

**HEARING LOSS AMONG PATIENTS RECEIVING ANTI-
TUBERCULOSIS TREATMENT**

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**THIS DISSERTATION IS SUBMITTED TO THE UNIVERSITY OF
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DEGREE**



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DECLARATION

I, **BENJAMIN TETTEH AMARTEY** do hereby declare that this dissertation which is being submitted in fulfillment of the requirements for the degree of MSc in Audiology is the result of my own independent research performed under supervision, and that except where otherwise other sources are acknowledged and duly referenced, this work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree. I hereby give permission for the Department of Audiology, Speech and Language Therapy to seek dissemination/publication of the dissertation in any appropriate format. Authorship in such circumstances to be jointly held between myself as first author and the project supervisors as subsequent authors.

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DEDICATION

This work is dedicated to my parents, Mr. Joshua Amartey and Mrs. Hannah Amartey.

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LIST OF ABBREVIATIONS

AC	Air conduction
AIDS	Acquired Immuno-deficiency Syndrome
ARV	Antiretroviral
AOAE	Automated otoacoustic emissions
BC	Bone conduction
BSA	British Society of Audiology
CDC	Centers for Disease Control and Prevention
CDR	Case Detection Rate
DOTS	Directly Observed Therapy, Short-course
DPOAE	Distortion product otoacoustic emission
ETB	Extrapulmonary TB
GHS	Ghana Health Service
GSS	Ghana Statistical Service
HIV	Human Immuno-deficiency Virus
IGRA	Interferon-gamma release assays
LTBI	Latent TB Infection
MDR	Multi-drug resistant
NTP	National TB Control Programme
OAE	Otoacoustic emissions
PTA	Pure tone Audiometry
PTB	Pulmonary TB
ROS	Reactive oxygen species
TB	Tuberculosis/Tubercle bacillus
TST	Tuberculin Skin Test
WHO	World Health Organization
XDR	Extensively-drug resistant

ABSTRACT

Background: Tuberculosis therapy is characterized by many side effects including hearing loss. It has been documented that the use of aminoglycosides for TB treatment is the cause of the associated hearing impairment. The consequential effect of hearing impairment on the patient is high. This has its long-term socio-economic effect (social isolation and stigmatization) on patients, families and public health in general. Hearing loss can compromise treatment compliance and also affect the quality of life of patients during and after treatment.

Aim: The aim of the study was to determine and establish the prevalence of hearing loss among patients receiving treatment for TB.

Method: A quasi-experimental, post-test only with non-equivalent control group design involving 60 consenting patients receiving treatment for TB at the chest clinic of the Tema General Hospital between February and May 2018 and a control group of 60 age and gender-matched uninfected volunteers constituted this study. Data on demographics and case history were collected using a structured questionnaire. The hearing status of participants was assessed using conventional pure tone audiometry and transient evoked otoacoustic emission tests. Data were analyzed using the SPSS statistical software package.

Results: A hearing loss prevalence of 20% was found among patients receiving treatment for TB. Out of the 60 patients on TB medications assessed, 12 presented with hearing loss that ranged from mild to severe. Patients who presented with the poor thresholds were all referred in the OAE. Hearing thresholds of patients receiving anti-TB medications were significantly elevated ($p < 0.05$) in comparison to the thresholds of the control group.

A statistically significant ($p < 0.05$) difference was observed between the hearing thresholds of patients receiving treatment and the uninfected volunteers especially at the high frequencies. A similar significant ($p < 0.05$) association was also found between exposure to TB medications and poor hearing thresholds.

Conclusion: Patients receiving treatment for TB usually demonstrate significantly elevated hearing thresholds which tend to be more pronounced at the high frequencies. Audiological management of these patients should, therefore, be an essential part of their therapeutic treatment plan. This will help improve their quality of life during and after treatment.

Keywords: Aminoglycoside, TB, hearing impairment, quasi-experimental, otoacoustic emissions, social isolation, stigmatization.

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND

Tuberculosis (TB) remains one of the deadliest infectious diseases responsible for mortality across the world (Agyeman & Ofori-Asenso, 2017). According to the World Health Organization (WHO), about 10.4 million people contracted TB in 2016 with 400 thousand of this number being HIV positive. Tuberculosis is present in every part of the World, but in 2016, Asia recorded the highest incidence of TB (45%) in the world with Africa coming second with an incidence of 25%. Seven countries in the world account for 64% of global TB infection rates. India has the highest TB infection rate in the world followed by Indonesia, China, Philippines, Pakistan, Nigeria and South Africa. Over 95% of TB cases and deaths occur in developing countries. Nigeria and South Africa account for the highest cases of TB in Africa (Raviglione & Sulis, 2016; WHO, 2018b). According to the WHO, HIV co-infection is increasing the burden of TB with TB accounting for 40% of HIV mortalities. It is widely known that people infected with HIV have a compromised immune system making them 20 to 30 times more likely to develop active TB (WHO, 2018b).

Tuberculosis was the greatest cause of mortality in the Gold Coast (now Ghana) (50% mortality in victims) and is still a silent killer today (7.8% mortality). In 2016, Ghana recorded 14, 632 new cases of TB, with a case detection rate (CDR) of 32%, and a TB-HIV co-infection rate of 2%. The current surveillance system in the country is detecting about 52 per 100,000 population (Ghana Health Service, 2017a, 2017b, 2017c).

According to the National Tuberculosis Control Program (NTP), a survey conducted in 2014 revealed that the burden of TB in Ghana (286 per 100,000 people) is four times higher than the WHO estimates (71 per 100,000 people) for the country (Ghana Health Service, 2017b). The degree of co-morbidity between TB and HIV/AIDS has also been found to be fueling the burden. Multi-drug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) have also emerged as a public health concern and a major threat to the effective control of TB. Treatment successes for drug resistant TB are still poor and the inability to detect and report such cases remain a huge problem (Agyeman & Ofori-Asenso, 2017). It is estimated that about 600,000 new cases of rifampicin resistance were reported globally in 2016 of which 490,000 were confirmed as MDR TB (WHO, 2018b).

Multidrug-resistant TB cases are being reported in Ghana in increasing numbers and the National TB Program (NTP) attributes it to increasing weakening support for patients care. The NTP reported that 77 cases of MDR TB in 2016, up from 60 recorded in 2015 are being treated (Ghana Health Service, 2017b). Drug resistance surveillance studies carried out in Ghana revealed a high prevalence of 24-36% MDR TB among previously treated patients (Forson, Kudzawu, Kwara, & Flanigan, 2010; Kato et al., 2014; Forson et al., 2018).

The high prevalence of drug resistant TB in Ghana has been attributed mainly to the high incidence of retreatment cases. Statistics indicate that of the approximately 15,000 patients that are diagnosed with TB every year in Ghana, retreatment cases constitute about 5-6% (Forson et al., 2018). Forson et al., (2018) further revealed that in a review of NTP data on patients who have undergone treatment in 2015, 46% were relapsed patients, 26% defaulted or failed treatment, and 27% were made up of extra-pulmonary TB, smear-negative pulmonary TB and patients who were unable to do a sputum smear (Forson et al., 2018). Studies carried out in other African and low-

income countries revealed that the treatment outcomes of retreatment regimens show success rates of only 50-60% which is worrying and gives cause for concern (Ottmani et al., 2006; Tabarsi et al., 2011; Nakanwagi-Mukwaya et al., 2013).

The prevalence of MDR TB is increasing globally. It has become a public health concern and requires treatment with aminoglycosides which are an essential part of second-line anti-TB drugs. However, ototoxic hearing loss is a major downside and limitation for their use. (Harris, Peer, & Fagan, 2012; Olusanya, Neumann, & Saunders, 2014; Sharma, Bhagat, Verma, Singh, & Singh, 2016).

Hearing loss is regarded as the “fourth highest cause of disability globally” (WHO, 2018a), and in 2018, WHO estimated that about 466 million people (5% of global population) have disabling hearing loss globally. About 432 million (91%) of this number are adults and 34 million (9%) are children. According to the WHO, the rate of disabling hearing loss has been on a steady rise during the past 10 years and it has been projected that by 2050, over 900 million people (1 in every 10 people) will have disabling hearing loss. The global estimates of disabling hearing loss are most prevalent in the South Asia, Asia Pacific and sub-Saharan Africa regions (WHO, 2018c).

It is estimated that about 110,625 (0.4% of national population) people have hearing loss in Ghana. About 50,125 of this number are males and about 60,500 are females (Ghana Statistical Service, 2013). Risk factors accounting for this impairment include genetics, birth complications, infectious diseases and medications used in treating drug-resistant TB. Hearing loss that is not addressed can result in an annual global cost of 750 billion dollars. An unaddressed hearing loss can impact people functionally, socially, emotionally and economically (WHO, 2018c).

1.2 PROBLEM STATEMENT

Tuberculosis remains one of the leading infectious diseases affecting a wide spectrum of individuals worldwide. The control of TB depends largely on the use of antibiotics of which aminoglycosides are included. Studies have shown that people undergoing treatment for TB tend to have side effects such as hearing impairment. This has been attributed to the use of aminoglycosides (Peloquin *et al.*, 2004; Sturdy *et al.*, 2011; Modongo *et al.*, 2014; Nizamuddin, S; Khan, 2015; Sogebi *et al.*, 2017).

The hearing defect experienced due to anti-TB medication will affect drug adherence when patients are of the impression that compliance leads to hearing loss. This is an important public health problem. Some socioeconomic consequences of hearing impairment include feelings of loneliness, frustration, isolation, low income, low educational attainment, unemployment and underemployment (Emmett & Francis, 2015; WHO, 2018c).

In many jurisdictions, the effect of anti-TB drugs on hearing has been well documented, outcomes from these studies have helped with the management of TB and the information obtained has also supported TB control programs. However, very little work has been done to establish hearing loss among these patients in Ghana. The prevalence of these cases is not known as very few studies have been done in that direction. Currently, auditory assessment is not a vital part of the management of patients on anti-TB treatment regimen in Ghana. There is a paucity of research data to drive or support policies on the auditory assessment of these patients. It is therefore imperative a study such as this is conducted. The outcomes from this study will provide important information for managing patients on treatment for TB, ensure a better post-treatment quality of life for them and also help in the control of TB.

This study sought to investigate the prevalence of hearing loss in patients undergoing treatment for TB.

1.3 SIGNIFICANCE OF STUDY

The data derived from this study will, first, help establish the prevalence of hearing loss among TB patients under treatment. Second, it will provide research data to help drive policies, protocols and local guidelines on auditory assessment and rehabilitation of patients with TB. This will ensure that auditory monitoring becomes an important part of the management of patients on anti-TB treatment. Third, the findings will ensure that audiologists become part of the multi-disciplinary team of professionals involved in TB management and treatment in Ghana.

1.4 AIM OF STUDY

The aim of the study was to determine and establish the prevalence of hearing loss among patients on treatment for TB.

1.5 OBJECTIVES OF STUDY

The study objectives are as follows:

1. To determine the prevalence of hearing loss among patients with TB receiving treatment.
2. To establish the degree of association between TB treatment regimen and hearing loss.
3. To compare the hearing thresholds of TB patients receiving treatment to the controls.

1.6 HYPOTHESES

The following hypothesis was set and tested in line with the stated objectives;

H₁= There will be a significant difference between the hearing thresholds of TB patients

receiving treatment and the control group.

H₂= There will be a significant association between TB therapy and hearing loss.

