A description of the hearing profile in gold miners with tuberculosis

By

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Abstract

Title : A description of the hearing profile in gold miners with tuberculosis
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Two of the primary occupational health threats to employees in the mining industry are noise-induced hearing loss (NIHL) and occupational lung diseases (OLD) with Tuberculosis (TB) included in the latter. The objective of this study was to investigate the hearing profile of a group of gold miners with and without TB to determine the effect of TB and its associated risk profile on hearing. Workers in AngloGold Ashanti mine in South Africa were recruited due to the fact that they present with these two health threats namely NIHL and TB. The audiological and medical surveillance data of 2698 subjects (between the years 2001 and 2009) were used in analyses. Hearing thresholds for the air conduction frequencies (0.5, 1, 2, 3, 4, 6, 8 KHz) in both ears were analysed in conjunction with biographic and occupational data. Subjects were divided into three groups, two experimental groups (Single TB treatment, n= 911 and Multiple TB treatment, n= 376) and one control group (n= 1411). A highly significant difference ($p<0.01$) was noted between the control group and both TB treatment groups across most frequencies and hearing parameters analysed, although the higher frequencies were more affected. Pair wise comparisons revealed the largest differences in hearing thresholds throughout between the control group and the multiple TB treatment groups. The smallest differences in hearing thresholds were evident between the two TB groups with the multiple TB treatment group presenting with the poorest thresholds. TB and its related risk profile had a pronounced influence on the decline of hearing thresholds. Thresholds for the multiple TB treatment group indicated more deterioration than the hearing thresholds of the single TB treatment group. This may point to the possibility that the influence of repeated TB on the subjects' hearing thresholds over time was more pronounced than a single incidence

of TB. It is still necessary however to separate the effects of the disease from the effects of the treatment on hearing.

Key words

Tuberculosis, noise-induced hearing loss, gold miners, tuberculosis treatment, Streptomycin, associated TB risk profile, ototoxicity, age, noise exposure

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Abbreviations

ANCOVA	Analysis of Covariance
ARVs	Antiretrovirals
CD4	Cluster of differentiation 4
CI	Confidence Intervals
DOTS	Direct Observe Therapy Short Course
DSM	Diagnostic and statistical manual of mental disorders
HAART	Highly Active Anti-Retroviral Therapy
HIV	Human immunodeficiency virus
IHCs	Inner Hair Cells
MDR TB	Multi-drug resistant TB
MHSA	Mine Health and Safety
NIHL	Noise-induced hearing loss
NMT	Nontuberculous mycobacterial disease
NRTIs	Nucleoside Analog Reverse Transcriptase Inhibitors
ODMWA	Occupational Disease in Mines and Work Act
OHCs	Outer Hair Cells
OLD	Occupational lung disease
PLH	Percentage loss of hearing
PTS	Permanent threshold shift
ROS	Reactive oxygen species
RSA	Republic of South Africa
SA	South Africa
SANS	South Africa National Standards
TB	Tuberculosis/*tubercle bacillus*
TSH	Thyroid stimulating hormone
TTS	Temporary threshold shift
TWA	Time-weighted average
XDR TB	Extreme-drug resistant TB

Chapter 1

Orientation and statement of the problem

1.1 Introduction

'Gold is almost universally considered to be the symbol of everything precious and of enduring value because of the effort required to extract it from nature and its scarcity relative to other metals' (Eisler, 2003:325). Unfortunately the human cost of mining remains high and may include certain social factors such as high density living and migrant labour conditions as well as health concerns connected to the mine workers' specific occupational environment such as exposure to excessive dust, noise, heat and radiation. According to the annual report to society in 2006, AngloGold Ashanti (one of the largest global gold mining companies) reported that the primary occupational health threats to employees were noise-induced hearing loss (NIHL) and occupational lung diseases (OLD) with Tuberculosis (TB) included in the latter (AngloGold Ashanti Report to Society, 2006). Both of these diseases are rated important health hazards and carry a high social and economic cost, not only for the individual concerned but for the industry as a whole. It can even be hypothesized that there might exist some kind of relationship between these two diseases as both pose a major challenge to the gold mining industry and its employees.

1.2 Overview of Tuberculosis and gold mining

Tuberculosis (abbreviated as TB for *tubercle bacillus)* is a common and deadly infectious disease caused by mycobacterium, mainly *Mycobacterium tuberculosis.* It has been called the perfect expression of an imperfect civilization (Bastian, Stapledon & Colebunders, 2003) as two billion people (a third of the world's population according to Haney, Raymond, Hernández, Seeman, and Berry, 1996) carry the TB bacteria, 8 to 10 million people (10% of infected individuals) catch the disease every year and two million (an estimated 5000 per day) die from it (World Health Organization [WHO], 2008). This ratio is unfortunately growing daily with the proliferation of the AIDS epidemic in sub-Saharan Africa (McInerney et al., 2007; Bastian et al., 2003) and specifically South Africa (Joint United Nations Programme on HIV/AIDS (UNAIDS,

2010). During the last decade annual TB case-notification rates among South African gold miners increased four-fold (Corbett et al., 2003) and the high prevalence of human immunodeficiency virus (HIV) greatly increases the risk of contracting TB (Sonnenberg et al., 2005; Ross & Murray, 2004).

It has also become increasingly apparent in the last 15 years that, despite meeting World Health Organization (WHO) targets for the detection and cure of TB, the incidence of TB among employees in the Southern Africa gold mining industry has risen sharply. According to Guild, Ehrlich, Johnston and Ross (2001) it has risen three times faster than those among coal and platinum miners. The incidence of pulmonary TB in 2006 has increased to 31 per 1,000 from 25 per 1,000 in 2005. Recent TB case findings reports indicate that between 85% and 90% of the current TB cohort (employees with TB) are also infected with HIV (AngloGold Ashanti Report to Society, 2006). Mr Nelson Mandela, former South African president, addressed this issue back in 2004 at the International AIDS conference in Bangkok by warning the global community that the fight against AIDS will be lost, unless much more is done in the fight against TB (WHO MediaCentre, 2004).

The primary cause of TB*, Mycobacterium tuberculosis,* is an aerobic bacterium that divides every 16 to 20 hours, an extremely slow rate compared with other bacteria, which usually divide in less than an hour. The bacterium usually attacks the lungs (75 % of the cases), but can also affect other parts of the body such as the kidney, spine, brain, lining of the abdominal cavity, lungs and heart, reproductive organs, skin etc. According to Guild et al. (2001) extra-pulmonary TB equals approximately 25 % of all cases and occurs relatively commonly in miners. Typical symptoms of pulmonary TB include persistent coughing, chest pain, shortness of breath, weight loss, fever, no appetite, weakness, chills and night sweating (Guild et al., 2001; Haney et al., 1996). If not treated properly, TB can be fatal (Centre for Disease Control and Prevention [CDC], 2008; Guild et al., 2001).

TB is transmitted by airborne droplets from person to person (Guild et al., 2001; Farmer, 1997; Haney et al., 1996), and infection can be acquired only from individuals with active pulmonary disease (CDC, 2008; Guild et al., 2001). In most individuals the initial tuberculosis infection is controlled by the immune system and the tuberculosis

bacilli may remain confined within special cells of the immune system called tubercles. Bacteria are inactive, but remain alive in the body, and can become active at a later stage when the infected individual's immune system is suppressed for one or another reason (Guild et al., 2001). This is called *latent TB.* Individuals with latent TB infection have no symptoms, but usually display a positive skin test reaction, and may develop active TB disease if they do not receive treatment for latent TB (Guild et al., 2001). An individual infected with TB but with a healthy immune system has a 10% lifetime chance of developing TB (CDC, March 2008). Of those who do go on the have the disease, over 90 % will do so within the first five years following infection (Guild et al., 2001).

The intensity of exposure to TB infection is by far the most important factor affecting TB incidence rates in any community (Guild et al., 2001). Another contributing factor influencing TB incidence rates in a specific community is the percentage of infected individuals who develop active TB (Guild et al., 2001). A number of factors have been identified that greatly increase the risk of developing active TB, of which increasing age, silica exposure, silicosis[1], HIV infection, working underground and migrant labour systems are the most relevant for the mining industry (Sonnenberg et al., 2005; Corbett et al., 2003; Guild et al., 2001). Other risk factors include substance abuse, severe kidney disease, diabetes mellitus, low body weight, and certain medical treatments (Guild et al., 2001).

Treatment for TB includes antibiotics to kill the bacteria usually applied over extended periods of time (at least 6 to 12 months) to entirely eliminate mycobacteria from the body. The standard first-line regimen (also specified by the National TB Control Programme, Hausler, 2000) for active TB is a combination of several antibiotics to reduce the risk of the bacteria developing antibiotic resistance and includes: *Isoniazid, Rifampicin, Pyrazinamide*, and *Ethambutol* for two months (five days/week), and then *Isoniazid* and *Rifampicin* alone for a further four months (five days/week). In re-treatment cases *Streptomycin* is added to the initial phase regimen (Guild et al., 2001; Hausler, 2000). The WHO strategy, well known as DOTS (directly observed therapy

[1] The most common occupational lung disease, caused by inhalation of crystalline silica dust, particularly in deeper level mining, and is marked by inflammation and scarring in forms of nodular lesions in the upper lobes of the lungs (UCSF Medical Centre, 2010).

short-course) remains the backbone of all efforts to control TB (Bastian et al. 2003; Guild et al., 2001) and is essential during the intensive phase as well as compulsory during the continuous phase of TB treatment in the mining industry (Guild et al., 2001; Hausler, 2000). The chain of transmission can be broken by isolating patients with active disease and starting effective anti-tuberculosis therapy. After only two weeks of such treatment, people with non-resistant, active TB generally cease to be contagious (ChemIDplus lite, National Library of Medicine, 2008)

Although not one of the above mentioned antibiotics, apart from *Streptomycin*, have any specific ototoxic side effect reported (Duggal & Sarkar, 2007; de Lima, Lessa, Aquiar-Santos & Medeiros, 2006; de Jager & van Altena, 2002; Peloquin et al., 2004; Hershfield, 1999; Carraso, 1981); and no direct relationship has yet been reported between the presence of TB and hearing loss, no studies could be found which have exclusively investigated the hearing status of TB-infected individuals who receive TB treatment. Side-effects of the drugs have included peripheral neuropathy associated with *Isoniazid* and *Ethambutol* (ChemIDplus lite, National Library of Medicine, 2008, Hershfield, 1999) and can basically be described as damage to the peripheral nervous system that is responsible for transmitting information from the brain and spinal cord to every other part of the body. *Rifampicin* has been described as promiscuous in its interactions with many other drugs used e.g. during antiretroviral treatment (United States National Library of Medicine, 2008; Brennan-Benson, Lyus, Harrison, Pakianathan & Macallan, 2005) and may complicate the co-treatment of TB and HIV as co-infection is one of the most important risk-factors due to the increased risk of drug-drug interaction, toxicity and paradoxic reactions (Munro et al., 2007; Dworkin et al., 2005; Breen et al., 2004; Patel et al., 2004; Bock & Reichman, 2002).

Apart from the few case studies mentioning extrapulmanory TB e.g. Tuberculous Otitis Media (Cho et al., 2006; Campbell, Chatton, Chusid & Yale, 1985) and Tuberculosis of the middle ear cleft (Ozcelik, Ataman & Gedikoglu, 1995), Tuberculous Meningites (Kuan, Kaga & Tsuzuku, 2007) and Miliary Tuberculosis (Stach, Westerberg & Roberson, 1998) leading to a sensory-neural hearing loss, no other specific literature could be found on a possible relationship between these two entities. It is possible that TB in itself or TB treatment and their interactions may contribute to aggravate the pre-existing risk of hearing loss amongst mine workers with TB. In addition to these

factors a person with TB already demonstrates a reduced immune response which may make them more susceptible to hearing loss due to a variety of reasons including drug-interactions, other opportunistic infections, and noise-exposure (Ryan, Harris & Keithly, 2002).

1.3 Overview on noise-induced hearing loss and gold mining

The other major occupational health threat mentioned by AngloGold Ashanti in their annual report to society in 2006 is noise-induced hearing loss (NIHL). NIHL is the most prevalent, irreversible industrial disease and the biggest compensable occupational hazard (Ologe, Akande & Olajide, 2006). According to Nelson, Nelson, Concha-Barrientos and Fingerhut (2005) using the results of 17 studies conducted in 12 countries, between 16% and 37% of disabling hearing loss in adults worldwide can be attributed to occupational noise, presenting an important socio-economic factor. Sixty-seven new cases of NIHL were identified in South Africa during 2006, which is a rate of two per 1,000 employees (AngloGold Ashanti Report to Society, 2006). This indicates a decrease from the four cases per 1,000 employees reported in 2005 and may be due to more effective hearing conservation programs that are in place. NIHL is also responsible for ±15% of all occupational disease claims submitted to the Rand Mutual Assurance Company (RMA) (the only insurance company that underwrites mines' compensation for occupational diseases in SA), excluding lung diseases, and accounts for ±45% of compensation benefits paid out by the RMA to claimants (Begley, 2006).

Noise-exposure levels related to an 8-hour working day (or a 40-hour working week), exceeding the occupational exposure limit of 85 dB(A) TWA, are considered to be dangerous to the auditory system (Sliwinska-Kowalska et al., 2006; Guild et al., 2001). It is now commonly accepted that mechanical damage as well as metabolic disturbances (in the inner ear) induced by intense sound exposure lead to noise-induced hearing loss (Heinrich & Feltens, 2006). NIHL is a sensory-neural hearing loss that usually manifests itself over a number of years and normally results in binaural impairment of hearing (Kurmis & Apps, 2007; Begley, 2006). It is predominantly noted in the high frequency region with a typical notch at 4 to 6 kHz (Sliwinska-Kowalska et al.,2006; Gates, Schmid, Kujuwa, Nam & D'Agostino, 2000). Depending on the type of noise exposure and the duration and intensity of the noise,

temporary (TTS) and permanent threshold shifts (PTS) can occur (Heinrich & Feltens, 2006; Henderson, Bielefeld, Harris & Hu, 2006). The wide-ranging working environment of gold miners being a confined area (Soer, Pottas & Edwards, 2002), as well as the fact that some of the equipment used during the mining process expose the workers to prominent levels of vibratory components (Bretlau, 2004), may also impact on the auditory effect that noise has on the gold miners.

Damaged cellular structures in response to intense noise exposure were identified particularly in the organ of Corti (Le Prell, Yamashita, Minami, Yamasoba & Miller, 2007; Heinrich & Feltens, 2006) where noise-induced signals are transferred via afferent neurons to the brain. After acoustic over-stimulation however, broken tip-links between the stereovilli and nerve ends were identified, resulting in disrupted mechano-electrical transduction which lead to a temporary noise-induced hearing loss. (Heinrich & Feltens, 2006). Confirmation for re-established signal transduction was obtained upon regeneration of the tip links over a period of time, suggesting recovery from temporary threshold shift induced by noise exposure. The short outer hair cells of the high frequency region were also found to be more vulnerable than the taller receptor cells in the low frequency area (Martin & Clark, 2006).

The mechanisms leading to temporary threshold shift (TTS), however, seems to be essentially different from those resulting in permanent threshold shifts (PTS) (Heinrich & Feltens, 2006). Different processes that are contributing to PTS have been described by various authors. One of these contributing factors is intense metabolic activity (after acoustic over-stimulation) (Miller & Schein, 2005). The intense metabolic activity drives the formation of excessive free radicals, damaging cellular lipids, proteins and DNA, leading eventually to cellular death (Henderson et al., 2006; Le Prell et al., 2006; Pouyatos, Gearhart, Nelson-Miller, Fulton & Fechter, 2006). Additional contributing factors include an increased blood flow to the cochlea upsetting its metabolic homeostasis (Le Prell et al., 2006) as well as alterations in the calcium homeostasis leading to irreversible hair cell damage (Heinrich & Feltens, 2006; Le Prell et al., 2006).

Individual susceptibility to NIHL as well as the degree of hearing loss varies greatly among individuals. This means that with the same exposure to noise some individuals

develop substantial hearing loss, whereas others develop little or no hearing loss at all (Bovo, Ciobra & Martini, 2007; Sliwinska-Kowalska et al., 2006). Noise-induced threshold shifts also depends on the interaction between intrinsic and environmental factors (Konings et al., 2007; Burgess and Williams, 2006; Sliwinska-Kowalska et al., 2006). Environmental factors or concurrent and contributing factors may include impulsiveness of noise, exposure paradigms, acoustic vibration, occupational exposure to certain chemicals, ototoxic drugs, infection or illness, temperature and smoking (Carlsson, Fransen, Stenberg, Bondeson, 2007; Kurmis & Apps, 2007). Several individual (biological) factors have also been studied in their role to aggravate NIHL. An association has been found between NIHL and elevated blood pressure (risk factor), cholesterol level (risk factor), and age (increasing effect with presbycusis) for example (Kurmis & Apps, 2007; Philp, 2007; Sliwinska-Kowalska et al., 2006; Frisina, 2001). In a study by Toppila, Pyykkö and Starck (2001) it was found that as the number of confounders increased, the noise exposure was overruled by these factors in the development of hearing loss. There is also increasing evidence that genetic mutations could determine an individual's intrinsic predisposition to noise damage (Bovo et al., 2007; Ologe et al., 2006). In theory, any contributing factor that weakens the ear functionally or structurally could therefore cause it to be more susceptible to develop hearing loss. It might even be possible that TB and/or TB treatment might contribute to the above mentioned process.

1.4 Research question

Although no specific literature could be found describing a relationship between TB and hearing loss it seems reasonable to assume that TB poses a general risk profile for hearing loss, especially in the mining industry. Therefore the research question arising from the discussion is: *How does the hearing profile of a group of gold miners with TB compare to the hearing profile of a control group of TB negative gold miners?*

1.5. Outline of dissertation

Chapters 2 and 3 will provide an in-depth overview on the two main areas related to this study i.e. Tuberculosis and Noise Induced Hearing Loss. Possible relationships and contributing/confounding factors are explored and relevant questions are asked in order to lead the way to a possible better understanding of the matter at hand and the possibility of interaction between the two subject matters. Chapter 4 will provide

insight in the methodology of the current study, chapter 5 will present the results and findings of the study, in chapter 6 these results will be discussed and chapter 7 will serve as a final conclusion of this study.

Electronic database and real-time online literature searches were primarily performed, mainly using the Scopus and Medline search engines. Topic-defined keyword searches were performed using mostly a Boolean descriptive tool e.g. 'noise-induced' AND 'occupation', and 'hearing loss' AND 'tuberculosis'. Figure 1.1 serves as a visual representation of the outline of these two chapters, indicating the most important subjects that will be discussed as well as possible relations to each other.

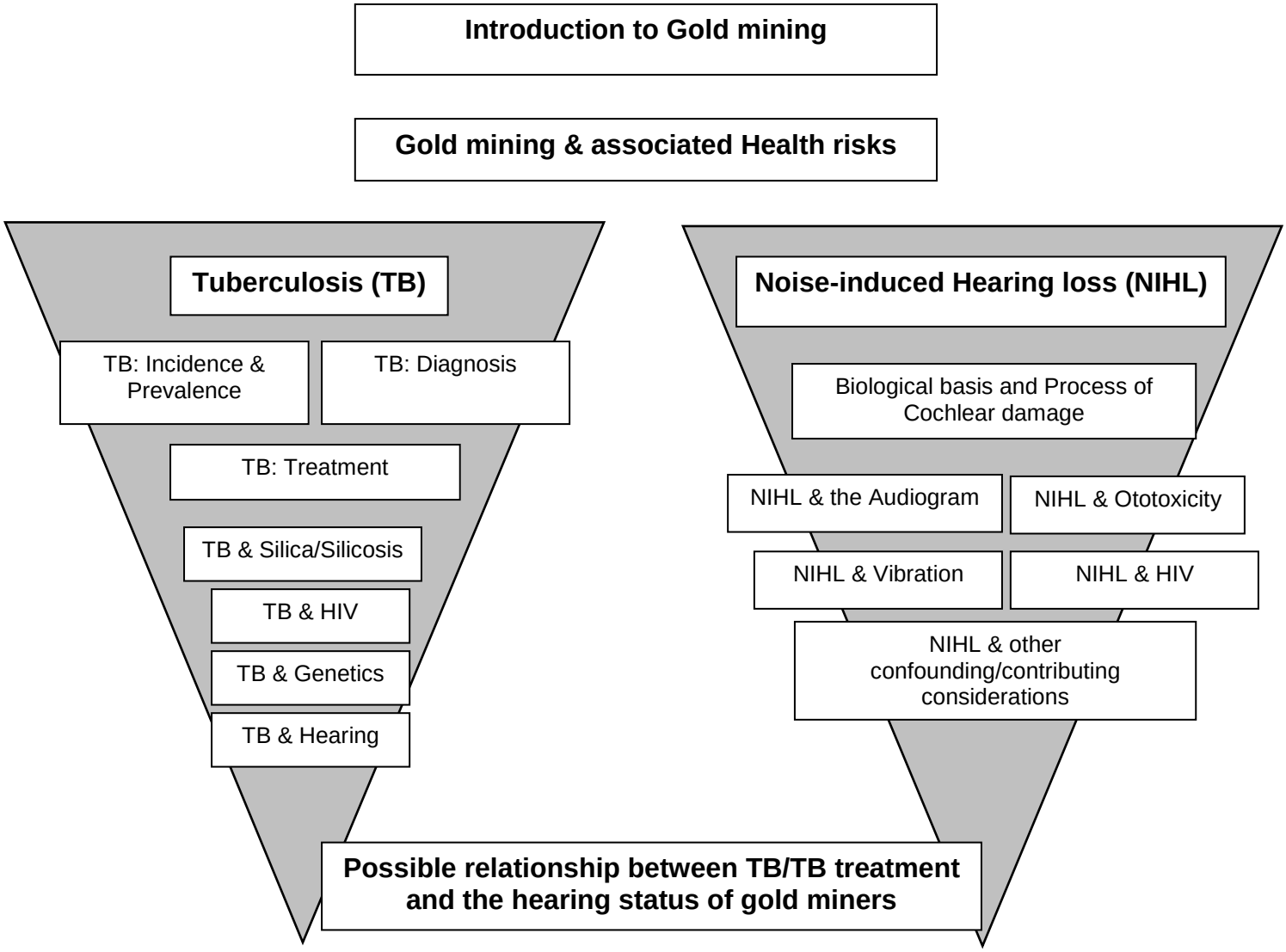


Figure 1.1 Outline of chapters 2 and 3

Chapter 2

Gold mining and Tuberculosis

2.1 Introduction to gold mining

Gold is a chemical element (symbol *Au* and an atomic number of 79) that is a highly sought-after precious metal for coinage, jewellery, and other forms of arts since the beginning of recorded history. The metal occurs as nuggets or grains in rocks, in veins and in alluvial deposits. It is dense, soft, shiny and the most malleable and ductile pure metal known. Pure gold has a bright yellow colour and lustre traditionally considered attractive, which it upholds without oxidizing in air or water. It has been a symbol of wealth and value all through-out history (Holden, 2001).

The gold mining industry in the Republic of South Africa (RSA) (for a large portion of the twentieth century the largest producer of gold in the world) started around 1886 when gold was discovered on the Witwatersrand (Eisler, 2003), although smaller deposits had previously been exploited. Currently, AngloGold Ashanti in South Africa, operates seven wholly owned underground mines situated in two geographical regions on the Witwatersrand Basin. These mines are Mponeng, Savuka and Tautona which comprise the West Wits operations (and will be the focus of this study) and Great Noligwa, Kopanang, Tau Lekoa and Moab Khotsong which makes up the Vaal River operations (AngloGold Ashanti, Annual Report 2007).

The discovery of gold in the Witwatersrand changed the face of mining in South Africa. No longer could gold be recovered by simple panning, as the gold was embedded in deep level rock and high level technology was needed to be able to extract and recover it. This meant that mining gold required huge sums of capital, and only large-scale mining companies could continue mining under these conditions. The great mining houses of modern times e.g. the Corner House (later Rand Mines and Rand Gold and Exploration Limited), Consolidated Gold Fields (later Gold Fields Limited), the Robinson Group and the Johannesburg Consolidated Investment Company (now JCI Limited) came into existence (AngloGold Ashanti, Gold in SA, 2007).

