left ear refer readings for 4000 Hz is 43 (63.24%) and the number of right ear refer readings is 37 (54.41%). The number of left ear refer readings at 6000 Hz is 52 (76.47%) and the number of right ear refer readings is 43 (63.24%). The left ears have a considerably higher number of refer results than the refer results for the right ears. Few differences in refer numbers at the low and mid frequencies are present at session three. In the total number of pass/refer readings (Figure 10), 6000 and 8000 Hz, have higher numbers of refer readings.

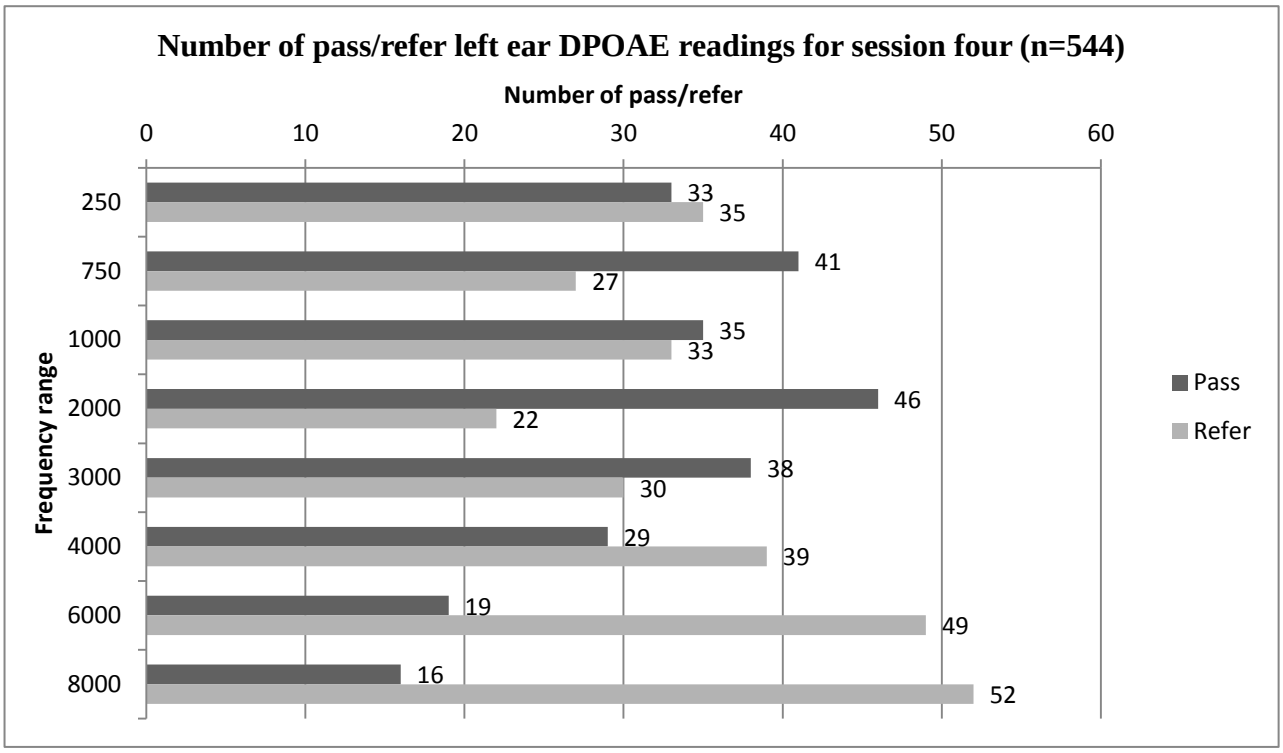


Figure 11

Number of pass/refer left ear DPOAE readings at session four

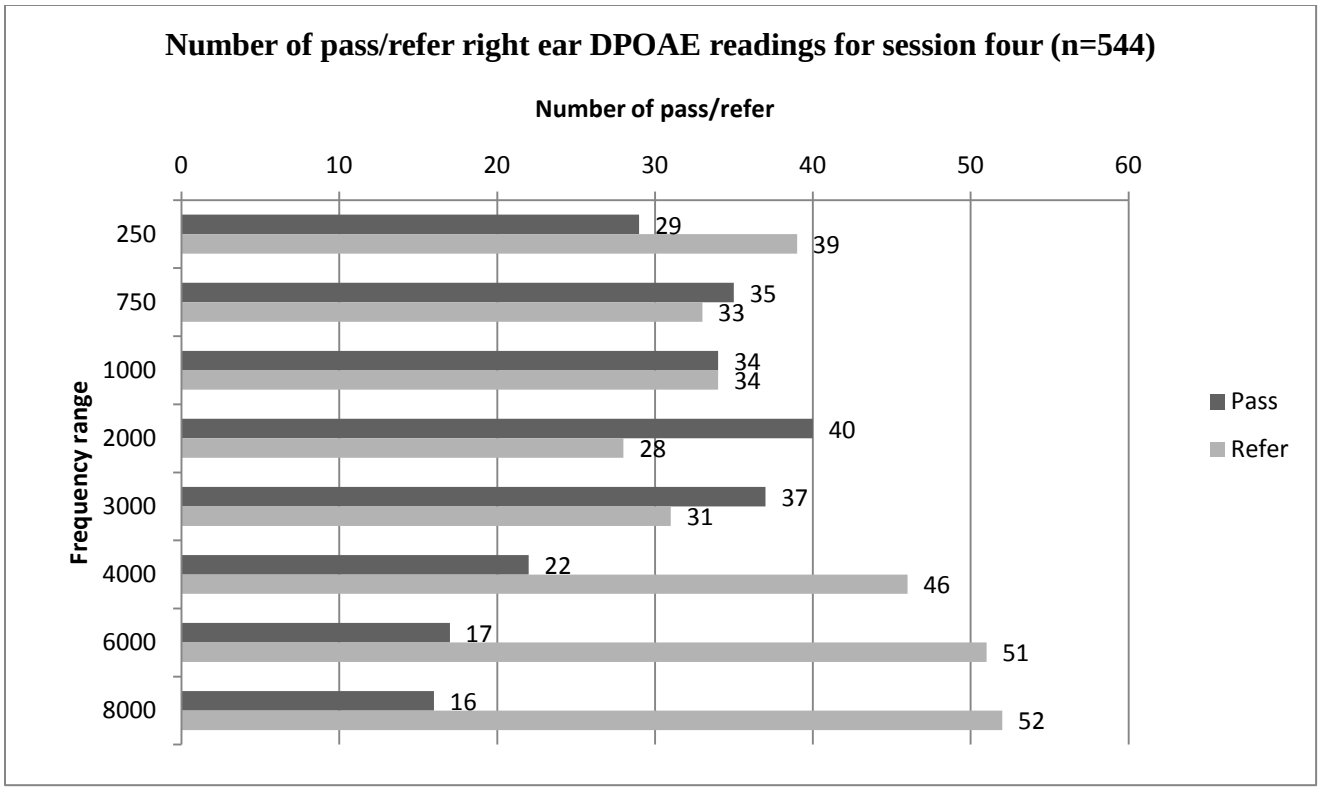


Figure 12

Number of pass/refer right ear DPOAE readings at session four

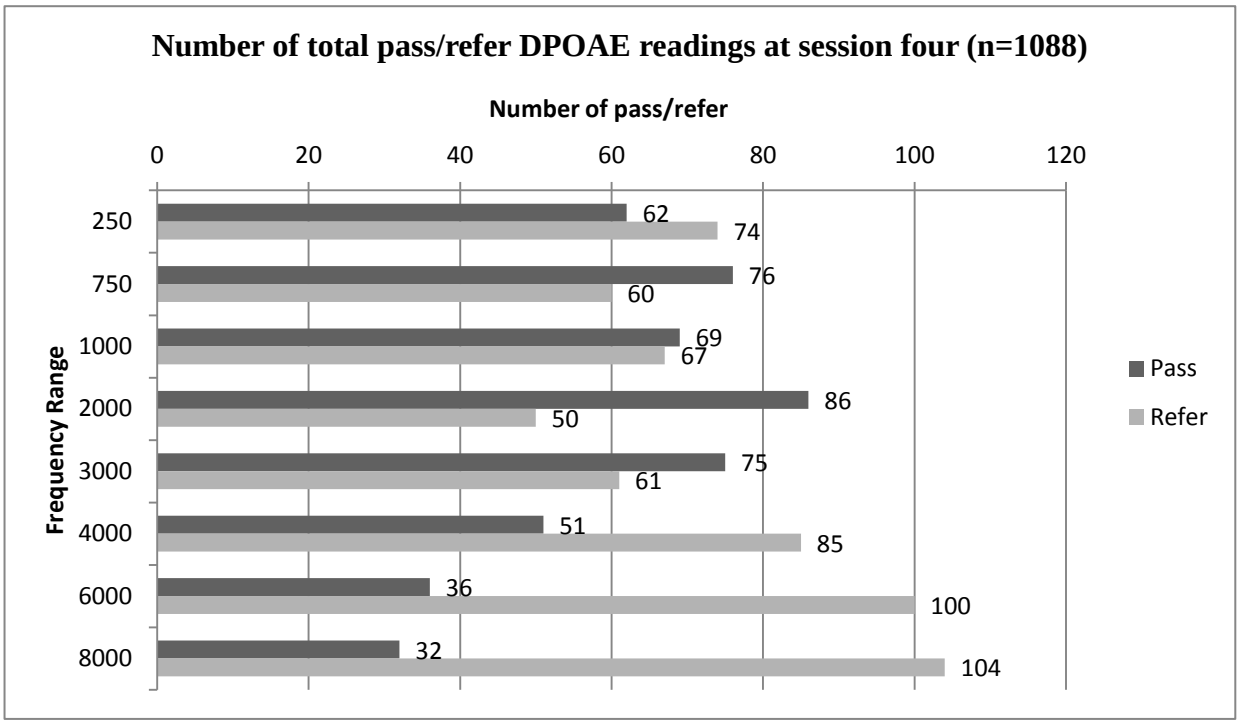


Figure 13

Number of total pass/refer DPOAE readings at session four

Slightly different to the third session, was the fourth DPOAE screening session; where differences between the numbers of pass/refer readings for left ear and right ear are visible at 2000 and 4000 Hz (Figure 11 and 12). However, the difference between this session and the third session is that now the right ear is showing higher refer numbers than the left ear was in the previous session. At 2000 Hz, the right ears have yielded 28 (41.18%) refer readings as opposed to the left ears that yielded 22 (32.35%) refer readings therefore indicating a higher percentage of pass readings at 2000 Hz for session four. Then at 4000 Hz, the right ears have yielded 46 (67.65%) refer readings as opposed to the left ears that yielded 39 (57.35%) refer readings. Again, little numerical difference between left and right ear readings exists in the low frequency range at session four. On average, at session four, the mean average of the total number of pass readings was 28.75 compared to the total number of refer readings, at 39.25. Therefore, despite larger numbers of pass readings at specific frequencies, the number of refer readings still exceeds pass readings at session four (Figure 13).

Considering the total pass/refer DPOAE readings for the second, third and fourth sessions i.e. Figures 7, 10 and 13; numerically, from frequencies 250-3000 Hz there appears to be a lack of consistency with regards to specific frequencies yielding a higher number of passes or a higher number of refers at each subsequent session. The readings shift from higher/lower referral rates to higher/lower pass rates at each frequency and at each subsequent session. Whereas at 4000-8000 Hz, the trend remains more constant, with remarkably lower pass numbers than refer numbers. This trend is in agreement with literature that supports DPOAEs as being sensitive to changes in hair cell function at higher frequencies (Hall, 2000).

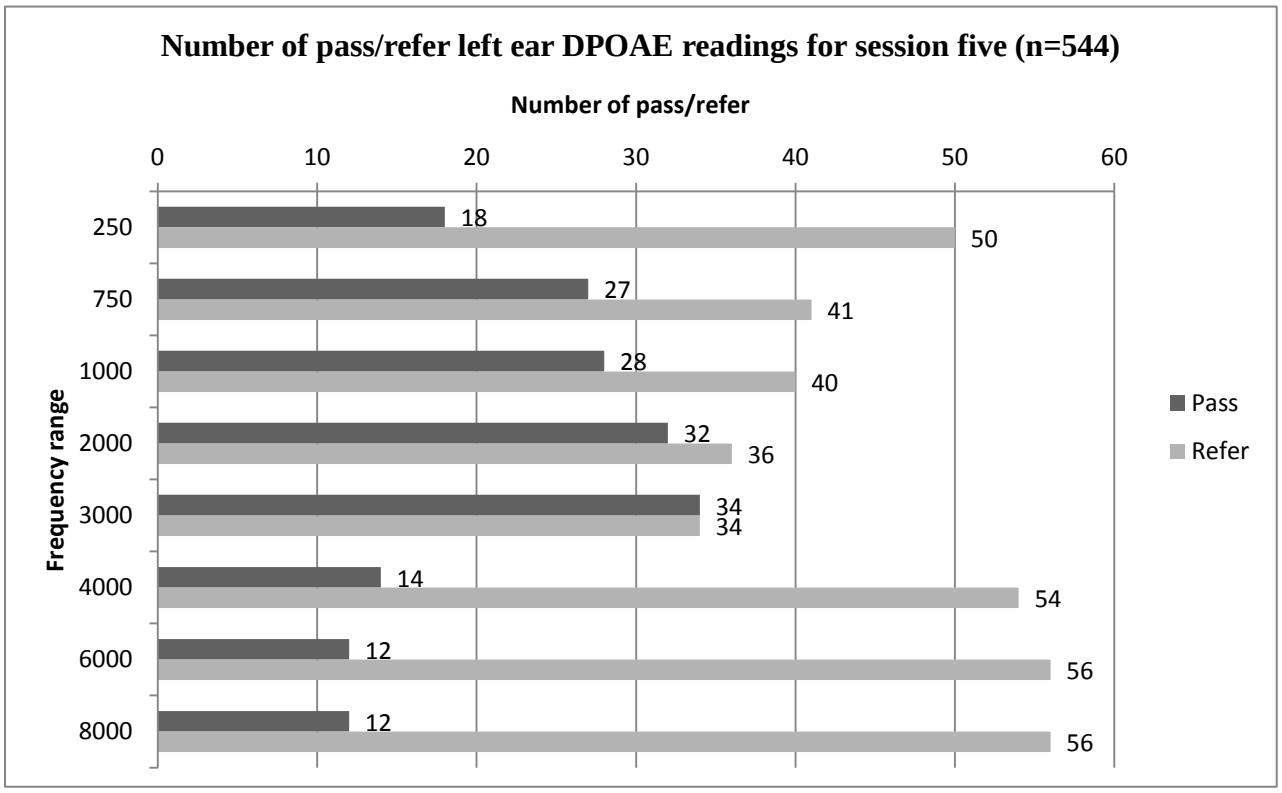


Figure 14

Number of pass/refer left ear DPOAE readings at session five

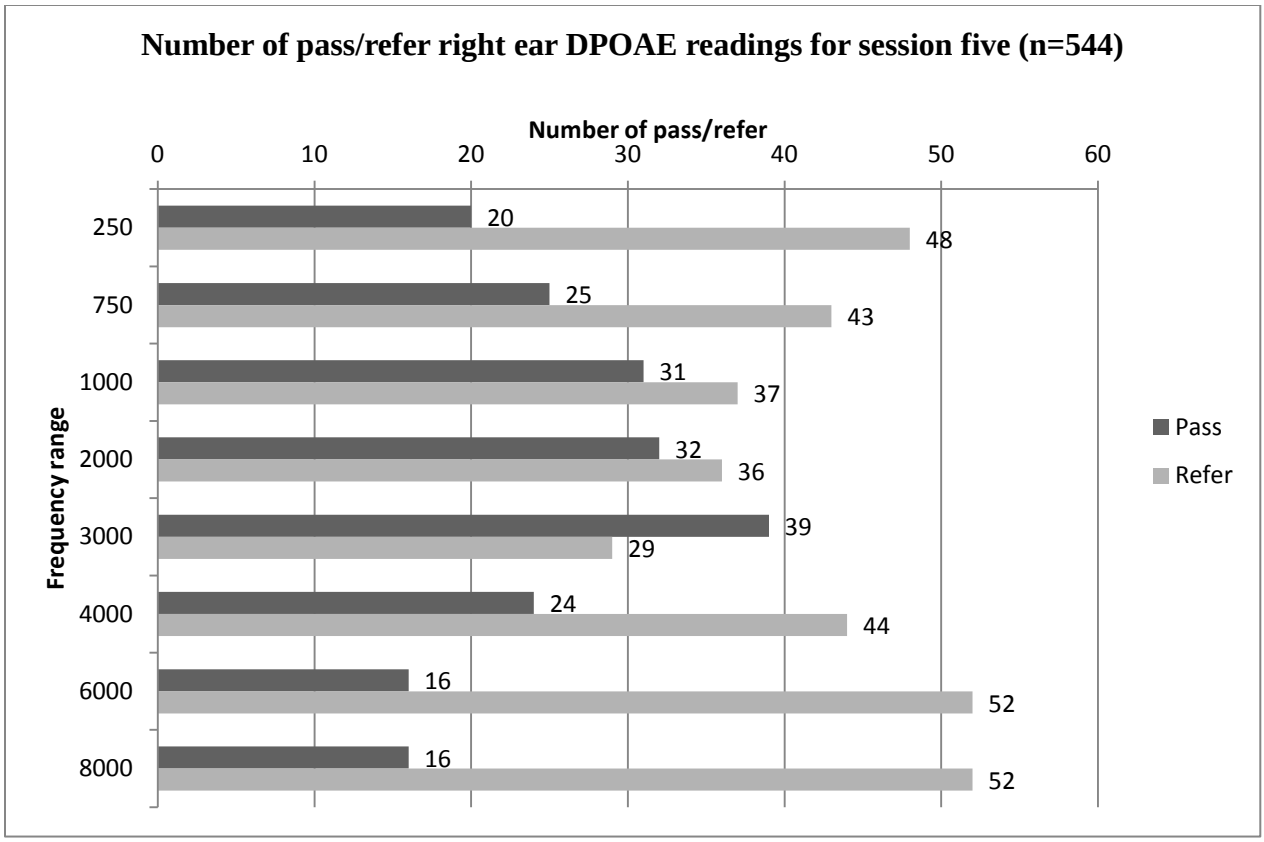


Figure 15

Number of pass/refer right ear DPOAE readings at session five

Only one large numerical difference between left and right ear DPOAE readings exists at session five; and that is at 4000 Hz (Figure 14 and 15). The left ear readings at 4000 Hz indicates 54 (79.41%) refer readings compared to 44 (64.71%) refer readings for the right ears. Whereas, across the other frequencies, little numerical differences between left and right ear DPOAE readings exists for the final audiological session.

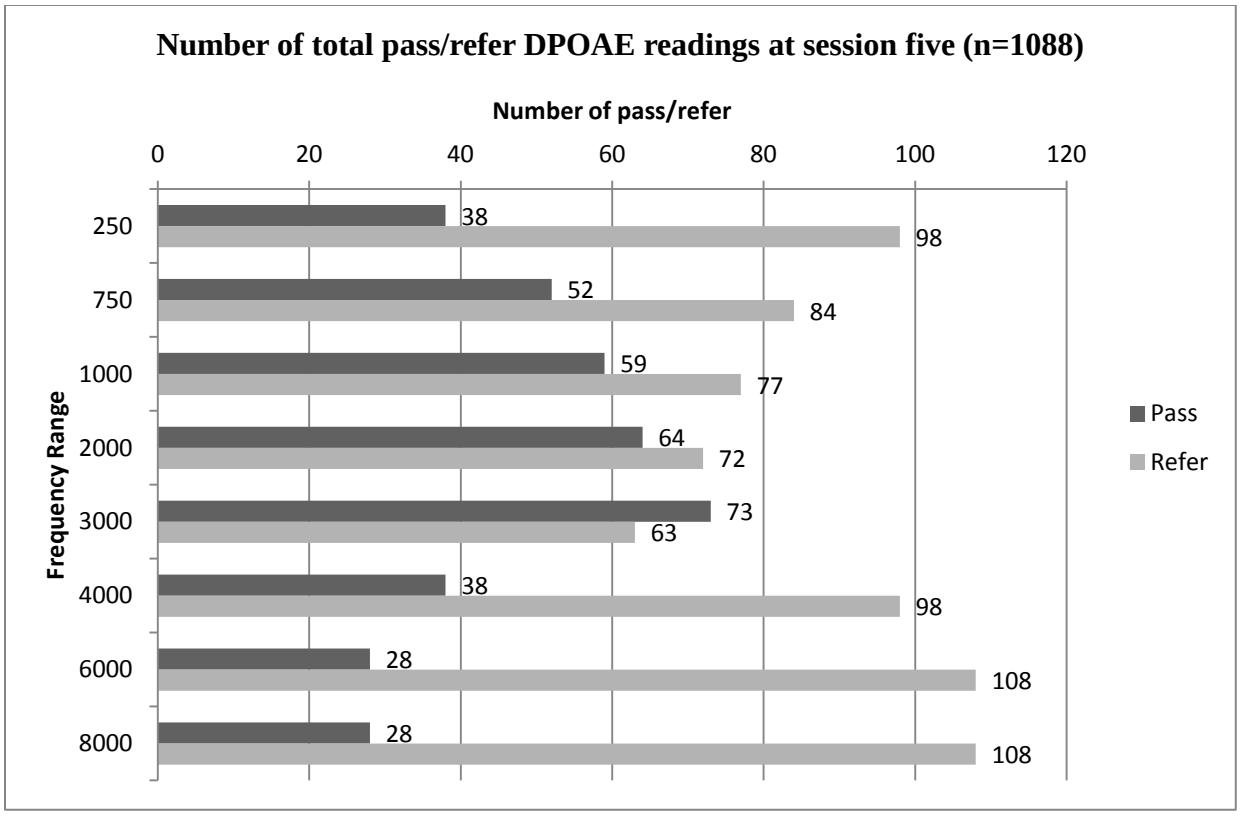


Figure 16

Number of total pass/refer DPOAE readings at session five

The total results of the fifth session of DPOAE assessments are depicted in Figure 16. The graph clearly shows the large number of refer readings at 250, 4000, 6000 and 8000 Hz. The low and mid frequency range again show a mixed number of refer and pass readings. In the total (i.e. combined left and right) number of pass/refer readings at session five in a group of adults on long-term MDR-TB treatment the refer readings far exceed the pass readings with mean averages of 25.38 pass and 42.63 refer readings. Therefore, at the fifth session of DPOAE screening in this group of adults on long-term MDR-TB treatment, the overall number of refer readings far exceed the number of pass readings on DPAOE results across all the tested frequencies.