CHAPTER TWO

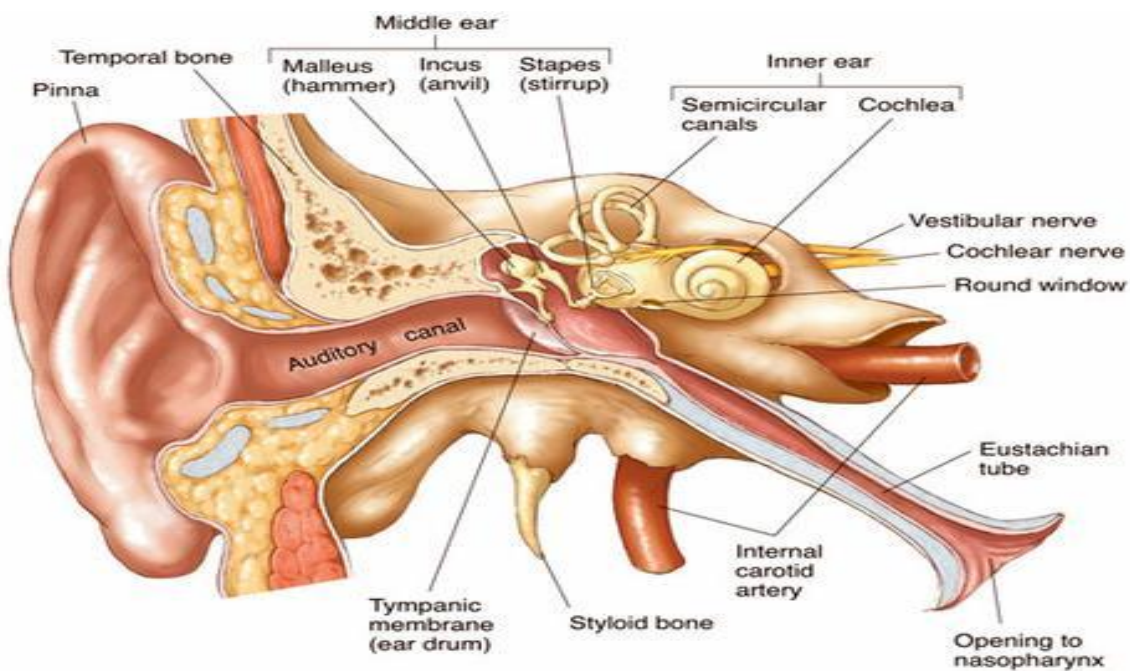
LITERATURE REVIEW

2.1 INTRODUCTION

The review of the anatomy and physiology of the auditory system, hearing loss, TB, hearing loss in patients on anti-TB regimen, association between TB treatment and hearing loss, and the pathophysiology of drug-induced hearing loss is presented in this chapter.

2.2 ANATOMY AND PHYSIOLOGY OF THE EAR

The hearing mechanism comprises the outer ear, middle ear and inner ear as shown in Figure 2.1.



Source: (Huch, 2013)

Figure 2.1: Parts of the auditory system

2.2.1 Outer Ear

The outer ear is made up of the auricle or pinna, the external auditory meatus, and the outer layer of the tympanic membrane. It plays the role of collection and resonating of sound. It helps in localizing the source of sound, and also serves to protect the tympanic membrane. The auricles are most visible as compared to the other portions of the out ear mechanism. There are individual differences in their size and shape. Their main function is to gather sound waves from the environment and channel them into the ear canal. They also help in sound localization and protection of the ear canal. They also boost sounds around 4500Hz through their role as resonators. The anatomy of the auricles enables them to deliver high frequency sounds efficiently than low frequency sounds (Martin & Clark, 2006; Stach, 2008).

The external auditory meatus is a narrow tube that leads from the concha of the auricle to the tympanic membrane. It is approximately 2.3 cm to 2.9 cm long and takes a downward bend as it nears the tympanic membrane. The outer two third of the external auditory meatus is lined with cartilage and the inner one third is skin-covered bone. The external auditory meatus channels sound to the tympanic membrane protects the tympanic membrane and enhances sounds around 2000-7000Hz as a result of its function as a resonator (Martin & Clark, 2006; Stach, 2008).

The tympanic membrane (ear drum) has a total area of 90mm. It is located at the end of the ear canal, where it is protected from trauma and, kept at a constant temperature and humidity. It is concave in shape and curves slightly inside. The tympanic membrane is vibrated when it is struck by acoustic pressure. The tympanic membrane is very thin, averaging about 0.07 mm, and has an extremely efficient vibrating surface. Its whole area is very rich in blood supply, which explains why it gives a reddish appearance when there is an infection or blood is brought to the area (Martin & Clark, 2006; Stach, 2008).

2.2.2 Middle Ear

The middle ear is an air-filled cavity situated within the temporal bone of the skull. It houses the ossicular chain, which consists of the 3 ossicles (malleus, incus, stapes) suspending in space, connecting the tympanic membrane to the oval window of the cochlea. These ossicles transmit sound-induced vibrations of the tympanic membrane to the cochlea through the oval window. The middle ear structures function as an impedance matcher, providing a bridge between the impedance of the air in the external auditory canal to the impedance of the fluid in the inner ear. First, the tympanic membrane's vibrating area is 17 times that of the oval window. Sound pressure collected over the surface of the tympanic membrane is concentrated on the smaller surface area of the oval window, resulting in an increased pressure. Also, the lever actions of the ossicles enable the malleus and incus to pivot. This results in increased stapedial footplate vibrations (Martin & Clark, 2006; Stach, 2008; Gelfand, 2016).

2.2.3 Inner Ear

The inner ear comprises the auditory and the vestibular labyrinths. The organs of equilibrium are housed in the vestibule and that of hearing are housed in the cochlea. The cochlea is filled with fluid and has a snail-shell shape. It has 2.5 turns and is located in the temporal bone. Within the cochlea lies the perilymph-filled scala vestibule and scala tympani. Between these two canals lie the endolymph-filled scala media (cochlea duct). The scala media is separated from the scala vestibule by the reissner's membrane and from the scala tympani by the basilar membrane. On the basilar membrane sits the organ of corti which is the sensory organ for hearing. The inner ear, or cochlea converts mechanical energy in the form of vibrations transmitted to the perilymph through the ossicular chain into electrical or neural impulses which is then taken to the brain

through the cochlea branch of the vestibulocochlea nerve where it is perceived as sound (Alberti, 2001; Martin & Clark, 2006; Stach, 2008; Gelfand, 2016).

2.2.4 Outer and Inner Hair Cells

The outer and inner hair cells are two sensory cells that play a vital role in hearing. They have different morphologies. The hair bundles of the inner hair cells are arranged linearly whereas those of the outer hair cells are arranged in a 'V' shape. There are three rows of 12,000 to 15,000 outer hair cells and one row of 3,000 inner hair cells. The outer and inner hair cells are separated from each other by Corti's arch. The hair cells have hair-like projections called stereocilia. These hair cells rest on the basilar membrane, and the stereocilia are in contact with the tectorial membrane. During stimulation, when the cilia bend in one direction, the nerve cells are roused. However, if they turn the other way, the nerve impulses are constrained; and if they turn to the side, there is no stimulation at all. Outer hair cells are involved in active cochlea process. They amplify small sounds thereby improving the sensitivity and the dynamic range of hearing. They are also responsible for 'sharpening' sounds in order to enhance frequency discrimination. The inner hair cells, however, transmit electrical sound-evoked signals to afferent auditory nerve fibres (Alberti, 2001; Martin & Clark, 2006; Stach, 2008; Gillespie & Müller, 2009; Hudspeth, 2014).

2.3 HEARING LOSS

Hearing ability is an indispensable human sense and very vital for an acceptable quality of life. Loss of hearing, therefore, is not only debilitating, but also stigmatized (Adeyemo, Oluwatosin, & Omotade, 2016a). Currently, hearing loss is one of the most dominant handicaps and prevalent sensory impairment in the world (Hesse, 2016; Mulwafu, Kuper, & Ensink, 2016). Hearing status is usually measured according to the lowest intensity of a sound signal that an individual can hear.

This is known as hearing threshold and it is quantified over a range of multiple frequencies that are stated in hertz (Hz). The commonly used frequencies include 250Hz, 500 Hz, 1000Hz, 2000Hz, 3000Hz, 4000Hz, 6000Hz and 8000Hz (Mahomed & De Wet Swanepoel , 2014). Hearing loss occurs in children and adults when hearing thresholds are found to be above 15dB and 25dB respectively (Mahomed & De Wet Swanepoel, 2014; World Health Organization, 2017).

2.3.1 Evaluation of Hearing Status

Hearing status is evaluated by using pure tone audiometry. It is regarded as the true test of hearing and also the gold standard for determining hearing thresholds. However, pure tone audiometry is just one of the tests in audiological test batteries, hence other tests are done to confirm and cross-check audiometric results. Pure tone audiometry employs air conduction (AC) and bone conduction (BC) pure tone signals to record hearing thresholds across multiple frequencies. Air conduction pure tones help determine the thresholds of sounds conducted through the entire auditory system (external, middle & inner ear) whilst BC allows for thresholds to be determined when the cochlea is stimulated directly. These tests can help determine the type, degree, configuration and symmetry of hearing loss. Using these two tests together can also enable the location pathological lesion causing hearing loss to be deciphered. Audiometric results are usually represented graphically on an audiogram (Mahomed & De Wet Swanepoel, 2014).

2.3.2 Types of Hearing Loss

Hearing loss is classified by the part of the auditory system (outer, middle or inner ear) that is affected. Hearing loss can, therefore, be conductive, sensorineural or mixed. Conductive hearing loss (CHL) is considered to be the second most prevalent form of all cases of hearing loss (Clarkson, Antunes, & Rubio, 2016). Conductive hearing loss occurs when sounds find it difficult

to get to the inner ear. This happens because sounds are not able to get past the outer and middle ear due to attenuation or reduced intensity of sound. This is mainly a problem of efficient sound transmission into the inner ear. Some common causes of conductive hearing loss include fluid in the middle ear, infections, Eustachian tube dysfunction, tympanic membrane perforation, impacted wax among others. Conductive losses can, however, be corrected with medicine or surgery (American Speech-Language-Hearing Association, 2018).

Any damage or dysfunction in the cochlea or the auditory nerve can result in sensorineural hearing loss. This type of loss causes loud sounds to become muffled. This has the tendency of affecting communication immensely (Henry & Heinz, 2013). In sensorineural hearing loss (SNHL), certain parts of the cochlea may be affected in several ways. These include the inner and outer hair cells, the spiral ganglion neurons, channel through which information is transmitted from the cochlea to the auditory brainstem (Kujawa & Liberman, 2006, 2009), and the stria vascularis, which produces endocochlea potential in the scala media of the cochlea (Liu et al., 2016). Factors accounting for SNHL include illnesses, exposure to loud noise, head trauma, ageing, genetic factors among others (ASHA, 2018a). Sometimes, damage can occur in the outer ear, middle ear and inner ear (cochlea). Such a loss has both conductive and sensorineural components and it is called mixed hearing loss. In cases of mixed hearing loss, the conductive component can be corrected through medical intervention (ASHA, 2018b).

2.4 TUBERCULOSIS

TB is a disease caused by *Mycobacterium Tuberculosis* (*M. Tuberculosis*). It is an air-borne disease and very infectious. Tubercle bacilli is another name given to *M. TB* and it is from this that the abbreviation TB is derived. (CDC, 2011; WHO, 2018b).

2.4.1 Mode of Transmission

Tuberculosis is mainly transmitted through air. *M. Tuberculosis* is contained in droplet nuclei released when an infected person sneezes, coughs or shouts. When the contaminated air is inhaled, it can lead to infection. These pathogens move from the mouth and nasal tract all the way to the alveoli of the lungs (Nicas, Nazaroff, & Hubbard, 2005).