Gold mining involves the science and technology for the discovery of this rare metal, in addition to its removal and sale in the marketplace (AngloGold Ashanti, Report to Society, 2008). According to geological understanding essentially all gold in rocks is found primarily in low concentrations. On average, gold in South African mines, is found in only 5.1 parts per million from rock extracted at depths of up to 3.5 kilometers below surface (Chamber of Mines of South Africa (Education), 2008) and the technology of extraction is expensive; mainly because the process requires gold mining companies to manipulate large quantities of ore for small results. From the hundred – and-fifty thousand metric tons of gold, which were mined during the last seven thousand years of history, around one third came from the Witwatersrand basin (Müller & Dirner, 2010).

Gold (in the West Wits operation) occurs in the laterally extensive quarts pebble conglomerate reefs, which are generally less than two meters thick and are widely considered to represent laterally extensive braided fluvial deposits. Gold generally occurs in a native form often associated with pyrite and carbon, with quartz being the main gangue material. Separate fan systems were developed at different entry points and these are preserved as distinct goldfields (AngloGold Ashanti, Report to Society 2008). The process of gold mining (hard rock mining) happens both above and below the surface of the earth and includes a variety of activities whilst making use of different instruments, machinery and processes. These processes include 1) finding the orebody, 2) mining: accessing the orebody through procedures like shaft sinking, tunnelling (to reach gold-bearing reefs), and stoping, 3) removing the ore through methods like drilling and blasting (into the gold-bearing face of the stopes), 4) transporting broken material to plants for treatment, 5) rock processing (crushing and milling the ore) and gold extraction (using chemicals) as well as 6) refining, gold pouring and finally 7) mine-site rehabilitation (AngloGold Ashanti, Report to Society 2008).

Mining operations are conducted at depths ranging from 1800m to 3777m below surface. In 2007, the West Wits operations produced 33 258 kg of gold, equivalent to 20 % of the group's total production (Country Report, South Africa West Wits operations, 2007). Furthermore there were 160 102 workers employed in South Africa's gold mining industry during 2009 (Chamber of Mines of South Africa), which is

a little less than in the PGMs industry with most employees, and more than double the number of employees in the coal mining industry.

2.2 Gold mining health risks

Shortly after the gold mining industry took off in South Africa, tuberculosis was recognised as an important health hazard (Guild et al., 2001). During these early days, black migrant miners were recruited from rural South Africa and other neighbourhood states, employed for short contract periods (six to nine months) and often stayed home for extended periods between contracts. Critical studies reported that extreme social and physical conditions (overcrowding, poor diet and poor working conditions), rendered the labour force excessively prone to tuberculosis and pneumonia (Eisler, 2003; Guild et al., 2001; Corbett et al., 1999). Between 1975 and 1991 the prevalence of TB rose even further, as the frequency of both TB and silicosis were indicated to increase with age and duration of service, whilst silicosis remained the most significant predictor of TB (Eisler, 2003, Corbett et al., 1999). These statistics showed a rapid increase in TB cases with the rise of the HIV pandemic during the 1990s, as HIV infection predisposes to TB (Sonnenberg et al., 2005; Corbett et al., 1999). Other contributing factors remained the crowdedness of the miners' living conditions, silica dust exposure, and an increase in the age of the work force (Eisler, 2003; Corbett et al., 2003; Corbett et al., 1999), signifying that TB was likely to remain the most important health hazard in South African mines.

2.3 Tuberculosis

'Tuberculosis is a social disease, and presents problems that transcend the conventional medical approach….its understanding demands that the impact of social and economic factors on the individual be considered as much as the mechanism by which tubercle bacilli cause damage to the human body' (Farmer, 1997:348).

2.3.1 Nature of Tuberculosis

Tuberculosis, a bacterial infection caused by *Mycobacterium tuberculosis*, has been known since earliest times as archeological findings from a number of Neolithic sites in Europe and sites from ancient Egypt to the Greek and Roman empires show evidence of a disease consistent with modern TB. It is now causing more deaths in the world than any other infectious disease (Mathema, Kurepina, Bifani & Kreiswirth, 2006). As

discussed previously, TB rates have also risen progressively throughout Africa during the last decade. Based on notifications to the Chamber of Mines in South Africa, the incidence of TB has increased dramatically in recent years; with a three times higher incidence amongst the gold miner population (Guild et al., 2001) than amongst other mining populations. When TB becomes active; the disease kills an estimated 60% of those who are not treated. This amounts to approximate 3 million deaths worldwide every year (Herchline & Amorosa, 2009). When treated, an estimated 90 % of patients who have an active tuberculosis infection survive (WHO, 2008; Guild et al., 2001)

TB is characterized by the formation of *tubercles*, or small rounded nodules, in tissue implanted in areas of high partial pressure of oxygen e.g. the lungs or renal cortex. Once inhaled by a tuberculin free person, the bacilli have four potential destinies: 1) they may be killed by the immune system, 2) they may multiply and cause primary TB, 3) they may become dormant and the host remains asymptomatic, or 4) they may reproduce after a latency period (reactivation disease) (Herchline & Amorosa, 2009).

As a person breathes bacterially contaminated air, the bacilli travel to the lungs through the *bronchioles*. At the end of the bronchioles are *alveoli*. Alveoli are balloon-like sacs where the blood receives oxygen from inhaled air and releases carbon dioxide into the exhaled air. Tuberculosis bacilli infect the alveoli, where the body's immune system, in the form of specific white blood cells called *macrophages,* attacks them. Tuberculosis bacteria, however, contains a complex cell wall that protects some bacteria inside the macrophage[2], and may overwhelm a person's immune system, especially if the immune system is already being compromised (e.g. when a person is HIV positive or has been exposed to silica dust) (Mathema et al., 2006). Although the most common site of tuberculosis infection is the lungs, the bacilli could break out of the tubercles in the alveoli and the infection can be carried through the blood stream or lymphatic system to other organs from the primary infection site (Mathema et al.,2006; Department of Health, 2004; Stach et al., 1998). Organisms deposited for example in the upper lung zones, kidneys, bones, and brain may find environments that support their growth, and several bacterial divisions may occur before specific immunity

[2] Protective immunity is characterized by granuloma formation that consists primarily of activated *M. tuberculosis*-infected macrophages and T cells.

develops and limits multiplication. Infants, very young children and people infected with e.g. HIV have an increased risk of developing this extra-pulmonary TB (Curtis, 2007).

As the body's immune system resists the infection and kill numerous bacilli, immune cells and local tissue die as well. These dead cells form masses called granulomas, where bacilli can survive but cannot grow. Granuloma also provides a local environment for communication of cells of the immune system. Within the granuloma, T lymphocytes (CD4+) secrete cytokines, which activate macrophages to destroy the bacteria with which they are infected (Mathema et al., 2006). As more lung tissue is destroyed and granulomas expand, cavities develop in the lungs, and sometimes expand into lung airways. This allows large numbers of bacilli to spread when the person coughs. As the granulomas grow in the lungs and destroy lung tissue, it may lead to more coughing and shortness of breath. These structures can also eat away at blood vessels, leading to bleeding in the lungs, resulting in possible blood sputum. As the disease develops, the presentation is variable in regard to severity, duration, therapeutic response, and tissue tropism. Although commonly a pulmonary infection, *M. tuberculosis* can infect a variety of tissues, such as the meninges, lymph nodes, and tissues of the spine. A number of external factors may influence the progression and nature of disease. These include co-morbid conditions that dampen the host immune system, such as poorly controlled diabetes mellitus, renal failure, chemotherapy, malnutrition, or intrinsic host susceptibility (Mathema et al., 2006). Recently, it has become apparent that HIV-infection, due to its profound suppression of the normal immune response, predisposes to much more severe forms of tuberculosis. In HIV-infected persons with TB, dissemination of tubercle bacilli and a variety of extrapulmonary manifestations are common (Mathema et al., 2006; Corbett et al., 2003).

The effect of free radicals (oxidative stress), and lower levels of antioxidants has also been reported in TB patients, largely due to poor immunity and malnutrition (Reddy, Murthy, Krishna & Prabhakar, 2004; Jack, Jackson & Hind, 1994). Mycobacteria can induce reactive oxygen species production by activating phagocytes, and although an important part of the host defence against mycobacteria, enhanced reactive oxygen species (ROS) generation may promote tissue injury and inflammation. This may contribute even further to immunosuppression (Reddy et al., 2004) and a prolonged

recovery time. Since some of the TB medication is also known to generate free radicals (in the inner ear) (Bardien et al., 2009), and the process of noise-induced hearing loss itself is also attributed to this phenomenon, this matter will be discussed later on and possible relationships will be considered.

Two other varieties of TB that are also worth mentioning in this general discussion of TB are MDR-TB and XDR-TB, where MDR-TB is defined as resistance of *M.tuberculosis* to *Isoniazid* and *Rifampicin* with or without resistance to other TB drugs (Guild et al., 2001). Selection for drug-resistant mutants in patients mainly occurs when patients are treated inappropriately or are exposed to, even transiently, sub-therapeutic drug levels, conditions that may provide adequate positive selection pressure for the emergence and maintenance of drug-resistant organisms. One of the contributing factors is the exceptional length of chemotherapy required to treat and cure infection with *M. tuberculosi*. The need to maintain high drug levels over many months of treatment, combined with the inherent toxicity of the agents, results in reduced patient compliance and subsequently higher likelihood of acquisition of drug resistance (Mathema et al., 2006; Department of Health, 2006). This condition is difficult and expensive to treat, and in the year 2000 the cure rate or for MDR-TB was less than 50% (Hausler, 2000).

XDR-TB, although identified in all regions of the world but most frequently found in the former Soviet Union and Asian countries, is showing resistance to most of the drugs currently used in TB treatment. A recent outbreak of XDR-TB in an HIV-positive population in KwaZulu-Natal, South Africa emphasized the urgency of the situation with alarming high mortality rates (WHO, 2006).

2.3.2 Incidence and prevalence of Tuberculosis

TB case rates have risen progressively throughout Africa during the last decade. Among gold miners the increase in TB case notification rates occurred in parallel with the increasing prevalence of HIV infection, which greatly increases susceptibility to TB (Guild et al., 2001). According to Corbett et al. (2003), TB incidence rates were the highest in the WHO African Region with an average of 290/100 000 per year. This number was estimated even higher within the gold mining industry at a rate of 3 000 per 100 000 individuals (AngloGold Ashanti, Report to Society, 2006). In 2008, 874

employees were diagnosed with TB, a rate of 26 per 1000 employees (AngloGold Ashanti, Report to Society, 2008). Nine percent (7-12%) of all new adult TB cases (15-49 years) were attributable to HIV infection, but the proportion was much greater in the WHO African Region (31%). In South Africa alone there were two million co-infected (HIV and TB) adults (Corbett et al., 2003), confirming that the HIV pandemic presents an enormous challenge to the control of the TB disease.

2.3.3 Diagnosis of Tuberculosis

Consequently it is of utmost importance to detect and start TB treatment as soon as possible. The presence of TB should be suspected in any individual who presents with one or more of the following symptoms: resistant cough for three weeks or more, sputum production (particularly if blood stained), chest pain, shortness of breath, loss of appetite, loss of weight, night sweats, fever and general fatigue and weakness (Department of Health, 2004; Hausler, 2000). Cough however, is a common symptom among miners, and cough alone is less likely to result in presentation to the health service. Nursing staff should therefore be trained to recognize these symptoms and investigate promptly (Guild et al., 2001). South African miners are one of the communities in which routine radiography is practised as part of active case detection (Guild et al., 2001).

TB can be diagnosed by its symptoms, chest radiography, sputum smear microscopy and by cultivation of M. tuberculosis, which is considered as the gold standard. Recent advances in molecular biology and a better understanding of the molecular basis of drug resistance in TB, have provided new tools for rapid diagnosis; however, the high cost of most of these techniques, and their requirement for sophisticated equipment and skilled personnel have precluded their implementation on a routine basis, especially in low-income countries (Perkins & Cunnigham, 2007; Pai, Kalantri & Dheda; 2006). In order to diagnose active TB, most mining companies in South Africa still rely on sputum microscopy (Guild et al., 2001). All patients with suspected pulmonary TB should have three sputum smears done over 2 days. In order to differentiate between TB and nontuberculous mycobacterial disease (NTM) (which is clinically indistinguishable from TB, but treated totally differently), all positive cultures should have the organism identified (Department of Health, 2004; Guild et al., 2001). Although a chest radiograph is required at diagnosis and following completion of treatment for

notification to and compensation assessment (Guild et al., 2001), the diagnosis of TB should not be based on chest radiograph alone as HIV infection alters the clinical and radiological presentation of TB. More than 90% of HIV-infected patients with TB will have an abnormal chest radiograph. Upper lobe infiltrates and cavities are the typical findings in reactivation tuberculosis, whereas intrathoracic lymphadenopathy and lower lobe disease are seen in primary tuberculosis. In HIV-infected persons with higher CD4 T-cell counts (e.g. >200 cells/mm^3) the radiographic pattern tends to be one of reactivation disease with upper lobe infiltrates with or without cavities. In HIV-infected persons who have a greater degree of immunosuppression (e.g. CD4 T-cell count <200 cells/mm^3), a pattern of primary disease with intrathoracic lymphadenopathy and lower lobe infiltrates is seen. As chest radiographs may appear normal in 7-14% of cases, a high index of suspicion must be maintained in evaluating an HIV-infected patient with symptoms suggestive of tuberculosis (Gooze & Daley, 2003).

TB comes with a high social and economic cost, both for the individual concerned and the industry as a whole. Historically, because of the increased risk of TB in silica-exposed gold miners, TB is considered an occupational disease in South Africa (AngloGold Ashanti, Report to Society, 2006). Improved employee health would lead to improved quality of life, improved productivity and reduced healthcare cost.

2.3.4 Treatment of Tuberculosis

Treatment regimens vary according to treatment category and site of disease. The following case definitions are used for treatment category: *New cases* are patients who have not previously been treated for TB for more than one month. *Re-treatment* cases are patients who have previously had more than one month of TB treatment and now require re-treatment. Re-treatment for TB may be required for relapse following previous cure, interruption of treatment or treatment failure (Guild et al., 2001). They are more likely to show resistance to one or more of the anti-TB drugs, so their sputum should be sent for culture and susceptibility testing (Department of Health, 2004; Hausler, 2000). People living with HIV/AIDS also have an increased risk of recurrence of TB after completing TB treatment (Glynn et al., 2004).

Adherence to TB treatment cannot be over-emphasized (McInerney et al., 2007). Although there may be side-effects to some of the TB drugs, the importance of

completing a course is of absolute importance. The best way to ensure that a patient completes treatment is with Directly Observed Treatment (DOT) (Ducati, Ruffino-Netto, Basso & Santos, 2006; Hopewell, Pai, Maher, Uplekar & Raviglione, 2006; Deaprtment of Health, 2004). The DOTS strategy is an internationally recommended strategy for controlling TB. The elements are: political commitment to direct resources towards TB control, identifying patients with sputum smear microscopy, directly observed treatment and provided patient-centred care, ensuring drug supply and use of standardised anti-TB treatment regimens, and monitoring treatment outcomes with TB recording and reporting systems (Hausler, 2000).

The treatment regimens for new and retreatment cases recommended by the National TB Council Programme are used and have already been mentioned in the previous chapter. These treatment regimens are internationally accepted as well (Ducati et al., 2006; Hopewell et al., 2006). TB treatment is the same for those who are infected with HIV and those who are not (Department of Health, 2004; Guild et al., 2001; Hausler, 2000). All patients who are infectious (smear positive) or clinically ill should be admitted to a TB facility for initial care. Once patients are clinically well and non-infectious (converted to smear negative), they may be discharged. They may return to work on treatment if clinically fit to do so (Guild et al., 2001). Health care providers may suggest preventive therapy (and even HAART) to HIV positive workers, enabling reduction of opportunistic infections while on TB treatment and of recurrence of TB once completed (Perkins & Cunningham, 2007; Guild et al., 2001).

When used correctly, the combination of the four initial drugs is effective in the treatment of TB where each drug has a specific part to play in the treatment process: *Isoniazid* (INH) and *Ethambutol* is a bacteriostatic agent that is able to reduce the number of actively dividing bacilli during the initial phase of therapy. *Rifampicin* is a bactericidal agent that kills the remaining bacteria, while *Rifampicin* and *Pyrazinamide* act well against the intracellular bacteria which are dormant inside macrophages and other cells. They also provide the best ‘sterilization’, in other words killing dormant bacteria very well in order to lower the number of relapses after a successful treatment (Department of Health, 2004; Hershfield, 1999). *Streptomycin* was the first drug used clinically for treatment of TB (1947-1952), as it was the only drug available at that time (Wilson, 2005). It is an aminoglycoside antibiotic that interferes with the bacterial

protein synthesis, and is now being used as a second-line drug due to its toxicity (Caminero, 2005; Hershfield, 1999), and only when the initial 4-drug therapy fails. Dr Zahan Eloff (Manager of Occupational Health at the West Wits Operation, AngloGold Ashanti Gold Mine) confirmed that Streptomycin is mostly used in re-treatment cases, but also in some first treatment cases when there is an indication of adverse effects of the first line medications, mostly hepatotoxicity (personal communication, November 2010). (International standards recommend to always include an aminoglycoside or capreomycin in retreatment (Caminero, 2007)). The adverse effects of *Streptomycin* include affecting the eighth Cranial Nerve's auditory and vestibular functions (ototoxicity) as well as nephrotoxicity (Department of Health, 2004; Hershfield, 1999).

Adverse reactions to drugs may be the consequence of intolerance, toxicity or hypersensitivity. In a study done by Torun et al. (2005) to investigate the frequency of treatment side-effects of MDR-TB in 263 patients, 182 cases (69.2%) developed one or more side effects and included: ototoxicity, psychiatric disorders, gastrointestinal disturbances, arthralgia, epileptic seizures, hepatitis and dermatological effects. *Isoniazid* may produce asymptomatic elevation of serum transaminases, overt hepatitis, or even more severe hepatitis. *Isoniazid* may also interfere with pyridoxine metabolism and thus produce peripheral neuropathy, and is also associated with hypersensitivity reactions such as skin rash. Hepatotoxicity occurs less frequently with Rifampin than with *Isoniazid*, but hypersensitivity reactions, thrombocytopenia, renal failure and flu-like symptoms may occur. *Pyrazinamide* may cause hypersensitivity reactions and gastrointestinal upset can occur. The most significant side-effect of *Ethambutol* is optic neuritis and the symptoms of this condition include blurred vision and colour blindness (Department of Health, 2004; Hershfield, 1999). Aminoglycosides (e.g. *Streptomycin*) appear to generate free radicals within the inner ear, with subsequent permanent damage to sensory cells and neurons resulting in permanent hearing loss (typically involving the first row of outer hair cells in the basal turn/higher frequencies first) (Bardien et al., 2009; Duggal & Sarkar, 2007).Table 2.1 is a list of possible adverse effects that might be caused by TB treatments.

Table 2.1 Frequency of reported side-effects of TB treatment, according to Furin et al. (2001); hearing related affects are listed in bold

Adverse Effect	Symptoms associated in the literature with these effects
Psychiatric	Presence of one or more of the following: depression, anxiety and/or psychotic symptoms as defined by DSM IV criteria
Peripheral nervous system	Peripheral neuropathy: numbness, tingling sensation, diminished or **absent reflexes**, **vestibular side effects**, nystagmus, dizziness and/or loss of balance.
Hypothyroidism	Serum thyroid stimulating hormone (TSH) greater than 10.0 IU/mL.
Central nervous system	Severe headache not relieved by non-prescriptive analgesics, possible seizure activity of any type as reported by patient or witnessed by another.
Otologic	**Hearing loss** confirmed by audiometry/ physical examination.
Musculoskeletal	Presence of joint pain, joint swelling, or persistent muscle aches.
Renal	A rise of 0.5 or more in serum creatinine from a patient's baseline.
Hepatitis	Elevation of serum transaminases or serum bilirubins to more than twice normal values.
Severe gastritis	Inflammation of upper GI tract, serious enough to cause bleeding.
Mild gastritis	Irritation of stomach, manifested by nausea, vomiting, pain and/or reflux.
Ocular	Presence of visual changes suggestive of optic neuritis, incl. vision loss, pain, loss of colour vision etc.
Dermatological	Any skin change incl. rush, bronzing, and/or photosensitivity reaction.

Apart from the aminoglycosides and capreomycin and its ototoxic actions (vestibular and/or auditory) (Curry, 2008), no other TB drug used in the standard first-time or re-treatment regimens has an affirmed ototoxic response. In a case report by Yerdelen & Tan (2008), a 78-year old man developed hearing loss while he was on a hemodialysis program and taking TB medication (combination therapy with *Isoniazid* and no *Streptomycin*). Yerdelen & Tan (2008) reports a further seven cases of end-stage renal failure with patients developing hearing loss, where *Isoniazid* is implicated. Although the authors state that it is difficult to confirm beyond any doubt that *Isoniazid* is the responsible drug due to multiple drug interactions etc., they had discontinued *Isoniazid* in four of the patients and documented improvement of hearing loss in two, progression in one and stable findings in the other.

The neurotoxic syndrome associated with *Isoniazid*, (Ethionamide, Cycloserine and Linezolid) is a well-known phenomenon (Yerdelen & Tan, 2008), ranging from peripheral neuropathy, optic neuritis, ataxia, dysarthria, psychiatric manifestations etc. *Isoniazid* induces these effects by inhibiting the phosphorylation of pyridoxine, resulting in decreased production of pyridoxal-5-phosphate, a coenzyme involved in multiple metabolic functions, including neurotransmission (Yerdelen & Tan, 2008). Although Pyridoxine prophylaxis (Curry, 2008) is included in most of the TB patients' treatment (to counteract the neurotoxic effect), the possibility of an interaction between impaired neurotransmission and the effect on the hearing status of the gold miners cannot be ignored.

TB and the different pathways where the hearing system can be involved, have been investigated. Although hearing loss can be a secondary cause of TB, the process of TB seems to have no explicit or proven effect on hearing. The already compromised immune system can cause the miners to be more susceptible to specifically NIHL. It might even be possible that the process of TB and the role of free radicals could aggravate a pre-existing NIHL, or predispose the miners to become more susceptible to develop a hearing loss. The diagnosis and treatment of TB as well as the side-effects caused by TB drugs have also been considered. Apart from *Streptomycin* (in the TB regimen) no other drug has ototoxicity as known side-effect, but it may be possible that other weaknesses in the body due to TB medication or other medication such as ARVs can exaggerate the already pre-existing risk of NIHL amongst mine-workers.

TB was classified as a compensable disease in 1916, although compensation was racially biased for more than 80 years. The Occupational Diseases in Mines and Works Act (ODMWA) was adjusted in the 1990's to remove racial discrimination for compensation, and a wage based system was introduced (Guild et al., 2001). The extremely high burden of lung disease in mine workers and ex-mine workers places enormous challenges on health service delivery systems and compensation authorities. As mentioned before, at present mine workers are currently compensated for cardio-respiratory TB. If the TB medication contributes to hearing loss or aggravates an already existing hearing loss, compensation should in all probability also be considered for them.

2.3.5 Effect of silica exposure and silicosis on the development of Tuberculosis

Silicosis is the most significant occupational lung disease in gold mining, and the overall TB rates are approximately three to four times higher in silica-exposed gold-miners than in non-silica exposed gold miners (Guild et al., 2001; Ross & Murray, 2004). The dangers of silicosis from the inhalation of silica (the second most common mineral on earth) dust produced by the processes (drilling, blasting, scraping) of hard rock mining, have long been recognised and occurs where crystalline silica particles are liberated (Eisler, 2003; Guild et al., 2001; Corbett et al., 1999). Quartz is a pure form of silica crystal, and newly fractured quartz is the most toxic variety of crystalline silica (Guild et al., 2001).

Silicosis is a condition that develops slowly over time. As a group, active miners include members with a mix of length of service. Members with a shorter length of service (e.g. <10 years) are unlikely to have detectable silicosis, even if they work in dust levels high enough to eventually cause the condition. The condition progresses slowly with continued mining exposure, and even when exposure ceases, the dust particles in the lungs continues to be biologically active and the condition continues to develop (Eisler, 2003; Guild et al., 2001; Corbett et al., 1999).