Table 6

Parameter estimates and Odds of DPOAEs for time and ear effect

	Parameters (B)	S.E.	Wald	df	*P*-value	Exp(B)	95.0% C.I.for EXP(B)	
							Lower	Upper
Ear(1)	-0.03	0.22	0.02	1	0.88	0.97	0.63	1.48
Time			7.73	4	0.01			
Session 1	0.93	0.38	6.01	1	0.01	2.54	1.21	5.36
Session 2	0.93	0.38	6.01	1	0.01	2.54	1.21	5.36
Session 3	0.83	0.38	4.65	1	0.03	2.29	1.08	4.87
Session 4	0.60	0.39	2.31	1	0.13	1.82	0.84	3.95

*key: S.E.-standard error; df-degrees of freedom; C.I.-confidence interval

On regression analysis of the parameter odds estimate for DPOAEs (Table 6), the effect of time on DPOAE changes was statistically significant ($p<0.05$) for sessions one to three. Whereas, these changes were not significant ($p=0.9$) for ear difference. Whereas, the Parameter estimates of odds of passing the DPOAE screening at monthly sessions are 2.54 times higher in first month (session one), than in the reference time (session five). Similar interpretation is applicable for the second and third session, where the Odds of passing the DPOAE was 2.25 and 2.29 higher in session two and session three respectively.

Therefore, at all five DPOAE screening sessions in this group of adults on long-term MDR-TB treatment, the overall number of refer readings far exceed the number of pass readings; DPOAE changes are significantly affected by time whereas, ear difference has little effect on DPAOE results across all the frequencies tested.

iii. Pure Tone Audiometry

Pure Tone Audiometry was conducted on all 68 participants, as per their audiological records. PTA was conducted as part of the audiological investigations and

was conducted monthly over a five-month period. PTA included conventional frequency range as well as high-frequency testing at 10 000 Hz and 12 500 Hz. For hearing to be clinically classified as 'normal', PTA thresholds need to be within 0-25 dB across the conventional frequency range (Roeser & Clark, 2007). Mean thresholds have been analysed by ear difference (left and right) in the total sample and then as the total sample (both left and right ears). The PTA results are not set out as initial, middle and final sessions, as are the DPOAEs, but are rather represented in line-graphs below, using the mean thresholds of each frequency tested at each monthly assessment. Regression analysis and analysis of covariance is used to statistically describe the significance of PTA threshold changes in the total sample (Table 7). The fifth session is the reference category and is therefore absence, as the absence of all the four sessions implies the fifth session is most important. The PTA results are then compared to the DPOAE results for frequencies and sessions where results showed comparable differences between left and right ears and the total sample.

Table 7

ANCOVA parameter estimates for ear and time effects for PTA results across all test frequencies

Parameter Estimates					
Dependent Variable: Pure Tone Audiometry					
	P-values				
	Ear	**Session 1**	**Session 2**	**Session 3**	**Session 4**
250 Hz	0.17	-4.50	-4.03	-2.7	-0.95
500 Hz	0.34	0.00	0.00	0.03	0.57
1000 Hz	0.73	0.00	0.00	0.05	0.34
2000 Hz	0.53	0.00	0.00	0.00	0.06
4000 Hz	0.31	0.00	0.00	0.02	0.00
6000 Hz	0.04	0.00	0.00	0.00	0.04
8000 Hz	0.79	0.00	0.00	0.00	0.07

10 000 Hz	0.70	0.00	0.00	0.00	0.07
12 500 Hz	0.04	0.00	0.00	0.00	0.27

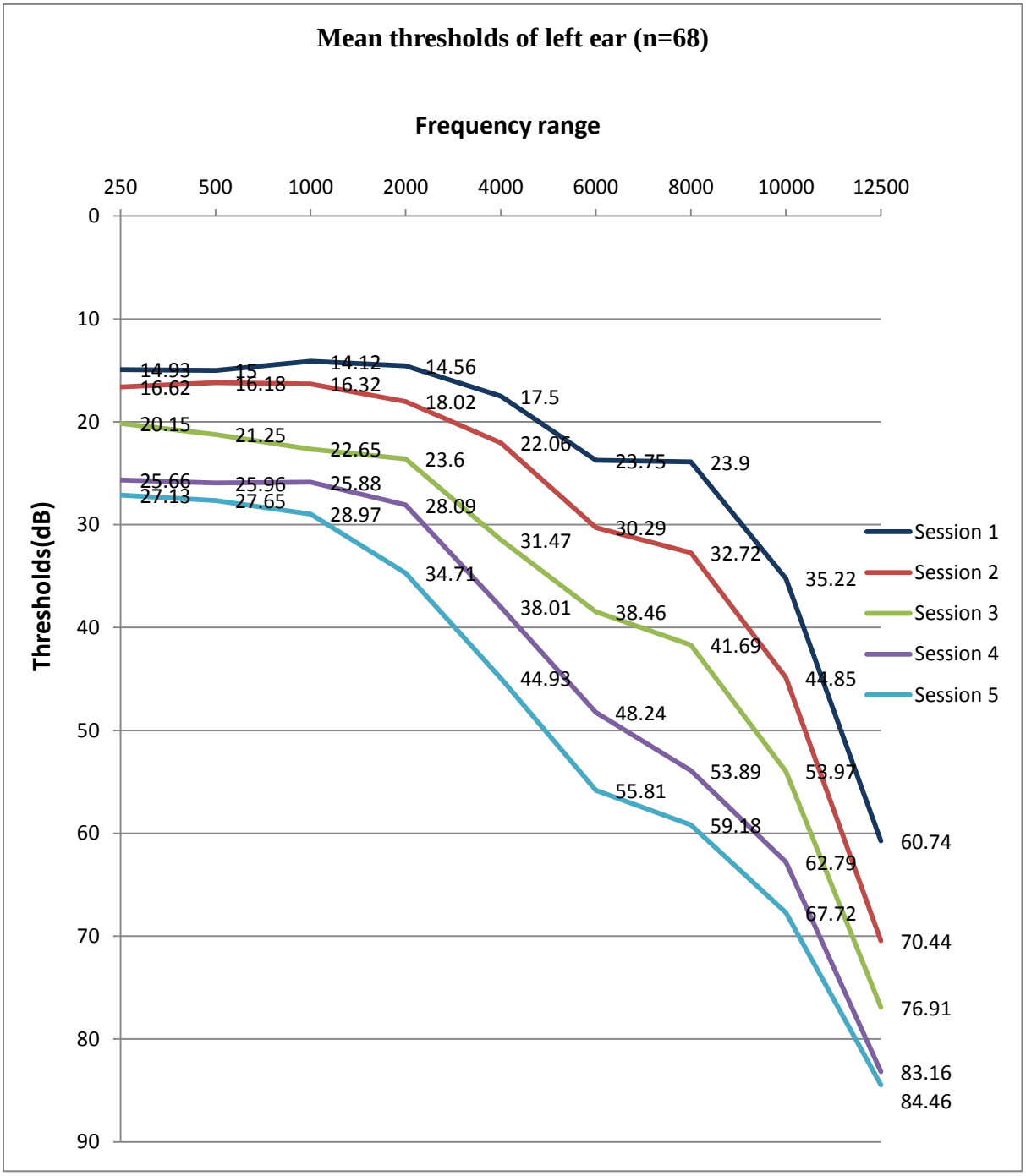


Figure 17

Mean thresholds of monthly PTA results for the left ear

Figure 17 gives a graphical representation of the monthly decline in PTA thresholds for the total sample (n=68) for left ears only. From session one through to session four, the mean thresholds at 250, 500 and 1000 Hz, were all within the normal range of hearing sensitivity for the left ears on the total sample i.e. less than 25 dB. This indicates that at these low frequencies, little change in left ear hearing thresholds, over four months of receiving treatment for MDR-TB, is evident in this group of adults. Whereas, at session five, the left ear thresholds across the entire frequency range are all above the 25 dB threshold for normal hearing sensitivity; showing that over an extended time period, changes in hearing sensitivity occur across the test frequency range. At frequency 2000 Hz, the mean threshold begins to decrease, but only at the fourth session of audiological assessment i.e. 28.09 dB. At this frequency, the change in hearing sensitivity would clinically be considered a mild hearing loss. However, on analysis of variance (Table 7), these changes at 2000 Hz at the fourth session, were found to be statistically non-significant as p=0.06. The remaining frequencies show a steady decline of PTA thresholds across all five audiological sessions, with the high frequencies, 8000-12 500 Hz, showing the greatest decline in PTA average and the severest hearing deficit. On analysis of variance, the p-values for these frequencies were p<0.05; therefore these changes were found to be statistically significant. Therefore the most significant changes in left ear hearing function occur at the higher frequencies in this group of adults on MDR-TB treatment.

The PTA results for the left ears from session one, show that clinically from frequency 250-8000 Hz, the hearing thresholds remain within the 25 dB normal hearing range; at 10 000 Hz the hearing changes from hearing within normal limits to a mild hearing loss, and then at the final frequency tested, the hearing slopes to a moderate-severe hearing loss. On analysis of variance, at 10 000 Hz, these changes were found to be statistically non-significant (p=0.07). Session two, begins with hearing within normal limits from 250-4000 Hz, and clinically changes from a mild hearing loss at 6000 and 8000 Hz, to a moderate hearing loss at 10 000 Hz, and finally to a moderate-severe hearing loss at 12 500 Hz. Statistically, on analysis of variance, the changes across the entire frequency range are considered significant (p<0.05). Clinically, the third session

shows changes in hearing sensitivity from hearing thresholds within normal limits from 250-2000 Hz, to a mild hearing loss at 4000 and 6000 Hz, to a moderate hearing loss at 8000 Hz and 10 000 Hz; and finally a severe hearing loss at the highest frequency tested. Again, on analysis of variance, the changes across the entire frequency range are considered significant ($p<0.05$). Session four shows the same hearing threshold changes as session three, but the clinical hearing changes are from hearing within normal limits to a mild hearing loss at an earlier frequency, namely 2000 Hz. The hearing severity at the highest frequency, 12 500 Hz (83.16 dB), is also severe, but at least 6 dB more severe than that at session three (76.91 dB). On analysis of variance, the changes in hearing function at 250, 4000 and 6000 Hz are considered significant ($p<0.05$). The significant changes have already occurred in the earlier sessions of testing, indicating that the greatest damage to the auditory system begins early on whilst drug treatment for MDR-TB begins. The last session of PTA reviews, clinically shows that hearing sensitivity ranges from mild to severe hearing loss from 250-12 500 Hz; with analysis of variance showing significant changes at 250, 4000 and 6000 Hz ($p<0.05$). Overall, the graph depicts the steady decline in left ear PTA thresholds across the frequency range and across the five sessions of audiological testing.

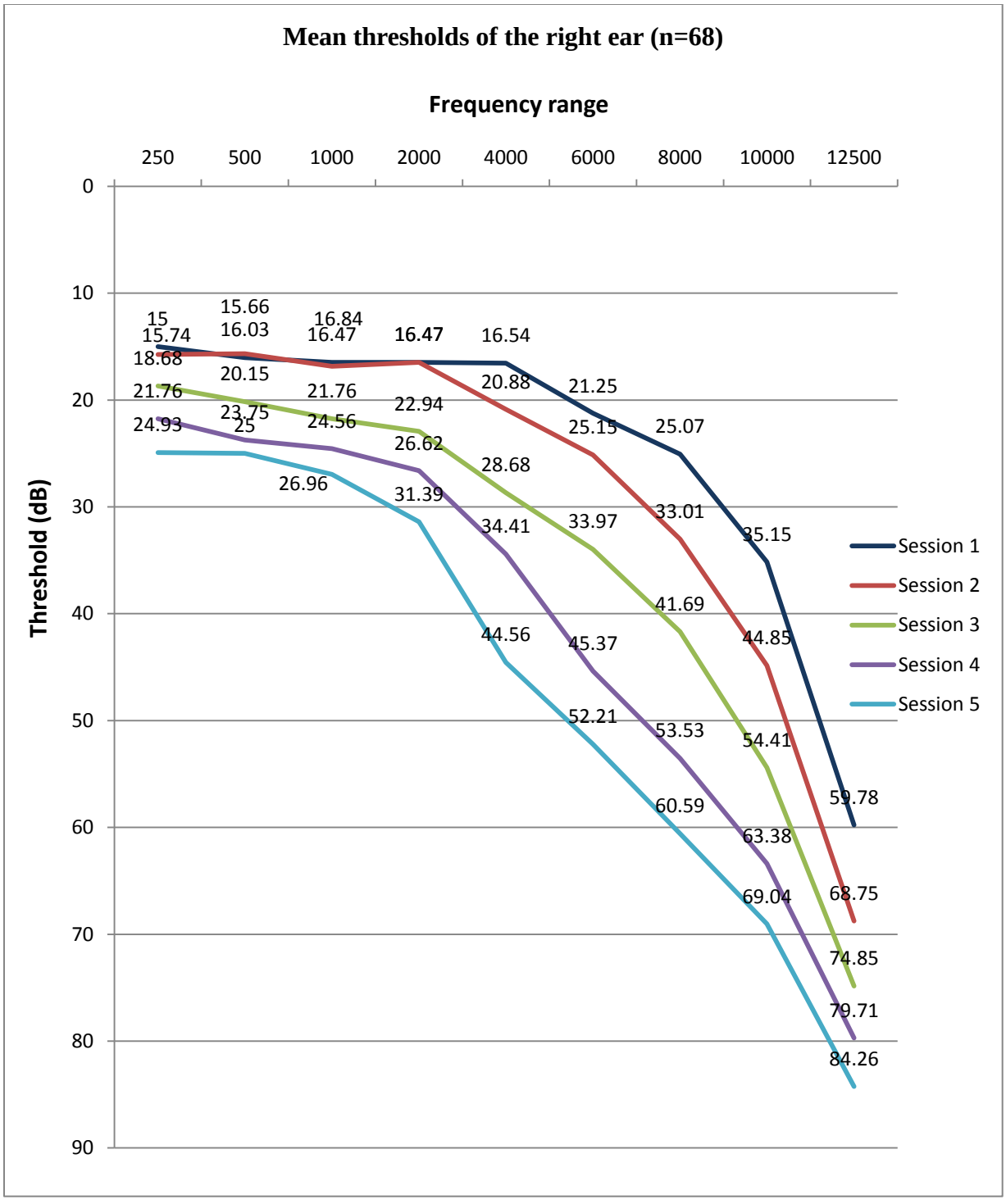


Figure 18

Mean thresholds of monthly PTA results for the right ear

Figure 18 gives a graphical representation of the monthly decline in PTA thresholds for the total sample (n=68) for right ears only. From session one through to session five, the mean thresholds at 250, 500 and 1000 Hz, were all within the normal range of hearing sensitivity for the right ears on the total sample; except for 1000 Hz at the fifth session falling just outside of the normal hearing value i.e. 26.96 dB. This indicates that in the right ear, there is little change in right ear hearing thresholds at these low frequencies, over the full five months of receiving treatment for MDR-TB is evident in this group of adults. For the remaining frequencies, the mean threshold begins to steadily decline over all five audiological sessions, with the high frequencies, 8000-12 500 Hz, showing the greatest decline in PTA average and the severest hearing deficit. The change in hearing sensitivity for the right ear occurs at frequencies greater than 1000 Hz at sessions three, four and five. More specifically, at session one, clinically hearing is within normal limits from 250-8000 Hz. The change in hearing sensitivity occurs at 10 000 Hz, where clinically the hearing is classified as a mild loss, and at 12 500 Hz, where the hearing is now classified as a moderate-severe hearing loss. On analysis of covariance (Table 7), these changes are considered statistically significant ($p<0.05$) at 10 000 Hz and 12 500 Hz. At session two, the hearing thresholds show changes from 8000 Hz through to 12 500 Hz; more specifically clinically classified as a mild (8000 Hz), moderate (10 00 Hz) and moderate-severe hearing loss respectively; and statistically, these changes are significant as $p<0.05$ on the analysis of covariance. The hearing thresholds shift again to earlier frequencies at session three, with the hearing loss beginning at 4000 Hz. From 250-2000 Hz the hearing thresholds are within normal limits; then hearing sensitivity changes to a mild hearing loss at 4000 and 6000 Hz, to a moderate hearing loss at 8000 Hz, to a moderate-severe hearing loss at 10 000 Hz; and finally a severe hearing loss at 12 500 Hz. The described changes in PTA thresholds are statistically significant ($p<0.05$) on analysis of covariance for session three. Session four shows the same hearing threshold changes as session three, but the hearing changes from hearing within normal limits to a mild hearing loss at an earlier frequency, 2000 Hz, and then sloping to a severe hearing loss at 12 500 Hz. The changes for session four, that are considered significant ($p<0.05$) are at 4000 Hz and 6000 Hz. The remaining changes at the other test frequencies are considered non-significant on analysis of covariance for session four. The

last session, shows that hearing sensitivity ranges from hearing within normal limits at 250 and 500 Hz, to a sloping mild to severe hearing loss from 1000-12 500 Hz. Overall, the graph depicts the steady decline in right ear PTA thresholds across the frequency range and across the five sessions of audiological testing.

The PTA thresholds between left and right ears show threshold and hearing severity differences, at certain sessions and frequencies. There is little clinical difference in the effect PTA thresholds have on hearing loss classification at session one, session three and session four for left and right ears. At session two, there is a difference between hearing thresholds for left and right ears; the left ear shows earlier signs of thresholds changes than the right does i.e. change seen at 6000 Hz in the left ear and change in the right ear results begins at 8000 Hz. The changes are clinically significant at 6000 Hz as the left ear presents with a mild hearing loss; and the right is still within normal limits. At the fifth session, the difference between left and right PTA threshold changes is that for the left ear results, the hearing loss is evident across the entire frequency range i.e. mild to severe hearing loss. Whereas, for the right ear results, the hearing loss is only evident at 1000 Hz, but slopes from hearing within normal limits to mild to severe hearing loss. On analysis of covariance, the ear effect at 6000 Hz and 12 500 Hz is considered significant ($p<0.05$) for PTA thresholds for left and right ears. Clinical changes at 6000 Hz correspond to the ear effect difference for left and right ears.

From this comparison (of left and right ear results), it can be said that despite hearing changes occurring at earlier and later frequencies at either left and right ear; overall in both set of ear results the trend is that for each subsequent session, the change in hearing sensitivity occurs at an earlier frequency. Therefore, it is clear that over time the hearing deteriorates for both left and right ear PTA threshold results.

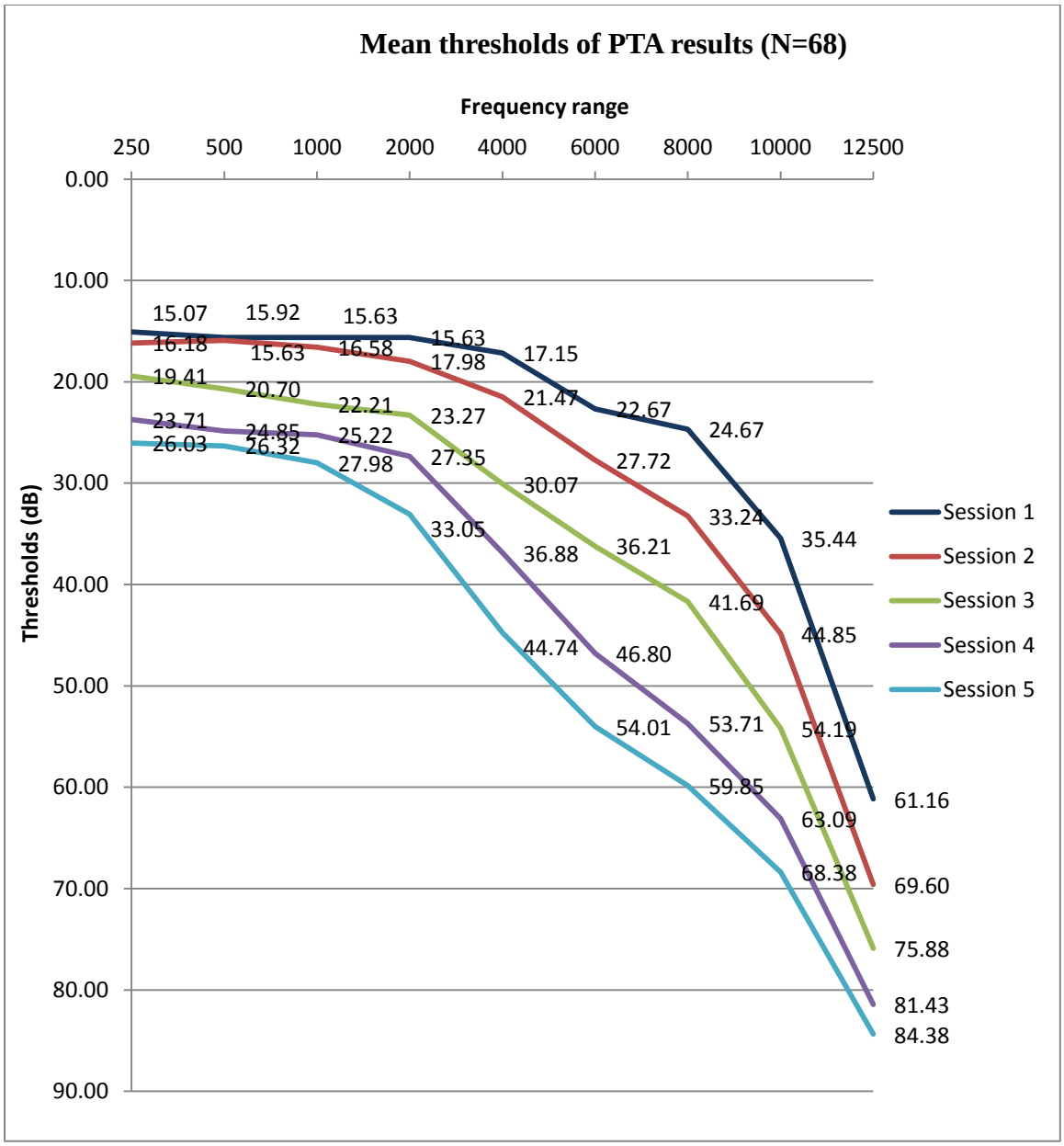


Figure 19

Mean thresholds of monthly PTA results

Figure 19 gives a graphical representation of the monthly decline in PTA thresholds for the total sample (N=68). From session one through to session four, the mean thresholds at 250, 500 and 1000 Hz were all within the normal range of hearing sensitivity for adults. Therefore no change in hearing sensitivity was observed at the low

frequencies for adults on long-term MDR-TB treatment. The remaining frequencies show a steady decline of PTA thresholds across all five audiological sessions, with the highest frequency, 12 500 Hz, showing the greatest decline in PTA average and the severest hearing deficit. Session one shows clinical changes in hearing sensitivity only at 10 000 Hz and 12 500 Hz, with mild and moderate-severe hearing losses respectively. On analysis of variance, these changes were found to be statistically significant ($p<0.05$) for both 10 000 Hz and 12 500 Hz. At session two the clinical changes in hearing sensitivity are seen at an earlier frequency i.e. a mild hearing loss at 4000 Hz, continuing onto a moderate-severe hearing loss at 12 500 Hz. The clinical changes in hearing sensitivity at session three are very similar to those of session two, except that the hearing loss continues onto a severe hearing loss at 12 500 Hz. For both session two and three, the changes seen at the respective frequencies described above, are significant on analysis of covariance ($p<0.05$). Session fours' clinical hearing changes are seen at 2000 Hz, where again the hearing loss slopes from mild to severe; however on analysis of covariance at this frequency, the changes are found to be non-significant ($p>0.05$). The final session shows that clinically all PTA thresholds range from mild to severe hearing losses across all test frequencies. Overall, the graph depicts the steady decline in PTA thresholds across the frequency range and across the five sessions of audiological testing. Therefore, changes in hearing are evident on PTA (up to 12 500 Hz) for adults on long-term MDR-TB treatment.