2.4.2 Pathogenesis of TB

The presence of the TB bacillus in the alveoli of the lungs constitutes the occurrence of an infection. Inside the alveoli, the tubercle bacilli are engulfed by the macrophages where they evade the effects of the phagocytosis, they survive within the macrophages where they rapidly proliferate and are released to infect other cells, tissues, organs and areas of the body (CDC, 2013). Some of these areas include the lymph nodes, kidney, apex of the lungs, brains, and bone (Nicas *et al.*, 2005). Specialized immune cells ingest some of the pathogens and keep the rest contained within 2-8 weeks. The strength of a person's immune system determines whether the bacilli will be able to be contained. If the bacilli are contained, such a condition is known as latent TB infection (LTBI). Individuals with LTBI are not infectious and do not fall sick or exhibit any symptom because the bacteria are inactive in their body. However, LTBI can always progress to full-blown TB disease at any time the immune system is compromised or suppressed. If the immune system is unable to control the bacilli, they multiply rapidly resulting in TB disease (CDC, 2013)

2.4.3 Sites of TB disease

Tuberculosis can occur at two sites namely pulmonary and extra-pulmonary sites. Tuberculosis disease that mostly affects only the lungs is referred to as pulmonary TB (PTB). It is responsible

for the majority of all cases of TB. Individuals with PTB have symptoms such as a cough and abnormal chest radiography. Such individuals may also be highly infectious (CDC, 2013b). Tuberculosis disease can occur in other areas of the body. Some of these areas include the spine, lymph nodes, pleura, brain, kidney, bones and joints. Extra-pulmonary TB (ETB) can occur simultaneously with PTB. This is the case especially among persons with HIV. Individuals with ETB are not infectious but can become infectious in some situations (CDC, 2013b).

2.5 DIAGNOSES OF TUBERCULOSIS

Tuberculosis like all infectious diseases can be detected presumptively at the clinical level and confirmed by specific laboratory methods. Active TB is diagnosed by finding bacilli in specimen from the respiratory tract (pulmonary TB) or in specimen derived from other sites in the body (Extra-pulmonary TB) (Dahman, Algosadi, Mohammed, Alahmari, & Ali, 2018). Any individual suspected to have been infected with TB is required to undergo a complete medical evaluation comprising of medical history, physical examination, test for *M. TB* infection (TST or IGRA), chest radiography and bacteriologic examination (CDC, 2013a; Dahman *et al.*, 2018).

2.5.1 Medical History

This explores history of direct exposure to TB, known exposure to any individual infected with TB, symptoms of TB and past history of diagnosis with TB or LTBI. Steps are also taken to identify co-morbidities like HIV that can pose a threat. Symptoms manifested by patients with pulmonary TB include coughs lasting 3 weeks or more, coughing up blood, chest pains, appetite loss, weight loss, night sweats, fever, and fatigue. Symptoms presented by patients with extra-pulmonary TB, on the other hand, are mostly related to the part of the body that is infected. (CDC, 2013a; Dahman *et al.*, 2018).

2.5.2 Physical Examination

Physical examination is done to determine the patient's overall physical condition. The information that is derived helps in choosing the appropriate diagnosis and identifying comorbidities that might affect treatment after diagnoses. Physical examination, however, is not only used in establishing TB infection or otherwise (CDC, 2013a; Dahman *et al.*, 2018).

2.5.3 Test for *M. Tuberculosis*

Detection of *M.TB* is accomplished through skin or blood tests. The skin test is the mantoux tuberculin skin test (TST) and the blood test is the interferon-gamma release assays (IGRAs). These tests are used to differentiate individuals infected with *M.TB* from those who have not been infected. Since these tests are not able to differentiate LTBI from TB disease, supplementary tests are required (CDC, 2013a; Dahman *et al.*, 2018).

2.5.4 Chest Radiography

The Chest Radiograph is mostly used in diagnosing PTB. In most cases, PTB presents with chest abnormalities on the radiograph. The standard assessment used in the detection of these chest abnormalities is a posterior-anterior radiograph of the chest. These abnormalities evident on the chest radiogram may be suggestive of TB, but cannot be solely used to diagnose TB. It can, however, be used to rule out TB disease in an individual who is HIV-negative, has positive TST reaction or IGRA and not manifesting symptoms of TB disease (CDC, 2013a; Dahman *et al.*, 2018).

2.5.5 Bacteriologic Examination

Examination of clinical samples (sputum, urine) has a serious diagnostic importance. It is important that the specimens are inspected and cultured in a laboratory specifically designed for detecting *M.TB*. Furthermore, drug susceptibility testing is performed to establish resistance to the first-line drugs. The result of this test determines the appropriate drugs that should be used to treat a particular patient (CDC, 2013a; Dahman *et al.*, 2018).

2.6 TREATMENT OF TUBERCULOSIS

Tuberculosis treatment can last for at least 6 months or longer. During the first 8 weeks of treatment, most of the bacteria are killed, but there are some organisms that require longer treatment hence patients must still complete additional 4 months of therapy in order to avoid relapse. An effective TB therapy must contain multiple drugs that the bacteria is vulnerable to. A four-drug regimen is the acceptable standard of care for the commencement of TB treatment. To prevent resistance by bacteria to drugs, treatment with a single drug is discouraged. The case management policy adopted by the WHO to help ensure adherence to therapy is the Directly Observed Therapy, Short-course (DOTS). It involves the designation of a health worker to monitor and document the intake of drugs by a patient undergoing treatment. This strategy has become necessary in order to minimize the development of drug resistance, treatment failure, and relapse (CDC, 2013c; WHO, 2017).

2.6.1 Categories of Treatment

Category I: This is applicable to new cases with sputum smear-positive or negative PTB and ETB. Patients who fall within this category are put on a 6-month treatment consisting of two months of rifampicin, isoniazid, pyrazinamide, and ethambutol followed by 4 months of isoniazid and

rifampicin. However, patients with ETB are put on treatment for up to nine months depending on the anatomical site of the infection. The intake of these regimens are supervised daily by the Health worker (NTP, 2012b; WHO, 2017)

Category II: In cases of relapse due to treatment failure or default, patients are put on an 8-month regimen consisting of 3 months of daily supervised rifampicin, isoniazid, pyrazinamide, and ethambutol, supplemented by streptomycin in the course of the first two months, followed by 5 months of daily rifampicin, isoniazid and ethambutol (NTP, 2012b; WHO, 2017).

Category III: For Children who are below 12 years, a 6-month regimen is given to them. This regimen consists of two months of isoniazid, rifampicin and ethambutol and four months of isoniazid and rifampicin (NTP, 2012b; WHO, 2017).

2.6.2 Phases of Treatment

Every TB therapy has two phases, a preliminary intensive phase and a later continuation phase. Usually, the intensive phase lasts for 2-3 months. Once treatment is commenced, the patient becomes less infectious. In the intensive phase, the standard regimen for drug-susceptible TB is made up of rifampin, isoniazid and pyrazinamide. Ethambutol is also added in order to protect against any resistance to one of the three main drugs. However, once susceptibility to the three core drugs is confirmed, Ethambutol can be discontinued. The risk of developing drug resistance is very high in this phase. This phase consists of two months of rifampicin, isoniazid, pyrazinamide, and ethambutol under the supervision of a health worker. The continuation phase spans 4 or 5 months and the patients are put on a regimen consisting of isoniazid and rifampicin. This phase is usually not supervised but requires patients to report to the treatment center once

every week. On monthly visits, however, reviewing of progress is done, counselling offered and new drugs supplied (NTP, 2012b; WHO, 2017). The first-line TB drugs are depicted in figure 2.2.



Source:(CDC, 2013c)

Figure 2.2: First-line TB medications (Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol)

2.7 DRUG-RESISTANT TUBERCULOSIS

There are instances where *M. tuberculosis* can become resistant to the first-line anti-TB drugs used in TB treatment. Any resistance to at least isoniazid and rifampicin is referred to as multidrug-resistant TB. The advent and spread of MDR TB are attributed to improper use of TB medications, poor quality drugs, use of single drugs, poor storage conditions, person-to-person transmission, and premature interruption of treatment (WHO, 2014, 2016). The treatment and management of MDR TB can be very difficult and expensive. This results in the development of even more severe resistance to anti-TB drugs called extra drug-resistant TB (XDR TB). The XDR TB is a very

uncommon type of MDR TB that does not respond to isoniazid and rifampicin, in addition to any fluoroquinolone and at least one of the three injectable second-line drugs (amikacin, kanamycin, or capreomycin). Second-line regimens are used in treating patients with confirmed or suspected MDR TB, poly-resistant TB, and rifampicin mono-resistance. These regimens are very expensive and have many side effects (NTP, 2012a; WHO, 2014, 2016). The treatment of MDR TB is in two phases: the injectable phase and the continuation phase. In the initial phase, the patient is initiated on an injectable drug for at least 8 months. The treatment progresses to the continuation phase after the first phase is completed. The continuation phase lasts for at least 12 months. The MDR TB treatment has a total duration of at least 18-24 months (NTP, 2012a; WHO, 2014). However, the WHO recently rolled out a shorter treatment regimen for MDR-TB. This shorter regimen spans 9-12 months (WHO, 2014, 2016).

2.8 TB-HIV CO-INFECTION

TB-HIV co-infection has been regarded as the deadliest dual epidemic (Panda et al., 2018). A high HIV prevalence is reported to be associated with increased rate of developing active TB as HIV accelerates the development of the disease during primary TB infections (Allen et al., 1992). Selwyn et al., (1989) also added that TB-HIV co-infection is generally due to the reactivation of latent TB infection in persons with HIV. Patients with TB-HIV co-infection undergo both anti-TB therapy and antiretroviral therapy concurrently. These therapies have well-known synergistic and additive effects on the outer hair cells resulting in SNHL (Katijah, 2010; Harris, Peer, *et al.*, 2012; Harris, Bardien, *et al.*, 2012).

2.9 RELATIONSHIP BETWEEN TUBERCULOSIS AND HEARING LOSS

TB-related hearing loss can be attributed to various causes including ototoxicity from aminoglycosides including streptomycin (Adeyemo, Oluwatosin, & Omotade, 2016b). Studies have reported significant side effects associated with TB treatment of which ototoxicity features prominently. These side effects have also been reported to have effect on treatment adherence and play a vital role in treatment default (Awofeso, 2008; Gülbay *et al.*, 2006). Ototoxicity due to aminoglycosides is regarded as one of the important etiological factors for hearing loss. These aminoglycosides are the most common cause of hearing loss especially among patients on anti-TB therapy (Adeyemo *et al.*, 2016b). Literature is replete with studies on the ototoxic side effects of anti-TB therapy.

Yang *et al.*, (2017) in a study to determine the side effects associated with the treatment of patients with MDR TB, retrospectively and consecutively reviewed the medical records of 256 patients who were initiated on anti-TB treatment regimen between January 2006 and December 2011. The results indicated that various side effects were evident in 95 (37.1%) of the patients. Ototoxicity was one of the most frequently observed side effects. It was observed in 4 patients (1.6%) and it was found to have occurred at mean 4.7 months after the start of the therapy.

Furthermore, a study to determine the side effects of anti-TB drugs was also investigated by Gülbay *et al.*,(2006). The records of 1,149 patients who have undergone anti-TB therapy were reviewed. The results revealed the main side effects of the therapy to be ototoxicity (1.7%).

In another study, Törün *et al.*, (2005) evaluated the side effects observed in 263 MDR TB patients in the course of treatment with anti-TB treatment regimen. The medical records of all patients enrolled in the study who received anti-TB therapy were reviewed. The results indicated that side

effects were evident in 182 cases (69.2%). Ototoxicity was confirmed as the most common side effect and it was detected in 110 cases (41.8%). Ototoxicity was defined in the study as the presence of tinnitus, hearing loss confirmed by pure tone audiometry, and vertigo. Ototoxic hearing loss is regarded as a common and one of the most frequently observed side effects experienced by patients on anti-TB therapy.

2.10 PATHO-PHYSIOLOGY OF AMINOGLYCOSIDE OTOTOXICITY

Ototoxicity is the result of the exposure of the inner ear to drugs and therapeutic agents leading to hearing impairment (Rybak & Ramkumar, 2007). The damage and functional impairment are usually in the inner ear and areas most affected include the cochlea, the vestibular systems as well as the vestibule-cochlea. Ototoxicity is mainly a result of exposures to ototoxic drugs or chemical agents (Roland & Rutka, 2004; Yorgason, Fayad, & Kalinec, 2006).