The majority of the mine labour force consists of Black workers conducting jobs such as drilling, ore removal, and stoping in the dustiest areas of the gold mine. Available information from recent studies (on retired and retrenched workers) indicate that Black mineworkers have a working lifetime risk of between 220/1 000 and 360/1 000 of developing radiological silicosis from gold mining (Guild et al., 2001).

Based on 2007 CDC data, the frequency of TB in Hispanic, Black and Asian populations were 7.6, 8.5, and 23.5 times higher, respectively, than in White populations. Race, nevertheless, is not clearly an independent risk factor as foreign-born persons account for example for 96% of TB cases among Asian populations, but only for 29% of TB among Black populations. Risk is best defined on social, economic, and medical factors (Herchline & Amorosa, 2009). These data furthermore indicated that TB rates in women decline with age, but increase in men with age. The reason for these differences may as well be social rather than biological in nature, but are noteworthy as the socio-economic and labour environment as well as ethnic

distribution amongst the mining workforce lends itself to certain populations being more susceptible to develop TB.

Both silica exposure and silicosis however are unambiguous risk factors for TB. The reason for the increased risk is not well understood, but it is thought that silica damages pulmonary macrophages, inhibiting their ability to kill mycobacteria as well as reducing lung function and leading to cell death (AngloGold Ashanti, Report to Society, 2006; Guild et al., 2001). Tuberculosis in a person with established silicosis is termed silicotuberculosis. The risk of developing TB increases with duration of exposure to silica dust even in the absence of silicosis (Nelson et al., 2010; Ross & Murray, 2004; Eisler, 2003). The presence of radiological silicosis (marked by inflammation and scarring in the form of nodular lesions), increases the risk for pulmonary TB approximately four fold, with the risk rising as radiological silicosis becomes more severe (Guild et al., 2001).

The presence of silicosis in the lungs can alter the natural history of TB and may change the radiological appearances. The interaction of TB and silicosis is very damaging to the lung, unless TB is diagnosed and treated early. In a study done by teWaterNaude et al. (2006), it was indicated that two jobs, namely driller and winch operator, contained a higher proportion of workers with pulmonary TB. These two jobs were also those with exposure to the highest quartz and dust concentrations. Their analysis indicated a significant association between measures of silica and dust exposure and pulmonary TB prevalence (independent of the presence of silicosis). The study also emphasised that the length of service is a rather poor proxy for exposure compared with indices that include gravimetric measures of intensity. It is therefore important to take the particular occupation of the individual mineworker as well as the exposure time in that occupation into account, before any assumption can be made towards an individual's specific risk and susceptibility to develop TB (this is the same for NIHL). The fact that TB incidence in gold miners is age-dependant, is likely to be at least partly due to the effect of silica exposure, since age and length of service are closely related (Nelson et al. 2010; Eisler, 2003; Guild et al.,2001).

2.3.6 Effect of HIV/AIDS on Tuberculosis

Acquired immunodeficiency syndrome (AIDS) can be called the epidemic of the 20th century (Moazzez et al., 1998). According to UNAIDS global report on AIDS (2010) there were an estimated 33.3 million people worldwide living with the human immunodeficiency virus (HIV - the virus causing AIDS). This number includes the estimated 2.6 million people who were newly infected with HIV in 2009. AIDS was also the cause of 1.8 million deaths worldwide in 2009.

Sub-Saharan Africa has been the heaviest affected by this modern-day outbreak as 34% of people living with HIV in 2009 resided in the 10 countries in Southern Africa; 31% of new HIV infections in the same year occurred in these 10 countries, as did 34% of all AIDS-related deaths. With an estimated 5.6 million [5.4 million–5.8 million] people living with HIV in 2009, South Africa's epidemic remains the largest in the world (UNAIDS, 2010).

According to WHO data (2009), at least one-third of the 33.2 million people living with HIV worldwide are infected with TB. It is estimated that the HIV/AIDS prevalence levels amongst employees at the AngloGold Ashanti operations in South Africa in 2007 remained stable, at around 30% of the workforce (AngloGold Ashanti Report to Society, 2007). It needs to be emphasized again that according to AngloGold Ashanti's 2006 Report to Society between 85% to 90% of the TB cohort are also infected with HIV. These figures are a clear indication of how closely intertwined the two diseases are, and how difficult it is to talk about the one without mentioning the other – especially in the gold mining industry.

HIV is a retrovirus that infects blood cells, resulting in life-long infection that leads to chronic illness characterised by progressive immunodeficiency and occurrence of opportunistic infections including TB. The immunosuppression that results from HIV infection leads to a greatly increased risk of TB disease following TB infection, both by increasing the rate of reactivation of the disease, and by increasing susceptibility to rapidly progressive disease following newly acquired infection. The increased susceptibility to TB is apparent from an early stage of HIV, and becomes more pronounced with increasing degree of immunosuppression (Sonnenberg et al., 2005; Guild et al., 2001)

The role for $CD4^+$ T cells in protecting against disease progression is emphasized by the marked susceptibility to TB in patients with advanced HIV-induced $CD4^+$ T-cell depletion. The natural course of HIV disease may also be influenced by *M. tuberculosis* infection. *M. tuberculosis* infection results in macrophage activation, which can house resident HIV virions, resulting in active expression of HIV antigens rather than the prolonged latency without antigenic expression of HIV proteins. Thus, HIV infection tends to accelerate the progression of TB, while in turn; the host immune response to *M. tuberculosis* can enhance HIV replication and may accelerate the natural course of HIV/AIDS (Mathema et al., 2006).

The prevalence of HIV has and will also increase as well as aggravate the burden of TB in miners exposed to silica (Rees & Murray, 2007; Dias et al., 2006). A recent study on the effect of HIV on silicosis and TB incidence in a Black population of South African gold mineworkers, found that HIV increased the incidence of TB by five times, and silicosis increased the incidence of TB by three times (Corbett et al., 2000). The co-existence of HIV and silicosis is an example of interaction or synergistic risk (Marks, 2006) and increases the incidence of TB multiplicatively by fifteen times (Nelson et al., 2010; Ross & Murray, 2004). This is a powerful contributor, especially because it is more difficult to diagnose TB in someone infected with HIV (Stoltz, 2008; Mathema, 2006).

2.3.7 Genetics in Tuberculosis

A variety of studies (also in twin studies) proposed that the course of tuberculosis is (highly) dependant on an individual's genetic susceptibility or make-up, suggesting that the innate mechanism of immune defence (among other factors) can often contribute to an infection (Jabado & Gros, 2005; Stead, 1992). Furthermore it is also suggested that the development of TB is the result of a complex interaction between the host and pathogen influenced by environmental factors (Selvaraj, 2004). These contributors make it difficult to pin-point the precise origin, although the most important fact to keep in mind is that TB weakens the immune system in general, and therefore may cause the workers to be more susceptible to other damage/infection somewhere else in the body.

2.3.8 Influence of Tuberculosis on hearing

Although Tuberculosis, according to the Occupational Diseases in Mines and Work Act as Amended, Act 208 of 1993, is compensable only if cardio-pulmonary organs are involved, other forms of extrapulmonary TB (as mentioned already) are also present – especially in the HIV infected population. These infections are often miss-diagnosed as the symptoms are systemic with local features most of the time (Hausler, 2000). Other forms of TB which have a direct influence on the hearing of the involved individuals may include: Tuberculous Otitis Media, Tuberculosis of the Nasopharynx, Tuberculosis induced changes to the osseous cranial base, Tuberculous Meningitis and Miliary Tuberculosis.

Tuberculous Otitis Media (one of the rarest forms of extrapulmonary TB) remains a significant challenge to the specialist. It is difficult to diagnose due to its symptoms having non-specific manifestations with respect to other types of chronic otitis media; often leading to a delay in specific treatment and an increased risk of complications such as facial paralysis and irreversible hearing loss (Vaamonde, Castro, Garcia-Soto, Labella, and Lozano, 2004; Ozcelick, Ataman, and Gedikoglu, 1995). In the specific studies mentioned here, the most frequent reason for consultation was refractory otorrhea, while most patients showed hearing loss and otorrhea of varying degree, and none reported a past history of TB. Multiple perforations of the tympanic membrane also seem to be a frequent consequence of the disease. The treatment of choice is the standard treatment used for other forms of TB, although the effects of treatment on hearing loss have been classed as ‘unpredictable’ (Vaamonde et al., 2004) as early treatment onset is the best guarantee for optimal recovery.

Nasopharyngeal TB also represents an uncommon form of TB. Enlargement of the neck lymph node and other symptoms referable to the ear and nose (tinnitus, nasal obstruction, hearing loss and otolgia) are presenting symptoms and direct observation of the nasopharynx reveals a combination of mass and irregularity. Nasopharyngeal TB is usually isolated, without pulmonary or systemic symptoms, and also aggravates the early diagnosis (Tse et al., 2003).

In a noteworthy study by Balboni et al. (2008), TB induced changes to the osseous cranial base with a potential effect on hearing is revealed. Although hearing loss, tinnitus, and vestibular problems, have been noted to occur in some individuals who

have developed TB, the exact means of such complications are not entirely understood but may include direct effects (e.g. drug toxicity on hair cells due to treatment) and/or indirect disturbances (e.g. loss of control of perilymph composition/pressure, altered cochlear blood flow, and increased turbulent venous flow by means of cranial-base ossification). In this study the authors suggested that premature ossification of two structures located on cranial base, the petro-occipital fissure and cochlear aqueduct in active TB patients, alters the homeostatic mechanisms of the ear in a way comparable to that seen in age-related hearing loss. This causes the aural symptoms such as hearing loss, tinnitus and vestibular fall-outs (Balboni et al., 2008), and may hold a possible explanation to the relationship between TB and hearing loss.

The relationship between sensory-neural hearing loss (SNHL) and meningitis has long been studied. Kuan et al. (2007) reported a case study of a 22-year-old male who died of tuberculous meningitis and concluded that the modiolus and cochlear aqueduct are the main routes for the spread of infection from the meningitis to the inner ear.

Stach et al. (1998) reported a single case of auditory disorder in the central nervous system due to miliary tuberculosis. This specific form of tuberculosis results in the formation of numerous small tubercles distributed throughout the central nervous system. These tubercles are referred to as miliary lesions because of their resemblance to millet seed (Stach et al., 1998). Although reports of auditory disorder secondary to this disease are rare, the authors summarized clinical data of a patient with a unilateral hearing disorder (of sudden onset), secondary to miliary tuberculosis. The auditory disorder was characterized by a profound hearing loss of retrocochlear origin; presenting with normal otoacoustic emissions but abnormal auditory evoked potential results (Stach et al., 1998). The case demonstrates that the TB, as a result of the formation of tubercles at a specific point in the auditory nervous system (although rare), is able to cause a hearing loss.

It remains difficult however, to separate the effects of the disease from effects of the treatment, which often consist of ototoxic antibiotics (Stach et al., 1998). Nonetheless, if TB or the treatment thereof has a negative influence on the hearing status of miners when being used during the treatment of occupational (cardio-pulmonary) TB, the

hearing loss caused or aggravated by the use of these treatments should also be investigated.

2.4 Conclusion

The contributing factors that clearly influence the development of TB include the severity of silicosis, the prevalence of TB in the population from which the workforce is drawn, as well as their age, general health and HIV status (Ross & Murray, 2004). The intensity of exposure to TB infection is by far the most important factor affecting TB rates in communities (Department of Health, 2004). The other aspect determining TB incidence rates in a community is the percentage of infected individuals who progress to active TB.

Even though the prevalence of TB in South Africa's gold mines are so high, there are only a few case studies available that report on extra-pulmonary TB and hearing loss and the recognized ototoxic effect of Streptomycin on hearing. There is no research available on the effect of TB on the hearing profile of gold miners and this phenomenon will be investigated in the present study.

Chapter 3

Noise-induced hearing loss

3.1 Background to noise-induced hearing loss

Noise has been increasingly recognised as a pervasive occupational hazard, rated under the top ten work related problems (Ologe et al., 2006) with many adverse effects including e.g. elevated blood pressure, reduced performance, sleeping difficulties, annoyance and stress, tinnitus and most importantly noise-induced hearing loss (NIHL) (Nelson et al., 2005). Noise is not only a health hazard to workers with significant implications for the individual's quality of life, but also serves as a serious financial threat to many industries, as it is responsible for a huge percentage of all occupational disease claims and compensation benefits being paid out (Begley, 2006). The South African mining industry introduced hearing conservation programmes (HCPs) in 1988 (Guild et al., 2001). Since labour-intensive methods common to many mineral extraction and processing operations were resulting in large numbers of people being routinely exposed to noise beyond the legally recognised safe limit of 85 dB(A)[3], HPCs consequently became compulsory. Research indicated that time-weighted average (TWA)[4] equivalent exposure levels in RSA mines, normalised to an 8-hour duration are generally between 90 and 100 dB(A), depending on the occupation. Some exposure levels even range between 95 and 110 dB(A). It has subsequently been estimated that between 68 and 80 % of mine workers are exposed at a TWA of 85 dB or greater, indicating a significant risk of hearing loss in the industry (Guild et al., 2001).

Occupational noise-induced hearing loss therefore describes an acquired hearing deficiency directly attributable to excessive workplace noise, stereotypically unmasked by a decline in communicative capacity. Clinically, affected individuals show a deteriorating appreciation for sounds within the high frequencies, typically noted as a threshold dip/hearing notch between 4000-6000 Hz on pure-tone audiometry testing

[3] (A) Means the logarithmic unit for the average level of a sound, as measured using a Sound Pressure Level meter's A-weighting network. This network applies weighting to the values for constituent frequencies of a sound in accordance with the human ear's sensitivity to them.
[4] TWA shows a worker's daily exposure to occupational noise (normalised to an 8 hour day), taking into account the average levels of noise and the time spent in each area.

(Dobie, 2008; Sliwinska-Kowalska et al., 2006; Gates et al., 2000). Interestingly, despite the almost universally-accepted diagnostic standard of the hearing notch, a recent study suggested that fewer than 38% of individuals with diagnosed occupational NIHL actually demonstrated this characteristic feature (Kurmis & Apps, 2007). In another study by Soer et al. (2002) this typical 'noise notch' was identified at 6 kHz. Rabinowitz et al. (2006) indicated that a notch could be identified in most audiograms of noise exposed workers.

Factors determining damage-risk criteria for NIHL are sound-pressure levels, spectral characteristics, duration of exposure, and individual susceptibility (Nanda & Tripathy, 2007; Miller & Schein, 2005; Mills & Going, 1982). While certain high-level noises impact sufficient energy to the cochlea (approximately 125 dB SPL or greater) to cause significant *mechanical* damage, much noise exposure is at such a level so as to *metabolically* challenge the cochlea as well. Exposure to excessive levels of noise leads to the production of reactive oxygen species (ROS) and other free radical molecules in the cochlea, and these ROS are capable of inducing cochlear damage as well as loss of function when infused into the cochlea (Kopke et al., 2002). The following section will consider the mechanism of noise induced hearing loss.

3.2 Biological basis for cochlear damage in noise-induced hearing loss

High-levels of noise exposure present special challenges to the auditory system. The damage caused by noise is pervasive and affects virtually all of the cellular subsystems of the inner ear (sensory cells, nerve endings, and vascular supply) (Le Prell et al., 2007; Henderson et al., 2006; Wang, Hirose & Liberman, 2002; Henderson & Hamernik, 1995). In order to really understand the ear's response to noise, it is necessary to have an overview of each part of the peripheral auditory system.

The geometry of the external auditory meatus (EAM) is that of a tube, closed at the one end by the tympanic membrane and open at the other end. Tubes open at one end have acoustic resonant properties that are described as follow: resonant frequency (f) = speed of sound / 4 X length of EAM. Because the average human EAM is approximately 25 mm long, the resonant frequency of the average human ear is around 3,200 Hz. Depending on the direction and frequency of the sound source, the sound pressure amplification can be as great as 20 dB in the mid-frequency range.

Thus, the resonant characteristics of the EAM help determine the acoustic energy delivered to the cochlea (Cummings et al., 2005; Walsh, Demkowicz & Charles, 2004; Henderson & Hamernik, 1995). With this in mind - industrial noise usually includes a broader spectrum of frequencies, and as the noise travels through the EAM, acoustic energy in the mid-frequency range resonates (are amplified), creating a band pass noise centred at 3,200 Hz at the tympanic membrane. This characteristic of the EAM is primarily responsible for the appearance of the '4 KHz notch' in NIHL audiograms, as studies of the basilar membrane vibration indicated that the point of maximum displacement (4 KHz) occurs half an octave above the frequency of stimulation (3.2 KHz) (Henderson & Hamernik, 1995). The large variability in peoples' susceptibility to NIHL may thus be partially explained by the variation in acoustic transfer characteristics of the external auditory meatus.

The primary function of the middle ear (ME) is to serve as an impedance matching transformer to partially compensate for the nearly 30-40 dB transmission loss that occurs when airborne sound is introduced to the fluid-filled cochlea (Martin & Clark, 2006). Variations exist in the size of the ossicles and middle ear space, but there are limited data regarding how individual variations in middle ear structures contribute to susceptibility to NIHL. However, the importance of the acoustic reflex (AR) on noise exposed individuals must be considered. Henderson and Hamernik (1995) mentioned a study by Coletti et al. where subjects were assessed and categorized on the basis of their reflex threshold, strength of contraction, resistance to adaptation, and latency. Workers with highly efficient reflexes (i.e. low thresholds, strong contraction, free of adaptation) developed substantially less permanent threshold shifts than workers with less effectual reflexes. Although a small study with only a few subjects, it is worth reflecting on as the possible effect of e.g. impaired neurotransmission (due to TB medication) on reflexes were considered earlier (Yerdelen & Tan, 2008).

While the EAM and ME are primarily responsible for the transmission of acoustic energy from air to the cochlea, the combined action of these systems transform the input (energy) in a relatively predictable manner which is directed by laws of acoustics and mechanics. Once the energy enters the cochlea however, the process becomes more complicated and involves a number of biological processes.

When sound is transmitted to the inner ear via the movement of the stapes footplate, it initiates a travelling wave that moves from the oval window to the point of maximum vibration along the basilar membrane (BM). The actual vibration patterns on the BM are determined by the physical characteristics of mass and stiffness. The mechanical (impedance) characteristics of the organ of Corti change systematically along its length (with the base 100-200 times stiffer than the apex), leading to the tonotopic encoding of the frequency of the incoming sound (Henderson & Hamernik, 1995), with high frequency stimuli causing for example maximal disturbance near the oval window (base). This mechanical structure and impedance are critical for maintaining the faithful representation of sound vibrations along the membrane (Henderson et al., 2006). Damage to or loss of the pillar cells, as explained below, also interferes with the local impedance of vibration, and may furthermore contribute to the loss of outer hair cells.

The travelling wave induces shearing between the tectorial membrane, reticular lamina, and organ of Corti, which cause the final mechanical motion of significance: movement of the stereocilia (delicate hair-like structures, arranged in staggered rows on the apical surface of the sensory cells i.e. the inner and outer hair cells). This mechanical process initiates a series of electromechanical events within the hair cells. Displacement of the BM toward the scala vestibula and bending of the stereocilia (stereovilli) towards the spiral ligament is excitatory, leading to an increased release of chemical transmitters at the basal surface of the hair cell. On the contrary, displacement of the BM, leads to a decreased release of neurotransmitters (Henderson et al., 2006). The process of NIHL however, as mentioned previously, involves more than only the sensory cells, but also includes supporting cells, nerve fibres and the vascular system of the cochlea (Cummings et al., 2005).

Damaged cellular structures in response to intense noise exposure were identified - particularly in the organ of Corti (Le Prell et al., 2007; Heinrich & Feltens, 2006; Cummings et al., 2005; Wang et al., 2002). The organ of Corti consists of supporting cells, as well as the two types of sensory cells, the inner (IHCs) and the outer hair cells (OHCs). The inner hair cells transfer signals via afferent neurons to the brain, whereas the vulnerable outer hair cells act as a cochlear amplifier by enhancing the basilar membrane movements. Both types of hair cells possess a bundle of sensory hairs (stereocilia/stereovilli) which react on sound stimulation by deflecting, thereby opening

non-specific ion channels[5], causing membrane depolarization, neurotransmitter release and finally a generation of action potentials in the attached cochlear nerves (Henderson et al., 2006). Following a traumatic noise exposure, damage or loss of OHCs however, is invariably greater than that of the IHCs. Reasons for this might be 1) OHCs experience a direct shearing force at their stereocilia, whereas the IHC stereocilia are stimulated by viscous drag. 2) OHCs have most of their long axis 'unprotected' from mechanical stress, whereas IHCs are 'supported' on all surfaces with supporting cells. 3) The OHCs are closer to the point of maximum basilar membrane travelling wave displacement than the IHCs (Henderson & Hamernik, 1995).

Stereocilia are bounded by a continuation of the plasma membrane of the cell. The arrangement of the stereocilia on the IHCs is more or less a linear arrangement, while the stereocilia on the OHCs have a 'V' or 'W' like configuration. The height of the stereocilia is graded by location, with the shortest cilia in the row facing the modiolus. The tallest cilia of the OHCs are in contact with the tectorial membrane, while the stereocilia of the IHCs may not have such attachments at all (Henderson & Hamernik, 1995). The cilia also contain a lengthwise arrangement of actin filaments with transverse interconnections, resulting in a stiff, hair-like structure. Adjacent stereocilia are interconnected by tip links thought to be instrumental in the gating process during transduction (Heinrich & Feltens, 2006). The cilia, however, appear to be the weakest link in the mechanical transduction process.

At the sub-cellular level, broken tip links were identified after acoustic over-stimulation, which resulted in reduced hair bundle stiffness, disrupted mechano-electrical transduction and temporary noise-induced hearing loss (Heinrich & Feltens, 2006; Wang et al., 2002). Evidence for re-established signal transduction was however obtained upon regeneration of the tip links over a period of time; suggesting recovery from temporary threshold shift (TTS) induced by noise exposure (Henderson et al., 2006; Cummings et al., 2005).

[5] Ion channels are proteins that are integral parts of the membranes of cells. Most of the cell's membrane is lipid and acts as a chemical and electrical barrier between the inside and outside of the cell. Ion channels have pores that act as conduits for ionic currents to pass through the membrane.

Besides injury to tip links, additional molecular deterioration with subsequent repair has been implicated to contribute to TTS after acoustic over-stimulation (Heinrich & Feltens, 2006; Cummings et al., 2005). A reduction in outer hair cell stiffness and cell length has also been reported after intense noise exposure, with recovery taking place over time. Furthermore, exposure to moderate levels of noise causes a buckling of supporting cells, resulting in a temporary loss of contact between the outer hair cell stereocilia and the tectorial membrane, most probably amount to a protective response – preventing longer lasting hair bundle deflection and excessive depolarization of outer hair cells membranes (Heinrich & Feltens, 2006). The short outer hair cells of the high-frequency region are more vulnerable than the taller receptor cells in the low-frequency area (Pouyatos et al., 2007; Cummings et al., 2005).

All of the processes mentioned above modulate calcium channel permeability and/or calcium homeostasis in at least some biological systems. In the outer hair cells, the opening of non-specific ion channels at the apical cell side during noise-induced perilymph movement causes membrane depolarization and calcium influx. The calcium increase correlates with a contraction of the organ of Corti and with a decrease of the amplitude of the cochlear potential. Depending on the time and intensity of noise exposure, longer lasting depolarization in the case of acoustic over-stimulation will lead to an increased calcium concentration in the outer hair cells, resulting in a much higher Ca^{2+} concentration than the outer hair cells can tolerate, leading to irreversible hair cell damage. To generally prevent any possible calcium overloading, outer hair cells possess many calcium-binding proteins, acting as calcium buffers. However evidence showed high amounts of loosely bound calcium in cellular debris of destroyed outer hair cells after acute noise trauma, indicating substantial calcium concentrations that most outer hair cells cannot tolerate (Le Prell et el., 2007; Heinrich & Feltens, 2006).

It can therefore also be assumed that noise exposure is causally related to physiological calcium-activated and mitochondrion-dependent processes in outer hair cells. Intensive noise exposure results in prolonged deflection of hair bundles, continued membrane depolarization and intracellular and intramitochondrial accumulation of Ca^{2+}. Under these conditions the high cellular Ca^{2+} -binding capacity of outer hair cells become saturated after several hours, and calcium overload in

mitochondria will finally lead to NO (nitric oxide) and ROS (reactive oxygen species) production. After noise damage has been imposed in OHCs (through free radicals damaging DNA, breaking down lipid and protein molecules, triggering cell death – Henderson et al., 2006), different mechanisms might be involved to signal the occurrence of hair cell damage to supporting cells and onwards (Heinrich & Feltens, 2006).