These changes, in the PTA thresholds for both left and right ears, were found to be statistically significant ($p<0.05$) for all the test frequencies (250-12 500 Hz). The statistically significant changes were evident from session one to session three for frequencies 250-12 500 Hz; and for session four at 4000-6000 Hz. The most important effect of all was the 'time' effect, as the study was most focused on the long-term effects of the MDR-TB medications on patients' hearing ability. Therefore, analysis of 'time' main effect is described below along with ear difference at each audiological test frequency for PTA thresholds.

Table 8

ANCOVA Test Results of Between-Subject Effects for Independent Variables (ear and time) for PTA frequencies (250-12 500 Hz) in total sample (N=68)

Tests of Between-Subjects Effects **Dependent Variable: Pure Tone Audiometry**									
	250 Hz	**500 Hz**	**1000 Hz**	**2000 Hz**	**4000 Hz**	**6000 Hz**	**8000 Hz**	**10000 Hz**	**12500 Hz**
Ear	0.17	0.34	0.73	0.53	0.31	0.04	0.79	0.70	0.04
Time	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Table 8 is a summary of the ANCOVA analysis of between-subjects results for the variables of ear and time in the total sample across the PTA frequencies. In the ANCOVA analysis, the interaction effects for the variable of time had *p*-values of < 0.05 across all the PTA test frequencies. Therefore the independent variable of time is significantly different from zero at all frequencies tested. Therefore the main hypothesis is rejected and the interaction effects of time are significant in this study. Whereas, the interaction effects for the variable of ear difference has *p*-values > 0.05 across the PTA test frequencies, except for one interaction effect at 12 500 Hz, which has a *p*-value of 0.04 for ear difference effect. Therefore for all the other ear interactions across the PTA frequencies, the hypothesis is accepted and the interaction effects of ear difference are non-significant.

Table 9

ANCOVA parameter estimates of time for PTA across all frequencies

Dependent Variable: Pure Tone Audiometry				
Parameter Estimates of Time				
	Session 1	**Session 2**	**Session 3**	**Session 4**
250 Hz	-11.01	-9.85	-6.62	-2.32
500 Hz	-10.74	-10.40	-5.63	-1.47
1000 Hz	-12.39	-11.40	-5.77	-2.76
2000 Hz	-17.47	-15.07	-9.78	-5.10
4000 Hz	-27.63	-23.27	-14.67	-7.87
6000 Hz	-31.39	-26.29	-17.79	-7.21
8000 Hz	-35.23	-26.62	-18.16	-6.14
10 000 Hz	-33.02	-23.53	-14.19	-5.29
12 500 Hz	-23.50	-14.78	-8.49	-2.94

Table 9 shows the parameter estimates of time for PTA across all test frequencies; the parameter estimates of time for each session are negative, therefore an increase can be expected. From table 9 it is obvious that the PTA threshold values, at each test frequency, for the parameter of time increases with each subsequent session. For example, at 250 Hz; at session one, the PTA thresholds increases by 11.01 dB, at the second session the thresholds increases by 9.85 dB, in the third session, by 6.62 dB and in the fourth month the thresholds increases by 2.32 dB. The same can be said for all the other frequencies; and furthermore, these consequent increases in PTA thresholds are considerably higher at each session and at each consecutive frequency. Therefore, as the test frequency increases with each additional sessional assessment, so the PTA thresholds worsen. Therefore, it is evident that the pure tone threshold results at each test frequency increase from month to month in adult patients on long-term MDR-TB medication.

iv. DPOAE results compared to PTA results

The audiological investigations that make up the audiological test battery cannot be viewed in isolation (Sweetow & Sabes, 2008). Since the otoscopic examinations and tympanograms had to correspond with the inclusion criteria of the study, no comparisons to the other audiological investigations need to be made as standard results were only accepted. However, the DPOAE and PTA results need to be viewed in a comparable manner, as results from one test need to correspond to the other test in order for the full audiological investigation to be permissible (Roeser, Valente & Hosford-Dunn, 2007). Therefore in this section results will be compared for the same sessions and for the same frequencies at which notable differences and similarities were found for DPOAEs and PTA thresholds. DPOAE results did not go past 8000 Hz whereas PTA results did; therefore no comparison can be made for the PTA results that were significant in showing hearing change i.e. at 10 000 and 12 500 Hz at any session.

The DPOAE readings at session one showed that at 4000 Hz, the number of left ear refer readings (34) were notably lower than the number of right ear refer readings (42). Whereas, for the PTA mean threshold at this frequency at session one, the difference between left and right ear thresholds were not of great clinical difference i.e. 17.5 dB and 16.54 dB respectively and these threshold readings fall within the range considered normal hearing. The ear difference effect at this 4000 Hz, at session one, was statistically non-significant. For the combined ear DPOAE readings at session one; both 2000 and 3000 Hz had notably larger pass readings (91) than refer readings (45). Clinically, the PTA mean thresholds for these frequencies were still within the normal limits for hearing sensitivity. Statistically, the PTA changes were statistically significant ($p<0.05$) at 2000-4000 Hz. Despite the larger number of pass DPOAE readings, there still existed a number of refer DPOAE readings; and despite the PTA thresholds still being within normal limits there was a decrease from 250-2000 Hz in PTA thresholds. Perhaps the high pass rates are in agreement with the PTA thresholds remaining within normal limits; and the number of refer DPOAE readings are in agreement with the change or decrease in thresholds. No other comparable differences at session one existed.

At the second session, clinically and statistically there was little comparison between the left and right results for DPOAE readings and PTA thresholds ($p<0.05$).

However, the overall results correspond clinically and statistically for DPOAEs and PTA at session two. The number of DPOAE refer readings at 4000-8000 Hz show an increase; and the change in hearing sensitivity for PTA results begins at 4000 Hz and continues on through to the remaining frequencies, and the *p*-values ($p<0.05$) are significant at session two and for frequencies 4000-8000 Hz.

Session three shows clinically comparable differences between left and right ears for DPOAEs, but not for PTA results and not statistically ($p>0.05$) for DPOAE ear difference effect. However, the left ear DPOAE refer readings at 4000 and 6000 Hz show an increase in numbers as does the number of total DPOAE readings at 6000 Hz (left and right); and the change in hearing sensitivity for the overall PTA results begins at 4000 Hz and continues on through to the remaining frequencies. The analysis of covariance for PTA thresholds changes at 4000 and 6000 Hz, and ear effect at 6000 Hz are statistically significant ($p<0.05$) at this session.

At session four, there are again clinically comparable differences between left and right ears for DPOAEs, but not for PTA results and not statistically ($p>0.05$) for DPOAE ear difference effect. For the comparison of the total PTA results and total DPOAE readings; at 2000 Hz the DPOAE readings show both refer and pass readings, but the number of pass readings are much higher than the number of refer readings at this frequency. The PTA threshold at 2000 Hz begins to change, and presents a mild hearing loss. This mild hearing loss corresponds to the number of refer readings at 2000 Hz. However, statistically the changes PTA threshold changes at 2000 Hz are non-significant at session four ($p>0.05$). Whereas at 4000-8000 Hz, the trend remains more constant, with remarkably lower pass numbers than refer numbers for DPOAEs and more severe hearing threshold changes from 4000 Hz onwards for PTA results. Statistically, only at 4000-6000 Hz are the changes in hearing thresholds significant ($p<0.05$) at session four; and the changes in DPOAE function are non-significant ($p>0.05$).

The fifth and final session for DPOAEs show large differences between the number of left and right ear DPOAE readings at 4000 Hz and the large refer numbers at 250, 4000, 6000 and 8000 Hz in the total (left and right ear) results. As for the PTA results, the hearing loss is clinically evident across the entire frequency range.

Therefore, these audiological results confirm that adults on MDR-TB treatment over an extended period of time show permanent audiological changes and decreased hearing abilities. On analysis of variance, the changes in hearing thresholds were found to be statistically significant ($p<0.05$) from session one to session three for frequencies 250-12 500 Hz; and for session four at 4000-6000 Hz. These differences are also considered statistically significant ($p<0.05$) for DPOAE and PTA results for sessions one (at 2000-4000 Hz), session two (at 4000-8000 Hz), session three and session four (both at 4000-6000 Hz). Similar for both left and right ears, the differences in PTA changes at session one to three (250-12 500 Hz) and session four (4000-6000 Hz) were statistically significant ($p<0.05$). Whereas, differences in ear effect for DPOAE readings were consider statistically non-significant ($p>0.05$) across all frequencies tested.

3.3 Results of the estimated total sample of adults who may present with changes in hearing following long-term MDR-TB treatment

3.3.1 DPOAEs

As mentioned earlier in the study, an overall pass/refer was allocated to each patient's DPOAE repeated measure done at each audiological session. This was based on a pass for more than 50% of the high frequencies (4000-8000 Hz). In this way the estimated number of adults who showed a change in hearing function (with regards to DPOAE function) could be calculated from the overall assigned pass/refer.

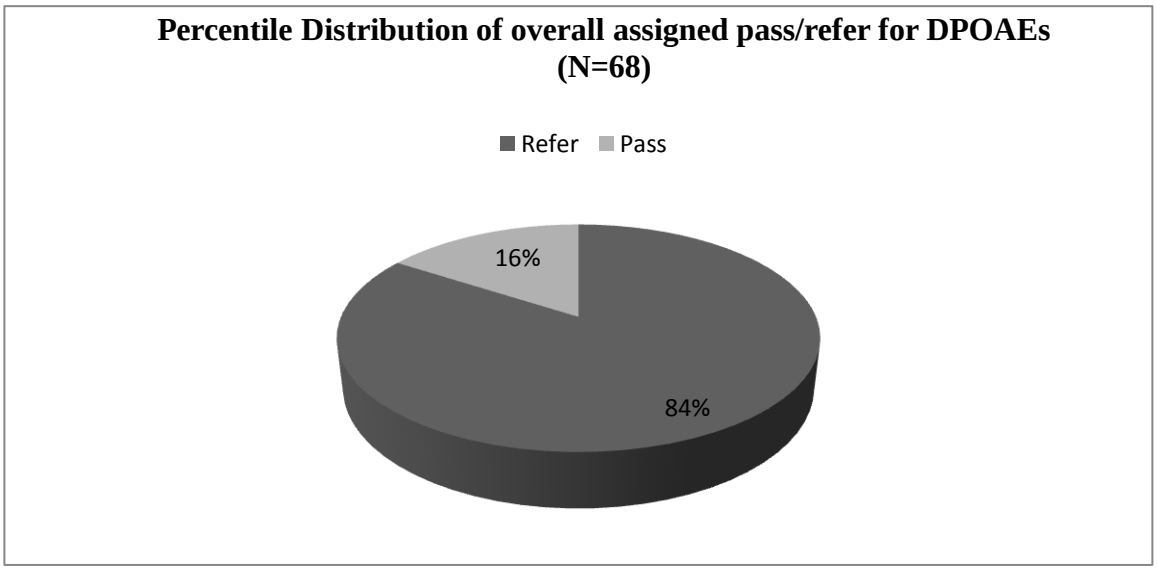


Figure 20

Percentile Distribution of the overall assigned pass/refer for DPOAEs

The pie chart (Figure 20) shows the percentile distribution of the overall assigned pass/refer for DPOAEs. Of the 68 patient files reviewed, the majority (57) of the sample (84%), over all five months of audiological assessments, were referred for DPOAEs.

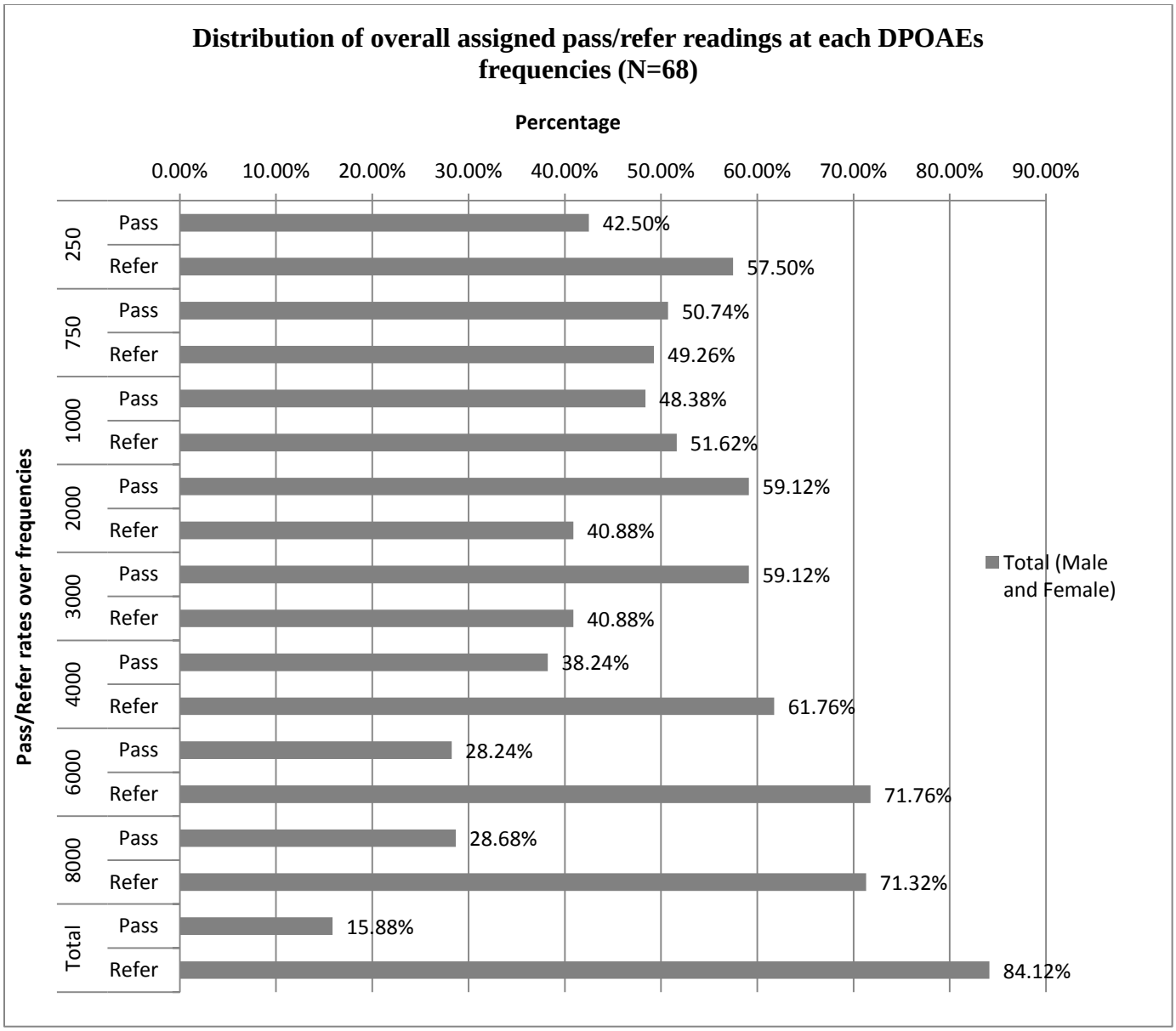


Figure 21

Distribution of the overall assigned pass/refer readings at each DPOAE frequency

A more detailed graph, figure 21, shows the distribution of the overall assigned pass/refer rates at each DPOAE frequency. Looking into the distribution of frequency-specific pass/refer rates is note-worthy as ototoxicity is said to be highly sensitive to DPOAE testing and is said to affect the high-frequencies first (Konrad-Martin et al., 2005). At frequency 250 Hz, the percentage of the number of assigned overall passes is

lower than the number of assigned overall refers for the total sample. For frequencies 750-1000 Hz, the number of pass/refer percentages are generally alike for the total sample readings. However, at frequencies 2000 Hz and 3000 Hz, the numbers of overall passes are higher than the number of overall refers in the total sample. This trend at 2000 and 3000 Hz, is consistent with the number of pass/refer readings for DPOAEs at each audiological investigation across the DPOAE frequency range. At the higher frequencies, 4000-8000 Hz, the number of overall assigned refers greatly exceeds the number of overall assigned pass numbers in the total sample.

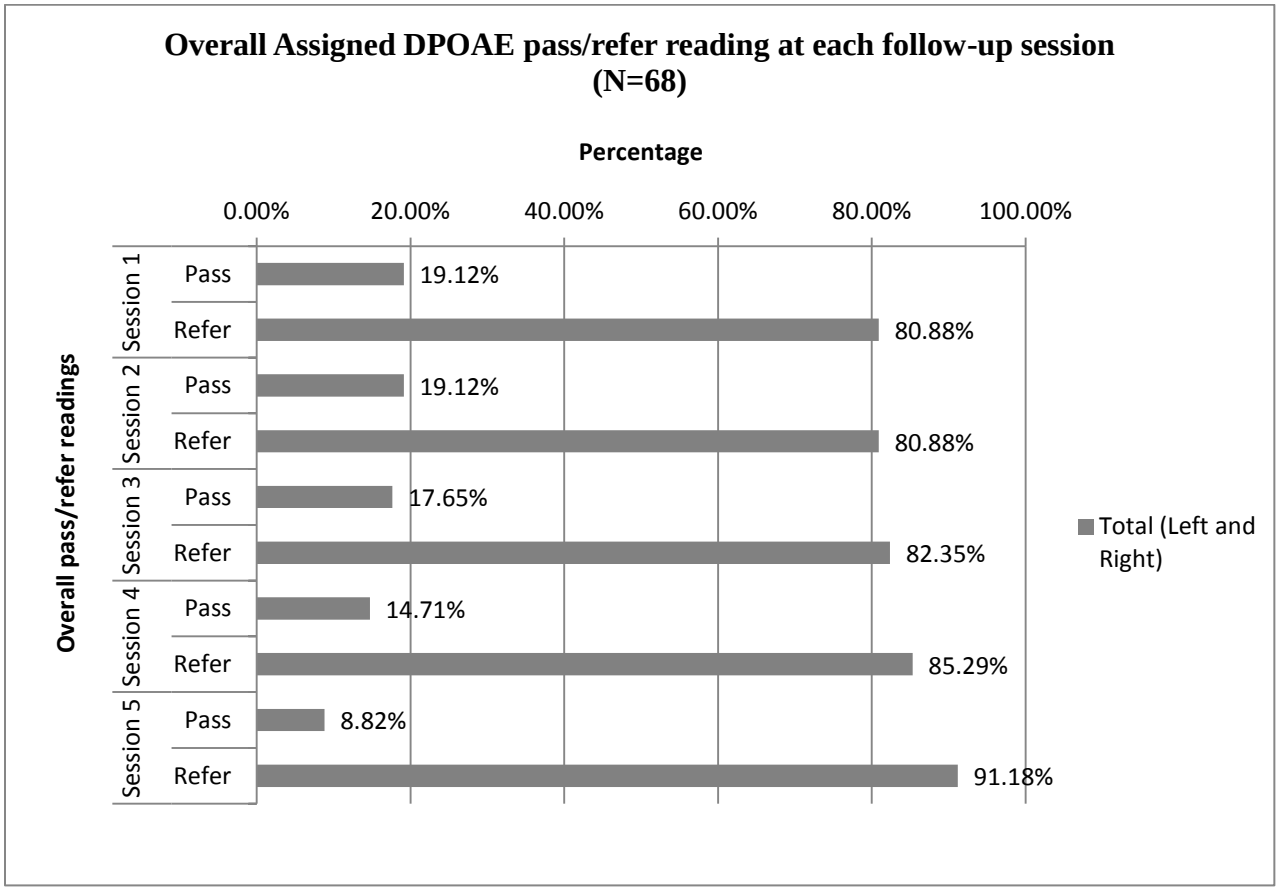


Figure 22

Overall assigned DPOAE pass/refer reading for total sample at each follow-up session

Figure 22, shows the percentage of the overall assigned pass/refer readings at each audiological session. The large percentage of refer readings over the small

percentage of pass readings are clearly visible from Figure 22. Furthermore, the gradual decline of pass readings at each subsequent audiological session is evident from the graph.

3.3.2 Pure-Tone Audiometry

The criteria set by ASHA (1994) according to their guidelines on management of ototoxic hearing loss, were used to indicate ototoxic hearing loss for each participant record, at each PTA assessment. These specific criteria are defined as (1) a 20dB decrease at any one test frequency, (2) a 10 dB decrease at any two adjacent test frequencies, or (3) a loss of response at three consecutive test frequencies where responses were previously obtained.

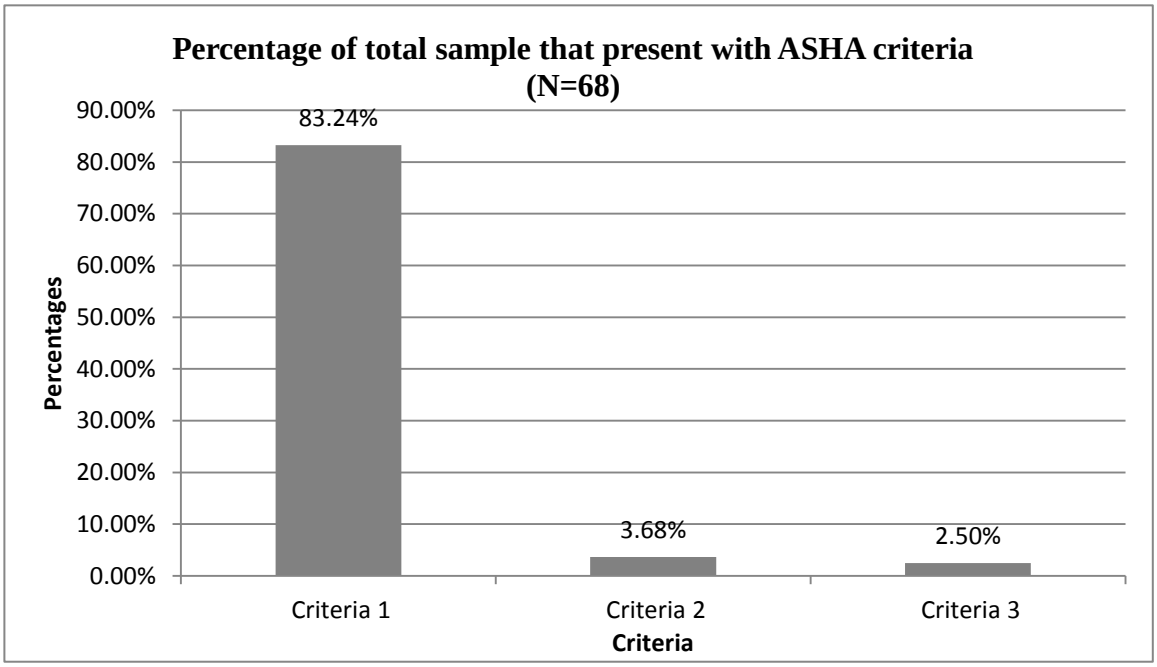


Figure 23

Percentage of total sample that present with ASHA (1994) criteria

The most common seen criteria in the records reviewed were type (1), 83.24% of the sample presented with this criterion. Most type (1) criteria were seen in the patient records reviewed and the 20 dB decrease in PTA threshold took place at the highest

frequencies (10 000 and 12 500 Hz) (Figure 23). This 20 dB decrease was evident from session one. Then gradually, over the remaining four sessions, 20dB decreases were seen across the preceding frequencies. The 20 dB drop gradually moved into the mid-range frequencies (3000-8000 Hz) and was even seen in the low range frequencies (250-2000 Hz) with some patient records. Only 3.68% of the records reviewed matched the second criterion, and an even lower percentage matched type (3), 2.5% of the total sample. Of the 68 patient records reviewed, 19 showed two of the three ASHA criteria for defining ototoxic hearing loss. More specifically, five showed criteria (1) and (3), 13 showed criteria (1) and (2) and one showed criteria (2) and (3).