Ototoxicity among TB patients is mainly due to antibiotics used in the treatment of TB called aminoglycosides. Aminoglycosides can affect the cochlea in which case they are said to be cochleotoxic, or vestibulotoxic when they affect the vestibular apparatus. Streptomycin is primarily vestibulotoxic, whereas amikacin, kanamycin and neomycin are essentially cochleotoxic. Damage to the cochlea can induce permanent hearing loss and tinnitus whilst damage to the vestibular system can result in dizziness (vertigo), ataxia, and/or nystagmus (Selimoglu, 2007). Aminoglycoside-induced hearing loss has a distinct pattern which shows the high frequencies (4000-8000Hz) being affected first with the lower frequencies affected later (Human *et al.*, 2010).

Aminoglycosides enter the inner ear fluids via the bloodstream following parenteral administration. Their presence is evident in the inner ear within a couple of minutes and may

plateau within 30 minutes to 3 hours following systemic administration (Schacht, 2004; Huth, Ricci, & Cheng, 2011). Huy *et al.*, (1986) identified the delayed presence of aminoglycosides in inner ear tissues long after the bloodstream has been rid of the drug. Despite having a shelf-life of 3-5 hours in serum, aminoglycosides can, however, stay longer in the inner ear fluids even months after treatment has ended. This explains the occurrence of post-treatment delayed hair cell death (Huy *et al.*, 1986; Schacht, 2004).

In the cochlea, aminoglycosides can be found in the hair cells and in some supporting cells. Although these drugs reach the inner ear shortly after administration, it, however, takes several days before hair cell destruction starts (Hashino & Shero, 1995; Hiel *et al.*, 1993). Once aminoglycosides enter the inner ear, they bind with irons which results in the formation of free radicals known as reactive oxygen species (ROS). This ROS activates and triggers active signal pathways that result in cell death from apoptosis. This apoptosis permanently destroys the outer hair cells leading to irreversible hearing loss. Initial effects of the aminoglycoside-induced hearing loss occur in the outer hair cells at the basal portion of the cochlea where high frequencies are processed and then progresses to the apical portion of the cochlea that processes low frequencies (Hiel *et al.*, 1993; Barclay & Begg, 1994; Schacht, 2004; Guthrie, 2008; Huth *et al.*, 2011; Karasawa & Steyger, 2011; Tabuchi *et al.*, 2011).

2.11 EFFECT OF ANTI-TUBERCULOSIS TREATMENT REGIMEN ON HEARING STATUS

Aminoglycosides used in the treatment of TB often induce ototoxic hearing loss by damaging the hair cells leading to their permanent loss (Kawamoto *et al.*, 2004). This affects hearing thresholds resulting in hearing impairment. This is very prevalent and has been investigated by several studies.

A study conducted by Javaid *et al.*, (2018) to determine the effects of aminoglycosides on the hearing status of MDR TB patients revealed the presence of ototoxicity in 36.83% of the study participants. This was a retrospective study of 543 MDR TB patients initiated on treatment with the injectable microbials amikacin and capreomycin. Baseline audiograms were obtained for all patients before the commencement of the therapy. Of the 200 patients confirmed of manifesting evidence of ototoxicity, hearing loss was reported in 59 of them, tinnitus in 69, and 73 of them showed evidence of both tinnitus and hearing loss. The study also mentioned age, gender, treatment duration along with aminoglycosides as risk factor for ototoxicity. Amikacin was also established as more ototoxic than capreomycin.

In a related study, Tiwari *et al.*, (2016) also investigated kanamycin-induced ototoxicity in 100 MDR TB patients receiving kanamycin during the intensive phase of their treatment for TB. Out of the 100 patients, ototoxicity symptoms were observed in 37 of them. Hearing loss was exclusively observed in 36 of the patients, whilst one patient presented with both hearing loss and vertigo. The study further revealed that, about 25 (67.6%) of the patients developed ototoxicity as a result of kanamycin within one month of treatment commencement, 4 (10.8%) during the second month, 1(2.7%) in the third month, 2(5.4%), 3(8.1%) and 2(5.4%) during the fourth, fifth and sixth months respectively. The study went on to disclose that, 35 of the patients had a mild sensorineural hearing loss while moderate sensorineural hearing loss was observed in 2 patients. Bilateral hearing loss evidenced in 36 of the patients.

Nizamuddin *et al.*, (2015) investigated the effect of second line aminoglycosides (amikacin, kanamycin and streptomycin) on the hearing status of MDR TB patients. This was a prospective study done from 2009 to 2014 that enrolled 84 patients with. Patients were put into three groups; group I ($n=27$) patients on amikacin, group II ($n=40$) patients on kanamycin and group III ($n=17$)

patients on streptomycin. Baseline audiograms were obtained before the commencement of treatment and pure tone audiometry was carried out every 3 months until the end of the treatment. The results established the evidence of hearing loss in 19 (22.7%) patients. High-frequency hearing loss was evident in 11 (58%) patients, low-frequency hearing loss was observed in 2 (10.5%) patients and the incidence of dead ear was evident in 6 (31.5%) patients. The study concluded that amikacin (47.36%, 9 cases out of 19 cases) was more ototoxic than kanamycin (36.84%, 7 cases out of 19 cases) and streptomycin (15.78%, 3 cases out of 19 cases).

Modongo *et al.*, (2014) analyzed the treatment outcomes of amikacin-based regimen and its effect on the hearing status of MDR TB patients using a retrospective cohort study. About 437 patients who received amikacin-based therapy between 2006 and 2012 were included in the study. About 288 (66%) of the sample size were HIV co-infected. The results indicated that 147 (54%) patients had hearing loss. Out of the 313 (72%) patients who completed treatment, 228 (73%) were cured. The study concluded that curing MDR TB was associated with longer amikacin treatment duration and higher dosage, however, these were also associated with the development of hearing loss.

Brits *et al.*, (2012) studied the consequence of TB on the hearing thresholds of gold miners by reviewing and analyzing the audiometric data of 2,698 gold miners who were with and without TB. Participants were put into three groups- single treatment ($n=911$), multiple treatment ($n=376$) and a control group comprising 1,411 participants. Bilateral hearing thresholds were analyzed in conjunction with biographic and occupational data. The results indicate that the hearing thresholds for the TB (experimental) groups were significantly ($p<0.01$) elevated compared to those of the control group. Also, hearing thresholds overtime also worsened significantly more ($p<0.01$) in the miners with TB compared to those without TB. In addition, the smallest difference in hearing

thresholds was noted between the single and multiple TB treatment groups, with the multiple treatment groups presenting with the poorest thresholds.

2.12 PREVALENCE OF HEARING LOSS AMONG PATIENTS ON ANTI-TUBERCULOSIS REGIMEN

2.12.1 Prevalence in the World

Literature abounds with prevalence studies on hearing loss among patients on anti-TB therapy. Few of such studies conducted in North America, Asia, Europe and South America are discussed.

Peloquin *et al.*, (2004) conducted a study on 87 patients in the United States of America to compare the prevalence of ototoxic hearing loss among patients receiving either of two recommended anti-TB regimens. The findings revealed ototoxicity in 32 (37%) of the patients initiated on the regimen.

Sharma *et al.*, (2016) carried out a study in India between 2012 and 2014 to investigate the extent of hearing loss in 100 MDR TB patients receiving kanamycin-based regimen. Baseline audiometry was conducted before the commencement of therapy and repeated after 1 week and 6 weeks of therapy. Results indicated the presence of ototoxicity in 18 patients. A high frequency hearing loss incidence of 14% was reported.

A study of 50 patients commencing TB treatment was also carried out in the United Kingdom between 2004 and 2009. A total of 50 patients were initiated on injectable aminoglycosides regimen in five (5) centres in the UK. Out of the 50 patients, 29/50 (58%) received amikacin, 11/50 (22%) were put on capreomycin, and 10/50 (20%) received streptomycin. Out of the total of 50

patients enrolled in the study, 14 patients developed ototoxicity which is equivalent to a prevalence of 28% (Sturdy *et al.*, 2011).

Furthermore, a descriptive study that analyzed the hearing status of 97 patients undergoing treatment for PTB was carried out in two reference Hospitals in Brazil between November and December 2009. The study included patients between 18 and 60 years who consented and were on anti-TB therapy. About 52 of the patients were initiated on a first-line regimen, and 45 were on second-line regimen. Interviews were employed to collect demographic and clinical data, whilst pure tone audiometry was used to collect data on hearing thresholds. Results showed evidence of hearing loss in 23 of the patients which correspond to a prevalence of 23.7% (Vasconcelos, Lima, Frota, Ruffino, & Kritski, 2012).

In addition, a study that assessed the hearing status of 64 patients with MDR TB who completed second-line aminoglycosides therapy from 2000 to 2006 was conducted in India. Patients were put into 3 groups: group I, 34 patients on amikacin, group II, 26 patients on kanamycin and group III, and 4 patients on capreomycin. Baseline audiograms were obtained and follow up audiological evaluation was also done. The authors reported high frequency (4000-8000Hz) SNHL in 12 patients representing 18.75% of the patients included in the study (Duggal & Sarkar, 2007).

A study was conducted in Portugal to evaluate the auditory status of MDR TB patients who completed anti-TB therapy between 2009 and 2012. It included 11 of the 22 patients (corresponding to 50% response rate) invited for evaluation. Patients underwent pure tone and speech audiometry, distortion product otoacoustic emissions testing (DPOAE) and tympanometry. The results revealed sensorineural hearing loss in 6 patients representing a prevalence of 60% (Ribeiro *et al.*, 2015).

2.12.2 Prevalence in Africa

Most of the prevalence studies on hearing loss stemming from anti-TB medications coming out of Africa are reported in Southern, Eastern and to some extent West Africa.

A study was conducted in Zambia to determine the extent of hearing loss among MDR TB patients receiving kanamycin therapy for 8 months in the initial phase. Extended high frequency pure tone audiometry was conducted before or within two weeks of treatment commencement in the first phase. In the second phase, extended high frequency audiometry was done after several months of treatment. The study reported a hearing loss prevalence of 92.1% representing 35 of the study participants. The relatively high proportion of patients with hearing loss when compared to similar studies is attributed to the extended high frequency audiometry used in assessing hearing status of patients, the high proportion of patients with HIV co-infection (76%) which in its self is a risk factor for hearing loss, and the exclusive use of kanamycin with known cochleotoxic effects (Mwansasu, Siziya, & Mpondo, 2017)

Also, a study was also conducted in South Africa to investigate cochlea-vestibular clinical and audiometric findings among 53 MDR TB and XDR-TB patients on treatment with second-line aminoglycosides. Evaluation of patients was done by employing otoscopy, diagnostic audiometry and tympanometry. Findings revealed a proportion of 47% of patients with significant hearing losses (Ramma & Ibekwe, 2012).

In addition, a prospective cohort study was conducted in Cape Town, South Africa to document the occurrence of ototoxic hearing loss among 151 MDR TB patients aged between 14 and 70 years. They underwent treatment with kanamycin (145 patients; 96%), streptomycin (5 patients; 3%) and capreomycin (1 patient; 1%). About 86 (57%) of the patients were confirmed of being

HIV-positive and the rest HIV-negative. Patients were evaluated using tympanometry and pure tone audiometry after their demographic data was collected. Pure tone was conducted monthly for 3 months. The findings revealed a high frequency (4000-8000Hz) hearing loss prevalence of 58% which is equivalent to 87 patients. The study concluded that the prospect of developing hearing loss was higher in HIV-positive patients (60/86; 70%) as compared to HIV-negative patients (27/65; 42%) (Harris, Bardien, *et al.*, 2012).

A retrospective cohort study conducted in Namibia compared the cumulative prevalence of hearing loss among 353 patients with MDR TB who have undergone amikacin and kanamycin-based therapy. Pure tone audiometry was carried out at baseline, intensive treatment phase and continuation phase of treatment. The findings showed the occurrence of hearing loss in 206 patients which represents a cumulative prevalence of 58% (Sagwa *et al.*, 2015).