In summary, permanent threshold shifts are observed under conditions causing irreparable damage to cells and altering its physiological state. These processes are described by various authors, concluding that noise exposure drives mitochondrial activity and free radical[6] production, reduces cochlear blood flow, causes excitotoxic neural swelling[7], and induces both necrotic[8] and apoptotic[9] cell death in the organ of Corti (LePrell et al., 2007; Pouyatos et al., 2007; Henderson et al., 2006).

With this as background: the use of generic animal models with reduced antioxidant potential have shown that, if the intrinsic free radical buffering system is altered or inefficient, then the cochlea can become much more vulnerable to noise (Pouyatos et al., 2007). Aminoglycoside appears to generate free radicals within the inner ear (primarily the outer hair cells and type I vestibular cells), with subsequent permanent damage to sensory cells & neurons resulting in permanent hearing loss (Duggal & Sarkar, 2007; Sha, 2005). The possibility might therefore exist, that if TB and/or TB medication compromises the immune system of the body, it may also have an influence on the cochlea's free radical buffering system.

3.3 Noise-induced hearing loss and the audiogram

[6] Contains one or more unpaired electrons, enabling them to alter the electron arrangement in stable molecules. Although essential for cellular life processes, in excess they damage cellular lipids, proteins, and DNA, and upregulate apoptotic pathways.
[7] Glutamate is thought to be a major neurotransmitter between the inner hair cell and the afferent cochlear nerve ending. It is hypothesized that with excessive sound stimulation; excessive synaptic glutamate concentrations are developed leading to overstimulation of glutaminergic receptors giving raise to metabolic cascades resulting in cell injury and death. Some of the potentially harmful cascades set in action by glutamate excitotoxicity may include increases in intracellular calcium, and the excessive production of nitric oxide (NO) and related free radicals such as peroxynitrite (Kopke eta al.,2002:1522; Henderson et al., 2006; Le Prell et al., 2007).
[8] The premature death of cells and living tissue, caused by external factors such as infection and trauma.
[9] The process of programmed cell death that may occur in multicellular organisms.

Exposure to workplace noise equal to or exceeding the permissible noise exposure level may cause a shift in hearing thresholds for the person with normal hearing. The widely assumed average picture of a NIHL will be a mild sensory-neural hearing loss in the frequencies below 2000 Hz, deteriorating to a moderate sloping hearing loss in frequencies above 2000 Hz (Nanda & Tripathey, 2007). According to a study done by Ologe et al. (2006) in a steel rolling mill in Nigeria, the average hearing threshold at 4000 Hz increased with increased levels of noise exposure. The outer hair cell loss shift towards high frequencies could be due to the fact that the cochlea has different susceptibility to ROS depending on the tonotopic location, making the hair cells at the basal turn more vulnerable to free-radical damage than apical OHCs (Sha, 2005). Loss of OHCs leads to elevated hearing thresholds (up to between 40-60 dB), along with loss of cochlear frequency tuning. However with more severe noise exposure, the pathology spreads to IHC death, loss of auditory nerve fibres and damage to the stria vascularis (Henderson et al., 2006).

A typical NIHL is in principle symmetrical, although studies indicate that the left ear is somehow more vulnerable (Sliwinska-Kowalska et al., 2006). Human laterality, with cortical pathways and a specifically more pronounced efferent auditory system on the right side, which reduces the susceptibility of right ear to cochlear insult, can serve as a possible explanation for this phenomenon (Nageris et al., 2007). Characteristically NIHL develops slowly over several years (Philp, 2007) as the result of exposure to continuous or intermitted loud noise (McReynolds, 2005), and affects not only the audibility but also the intelligibility of speech (McBride, 2004).

The main criterion for assessing hearing status (at mines) is percentage loss of hearing (PLH). Shifts in PLH are identified by comparing the present value with that from the baseline audiograms or previous audiograms. According to the Mine Health and Safety Act (MHSA, Act 29 of 1996) Instruction 171 and South Africa National Standards (SANS 10083), a system of medical surveillance for all employees in any working place where the equivalent, continuous A-weighted sound pressure level, normalised to a 8 hour working day or a 40 hour working week exceeds 85 dB(A), should be maintained (Begley, 2006). PLH is derived by combining the patient's hearing threshold levels at 0.5, 1, 2, 3 and 4 KHZ, using the weighted tables available from the Compensation Commissioner. A shift of ten per cent or more in PLH, as compared with the baseline

audiogram has been accepted as the level at which a compensation claim may exist (Workmen's Compensation Commissioner Instruction 171, 2001; Guild et al., 2001). Figure 3.1 is an illustration of a typical NIHL over time.

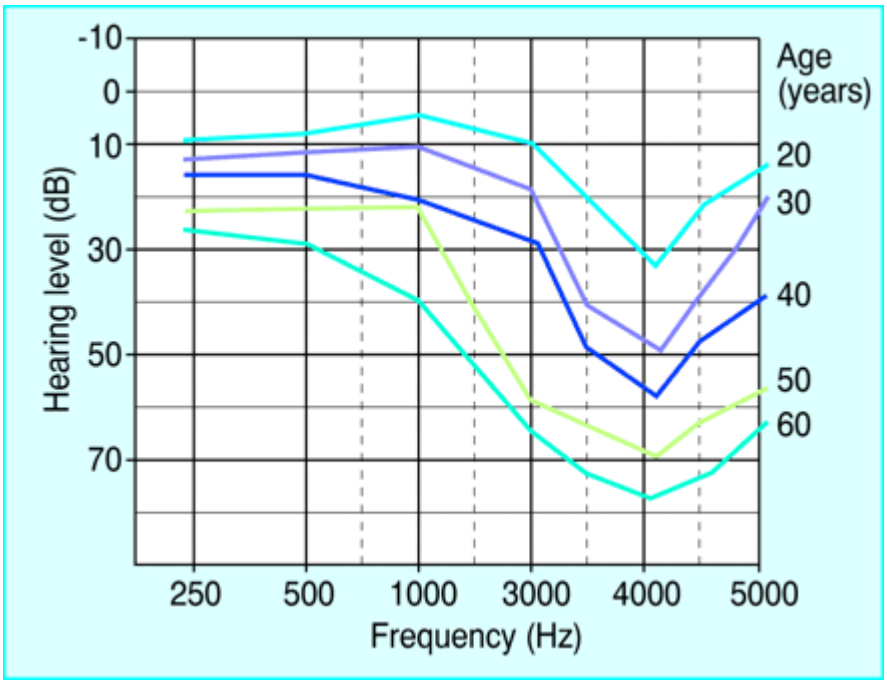


Figure 3.1 NIHL over years (Jones, 1996)

Against above background, hearing impairment in general may comprise the following symptoms as described in Table 3.1 (table adapted from Campo et al., 2009):

Symptoms	Description
Loss of hearing sensitivity	When the level of sound is below the individual's threshold of detection, it is not perceived.
Compressed loudness function	In the frequency region where there is a loss of sensitivity, the rise in loudness as a function of sound level is somewhat distorted.

Symptoms	Description
Loss of temporal resolution	The ability to detect gaps in an ongoing sound is generally reduced when there is substantial loss of hearing sensitivity.
Loss of spatial resolution	The ability to localize sound sources is reduced.
Persistent ongoing tinnitus	This is a relative common symptom among individuals with occupational hearing impairment, and it may impair concentration and interfere with rest and sleep. This, in turn, can result in a severe handicap (psychosocial disadvantages) because of the physical and psychological stress involved.

3.4 Ototoxicity and noise-induced hearing loss

Ototoxicity, which implies damage to the ear by toxins, can be caused by certain therapeutic agents (pharmaceuticals) or exposure to certain chemicals/solvents e.g. styrene, xylenes, and hydrogen cyanide. The effect of exposure to certain organic solvent mixtures has an adverse effect on 1) standard pure-tone thresholds, 2) on high frequency averages as well as 3) on central auditory function (Fuente et al., 2009). Noise exposure has also been reported to interact synergistically with several toxins (Campo et al., 2009; Morata, 2007).

Ototoxicity from especially aminoglycoside antibiotics (such as *Streptomycin* used in the standard re-treatment of TB in mine workers) is well known, and may act cochleotoxic as well as vestibulotoxic. After administration, they can penetrate the cochlea through the stria vascularis (Campo et al., 2009), before reaching the cochlear hair cells in which they can be stored for several months. Cochlear toxicity proceeds stepwise in the damaging of the cochlear structures - affecting the inner row of outer hair cells first, followed by the outer rows of hair cells, then by the inner hair cells (Duggal & Sarkar, 2007; Lyos et al., 1992). The progression of hair cell loss also tends to be from the basal to apical side. The pathology has furthermore been localized to the stria vascularis, spiral ligament, and spiral prominence. Several theories of the mechanism of damage have been proposed, incl. damage to the hair cells and

disruption of the metabolism in the stria vascularis and spiral ligament, which leads to changes in cationic differences of the perilymph and endolymph. These drugs also appear to generate free radicals within the inner ear that trigger apoptotic and necrotic cell death. Generally the risk of ototoxicity has been associated with older age and larger cumulative dose received (Peloquin et al., 2004), as well as prior exposure to aminoglycosides and previous noise exposure (Lyons, 1992).

A sensory-neural (permanent) hearing loss due to ototoxicity ranges from minimal to severe, usually starting in high frequencies (and may progress to the lower frequencies later on), involving speech frequencies (Duggal & Sarkar, 2007). In some cases the hearing loss may be unilateral (Lyos, 1992). Case presentations with tinnitus have also been reported, and once again, noise exposure and some types of aminoglycoside interact synergistically (Campo et al., 2009; Mills and Going, 1982), in order to aggravate the effect of the treatment on the hearing status of the gold miners. It is therefore important to note that ototoxic medication as well as noise has a greater influence on the higher frequencies (Duggal & Sarkar, 2007; Ologe et al., 2006; Sliwinska-Kowalska et al., 2006). Aminoglycoside ototoxicity can progress after discontinuation of the drug (Duggal & Sarkar, 2007) and is known to persist in the inner ear tissues for 6 months or longer after administration (Bardien et al., 2009). Ototoxicity is determined by comparing baseline data, ideally obtained prior to ototoxic drug administration, to the results of subsequent monitoring tests (Duggal & Sarkar, 2007). Aminoglycoside-induced hearing loss may have a major impact on the ability of affected individuals to remain effective and secure their jobs, and should be contemplated as a possible compensable (occupational) disease.

The effects of combined exposure to various (ototoxic) substances e.g. loop diuretics and aminoglycoside, as well as to other (toxic) substances and noise, should also be considered carefully. The aminoglycosides primarily damage auditory hair cells, whereas loop diuretics damage the stria vascularis (Campo et al., 2009). Thus, combined treatment results in two sites of injury within the cochlea. It has to be emphasized that the hair cells are dependent on the stria vascularis for maintaining normal inner ear fluid composition. Moreover, damage to the stria vascularis may result in increased entry of the aminoglycosides into the inner ear fluid. Some studies also

indicate that the administration of ototoxic drugs such as aminoglycosides produces increased susceptibility to noise-induced damage (Campo et al., 2009).

3.5 Hearing loss and vibration

The inner ear is not only vulnerable to noise-induced injury, but also to vibration-induced injury (VHL). A few studies have attempted to answer the question whether the mechanisms underlying noise-induced hearing loss are the same as for vibration-induced hearing loss, as many of the gold miners are also subjected to vibration through the machinery and transportation equipment they use. In a remarkable study done by Bretlau et al. (2004) comparing the protective efficacy of antioxidants and neurotrophins on vibration-induced as well as noise-induced hearing losses, it was found that although these agents have been shown to reduce the effects of NIHL, there were some differences in their protective effect against VHL. It has however been shown in a study by Palmer et al. (2002), as well as mentioned by Morita (2007) and Carlsson et al. (2007), that workers exposed to occupational sources of hand transmitted vibration (HTV) often suffer from hearing loss, as well as vibration induced white finger (VWF)/Raynauds's syndrome (and vice versa) and other features of the hand-arm vibration syndrome. In several surveys of forestry workers, hearing thresholds were worse in men with 'finger blanching' than in their colleagues of similar age considered to have similar exposures to noise and vibration. Such findings have encouraged the hypothesis that sympathetic vasoconstriction observed in VWF affects cochlear blood flow, rendering the worker more vulnerable to (sensory-neural) hearing loss. One concern with such an interpretation may be the degree to which this occupational hazard of vibration will account for another confounding influence on NIHL. Nevertheless, it is important to mention all possible contributing factors, in order to clearly understand the matter at hand.

3.6 Effect of HIV/AIDS on noise-induced hearing loss

There is an increased awareness that HIV may also cause hearing changes, possibly due to its neurotropic nature with direct involvement of the eighth cranial nerve (Dias, Chunderdoojh & Hurkchund, 2006). It is believed that between 21% and 49% of HIV-infected patients develop a sensory-neural hearing loss, which predominantly involves the higher frequencies. Although hearing loss can also be seen in symptom-free HIV positive patients, the degree of SNHL is usually correlated with the severity of the disease (Bektas, Martin, Stagner, Lonsbury-Martin, 2008).

The hearing loss observed in HIV-infected patients has been attributed to a number of sources including neurotrophism of the virus, neurological complications of AIDS-related opportunistic infections of the CNS such as toxoplasmosis, cytomegalovirus, TB, cryptococcosis and neurosyphillis, direct invasion of the cochlea from local opportunistic infections or malignancies incl. Kaposi's sarcoma and lymphoma, otitis media due to bacterial pathogens, and drug use due to the accompanying infections. It can be hypothesized that a relatively significant percentage of the hearing loss observed in HIV+ patients is due to the use of ototoxic drugs such as the antibiotics commonly used to treat opportunistic infections that complicate the disease (e.g., aminoglycoside compounds and amphotericin B). However, in up to 50% of HIV-infected individuals with SNHL, no cause can be identified to explain the associated hearing loss (Bektas et al., 2008).

Abnormal audiological results in a variety of studies with HIV-infected individuals were nevertheless found, presenting with irregular and different types of audiograms, involving different frequencies (mostly the higher frequencies), and presenting all types of hearing losses (sensory-neural, conductive and central). A combination of factors, as mentioned above, should be taken into account when explaining this phenomenon, for example the role of opportunistic infections, tumours, antiretroviral medication, ototoxic medication and ongoing noise exposure (Dias, Chunderdoojh & Hurkchund, 2006; Khoza & Ross, 2002, Chandrasekhar et al., 2000).

Bektas et al. (2008) mentions a few case studies where HIV patients, 35 years and older who received antiretroviral therapy, experienced hearing loss. This relationship was not always found in younger patients who received antiretroviral therapy (Bektas et al, 2008). Simdon, Watters, Barlett and Connick (2001) discussed three specific cases of possible nucleoside analog reverse transcriptase inhibitors (NRTI) associated ototoxicity in HIV-infected patients, all of whom were older than 45 years of age, had a history of noise-induced hearing loss, and reported tinnitus and deterioration in hearing in the setting of antiretroviral therapy. Reductions in mitochondrial DNA content induced by NRTIs, as well as mitochondrial DNA mutations associated with aging and HIV infection, all may contribute to auditory dysfunction in older patients with HIV infection.

The NRTIs continue to be the most common antiretroviral drug group used to treat HIV infected patients. NRTIs act as chain terminators of mitochondrial deoxyribonucleic acid (DNA) and as such cause damage to mitochondrial DNA (Bektas et al., 2008). NRTIs constitute the only antiretroviral drug group that has been proposed in some reports to cause hearing loss. Since all identified inherited mitochondrial anomalies cause hearing loss, it is very likely that NRTI-related ototoxicity, if it exists, is related to mitochondrial damage.

Therefore if 85% to 90% of the TB cohort are also infected with HIV (AngloGold Ashanti Report to Society, 2006), and the synergistic effect of noise and drugs and/or various industrial chemicals (Campo et al., 2009; Morata, 2007) is so well established, it is clear that the cause of hearing loss may be categorized within one or more groups, i.e. 1) Aids-related lesions in cochlea and/or auditory pathways of the CNS, 2) ototoxicity produced by drugs used in the therapy for AIDS-related conditions (which include TB), 3) an already existing (noise-induced) hearing loss aggravated by one of the above.

3.7 Other confounding variables in noise-induced hearing loss

Given the timeframe across which occupational-related hearing damage takes place, and the resulting delay until symptomatic presentation, the role of contributing and/or confounding environmental exposure on NIHL development is difficult to determine. Clinically, diagnosis of pure occupational-related NIHL is being complicated by the potential for concurrent and retrospective confounding and/or contributory non-work related noise-exposure, lifestyle considerations (e.g. smoking and alcohol consumption), exposure to ototoxic drugs, chemical exposure, infection or illness (e.g. HIV/AIDS and TB), prolonged exposure to part- or whole-body acoustic vibration, genetic factors (Kurmis & Apps, 2007) and age (Nanda & Tripathy, 2007).

Humans show differing susceptibility to noise damage even under very carefully controlled exposure conditions (Ologe et al., 2006, Henderson and Hamernik, 1995). Individual susceptibility to NIHL also depends on the interaction between intrinsic and environmental factors (Sliwinska-Kowalska et al., 2006, Konings et al., 2007) and includes as mentioned before impulsiveness of noise, exposure paradigm, distance from the noise source (Dogru et al., 2003), direction of sound waves (Dogru et al.,

2003), noise exposure beyond the workplace, co-exposure to noise and vibration, ototoxic drugs, temperature, smoking etc. Individual factors playing a role to aggravate NIHL are e.g. elevated blood pressure, elevated cholesterol levels, cardiovascular events, diabetes mellitus, too high/too low body mass index (Fransen et al., 2008), being a man, increasing age, and having blue eyes (having less melanin content in the eyes) (Sliwinska-Kowalska et al., 2006). In an interesting study by Toppila, Pyykkö and Starck (2001) it was found that as the number of confounders increased, the noise exposure was overruled by these factors in the development of hearing loss.

Although environmental and intrinsic factors have been studied thoroughly, knowledge of the genetic factors that are responsible for NIHL is limited. Evidence of heritability for NIHL in humans are rare, but has been investigated by some. Carlsson et al. (2005) for example found no significant difference between susceptible and resistant groups being exposed to noise, concluding that genetic variation of antioxidant enzymes played no major role in the susceptibility to NIHL. However, in a rather large study conducted a few year later using the audiometric data of more than 5500 noise-exposed labourers – significant interaction between noise exposure levels and certain genotypes (Konings et al., 2007) was indicated, confirming the complexity of NIHL. Morita et al. (2007), Davis et al. (2001), etc. also confirmed that the susceptibility to NIHL is associated with the *Ahl* gene (the gene that is responsible for age-related hearing loss). NIHL has furthermore been found to be significantly more frequent in workers with blood group O compared to those with other blood groups, signifying susceptibility to certain conditions (Dogru et al., 2003). It is therefore important to mention in conclusion, that not all miners will demonstrate the same susceptibility to develop NIHL, even if all other contributing factors remain exactly the same.

Age for example is another contributing factor when examining NIHL, since the same genes responsible for age-related hearing loss (presbyacusis) have also been indicated to be responsible for NIHL (Fransen et al., 2008; Morita et al., 2007; Sliwinska-Kowalska et al., 2006; Davis et al., 2001). It was therefore critical to adjust for this contributing factor. It is further assumed that the effects of presbyacusis add linearly to the effects of occupational noise exposure (Morita, 2007; Mills & Going, 1982), presumably depending on the specific type of prebyacusis that is involved. Neural presbyacusis, where the major pathology is indicated by losses of spiral

ganglion cells, cannot exhibit the same effects as for example a typical NIHL. Dobie (2008) argues that the contribution of excessive noise exposure (occupational noise) is overestimated as the contributions of aging and noise are difficult to separate. He argues that NIHL becomes apparent in middle age, when occupational noise exposure ceases, but age-related threshold shifts are added to prior noise-induced shifts, resulting in a significant impairment (Dobie, 2008). In addition, more than 20% of NIHL patients struggles with tinnitus (Kurmis & Apps, 2007), aggravating the symptoms even more.

Cigarette smoking has been strongly associated with an increasing frequency of hearing loss, acting synergistically with occupational excessive noise exposure to accelerate both the severity and rate-of-acquisition of impairment (Kurmis & Apps, 2007, Fransen et al., 2008). Smoking in combination with elevated diastolic blood pressure and the presence of Raynaud's disease (white finger disease) seems to aggravate NIHL, although smoking alone is already increasing the risk substantially (Carlsson et al., 2007). One of the explanations may be that the smoke being inhaled contains free radicals which enter circulation and these modulate antioxidant enzymes activities of the blood. Smoking has also been implicated as a direct ototoxin (nicotine effect) and as an inducer of ischaemia in the cochlea (Carlsson et al., 2007). The combined effect of noise exposure and smoking on hearing is therefore not interactive but additive (Uchida et al., 2005).

3.8 Conclusion

It is obvious from the discussion above that the investigation of the hearing status of gold miners is a complicated matter. There are many contributing as well as confounding factors that have to be considered and adjusted for in comparing the hearing status of gold miners who are TB negative with the hearing status of gold miners who are TB positive and are receiving TB treatment. It is however comprehensible that having a hearing loss will substantially affect an individual's capacity to interact, work, and function effectively in an increasingly communication-intense society, on top of other difficult-to-quantify influences on quality-of-life. It is therefore our duty and role as audiologist to investigate, to clarify and ultimately to contribute to the hearing wellness of these mine workers.

Chapter 4

Methodology

4.1 Introduction

'The goal of science is knowledge. The goal of research is to draw inferences about a study sample and ultimately about the real world. The challenge is to minimize error. Adherence to scientific principles and accepted scientific practices minimizes error and facilitates accurate inferences. Research integrity and responsible conduct of research is critical to the research process, maintain trust in science, and preventing harm to those that research is meant to benefit.' (Jones & Mock, 2007:60)

The problem underlying this research project has already been stated in Chapter 1. The processes that were involved to draw inferences about the study population will be discussed in this chapter.

4.2 Research aims

The primary aim of the study was achieved by describing and comparing the hearing profiles of three groups; i.e. a control group, a single TB treatment group and a multiple TB treatment group. The effect of certain variables on the hearing of the control and two experimental groups were also described in order to reach the primary aim. The primary and sub-aims are listed below.

Primary Aim

To compare the hearing profile of gold miners with and without tuberculosis.

Sub-Aims

- To compare and describe hearing thresholds for two experimental groups (*TB positive - single treatment and TB positive – multiple treatment*) and a control group (*TB negative*).
- To compare and describe hearing thresholds for two experimental groups (*TB positive - single treatment and TB positive – multiple treatment*) and a control group (*TB negative*), considering the co-variable of noise exposure.

4.3 Research design

This study followed a quasi-experimental design that was quantitative in nature. Quasi-experiments are those that satisfy all of the requirements of a true experiment with the exception of random assignment (Maxwell & Satake, 2006), and in this study the subjects were classified on the basis of a specific condition i.e. TB and TB treatment or re-treatment. The hypothesis was tested by using a retrospective cohort study. A retrospective cohort design uses data that were collected in the past to determine the relationship between a set of potential risk factors and an outcome that is measured (DeForge, 2010). The data for this study were collected over a number of years by the occupational health department at the West Wits operation of the AngloGold Ashanti Gold Mine in the Witwatersrand. By assembling the cohort of TB negative and TB positive subjects into comparison groups (control, single TB treatment, multiple TB treatment), it was possible to compare and describe their hearing status and the effect of variables such as age, type of noise exposure and length of noise exposure on the subjects' hearing.

Convenience sampling was used to select the subjects for the two experimental groups as all subjects at the West Wits operation infected with TB, who received TB treatment or re-treatment, and gave informed consent, between the year 2001 and 2009 were selected (McMillan & Schumacher, 2006). Matched sampling was used to select the subjects for the control group (subjects not infected with TB) in order to detect a statistical significance between the groups that can be attributed to the influence of the independent variable (TB and/or TB treatment) (Maxwell & Satake, 2006). Variables such as age at test, type of noise exposure and length of noise exposure between the audiograms, were matched within these three groups.