Of the 68 patient records reviewed, all 67 presented with sensorineural hearing loss of some degree and configuration, according to the ASHA (1994) criteria for defining ototoxic hearing loss. Therefore it can be estimated that 98.53% of the group of adults had changes in hearing following long-term MDR-TB treatment. Only one patient, a female, showed no signs of ototoxic hearing loss. Her hearing was within normal limits for all PTA thresholds, except for one response at 12 500 Hz which was 30dB. However, no normative thresholds for HFA are available (Gordon et al., 2005). Her DPOAE readings began with pass readings at the first and second session, but the subsequent sessions were mostly refer readings across the DPOAE frequency range. This may indicate that her hearing was at risk given the DPOAE findings and there is research to suggest that DPOAEs may be reduced before threshold shifts occur at PTA (Bhagat, 2009). It would have been beneficial had she attended follow-up sessions to monitor her hearing status and see if a hearing loss, due to ototoxicity, did develop over a longer period of time. In the total sample of patient records reviewed in this study, all 68 patient records showed a change in hearing function, be that changes in DPOAE function and/or changes in PTA thresholds, following long-term treatment for MDR-TB.

3.4 Statistical results of the relationships between the audiological findings and variables in the total sample

In this section, the possible relationships between the audiological findings (DPOAEs and PTA) and the following factors: age and gender were investigated using inferential statistics.

3.4.2 Logistical regression for DPOAE results in the total sample

This section of the study intended to predict the probability of pass or refer in the DPOAE results.

Table 10

Parameter estimates and Odds of DPOAEs for age and gender effects

	Parameters (B)	S.E.	Wald	df	*P*-value	Exp(B)	95.0% C.I.for EXP(B)	
							Lower	Upper
Age	-0.07	0.01	28.88	1	0.00	0.93	0.91	0.95
Gender(1)	-0.03	0.22	0.02	1	0.89	0.97	0.63	1.50
Constant	-0.01	0.55	0.00	1	0.98	0.99		

Table 10 represents the independent variables (age and gender effects) that may have significantly affected the DPOAE results over the five DPOAE screening sessions. The table clearly indicates that age is statistically significant ($p<0.05$), whereas the gender effect is non-significant ($p>0.05$). The Odds of a DPOAE result as being a pass reading, decreases by 0.93 as a patient's age increases every year i.e. the effects of aging, as the parameter of age is negative. That is, generally the probability of passing on DPOAEs decreases with a patient's age. For that reason, hearing function related to DPOAE results, decreases as a result of presbyacusis; but more significantly, the chances of passing DPOAE testing decreases as patients continue through monthly assessments related to ototoxic hearing loss, as seen in the DPOAE results section.

3.4.2 Analysis of Covariance (ANCOVA) for PTA results in the total sample

Table 11

ANCOVA Test Results of Between-Subject Effects for Independent Variables (age and gender) for PTA frequencies (250-12500 Hz) in total sample (N=68)

Tests of Between-Subjects Effects									
Dependent Variable: Pure Tone Audiometry									
	250Hz	**500Hz**	**1000Hz**	**2000Hz**	**4000Hz**	**6000Hz**	**80000Hz**	**10000Hz**	**12500Hz**
	***p*-value**	***p*-value**	***p*-value**	***p*-value**	***p*-value**	***p*-value**	***p*-value**	***p*-value**	***p*-value**
Age	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Gender	0.22	0.73	0.62	0.76	0.02	0.04	0.05	0.16	0.08
R value	0.07	0.06	0.07	0.08	0.15	0.18	0.21	0.25	0.28

Table 11 is a summary of the ANCOVA analysis of between-subjects results for the variables of gender and age in the total sample across the PTA frequencies. In the ANCOVA analysis, across all the PTA test frequencies, the interaction effects for the variable of age had *p*-values of < 0.05. Therefore the independent variable of age is significantly different from zero. Therefore the hypothesis is rejected and the interaction effects of age are significant in this study. Whereas, the interaction effects for the variable of gender is non-significant ($p > 0.05$) across the PTA test frequencies, except for the interaction effect at 4000-8000 Hz ($p<0.05$). Therefore for all the other gender interactions across the PTA frequencies, the hypothesis is accepted and the interaction effects of gender are non-significant. However for 4000-8000 Hz, the gender interaction effect is significant. These results will be discussed further in the next chapter of this study.

The R-squared values, indicates the total variance that the four interaction variables of gender, ear and time, have on PTA threshold results, whilst controlling for the effects of age (the covariate). At 250-2000 Hz, the total variance for PTA thresholds range between 61–83, and from 4000-12 500 Hz, the total variance increases to 146 and

continues to increase to 278. This means that after controlling for the age effect on the response variable, by accounting for age-related hearing loss in the exclusion criteria, the other variables explain the remaining variation in PTA thresholds. It has already been stated that ear effect was only found to be clinically significant at session two (6000 Hz) and session five (12 500 Hz). The R-values at these frequencies suggest that age was accountable for 25% of the PTA changes at 6000 Hz and 49% of PTA changes at 12 500 Hz. 25% is minimal in comparison the remaining 75% change that the other variables may be accountable for. Whereas, 49% is a larger percentage that age may be accountable for. The interaction effects of all the variables will be discussed in the next chapter.

Table 12

ANCOVA parameter estimates for age and gender for PTA results across all test frequencies

Parameter Estimates		
Dependent Variable: Pure Tone Audiometry		
P-values		
	Gender	**Age**
250 Hz	0.22	0.42
500 Hz	0.73	0.38
1000 Hz	0.62	0.47
2000 Hz	0.76	0.49
4000 Hz	0.02	0.45
6000 Hz	0.04	0.57
8000 Hz	0.05	0.62
10 000 Hz	0.16	0.86
12 500 Hz	0.08	1.27

Table 12 shows the parameter estimates of gender and age for PTA of the dummy variables resulting from the categorical variables, across all test frequencies. Table 12 shows that across all the PTA test frequencies, 250-12 500 Hz, only gender is statistically significant ($p<0.05$) at 4000-8000 Hz. Age is non-significant ($p>0.05$) and the positive parameters of age at each frequency, indicate that the older the person, the higher the PTA threshold at each frequency. An increase of one year in age results in the increase of the PTA threshold at that frequency; and it is evident that age steadily increases in this group of adults on MDR-TB treatment. The current study did control for age-related hearing loss by excluding records of patients older than 49.11 years old.

CHAPTER FOUR
DISCUSSION

4.1 Introduction

As research literature supports, the relationship between anti-tuberculosis medications and hearing loss (Duggal & Sarkar, 2007; Human et al., 2010) has been well documented. The current study looks at this relationship and adds relevance to the audiological and pharmaceutical fields within a South African context. The results following the retrospective review of hearing function in adults on long-term MDR-TB treatment are discussed below in order of the audiological investigations they underwent.

4.2 Discussion of the sample

The sample consisted of 35 (51%) female records and 33 (49%) male records, between the ages of 18.00 and 49.11 years with a mean age of 33.4 years. The relatively small sample size, in relation to the large number of adults with MDR-TB within KwaZulu-Natal, was limited to available records that corresponded with the inclusion and exclusion criteria of the study. Therefore those records that indicated ages below 18.00 years and above 49.11 years, poor monthly adherence to audiological assessments, case history of previous hearing loss or conductive hearing loss, and defaulting of MDR-TB drug regimens were not considered in this retrospective study. However, the fact that the data were collected from a public health service hospital which provides health care service to the majority of South Africans, as opposed to a hospital within the private sector, the sample is more representative of the South African population. Acknowledgement has been made that the data were collected from only one institute, and generalisation to the larger South African population living with MDR-TB is limited. The proportion of male (49%) to female (51%) patient files was very similar in the total number of patient files reviewed. Therefore, gender effects, if any can be more equally discussed in this study.

4.3 Otoscopic examination and Tympanograms

In accordance with the inclusion and exclusion criteria set out for this study, only patient records with obstruction-free ear canals and Type A tympanograms at each audiological investigation, were considered for review. According to their

records, all 68 patient records revealed obstruction-free ear canals and Type A tympanograms at all five audiological sessions, including the baseline audiological investigation. These audiological tests were repeated measures, therefore the chances of false-positives arising are reduced and the results are more reliable and valid. The presence of type A tympanograms was used as an inclusion criterion to rule out common audiological impairments such as middle-ear infections and wax obstructions, that may confound the findings of this study. The implications of having conductive hearing losses in this study, would affect DPOAE and PTA results in a different way that a sensorineural hearing loss would; and therefore confounding variables would enter into this study. Conductive losses typically affect the lower frequencies in PTA, and DPOAEs results are usually absent (Glattke & Robinette, 2007; Martin & Clarke, 2003). A Type A tympanogram indicates normal middle-ear pressure and compliance or a sensorineural hearing loss, where all other types indicate other abnormal findings (Margolis & Hunter, 2000). Therefore it can be assumed that the patients, whose records were reviewed, presented either with normal hearing or a sensorineural hearing loss on tympanometry during their five months of audiological investigations. Further audiological testing is needed to verify findings and validate audiological testing using the cross-check principle (Shoup & Roeser, 2007). Therefore audiological testing has to be conducted in a battery of measures in order for accurate outcomes to be obtained (Sweetow & Sabes, 2008). Therefore it can be assumed that, in conjunction with the findings of DPOAEs and PTA, patients who presented with type A tympanograms were presenting with a probable sensorineural hearing loss.

4.4 DPOAEs

Screening DPOAEs were conducted at each audiological session, and yielded either a pass or refer reading for frequencies 250-8000 Hz. DPOAEs are a measurement of function and not threshold; a pass reading indicated that outer-hair cell function at that frequency was intact and hearing function as a result is unchanged. A refer reading indicated the opposite, and that hearing function would be altered by damage to the outer-hair cells of the cochlear (Bhagat, 2009). DPOAEs are considered a benchmark for detecting hearing dysfunction related to ototoxic hearing damage (Glattke & Robinette, 2007; Hall, 2000). The DPOAE results in this study were clinically and statistically investigated according to the changes the results had

on hearing function over time and also if other variables such as age, gender and ear difference impacted on these changes over time.

The left and right ear DPOAE findings at all five sessions revealed some numerical differences in pass and refer readings for certain frequencies at certain sessions. However no definite trend could be ascribed to these findings and fluctuating differences between left and right ear readings were evident. The fluctuating differences can be explained by some of the literature that suggests lower frequencies are not as affected by ototoxic medication as the higher frequencies (Campbell, 2007) because the pathophysiological and pharmacological mechanism of aminoglycosides drugs operate in such a way that hair-cells responsible for higher-frequency function are damaged first, followed by the mid- and lower-frequency hair-sites (Steyger & Karasawa, 2008). Statistically, the ear performance effect was non-significant across all five sessions. Indicating that in this study, no ear performed better or worse for DPOAEs. The above findings imply that the changes in hearing have taken on a more bilateral configuration; indicative of an ototoxic induced hearing loss (Konrad-Martin et al., 2005; Steyger & Karasawa, 2008). Specific literature could not be found suggesting ear difference in DPOAEs in the presence of ototoxic induced hearing loss. Conversely, the congruency in findings can be explained by literature regarding the close correlation between left and right ear responses for DPOAEs (Hall, 2000) and in a study by McFadden, Martin, Stagner and Maloney (2009) on DPOAE differences, no ear difference in DPOAE results were found.

The total (left and right ear) readings from this current study, with regards to the overall number of refer readings across the five sessions, were interesting in that the results revealed high numbers of refer readings. This is not surprising because in the presence of hearing dysfunction, DPOAE results will present as refer readings (Hall, 2000). Similar studies that looked at ototoxicity and hearing function did not include OAEs in their investigations (De Jager &Van Altena, 2002; Peloquin et al., 2004); so no comparisons to this current study could be made. However, large volumes of research exist regarding OAE sensitivity to pre-clinical changes and their value in detecting frequency-specific hearing damage in OHC functioning (Hall, 2000 & Konrad-Martin et al., 2005). This makes DPOAEs highly valuable in early detection of ototoxic hearing loss. This lack of information with regards to DPOAEs and ototoxicity highlights the need for more studies to be conducted in this context

that will include DPOAEs as part of the audiological investigations, so that effective and sufficient audiological data is available regarding this population of adults.

As for the total DPOAE readings and the calculated number of adults who showed a change in hearing function (with regards to DPOAE function) over all five sessions and across all eight frequencies tested; these results were significant in this study as they revealed the presence of hearing dysfunction (i.e. refer readings) starting from session one at all the test frequencies through to session five. This is unexpected because this study's exclusion criteria stipulated participants with records of history of hearing loss and middle-ear pathologies be excluded; it was assumed that the records reviewed would be of patients with normal hearing sensitivity from the initial audiological assessment. Thus implying patients would present with a considerable number of pass readings for the DPOAE frequencies at the initial evaluation. However, most records reviewed displayed refer readings, as early as the initial evaluation and at the low frequencies. These results indicate that a hearing loss was already beginning when audiological measurements began, because OAEs are highly sensitive to pre-clinical (i.e. PTA threshold) changes (Konrad-Martin et al., 2005) especially changes related to ototoxicity (Khoza, 2007). Similarly, De Jager & Van Altena (2002) reported on the rapid appearance of ototoxic hearing loss within five days of drug administration. The presence of both pass and refer readings at all sessions and all frequencies could be due to three effects; firstly DPOAEs aid in the early identification of the start of ototoxic hearing loss, secondly that OAE's are present in 99% of all ears (Hall, 2000) and thirdly that no DPOAE changes can occur in early exposure of ototoxic drugs (Bhagat, 2009). The large percentage (84%) of the sample that showed a refer reading for DPOAEs revealed that the majority of the patients' whose records were reviewed, showed a change in hearing function for DPOAEs over time. As with the above findings, the leading features in all the results are the high number of refer readings, as opposed to the number of pass readings at high frequencies (i.e. 6000-8000 Hz) across all five sessions. This above trend is consistent with literature (Campbell, 2007; Duggal & Sarkar, 2007; Konrad-Martin et al., 2005) that supports the notion that ototoxic hearing loss is characterized by changes in high-frequency hearing function, followed by changes in the mid and low frequencies (Konrad-Martin et al., 2005).

Another variable that was investigated with relation to changes in DPOAE function was that of gender effect. There was also no statistical significance with

regard to gender differences in the DPOAE results across all five sessions and all frequencies. This finding is consistent with literature by Schmuziger et al. (2006) who assert that DPOAE amplitude is not influenced by gender. With regards to age as a variable affecting hearing fucntion related to DPOAEs, age was found to be statistically significant ($p<0.05$). That is, the probability of obtaining a pass result for DPOAEs decreases with age. These findings are supported by literature regarding the poor performance on OAEs with the deterioration of hair-cell function due to age (Hall, 2000), but most specifically at the ultra-high frequencies. The findings, in the current study, are concerning as age-related hearing loss was mostly accounted for in the exclusion criteria of this study. More research is required to confirm this age-related association in the presence of ototoxic hearing loss.

For that reason, the statistical significance that time has on DPOAE functioning when ototoxic treatment is present needs to be discussed. The statistical value of p (<0.05) for the time effect across sessions one to three were significant, and the odds of passing the DPOAE screening gradually decreases from session one through to session four; therefore over time the damage to outer hair cell functioning increased. In studies by Duggal and Sarkar (2007) and Li and Steyger (2009) regarding aminoglycosides and ototoxicity, prolonged exposure to ototoxic medication causes hair-cell damage in the cochlea that begins in the high-frequency range and progresses into the lower and mid-frequency range of the cochlea. Interestingly, the p-value at session four was non-significant ($p>0.05$). This could be attributed to the fact that all significant changes in hair cell function had already occurred, at the earlier sessions (De Jager & Van Altena, 2002; Li & Steyger, 2009) and that variability in the progression of ototoxic hearing loss is documented (Mudd et al., 2010). This highlights the need for standardised audiological ototoxic monitoring programmes, so that these changes can be identified early in the treatment process of MDR-TB and more information about such variability regarding ototoxic hearing loss patients can be obtained and better patient counselling and care can take place.

The hearing function related to DPOAE results, may decrease as a result of age; but more significantly, the chances of passing DPOAE testing decreases as patients continue through monthly assessments related to ototoxic hearing loss. A number of audiological disorders affect DPOAEs; such conditions include increasing age and ototoxicity and can present similarly in DPOAE results. The changes seen in

DPOAE function in this study are more related to ototoxic hearing loss as age was accounted for in the exclusion criteria of the study. It is clear from the above that the DPOAE screening in this population of adults on long-term MDR-TB treatment, has revealed the prolonged effects ototoxic medication has on hair cell function, specifically the primary effects on the higher frequency regions of the cochlea. Current findings suggest the need for further studies regarding audiological investigations into ototoxic hearing loss with DPOAEs be conducted so that literature pertaining to this context can account for variables such as age, gender and ear.

4.5 High-Frequency Pure Tone Audiometry

The next audiological investigation that was clinically and statistically analysed was that of PTA threshold results. PTA was conducted at all five sessions and the tested frequency range went up to 12 500 Hz. Internationally, PTA forms the basis of any hearing assessment (Roeser & Clark, 2007) and PTA is conducted to determine the presence, type, and degree of hearing loss in the peripheral auditory system based on behavioral responses to acoustic stimuli (ASHA, 2004). Intensity changes in hearing function were expressed in dB and clinical changes were described using Silman and Silverman's (1991) classification of hearing loss system according to the mean thresholds for left ear, right ear and total threshold results.

The results for left and right ear mean thresholds indicated that no changes in hearing thresholds at low frequencies (250-1000 Hz) from session one to session four occured, but rather at higher frequencies. Similarly, at session one the PTA thresholds for left and right ears were all within normal limits across the conventional PTA frequency range. Hearing changes in PTA were evident at the ultra-high frequencies (10 000 and 12 500 Hz). This collection of findings for left and right ear threshold results at session one, could be explained in two ways. Namely, that changes in hearing function due to ototoxic agents are characterised by damage to the high-frequency in the cochlea (Harrell, 2002); and if any earlier damage to hearing function was present, PTA is not sensitive enough to detect early onset-ototoxic hearing loss, like DPOAEs are (Bhagat, 2009; Konrad-Martin et al., 2005). Therefore ototoxic audiological protocols should include multiple audiological investigations that can supplement and validate audiological findings (ASHA, 1994; WHO, 2010d).

Overall, there was steady decline in left and right ear PTA thresholds across the frequency range and across the five sessions of audiological testing. The most

significant clinical changes occurred at the fifth session and at the highest frequencies in this group of adults on MDR-TB treatment. In a study by Duggal and Sarkar (2007), that also looked at the audiological outcomes of patients with MDR-TB on long-term treatment, found similar results with regards to sloping high frequency hearing loss. Likewise, in another study by De Lima et al. (2006), which investigated hearing impairment in individuals with TB using HFA testing, found the hearing loss was most severely affected at the high frequencies, and mostly bilateral and sensorineural in nature. These findings in relation with this currents study's findings means a trend can be established in developing countries on the presentation of hearing changes in patients on long-term MDR-TB treatment.

Surprisingly, ear and gender had some significant standing at a few frequencies at some of the sessions, but little overall clinical significance at session one, session three and session four for each separate set of ear results. Literature previously published explains these inconsistent findings with regards to ear and gender effects. Inter-patient variations do exist and ototoxicity can be unpredictable, with individual variations in degree and range of hearing loss, susceptibility to ototoxic hearing loss and onset of hearing loss being evident (Begg & Barclay, 1995; Mudd et al., 2010). Another study investigating HFA (Wiley et al., 1998) found similar significant ear and gender effects at some lower frequencies, but no gender differences were observed in their threshold sensitivity at high frequencies. The inability for this current study, and others, to provide definite trends in gender and ear findings suggest that the hearing losses described had taken on a very bilateral configuration indicative of an ototoxic induced hearing loss (Konrad-Martin et al., 2005; Steyger & Karasawa, 2008); and additional studies need to be done in South Africa to offer more research regarding these trends. A bilateral hearing loss severely impacts on an individual's communicative abilities, more than a unilateral hearing loss (Khoza, 2007). Providing counselling and rehabilitative measures, such as hearing amplification, may help patients deal with impaired localisation of sound skills and possible communication difficulties.

In further describing the hearing loss in the sample that presented with clinical hearing loss in this study, the final results revealed a distinct mild-profound sloping SNHL. These results are consistent with literature that describes ototoxic hearing loss as a bilateral sensorineural hearing loss (Castillo & Roland, 2007). The severity of the hearing loss was more evident in the fifth PTA session. Statistically, the interaction

effects of time and age were significant across the entire five sessions and across the entire frequency range.

Similarly, a study with adults aged 48-92 years old found that hearing sensitivity, for ultra-high frequencies, increased with advancing age (Wiley et al., 1998). The study by Wiley et al. (1998) is useful in explaining the significance age had on the hearing threshold changes in the current sample. Other studies are in agreement that advancing age is a risk factor in the development of hearing loss in the presence of ototoxic medications (Kondrad-Martin et al., 2005). However, this current study controlled for advanced age by excluding participant records over 49.11 years of age. Other studies evidenced that ototoxicity is more common in adults than in neonates and children (Mudd et al., 2010). Therefore, the findings that age was significant have more implications regarding the need for ototoxic monitoring programs in the adult population.

Current findings in as far as PTA threshold changes are concerned revealed that time has a significant effect on thresholds when ototoxic treatment is being administered. Audiological changes were present in earlier sessions, but less severe and only at later frequencies. These findings are consistent with studies mentioned earlier (Duggal & Sarkar, 2007; De Jager & Van Altena, 2002), that also investigated HFPTA in adults on long-term treatment for MDR-TB. Findings from all these studies revealed mild-severe sloping sensorineural hearing losses that are consistent with research regarding the characteristics of ototoxic hearing loss (Castillo & Roland, 2007) and that lengthy exposure to ototoxic agents causes this type and degree of hearing loss. The presence of such a profound hearing loss has implications for the quality of life that such patients face and the role audiologists have on early and effective ototoxic monitoring programmes.