2.12.3 Prevalence in West Africa

Prevalence studies on hearing loss among TB patients undergoing therapy found in the West Africa sub-region have all been conducted in Nigeria. One of such studies was carried out at the University of Port Harcourt Teaching Hospital between January and May 2013. The study investigated the effect of second-line anti-TB drugs on the hearing status of 28 patients with MDR-TB. Baseline audiograms were obtained from the patients before the commencement of therapy. Pure tone was again conducted 3 months after the initiation of therapy. Patients were put on kanamycin, levofloxacin, pyrazinamide and cycloserine. The study reported a hearing loss prevalence of 61% (Ibekwe & Nwosu, 2016).

In a related study conducted in Nigeria, the incidence of aminoglycoside-induced hearing loss was ascertained in 70 patients with MDR on anti-TB therapy. Baseline audiograms were obtained and

serial pure tone audiometry (PTA) were conducted at 4 weekly intervals until discharge after being on admission for 4 months. Aminoglycoside-induced hearing loss was confirmed by comparing Serial to baseline PTA. The study reported ototoxicity in 16 of the patients which correspond to a prevalence of 22.9% (Sogebi, Adefuye, Adebola, Oladeji, & Adedeji, 2017). The present study is the very first in Ghana that borders on hearing loss resulting from anti-TB medications.

2.13 RESEARCH GAP

Although a significant number of studies have been conducted in other jurisprudence on the prevalence of ototoxic hearing loss among patients undergoing anti-TB therapy, no such study has been done in Ghana. Currently, the prevalence of hearing loss among TB patients receiving therapy in the country is unknown and this presents a gap in literature. Also with a high prevalence of TB in Ghana, it implies that there is likely going to be a significant number of TB patients that will proceed to aminoglycoside-based treatment. In addition, MDR TB prevalence has been on the increase in recent times and a case of XDR-TB was recently also recorded in the country for the first time (Appiah, 2017; Odhiambo, 2017; Yusif, 2018). Presently, there are no protocols, policies or specific guidelines in place to monitor ototoxicity that may arise from aminoglycoside-based therapy. This is largely due to the unavailability of data to help in that regard. It is based on this necessity that the current study was designed to address some of these gaps in literature by determining and establishing the prevalence of hearing loss among patients receiving anti-TB therapy.

CHAPTER THREE

METHODOLOGY

3.1 INTRODUCTION

This chapter explains the methodology that was employed for the study. The chapter looks at the study design, study area, study population, sampling techniques, research instruments, data collection procedures and tools, infection control, data management plan and analysis and ethical consideration.

3.2 STUDY DESIGN

The design employed for this study was a quasi-experimental, post-test only with non-equivalent control group. This study design is deemed ideal in the face of “practical and ethical barriers to conducting randomized controlled trials” (Grimshaw, Campbell, Eccles, & Steen, 2000). Hearing loss constituted the dependent variable and the treatment regimen constituted the independent variable.

3.3 STUDY AREA

The study was conducted at the Tema General Hospital. Study participants were enrolled from the Chest Clinic of the Tema General Hospital. The hearing assessments were also conducted at the Chest Clinic.

3.3.1 Profile of Study Area

The Tema metropolis is among the 13 districts constituting the Greater Accra Region of Ghana. It is a harbour city located in the southeastern part of Ghana. There are several health facilities

within the metropolis. These include private health facilities, health centers, a polyclinic and the Tema General Hospital.

3.3.2 Tema General Hospital

The Tema General Hospital is the main government hospital providing healthcare for the entire metropolis and beyond. It was established in 1954 and currently serves as the major referral centre for all major clinics and hospitals within the metropolis. The Chest Clinic is one of the specialized clinics run by the hospital. The clinic attends to both in-patients and out-patients with TB.

3.4 STUDY POPULATION

The target population of this study consisted of male and female patients diagnosed with TB and attending the Chest Clinic of the Tema General Hospital.

3.5 SAMPLING

3.5.1 Sample Size

A recent study conducted in Nigeria reported the proportion of TB patients with hearing loss at 22.9% (Sogebi, Fadeyi, *et al.*, 2017). Based on this proportion, the sample size was calculated using the equation below;

$$n = \frac{Z^2 p(1 - p)}{E^2}$$

where

n is the estimated minimum sample size

E is the allowable confidence level (margin of error) (0.1)

Z is the critical score for 90% confidence interval (1.645)

P is the proportion of TB patients with hearing loss in the population (0.229)

Using the assumed values, a minimum sample size of 48 participants was generated. However, 60 participants were recruited into the study.

3.5.2 Sampling Method

The purposive sampling technique was employed to recruit participants for the study.

3.5.3 Sampling Procedure

Patients who visited the chest clinic during the period of the study and consented to be part of the study were included in the treatment group. Healthy volunteers who consented were included in the control group. The patients recruited into the study were grouped into treatment (60 participants) and control (60 participants). The treatment group was defined as patients with confirmed diagnosis of TB and undergoing treatment with either first-line anti-TB drugs, whilst the control group was defined as healthy consenting volunteers. The treatment and control groups were matched based on age and gender.

3.6 INCLUSION AND EXCLUSION CRITERIA

3.6.1 Inclusion Criteria

All consenting patients diagnosed with TB from age 18 to 50 years attending the Chest Clinic of the Tema General Hospital.

3.6.2 Exclusion Criteria

The following criteria were used:

- Patients aged below 18 and above 50 years
- Patients on TB treatment for less than one month.
- Patients taking or have taken any ototoxic medications within the last three months.
- Patients with ear infection or discharge.

3.7 INSTRUMENTATION

3.7.1 Otoscope

The Heine otoscope was used to examine the external auditory canal of the participants. An otoscope is an audiological device composed of a head and a handle. The head contains a light source and a magnifying lens. The switch is located on the handle whilst the front end of the otoscope has an attachment for specula. Otoscopy was done to detect ear infections, impacted wax, foreign body and perforated eardrum.

3.7.2 Transient-Evoked Otoacoustic Emission

The Echo-screen TS SET transient-evoked otoacoustic emission (TEOAE) was used to assess hair cells motility in participants. The Echo-screen TS SET TEOAE is a fast, reliable and easy to use OAE device used in detecting hearing loss in newborns and adults. It detects hearing loss by employing automated otoacoustic emissions (AOAE) which includes TEOAE technology. The device has a miniature probe containing a loudspeaker and a microphone. The loudspeaker generates the acoustic stimuli and the microphone records the sound produced by the cochlea. The probe is usually inserted into the ear of the patient and a click or tone burst is presented. The

testing frequency range of the TEOAE is 500-4000Hz. When the probe is inserted into the ear, the loudspeaker generates a stimulus that is propagated all the way into the cochlea. Once in the cochlea, it causes the activation of outer hair cells. The energy associated with the outer hair cells movement is propagated back into the ear canal to be detected by the microphone. The recorded stimulus is analyzed and the presence of OAE is confirmed. The Echo-screen TS SET TEOAE is depicted in Figure 3.1.

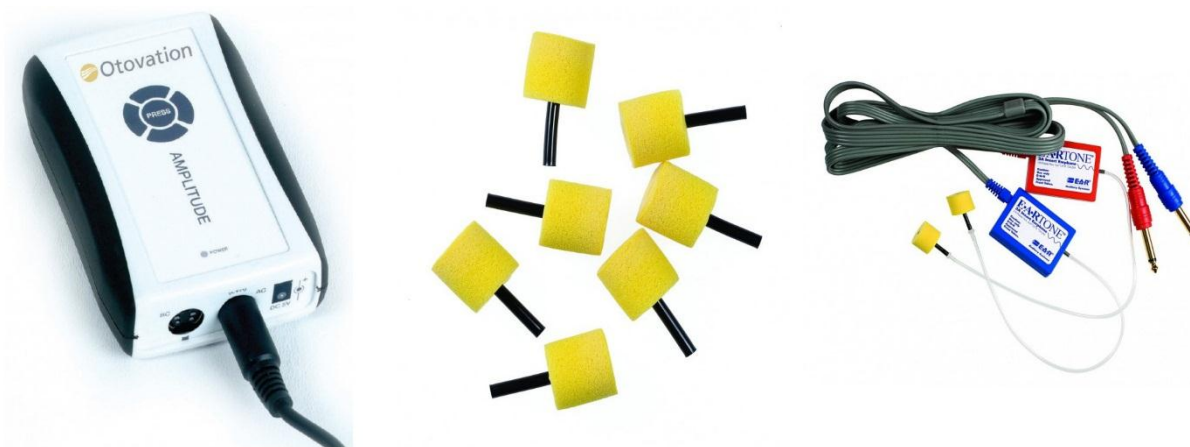


Source: (Natus company, n.d.)

Figure 3.1: Echo-screen TS SET Transient-evoked otoacoustic emission

3.7.3 Otovation Amplitude T3 Diagnostic PC-based Audiometer

The otovation amplitude T3 diagnostic pc-based audiometer was used in assessing the hearing status of participants. It is a wireless audiometer that can be used for non-invasive air and bone conduction and speech audiometric testing with masking within the range of 125Hz to 8 KHz in varying intensity levels. It comes with a wrist strap, rechargeable batteries, DC 5V power supply, air conduction inserts, bone conductor oscillator and USB Bluetooth adapter. It has a patient response button on the autopod (amplitude T3 handheld unit) and was calibrated according to ANSI S3.6-2004 standard. The otovation amplitude T3 audiometer is depicted in Figure 3.2;



Source: PCWerth (2018)

Figure 3.2: Otovation Amplitude T3 wireless Audiometer and E-A-RTONE 3A Insert ear tips.

3.8 DATA COLLECTION PROCEDURE

3.8.1 Test Protocol

It is generally not recommended to use a single audiological test for the assessment of hearing sensitivity. The application of multiple test batteries allows for a confident diagnosis to be reached (Diefendorf, 2009). Pure tone audiometry and TEOAE were selected and used in assessing hearing sensitivity in this study. In selecting the test batteries for this study, the most cost-effective test batteries with the highest validity and reliability were selected (Ghafari, 2012).

3.8.2 Test Environment

The tests were conducted at the Chest Clinic in a quiet room with a measured ambient noise level of 30 dBA which is lower than the permissible ambient noise level (>35dBA) recommended for audiometry by the British Society of Audiology (BSA, 2017).

3.8.3 Review of Medical Records and Interview

The purpose of the study including the benefits was explained to the patients in order to enable them to make informed decision. Patients who consented to participation in the study were made to sign or thumbprint the consent form. A structured questionnaire targeting key demographical and case history information was utilized in gathering all-important demographic data, case history information, co-morbidities that could have confounded the study, and auditory data (Khoza-Shangase, 2011).

3.8.4 Otoscopy

Otoscopic examination was carried out to assess the participants' ears for signs and presence of impacted wax, tympanic membrane perforation, collapsed ear canals, foreign body and obstructions in the external ear canal (Khoza-Shangase, 2011). Only participants who passed the otoscopic examination progressed to the next stage.

3.8.5 Pure Tone Audiometry

Conventional (250Hz-8000Hz) PTA was conducted on all participants who underwent and passed otoscopic examination using a calibrated otovation amplitude T3 diagnostic pc-based audiometer with EAR 5A inserts and radiocar B-71 bone conductor. Daily biological calibration, functional inspection and performance checks were done before the commencement of the hearing assessment. Before the commencement of the assessment, participants were given appropriate explanations and instructions concerning the assessment procedures and tests and repeated in the course of the procedures when the need arose. Participants' were fitted with the insert earphone with the appropriate insert ear tip size.

Testing began in the better hearing ear (according to the participants' account) and at 30dBHL at 1000Hz, using an ascending approach. Next, 2000Hz, 3000Hz, 4000Hz, 6000Hz, 8000Hz, 500Hz and 250Hz were tested in that order. However, for the first ear, only 1000Hz was retested. The opposite ear was also tested using the same order. The tests were conducted using standard audiometric procedures (BSA, 2017).

In bone conduction pure tone, the bone vibrator was placed over the mastoid prominence of the worse ear. It was placed exactly behind the pinna and measures were put in place so that it doesn't

touch the pinna or rest on the hair. The vibrator was held firmly by a headband. Bone conduction testing was also done using standard audiometric procedures (BSA, 2017).