Deductive reasoning, beginning with the aim and sub-aims, was used to draw logical conclusions. Objectivity in data analyses was retained by conducting certain statistical procedures and using objective criteria to evaluate the outcomes of the analyses. In this study previously obtained hearing thresholds were used to describe and compare the hearing status of gold miners with and without TB.

4.4 Ethical considerations

Jones and Mock (2007) mentioned that if a universal code for research conduct could be written, the following principles should be included for research involving humans, i.e. respect for persons, beneficence, and justice. As long as human participants are used in research, their treatment during, and benefit from the research process should remain an important consideration (Jones & Mock, 2007). A research collaboration agreement was reached between the University of Pretoria and AngloGold Ashanti to investigate the effect of TB and TB treatment on the hearing of the gold miners. The study protocol was reviewed and approved by ethics committees at the University of Pretoria and AngloGold Ashanti. The ethical aspects described below were therefore taken into account in the planning of this research project.

Respect for the privacy of research participants

In order to ensure the privacy and confidentiality of all participants (Maxwell & Satake, 2006), no individuals were named in the research report. This was achieved by assigning a code to each subject. No names were used during this study and all personal information remained confidential. Data was processed, analysed and discussed according to these codes to make the best possible effort to maintain confidentiality. This was clearly explained in the informed consent letter provided to all possible participants.

Informed consent

According to Maxwell and Satake (2006), informed consent is a fundamental ethical principle which consist of the following components – the subjects should be informed in writing about the general goals, the specific procedures and significance of the study, the risks or harm (if any), the benefits or reimbursement (if any), the plans for disseminating findings, and the measures such as data-coding procedures used to safeguard confidentiality of participants. It is also important to make it clear that

participation is voluntary and can be terminated at any time without negative consequences. Subsequently, written informed consent was obtained for the present study by having each participant (in the two experimental groups) signing the appropriate form (attached as Appendix 3), after they have read through a letter explaining the goals and procedures of the study. Where necessary a translator was used to explain the content of the letter to possible participants who were not English literate.

Beneficence and non-malfeasance

As the study was a record review and already known outcomes were used, no tests were involved to cause any physical, social or emotional harm to the participants. Due to the nature of this study, access to the medical files of the participants was needed, and this was therefore clearly explained in the letter of consent, as well as how participants' confidentiality would be safeguarded. The letter also explained that the information gathered would provide useful data to the field of audiology through publication of the results upon conclusion of the study. The letter also informed subjects that all data obtained in the study would be stored for a minimum of fifteen years for record-keeping purposes. There were no incentives or rewards (financial or other) offered for participation in the study.

4.5 Research Subjects

In this section the research population, sampling method, subject selection criteria and a description of the research subjects are discussed.

4.5.1 Research population

The study was performed on the records of 2698 subjects from the AngloGold Ashanti goldmine in the Witwatersrand area, South Africa. The audiological and medical data of the subjects (between the years 2001 and 2009) who were working in the Mponeng, Tautona or Savuka mines at AngloGold Ashanti were used and analysed during this study.

4.5.2 Sampling method

The selection process that was followed can be described as a non-random selection method. Two sampling techniques were used. Convenience sampling (McMillan &

Schumacher, 2006) was used to select the two experimental groups as all subjects infected with TB, who received TB treatment or re-treatment between the year 2001 and 2009 were selected (1287 subjects). Match sampling is a control procedure specifically designed to control the degree to which subjects in different groups are allowed to differ by pairing them according to particular characteristics (Maxwell & Satake, 2006). This technique and was used to select the subjects for the control group (1418 subjects). This technique is essential for detecting a statistical significance between the groups that can specifically be attributed to the influence of e.g. a treatment or multiple treatment (Maxwell & Satake, 2006). Variables such as age at test, type of noise exposure and length of noise exposure between audiograms, were matched within these three groups.

4.5.3 Criteria for subject selection

Subjects were selected according to set criteria as discussed below in order to establish an internal validity. This is the extent to which it will be possible to justify the causal inferences based on observed changes in the dependant variable (hearing status) in response to variations in the independent variable (not being infected with TB at all, infected with TB and received treatment, or infected with TB and received re-treatment) (Guild et al., 2001). Selection criteria are discussed under the following headings i.e. TB status and TB treatment, age and type of noise exposure.

TB status and TB treatment

South African miners are one of the few communities in the world in which routine radiography is practised (Guild et al., 2001), in order to actively detect TB cases. This forms part of their annual medical surveillance routine, and once TB is detected and confirmed by sputum smears, they are started on treatment. TB positive subjects who gave consent to use their medical records in this study, were divided to form the two experimental groups, i.e. TB positive – single treatment, and TB positive – multiple treatment. As this study forms part of a bigger research study on the audiological records of workers at the same mine, a control group (TB negative) was selected from them and matched against the two experimental groups for age and noise exposure.

- *Control group*

  These subjects have not been positively diagnosed with TB, as no specific symptoms linked to TB e.g. persistent coughing, night sweats and weight loss had

been reported. Variables such as age at test and type of noise exposure were matched against the two experimental groups.

- *Single TB treatment group*

  Diagnosed with Pulmonary TB (diagnosed by chest radiography, positive sputum culture or positive AFB sputum) and received TB medication according to the treatment protocol for pulmonary TB. Treatment regimens for the mining industry are according to the Department of Health as summarised in table 4.1 (Guild et al., 2001).

- *Multiple TB treatment group*

  Diagnosed with Pulmonary TB more than once (diagnosed by chest radiography, positive sputum culture or positive AFB sputum) and received TB medication according to the re-treatment protocol for pulmonary TB. Treatment regimens for the mining industry are according to the Department of Health as summarised in table 4.1 (Guild et al., 2001).

Table 4.1 Summary of the National TB control programme treatment guidelines

Type of Treatment	Medication
New TB	2RHZE / 4RH *
Re-treatment TB	2RHZES / 1RHZE / 5RHE *
Treatment frequency	5 days/week (initial) 5 or 3 days/week (continuation)
DOTS (intensive phase)	Yes
DOTS (continuation phase)	Yes

***H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin**

Age

To keep the contributing effect of age of hearing loss omissible, the subjects were chosen over a wider age range (20 – 65 years of age) and matched within each group (control, TB single treatment and TB multiple treatment). TB incidence in gold-miners is strongly age-dependant, with a progressive increase in TB disease rates with rising age (Corbett et al., 2003; Guild et al., 2001). This is likely to be at least partly due to

the effect of silica exposure, since age and length of service are in close association with one another and with cumulative silica exposure (Guild et al., 2001). Age also plays a role in the deterioration of the hearing status of individuals (Fransen et al., 2008; Morita et al., 2007; Sliwinska-Kowalska et al., 2006; Davis et al., 2001;). Aging produces alterations in many areas of the auditory system, and can be expected in men by their early 60s (Dobie, 2008; Martin & Clark, 2006).

Type of noise exposure

Subjects were selected and matched in their different groups (control, TB single treatment and TB multiple treatment) according to their current exposure level to workplace noise. Exposure levels were described in terms of a specific occupation, as specific occupations are matched with different exposure levels e.g. pneumatic rock drill equals ~108 dB (A) (Phillips, Heyns & Nelson, 2007). Data received from the occupational health division at the mine, indicated noise exposure levels for drillers ranging between 110 dBA and 133 dBA. A noise exposure level is measured in compliance with Instruction 171 and is done through the use of a “dose badge”, a personal dosimeter worn by the mine worker for the duration of his shift.). Company Policy also states that every employer exposed to noise levels above 85 dB (A) must wear hearing protection equipment which are provided and monitored by the mine. The different exposure levels/occupations were then categorized in 4 groups namely: 1) above surface noise exposure, 2) below surface noise exposure, 3) no noise exposure and 4) uncertain levels of noise exposure e.g. students and trainees. These subgroups (1 & 2 Noise) were compared to (3 & 4 – No) Noise) (see Table 4.4). In order to narrow the analysis down and to use a group with homogenous noise exposure (termed homogenous noise exposure groups), two alternative subgroups were also analysed and compared within the three groups i.e. drillers (high levels of noise exposure) vs. admin workers (at present no noise exposure) (see Table 4.5).

4.5.4 Description of research subjects

Data were selected from audiometric and medical records of the subjects (mostly black males), made available by the mine’s occupational health department. Data included the following information on the subjects: a company number, audiogram test dates, type of audiogram, thresholds for the air conduction frequencies at 0.5, 1, 2, 3, 4, 6, 8 KHz in both the left and right ear, job description, percentage binaural impairment

(PBI), percentage monaural impairment left (PMIL), percentage monaural impairment right (PMIR), percentage loss of hearing (PLH), gender, race, age tested, working years, TB status, and type of TB treatment.

The following tables serve as descriptions of the research subjects, how they were divided into different groups and categories and the number of subjects in each group.

Table 4.2 Number of subjects in each group and mean age

Group	N	Mean 'age at test' (SD 'age at test')
Control	1411	38.55 (10.27)
Single TB	911	43.30 (7.00)
Multiple TB	376	44.74 (6.61)
Total	2698	41.02 (9.20)

Table 4.3 Age categories of subjects

Age category	Control	Single TB	Multiple TB
< 30 yrs			
n	346	34	3
Frequency %	24.52	3.73	0.80
31- 40 yrs			
n	478	287	98
Frequency %	33.88	31.50	26.06
41- 50 yrs			
n	384	447	198
Frequency %	27.21	49.07	52.66
51- 60 yrs			
n	189	142	75
Frequency %	13.39	15.59	19.95
> 60 yrs			
n	14	1	2
Frequency %	0.99	0.11	0.53
Total	**1411**	**911**	**376**
	100.00	**100.00**	**100.00**

Figure 4.1 is a bar chart representing the number of subjects in each age category as a frequency. There were eight subjects according to the original data received from the mine (14, 15, 17, 66, 68, 72, 75, 79 years of age), who could not be fitted in these age categories, and therefore their data was not used in this study.

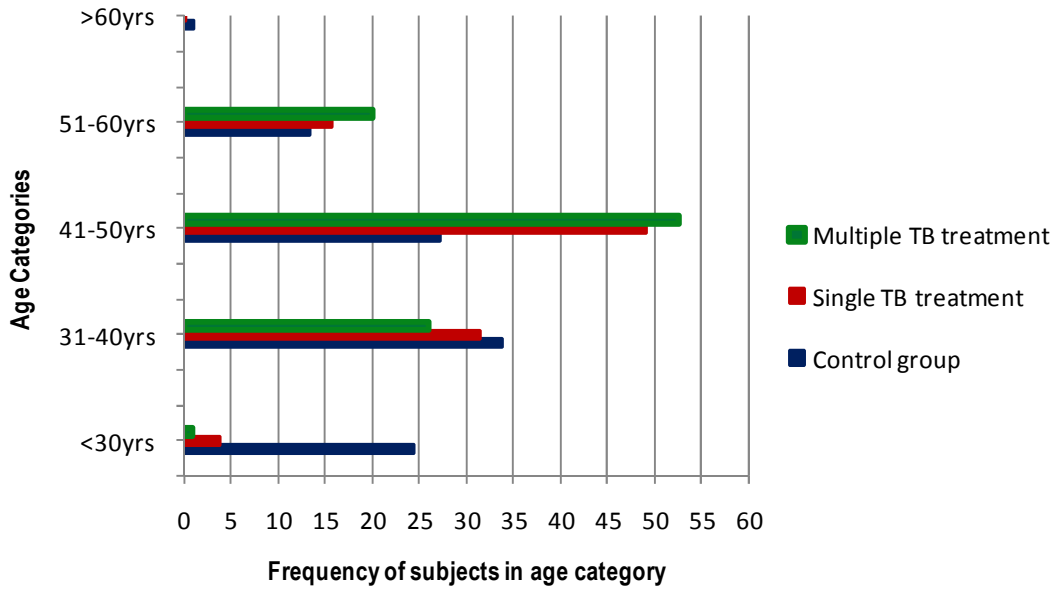


Figure 4.1 Age categories of subjects

The alternative noise exposure levels/occupations (see paragraph 4.5.3) was also one of the variables that was measured in order to describe their relation to the hearing status of the gold miners. Table 4.4 and 4.5 provide groups and the number of subjects in each group.

Table 4.4 Noise vs. no noise exposure groups

Group	Noise	No noise
Control	1026	392
Single TB	704	210
Multiple TB	278	98
Total	2008	700

Table 4.5 Driller vs. admin staff exposure groups

Group	Driller	Admin
Control	116	50
Single TB	144	39
Multiple TB	70	11
Total	330	100

4.6 Data collection personnel, equipment and requirements

In terms of the Mine Health and Safety Act (MHSA, Act 29 of 1996) Instruction 171 and South Africa National Standards (SANS 10083), it is the responsibility of the employer to establish and maintain a system of medical surveillance for all employees in any working place where the equivalent, continuous A-weighted sound pressure level, normalised to a 8 hour working day or a 40 hour working week exceeds 85 dB (A) (Begley, 2006). With the change in compensation legislation (Instruction 171 supplement on 16 November 2001), it became compulsory by law that a baseline audiogram had to be conducted for all such individuals within two years after this legislation was published and within thirty days for new employees who had not worked previously. The mine concerned in this study complied with these regulations and this is the reason why audiograms from the year 2001 onwards were considered. These baseline audiograms then serve as the individual's baseline for the rest of their working careers. From this baseline each individual's percentage loss of hearing (PLH) can be calculated.

In the section that follows the requirements for personnel, equipment and procedural requirements in the collection of data (used in this study) at the mine will be discussed.

4.6.1 Personnel requirements for medical surveillances and audiometric testing

Medical surveillance is the direct responsibility of occupational health and occupational medical practitioners (Guild et al., 2001), who are registered with the South African Nursing Council and Health Professions Council of South Africa. The following table describes the requirements for personnel conducting the various audiometric evaluations. The personnel responsible for conducting the audiograms used in this study were subjected to these requirements.

Table 4.6 Requirements for personnel conducting audiometric tests (Guild et al., 2001)

Screening audiometry (Baseline, periodic screening, monitoring and exit)	Diagnostic audiometry (Specialist evaluation)
Audiometrist registered with the Health Professions Council of South Africa as an audiometrist or hearing aid acoustician, or holding a certificate in audiometry issued by an institution recognised and approved by the DME; Occupational medical practitioner registered with the Health Professions Council of South Africa; Audiologist, i.e. a graduate in speech therapy and/or Audiology registered with the Health Professions Council of South Africa; Medical Practitioner specialising in otorhinolaryngology and registered with the Health Professions Council of South Africa	Audiologist, i.e. a graduate in speech therapy and/or Audiology registered with the Health Professions Council of South Africa; Medical Practitioner specialising in otorhinolaryngology (ENT) and registered with the Health Professions Council of South Africa

4.6.2 Apparatus requirements for determining hearing thresholds

Audiometry is the process where an individual's hearing threshold levels are determined over a specified range of audio frequencies. As a minimum requirement, these should include 500; 1 000; 2 000; 3 000; 4 000, 6000 Hz and 8 000 Hz, but may also include 125 and 250 Hz (Guild et al., 2001). Table 4.7 includes the frequencies to be included for screening and diagnostic audiometry according to Guild et al. (2001).

Table 4.7 Audiometer requirements (Guild et al., 2001)

Type of audiometer	Test frequencies
Screening	0.5; 1; 2; 3; 4; 6; and 8 kHz
Diagnostic	0.25; 0.5; 1; 2; 3; 4; 6; and 8 kHz

The audiometer used in the screening set-up at the occupational health facility of West Wits is the Tremetrics RA 600 Type 4 audiometer (serial no 971499) with TDH 39 headphones. Up to ten workers can be tested simultaneously using the audiometer's automatic testing procedure and specifically designed software (Everest). This allows for automatic and simultaneous testing of more than one client at a time, as well as saving the information to a database. Diagnostic testing is conducted in another facility by using the GSI 61 audiometer (serial no AA041138).

Acoustic enclosures or soundproof rooms for audiometric testing comply with the requirements for background noise and environmental conditions specified in SANS 10182:2006. Table 4.8 provides the background noise limits for air- and bone-conduction.

Table 4.8 Background noise limits for audiometry (Guild et al., 2001)

Type of audiometry	Maximum unweighted sound pressure level (dB) at give centre frequency (Hz): SANS 10182: 2006						
	125	**250**	**500**	**1000**	**2000**	**4000**	**8000**
Screening	52,0	38,5	22,0	24,0	31,0	37,0	35,5
Diagnostic							
Air-conduction	29,0	21,0	20,5	24,0	31,0	37,0	35,5
Bone-conduction	22,5	14,5	10,5	9,5	9,0	5,0	12,5

The following audiometer calibration and verification requirements were met:

- Screening and diagnostic audiometers had a valid calibration certificates at the time of commissioning of this study (see Appendix IV – calibration certificate).
- Calibration service providers had the necessary training and equipment, and demonstrate traceability to the National Acoustic Standard. Calibration is annually done by ACTS, Audiometric Calibration and Training Services.
- Personnel conducting audiometry validated the accuracy and calibration continuity of audiometers on a weekly basis by means of subjective or biological calibration checks. These records are retained for record keeping.
- Each day, prior to testing, the personnel conducting audiometry confirmed the correct functioning of the audiometer, inspected all cables and connections, confirmed proper function of patient's response button, and performed a listening check to ensure the absence of unwanted sounds.

4.6.3 Procedural requirements for collection of hearing threshold data

The following are included to demonstrate the different protocols that need to be followed by the occupation health and occupational medical practitioners in order to collect the data on hearing thresholds. These requirements were also followed during the collection of data for this study:

Routine screening audiometry makes use of basic air-conduction procedures to record baseline, periodic screening, monitoring and exit audiograms (Guild et al., 2001). Diagnostic testing is only done when a medical opinion recommends a specialist evaluation for purpose of investigating ear pathology, inconsistent baseline results or a potential compensation claim for NIHL. These results were also included in the database that was used to collect data. The following table gives the application, purpose and procedural requirements for audiometric testing.

Table 4.9 Application, purpose and procedural requirements for audiometric testing (Guild et al., 2001)

Type of audiometry	Application	Purpose	Procedural requirements
Baseline	Before allocation to work in a noise zone (TWA ≥ 85 dB) or within 30 days of commencing such work.	To provide a reference for evaluating any further changes in hearing status.	Before testing, a 16-h period with no exposure to noise > 85 dB. Use better of two audiograms that are within 10 dB at 0.5; 1; 2; 3 and 4 kHz. Incorporate results into medical surveillance records.
Periodic Screening	Annually for noise-exposed individuals (TWA ≥ 85 dB)	To quantify any permanent hearing loss that results from exposure to noise.	Before testing, a 16-h period with no exposure to noise > 85 dB. Incorporate results into medical surveillance records.
Monitoring	6-monthly for high-risk exposure (TWA ≥ 105 dB), subject to employer's code of practice.	To identify temporary threshold shifts and enable the prevention of permanent hearing loss.	Conduct testing as soon as possible after exposure to noise, i.e. at the end of the working shift.
Exit	On conclusion of employment in a noise zone (TWA ≥ 85 dB) or on employee's termination.	To provide records of hearing levels on conclusion of employment in the zone.	Before testing, a 16-h period with no exposure to noise > 85 dB. Incorporate results into medical surveillance records.
Diagnostic	When a medical opinion recommends a specialist evaluation for purpose of investigation ear pathology, inconsistent baseline results or a potential compensation claim for NIHL.	To enable a specialist evaluation of hearing status as required; To support a possible compensation claim, where indicated.	Before testing, a 16-h period with no exposure to noise >85 dB: Use of hearing protection devices to limit noise emission during this period is not acceptable; Mandatory test frequencies are 0.5; 1; 2; 3; 4; 6; or 8 kHz.

4.7 Data collection procedures

The medical surveillance records of the subjects at the three different mines (Tautona, Savuka and Mponeng) at AngloGold Ashanti were used to select and match the subjects within the three different groups (control, single TB treatment and multiple TB treatment). As mentioned before, the medical surveillance is the direct responsibility of occupational health and occupational medical practitioners. The occupational medical/health department accessed the mine's electronic database and exported all required information to Excel spreadsheets – this included: a company number, test dates, type of audiogram, thresholds for the air conduction frequencies at 0.5, 1, 2, 3, 4, 6, 8 KHz in both the left and right ear, job description, percentage binaural impairment (PBI), percentage monaural impairment left (PMIL), percentage monaural impairment right (PMIR), percentage loss of hearing (PLH), gender, race, age tested, working years, TB status and type of TB treatment. The audiometric records consisted of pure-tone air conduction audiograms for right and left ear respectively. Some audiograms (approximately 30 per cent) were obtained from a diagnostic evaluation, other from a baseline, periodic screening, monitoring or exit assessments.

Once informed consent (Appendix 3) was obtained from all potential subjects to access their medical records on the mine's electronic database (see section 4.4), subjects' medical history was followed to identify the single TB treatment and multiple TB treatment groups. These data were exported to Excel spreadsheets by the occupational medical department of the involved mines. The control group was selected from the same dataset mentioned, but only subjects who are TB negative were selected. This was done in order to control for age, exposure to different noise levels and years of exposure in the two experimental groups.

4.8 Data processing and analysis

According to Maxwell and Satake (2006) statistical analysis allow the researcher to find patterns and meaning in numerical data. Once the data was received from the mine and converted to a single Microsoft Excel data sheet, data-cleaning was conducted. Audiogram data was for example disregarded in all rows where no response (NR) values were recorded in more than four frequencies in one ear. All rows where an audiogram error code was recorded in threshold value cells between 500-4000Hz were also deleted. The reason for this is that the values at these frequencies were important

for the calculations of hearing impairment e.g. PLH. No hearing impairment calculations (Instruction 171) were possible without values at these frequencies. Where NR values were recorded for one or two frequencies (mostly high frequencies), and where results correlated with previous audiogram results (within 10dB's), maximum values (100dB) were given. Audiogram data were furthermore disregarded in all rows where one ear had normal threshold values and the other NR values. These results most likely indicated a unilateral functional hearing loss (malingering) as inter-aural attenuation makes this scenario impossible. Where no date of birth was recorded, the subject could not be assigned to an age group, and the data were not useful.

After data-cleaning the researcher consulted with a statistician (Prof Piet Becker from the Medical Research Council) who assisted in conducting the statistical analysis on the data set by means of a statistical analysis system (StataCoro. 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP). Both descriptive and inferential statistics were employed. Descriptive statistics served to organize and summarize this particular set of observations in a manner convenient for numerically evaluating the attributes of the available data (Maxwell & Satake, 2006). Tables and line graphs were primarily used to provide a visual and readily interpretable summary of the data. Measures of central tendency (means), measures of variability (standard deviations) and correlation techniques were used. Inferential statistics allowed the researcher to generalize findings from the study sample to a similar group (population) from which the sample were drawn (Maxwell & Satake, 2006). Analysis of covariance (ANCOVA), pair wise comparisons[10] and 95% confidence intervals[11] were used to establish whether statistically significant relationships existed between the variables. Note that the 95% CI were small (typical range 2-4dB) compared to the standard deviations (typical values 11-20) because of the following definition of the CI applied in this study:

$$x - 1.96\,\frac{sd}{\sqrt{n}};\; x + 1.96\,\frac{sd}{\sqrt{n}}$$

[10] Pair wise comparisons are methods for analyzing multiple population means in pairs to determine whether they are significantly different from one another (Maxwell and Satake, 2006).

[11] A confidence interval is a range in which an unknown population parameter is likely to be included (Qiaoyan, Zhoa & Yang, 2010). The 95% confidence intervals is an indication that 95 % of the time the confidence intervals will contain this population parameter, concluding the results are significant as the mean thresholds are included in the confidence intervals.

Narrow CI in the presence of large SDs is ascribed to the small Standard Error as a result of the large sample size. During pair wise comparisons an F value was reported. Given a null hypothesis and a significance level ($p < 0,05$ = significant and $p < 0,01$ = highly significant), the corresponding F test rejects the null hypotheses if the value of the F statistic is large.