ASHA (1994) established three criteria to interpret PTA thresholds as being an ototoxic hearing loss or not. ASHA established these criteria because monitoring for ototoxicity is not a common practice among audiologists and ototoxic treatment procedures. Measurement and monitoring procedures tend to be inconsistent, and criteria for interpreting audiological results do not exist (ASHA, 1994). In this study it was found that the majority of the records showed type (1) criterion (83.24%); and only a small percentage of the records reviewed showed type (2) and type (3) criteria i.e. 3.68% and 2.5% respectively. As discussed, ototoxicity causes damage to the auditory structures responsible for high-frequency sound interpretation first. This is

seen in the large percentage of type (1) criteria where 20 dB drops in responses are evident across the monthly sessions; and the criterion was most evident at the highest frequencies (i.e. 8000-12 500 Hz). This criterion was most evident at session one and gradually, over the remaining four sessions, 20 dB drops were seen across the preceding frequencies. All the patients had already begun MDR-TB drug administration before being referred for audiological investigations. This decrease in hearing sensitivity is consistent with literature which shows evidence of hearing loss seen within five days of aminoglycoside treatment commencement (De Jager & Van Altena, 2002). The time of onset of ototoxic hearing loss is unpredictable; and hearing loss may be evident after a single dose of treatment is given or several weeks after treatment has ended (De Jager & Van Altena, 2002). Risk factors and genetic predisposition may play a role in the development, and rate of development, of ototoxicity (De Jager & Van Altena, 2002; Konrad-Martin et al., 2005). This literature may explain the earlier appearance of ototoxic hearing loss in some patients than in others. The hearing loss gradually moved into the mid range frequencies and was even seen in the low range frequencies with some patients. Hearing loss due to ototoxicity is predominantly in the high frequencies (Økstad, Laukli & Mair, 1988) and is most pronounced in the ultra-high frequencies (Dreschler, van der Hulst, Tange & Urbanus, 1985; De Seta, Bertoli & Filipo, 1985). The hearing loss gradually becomes evident in the lower frequencies throughout the treatment course (Fausti et al., 1994; De Jager & Van Altena, 2002; Schacht, 1998). Over time, highly ototoxic regimens can cause severe to profound hearing losses across the frequency spectrum (Duggal & Sarkar, 2007). The ASHA (1994) criteria used to indicate and define ototoxic hearing loss can all be done using pure-tone audiometry assessment, what is important is the frequency range that is incorporated to detect the three criteria i.e. HFA. HFA is successful in the early detection of ototoxicity (Dreschler et al., 1985) and is important in monitoring programmes as it provides warnings to take preventative and managerial measures before the frequencies, at which conversational speech occur, are affected (Schmuziger et al., 2007).

A large limitation of using HFA is that there are no normative values for HFA thresholds (Schmuziger et al., 2007), due to issues such as lack of calibration standardisation, instrumentation, difference in testing procedures and inter-subject threshold variability (Gordon et al., 2005; De Set et al., 1985). Yet it is the most valuable and used measurement for detecting ototoxic-induced hearing loss (Frank,

1990; Gordon et al., 2005). Intra- and inter-subject variability are said to be due to the complex physical interactions of HF pure tones that may result in standing waves in the ear canal (Schmuziger et al., 2007).

Despite the limitations of HFA use, a number of studies can justify the relevance and value of HFA with regards to repeatability and some threshold estimates. Dreschler et al. (1985) reported that HF reproducibility is almost as good as the reproducibility of the conventional frequency range (250-8000 Hz). Frank (1990) conducted HFA (10 000-20 000 Hz) with circumaural headphones, on 100 normal hearing adults, with an age range of 18-28 years old. The study found that test-retest thresholds were within the clinically acceptable range of ±1 0dB for each ear, for 95% of the subjects. Frank and Dreisbach (1991) found that HF thresholds were also repeatable and within a clinically acceptable range of ±10 dB in a study conducted with 50 otologically normal, mixed gender subjects using HFA with circumaural headphones. In a later study by Frank (2001), repeated thresholds for HFA were well within ±10 dB and had exceptionally low false-positive rates in reference to the ASHA (1994) criteria for a significant threshold shift due to ototoxicity. Another study by Schmuziger et al. (2004) made use of 138 otologically healthy mixed gender subjects with an age range of 12-51 years old. The study indicated 94% test-retest repeatability was within 10 dB for frequencies 500-16 000 Hz, with the 500-12 500 Hz having excellent and the best repeatability with circumaural headphones. More recent studies investigate HFA thresholds. As reported by Comastri, Martin, Simon, Angarano, Dominguez, Luzzi, Lanusse, Ranieri and Boccio (2008), 70 patients of both genders, who were considered normal subjects, aged between 20 and 50 years presented with hearing within normal limits when tested at frequencies 8000-14 000 Hz. In another study by Singh, Saxena and Varshney (2009), 50 normal patients of differing ages and gender with no history of hearing loss, ototoxic drug or noise exposure, were tested using ultra-high frequency PTA (8000-20 000 Hz). In the age groups ranging from 10-50 years old, the patients presented with hearing thresholds within normal limits for the ultra-high frequencies tested. The above findings lend to the reliability of the audiological findings, especially the value of HFA, in the current study.

It is here that converging evidence from all the audiological investigation reviewed can be applied. The type A tympanograms can now be confirmed as a sensorineural hearing loss, as opposed to the other alternative (i.e. normal hearing)

with certainty. The DPOAE and PTA results show similar patterns of change in that the low- and mid-frequencies are affected by peripheral ear damage earlier than expected but with less severity; and the most change in ear function is seen at the high frequencies at the final audiological session; due to the pathophysiological and pharmacological mechanisms that aminoglycosides drugs show over long exposure times (Steyger & Karasawa, 2008). All the audiological test results indicate that this group of adults presented with sensorineural hearing loss of some degree and configuration over the five session time period. Some of these variations in the presentation, degree and range of hearing loss did exist for the ototoxic induced hearing loss (Konrad-Martin et al., 2005) as seen in this sample. Similar damaging effects on the human cochlea and other auditory changes can present as some of the criteria of ototoxic hearing loss, such as presbyacusis (Økstad, Laukli & Mair, 1988), HIV-related hearing loss (Roland, Alexiades, Jackman, Hillman & Shapiro, 2003) and excessive noise exposure (Schmuziger et al., 2007). However pre-existing HL, NIHL and presbyacusis were accounted for as exclusion criteria in this study. Therefore within this time frame, the only remaining possible hearing deficit in this study is that of ototoxicity.

CHAPTER FIVE
CONCLUSION, LIMITATIONS AND RECOMMENDATIONS

5.1 Theoretical Framework and Context of Study

TB remains a world-wide pandemic; with MDR-TB on the rise globally (WHO, 2009a) and as of 2010, South Africa had about 11 000 cases of MDR-TB (2010b). Along with the increasing MDR-TB infections, the use of aminoglycosides is also on the rise in South Africa (Human et al., 2010). The ototoxic effects of MDR-TB treatment cause permanent, sensorineural hearing loss (Human et al., 2010) that has negative effects on an individual's life socially, vocationally and emotionally (Ross & Deverell, 2004; Khoza-Shangase et al., 2009; Swanepoel, 2006). Despite the above findings, no standardised ototoxic monitoring programme is available to audiologically identify, monitor and manage such patients so that appropriate counselling and rehabilitative measures can take place. There is also no uniform drug regimen that will best facilitate the treatment of MDR-TB but also address adverse side-effects of the treatment. The record review took place at Murchison Hospital in KwaZulu-Natal province. This province has one of the worlds and South Africa's highest MDR-TB rates (WHO, 2010b; Zager & McNerney, 2008). This theoretical framework provided a necessary and urgent milieu for the content and context of this study.

The aminoglycosides are an umbrella term for anti-TB drugs. They have been used to treat TB since the 1940's (Begg & Barclay, 1995; Konrad-Martin et al., 2005). However, MDR-TB is resistant to first-line anti-tuberculosis drugs (Zager & McNerney, 2008). Well documented adverse effects of anti-TB drugs have been reported (Duggal & Sarkar, 2007) and undoubtedly the most significant limitation of the therapeutic use of aminoglycosides is their toxic and adverse effects on the auditory system (Konrad-Martin et al., 2005; Schacht, 1998). It would seem that preventing further cases of MDR-TB would require following an effective antituberculosis drug therapy regime. However, managerial supervision and provision of services appears to be a large hindrance to these regimens (Villarino et al., 1992). In South Africa such services are limited and resources scarce. Hospital institutions need to reduce patient-patient transmission of MDR-TB and improve early detection and management of infectious and at-risk patients. Many patients may go undetected

and remain infectious for prolonged periods of time due to ineffective medical management and long waiting periods for test results (Villarino et al., 1992).

There are studies that investigated the effects of first-line anti-TB drugs on hearing function; they revealed ototoxic irreversible hearing loss, with permanent damage to auditory and vestibular systems (Khoza-Shangase et al., 2009; Konrad-Martin et al., 2005; Li & Steyger, 2009; Peloquin et al., 2004; Schact, 1998). Few studies have investigated the effects of second-line anti-TB drugs on hearing function. The few studies that have investigated the changes in hearing function with long-term use of aminoglycosides, found compelling research with regards to the initial damage being present at the high-frequencies and gradually progressing into the mid- and low-frequencies of hearing range (Duggal & Sarkar, 2007; Jager & Van Altena, 2002). These studies did not include ototoxic-sensitive audiological tests, such as HFPTA or DPOAEs, or age, gender and ear effects in their findings. Therefore the results from this study are useful as all these factors were investigated.

The effects of HIV in this environment cannot be excluded, given the high prevalence of HIV in South Africa, particularly in KwaZulu-Natal (UNAIDS, 2009), and the high co-infection percentage between HIV and MDR-TB (Suchindran et al., 2009). However, HIV status and blood cell counts were not included in this study as the information was not readily available and the nature of a record review is that the researcher is limited to the data that already exists. Even if the researcher had requested for permission of HIV status and ARV regimens, those HIV positive patients could not be excluded as the sample needed to be a realistic representation of the population at hand; and many patients whose records were reviewed during the data collection had passed away. There is some index of suspicion on the nature of some of the audiological findings that HIV manifests in its own related hearing loss. However, the results indicated a typical-ototoxic hearing loss; with a high-frequency sensorineural hearing loss. Whereas literature suggests, HIV related hearing loss can be conductive, sensorineural and/or central, it can range from mild to profound, it can be gradual or sudden, stable or fluctuating and can be bilateral or unilateral. Otitis media is common and the hearing loss characteristics are often related to the progression of the disease (Khoza, 2007).

There is no standardised ototoxic-sensitive audiological monitoring programme in this country, despite high numbers of TB, MDR-TB and HIV in our population (UNAIDS, 2009; WHO 2010b) and the unquestionable literature regarding

permanent hearing damage from treatment regimens for these infectious conditions (Khoza-Shangase et al., 2009; Duggal & Sarkar, 2007; Human et al., 2010). Therefore the outcomes of this study provide guidance and research data for the establishment of such ototoxic monitoring programmes in a South African context.

5.2 Summary of Main Findings

MDR-TB is a present and concerning illness in South Africa (WHO, 2010b). The study highlighted the severity and prevalence of hearing loss in an adult population receiving long-term MDR-TB treatment in South Africa. While investigating the hearing function in adults on long-term treatment for MDR-TB, findings from the current study indicated that adults receiving long-term MDR-TB presented with significant ototoxic hearing losses.

- All 68 records reviewed revealed clinically clear otoscopic examinations and type A tympanograms at each audiological sessions
- Changes in hearing function were seen in DPOAE and PTA results at all five audiological sessions and across all frequency ranges, with the time effect being the most significant variable in the data
- 84% of the total sample presented with overall refer readings for DPOAEs
- 98.53% of the group of adults presented with criteria indicative of ototoxic hearing loss
- On clinical PTA results, 67 of the 68 records reviewed revealed a mild-profound sloping SNHL
- In the total sample of patient records reviewed in this study, all 68 patients showed a change in hearing function, be that changes in DPOAE function and/or changes in PTA thresholds, following long-term treatment for MDR-TB
- In summary, the hearing loss was mainly bilateral for the clinical PTA results
- Variations in the effects of gender and ear difference were minimal and variations in the presentation of ototoxic hearing loss is common
- Similar presentation, to ototoxic hearing loss, of other degenerative conditions exists; however these conditions were accounted for as exclusion criteria in this study. Therefore the only remaining possible hearing deficit in this study was that of ototoxicity

5.3 Limitations of the Current Study

The study set out to investigate hearing function in a group of adults on long-term MDR-TB, and provide relevant data regarding ototoxic hearing loss and in turn potential future recommendations for appropriate ototoxic monitoring programmes in South Africa. The nature of the study was that of a retrospective records review; therefore many of the limitations in the study are directly related to the fact that the researcher was limited to the information already available. The findings of this study need to be considered in relation to identified limitations of the research:

- The hospital, at which the data were collected, was limited to screening DPOAEs up to 8000 Hz and not diagnostic DPOAE's. DPOAE accuracy is increased when clinical information such as signal-to-noise ratio and primary-tone frequencies are available (Bhagat, 2009). Had the hospital site had access to diagnostic OAE machinery that tested up to the same frequency that the PTA tested up to, more frequency specific results could have been obtained, more comparable high frequency results could have been made, and results described in more detail; increasing the study's validity. However, despite this limitation, the researcher accounted for the limitation by ensuring only records with consistent results for all audiological assessments were reviewed so that repeatability strengthened the validity of the audiological test results.
- As mentioned previously in the literature review; there exists a close link between HIV and TB (Gandhi et al., 2006; Goozé & Daley, 2003; Khoza, 2007; Lawn et al., 2006). However, this study did not consider patients' HIV status. Therefore, there was no co-investigation of hearing function with the possibility of patients having HIV/AIDS, or those possibly on ARV treatment for HIV and the interactions such treatments may have with MDR-TB treatments or the manifestations that HIV has on patients' audiological system. There have been studies investigating the ototoxic effects of ARV's and in combination with MDR-TB treatment may prove even more ototoxic (Khoza-Shangase et al., 2009). Furthermore, it was reported in UNAIDS (2006), that approximately 18.8% of adults, in South Africa, aged 18-49 years old were infected with HIV. Therefore based on these statistics, the sample in this current study were between the ages of 18-49 years, it can be assumed that a percentage of the sample were possibly infected with HIV and possibly on treatment for HIV. For that reason, it would have been useful in this current

study to obtain patient information regarding possible HIV infection and treatment, so this could have been taken into account and or controlled for.

- Patient case history was collected from patient records and subject to information probed by the Murchison audiologist at the time the patient was seen at the hospital. There is well-documented research (Konrad-Martin et al., 2005) that states a genetic predisposition exists for ototoxic hearing loss. Therefore it would have been useful to include a thorough family history when starting a patient on ototoxic medication so those patients who are more at risk can be better counseled regarding their higher risk rates for the development of ototoxic hearing loss. This allows for patients to be better managed and monitored (Konrad-Martin et al., 2005) with regards to best practice standards for audiological care (ASHA, 2004).
- As mentioned previously in the methodology section, it was a pre-existing limitation that record reviews are confined to the available and existing information. Therefore patient records did not include information or details on previous ototoxic drug regimens for other medical conditions or previous ototoxic exposure. Therefore to account for this limitation the researcher excluded any patient record that stated a previous hearing loss of any kind.
- The audiological assessment in patients' records did not account for tinnitus assessment or management. The incidence of tinnitus with ototoxic hearing loss is unknown, as is the relationship between the two; tinnitus can occur with or without ototoxic hearing loss. Having had this information, on whether the patients in this study experienced tinnitus, would have added value in describing hearing function in the presence of ototoxic treatments.
- Making use of statistics from global organisations comes with the drawback of having to deal with countries' compliance in providing up-to-date data on infectious conditions such as HIV, TB and MDR-TB. Mathematical models allow for the generation of global estimates on such conditions. This is the case with most African countries, where large gaps in information exist due to poor patient compliance with treatment, poor diagnostic measures for determining incidences of such conditions and lack of infrastructure and basic medical care (WHO, 2010a).
- Due to the fact that the researcher was dependent on available patient records and whether patients' information matched the inclusion criteria, a larger

sample size could not be gathered. A larger sample size would allow for greater generalisation of the results and findings of the current study. Yet it gives insight into the reality of the current situation within the South African context, where audiological data is not readily available in a population where hearing loss is common in conditions such as TB and MDR-TB.

5.4 Conclusions

This study set out to review the audiological findings of adults on long-term MDR-TB medication. MDR-TB is a present and concerning illness in South Africa (WHO, 2010b). This study has highlighted the severity and prevalence of hearing loss in a South African adult population receiving long-term MDR-TB treatment and prompted the development of an ototoxic monitoring programme to meet the standards of audiological services in South Africa.

In a group of adult patients receiving long-term MDR-TB treatment, all records reviewed showed hearing damage in some form and degree in both DPOAE and PTA results. The hearing loss was evidently found to be due to ototoxic damage to the ear structures. Findings from the study regarding the audiological changes that occur in patients with ototoxic hearing loss, has implications for when audiological management programmes should be implemented. As was evident from both the DPOAE and PTA testing, changes in hearing function were seen from session one, regardless of age, gender or ear performance. It is strongly suggested that audiological monitoring be implemented as soon as MDR-TB treatment commences or, better yet, as soon as the diagnosis of MDR-TB be confirmed so baseline results can be obtained. The high co-morbidity rate between MDR-TB and HIV also has implications for the implementation of an effective and efficient audiological monitoring programme. This population of people are at risk of contracting opportunistic infections. Monitoring systems can help identify and in-turn treat such infections so that further audiological deteriorating can be avoided. Guidelines for the control and prevention of MDR-TB transmission also need to be formulated and implemented in HIV units (Easterbrook, 1996).

Audiological findings from all 68 records indicated that this group of adults presented with sensorineural hearing loss of some degree and configuration over time. The DPOAE and PTA results showed similar patterns of damage as indicated by their audiological implications. The changes began, early, in the high frequencies and then

gradually progressed into the low- and mid-frequencies. The final set of audiological results, indicating the time frame at which ototoxic treatment was the longest, presented with the most significant change in ear function. The cause of the hearing loss was confidently found to be due to ototoxicity due to the drugs pathophysiological mechanisms, the accountability for other auditory dysfunctions as being the cause and the ototoxic-like-characteristics of the hearing loss detected in all audiological tests reviewed in this study.

5.5 Recommendations for Future Directions

Despite the current study presenting with limitations, the study investigated the hearing function of adults on long-term MDR-TB in South Africa. It provided results and insight into the rapid and severe hearing loss that these patients presented with once on MDR-TB treatment. In addition to the valuable data on hearing function, it provides insight and opportunity about the role audiologists in South Africa need to play in the development and maintenance of an ototoxic monitoring programme to meet the standards of audiological services in South Africa. Furthermore, medical staff need to be on high alert for any signs of MDR-TB, especially in immune-compromised patients with HIV (Easterbrook, 1996).

De Jager and Van Altena (2002) found that patients are unlikely to complain of hearing loss until considerable hearing damage has been done. Therefore the ideal programme needs to include aspects of the audiological test battery that will be sensitive and specific to early detection and monitoring of ototoxic hearing loss. It needs to adhere to international and best-practice guidelines and standards; but also needs to be adapted for the South African context. Best-practice suggests the inclusion of detailed case history that includes probing on genetic predisposition to ototoxicity, HFA and diagnostic DPOAEs (ASHA, 2004). The inclusion of tinnitus information, as a part of the audiological assessment would optimise management for patients with ototoxic hearing loss (Konrad-Martin et al., 2005).

As mentioned in the literature review, MDR-TB is a life-threatening condition and the use of treatment that is ototoxic is warranted to preserve life. The preservation of quality of life also falls within the scope of practice of medical professionals who are involved in the treatment, care and management of individuals with MDR-TB (Fausti et al., 2005). The *WHO Guidelines for the Treatment of TB* (2010d), state that patients on treatment for MDR-TB should be monitored for the known adverse side

effects of drug-regimens and major adverse reactions. Monitoring ototoxic hearing loss may not prevent the ototoxic effects of the treatment; however evidence-based modifications to the dosing regimens may lower the adverse effects. This includes dividing dosages, using ancillary drugs, reducing the dosage or replacing the drugs (Campbell, 2007; Lüllmann et al., 2000; Gupta et al., 2008). More studies on the above need to be explored in relation to specific changes seen in the ototoxic hearing loss. Furthermore, an audiological monitoring programme will allow for the evaluation of rehabilitation measures, the confirmation of stable hearing thresholds and also function as an on-going counselling tool regarding the ototoxic hearing loss. Monitoring should ideally continue for at least six months after the cessation of treatment (Mudd et al., 2010) and appropriate hearing loss management and rehabilitation measures should take place to offer patients ,with ototoxic hearing loss, a better quality of life. Part of the role and duty of audiologists, is to provide effective and appropriate rehabilitation to patients diagnosed with hearing impairment. It is in audiologists' professional capacity to maximize the patient's residual hearing and offer education on their condition and possible treatment options (Martin and Clark, 2003). Further research studies need to be conducted to decide on optimal length of the monitoring programme in this context.

Other options to prevent or slow down ototoxic damage is to include protective antioxidants (Schacht, 1998; Steyger & Karasawa, 2008); these antioxidant agents may be too expensive and complex to be included in developing countries treatment protocols, but research showing high numbers of ototoxic hearing loss in the South African context is needed to advocate for such agents to be recommended to this country and other developing countries. Also drug regimens are often chosen on the basis of the local community's resistance pattern (Gupta et al., 2008) and costs. More studies involving the effects of MDR-TB treatment are needed to change drugs and dosages and advocate for cost-effective but protective or anti-ototoxic drug treatments in South Africa. A rapid genetic screening method has been established that is easy, cost effective and efficient at detecting mutations in MDR-TB positive patients prior to the start of aminoglycoside treatment in order to lower the incidence of ototoxic-induced hearing loss (Human et al., 2010). Another interesting study that would give valuable information regarding the outcomes of audiological monitoring programmes in patients with MDR-TB, would be to compare treatment outcomes of partially hospitalized patients with outcomes of patient solely treated as outpatients.

Such a study would also give compellingly demonstration on the advantages of hospitalizing MDR-TB patients and the outcomes this has on MDR-TB incidence and infection rates.

Therefore, it is recommended that further studies in South Africa be done involving the establishment of standardised guidelines for audiological monitoring, within a multidisciplinary team to advocate, effectively assess and manage patients on MDR-TB treatment. Proposed inclusion of the following into an ototoxic-monitoring programme for the South Africa population, based on the findings of this study suggests:

- The following information needs to be obtained in a detailed case history and any changes during the monitoring time need to be obtained: previous or existing hearing loss, family history related to ototoxic hearing loss, the presence of tinnitus, commencement and end-date of ototoxic drug treatments.
- The inclusion of DPOAEs, preferably diagnostic DPOAEs and HFPTA (at least up to 12 500 or 14 000 Hz) in the audiological investigations based on their sensitivity to the early and specific detection of ototoxic hearing damage.
- Counselling measures need to be implemented from the start of monitoring and continue throughout the monitoring process. From this set of results and other literature, aspects regarding the type, degree and severity of the expected hearing loss need to be addressed as well as rehabilitation options post-treatment.