Masking was performed using standard audiometric procedures whenever any of these three (3) indications were realized;

- When the difference between the right and left unmask AC thresholds is 55dB or more.
- When there is an Air-bone gap of 10dB and above.
- When the first condition has not been applied, but the difference between the BC threshold of one ear and the unmasked AC threshold of the other ear is 55dB or more (BSA, 2017).

3.8.6 Otoacoustic Emission

The status of the hair cells in the cochlea of participants was assessed using the Echo-screen TS SET transient-evoked otoacoustic emissions (TEOAE) test. A probe containing a miniature loudspeaker and a microphone was inserted to the ears of the participant. A click or tone burst stimulus was presented into the participant's ears via the loudspeaker in the probe. In response to the acoustic stimulus presented, the cochlea also generated sound waves which are picked up, measured, recorded and analyzed by the microphone in the probe. The outcomes were categorized into pass or refer depending on the integrity of the cochlea.

3.9 INFECTION CONTROL

Infection control measures recommended by Kemp & Bankaitis, (2000) were adhered to in order to curb cross infection. These included;

- regular hand washing

- wearing of hand gloves and face mask
- Appropriate disposal of waste (used gloves, wipes)
- Clean OAE probe tips and insert ear tips were utilized in assessing each participant and they were cleaned and disinfected after use.
- Otoscopic specula were cleaned and sterilized after use.

3.10 DATA MANAGEMENT PLAN

Data was managed in order to conceal and protect the identity of the participants. This was done by identifying the participants with reference codes. Completed questionnaires were securely kept under lock and key and were only accessible to the Principal Investigator. Soft copies of the data were placed on a password-protected personal computer. The quantitative data that was generated was analyzed, coded, and entered into the Statistical Package for Social Studies (SPSS) software.

3.11 DATA ANALYSIS

Statistical Analysis was performed with the SPSS statistical software. A general overview of the data was given by standard descriptive statistics. The Independent t-test was used for paired comparisons between results for groups according to demographics and hearing thresholds. Chi-square test was performed to reveal associations between exposure to TB medications and auditory thresholds. A level of significance of 0.05 was used in the data analysis.

3.12 ETHICAL CONSIDERATIONS

Ethical clearance was granted by the Ethics and Protocol Review Committee (EPRC) of the School of Biomedical and Allied Health Sciences (SBAHS). Permission and authorization were granted for the data collected by the Chief Medical Officer of the Tema General Hospital. Methods and

objectives of the study and the process of assessment were fully explained to the patients. Participants were assured of absolute confidentiality of information with regards to data on their medical history and hearing status. Informed consents were obtained from patients before the commencement of the study

CHAPTER FOUR

RESULTS

4.1 INTRODUCTION

The details of the results of the study comprising demographics, characteristics of the treatment group, distribution of pure tone audiometric and otoacoustic emission results, as well as degrees of hearing loss and tests of associations are presented in this Chapter.

4.2 DEMOGRAPHIC CHARACTERISTICS

4.2.1 Gender, age, TB and HIV demographics

The study explored the demographic characteristics (gender, age, type of TB and HIV status) of the 120 participants (60 each in the treatment and control groups) of the study. The findings indicated that females were the most prevalent gender ($n=33$, 55%) in both the treatment and control groups as compared to males ($n=27$, 45%). The mean of the ages of participants were 37.97 (9.17) years for the treatment group and 34.17 (9.16) years for the control. The minimum age of the participants enrolled in the study was 18 and the maximum 50 years. Participants within the age range of 40-50 years were the most prevalent in the treatment group ($n=29$, 48%), whilst the least prevalent ($n=13$, 23%) were 18-29 years. For the control group, the most prevalent age range was 18-29 years ($n=22$, 36%). Participants who presented with pulmonary TB in the treatment group were more prevalent ($n=49$, 81.7%) compared to those who presented with extra-pulmonary TB ($n=11$, 18.3%). Majority of the participants in the treatment group presented with negative HIV status ($n=54$, 90%) than positive HIV status ($n=6$, 10%). Table 4.1 presents a breakdown of the gender, age, type of TB and HIV demographics.

Table 4.1: Gender, age, TB and HIV demographics

Demographic variable		Treatment Group		Control Group		Total	
		Frequency	Percent %	Frequency	Percent %	Freq	Percent %
Gender	Male	27	45	27	45	54	45
	Female	33	55	33	55	66	55
	Total	60	100	60	100	120	100
Age (years)	18-29	13	23	22	36	35	29
	30-39	18	30	19	32	37	31
	40-50	29	48	19	32	48	40
	Total	60	100	60	100	120	100
TB Type	ETB	11	18.3			11	18.3
	PTB	49	81.7			49	81.7
	Total	60	100			60	100
HIV Status	Positive	6	10			6	10
	Negative	54	90			54	90
	Total	60	100			60	100

4.2.2 Characteristics of the Treatment Group

The findings of the study indicated that new cases of TB were the most prevalent ($n=46$, 76.7%) compared to retreatment cases ($n=14$, 23.3%) in the treatment group. Also, all the participants enrolled in the treatment group were on first-line anti-TB medication ($n=60$, 100%). The last phase of TB treatment was more prevalent ($n=40$, 66.7%) than the first phase of treatment ($n=20$, 33.3%). Data on duration of treatment revealed that 1-2 months and 3-4 months were more

prevalent ($n=18$, 30% each), whereas 9-12 months ($n=1$, 1.7%) was the least prevalent. The characteristics of the Treatment group are presented in Table 4.2.

Table 4.2: Characteristics of the Treatment Group

Variable		Treatment Group	
		Number	Percent %
Cases	New	46	76.7
	Retreatment	14	23.
	Total	60	100
Regimen	First-line	60	100
	Second-line	-	-
	Total	60	100
Phases	First phase	20	33.3
	Last phase	40	66.7
	Total	60	100
Treatment duration	1-2 months	18	30
	3-4 months	18	30
	5-6 months	11	18.3
	7-8 months	12	20
	9-12 months	1	1.7
	Total	60	100

4.3 DISTRIBUTION OF AUDIOMETRIC DATA

4.3.1 Distribution of maximum and minimum pure tone AC and BC thresholds

Pure tone air conduction and bone conduction thresholds at test frequencies in the right and left ears were recorded for the treatment and control groups. In the treatment group, the highest means and standard deviation of AC and BC thresholds were recorded at [AC: right ear= 18.71 \pm 12.3; left ear= 19.58 \pm 11.66] and [BC: right ear=37.50 \pm 8.39; left ear= 39.17 \pm 9.25] were recorded at 8000Hz and 4000Hz respectively. The means and standard deviation for the lowest AC thresholds were recorded at 250Hz [right ear=15.67 \pm 6.28; left ear= 16.92 \pm 5.62]. The highest means and standard deviations for AC and BC thresholds in the treatment group were recorded at high frequencies (2-8 KHz). Tables 4.3 and 4.4 presents a breakdown of the maximum and minimum pure tone BC and AC thresholds compared to the overall mean and standard deviation at test frequencies.

Table 4.3: Distribution of maximum and minimum pure tone bone-conduction thresholds compared to overall mean and standard deviation at test frequencies.

Bone conduction thresholds dBHL				
Treatment Group				
Frequency (Hz)	Ears	Maximum	Minimum	Mean \pm
500	Right	30	15	22.50 \pm 5.87
	Left	35	15	22.50 \pm 6.91
1000	Right	40	15	26.67 \pm 7.79
	Left	30	15	25.83 \pm 6.34
2000	Right	40	10	29.17 \pm 7.64
	Left	40	25	32.50 \pm 4.52
4000	Right	55	30	37.50 \pm 8.39
	Left	55	30	39.17 \pm 9.25

Table 4.4: Distribution of maximum and minimum pure tone air-conduction thresholds compared to the overall mean and standard deviation at test frequencies.

Air conduction thresholds dBHL							
Freq (Hz)		Treatment Group			Control Group		
	Ears	Maximum	Minimum	Mean \pm SD	Maximum	Minimum	Mean \pm SD
250	Right	30	5	15.67 \pm 6.28	25	5	15.33 \pm 5.44
	Left	30	5	16.92 \pm 5.62	25	5	17.00 \pm 4.71
500	Right	30	5	15.63 \pm 6.30	25	5	15.33 \pm 5.81
	Left	30	5	17.33 \pm 5.46	25	10	16.67 \pm 4.19
1000	Right	40	5	16.79 \pm 7.24	25	5	16.17 \pm 5.92
	Left	30	5	16.75 \pm 6.07	25	5	16.58 \pm 4.74
2000	Right	40	5	15.83 \pm 7.54	25	5	15.00 \pm 6.18
	Left	45	5	16.79 \pm 7.12	25	5	15.33 \pm 4.86
3000	Right	45	0	17.21 \pm 8.09	25	5	15.75 \pm 6.16
	Left	45	5	17.46 \pm 8.10	25	5	16.67 \pm 4.84
4000	Right	60	0	17.25 \pm 9.99	25	0	15.58 \pm 5.83
	Left	55	0	18.25 \pm 9.61	25	5	17.58 \pm 4.56
6000	Right	80	0	17.92 \pm 11.4	25	0	15.83 \pm 6.19
	Left	75	0	18.88 \pm 11.1	25	5	16.92 \pm 4.97
8000	Right	80	5	18.71 \pm 12.3	25	5	15.75 \pm 6.02
	Left	80	0	19.58 \pm 11.7	25	0	18.33 \pm 5.94

dB=decibels, HL=Hearing loss, Sd=Standard deviation, Hz=Hertz

4.3.2 Degree of hearing loss in Treatment and Control groups

Out of the 60 participants recruited into the treatment group, 48 (80%) presented with normal hearing thresholds whilst 12 (20%) presented with varying degrees of SNHL. They consisted of 4 (6.7%) participants with mild SNHL, moderate ($n=5$, 8.3%), moderately severe ($n=2$, 3.3%), and severe ($n=1$, 1.7%). None of the participants presented with profound SNHL and normal hearing threshold was recorded in 48 (80%) of the participants in the treatment group. The most prevalent degree of loss was moderate SNHL ($n=5$, 8.3%) with the least prevalent being severe SNHL. The SNHL recorded were all bilateral and symmetrical in all the participants who presented with hearing loss. All the participants recruited into the control group presented with normal hearing thresholds ($n=60$, 100%). Table 4.5 gives the breakdown of the degree of hearing loss recorded in the treatment and control groups.

Table 4.3: Degree of hearing loss in each ear in treatment and control groups

Degrees	Treatment Group				Control Group			
	Right ear		Left ear		Right ear		Left ear	
	Freq	%	Freq	%	Freq.	%	Freq.	%
Normal	48	80	48	80	60	100	60	100
Mild	4	6.7	4	6.7				
Moderate	5	8.3	5	8.3				
Moderately severe	2	3.3	2	3.3				
Severe	1	1.7	1	1.7				
Profound	-	-	-	-				
Total	60	100		100	60	100	60	100

4.3.3 Distribution of OAE results

Findings from the OAE test indicated that 48 (80%) participants in the Treatment group presented with passes in both ears whereas 12 (20%) participants were referred in both ears. However, all participants in the control group recorded passes in both ears. Overall, out of the 240 ears assessed, 216 (90%) recorded passes in both groups whilst 24 (10%) ears recorded referrals. Table 4.6 presents the distribution of OAE results for the participants in the Treatment and Control groups.

Table 4.4: Distribution of OAE results for both ears in the treatment and control groups.