Analysis of hearing threshold parameters was done using the ANCOVA with covariates such as age, exposure time (between first and most recent audiogram), and first audiogram thresholds values. Age was adjusted for during the analysis of the hearing thresholds, due to the fact that age is an important contributor to hearing loss (Nanda & Tripathy, 2007; Morata, 2007; Sliwinska-Kowalska et al., 2006). The average age of the subjects in each group, as well as the average threshold value at the specific frequency involved, and adjusted the threshold according to the slope of the threshold/age was calculated. The same was done to adjust for exposure time and first audiogram threshold values. In other words, statistically all subjects in the same group were set to an equal average age, by adjusting the frequency threshold values, before doing pair wise comparisons.

The data were organized in various hearing threshold and noise exposure parameters in order to explore the effect of TB and TB treatment on the miners' hearing status. Table 4.10 includes the different hearing threshold parameters that were considered and analysed as well as the reason for the specific analysis.

Table 4.10 Hearing threshold parameters

Hearing threshold parameters	Reason for observation and analysis
1) All frequencies (0.5, 1, 2, 3, 4, 6, 8 kHz): **1.1** First audiogram recorded (left & right ears) **1.2** Last audiogram recorded (left & right ears)	These analyses were done in order to gain an overview of all the hearing frequencies of the subjects in the three groups (control, single TB treatment and multiple TB treatment), as well as the decline of the hearing thresholds from the first audiogram recorded to the last audiogram recorded. It was also necessary to compare what the effect of various variables such as time exposure, noise exposure and age was on the hearing thresholds (audiograms) of the subjects. Age was adjusted for during the observation and description of the hearing thresholds, due to the fact that age is an important contributor to hearing loss (Nanda & Tripathy, 2007; Morata, 2007; Sliwinska-Kowalska et al., 2006). In the same way exposure time between the two audiograms as well as hearing thresholds at the first audiogram recorded was adjusted for.
2) Highest frequencies: **3.1** Left ears - (6 & 8 kHz) – last audiogram **3.2** Right ears - (6 & 8 kHz) – last audiogram	6 and 8 kHz were analysed separately, due to the fact that the effect of ototoxic medication spreads from the apical (high frequencies) to the basal end (low frequencies) of the cochlea (Duggal & Sarkar, 2007).
4) Percentage loss of hearing (PLH): **4.1** PLH (left ears) – last audiogram **4.2** PLH (right ears) – last audiogram	PLH was compared and analysed in order to determine if differences occur in the observed hearing status of subjects when calculating and describing it according to different classification/weighing systems, such as PLH or using more high frequencies in the calculation. Currently a shift in 10% or more in PLH, as compared with the baseline audiogram, has been accepted as the level at which a compensation claim may exist (Guild et al.,2001).

Table 4.11 includes the different hearing threshold parameters that were considered and analysed while the co-variable of noise exposure was considered using two alternative classification schemes.

Table 4.11 Hearing threshold parameters with noise exposure as co-variable

Hearing threshold parameters with the co-variable of noise exposure	Reason for observation and analysis
1) Noise vs. No Noise **1.1 Noise:** Low frequency average (0.5, 1, 2 kHz) (left & right ears) – last audiogram High frequency average (3, 4, 6 kHz) (left & right ears) – last audiogram **1.2 No Noise:** Low frequency average (0.5, 1, 2 kHz) (left & right ears) – last audiogram High frequency average (3, 4, 6 kHz) (left & right ears) – last audiogram **1.3 Noise vs. No Noise:** Differences in hearing threshold values (0.5 to 8 kHz, left & right ears) between the first and last audiogram recorded	These analyses were done in order to compare the effect of different exposure levels on the subjects in the three groups' (control, single TB treatment and multiple TB treatment) hearing thresholds. Once again age was adjusted for during the analysis, due to the fact that age is an important contributor to hearing loss (Nanda & Tripathy, 2007; Morata, 2007; Sliwinska-Kowalska et al., 2006). Hearing thresholds for the first and last audiogram recorded were compared, in order to observe the possible effect of age, time of noise exposure (between the first and last audiogram recorded) and/or TB/TB treatment on hearing thresholds. During the observation and description of the hearing thresholds, age, hearing threshold at the first audiogram as well as time of exposure between the first and last audiogram recorded was adjusted for.
2) Drillers vs. Admin Staff **2.1 Drillers:** Low frequency average (0.5, 1, 2 kHz) (left & right ears) – last audiogram High frequency average (3, 4, 6 kHz) (left & right ears) – last audiogram **2.2 Admin Staff:** Low frequency average (0.5, 1, 2 kHz) (left & right ears) – last audiogram High frequency average (3, 4, 6 kHz) (left & right ears) – last audiogram	In order to narrow the comparison down, the hearing thresholds of these two HEG groups (drillers - high levels of noise exposure and admin workers - almost no occupational noise exposure), were compared and described, while adjusting for age.

4.9 Validity and Reliability

Validity refers to the degree that the scientific explanations of certain phenomena represent reality, and to the truthfulness of findings and conclusions (McMillan & Schumacher, 2006). In the following table the researcher indicates how the different types of validity were met in this study.

Table 4.12 Validity in this study

Type of validity	Description
Statistical conclusion validity - determining whether a relationship exists between two or more variables (McMillan & Schumacher, 2006).	The services of a statistician (Prof P Becker) from the medical research council (MRC) were used to ensure that the data were handled in a knowledgeable way, while giving the researcher guidance in the interpretation of the findings.
Internal validity - refers to the degree that causal inferences can be justified based on observed changes in the dependant variable (hearing loss) in response to systematic variation in the independent variable (TB and/or TB medication) (Maxwell & Satake, 2006).	By matching subjects on extraneous variables and adjusting for variables such as age-tested, time exposure between audiograms used and hearing thresholds at first audiogram, the possibility of confounding results were kept to a minimum. Threats to the internal validity of this study might include the following: although all subjects were selected from one mine and variables matched within the groups, there might be within-subject variability e.g. subject variation due to historical influences or other medical treatments (Maxwell & Satake, 2006; McMillan & Schumacher, 2006) that have not been counteracted for. Attrition (mortality) may also be a threat to internal validity (McMillan & Schumacher, 2006), as some of the subjects might have passed away during the time period of this study.
Construct Validity - the extent to which the results support the theory behind the research. This is closely related to generalizability of the results to the greater population (McMillan & Schumacher, 2006).	The construct validity of this study is of high quality as a retrospective study was completed in an environment where both the dependant as well as independent variables are two of the highest ranked threats and role players in the mining industry.
External Validity - the degree to which the findings of this research project can be generalize to other populations (McMillan & Schumacher, 2006), settings, treatment variables or measurement variables (Maxwell & Satake, 2006).	Due to the fact that the most important variables like age, noise exposure levels and years of exposure were matched and controlled, it was possible to establish and describe a correlation between the miners' hearing status and TB and/or TB treatment. The population's external validity (McMillan & Schumacher, 2006) is however limited to the gold mining industry as other characteristics such as silicosis, migrant living conditions etc. are specific to this population.

Reliability refers to the consistency of measurement, in other words it refers to the extent to which the results are similar over different structures of the same instrument

or instances of data collection (McMillan & Schumacher, 2006). The amount of error variance in test scores, or the reliability, is determined empirically through a range of procedures, and is usually reported as a reliability coefficient. (McMillan & Schumacher, 2006). The reliability of the findings of this research project is related to the accuracy with which data collection, according to the specified standards, were executed as all of the standards remained consistent. Confidence intervals were also reported.

4.10 Conclusion

This chapter was introduced by a motivation for selecting the research methodology to be described in this chapter. The main-aim and sub-aims of the study were formulated, followed by the research design used to achieve the aims of this study. Ethical considerations were then discussed. Following this, the sample that took part in this study was considered. Audiometric data, personnel, equipment and procedural requirements used for collection of the data at the mine was described, followed by procedures used for data analysis. Finally, issues of validity and reliability were addressed as they relate to the current study.

Chapter 5

Results

5.1 Introduction

The primary aim of this study was to describe and compare the hearing status of a group of gold miners with and without tuberculosis. The group of gold miners with tuberculosis were divided in two groups, i.e. those who received a single TB treatment, and those who received multiple TB treatment. The reason for dividing the TB group is that *Streptomycin*, a known ototoxic medication, is included in the re-treatment regimen for tuberculosis (Guild et al., 2001), and may have a more pronounced effect on the hearing of those subjects. The results of the current study will be presented according to the sub-aims of the study. Figure 5.1 graphically displays how the main aim of the study was addressed by addressing the sub-aims.

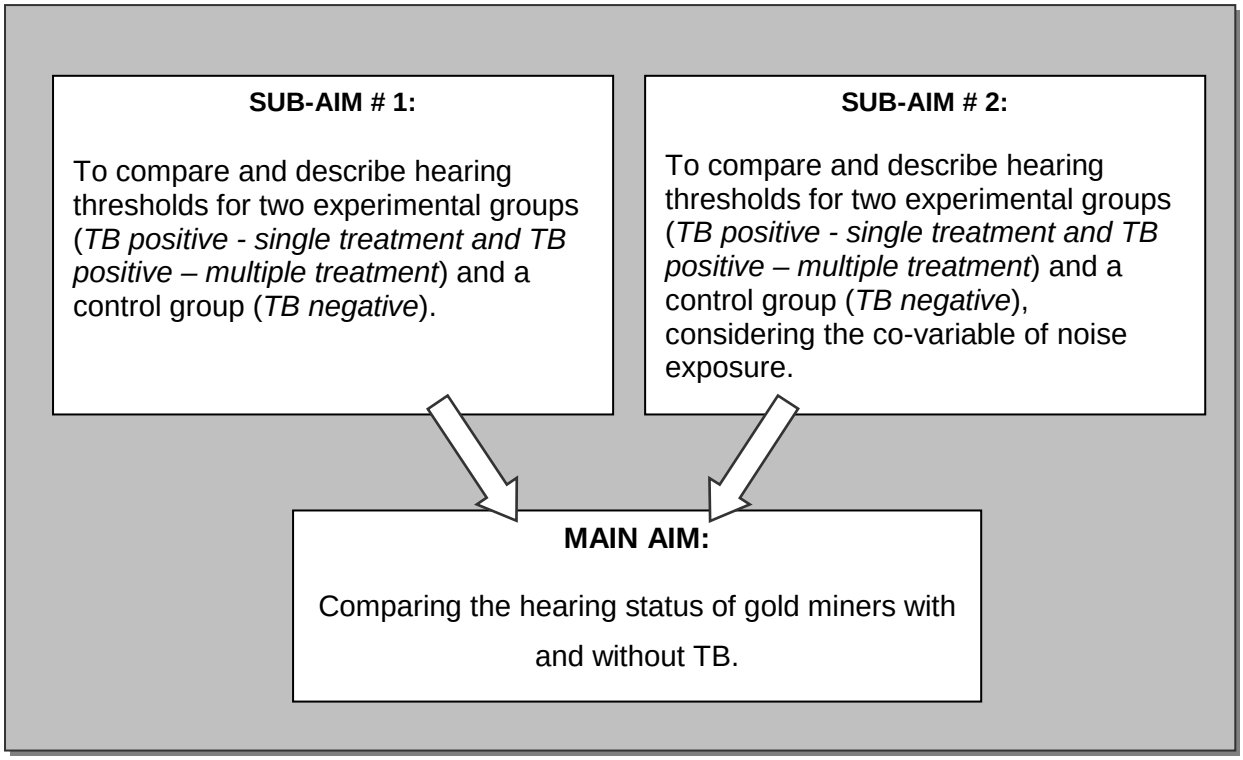


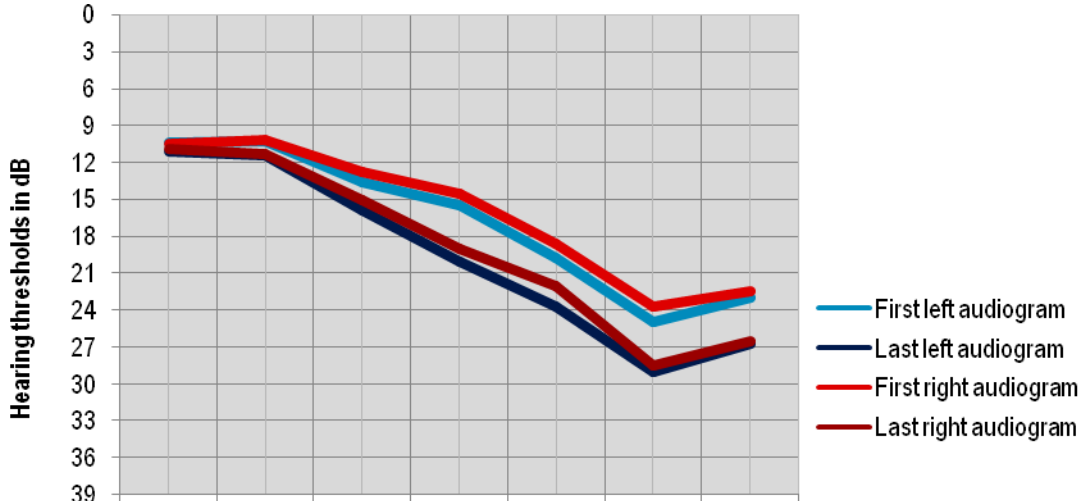
Figure 5.1 Graphic representation of the main aim and sub-aims of the study

5.2 Sub-aim # 1: Hearing threshold parameters across groups

Analysis of various hearing threshold parameters was done using the ANCOVA with covariates such as age, exposure time (between first and most recent audiogram), and first audiogram threshold values to observe, analyse and compare the effect of TB, TB treatment, age and continuous noise exposure on hearing.

5.2.1 Mean hearing thresholds across all frequencies

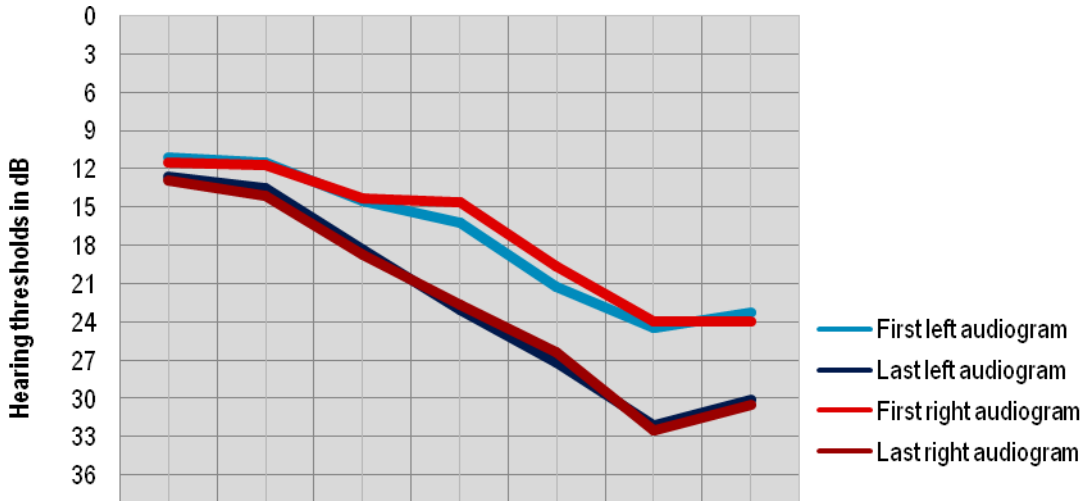
These observations and descriptions were done for the first and last audiogram recorded, across all frequencies (0.5, 1, 2, 3, 4, 6, 8 kHz), for the left and right ears respectively. It was done in order to form a broader representation of the hearing status of the subjects in the three groups (control, single TB treatment and multiple TB treatment) while adjusting for ‘age at test’ – in other words adjusting for the age of the subject when the audiogram involved was recorded. These corrections were done due to the fact that age has a known influence on hearing. The mean age for the covariate ‘age at test’ was calculated at 37.6 years for the first audiograms and 42.5 years for the last audiograms. Figures 5.2 to 5.4 are visual representations of the means of these hearing thresholds, and serve as illustrations of the progress of the hearing loss from the first audiogram recorded to the last audiogram recorded (in each group). The average number of years between the first and last audiogram recorded for all subjects was 4.9 years.



	0.5	1	2	3	4	6	8
First left audiogram	10.4	10.3	13.6	15.55	19.8	25	23
Last left audiogram	11.1	11.5	15.9	20.1	23.7	29	26.8
First right audiogram	10.5	10.2	12.8	14.6	18.6	23.7	22.5
Last right audiogram	10.9	11.3	15.1	19.1	22.1	28.5	26.5

Frequencies in kHz

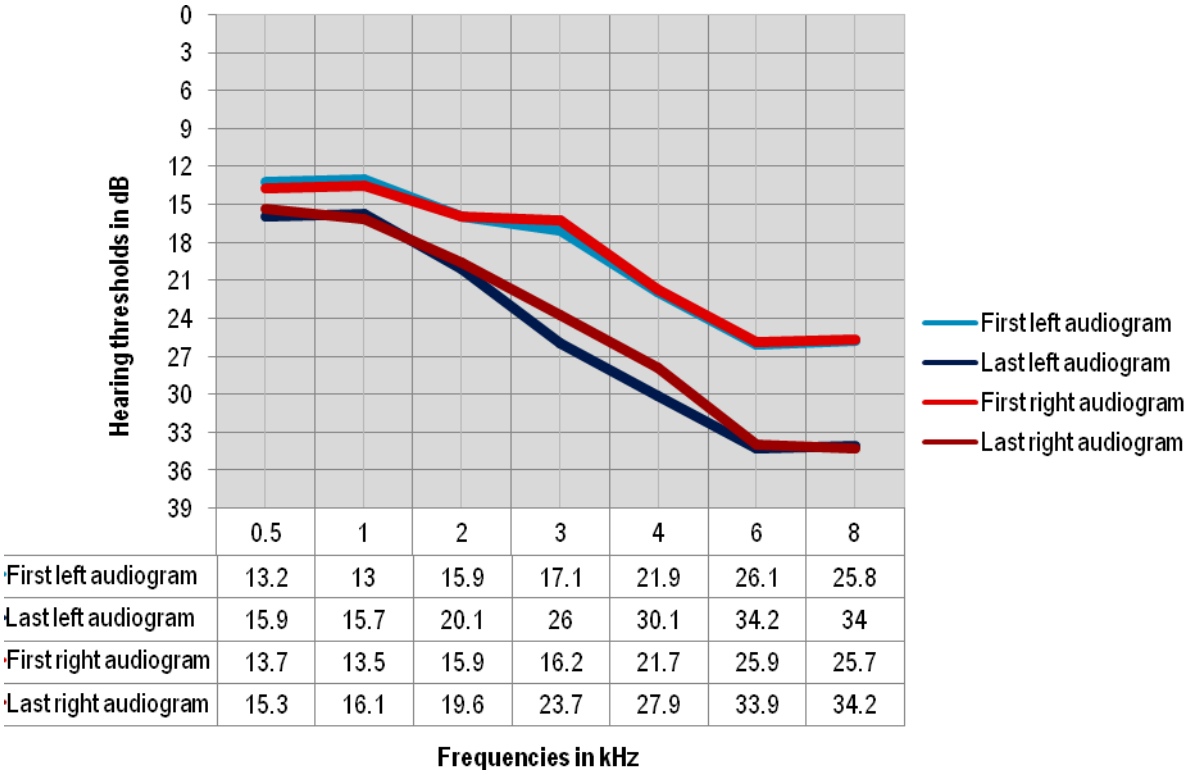
Figure 5.2 Control group: mean thresholds for first and last audiograms



	0.5	1	2	3	4	6	8
First left audiogram	11.1	11.5	14.5	16.2	21.2	24.5	23.3
Last left audiogram	12.6	13.5	18.3	23.1	27.2	32.1	30.1
First right audiogram	11.5	11.7	14.3	14.6	19.6	24	24
Last right audiogram	12.9	14.1	18.7	22.6	26.4	32.5	30.5

Frequencies in kHz

Figure 5.3 Single TB group: mean thresholds for first and last audiograms



	0.5	1	2	3	4	6	8
First left audiogram	13.2	13	15.9	17.1	21.9	26.1	25.8
Last left audiogram	15.9	15.7	20.1	26	30.1	34.2	34
First right audiogram	13.7	13.5	15.9	16.2	21.7	25.9	25.7
Last right audiogram	15.3	16.1	19.6	23.7	27.9	33.9	34.2

Figure 5.4 Multiple TB group: mean thresholds for first and last audiograms

Control group

It is clear from the graphs that there was a larger shift in average hearing thresholds (from the first to the last audiogram) in the two experimental groups than in the control group. The low frequency thresholds (0.5 and 1 kHz) of the control group in both the first and last audiograms were not affected. A very gradual down slope in the threshold values towards the high frequencies was visible in the control group's first audiograms, with only hearing thresholds at 6 and 8 kHz being out of the normal range (≥ 20 dB, according to Jerger's categorization, Hall & Mueller, 1997). The same pattern was visible in the graphs of the last audiograms, although the slope was slightly steeper, and hearing thresholds at 4 kHz were also out of the normal range (≥ 20 dB). The largest drop in hearing thresholds was between 2 and 3 kHz and between 4 and 6 kHz, with 6 kHz being the most elevated hearing threshold (notch in hearing thresholds). The left ears' hearing thresholds values in the first and last audiograms were slightly more affected than the hearing thresholds values for the right ears.

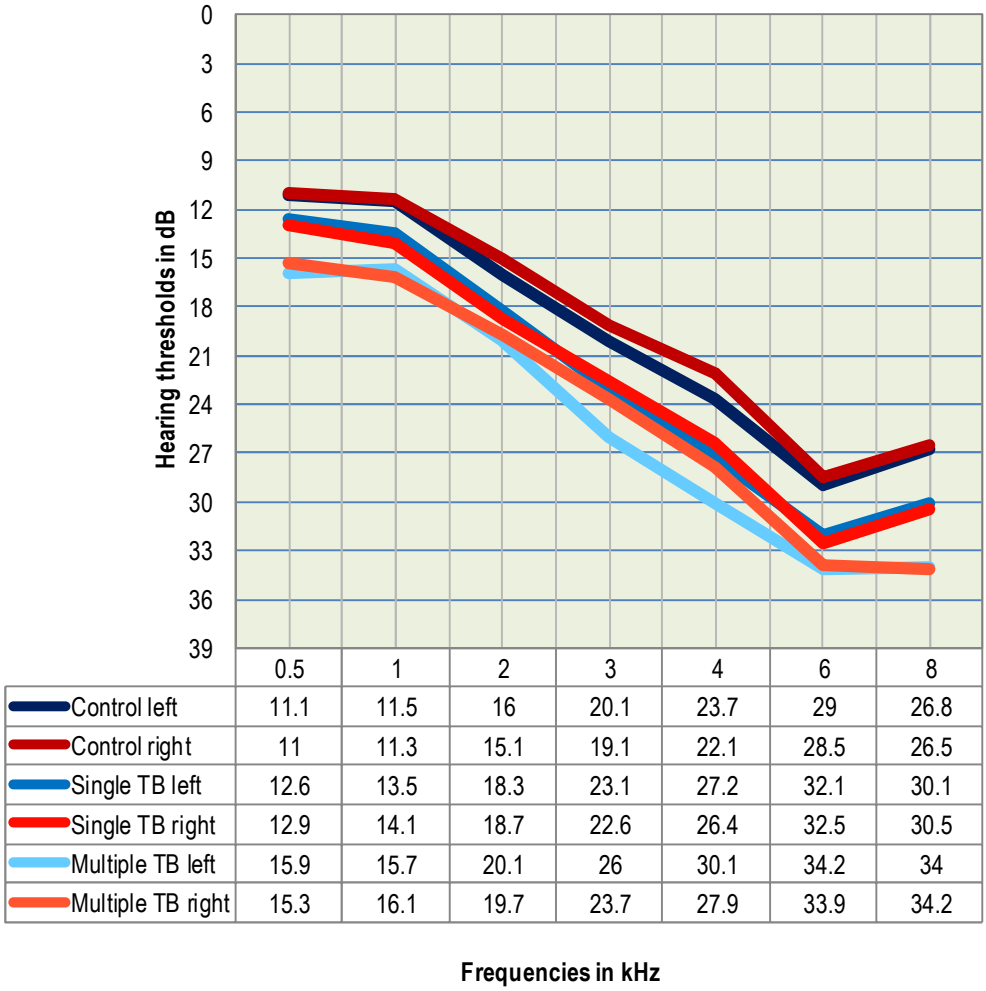
Single TB treatment group

There was a more definite difference between the first and last audiograms in the single TB group than in the control group. The low frequency hearing thresholds (0.5 and 1 kHz) of the last audiograms were slightly more affected, and the down slope towards the high frequencies was steeper than the slope in the last audiograms of the control group. Although only a small deterioration in the hearing status between 2 and 3 kHz was visible in the first audiograms, with a slightly steeper fall between 3 and 4 kHz and 4 and 6 kHz, there was a consistent deterioration in the hearing threshold between 2 and 3 kHz, 3 and 4 kHz and from 4 and 6 kHz in the last audiograms of the single TB group. 6 kHz could once more be identified as the most elevated hearing threshold in both the first and last audiograms (notch in hearing thresholds). 8 kHz was slightly more affected than in the control group, with the threshold values at 8 kHz in the right ears' first audiogram almost the same as the 6 kHz threshold values. The hearing threshold values in the left ear of the first audiograms were slightly more affected than the hearing thresholds of the right ear. The left and right ears' hearing thresholds for the last audiograms were however nearly the same.