REFERENCES

Alan, A. (2002). *Categorical Data Analysis*. Hoboken: John Wiley and Sons.

American Speech-Language-Hearing Association. (1994). Audiologic management of individuals receiving cochleotoxic drug therapy. (*American Speech-Language-Hearing Association) Practice Policy*. doi: 10.1044/policy.GL1994-00003

American Speech-Language-Hearing Association. (2004). *Scope of practice in Audiology* [Scope of Practice]. Retrieved October 24, 2008. doi:10.1044/policy.SP2004-00192

American Speech-Language-Hearing Association. (2010). *Code of ethics* [Ethics]. Retrieved June 17, 2010. doi:10.1044/policy.ET2010-00309

Amor, B.Y., Nemser, B., Singh, A., Sankin, A., & Schluger, N. (2008). Underreported threat of multidrug-resistant tuberculosis in Africa. *Emerging Infectious Diseases, 14*(9), 1345-1352. doi: 10.3201/eid1409.061524

Armitage, P., Berry, G., & Matthews, J. (2009). *Statistical Methods in Medical Research*. (4th ed.). Massachusetts: Blackwell Science Ltd.

Aziz, M.A., Wright, A., Laszlo, A., De Muynck, A., Portaels, F., Van Deun, A., et al. (2006). Epidemiology of antituberculosis drug resistance (The global project on anti-tuberculosis drug resistance surveillance): an updated analysis. *The Lancet, 368*(9553), 2142-2154.

Bardien, S., Human, H., Harris, T., Hefke, G., Veikondis, R., Schaaf, H.S., et al. (2009). A rapid method for detection of five unknown mutations associated with aminoglycoside-induced deafness. *BioMed Central Medial Genetics, 10*(20). Retrieved November 25 2009, from Open Access database. doi: 10.1186/1471-2350-10-2

Bhagat, S. (2009). Analysis of Distortion Product Otoacoustic Emission Spectra in Normal-Hearing Adults. *American Journal of Audiology, 18*, 60-68.

Begg, E.J., & Barclay., M.L. (1995). Aminogylcosides – 50 years on. *British Journal of Clinical Pharamacology*, 39: 597-603.

Bess, F.H., & Humes, L.E. (2008). *Audiology: The Fundamentals.* (4th ed.). Philadelphia: Lippincott Williams & Wilkins.

Beiter, R.C., & Talley, J.N. (1976). High-frequency audiometry above 8 000hz. *International Journal of Audiology, 15*(3), 207-214. Abstract retrieved from Informahealthcare. http://informahealthcare.com/doi/pdf/10.3109/00206097609071777

Campbell, K.C.M. (2007). *Pharmacology and ototoxicity for audiologists*. New York: Thomson Delmar Learning.

Carhart, R., & Jerger, J. F. (1959). Preferred method for clinical determination of pure-tone thresholds. *Journal of Speech and Hearing Disorders, 24*, 330–345.

Castillo, M.P., & Roland, P.S. (2007). Disorders of the auditory system. In R.J. Roeser, M. Valente, & H. Hosford-Dunn (Eds.), *Audiology Diagnosis* (2nd ed., pp. 77-99). New York: Thieme Medical Publishers, Inc.

Centers for Disease Control and Prevention. (2010). Tuberculosis: Elimination. Retrieved June 23, 2010 from www.cdc.gov/tb/publications/factsheets/elimination/tb.htm

Centers for Disease Control and Prevention. (2011a). Tuberculosis: Elimination. Retrieved December 04, 2010 from http://www.cdc.gov/tb/events/WorldTBDay/resources_global.htm

Centers for Disease Control and Prevention. (2011b). Tuberculosis: Elimination. Retrieved December 04, 2010 from http://www.cdc.gov/tb/publications/factsheets/general/LTBIandActiveTB.htm

Centers for Disease Control and Prevention. (2011c). Tuberculosis: Elimination. Retrieved December 04, 2010 from

http://www.cdc.gov/tb/publications/factsheets/treatment/drugresistanttreatment.htm

Chabon, S.S., & Morris, J. (2005, June/July). Raising Ethical Awareness in the Practice of Speech-Language Pathology and Audiology: A 24/7 Endeavor. *CSHA Magazine*, 6-8. Retrieved October 06, 2008 from http://www.csha.org/raisingethicalawareness

Comastri, S.A., Martin, G., Simon, J.M., Angarano, C., Dominguez, S., Luzzi, F., Lanusse, M., Ranieri, M.V., and Boccio, C.M. (2008). Contrast sensitivity tests and conventional and high frequency audiometry: information beyond that required to prescribe lenses and headsets. *American Institute of Physics, 992*(1), 63-68.

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

De Lima, M.L.L.T., Lessa, F., Aguiar-Santos, A.M., & Medeiros, Z. (2006). Hearing impairment in patients with tuberculosis from Northeast Brazil. *Rev. Inst. Med. trop. Sao Paulo, 48*(2), 99-102. doi: 10.1590/S0036-46652006000200008

De Seta,E., Bertoli, G.A., & Filipo, R. (1985). High-Frequency Audiometry above 8 kHz. *Audiology, 24*, 254-259.

Draper, N.R., & Smith, H. (1998). *Applied Regression Analysis*. New York: Wiley.

Dreschler, W.A., van der Hulst, R.J.A.M., Tange, R.A., & Urbanus, N.A.M. (1985). The Role of High-Frequency Audiometry in Early Detection of Ototoxicity. *Audiology, 24*, 387-395.

Duggal, P., & Sarkar, M. (2007). Audiological monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. *BioMed Central Ear, Nose and Throat Disorders, 7*(5). Retrieved November 25 2009, from Open Access database. doi: 10.1186/1472-6815-7-5

Dye, C. (2009). Drug resistant tuberculosis: biology, epidemiology and control. In Gillespie, S. (Ed.), *Antibiotic resistance: From genes to global prevalence*. The Biomedical & Life Sciences Collection, Henry Stewart Talks Ltd, London. Retrieved June 24, 2010 from http://hstalks.com/lib.php?t=HST98.2444_1_2&c=252

Dye, C., Espinal, M.A., Watt, C.J., Mbiaga, C., & William, B.G. (2002). Worldwide incidence of multidrug resistant tuberculosis. *The Journal of Infectious Diseases, 185*,(8), 1197-1202.

Easterbrook, P. (Ed.). (1996). Multidrug resistant tuberculosis: practical lessons for HIV units [Special issue]. *Genitourinary Medicine, 72*, 313-314.

Editors of Springhouse. (2005). *Professional Guide to Diseases*. (8th ed.). Publications International: Lippincott Williams & Wilkins.

Fausti, S.A., Larson, V.D., Noffsinger, P.D., Wilson, R.H., Phillips, D.S., & Fowler, C.G. (1994). High-frequency Audiometric Monitoring Strategies for Early Detection of Ototoxicity. *Ear & Hearing, 15*, 232-239.

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

Fausti, S.A., Wilmington, D.J., Helt, P.V., Helt, W.J., & Konrad-Martin, D. (2005). Hearing and health care: The need for improved hearing loss prevention and hearing conservation practices. *Journal of Rehabilitation and Research Development, 42*(4), 45-62.

Fife-Shaw, C. (2002). Bivariate Statistical Analyses. In G.M. Breakwell, S. Hammond, & C. Fife-Shaw (Eds.), *Research methods in Psychology* (pp. 350-371). London: SAGE Publication Ltd.

Fire, K. M. (1995). Interpretation of Clinical Test Results. In L.G. Wall (Ed.), *Hearing for the Speech-Language and Health Care Professional* (pp. 171-217). Massachusetts: Butterworth-Heineman.

Fowler, C.G., & Shanks, J.E. (2002). Tympanometry. In J. Katz (Ed.), *Handbook of Clinical Audiology* (5th ed., pp. 175-204). New York: Lippincott Williams & Wilkins.

Frank, T. (1990). High-Frequency Hearing Thresholds in Young Adults Using a Commercially Available Audiometer. *Ear and Hearing, 11*(6), 450-454.

Frank, T., & Dreisbach, L.E. (1991). Repeatability of High-Frequency Thresholds. *Ear and Hearing, 12*(4), 294-295.

Frank, T. (2001). High-frequency (8-16 kHz) reference thresholds and intra-subject threshold variability relative to ototoxic criteria using a Sennheiseer HAD 200 earphone. *Ear & Hearing, 22,* 161-168.

Gandhi, N.R., Moll, A., Sturm, A.W., Pawinski, R., Govender, T., Lalloo, U., et al. (2006). Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *The Lancet, 368* (9547), 1575-1580.

Gelfand, S. A. (2001). *Essentials of Audiology* (2nd ed.). New York: Thieme Medical Publishers Inc.

Gelman, A., & Hill, J. (2007). *Data analysis using regression and multilevel/hierarchical models*. New York: Cambridge University Press.

Gibbon, C.J. (2005). *South African medicines formulary*. (7th ed.). Cape Town: CTP.

Glattke, T.J., & Robinette, M. (2007). Otoacoustic Emissions. In R.J. Roeser, M. Valente, & H. Hosford-Dunn (Eds.), *Audiology Diagnosis* (2nd ed., pp. 478-496). New York: Thieme Medical Publishers, Inc.

Goozé, L., & Daley, C.L. (2003). *Tuberculosis and HIV*. HIV InSite Knowledge Base Chapter. Retrieved May 23, 2010 from UCSF database. http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-05-01-06

Gordon, G.S., Phillips, D., Helt, W.J., Konrad-Martin, D., & Fausti, S.A. (2005). The evaluation of insert earphones for high-frequency bedside ototoxicity monitoring. *Journal of Rehabilitation Research & Development, 42*, 353-362.

Grove, S. K. (2005). *The Practice of Nursing Research: conduct, critique and utilization*. (4th ed.). Philadelphia: Saunders.

Gupta, R., Espinal, M.A., & Raviglione, M.C. (2008). Treatment of Multidrug-Resistant Tuberculosis (Update). In Fauci, A.S., Braunwald, E., Kasper, D.L., Hauser, S.L., Longo, D.L., Jameson, J.L., & Loscalzo, J.: Harrison's principles of internal medicine,http://0-www.accessmedicine.com.innopac.wits.ac.za/updatesContent.aspx?aid=395649.

Hall, J.W. (2000). *Handbook of OAE's*. Canada: Singular Publishing.

Hallmo, P., Sundby, A., & Mair, I.W. (1994). Extended high-frequency audiometry. Air- and bone-conduction thresholds, age and gender variations. *Scandinavian Audiology, 23*(3), 165–170.

Harrell, R.W. (2002). Puretone Evaluation. In J. Katz (Ed.), *Handbook of Clinical Audiology* (5th ed., pp. 71-87). New York: Lippincott Williams & Wilkins.

Health Professionals Council of South Africa. (2008). *Guidelines for Good Practice in the Health Care Professions: General Ethical Guidelines for Health Researchers*. Booklet 6. Pretoria: HPCSA. Retrieved July 1, 2010, from, http://www.hpcsa.co.za/conduct_generic_ethical_rules.php

Howell, D. C. (2008). *Fundamental Statistics for the Behavioural Sciences*. Belmont: Thomson/Wadsworth Learning Inc.

Human, H., Hagen, C.M., de Jong, G., Harris, T., Lombard, D., Christiansen, M., & Bardien, S. (2010). Investigation of mitochondrial sequence variants associated with aminoglycoside-induced ototoxicity in South Africa TB patients on aminoglycosides. *Biochemical and Biophysical Research Communication, 393*, 751-756.

Idemyor, V. (Ed.). (2007). HIV and tuberculosis coinfection: Inextricably linked liaison [Special issue]. *Journal of the National Medical Association, 99*(12), 1414-1419.

Irwin, D.L., Pannbacker, M., Powell, T.W., & Vekovious, G.T. (2007). *Ethics for speech-language pathologists and audiologists: An Illustrative Casebook*. USA: Thomas Delmar Learning.

Jordan, J.A., & Roland, P.S. (2000). Disorders of the Auditory System. In R.J. Roeser, M. Valente, & H. Hosford-Dunn (Eds.), *Audiology Diagnosis* (pp. 85-108). New York: Thieme Medical Publishers, Inc.

Karim, S.S.A. (2008). XDR- and MDR-TB in rural South Africa is caused by exogenous reinfection. *Journal Watch HIV/AIDS Clinical Care*. Abstract obtained May 5, 2010 from http://aids-clinical-care.jwatch.org/cgi/content/full/2008/1027/3

Kemper, E. A., Stringfield, S., & Teddlie, C. (2003). Mixed Methods Sampling Strategies in Social Science Research. In A. Tashakkori, & C. Teddlie (Eds.), *Handbook of mixed methods in social & behavioral research* (pp.273-297). United Kingdom: Sage Publishers.

Khoza, K. (2007). *An investigation and monitoring of the auditory status in a group of adults with AIDS receiving antiretroviral and other therapies attending a HIV/AIDS clinic in Johannesburg, South Africa*. *Johannesburg:* University of the Witwatersrand.

Khoza-Shangase, K., Mupawose, A., & Mlangeni, N.P. (2009). Ototoxic effects of tuberculosis treatments: How aware are the patients? *African Journal of Pharmacy and Pharmacology, 3*(8), 391-399.

Kliiman, K., & Altraja, A. (2009). Predictors of extensively drug-resistant pulmonary tuberculosis. *Annals of Internal Medicine, 150*(1), 766-775.

Knechel, N.A. (2009). Tuberculosis: Pathophysiology, clinical features, and diagnosis. *American Association of Critical-Care Nurses, 29*(2), 34-43.

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

Lawn, S.D., Bekker, L.G., Middelkoop, K., Myer, L., & Wood, R. (2006). Impact of HIV infection on the epidemiology of tuberculosis in a peri-urban community in South Africa: The need for age-specific interventions. *Clinical Infectious Diseases, 42*, 1040-1047.

Li, H., & Steyger, P.S. (2009). Synergistic ototoxicity due to noise exposure and aminoglycoside antibiotics. *Noise Health, 11*(42), 26-32.

Lüllmann, H., Mohr, K., Ziegler, A., & Bieger, D. (Eds.). (2000). *Colour atlas of pharmacology* (6th ed.). Stuttgart: Thieme.

Margolis, R.H., & Hunter, L.L. (2000). Acoutsic Immittance Measurements. In R.J. Roeser, M. Valente, & H. Hosford-Dunn (Eds.), *Audiology Diagnosis* (pp. 381-424). New York: Thieme Medical Publishers, Inc.

Martin, F.N., & Clark, J.C. (2003). *Introduction to Audiology*. (8th ed.). Boston: Allyn and Bacon.

Mayo Foundation for Medical Education and Research. (2011). Tuberculosis. Retrieved December 04, 2011, from http://www.mayoclinic.com/health/tuberculosis/ds00372/dsection=complications

McBurney, D. H., & White, T.L. (2007). *Research Methods*. (7th ed.). Australia: Wadsworth.

McFadden, D., Martin G.K., Stagner, B.B., & Maloney, M.M. (2009). Sex differences in distortion-product and transient-evoked otoacoustic emissions compared. *Journal of the Acoustical Society of America, 125*(1), 239-246.

Mudd, P.A., Edmunds., AL., Glatz., F.R., Campbell K.C.M., & Rybak., L.P. (2010). Inner Ear, Ototoxicity. eMedicine: Otolaryngology and facial plastic surgery update July 1, 2010. http://emedicine.medscape.com/article/857679-overview

Muma, R.D., Lyons, B.A., Borucki, M.J., & Pollard, R.B. (1997). (2nd ed.). *HIV Manual for Health Care Professionals*. Connecticut: Appleton & Lange.

Njaramba, P.J. (2005). *Managing multidrug-resistant tuberculosis in hospitalised patients at Sizwe Tropical Diseases Hospital: A five year review of treatment outcomes*. (Unpublished master's thesis). University of the Witwatersrand, Johannesburg.

Økstad, S., Laukli, E., & Mair, I.W.S. (1988). High-Frequency Audiometry: Comparison of Electric Bone-Conduction and Air-Conduction Thresholds. *Audiology, 27*, 17-26.

Peloquin, C.A., Berning, S.E., Nitta, A.T., Simone, P.M., Goble, M., Huitt, G.A., et al. (2004). Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. *Clinical Infectious Diseases, 38*, 1538-1544.

Provincial Decision-Making Enabling. (2005). A profile of KwaZulu-Natal: Demographics, poverty, inequality and unemployment. Background Paper 2005:1(5). PROVIDE Project, Elsenburg. Retrieved June 30, 2010 from www.elsenburg.com/provide

Rappaport, J.M., & Provencal, C. (2002). Neuro-otology for audiologists. In J. Katz (Ed), *Handbook of Clinical Audiology* (5th ed., pp. 9-32). New York: Lippincott Williams & Wilkins.

Roeser, R.J., Buckley, K.A., & Stickney, G.S. (2000). Pure Tone Tests. In R.J. Roeser, M. Valente, & H. Hosford-Dunn (Eds.), *Audiology Diagnosis* (pp. 227-251). New York: Thieme Medical Publishers, Inc.

Roeser, R.J., & Clark, J.L. (2007). Pure-Tone Tests. In R.J. Roeser, M. Valente, & H. Hosford-Dunn (Eds.), *Audiology Diagnosis* (2nd ed., pp. 238-260). New York: Thieme Medical Publishers, Inc.

Roeser, R.J., Valente, M., & Hosford-Dunn, H. (2007). Diagnostic Procedures in Audiology. In R.J. Roeser, M. Valente, & H. Hosford-Dunn (Eds.), *Audiology Diagnosis* (2nd ed., pp. 1-16). New York: Thieme Medical Publishers, Inc.

Roland, J.T. Jr., Alexiades, G., Jackman, A.H., Hillman, D., & Shapiro, W. (2003). Cochlear Implantation in Human Immunodeficiency Virus-Infected Patients. *Otology & Neurotology, 24(*6), 892-895.

Ross, E., & Deverell, A. (2004). *Psychological approaches to health, illness and disability: A reader for health care professionals*. Pretoria: Van Schaik Publishers.

Schacht, J. (1998). Aminoglycoside ototoxicity: Prevention in sight*? Otolaryngology - Head and Neck Surgery, 118*(5), 674-677.

Schiavetti, N., & Metz, D.E. (2002). *Evaluating Research in Communication Disorders*. (4th ed.). Boston: Allyn & Bacon.

Schmuziger, N., Probst, R., & Smurzynski, J. (2004). Test-Retest Reliability of Pure-Tone Thresholds from 0.5 to 16 kHz using Sennheiser HAD 200 and Etymotic Research ER-2 Earphones. *Ear & Hearing, 25*, 127-132.

Schmuziger, N., Lodwig, A., & Probst, R. (2006). Influence of artifacts and pass/refer criteria on otoacoustic emission hearing screening. *International Journal of Audiology, 45*, 67-73.

Schmuziger, N., Patscheke, J., & Probst, R. (2007). An Assessment of Threshold Shifts in Nonprofessional Pop/Rock Musician Using Conventional and Extended High-Frequency Audiometry. *Ear & Hearing, 28*(5), 643-648.

Sharma, A., & Garavaglia. S. (1998). *A Smart Guide to Dummy Variables: Four Applications and a Macro*. New Jersey: Murray Hill. Retrieved February 08, 2012, from http://www.ats.ucla.edu/stat/sas/library/nesug98/p046.pdf

Shoup, A.G., & Roeser, R.J. (2007). Audiological Evaluation of Special Populations. In R.J. Roeser, M. Valente, & H. Hosford-Dunn (Eds.), *Audiology Diagnosis* (2nd ed., pp. 314-334). New York: Thieme Medical Publishers, Inc.

Silman, S., & Silverman, C.A. (*1991*). *Auditory Diagnosis: Principles and Applications*. San Diego: Singular Publishing Group.

Simpson, T. H., Schwan, S. A., & Rintel-mann, W. F**.** (1992). Audiometric test criteria in the detection of cisplatin ototoxicity. *Journal of the American Academy of Audiology, 3*, 176–185.

Singh, R., Saxena, R., & Varshney, S. (2009). Early detection of noise induced hearing loss by using ultra high frequency audiometry. *The Internet Journal of Otorhinolaryngology*, *10*(2), 1-5.

South African Constitution. (1996). *Bill of Rights*. Children, Sect. 28, Chap. 2. Retrieved June 7, 2009 from, http://www.info.gov.za/documents/constitution/1996/96cons2.htm Website last modified: 19 August 2009 12:08:27.

Statistical Package for the Social Sciences. (2012). http://www-01.ibm.com/software/analytics/spss. Copyright SOFTONIC INTERNATIONAL S.L. © 1997-2012

Stach, B.A. (2003). *Comprehensive dictionary of Audiology: Illustrated*. (2nd ed.). Canada: Delmar Learning- Thomson Inc.

Statistics South Africa. (2009). *Mid-year population estimates*. Retrieved June 24, 2010 from, http://www.statssa.gov.za/publications/statsdownload.asp?PPN=P0302&SCH=4437

Steyger, P.S., & Karasawa, T. (2008). Intra-cochlear trafficking of aminoglycosides. *Communicative and Integrative Biology*, *1*(2), 140-142.

Suchindran, S., Brouwer, E.S., & Van Rie, A. (2009). Is HIV infection a risk factor for multi-drug resistant tuberculosis? A systematic review. *PLoS ONE* 4(5): e5561. Retrieved November 25, 2009, from Open Access database. doi:10.1371/journal.pone.0005561

Swanepoel, D. W. (2006). Audiology in South Africa. *International Journal of Audiology, 45*(5), 262-266. doi: 10.1080/14992020500485650

Sweetow, R.W., & Sabes, J.H. (2008). Audiologic Testing. In A.K. Lalwani (Ed.), *Current Diagnosis & Treatment in Otolaryngology: Head & Neck Surgery* (2nd ed., pp. 596-606). USA: The McGraw-Hill Companies, Inc.

Trochim, W.M. (2006). *The Research Methods Knowledge Bases*. (3rd ed.). Retrieved June 24, 2010 from http://www.socialresearchmethods.net/kb/order/php

Turkkan, J. S. (2000). General Issues in Self Report. In A.A. Stone, C.A. Bachrach, J.S. Turkkan, J.B. Jobe, H.S. Kurtzman, & V.S. Cain (Eds.), *The science of self-report: Implications for research and practice* (pp. 1-3). New Jersey: Lawrence Erlbaum Associates.

UNAIDS. (2006). *2006 Report on the global AIDS epidemic: Executive summary / UNAIDS. "A UNAIDS 10th anniversary special edition.* Geneva.

UNAIDS. (2009). Aids epidemic update. Geneva: UNAIDS. Retrieved June 24, 2010 from http://data.unaids.org/pub/Report/2009/JC1700_Epi_Update_2009_en.pdf

Vasquez, R., & Mattucci, K.F. (2003). A proposed protocol for monitoring ototoxicity in patients who take cochleo- or vestibulotoxic drugs. *Ear, Nose & Throat Journal, 82*(3), 181-184.

Villarino, M.E., Geiter, L.J., & Simone, P.M. (1992). The multidrug-resistant tuberculosis challenge to public health efforts to control tuberculosis. *Public Health Reports, 107*(6), 616-625.