		Treatment Group		Control Group			
		Right ear (%)	Left ear (%)	Right ear (%)	Left ear (%)	Total	%
OAE	Pass	48 (80)	48 (80)	60 (100)	60 (100)	216	(90)
	Refer	12 (20)	12 (20)			24	(10)
Total		60 (100)	60 (100)	60 (100)	60 (100)	240	(100)

OAE= Otoacoustic Emissions

4.4 TEST OF DIFFERENCE BETWEEN MEANS

The treatment group differed significantly ($p < 0.05$) from the control group with respect to mean hearing thresholds at the high frequencies (2000, 3000, 4000Hz) in the two ears. The mean hearing threshold of the treatment group is greater than that of the control group at the 0.05 level of significance. However, no significant difference ($p > 0.05$) was recorded between the two groups with respect to the low frequency mean averages (500, 1000, 2000Hz) in the two ears. The differences in hearing threshold mean between the treatment and controls were larger for the high frequency averages than for the low frequency averages. The breakdown of the Independent t-test on the mean differences between the Treatment and Control groups is presented in Table 4.7.

Table 4.5: Independent t-test on the mean differences between the treatment and control groups hearing thresholds

Hearing Threshold Parameter (Hz)	Ear	Treatment Group mean \pm	Control Group mean \pm	p-value
2000, 3000, 4000	Right	18.68 \pm 9.03	15.70 \pm 4.093	0.021
	Left	18.93 \pm 9.60	15.90 \pm 3.740	0.024
500, 1000, 2000	Right	16.95 \pm 6.98	15.50 \pm 3.96	0.164
	Left	17.70 \pm 6.53	16.17 \pm 3.45	0.111

$\alpha= 0.05$, dB=decibels, Hz=Hertz, Sd=Standard Deviation

4.5 TEST OF ASSOCIATIONS

Findings from the study indicated a significant association ($\chi^2=13.333$, $p<0.05$) between OAE referrals and the treatment group. It reveals a significant association between TB therapy and OAE referral. For the association between audiometry findings and exposure to TB medications, a statistically significant association was also observed between abnormal audiometry findings and exposure to TB medications ($\chi^2=13.333$, $p<0.05$). The associations between OAE results and tuberculosis treatment as well as the association between audiometric findings and TB exposure are presented in Tables 4.8 and 4.9 respectively.

Table 4.6 Association between OAE results and TB therapy

		Otoacoustic Emissions		χ^2	df	p-value
		Pass	Refer			
Group	Treatment	48	12	13.333	1	0.000
	Control	60	-			

$\alpha = 0.05$

Table 4.7: Association between audiometry findings and exposure to TB medication

Variable	Normal audiometry findings		Abnormal audiometry findings		χ^2	df	p-value
	n	%	n	%			
	On medication	48	44.4	12			
No medication	60	55.6					

$\alpha = 0.05$

CHAPTER FIVE

DISCUSSION

5.1 INTRODUCTION

The present study investigated hearing loss among patients on anti-TB regimen and a matched control of healthy volunteers. In view of this, objectives were set and two hypotheses were also set and tested. The results revealed poor hearing thresholds among the patients receiving treatment compared to the healthy controls. Findings are discussed in light of the stated objectives and hypotheses and in relation also to relevant previous works.

5.2 PREVALENCE OF HEARING LOSS AMONG PATIENTS ON ANTI-TB REGIMEN

In this present study, a hearing loss prevalence of 20% was reported among patients on TB treatment. The proportion of patients who had their hearing affected in this study is consistent with the findings reported in other studies conducted all over the world. These included findings reported by Duggal & Sarkar, (2007), 18.75% and Javaid *et al.*, (2018), 36.83% in Asia, De Jager & Van Altena, (2002), 18% and Sturdy *et al.*, (2011), 28% in Europe, Vasconcelos *et al.*, (2012), 23.7% in South America, Peloquin *et al.*, (2004), 37% in North America, Ramma & Ibekwe, (2012), 47% and Sagwa *et al.*, (2015), 58% in Southern Africa, Ibekwe & Nwosu, (2016), 61% and Sogebi, Fadeyi, *et al.*, (2017), 22.9% in West Africa. The wide variations in the hearing loss prevalence could be ascribed to the difference in audiology test used. Whereas conventional pure tone audiometry was used in this study, most of the other studies employed high frequency pure tone audiometry which is able to assess hearing above 8000Hz. In addition, all the patients recruited into the treatment group were on first-line drugs, whilst in other studies, patients on second-line drugs with known ototoxic effects were recruited.

The high prevalence of hearing loss reported among TB patients undergoing treatment and on first line drugs in this study can be attributed to the fact that 50% (6) of the patients presented with hearing loss were also TB-HIV co-infected. This finding is consistent with findings from a study by Harris, *et al.*, (2012) who established that the probability of developing hearing loss was higher (about 4 times) in TB-HIV co-infected patients compared to HIV negative patients.

5.3 IMPACT OF TB THERAPY ON HEARING THRESHOLDS

A significant proportion of the patients initiated on TB treatment presented with poor hearing thresholds in this study. This finding is consistent with works by Törün *et al.*, (2005); Gülbay *et al.*, (2006); Yang *et al.*, (2017) who unanimously established that ototoxic hearing loss is a common and frequently observed side effect experienced by patients undergoing TB treatment. Another study which supported this finding was conducted by Mwansasu *et al.*, (2017) to investigate the degree of hearing loss among TB patients on therapy. The study concluded that a substantial proportion of patients with TB initiated on anti-TB regimen ended up with significant hearing loss.

The poor thresholds reported in this study were all bilateral and evident in the high frequencies which is consistent with findings by Nizamuddin *et al.*, (2015); Sagwa *et al.*, (2015); Sharma *et al.*, (2016), and Tiwari *et al.*, (2016). These studies concluded that ototoxic hearing loss is bilateral and is evident in the high frequencies. In addition, the majority of the patients on retreatment in this study presented with hearing loss and this is consistent with findings by Modongo *et al.*, (2014) who postulated that longer treatment duration was associated with the development of hearing loss.

5.4 COMPARISON BETWEEN THE HEARING THRESHOLDS OF PATIENTS ON ANTI-TB REGIMEN AND NON-INFECTED VOLUNTEERS.

The poorest hearing thresholds in this study were recorded by patients on anti-TB regimen since the mean and standard deviations of the AC thresholds of the treatment group were higher than in the controls. This result is consistent with findings from a study conducted by Brits *et al.*, (2012) which compared the hearing status of gold miners with and without TB. The study concluded that the hearing status of miners who presented with TB was higher or poorer than those without TB.

Higher hearing threshold differences were recorded in the high frequencies than in the lower frequencies between the treatment and control groups. This is congruous with findings by *Sha et al.*, (2001); Huth *et al.*, (2011); Karasawa & Steyger, (2011) and Tabuchi *et al.*, (2011) who concluded that the base of the cochlea where high frequencies are transduced are more vulnerable than the apical end where low frequencies are transduced. This explains why high frequency losses precede low frequency losses in drug-induced hearing losses. It also explains why hearing thresholds at higher frequencies in the present study were remarkably different between the two groups.

5.5 HYPOTHESIS 1

The first hypothesis which postulated that there will be a significant difference between the hearing thresholds of patients receiving treatment and those not on therapy in the high frequency categories was supported by the data collected. Differences with respect to hearing thresholds in group means were noted in all frequency categories. However, the differences that were statistically significant ($p < 0.05$) were found between the treatment and control groups in the high frequency categories. The hypothesis is consistent with the findings from a study conducted by Brits *et al.*, (2012) who reported that a highly significant difference exists between the hearing thresholds of patients undergoing treatment for TB and those not infected with TB.

The study also revealed a significant ($p < 0.01$) elevation of the hearing thresholds of the single and multiple treatment groups compared to those of the controls. However, there were no significant differences in the mean hearing threshold of TB patients on treatment and uninfected persons in the low frequency categories. In addition, Brits *et al.*, (2012) also reported that differences in thresholds were more pronounced in the high frequencies compared to the low frequencies and this agrees with the findings from the present study. This hypothesis is also supported by a study conducted by Vasconcelos *et al.*, (2012) in which irreversible hearing losses ranging from mild to severe were reported among patients initiated on TB medications. The findings also revealed that auditory thresholds were worse at the high frequencies.

5.6 HYPOTHESIS 2

The second hypothesis stated that there will be a significant association between TB therapy and elevated hearing thresholds. This was also supported by the data collected. A test of association between hearing status and the two group revealed a statistically significant association ($p < 0.05$) between treatment group and OAE referral. All the patients referred in the OAE and also demonstrated hearing loss of varying degrees were found to be in the treatment group and also undergoing therapy. Another test of association conducted to explore the association between audiometry findings and exposure to TB medications also reported a statistically significant association between abnormal audiometry findings and exposure to TB medications.

These results are consistent with findings from studies conducted by Duggal & Sarkar, (2007); Sagwa *et al.*, (2015); Ibekwe & Nwosu, (2016) and Sogebi, Fadeyi, *et al.*, (2017) who compared baseline hearing thresholds with post-treatment hearing thresholds of patients initiated on anti-TB regimen. Their findings revealed that most of the patients presented with elevated thresholds at the end of the therapy. Based on this, they unanimously concluded that TB therapy is associated with reduced hearing thresholds. The hypothesis was also supported by a study conducted by Mwansasu *et al.*, (2017) which established that a significant proportion of patients enrolled on TB therapy end up demonstrating poorer hearing thresholds. Sagwa *et al.*, (2015) also concluded that reduced hearing thresholds in patients with TB are an outcome of TB treatment.

CHAPTER SIX

CONCLUSION, RECOMMENDATIONS AND LIMITATIONS

6.1 CONCLUSIONS

Hearing loss among patients initiated on anti-TB medications is on the increase and this has the tendency of affecting the quality of life of patients during and after treatment. However, unlike other parts of the world where routine auditory assessment and monitoring have been integrated into the management of patients undergoing TB therapy in order to minimize and mitigate the occurrence of hearing loss, that cannot be said of Ghana. Research data needed to drive policies in that regard is unavailable.

The current study, therefore, endeavoured to determine and establish hearing loss among patients receiving treatment for TB at the Chest Clinic of the Tema General Hospital. Audiological test batteries like PTA and OAE were utilized in the assessment whilst descriptive and inferential statistics were employed to analyze the test results. The study revealed elevated hearing thresholds among the patients receiving treatment as compared to the controls. The patients presented with various degrees of hearing losses and this finding is consistent with findings from studies that have been conducted in other parts of the world. This study on the basis of outcomes obtained concluded that patients on anti-TB therapy are more likely to end up with significant hearing impairment due to the side effects of the treatment regimen.

6.2 RECOMMENDATIONS

Based on the outcomes revealed in this study, the following were recommended:

- Guidelines, policies and protocols on auditory assessment and monitoring of patients with TB in Ghana should be developed.
- Audiological management should be made an integral part of the therapeutic treatment plan for patients with TB.
- Audiologists should become part of the multi-disciplinary team of professionals involved in TB management.
- Future studies should utilize extended high frequency audiometry since this is more sensitive in detecting hearing loss before they become evident in conventional audiometry.
- Future studies should also employ prospective cohort study design and focus mainly on MDR TB patients on second-line anti-TB therapy.
- The study can also be replicated using a larger sample size and various study sites.

6.3 LIMITATIONS

Although the outcomes revealed by this study are weighty, caution should be exercised in its interpretation and generalization as a result of some limitations identified with the methodology. These limitations included the use of a small sample size. The inability to perform tympanometry, extended high frequency audiometry and DPOAE, the inability to predict treatment compliance and whether aminoglycosides were the actual causes of the hearing loss observed were all limitations of this study. Patients with HIV/AIDS and on antiretroviral therapy (ARV) were included in the study and this precluded total control over confounding variables that could have influenced the results since ARVs are known to be ototoxic and also for their interactions with other therapies. The major handicaps of this study were however financial and time constraints. Nonetheless, the outcomes from this study underscore the need for the auditory monitoring of patients initiated on anti-TB therapy because of ototoxicity concerns.