Multiple TB treatment group

The differences in hearing status between the first and last audiograms were again more distinct in the multiple TB group than in the control group. The hearing thresholds of the first audiograms of this group were already more affected than the hearing thresholds of the first audiograms of especially the control group, but also of the single TB group. Although the deterioration in hearing status between 2 and 3 kHz in the first audiograms was very small, there was a consistent drop in hearing threshold values between 2 and 3 kHz, 3 and 4 kHz and 4 and 6 kHz in the last audiograms of the multiple TB group. 6 and 8 kHz could now be identified as the most elevated hearing thresholds in both the first and last audiograms (no notch in hearing thresholds). The hearing thresholds of the right and left ears for the first audiograms were nearly the same (threshold values for the left ears were slightly more affected than those of the right ears), but in the last audiograms the left ears' hearing status were more affected than the right ears' hearing status (especially between 2 and 6 kHz).

Figure 5.5 is a representation of all the last audiograms recorded (left ears – blue lines and right ears - red lines) for the three groups.



	0.5	1	2	3	4	6	8
Control left	11.1	11.5	16	20.1	23.7	29	26.8
Control right	11	11.3	15.1	19.1	22.1	28.5	26.5
Single TB left	12.6	13.5	18.3	23.1	27.2	32.1	30.1
Single TB right	12.9	14.1	18.7	22.6	26.4	32.5	30.5
Multiple TB left	15.9	15.7	20.1	26	30.1	34.2	34
Multiple TB right	15.3	16.1	19.7	23.7	27.9	33.9	34.2

Figure 5.5 Left and right ears – last audiograms across all groups

From figure 5.5 it is clear that there was a difference between the three groups, although a smaller difference existed between the two TB groups than between the control and TB groups. It also was apparent from the results that the left ears' hearing thresholds in all three groups, and especially in the frequencies above 2 kHz, were slightly more affected than those of the right ears. This is especially evident in the control and multiple TB treatment groups. The left and right ears in the single TB treatment group were almost the same.

In order to narrow the observations and analysis of hearing thresholds down, and to be more specific in the description of the hearing status of gold miners, different hearing threshold parameters were used.

5.2.2 Mean hearing thresholds across frequency categories

These analyses were done on the last audiograms recorded, for the two frequency categories ('high' and 'low') in the left and right ears respectively. The reason for analysing the last audiograms first was to form a representation of the subjects' hearing status as it was after a few years of TB/TB treatment and/or noise exposure. The frequency categories consisted of low frequency averages (0.5, 1, 2 kHz - left & right ears) and high frequency averages (3, 4, 6 kHz - left & right ears). The reason for analysing the lower and higher frequencies separately was to be able to make a more specific comparison between the low and high frequency hearing thresholds, due to the fact that ototoxic medication as well as noise and age have a greater influence on the higher frequencies, while for example the PLH's weighting is highest for hearing loss at 1 kHz and lowest for hearing loss at 4 kHz – and will not necessarily present the true influence of a hearing loss if it was only located in the higher frequency area. The frequency categories within the three groups were compared using analysis of covariance (ANCOVA) with age at most recent test as covariate. This correction was done due to the fact that age has a known influence on hearing. Table 5.1 reports the mean, standard deviations and 95% confidence intervals (CI) for the observed threshold values in the 'high' and 'low' frequency categories. The reported p-value is corrected for age since adjustments for 'age at test' have been made across groups.

Table 5.1 Mean hearing thresholds across frequency categories for the last audiograms *(Green = significant at 1% level; Blue = significant at 5% level; Purple = not significant)*

Hearing Threshold Parameter		Control group (n = 1411)	Single TB Treatment (n = 911)	Multiple TB treatment (n = 376)	P-value
Left average low (0.5 + 1 + 2 kHz)	*mean*	11.2	15.2	18.4	p < 0.01
	sd	(11.5)	(12.5)	(18.4)	
	95 % CI	*[10.5 - 11.8]*	*[14.4 - 16]*	*[17.2 - 19.7]*	
Right average low (0.5 + 1 + 2 kHz)	*mean*	10.9	15.6	18.1	p < 0.01
	sd	(11.1)	(13.5)	(13.4)	
	95 % CI	*[10.2 - 11.5]*	*[14.8 - 16.4]*	*[16.9 – 19.3]*	
Left average high (3 + 4 + 6 kHz)	*mean*	20.8	28.2	32.3	p < 0.01
	sd	(16.2)	(17.5)	(17.2)	
	95 % CI	*[19.9 - 21.6]*	*[27.1 – 29.3]*	*[30.6 – 34]*	
Right average high (3 + 4 + 6 kHz)	*mean*	19.7	27.9	30.6	p < 0.01
	sd	(16.4)	(18)	(16.9)	
	95 % CI	*[18.7 - 20.5]*	*[26.8 – 28.9]*	*[28.9 - 32.4]*	

The groups (control, single TB treatment and multiple TB treatment) in all frequency categories with respect to mean hearing threshold differed significantly ($p < 0.01$). The differences between the groups were larger for the high frequency averages than for the low frequency averages. The difference between the hearing threshold means for the control and two TB groups was larger than the difference between the two TB groups. The average hearing thresholds of the multiple TB group were most affected, and the left ears more than the right ears. The 95% confidence intervals are an interval estimate of the population parameter. In other words there is a 95% confidence level that the population parameter is included in the confidence intervals. It is also noticeable that the 95%CI intervals for the three groups were not overlapping, but were successively higher for each of the three groups (control, single TB treatment and multiple TB treatment). The highest 95% CI level for the control group did not overlap with the minimum 95% CI level of the single TB treatment group.

Table 5.2 indicates the results of the pair wise comparisons between the three groups for the hearing threshold means of the frequency categories (last audiogram recorded), after adjustment for 'age at test' has been done. In other words these comparisons indicate whether there exist significant differences in average hearing thresholds for the low average (left & right ears) as well as high average (left & right ears) hearing thresholds between the three groups. Correction for 'age at test' was done due to the fact that age has a known influence on hearing. The mean value of the covariate 'age at test' was 41 years.

Table 5.2 Pair wise comparisons across frequency categories *(Green = significant at 1% level; Blue = significant at 5% level; Purple = not significant)*

Test of the significance of difference between groups (F-test)	F-value: Left average low frequency category	F-value: Right average low frequency category	F-value: Left average high frequency category	F-value: Right average high frequency category
Control - Single TB treatment	12.5	25.4	1.4	37.7
(P-value significance)	(p < 0.01)	(p < 0.01)	(p < 0.01)	(p < 0.01)
Control - Multiple TB treatment	40.6	40.1	4.1	38.1
(P-value significance)	(p < 0.01)	(p < 0.01)	(p < 0.01)	(p < 0.01)
Single TB treatment - multiple TB treatment	13.4	6.5	9.9	2.6
(P-value significance)	(p < 0.01)	(p < 0.05)	(p < 0.01)	(p > 0.05)

Corrected for age, the differences between the control and TB groups in all four frequency categories were highly significant ($p < 0.01$), with the largest difference between the control and multiple TB treatment groups. The smallest difference was between the two TB groups, with the differences in the left ear (low and high frequency average categories) still significant at a 1% level, the difference in the right ear for the low frequency average category significant at a 5% level, and no significant differences between the two TB groups for the right ears' high frequency average category.

5.2.3 Change in mean hearing thresholds across frequency categories over time

The change in hearing threshold means from the first to last audiograms across the above mentioned frequency categories within the three groups was calculated and compared using analysis of covariance (ANCOVA) with 'age at test', 'hearing thresholds at the first audiogram' and 'time exposure between the two audiograms' as covariates. This was done in order to observe the possible effect of time of exposure/age on the hearing thresholds in the low vs. high frequency categories. Table 5.3 reports the mean and standard deviations for the observed shifts in hearing threshold values from the first to the last audiograms in the 'high' and 'low' frequency categories. The reported p-value is after adjustments for the covariates have been made. The mean age of the covariate 'age at first test' was calculated to be 37.6 years, the mean hearing threshold value for 'hearing threshold at first audiogram' was 12.3 dB, and the mean time of exposure between the two recorded audiograms was 4.9 years.

Table 5.3 Change in mean hearing threshold values (from the first to last audiograms) across frequency categories (Positive value indicates deterioration in hearing thresholds). *(Green = significant at 1% level; Blue = significant at 5% level; Purple = not significant)*

Hearing Threshold Parameter		Control group (n = 834)	Single TB Treatment (n = 923)	Multiple TB Treatment (n = 373)	P-value
Left average low (0.5 + 1 + 2 kHz)	*mean*	0.8	2.9	3.5	p < 0.01
	sd	(9.4)	(9.9)	(11.2)	
Right average low (0.5 + 1 + 2 kHz)	*mean*	0.7	3.13	2.9	p < 0.01
	sd	(8.9)	(11.9)	(11.8)	
Left average high (3 + 4 + 6 kHz)	*mean*	3.1	7.6	9	p < 0.01
	sd	(10.2)	(12.1)	(13.9)	
Right average high (3 + 4 + 6 kHz)	*mean*	3.2	8.5	7.9	p < 0.01
	sd	(10.2)	(13.9)	(13.9)	

The groups (control, single TB treatment and multiple TB treatment) in all frequency categories differed significantly ($p < 0.01$) with respect to the differences between the mean hearing threshold values of the first and last audiograms. The differences in hearing threshold means between the groups were much larger for the high frequency

average than for the low frequency average. This indicates that there was a much larger shift in the hearing thresholds from the first to the last audiograms in the high frequencies, than in the low frequencies across groups. There was less deterioration visible in the hearing threshold changes in the control group, than in the experimental groups. In addition it was clear that the changes in hearing threshold means were larger between the control and two TB groups than between the two TB groups. These shifts however were larger for the right ear averages in the single TB treatment group, but larger for the left ear averages in the multiple TB treatment group.

Table 5.4 reports the results of the pair wise comparisons between the three groups for the changes in the hearing threshold means from the first to the last audiograms across frequency categories, while adjusting for ‘age at test’, ‘hearing threshold at the first audiogram’ and ‘time exposure between audiograms’. These corrections were made due to the fact that age has a known influence on hearing. Furthermore, the first audiograms used in this study are not necessarily the first audiograms recorded in the subjects’ working career, and therefore it is possible that there were already hearing threshold shifts present in these first audiograms which needed to be adjusted for. Lastly the correction for time exposure between the first and last audiograms was critical since not all of the subjects had the same time exposure between the two recorded audiograms. The mean age of the covariate ‘age at first test’ was calculated to be 37.6 years, the mean hearing threshold value for ‘hearing threshold at first audiogram’ was 12.3 dB, and the mean time of exposure between the two recorded audiograms was 4.9 years.

Table 5.4 Pair wise comparison for the changes in mean hearing thresholds (from the first to the last audiogram) across frequency categories *(Green = significant at 1% level; Blue = significant at 5% level; Purple = not significant)*

Test of the significance of difference between groups (F-test)	F-value: Left average low frequency category	F-value: Right average low frequency category	F-value: Left average high frequency category	F-value: Right average high frequency category
Control – Single TB treatment	25.4	37.3	38.1	51.2
(P-value significance)	(p < 0.01)	(p < 0.01)	(p < 0.01)	(p < 0.01)
Control – Multiple TB treatment	34.4	31.3	53.6	32.4
(P-value significance)	(p < 0.01)	(p < 0.01)	(p < 0.01)	(p < 0.01)
Single TB treatment – multiple TB treatment	3.7	0.5	6.2	0.0
(P-value significance)	(p > 0.05)	(p > 0.05)	(p < 0.05)	(p > 0.05)

Adjusted for the covariates, the differences between the control and TB groups were highly significant ($p < 0.01$) across all frequency categories, with the largest differences between the control and multiple TB treatment groups (highest F values). There were however no significant differences between the two TB groups ($p > 0.05$), apart for the left ear high frequency group, which was significantly different at the 5% level of significance.

5.2.4 High frequency hearing thresholds (6 and 8 kHz) for the last audiograms

The hearing threshold values for 6 and 8 kHz (for the left and right ear respectively), within the three groups were compared using analysis of covariance (ANCOVA) with 'age at test' as covariate. This was done in order to see the possible effect of TB/TB medication and/or age/time of noise exposure on the subjects' high frequencies hearing thresholds. Literature underlines the fact that noise exposure as well as ototoxic medication has the largest effect on higher hearing frequencies. Table 5.5 reports the mean, standard deviations and 95% confidence intervals (CI) for the

observed threshold values at 6 and 8 kHz. The reported p-value is after adjustments for 'age at test' has been made.

Table 5.5 Mean high frequency hearing thresholds (6 and 8 kHz) for the last audiograms *(Green = significant at 1% level; Blue = significant at 5% level; Purple = not significant)*

Hearing Threshold Parameter		Control group (n = 1418)	Single TB Treatment (n = 913)	Multiple TB-Treatment (n = 374)	P-value
Left 6 kHz	*mean*	25.6	32.8	36.4	p < 0.01
	sd	(18.4)	(19.4)	(19.7)	
	95% CI	*[24.6 - 26.6]*	*[31.5 – 34]*	*[34.4 - 38.3]*	
Right 6 kHz	*mean*	24.8	33.2	35.8	p < 0.01
	sd	(18.2)	(19.6)	(18.9)	
	95% CI	*[23.9 - 25.8]*	*[32 - 34.4]*	*[33.9 - 37.7]*	
Left 8 kHz	*mean*	23.4	30.8	36.2	p < 0.01
	sd	(20.2)	(21.4)	(23.2)	
	95% CI	*[22.3 - 24.5]*	*[29.4 - 32.2]*	*[34.1 - 38.4]*	
Right 8 kHz	*mean*	22.8	31.3	36.2	p < 0.01
	sd	(19.4)	(21.3)	(21.8)	
	95% CI	*[21.8 - 23.9]*	*[30 - 32.6]*	*[34.1 - 38.2]*	

The groups (control, single TB treatment and multiple TB treatment) in all of the tested high frequency categories differed significantly ($p < 0.01$) with respect to mean hearing threshold. It is evident that the hearing threshold means at 6 kHz was the most elevated threshold in the control and single TB group. 8 kHz was equally affected to 6 kHz in the multiple TB group. The differences between the control and both TB groups were again more pronounced than between the two TB groups. It is evident that differences in the right ears' hearing threshold values (6 & 8 kHz) between the control and single TB treatment group were larger than for the left ears. The differences between the hearing threshold values (6 & 8 kHz) of the single TB treatment and multiple TB treatment groups were however larger for the left ears.

Table 5.6 reports the results of the pair wise comparisons between the three groups for the hearing threshold values of the higher frequencies (6 & 8 kHz at the last

audiogram), after adjustment for 'age at test' has been done. Correction for 'age at test' was done due to the fact that age has a known influence on hearing and especially on the higher frequencies. The mean age of the covariate 'age at test' was 41 years.

Table 5.6 Pair wise comparisons for the high frequency hearing thresholds (6 and 8 kHz) for the last audiograms *(Green = significant at 1% level; Blue = significant at 5% level; Purple = not significant)*

Test of the significance of difference between groups (F-test)	F-value: Left 6 kHz	F-value: Right 6 kHz	F-value: Left 8 kHz	F-value: Right 8 kHz
Control – Single TB treatment	13.7	32.2	11.5	26.3
(P-value significance)	(p < 0.01)	(p < 0.01)	(p < 0.01)	(p < 0.01)
Control – Multiple TB treatment	24.8	29.8	36.3	48.2
(P-value significance)	(p < 0.01)	(p < 0.01)	(p < 0.01)	(p < 0.01)
Single TB treatment – multiple TB treatment	4.8	1	11.8	9.5
(P-value significance)	(p < 0.05)	(p > 0.05)	(p < 0.01)	(p < 0.01)

Adjusted for age, the differences between the control and two experimental groups were highly significant ($p < 0.01$), with the largest differences between the control and multiple TB treatment groups. The differences between the two TB groups in the 8 kHz categories were also recorded at a 1% level of significance, and the differences in the left ear 6 kHz category at a 5% level of significance. There was however no significant difference between the two TB groups in the right ears' 6 kHz category.

5.2.5 Percentage loss of hearing (PLH) for the last audiograms

The mean as well as standard deviations and 95% confidence intervals (CI) for the percentage loss of hearing (PLH) (Instruction 171) was calculated within the three groups, using analysis of covariance (ANCOVA) with 'age at test' as covariate. PLH was compared and analysed in order to determine whether differences exist in the

observed hearing status of subjects when calculating and describing their hearing statuses according to different classification or weighing systems. For example, when using PLH the weighting is highest for hearing loss at 1 kHz and lowest for hearing loss at 4 kHz, which may give a different image than when placing more weight on the high frequencies (including 6 kHz). The reported p-value is after adjustments for 'age at test' has been made.

Table 5.7 Percentage loss of hearing for the last audiograms *(Green = significant at 1% level; Blue = significant at 5% level; Purple = not significant)*

Hearing Threshold Parameter		**Control group (n = 1418)**	**Single TB Treatment (n = 914)**	**Multiple TB Treatment (n = 375)**	**P-value**
PLH	*Mean*	4.3	7.2	8.5	p < 0.01
	sd	(8)	(11)	(10.8)	
	95% CI	*[3.8 - 4.8]*	*[6.6 - 7.8]*	*[7.5 - 9.5]*	

The group means for PLH in each group differed significantly ($p < 0.01$). The differences between the control and both TB groups were larger than the differences between the two TB groups. It is apparent that differences exist in the hearing status of the subjects when different classification/weighting systems are used to calculate a hearing loss. With PLH there was for example a slightly smaller difference between the groups than when 6 kHz was included in the high hearing threshold means (3 + 4 + 6 kHz), and the difference between the groups was larger.

Table 5.8 provides the results of the pair wise comparisons between the three groups for the PLH, after adjustment for 'age at test' has been done. Correction for age' was done due to the fact that age has a known influence on hearing and especially on the higher frequencies. The mean age of the covariate 'age at test' was calculated as 41 years.

Table 5.8 Pair wise comparisons for the PLH for the last audiograms *(Green = significant at 1% level; Blue = significant at 5% level; Purple = not significant)*

Test of the significance of difference between groups (F-test)	F-value: PLH
Control – Single TB treatment	8.8
(P-value significance)	(p < 0.01)
Control – Multiple TB treatment	14.2
(P-value significance)	(p < 0.01)
Single TB treatment – multiple TB treatment	2.4
(P-value significance)	(p > 0.05)

Compensated for age, the differences between the control and two TB groups were highly significant ($p < 0.01$), with the biggest difference between the control and multiple TB treatment groups. There existed no significant difference between the PLH values for the two TB groups.

5.3 Sub-aim # 2: Hearing threshold parameters across groups, considering noise exposure co-variable

Analysis of two noise exposure indicators ('noise exposure' vs. 'no noise exposure' and drillers vs. admin staff) was done using the ANCOVA with age as covariate. All frequencies as well as the same frequency categories (low average left & right and high average left & right) were used in order to analyse and compare the effect of noise exposure on the subjects' (with and without TB) hearing status.

5.3.1 Mean hearing thresholds across frequency categories with noise exposure co-variable

These analyses were done in order to compare the effect of different exposure levels (noise and no noise) on the subjects in the three groups' (control, single TB treatment and multiple TB treatment) average hearing thresholds. The different exposure levels/occupations were categorized in four groups namely: 1) above surface noise

exposure, 2) below surface noise exposure, 3) no noise exposure and 4) uncertain levels of noise exposure e.g. students and trainees. These averages of the 'noise exposure' groups (1 & 2 Noise) were compared to the averages of the 'no noise exposure' groups (3 & 4 – No Noise).

The last audiograms recorded for the 'high' and 'low' frequency categories, left and right ears respectively, were used during these analyses. The frequency categories consisted of low frequency average categories (0.5, 1, 2 kHz - left & right ears) and the high frequency average categories (3, 4, 6 kHz - left & right ears), in each case the left and right ears separately. The reason for analyzing the lower and higher frequencies separately was to be able to make a more specific comparison between the low and high frequency hearing thresholds, due to the fact that ototoxic medication as well as noise and age have a greater influence on the higher frequencies. Table 5.9 reports the mean threshold values and standard deviations for these frequency categories. The reported p-values are after adjustments for 'age at test' have been made.

Table 5.9 Mean hearing thresholds across frequency categories for the last audiograms in the 'noise exposure' vs. 'no noise exposure' groups *(Green = significant at 1% level; Blue = significant at 5% level; Purple = not significant)*

Hearing Threshold Parameter	Noise exposure groups		Control group (n= 1026 noise +392 no noise)	Single TB Treatment (n= 704 noise +210 no noise)	Multiple TB Treatment (n= 278 noise +98 no noise)	P-value for noise vs. no noise
Left average low (0.5 + 1 + 2 kHz)	**Noise**	*mean*	11.3	14.9	17.4	p > 0.05
		sd	(11.5)	(12.8)	(13.8)	
	No Noise	*mean*	10.7	16.1	21.3	
		sd	(11.2)	(11.5)	(15.2)	
Right average low (0.5 + 1 + 2 kHz)	**Noise**	*mean*	10.9	15.5	17.1	p > 0.05
		sd	(10.7)	(13.7)	(12.4)	
	No Noise	*mean*	10.6	16.1	21	
		sd	(11.9)	(13)	(15.4)	
Left average high (3 + 4 + 6 kHz)	**Noise**	*mean*	21.2	27.8	31	p > 0.05
		sd	(16.3)	(17.8)	(17)	
	No Noise	*mean*	19.7	29.6	36	
		sd	(15.9)	(17.9)	(17.1)	
Right average high (3 + 4 + 6 kHz)	**Noise**	*mean*	20.3	27.3	29	p > 0.05
		sd	(16.6)	(17.7)	(15.9)	
	No Noise	*mean*	27.8	29.8	35.4	
		sd	(15.5)	(19)	(18.7)	

No significant differences exist between the hearing threshold means of the 'noise exposure' and 'no noise exposure' groups within each of the four frequency categories. It is evident from the table that the hearing threshold means for the 'noise exposure' groups were always slightly higher than for the 'no noise exposure' groups in the control group. In the two experimental groups, the hearing threshold means for the 'no noise exposure' groups across all frequency categories were more elevated than the hearing threshold means of the 'noise exposure' groups. The only observable differences between left and right ears were present in the high frequency average categories of the multiple TB group. In this category the left ears' high frequency averages were more elevated then those of the right ears, in both the 'noise exposure' and 'no noise exposure' groups.

Once the adjustment for age has been made (calculating the average ‘age at test’ on 41 years of age), no significant differences exist between the ‘noise exposure’ and ‘no noise exposure’ groups across all frequency categories. This correction for age was necessary due to the fact that age has a known influence on hearing.

5.3.2 Mean hearing thresholds across frequency categories for two employment groups

In order to narrow the analysis down, an alternative method of noise exposure classification was also analysed and compared viz. drillers (definite high levels of noise exposure) vs. admin workers (almost no noise exposure at work when last audiogram were recorded). Table 5.10 reports the hearing threshold means and standard deviation in each of the frequency categories, between the drillers and admin staff. The reported p-values are after adjustments for ‘age at test’ have been made.