Wall, L. G. (1995). Hearing for School Aged Children, Adults and the Elderly. In L.G. Wall, (Ed.), *Hearing for the Speech-Language and Health Care Professional* (pp. 141-170). Massachusetts: Butterworth-Heineman.

Wiley, T.L., Cruickshanks, K.J., Nondahl, D.M., Tweed, T.S., Klein, R., & Klein, B.E.K. (1998). Aging and High - Frequency Hearing sensitivity. Journal of Speech, Language and Hearing Research, 41, 1061-1072.

Wisker, G. (2001). *The Postgraduate Research Handbook: Succeed with your MA, Mphil, EdD and PhD*. New York: Palgrave.

Wolfgang, R., Schönfeld, U., Mansmann, U., Fischer, R., & Gross, M. (1998). Extended high frequency audiometry in pre-school children. *Audiology, 37*(5), 285-294. Retrieved October 30, 2009 from ProQuest database.

World Health Organization. (2004). Age-standardized Death Rates by Cause and Region. Geneva: WHO. Retrieved June 23, 2010, from, www.who.int/entity/gho/mortality_burden_disease/regions/situation_trends_deaths/en/

World Health Organization. (2008). WHO Report 2008: Global tuberculosis control – surveillance, planning, financing. Geneva: WHO. WHO/HTM/TB/2008.376.

World Health Organization. (2009a). Ten facts about tuberculosis. Geneva: World Health Organization /Gary Hampton. Retrieved June 24, 2010, from, http://www.who.int/features/factfiles/tuberculosis/en/

World Health Organization. (2009b). Tuberculosis and gender. Geneva: World Health Organization. Retrieved June 17, 2010, from, http:// www.who.int/entity/tb/challenges/gender/en/

World Health Organization. (2009c). *Country health portfolio*. Geneva: World Health Organization. Retrieved June 17, 2010, from, http://apps.who.int/whosis/database/core/core_select_process.cfm?countries=zaf&indicators=TBIncidenceRate&indicators=TBPrevRate

World Health Organization. (2010a). Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. Geneva: World Health Organization. ISBN**:** 978 92 4 159919 1f

World Health Organization. (2010b). *World health statistics*. Geneva: World Health Organization. Retrieved June 17, 2010, from, http://www.who.int/whosis/whostat/2010/en/

World Health Organization. (2010c). Drug- and multidrug-resistant tuberculosis (MDR-TB) – Frequently asked questions. Geneva: World Health Organization. Retrieved June 17, 2010, from http://www.who.int/entity/tb/challenges/mdr/faqs/en

World Health Organization. (2010d). Treatment of tuberculosis: guidelines – 4th ed. Geneva: WHO. WHO/HTM/TB/2009.420

World Health Organization. (2010e). *World health statistics*: *Compendium, interim version*. Geneva: World Health Organization. Retrieved June 17, 2010, from, http://www.who.int/entity/whosis/indicators/WHS10_IndicatorCompendium_20100513.pdf

World Health Organization. (2010f). *WHO model list of essential medicines*. Geneva: World Health Organization. Retrieved June 17, 2010, from, http://www.who.int/medicines/publications/essentialmedicines/en/index.html

Zager, E.M., & McNerney, R. (2008). Multidrug-resistant tuberculosis. *BMC Infectious Diseases, 8*(10). Retrieved August 12, 2009, from http://www.biomedcentral.com/1471-2334/8/10

Zignol, M., Hosseini., M.S., Wright, A., Weezenbeek, C.L., Nunn, P., Watt., et al. (2006). Global incidence of multidrug resistant tuberculosis. *The Journal of Infectious Diseases, 194*(4), 479-485.

APPENDICES

Appendix A: Data capturing spreadsheet

Part. Code	Dates seen	Gender	D.O.B	Ear	OE	Tymp	DPOAEs								PTA									Admission/ D/C	Hearing Hx	TB regimen	Audio Mx
							250	500	1	2	4	6	8	P/R	250	500	1	2	4	6	8	10	12.5				

Appendix B: Information Letter for Hospital Site

ATT: Dr. W. Hardy

Thank you for allowing me the opportunity to send this research proposal through regarding completing my masters in Audiology. My name is Angela Kavallieratos; I am a Masters student from the department of Speech Pathology and Audiology at the University of Witwatersrand. I will be conducting research for fulfilment of my Masters degree in Audiology. I will be conducting research regarding the effects of ototoxic drug administration for Multiple Drug Resistant Tuberculosis (MDR-TB). The aim of this proposed retrospective research is to determine the hearing function in adults with MDR-TB. Therefore I would like to review past patient audiological records from Murchison Hospital. Information regarding the hospital as well as the patients whose records will be reviewed will remain strictly confidential. Patient identifying information will not be published in results and patient details will remain anonymous. Ethical clearance is pending from the University of Witwatersrand Human Research Ethics Committee.

It would therefore be much appreciated if the hospital would grant me permission to collect and utilize data from the MDR-TB unit for the purpose of completing my masters. The data and findings of my proposed research would be made available to the hospital on request for future quality improvement.

Your anticipated participation in this study is greatly appreciated. Should you require the results of this study please indicate so and these will be provided in due time.

Should you have any queries regarding the above please do not hesitate to contact me.

Ms. Angela Kavallieratos 084 473 3154

Supervisor: Mr. Victor Andrade 011 717 4570

Co-supervisor: Dr. Katijah Khoza- Shangase 011 717 4565

Appendix C: Permission Letter from the Hospital Site

HEALTH
KwaZulu-Natal

MURCHISON HOSPITAL
Main Harding / Kokstad Road
Private Bag 701, Port Shepstone, 4240
Tel.: 039 – 687 7311 Fax. 039 - 687 7497
Email: silindile.mabaso@kznhealth.gov.za
www.kznhealth.gov.za

Reference:
Enquiries:
Tel: (039) 687 7311 Ext. 106
18 March 2010

TO: Miss Angela Kavallieratos

Re: Request for permission to perform research at Murchison District Hospital

Dear Angela,

Thank you for your letter received 16th March 2010.

Murchison Hospital would be happy to assist in your research project and grant you permission to conduct research at the hospital and access to patient data, under the following conditions:

1. Ethical approval for the study is obtained from the relevant supervisory authority
2. If your research proposal is altered, prior approval must be obtained from management
3. The research once completed will be made accessible to the hospital.

Signed,

MEDICAL MANAGER
DR. W. HARDY

SENIOR MEDICAL SUPERINTENDENT
MURCHISON HOSPITAL
PRIVATE BAG 701
PORT SHEPSTONE 4240

Appendix D: Ethical clearance certificate obtained from Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Miss Angela Kavallieratos

CLEARANCE CERTIFICATE	**M10913**
PROJECT	Hearing Function in Adults with Multi-Drug Resistant -TB: a Retrospective Review
INVESTIGATORS	Miss Angela Kavallieratos.
DEPARTMENT	Department of Speech Pathology & Audiology
DATE CONSIDERED	01/10/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 01/10/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : V de Andrade

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix E: Approval of Proposal of MA Audiology

Faculty of Humanities - Postgraduate

Private Bag 3, Wits 2050, South Africa • Tel: +27 11 717 4007/8 • Fax: 086 538 5279 • E-mail: Nadia.Mohamed@wits.ac.za

Student Number: 0500021J

Ms A Kavallieratos
P O Box 84175
Greenside
2034

29 September 2010

Dear Ms Kavallieratos

APPROVAL OF PROPOSAL FOR THE DEGREE OF MASTER OF ARTS BY RESEARCH

I am pleased to be able to advise you that the readers of the Graduate Studies Committee have approved your proposal entitled "Hearing function in adults with multiple drug resistant - TB: A retrospective review". I confirm Dr V De Andrade has been appointed your supervisor.

The research report is normally submitted to the Faculty Office by 15 February. If you have started the beginning of the year, and for mid-year the deadline is 15 August. All students are required to RE-REGISTER at the beginning of each year.

You are required to submit 2 bound copies and 2 unbound or 1 CD in pdf (Adobe) format of your Research to the Faculty Office. The 2 bound copies go to the examiners and are retained by them and the 2 corrected unbound copies are eventually sent to Archives and to the Library.

Please note that should you miss the deadline of 15 February you will be required to submit an application for extension of time and register for the research report extension. Any candidate who misses the deadline of 15 February will be charged full fees for the year.

I should be glad if you keep us informed of any changes of address during the year.

Note: All MA and PhD candidates who intend graduating shortly must meet your ETD requirements at least 6 weeks after your supervisor has received the examiners reports. **Students must remain registered at the Faculty Office until graduation.**

Yours sincerely

Nadia Mohamed
Postgraduate Division
Faculty of Humanities
Private Bag X 3
Wits, 2050

Appendix F: Calibration Certificate

hass

The Ear Institute, 1240 Webb Str. Queenswood Pretoria. Tel: (012) 333-3133 Fax: (012) 333-1124

H.A.S.S. Industrial (Pty) Ltd

Certificate of Calibration
No. C 192162/08

This certificate is issued in accordance with the conditions of the South African Bureau of Standards (SABS 0154-1; 0154-2). It is a correct record of measurements made. Copyright protected. This certificate may not be reproduced, except with the prior written approval of H.A.S.S. Industrial (Pty) Ltd.

Calibrated for:	**Murchison Hospital** **82 Main Harding Rd** **Port Shepstone** **KZN**
Calibration of:	**Obiter 922 Diagnostic Audiometer**
Manufacturer:	**Madsen**
Serial Number:	**192162**
Calibration procedure:	Complete diagnostic calibration: Audiometer (Obiter) Earphones (TDH 39: Right s/n 77463 Left s/n 74463; Bone Vibrator (B71) & Free Field.
Traceability:	The calibration was performed using instruments traceable to national standards.
Date of Calibration:	**2008-03-17** **Cal. Due Date:** **2009-03-17**
Results:	The instrument complies with the requirements for use of a Type 1 Audiometer. (Air; Bone & Free Field)
Remarks:	None
Calibrated by:	Waldo Hanekom Signature

NOTE: The values in this certificate are correct at the time of calibration. Subsequently the accuracy will depend on such factors as the care exercised in the handling and use of the instrument and the frequency of use. Re-calibration should be performed annually to ensure that the instrument's accuracy remains within the desired limits.

Appendix G: Calibration Certificate

hass

The Ear Institute, 1240 Webb Str. Queenswood Pretoria. Tel: (012) 333-3133 Fax: (012) 333-1124

H.A.S.S. Industrial (Pty) Ltd

Certificate of Calibration
No. C AS 063515/08

This certificate is issued in accordance with the conditions for calibration of the instrument as described by the manufacturer or the South African Bureau of Standards (SABS 0154-1; 0154-2) were applicable. It is a correct record of measurements made. Copyright protected. This certificate may not be reproduced, except with the prior written approval of H.A.S.S. Industrial (Pty) Ltd.

Calibrated for:	**Murchison Hospital** **82 Main Harding Rd** **Port Shepstone** **KZN**
Calibration of:	**GSI 38 V.3 Tympanometer**
Manufacturer:	**GSI**
Serial Number:	**AS 063515**
Calibration procedure:	Complete probe and pressure calibration as described in the manufacturers specification.
Traceability:	The calibration was performed using instruments traceable to national standards.
Date of Calibration:	**2008-03-17** **Cal. Due Date:** **2009-03-17**
Results:	The instrument complies with the requirements for use as specified by the manufacturer.
Remarks:	None
Calibrated by:	Waldo Hanekom

Signature

NOTE: The values in this certificate are correct at the time of calibration. Subsequently the accuracy will depend on such factors as the care exercised in the handling and use of the instrument and the frequency of use. Re-calibration should be performed annually to ensure that the instrument's accuracy remains within the desired limits.

Appendix H: Calibration Certificate

HASS GROUP

Ear Institute, 1240 Webb Str. Queenswood Pretoria. Tel: (012) 333-3131Fax: (012) 333-2298

H.A.S.S. Industrial (Pty) Ltd

Certificate of Calibration
No. C 192162/09

This certificate is issued in accordance with the conditions of the South African Bureau of Standards (SABS 0154-1; 0154-2). It is a correct record of measurements made. Copyright protected. This certificate may not be reproduced, except with the prior written approval of H.A.S.S. Industrial (Pty) Ltd.

Calibrated for:	**Murchison Hospital** **82 Main Rd Harding** **Port Shepstone** **KZN**
Calibration of:	**Madsen Orbiter 922**
Manufacturer:	**Madsen Electronics**
Serial Number:	**192162**
Calibration procedure:	Complete diagnostic calibration: Audiometer (Orbiter 922) Earphones (TDH 39: Right s/n 77463 Left s/n 74463; Bone Vibrator (B71) & Free Field System.
Traceability:	The calibration was performed using instruments traceable to national standards.
Date of Calibration:	**2009-03-04** **Cal. Due Date:** **2010-03-04**
Results:	The instrument complies with the requirements for use of a Type 1 Audiometer. (Air; Bone & Free Field System)
Remarks:	None
Calibrated by:	Waldo Hanekom Signature

NOTE: The values in this certificate are correct at the time of calibration. Subsequently the accuracy will depend on such factors as the care exercised in the handling and use of the instrument and the frequency of use. Re-calibration should be performed annually to ensure that the instrument's accuracy remains within the desired limits.

Appendix I: Calibration Certificate

Stanyer Electroserve cc.

SALES, SERVICE AND REPAIRS TO
MEDICAL AND ACOUSTIC INSTRUMENTATION
ck 94/05783/23

P.O. Box 273,
Gillitts, 3603,
Tel: 031-7090710
Fax: 031-7028778

No. 2 Gilro Park
34 Gillitts Road
Pinetown
3610

Certification of Standard Calibration

Company Name & Address

.....Murchison Hospital.....
.....
.....

Make	Model	Serial no.	Left ear	Right ear	Pre. cal.	Post cal.	Cert. no.
Madsen	OB822CE922	192167	C197958	C425705	96.0	96.0	9266

		Air/Pure tone			N.B. Noise			Bone con.		Free/Warble			Free/N/B		
Freq. Hz	Freq. Meas.	Left	SABS 70dB	Right	Left	SABS 70dB	Right	SABS 40dB	M.V	FF1	SABS 70dB	FF2	FF1	SABS 70dB	FF2
125	125	116.4	115	115.4	119.6	118	118.4				90			90	
250	250	98.4	97	98.0	100.1	100	100.2	90.5 +10	89.8	82.4	81	81.0		80.5	
500	500	83.7	83.5	83.5	85.9	86.5	86.2	82.0 +12	81.6	75.9	76	76.2		74.5	
750	749	79.9	79	79.1	86.4	82	82.8	72.0 +12	72.2	75.5	74.5	74.3		71.5	
1 K	1000	78.2	77.5	77.5	80.2	80.5	80.7	66.5 +12	65.6	74.8	74	74.9		71	
1K5	1498	78.4	77.5	77.3	81.6	80.5	81.4	61.5 +11	61.4	73.1	72.5	73.4		72.5	
2 K	2000	80.2	79	79.1	82.8	82	82.1	57.0 +12	57.4	71.4	71	71.8		72.5	
3 K	3000	81.1	81.5	81.3	84.7	84.5	84.7	55.0 +11	55.2	66.1	66.5	66.9		68	
4 K	4000	82.4	82	81.8	84.9	85	85.2	56.0 +6	55.7	67.0	66	67.2		67	
6 K	6000	86.0	86	86.1	89.0	89.5	89.4	53.0 +5	53.8	76.0	76.5	77.1		73.5	
8 K	8000	86.2	85.5	86.1	89.0	89.5	89.7	54.0 +10	55.0	84.4	85	85.1		81.5	

LIN	95	90	85	80	75	70	65	60	55	50	45	40	35	30
4000H														

Booth Levels

Booth Type: NSB

Frequency	8 K	4 K	2 K	1 K	500	250	125
Screen	35.5	37	31	24	22	38.5	52
Diagnostic	35.5	37	31	24	22	21	29
Levels	14.9	15.6	15.8	17.0	18.6	17.2	13.7

Screening (N) (ATT+25Db		ATT LIN (1K TAPE+F	
Left	Right	Left	Right

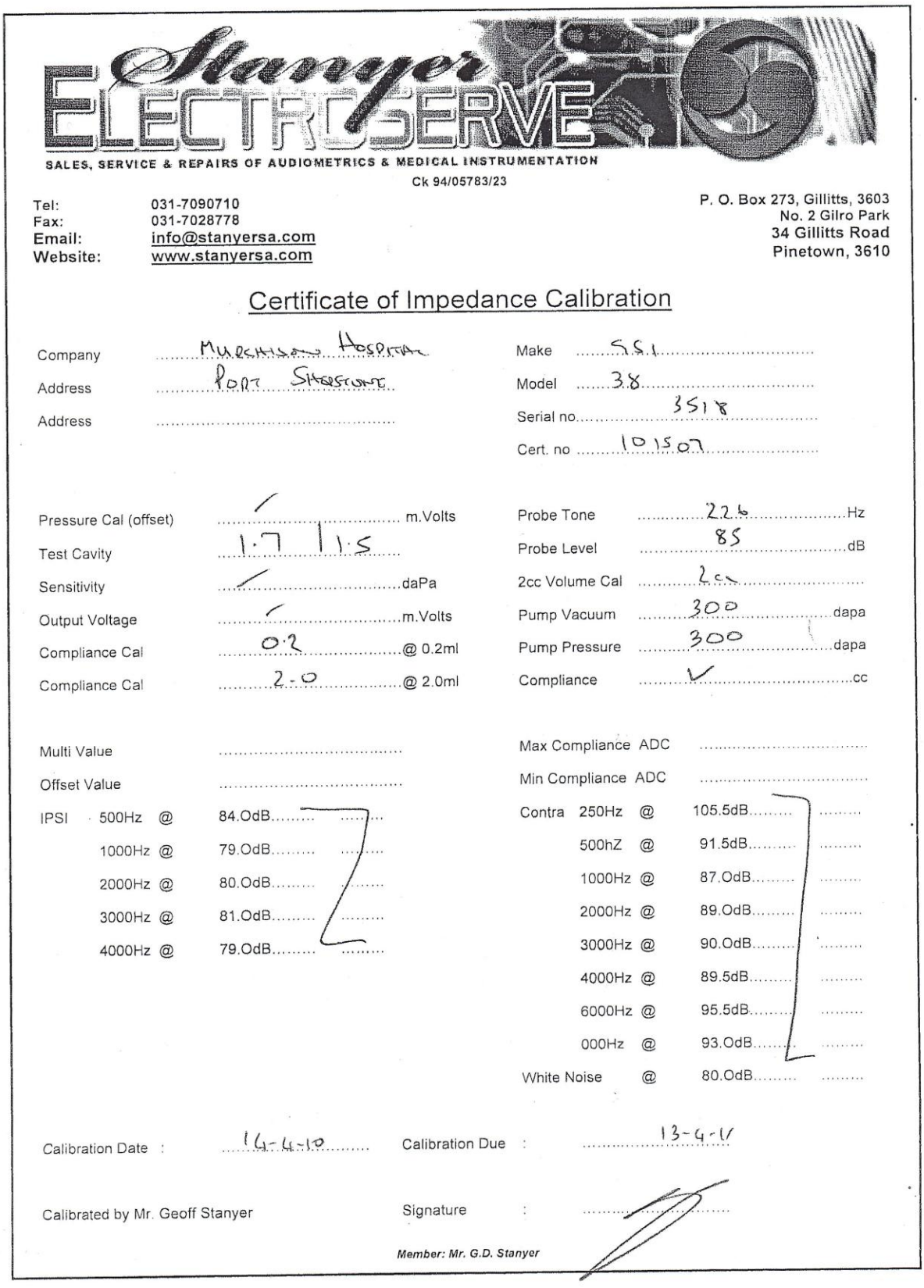
Calibration Date: 18.6.09 Calibration Due : 17-6-10

Calibrated by Mr. G.D. Stanyer / Mr. P.T. Stanyer Signature :

Certified in Noise Measurement and Calibration

Member: Mr. G.D. Stanyer

Appendix J: Calibration Certificate



Stanyer ELECTROSERVE

SALES, SERVICE & REPAIRS OF AUDIOMETRICS & MEDICAL INSTRUMENTATION

Ck 94/05783/23

Tel: 031-7090710
Fax: 031-7028778
Email: info@stanyersa.com
Website: www.stanyersa.com

P. O. Box 273, Gillitts, 3603
No. 2 Gilro Park
34 Gillitts Road
Pinetown, 3610

Certificate of Impedance Calibration

Company ..... Murchison Hospital
Address ..... Port Shepstone
Address .....

Make ..... SS1 .....
Model ..... 38 .....
Serial no ..... 3518 .....
Cert. no ..... 101507 .....

Pressure Cal (offset)	✓ m.Volts	Probe Tone	226 Hz
Test Cavity	1·7 | 1·5	Probe Level	85 dB
Sensitivity	✓ daPa	2cc Volume Cal	2cc
Output Voltage	✓ m.Volts	Pump Vacuum	300 dapa
Compliance Cal	0·2 @ 0.2ml	Pump Pressure	300 dapa
Compliance Cal	2·0 @ 2.0ml	Compliance	✓ cc

Multi Value .....
Offset Value .....