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APPENCICES

APPENDIX I: QUESTIONNAIRE ON A STUDY

DEMOGRAPHICS:

Reference Code: _____

Age _____ Sex: M F Occupation _____

Contact _____

TB Type: PTB ETB MDR HIV: P+ N-

Newly diagnosed Retreatment/Relapse

Treatment regimen: First-line Second-line

Date of treatment commencement: _____

First Phase Last Phase

Treatment duration: 1-2 months 3-4 months 5-6 months 7-8months 9-12months

1-2yrs

QUESTIONS:

1. Do you notice any tinnitus (ringing) in your ears? YES NO
2. Are you presently taking any other ototoxic drug? YES NO
3. Are you hypertensive? YES NO

4. Have you had a head injury before? YES NO
5. Have you had ear surgery before? YES NO
6. Have you had severe jaundice before? YES NO
7. Have you had meningitis before? YES NO
8. Do you have any kidney problem? YES NO
9. Do you have any history of hearing loss in your family? YES NO
10. Do you have any history of ear discharge or pain? YES NO

APPENDIX II: AUDIOMETRIC DATA COLLECTION FORM

CODE:		AGE:		M/ F		DATE :		
PURE TONE AUDIOMETRY RESULTS								
	250 Hz	500 Hz	1000 Hz	2000 Hz	3000 Hz	4000 Hz	6000 Hz	8000 Hz
Left Ear								
Right Ear								
BONE CONDUCTION RESULTS								
Left Ear								
Right Ear								
OAE	PASS	REFER						
Right Ear								
Left Ear								

APPENDIX III: PARTICIPANT INFORMATION FORM

Title of research: Hearing loss among patients receiving anti-tuberculosis treatment

Principal Investigator: Benjamin Tetteh Amartey

Department of Audiology, Speech and Language Therapy

Master of Science in Audiology

Mob: 0246845026; Email: benjiroz3@gmail.com

General Information about Research

I am a graduate student of the Department of Audiology, Speech and Language Therapy, School of Biomedical and Allied Health Sciences, University of Ghana. In fulfillment of the requirements to obtain a Master of Science degree in Audiology, I am undertaking a research on “**Hearing loss among patients receiving anti-tuberculosis treatment**” under the supervision of Dr Neal Boafo and Dr Enid Owusu of the University of Ghana School of Biomedical and Allied Health Sciences. The purpose of the study is to assess the hearing thresholds of patients on anti-TB treatment regimen and find the relationship between the treatment regimen and hearing loss.

Your involvement, cooperation and commitment as a participant in this research are of utmost importance to the researcher. This participant information sheet seeks to provide detailed information about the research in order to provide grounds for you to make a voluntary and informed decision before participating in the research.

Explanation of procedure

The study will employ a structured questionnaire to collect personal information about you and your medical records will also be reviewed. Various tests will be done to assess the status of your outer and middle ear. A hearing test will finally be conducted to assess your hearing threshold.

Possible Risks and Discomforts

There are no risks for participation in this study since the testing equipment and procedure does not give any side effects. Steps will also be taken to ensure infection control.

Voluntary Participation and Right to Leave the Research

Participation in this study is voluntary. You have the right to withdraw at any time or refuse to participate entirely without any jeopardy to you whatsoever.

Contacts for Additional Information

For any information, clarification or questions about the study, please contact the principal investigator, Benjamin Tetteh Amartey on 0246845026.

Confidentiality

Your real name or any other data that can be used to identify you will not be used at any point in time during the data collection. You will be given a code as identification. All information provided will remain confidential and will only be reported as group data with no identifying information. All data, including health records and test results, will be kept secured and only those directly involved with the study will have access to them.

Possible Benefits

Participating in the study provides you with the opportunity of knowing your hearing status and the presence or not of any hidden hearing problem at no cost.

Alternatives to Participation

In the event of any noticed problem, you will be referred for further diagnostic testing and the necessary action as needed.

Your rights as a Participant and complaints

This research has been reviewed and approved by the Ethical and Protocol Review Committee of the Department of Audiology, Speech and Language Therapy of the School of Biomedical and Allied Health Sciences, College of Health Sciences, University of Ghana. This committee has reviewed, evaluated and decided on the scientific and ethical merits of research protocols that are consistent with best practices to ensure that your rights as a participant are strictly protected. However, any questions regarding any rights issues in this research should be directed to the Ethical and Protocol Review Committee of the Department of Audiology, Speech and Language Therapy of the School of Biomedical and Allied Health Sciences, College of Health Sciences, University of Ghana.

APPENDIX IV: CONSENT FORM

INFORMED CONSENT

The document describing the benefits, risks and procedures for the research: **Hearing loss in patients on anti-TB treatment** has been read and / or explained to me. I have been given an opportunity to have any questions about the research asked and answered to my satisfaction. I agree to participate as a volunteer.

Date

Signature or Thump print of volunteer

If volunteers cannot read the form themselves, a witness must sign here:

I was present while the benefits, risks and procedures were read to the volunteer. All questions were answered and the volunteer has agreed to take part in the research.

Date

Signature or Thump print of volunteer

I certify that nature and purpose, the potential benefits, and possible risks associated with participating in this research have been explained to the above individual.

Date

Signature or thumb print of Person who Obtained Consent

APPENDIX V: TEOAE TECHNICAL SPECIFICATION

Technical Specifications of Echo-screen TS SET Transient-evoked otoacoustic emission

Design parameter	Specification
Weight	550g
Size	230*95*53mm
Power consumption	1.2 watts Max
Operating time	>10 hrs with fully charged battery
Display	128*64 dot graphic LCD (backlight)
Keyboard	5 keys
Evaluation method	Echo-screen device binomial statistics
Click rate	Approx. 60Hz
Display	Statistical waveform, measurement progress, TEOAE significant level, Noise level
Applied standards	EN 60601-1+A1+A2
	EN 60601-1-2
	EN 60601-2-26
	EN 60601-2-40

APPENDIX VI: OTOVATION AMPLITUDE T3 AUDIOMETER TECHNICAL SPECIFICATION

Technical Specifications of Otovation Amplitude T3 Diagnostic PC-based Audiometer

Design parameter	Specification
Safety Standards	IEC 60601-1, IEC 60601-1-1
Emissions Standard	IEC 60601-1-2
Audiometry Standards	IEC 60645-1, Type 3/4 ; ANSI S3.6:2004, Type 3/4 , ISO 389
Tone Presentation	Steady, Pulse, or Warble
Calibration	ANSI S3.6-2004 standard
Frequencies	125,250,500,750,1k,1.5k,2k,3k,4k,6k,8kHz
Output levels	AC:-10 to 110dB HL at center frequencies depending on transducer used. BC:-10 to 75 dB HL at center frequencies.
Increment	+/-1,2, or 5 dB user selectable
dB Deviation	+/- 1dB
Pure Tone Accuracy	+/-1%
Distortion	Less than 1.0% THD



UNIVERSITY OF GHANA
DEPARTMENT OF AUDIOLOGY, SPEECH
AND LANGUAGE THERAPY
SCHOOL OF BIOMEDICAL AND ALLIED HEALTH SCIENCES

Ref. No.:

29th Nov, 2017

The Medical Superintendent
Tema General Hospital
Tema

Dear Sir/Madam,

INTRODUCTION OF MSc AUDIOLOGY RESEARCH STUDENT: MR. B.T.AMARTEY

Mr. BENJAMIN TETTEH AMARTEY (10241594) is a final year MSc Audiology student of the Department of Audiology, Speech and Language Therapy of the University of Ghana School of Biomedical and Allied Health Sciences (SBAHS), Korle Bu.

He is carrying out a research study in hearing loss with emphasis on tuberculosis infection under the supervision of Dr. Neal Boafo (Audiologist) and Dr. Enid Owusu (Bacteriologist) both of SBAHS. His topic is "HEARING LOSS AMONG PATIENTS ON ANTI-TUBERCULOSIS TREATMENT REGIMEN". The study site for his research study is the Tema General Hospital during the period February to March 2018. An initial assessment of the candidate's research proposal has been done by the Department's Ethical Review and Protocol Committee (DEPRC).

In this regard, the Department is pleased to introduce Mr. B.T. Amartey to you and humbly requests your kind permission to grant him access to perform his research studies in your hospital. The Department considers this as an opportunity to collaborate with your hospital in scientific and clinical research for the common good of Tema General Hospital, SBAHS, and the country as a whole. Your earnest and kind consideration would be greatly appreciated. Thank you.

Yours sincerely,

Dr. S. ANIM-SAMPONG
(Ag. Head of Department)
cc: Dean, SBAHS

DEPARTMENT OF AUDIOLOGY
SPEECH & LANGUAGE THERAPY
SCHOOL OF BIOMEDICAL AND ALLIED
HEALTH SCIENCES

COLLEGE OF HEALTH SCIENCES

P. O. Box KB 143, Korle Bu, Accra, Ghana.

• Telephone: +233 (0) 302 687 974/5

• Email: asl.sbahs@ug.edu.gh

• Website: www.sbahs.ug.edu.gh



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DEPARTMENT OF AUDIOLOGY, SPEECH AND LANGUAGE THERAPY
SCHOOL OF BIOMEDICAL AND ALLIED HEALTH SCIENCES

Ref. No.:

29th Nov, 2017

The Medical Superintendent
Tema General Hospital
Tema



Dear Sir/Madam,

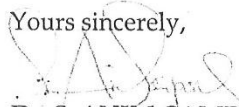
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Yours sincerely,


Dr. S. ANIM-SAMPONG
(Ag. Head of Department)

cc: Dean, SBAHS
DEPARTMENT OF AUDIOLOGY
SPEECH & LANGUAGE THERAPY
SCHOOL OF BIOMEDICAL AND ALLIED
HEALTH SCIENCES

Approved
[Signature]
15/2/18

COLLEGE OF HEALTH SCIENCES

FOR DATA COLLECTION AT THE CHEST CLINIC
TOPIC hearing loss among patients on anti-tuberculosis treatment regimen.
TEMA GENERAL HOSPITAL
DATE 20-2-18

INTRODUCTORY LETTER FOR CLINICAL EXPERIENCE

The following Master of Science in Audiology student(s)
From the School of Biomedical and Allied Health Sciences, University of Ghana
is/are reporting to your ward/unit for their/her/his practical experience in
nursing/midwifery from 20-2-18 to 31-3-18

Kindly give them/ him/ her necessary support.

1. Benjamin Tetteh Amartey
- 2.
- 3.

DEP. DIRECTOR OF NURSING SERVICES
TEMA GENERAL HOSPITAL
NB: SHOULD RUN TIMES SUITABLE TO THE WARD.

ORIENTATION CARRIED OUT.

20/2/18



UNIVERSITY OF GHANA
SCHOOL OF BIOMEDICAL AND ALLIED HEALTH SCIENCES

30th January, 2018.

Mr. Benjamin Tetteh Amartey,
Dept. of Audiology, Speech and Language Therapy,
SBAHS,
Korle-Bu.

Dear Mr. Amartey,

ETHICS CLEARANCE

Ethics Identification Number: SBAHS – ASLT./10241594/SA/2017-2018.

Following a meeting of the Ethics and Protocol Review Committee of the School of Biomedical and Allied Health Sciences held on Tuesday 30th January, 2018. I write on behalf of the Committee to approve your research proposal as follows:

TITLE OF RESEARCH PROPOSAL: HEARING LOSS AMONG PATIENTS ON ANTI-TUBERCULOSIS TREATMENT.

This approval requires that you submit three-monthly review reports of the protocol to the Committee and a final full review to the Committee on completion of the research. The Committee may observe the procedures and records of the research during and after implementation.

Please note that any significant modification of the research must be submitted to the Committee for review and approval before its implementation.

You are required to report all serious adverse events related to this research to the Committee within seven (7) days verbally and fourteen (14) days in writing.

As part of the review process, it is the Committee's duty to review the ethical aspects of any manuscript that may be produced from this research. You will therefore, be required to furnish the Committee with any manuscript for publication.

This reviewed report is valid till 31st. August, 2018.

Please always quote the ethical identification number in all future correspondence in relation to this protocol.

Thank you.

Yours sincerely,

Dr. S. D. Amanquah
(Chairman, Ethics and Protocol Review Committee)

Cc: Dean
Head, Dept. of Audiology, Speech and Language Therapy,
School Administrator

COLLEGE OF HEALTH SCIENCES

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