IPSI	500Hz @	84.OdB	Contra	250Hz @	105.5dB
	1000Hz @	79.OdB		500hZ @	91.5dB
	2000Hz @	80.OdB		1000Hz @	87.OdB
	3000Hz @	81.OdB		2000Hz @	89.OdB
	4000Hz @	79.OdB		3000Hz @	90.OdB
				4000Hz @	89.5dB
				6000Hz @	95.5dB
				000Hz @	93.OdB
			White Noise	@	80.OdB

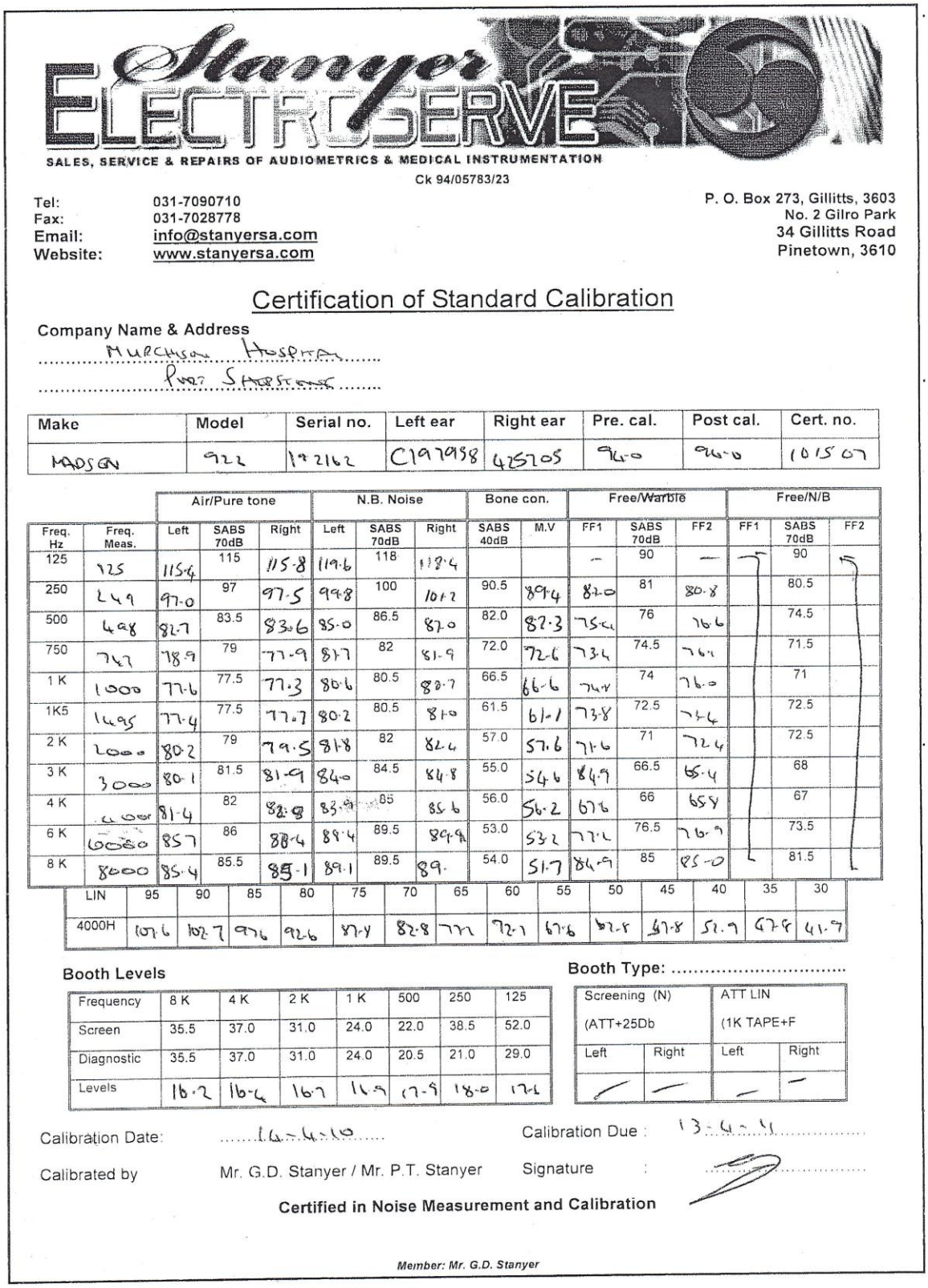
Max Compliance ADC .....
Min Compliance ADC .....

Calibration Date : 16-4-10 Calibration Due : 13-4-11

Calibrated by Mr. Geoff Stanyer Signature : .....

Member: Mr. G.D. Stanyer

Appendix K: Calibration Certificate



Stanyer ELECTROSERVE

SALES, SERVICE & REPAIRS OF AUDIOMETRICS & MEDICAL INSTRUMENTATION

Ck 94/05783/23

Tel: 031-7090710
Fax: 031-7028778
Email: info@stanyersa.com
Website: www.stanyersa.com

P. O. Box 273, Gillitts, 3603
No. 2 Gilro Park
34 Gillitts Road
Pinetown, 3610

Certification of Standard Calibration

Company Name & Address

Murchison Hospital
Post Stanger

Make	Model	Serial no.	Left ear	Right ear	Pre. cal.	Post cal.	Cert. no.
MADSEN	922	972162	C197958	425705	96-0	96-0	101507

		Air/Pure tone			N.B. Noise			Bone con.		Free/Warble			Free/N/B		
Freq. Hz	Freq. Meas.	Left	SABS 70dB	Right	Left	SABS 70dB	Right	SABS 40dB	M.V	FF1	SABS 70dB	FF2	FF1	SABS 70dB	FF2
125	125	115.4	115	115.8	119.6	118	118.4			–	90	—		90	
250	249	97.0	97	97.5	99.8	100	101.2	90.5	89.4	82.0	81	80.8		80.5	
500	498	82.7	83.5	83.6	85.0	86.5	87.0	82.0	87.3	75.4	76	76.6		74.5	
750	747	78.9	79	77.9	81.7	82	81.9	72.0	72.6	73.4	74.5	76.4		71.5	
1 K	1000	77.6	77.5	77.3	80.6	80.5	80.7	66.5	66.6	74.4	74	76.0		71	
1K5	1495	77.4	77.5	77.7	80.2	80.5	81.0	61.5	61.1	73.8	72.5	74.4		72.5	
2 K	2000	80.2	79	79.5	81.8	82	82.4	57.0	57.6	71.6	71	72.4		72.5	
3 K	3000	80.1	81.5	81.9	84.0	84.5	84.8	55.0	54.6	84.9	66.5	65.4		68	
4 K	over	81.4	82	82.8	83.9	85	85.6	56.0	56.2	67.6	66	65.4		67	
6 K	6000	85.7	86	88.4	89.4	89.5	89.9	53.0	53.2	77.2	76.5	76.9		73.5	
8 K	8000	85.4	85.5	85.1	89.1	89.5	89.	54.0	51.7	84.9	85	85.0		81.5	

LIN	95	90	85	80	75	70	65	60	55	50	45	40	35	30
4000H	107.6	102.7	97.6	92.6	87.4	82.8	77.7	72.1	67.6	62.8	57.8	52.9	47.8	41.7

Booth Levels

Frequency	8 K	4 K	2 K	1 K	500	250	125
Screen	35.5	37.0	31.0	24.0	22.0	38.5	52.0
Diagnostic	35.5	37.0	31.0	24.0	20.5	21.0	29.0
Levels	16.2	16.4	16.7	16.9	17.9	18.0	17.1

Booth Type: .....

Screening (N) (ATT+25Db		ATT LIN (1K TAPE+F	
Left	Right	Left	Right
✓	—	—	—

Calibration Date: 16-4-10

Calibration Due : 13-4-11

Calibrated by Mr. G.D. Stanyer / Mr. P.T. Stanyer

Signature :

Certified in Noise Measurement and Calibration

Member: Mr. G.D. Stanyer

Appendix L: Pure Tone Audiometry Thresholds for total sample

	Months	Mean	Standard Deviation	Range
Pure Tone Audiometry 250 Hz	1	15.074	15.295	105
	2	16.176	15.156	85
	3	19.412	21.231	110
	4	23.713	23.238	100
	5	26.029	25.071	110
Pure Tone Audiometry 500 Hz	1	15.63	16.247	95
	2	15.919	15.241	85
	3	20.699	22.829	115
	4	24.853	25.188	115
	5	26.324	26.199	110
Pure Tone Audiometry 1000 Hz	1	15.63	17.185	95
	2	16.581	18.04	100
	3	22.206	25.201	125
	4	25.221	27.527	125
	5	27.978	29.284	120
Pure Tone Audiometry 2000 Hz	1	15.63	17.645	120
	2	17.978	19.526	110
	3	23.272	27.53	120
	4	27.353	28.29	125
	5	33.051	31.996	130
Pure Tone Audiometry 4000 Hz	1	17.148	19.958	130
	2	21.471	22.045	120
	3	30.074	30.043	120
	4	36.875	31.64	115
	5	44.743	33.263	120
Pure Tone Audiometry 6000 Hz	1	22.667	20.758	125
	2	27.721	24.128	120
	3	36.213	31.923	115
	4	46.801	32.833	115
	5	54.007	31.971	115
Pure Tone Audiometry 8000 Hz	1	24.667	23.182	120
	2	33.235	26.257	110
	3	41.691	32.118	105
	4	53.713	30.368	110
	5	59.853	29.161	115
Pure Tone Audiometry 10000 Hz	1	35.444	25.3	105
	2	44.853	26.659	100
	3	54.191	26.807	90
	4	63.088	24.751	85
	5	68.382	24.228	95
Pure Tone Audiometry 12500 Hz	1	61.157	26.957	95
	2	69.596	26.063	95
	3	75.882	24.75	95
	4	81.434	21.343	85
	5	84.375	21.007	90

Appendix M: Pure Tone Audiometry Thresholds for left and right ears

		Mean	Standard Deviation	Range
Pure Tone Audiometry 250 Hz	Left ear	21.209	21.975	110
	Right ear	18.997	19.541	105
Pure Tone Audiometry 500 Hz	Left ear	21.522	22.829	120
	Right ear	19.884	21.196	120
Pure Tone Audiometry 1000 Hz	Left ear	21.91	25.249	130
	Right ear	21.163	23.529	125
Pure Tone Audiometry 2000 Hz	Left ear	24.149	26.825	130
	Right ear	22.805	25.786	130
Pure Tone Audiometry 4000 Hz	Left ear	31.254	30.279	130
	Right ear	28.939	28.895	130
Pure Tone Audiometry 6000 Hz	Left ear	39.896	31.327	125
	Right ear	35.174	30.431	120
Pure Tone Audiometry 8000 Hz	Left ear	43.045	31.032	120
	Right ear	42.282	31.235	120
Pure Tone Audiometry 10000 Hz	Left ear	53.701	28.367	105
	Right ear	52.747	27.983	100
Pure Tone Audiometry 12500 Hz	Left ear	76.497	24.869	95
	Right ear	72.616	25.94	100

Appendix N: Statistical results from ANCOVA and Regression analyses

Tests of Between-Subjects Effects Dependent Variable: Pure Tone Audiometry 250 Hz					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**P-value**
Corrected Model	20917.368(a)	7	2988.2	7.367	0
Intercept	1330.73	1	1330.7	3.281	0.071
Gender	606.79	1	606.79	1.496	0.222
Ear	780.28	1	780.28	1.924	0.166
Time	12202.6	4	3050.7	7.521	0
Age	7949.2	1	7949.2	19.597	0
Error	272177	671	405.63		
Total	567100	679			
Corrected Total	293095	678			
R Squared = .071 (Adjusted R Squared = .062)					

Parameter Estimates Dependent Variable: Pure Tone Audiometry 250 Hz						
					95% Confidence Interval	
Parameter	**B**	**Std. Error**	**t**	**P-value**	**Lower Bound**	**Upper Bound**
Intercept	9.861	3.965	2.487	0.013	2.074	17.647
[Gender=1]	1.96	1.603	1.223	0.222	-1.187	5.107
[Gender=2]	0*	.	.	.	.	.
[Ear=1]	2.145	1.546	1.387	0.166	-0.892	5.181
[Ear=2]	0*	.	.	.	.	.
[Time=1]	-11.013	2.447	-4.501	0	-15.82	-6.208
[Time=2]	-9.853	2.442	-4.034	0	-14.65	-5.057
[Time=3]	-6.618	2.442	-2.71	0.007	-11.41	-1.822
[Time=4]	-2.316	2.442	-0.948	0.343	-7.112	2.479
[Time=5]	0*	.	.	.	.	.
Age	0.422	0.095	4.427	0	0.235	0.61
* This parameter is set to zero because it is redundant						

Tests of Between-Subjects Effects Dependent Variable: Pure Tone Audiometry 500 Hz					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	20190.292(a)	7	2884.33	6.275	0
Intercept	2472.133	1	2472.13	5.378	0.021
Gender	55.089	1	55.089	0.12	0.729
Ear	414.034	1	414.034	0.901	0.343
Time	13287.52	4	3321.88	7.227	0
Age	6309.141	1	6309.14	13.726	0
Error	308434.4	671	459.664		
Total	619350	679			
Corrected Total	328624.7	678			
R Squared = .061 (Adjusted R Squared = .052)					

Parameter Estimates Dependent Variable: Pure Tone Audiometry 500 Hz						
					95% Confidence Interval	
Parameter	**B**	**Std. Error**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**
Intercept	12.685	4.221	3.005	0.003	4.397	20.974
[Gender=1]	0.591	1.706	0.346	0.729	-2.759	3.94
[Gender=2]	0*	.	.	.	.	.
[Ear=1]	1.562	1.646	0.949	0.343	-1.67	4.794
[Ear=2]	0*	.	.	.	.	.
[Time=1]	-10.739	2.605	-4.123	0	-15.854	-5.625
[Time=2]	-10.404	2.6	-4.002	0	-15.509	-5.299
[Time=3]	-5.625	2.6	-2.163	0.031	-10.73	-0.52
[Time=4]	-1.471	2.6	-0.566	0.572	-6.576	3.634
[Time=5]	0*	.	.	.	.	.
Age	0.376	0.102	3.705	0	0.177	0.576
* This parameter is set to zero because it is redundant						

Tests of Between-Subjects Effects Dependent Variable: Pure Tone Audiometry 1000 Hz					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	27005.980(a)	7	3858	6.887	0
Intercept	1296.2	1	1296.2	2.314	0.129
Gender	134.806	1	134.806	0.241	0.624
Ear	66.263	1	66.263	0.118	0.731
Time	15672.01	4	3918	6.994	0
Age	9796.674	1	9796.67	17.487	0
Error	375901.1	671	560.21		
Total	717700	679			
Corrected Total	402907.1	678			
R Squared = .067 (Adjusted R Squared = .057)					

Parameter Estimates Dependent Variable: Pure Tone Audiometry 1000 Hz						
					95% Confidence Interval	
Parameter	**B**	**Std. Error**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**
Intercept	12.489	4.66	2.68	0.008	3.339	21.639
[Gender=1]	-0.924	1.883	-0.491	0.624	-4.622	2.774
[Gender=2]	0*	.	.	.	.	.
[Ear=1]	0.625	1.817	0.344	0.731	-2.943	4.193
[Ear=2]	0*	.	.	.	.	.
[Time=1]	-12.394	2.876	-4.31	0	-18.04	-6.747
[Time=2]	-11.397	2.87	-3.971	0	-17.033	-5.761
[Time=3]	-5.772	2.87	-2.011	0.045	-11.408	-0.136
[Time=4]	-2.757	2.87	-0.961	0.337	-8.393	2.878
[Time=5]	0*	.	.	.	.	.
Age	0.469	0.112	4.182	0	0.249	0.689
* This parameter is set to zero because it is redundant						

Tests of Between-Subjects Effects Dependent Variable: Pure Tone Audiometry 2000 Hz					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	39049.140(a)	7	5578.45	8.712	0
Intercept	1973.478	1	1973.48	3.082	0.08
Gender	59.884	1	59.884	0.094	0.76
Ear	255.563	1	255.563	0.399	0.528
Time	27048.26	4	6762.06	10.56	0
Age	10508.05	1	10508	16.41	0
Error	429657.9	671	640.325		
Total	842675	679			
Corrected Total	468707.1	678			
R Squared = .083 (Adjusted R Squared = .074)					

Parameter Estimates Dependent Variable: Pure Tone Audiometry 2000 Hz						
					95% Confidence Interval	
Parameter	**B**	**Std. Error**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**
Intercept	16.548	4.982	3.322	0.001	6.766	26.331
[Gender=1]	-0.616	2.014	-0.306	0.76	-4.569	3.338
[Gender=2]	0*	.	.	.	.	.
[Ear=1]	1.227	1.943	0.632	0.528	-2.587	5.042
[Ear=2]	0*	.	.	.	.	.
[Time=1]	-17.472	3.074	-5.683	0	-23.509	-11.436
[Time=2]	-15.074	3.069	-4.912	0	-21.099	-9.048
[Time=3]	-9.779	3.069	-3.187	0.002	-15.805	-3.754
[Time=4]	-5.699	3.069	-1.857	0.064	-11.724	0.327
[Time=5]	0*	.	.	.	.	.
Age	0.486	0.12	4.051	0	0.25	0.721
* This parameter is set to zero because it is redundant						

Tests of Between-Subjects Effects Dependent Variable: Pure Tone Audiometry 4000 Hz					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	86568.781(a)	7	12367	16.369	0
Intercept	8448.606	1	8448.61	11.183	0.001
Gender	3945.982	1	3945.98	5.223	0.023
Ear	785.83	1	785.83	1.04	0.308
Time	68292.21	4	17073.1	22.598	0
Age	9166.387	1	9166.39	12.133	0.001
Error	506951.8	671	755.517		
Total	1207925	679			
Corrected Total	593520.5	678			
R Squared = .146 (Adjusted R Squared = .137)					

Parameter Estimates Dependent Variable: Pure Tone Audiometry 4000 Hz						
					95% Confidence Interval	
Parameter	**B**	**Std. Error**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**
Intercept	31.11	5.412	5.749	0	20.484	41.736
[Gender=1]	-4.998	2.187	-2.285	0.023	-9.293	-0.704
[Gender=2]	0*	.	.	.	.	.
[Ear=1]	2.152	2.11	1.02	0.308	-1.991	6.296
[Ear=2]	0*	.	.	.	.	.
[Time=1]	-27.628	3.339	-8.273	0	-34.185	-21.071
[Time=2]	-23.272	3.333	-6.982	0	-29.817	-16.727
[Time=3]	-14.669	3.333	-4.401	0	-21.214	-8.124
[Time=4]	-7.868	3.333	-2.36	0.019	-14.412	-1.323
[Time=5]	0*	.	.	.	.	.
Age	0.453	0.13	3.483	0.001	0.198	0.709
* This parameter is set to zero because it is redundant						

Tests of Between-Subjects Effects Dependent Variable: Pure Tone Audiometry 6000 Hz					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	118388.919(a)	7	16912.7	21.38	0
Intercept	13030.41	1	13030.4	16.472	0
Gender	3284.715	1	3284.72	4.152	0.042
Ear	3497.753	1	3497.75	4.422	0.036
Time	91981.58	4	22995.4	29.069	0
Age	14340.69	1	14340.7	18.128	0
Error	530804.8	671	791.065		
Total	1604225	679			
Corrected Total	649193.7	678			
R Squared = .182 (Adjusted R Squared = .174)					

Parameter Estimates Dependent Variable: Pure Tone Audiometry 6000 Hz						
					95% Confidence Interval	
Parameter	**B**	**Std. Error**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**
Intercept	35.175	5.538	6.352	0	24.301	46.048
[Gender=1]	-4.56	2.238	-2.038	0.042	-8.955	-0.166
[Gender=2]	0*	.	.	.	.	.
[Ear=1]	4.541	2.159	2.103	0.036	0.301	8.781
[Ear=2]	0*	.	.	.	.	.
[Time=1]	-31.396	3.417	-9.188	0	-38.106	-24.687
[Time=2]	-26.287	3.411	-7.707	0	-32.984	-19.59
[Time=3]	-17.794	3.411	-5.217	0	-24.491	-11.097
[Time=4]	-7.206	3.411	-2.113	0.035	-13.903	-0.509
[Time=5]	0*	.	.	.	.	.
Age	0.567	0.133	4.258	0	0.306	0.829
* This parameter is set to zero because it is redundant						

Tests of Between-Subjects Effects Dependent Variable: Pure Tone Audiometry 8000 Hz					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	138181.343(a)	7	19740.2	25.561	0
Intercept	18428.09	1	18428.1	23.862	0
Gender	3014.376	1	3014.38	3.903	0.049
Ear	57.41	1	57.41	0.074	0.785
Time	112955.7	4	28238.9	36.566	0
Age	16857.49	1	16857.5	21.828	0
Error	518195.4	671	772.273		
Total	1891975	679			
Corrected Total	656376.7	678			
R Squared = .211 (Adjusted R Squared = .202)					

Parameter Estimates Dependent Variable: Pure Tone Audiometry 8000 Hz						
					95% Confidence Interval	
Parameter	**B**	**Std. Error**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**
Intercept	41.277	5.471	7.544	0	30.534	52.02
[Gender=1]	-4.369	2.211	-1.976	0.049	-8.711	-0.027
[Gender=2]	0*	.	.	.	.	.
[Ear=1]	0.582	2.134	0.273	0.785	-3.608	4.771
[Ear=2]	0*	.	.	.	.	.
[Time=1]	-35.233	3.376	-10.435	0	-41.862	-28.603
[Time=2]	-26.618	3.37	-7.898	0	-33.235	-20.001
[Time=3]	-18.162	3.37	-5.389	0	-24.779	-11.545
[Time=4]	-6.14	3.37	-1.822	0.069	-12.757	0.477
[Time=5]	0*	.	.	.	.	.
Age	0.615	0.132	4.672	0	0.357	0.873
* This parameter is set to zero because it is redundant						

Tests of Between-Subjects Effects Dependent Variable: Pure Tone Audiometry 10000 Hz					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	136818.430(a)	7	19545.5	32.732	0
Intercept	22754.05	1	22754	38.106	0
Gender	1168.471	1	1168.47	1.957	0.162
Ear	91.454	1	91.454	0.153	0.696
Time	97184.21	4	24296.1	40.688	0
Age	32701.84	1	32701.8	54.765	0
Error	400675.3	671	597.132		
Total	2460525	679			
Corrected Total	537493.7	678			
R Squared = .255 (Adjusted R Squared = .247)					

Parameter Estimates Dependent Variable: Pure Tone Audiometry 10000 Hz						
					95% Confidence Interval	
Parameter	**B**	**Std. Error**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**
Intercept	40.815	4.811	8.483	0	31.368	50.262
[Gender=1]	-2.72	1.944	-1.399	0.162	-6.538	1.098
[Gender=2]	0*	.	.	.	.	.
[Ear=1]	0.734	1.876	0.391	0.696	-2.95	4.418
[Ear=2]	0*	.	.	.	.	.
[Time=1]	-33.015	2.969	-11.12	0	-38.845	-27.186
[Time=2]	-23.529	2.963	-7.94	0	-29.348	-17.711
[Time=3]	-14.191	2.963	-4.789	0	-20.01	-8.373
[Time=4]	-5.294	2.963	-1.787	0.074	-11.113	0.524
[Time=5]	0*	.	.	.	.	.
Age	0.857	0.116	7.4	0	0.629	1.084
* This parameter is set to zero because it is redundant						

Tests of Between-Subjects Effects Dependent Variable: Pure Tone Audiometry 12500 Hz					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	121966.490(a)	7	17423.8	36.788	0
Intercept	38460.14	1	38460.1	81.203	0
Gender	1463.13	1	1463.13	3.089	0.079
Ear	2114.39	1	2114.39	4.464	0.035
Time	48182.17	4	12045.5	25.432	0
Age	71100.43	1	71100.4	150.118	0
Error	317332.5	670	473.631		
Total	4205200	678			
Corrected Total	439299	677			
R Squared = .278 (Adjusted R Squared = .270)					

Parameter Estimates Dependent Variable: Pure Tone Audiometry 12500 Hz						
					95% Confidence Interval	
Parameter	**B**	**Std. Error**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**
Intercept	38.765	4.294	9.028	0	30.333	47.196
[Gender=1]	3.049	1.735	1.758	0.079	-0.357	6.455
[Gender=2]	0*	.	.	.	.	.
[Ear=1]	3.533	1.672	2.113	0.035	0.25	6.816
[Ear=2]	0*	.	.	.	.	.
[Time=1]	-23.495	2.649	-8.869	0	-28.696	-18.293
[Time=2]	-14.779	2.639	-5.6	0	-19.961	-9.597
[Time=3]	-8.493	2.639	-3.218	0.001	-13.675	-3.311
[Time=4]	-2.941	2.639	-1.114	0.265	-8.123	2.241
[Time=5]	0*	.	.	.	.	.
Age	1.267	0.103	12.252	0	1.064	1.47
* This parameter is set to zero because it is redundant						