Table 5.10 Mean hearing thresholds across frequency categories for the last audiograms in the drillers vs. admin staff groups *(Green = significant at 1% level; Blue = significant at 5% level; Purple = not significant)*

Hearing Threshold Parameter	Drillers vs. Admin staff		Control group (n=116 drillers + 50 admin)	Single TB Treatment (n=144 drillers + 39 admin)	Multiple TB Treatment (n= 70 drillers + 11 admin)	P-value for driller vs. admin staff
Left average low (0.5 + 1 + 2 kHz)	**Driller**	*mean*	14.9	18.9	22	p > 0.05
		sd	(13.2)	(14.8)	(15.7)	
	Admin	*mean*	9.9	17.4	17.7	
		sd	(8.6)	(11.1)	(11.2)	
Right average low (0.5 + 1 + 2 kHz)	**Driller**	*mean*	14.1	17.7	20.3	p > 0.05
		sd	(10.8)	(12)	(12.1)	
	Admin	*mean*	10.2	15.8	17	
		sd	14.1	(10.5)	(10.6)	
Left average high (3 + 4 + 6 kHz)	**Driller**	*mean*	26.2	35.7	37.8	p > 0.05
		sd	(16.3)	(17.5)	(16.9)	
	Admin	*mean*	19.1	31	31.7	
		sd	(15.6)	(17.1)	(12.7)	
Right average high (3 + 4 + 6 kHz)	**Driller**	*mean*	25	33.2	34.5	p > 0.05
		sd	(14.4)	(15.6)	(16.1)	
	Admin	*mean*	16.9	31.4	34.7	
		sd	(16.3)	(18.5)	(16.3)	

No significant differences exist in hearing threshold averages between any of the drillers and admin staff groups within each of the frequency categories once adjustment for age has been made (the average 'age at test' was 45.8 years of age). This correction for age was necessary due to the fact that age has a known influence on hearing. The differences that do exist in the hearing threshold averages between the driller and admin staff groups were however larger than the differences between the 'noise exposure' vs. 'no noise exposure' groups. The hearing thresholds of the drillers were more affected than those of the admin staff, and the left ears more than the right ears. The most affected group was the drillers in the multiple TB group.

5.3.3 Change in mean hearing thresholds across all frequencies in noise exposed and unexposed groups

The differences in hearing threshold means between the first and last audiograms across all frequencies (0.5 – 8 kHz) within the three groups were calculated and compared using analysis of covariance (ANCOVA) with 'age at test', 'hearing thresholds at the first audiogram' and 'time exposure between the two audiograms' as covariates. This analysis was done between the 'noise exposure' and 'no noise exposure' groups in order to observe the possible effect of noise exposure and time of exposure/age on the hearing thresholds at separate frequencies. Figure 5.6 provides a visual representation of the differences in hearing threshold means (between the first and last audiogram) across all frequency.

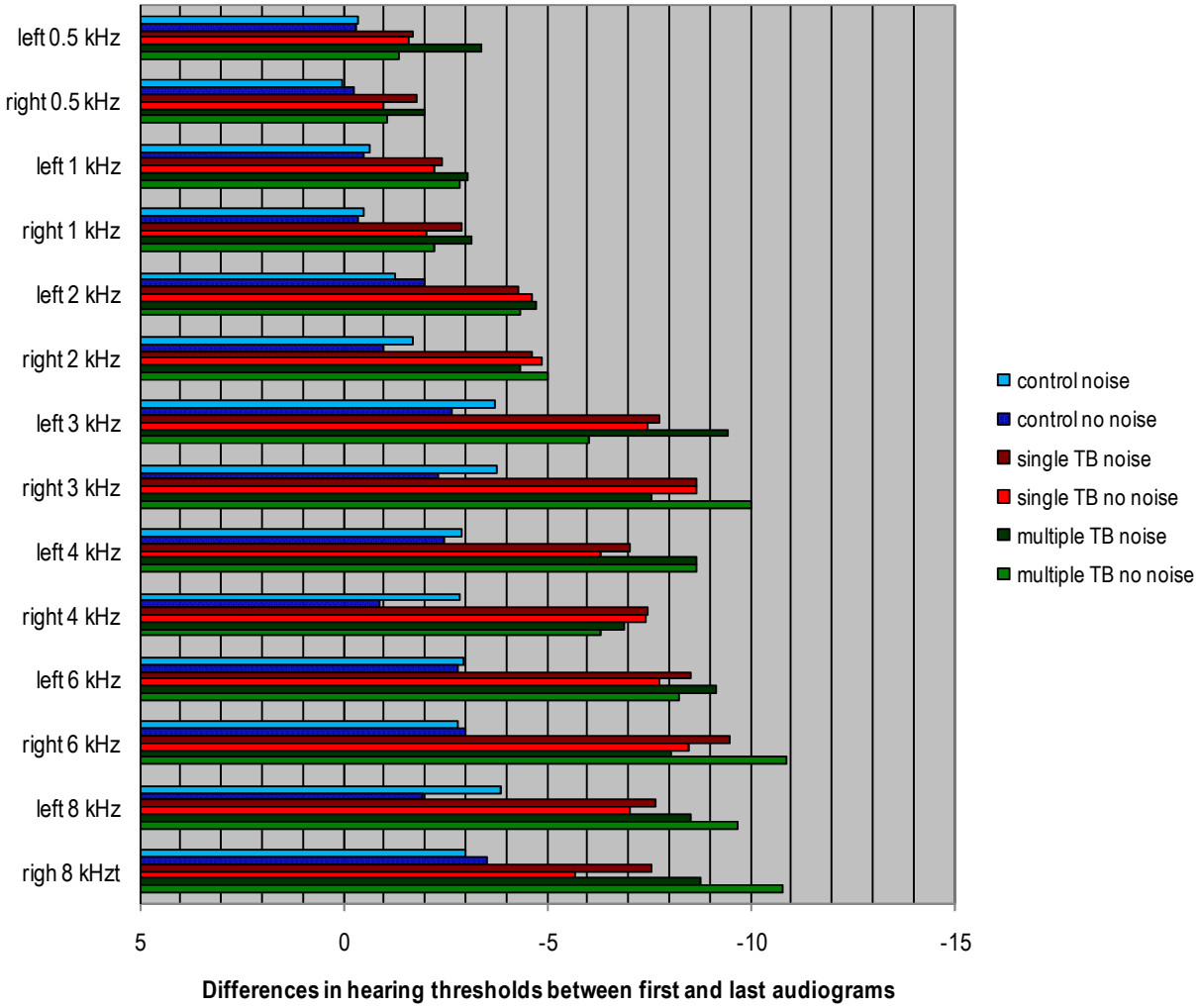


Figure 5.6 Change in mean hearing thresholds across all frequencies in noise exposed and unexposed groups (a negative value indicates deterioration in hearing thresholds).

Table 5.11 reports the mean, and standard deviations for the observed changes in hearing threshold from the first to the last audiograms in the 'noise exposure' and 'no noise exposure' categories. The reason for the statistics having a negative value is that the threshold values of the last audiograms were subtracted from the threshold values of the first audiogram. The reported p-values are after adjustments for the covariates have been made.

Table 5.11 Changes in hearing threshold values from the first to the audiograms across all frequencies in 'noise exposure' vs. 'no noise exposure' groups *(Green = significant at 1% level; Blue = significant at 5% level; Purple = not significant)*

Hearing Threshold Parameter	Noise exposure groups		Control group (n= 645 noise +188 no noise)	Single TB Treatment (n= 695 noise +204 no noise)	Multiple TB Treatment (n= 274 noise +98 no noise)	P-value for noise vs. no noise
Left 0.5 kHz	**Noise**	*mean*	-0.4	-1.7	-3.4	p > 0.05
		sd	(11.8)	(12.8)	(12.8)	
	No Noise	*mean*	-0.3	-1.6	-1.4	
		sd	(11.2)	(12)	(15)	
Right 0.5 kHz	**Noise**	*mean*	0.0	-1.8	-2	p > 0.05
		sd	(10.4)	(13.7)	(14.2)	
	No Noise	*mean*	-0.3	-1	-1	
		sd	(11.4)	(13.7)	(14.5)	
Left 1 kHz	**Noise**	*mean*	-0.6	-2.4	-3	p > 0.05
		sd	(10.1)	(11.1)	(11)	
	No Noise	*mean*	-0.5	-2.2	-2.9	
		sd	(11.4)	(11.1)	(15.3)	
Right 1 kHz	**Noise**	*mean*	-0.5	-2.9	-3.1	p > 0.05
		sd	(9.6)	(13.4)	(13)	
	No Noise	*mean*	-0.4	-2	-2.3	
		sd	(10.6)	(13.4)	(12.3)	
Left 2 kHz	**Noise**	*mean*	-1.3	-4.3	-4.8	p > 0.05
		sd	(10)	(11.6)	(11.5)	
	No Noise	*mean*	-2	-4.6	-4.3	
		sd	(10.4)	(10.9)	(15.7)	

Right 2 kHz	**Noise**	*mean*	-1.7	-4.9	-3.7	p > 0.05
		sd	(9.9)	(14)	(12.5)	
	No Noise	*mean*	-1	-4.8	-5	
		sd	(10.4)	(12.9)	(11.5)	
Left 3 kHz	**Noise**	*mean*	-3.7	-7.8	-9.5	p > 0.05
		sd	(11)	(13.4)	(12.8)	
	No Noise	*mean*	-2.6	-7.5	-6	
		sd	(11)	(13.9)	(14)	
Right 3 kHz	**Noise**	*mean*	-3.8	-8.7	-7.6	p > 0.05
		sd	(11)	(14.6)	(13.8)	
	No Noise	*mean*	-2.3	-8.8	-10	
		sd	(11.7)	(14.8)	(14.3)	
Left 4 kHz	**Noise**	*mean*	-3	-7	-8.6	p >0.05
		sd	(12.3)	(14.3)	(15.5)	
	No Noise	*mean*	-2.5	-6.3	-8.8	
		sd	(11)	(14.3)	(18.1)	
Right 4 kHz	**Noise**	*mean*	-2.9	-7.5	-6.9	p > 0.05
		sd	(11.6)	(15.9)	(15.9)	
	No Noise	*mean*	-0.9	-7.4	-6.3	
		sd	(11.6)	(15.5)	(17.02)	
Left 6 kHz	**Noise**	*mean*	-3	-8.5	-9.132	p > 0.05
		sd	(23.9)	(15.6)	(18.299)	
	No Noise	*mean*	-2.8	-7.8	-8.214	
		sd	(15.6)	(15.5)	(18.51)	
Right 6 kHz	**Noise**	*mean*	-3.9	-9.5	-8	p > 0.05
		sd	(13.9)	(18)	(18.5)	
	No Noise	*mean*	-3	-8.1	-10.9	
		sd	(15.2)	(16.9)	(19.2)	
Left 8 kHz	**Noise**	*mean*	-2.8	-7.7	-8.5	p > 0.05
		sd	(15.2)	(17.5)	(19.7)	
	No Noise	*mean*	-2	-7	-9.7	
		sd	(16.7)	(17.7)	(21.8)	
Right 8 kHz	**Noise**	*mean*	-2.6	-7.6	-8.7	p > 0.05
		sd	(14.3)	(19.4)	(18.4)	
	No Noise	*mean*	-3.6	-5.7	-10.8	
		sd	(16.1)	(17.4)	(19.3)	

There were no significant differences in the shift of hearing threshold means (from the first to the last audiograms) involving the ‘noise exposure’ vs. ‘no noise exposure’ groups in any frequency. In the control group there were nearly always larger hearing threshold shifts in the ‘noise exposure’ group than in the ‘no noise exposure’ group. In the two experimental groups however, there was no consistent pattern in the hearing threshold shifts involving the ‘noise exposure’ and ‘no noise exposure’ groups. The shifts in hearing threshold means (from the first to the last audiogram) were always larger in the two experimental groups than in the control group – even in the lower frequencies. In some of the frequencies the shifts in hearing threshold means from the first to the last audiograms were larger in the ‘no noise exposure’ groups than in the ‘noise exposure’ group. In other frequencies the shifts were reversed. The largest shifts in hearing threshold means from the first to the last audiogram were consistently in die multiple TB groups, and for most frequencies in the left ear. In two cases (multiple TB treatment 6 & 8 kHz) the largest shifts in hearing threshold means were however in the right ear. In three cases (3, 4, 6 kHz right) the shift in hearing threshold means were slightly more elevated in the ‘noise exposure’ category of the single TB treatment group, than in the multiple TB treatment group. In most single TB treatment frequencies the change in hearing threshold means for the two exposure groups were virtually the same.

Once corrections for age and time exposure between the audiograms as well as the hearing threshold at the first audiogram have been done (setting the average ‘time exposure’ to - 4.9 years), there was no significant difference between the ‘noise exposure’ and ‘no noise exposure’ groups across all the frequencies. These corrections were done due to the fact that age has a known influence on hearing. Furthermore, the first audiograms used in this study were not necessarily the first audiograms recorded in the subjects’ working career, and therefore it is possible that there were already hearing threshold shifts present in these first audiograms which needed to be adjusted for. Lastly the correction for time exposure between the first and last audiograms was crucial since not all of the subjects had the same amount of time exposure between the two recorded audiograms, which might have influenced the statistics.

5.4 Conclusion

From the results it can be concluded that there were significant differences between the hearing status of gold miners in the control group (not infected with TB) and the hearing status of gold miners in the two experimental groups (infected with TB and receiving TB treatment). Using different hearing threshold parameters to observe and analyse the hearing status of the three groups, most hearing threshold parameters differed significantly between the groups. There was no mean hearing threshold worse than 35 dB, which can possibly be explained by the fact that that there were a large number of subjects in this study and although many of them had mild, moderate and even severe hearing losses, the larger number of subjects with normal hearing thresholds normalized the distribution. A notch in hearing thresholds were recorded at 6 kHz in the control and single TB treatment groups. This notch at 6 kHz was not observed in the multiple TB treatment group. The largest differences between groups were observed between the control and multiple TB treatment group, and the smallest differences between the two TB groups. When compared over time, the differences between the groups became even larger, and the increase in the high frequency hearing thresholds became more pronounced. Although highly significant differences were present between the three groups at all frequency categories (left average low, right average low, left average high and right average high), the largest differences were in the high frequency categories. There were also significant differences observed between the three groups when the high frequency average (6 and 8 kHz) and PLH were analysed. It was observed that the hearing threshold values for the left ears were slightly more affected than the hearing threshold values of the right ears. There were however no significant differences between the three groups when they were organized into noise exposure groups (‘noise exposure’ vs. ‘no noise exposure’ and drillers vs. admin staff). The differences between the hearing thresholds of the drillers vs. admin groups were nevertheless larger than the differences between the ‘noise exposure’ vs. ‘no noise exposure’ groups.

Chapter 6

Discussion of the results

6.1 Introduction

It is clear from the discussion in the literature overview and the results of the study that the research of hearing status in gold miners (with and without TB) is a multifaceted topic. There are many contributing as well as confounding factors that have to be considered and adjusted for. A large study sample (n = 2698) was used in this project which assisted in providing better estimates of the population parameters. The law of large numbers states that larger samples provide better estimates of a population's parameters than do smaller samples (Lohmeier, 2010). Therefore, as the sample sizes increase the variability between sample statistics decreases which allow better estimates of the true population parameters. The fact that average age in the two experimental groups was higher than that of the subjects in the control group (see table 4.3), should be understood against the background information that the incidence of TB in gold miners is age-dependent (Guild et al. 2001). 'Age at test' was however adjusted for during all analyses by calculating the average age of the subjects in each group, as well as the average threshold value at the specific frequency involved, and adjusted the threshold according to the slope of the threshold/age. The aim of this chapter is to discuss all findings and to interpret the significance thereof. These findings will be discussed according to the sub-aims (hearing threshold parameters and hearing threshold parameters considering the co-variable of noise exposure).

6.2 Sub-aim # 1: Hearing threshold parameters across groups

Analysis of various hearing threshold parameters was done using the ANCOVA with covariates such as age at test, exposure time (between first and most recent audiogram), and first audiogram thresholds values. Different hearing threshold parameters were used in order to observe, analyse and compare the effect of TB, TB treatment, age and continuous noise exposure on different hearing frequencies.

6.2.1 Mean hearing thresholds across all frequencies

Control group: first and last audiograms

There was a small difference visible between the hearing thresholds of the first and last audiograms, although the difference was larger in the high frequencies than in the low frequencies (where the difference was very small). The slight downward slope towards the higher frequencies, which was steeper in the last audiograms than in the first audiograms, may be attributed to factors such noise exposure and age. Previous reports also indicated that the high frequency outer hair cells in the cochlea are more vulnerable (Sha, 2005; Henderson & Hamernik, 1995), and considering that these audiograms were not the first audiograms recorded for most subjects (but only the first in the period between 2001 and 2009), and that most of them had already been exposed to noise for a few years; it is possible that even after adjustment for age (years of noise exposure), the high frequencies (≥ 4 kHz) were mildly affected.

The largest drop in hearing threshold means (especially in the last audiograms) was between 2 and 3 kHz, 3 and 4 kHz and 4 and 6 kHz and is typical of hearing losses due to excessive occupational noise exposure (American College of Occupational and Environmental Medicine [ACOEM] Evidence-based statement, 2003). As mentioned above, the high frequency parts of the cochlea are most vulnerable to noise damage due to aspects such as the acoustic resonant properties of the auditory external meatus and the tonotopical arrangement of the hair cells in the cochlea. The high frequency hair cells at the basal side of the cochlea are at the maximum point of basilar displacement during acoustic overstimulation, leading to maximum shearing of hair cells, broken tip links, calcium overload in the mitochondria, increased free radical production and eventually cell death (Sha, 2005; Henderson & Hamernik, 1995). The reason for 6 kHz being the most elevated hearing threshold in both audiograms, and not 4 kHz as the perception is when NIHL is involved (Dobie, 2008; Sliwinska-Kowalska et al., 2006) might be due to the type of noise gold miners are exposed to, creating a band-pass at a slightly higher frequency. This phenomenon has been reported previously by other researchers such as Soer et al. (2002) in their study to describe the characteristics of noise induced hearing loss in gold miners, as well as in the ACOEM Evidence-based statement (2003). It consequently appears that noise

exposure as well as time/length of exposure and age contributes to deterioration in the hearing status of these miners.

The hearing thresholds of the left ears in both the first audiograms and last audiograms were in addition slightly more affected than the hearing thresholds of the right ears. This phenomenon (that the left ear is somehow more vulnerable and develops more hearing loss than the right ear), has also been reported by other researchers such as Nageris et al. (2007) and Sliwinska-Kowalska et al. (2006).

Single TB group – first and last audiograms

There was a more pronounced difference between the first and last audiograms in the single TB group than there was in the control group. The low frequency thresholds (0.5 and 1 kHz) of the last audiograms were slightly more affected, and the down slope towards the high frequencies was steeper than the slope in the last audiograms of the control group. This can be attributed to factors such as noise and age (as seen in the control group), but TB and TB medication (and possible related illnesses) can be a third contributing factor. It is important to mention that even though there is limited research or case studies on the effect of TB or TB treatment on hearing to confirm findings, and although most of these studies are reporting on extrapulmonary TB cases (Balboni et al., 2008; Kuan, 2007; Vaamonde, 2004; Stach et al., 1998), it is clear that TB/TB treatment had a more pronounced effect on these subjects' hearing status than noise/age alone. Stach et al. (1998) confirms however that it remains difficult to separate the effects of the disease from the effects of the treatment, as also seen in these results.

It is therefore evident that the possible related risk profile of gold miners who are TB positive and received TB treatment and the complexity of such a profile also needs to be considered, and includes a few aspects. *Streptomycin* (used during re-treatment of TB and even sometimes as part of first line treatment) appears to generate free radicals within the inner ear, with subsequent permanent damage to sensory cells and neurons resulting in permanent hearing loss (Bardien et al., 2009; Duggal & Sarkar, 2007). Although to a lesser extent, the neurotoxic syndrome associated with *Isoniazid* (used in the treatment of TB) is a known phenomenon (Yerdelen & Tan, 2008), and the possibility of an interaction between impaired neurotransmission and the effect on the

hearing status of the gold miners cannot be ignored. It is furthermore essential to keep in mind that between 85% and 90% of the current TB cohort are infected with HIV (AngloGold Ashanti Report to Society, 2006), and the role of immune-suppression, opportunistic infections, tumours, antiretroviral and ototoxic medication (Dias, Chunderdoojh & Hurkchund, 2006; Khoza & Ross, 2002; Chandrasekhar et al., 2000) on the hearing status of the miners cannot be ignored or simplified.

The notch in the hearing thresholds at 6 kHz was slightly less in this experimental group than in the control group, with no notch (6 and 8 kHz being equally affected) in the right ears' first audiogram. It is possible that the effect of TB and TB treatment is responsible for this phenomenon. The left ears' hearing thresholds of the first audiograms were slightly more affected than the hearing thresholds of the right ears, and can once more be attributed to the left ear being more vulnerable and developing more hearing loss than the right ear (Nageris et al., 2007; Sliwinska-Kowalska et al., 2006). The left and right ears' hearing thresholds for the last audiograms in this group were however nearly the same. The reason for no particular difference between the left and right ears in the single TB groups is not clear.

Multiple TB group – first and last audiograms

The differences in hearing status between the first and last audiograms were once again more distinct in the multiple TB group than in the control group. The hearing thresholds of the first audiograms of the multiple TB group were however already more affected than the hearing thresholds of the first audiograms of especially the control group, but also of the single TB group. This can be attributed to the fact that TB and/or TB treatment could have already influenced the hearing status of these miners. A possible reason for this phenomenon not being so evident in the single TB group is that the effect of TB and/or single TB treatment on the hearing status of gold miners has more of a long term influence, than immediate visible consequences. There was no notch in the hearing thresholds in the first or last audiograms of this group visible (6 and 8 kHz being equally affected) and can possibly be attributed to the effect of ototoxic medication (Duggal & Sarkar, 2007). The hearing thresholds of the right and left ears for the first audiograms were nearly the same (left slightly worse than right), but in the last audiograms the left ears' hearing status was more affected than the right

ears' hearing status (especially between 2 and 6 kHz) (Nageris et al., 2007; Sliwinska-Kowalska et al., 2006).

Characteristically NIHL develops slowly over several years (Philp, 2007) and although the lower frequencies (0.5 and 1 kHz) in all three groups (even with the last audiograms) were less affected, and the downwards progress from 1 kHz in all three groups was slightly steeper than with the first audiograms recorded, it was apparent that the deterioration in the two experimental groups (from the first to the last audiograms) was larger than in the control group. Results therefore indicate that the effect of TB status and TB treatment (possibly in combination with continued noise exposure and/or a related risk profile), had a more pronounced effect on the hearing status of gold miners than noise exposure alone. This is also illustrated by the smaller differences between the two experimental groups, than between the control and experimental groups.

With the above results in mind, previous studies confirmed that when the intrinsic free radical buffering system is altered or inefficient (e.g. by TB/TB medication), then the cochlea can become much more vulnerable to noise (Pouyatos et al., 2007; Duggal and Sarkar, 2007; Sha, 2005) as its anti-buffering system is compromised. Sha, Taylor, Forge and Schacht (2001) reported in a study with guinea pigs that the outer hair cells of the cochlea differed in their vulnerability towards free radicals, with the basal hair cells (high frequencies) being more vulnerable than the hair cells in the apex (low frequencies). As the cochlea is exposed to higher levels of free radicals it can also become more susceptible to the development of age-related hearing loss, as the effect of oxidative stress are damaging to most cells with specific deletions within the mitochondrial DNA, and cells become bioenergetically deficient (Durackova, 2010; Miura & Endo, 2010; Seidman et al., 2000). Furthermore Balboni et al. (2008) argued that TB might alter the homeostatic mechanisms of the ear in a way comparable to that seen in age-related hearing loss. This causes the aural symptoms such as hearing loss, tinnitus and vestibular fall-outs.

6.2.2 Mean hearing thresholds across frequency categories

The reason for analyzing the lower and higher frequency averages separately was to investigate whether ototoxic medication as well as noise and age had a greater influence on the higher frequencies (this phenomenon is also reported by Bardien et al., 2009; Duggal & Sarkar, 2007; Ologe et al., 2006; Sliwinska-Kowalska et al., 2006; Sha et al., 2001). A highly significant difference ($p < 0.01$) was found in the group means of the three groups in all frequency categories, indicating that the differences observed and discussed in the previous section between the three groups were statistically significant. The largest differences in hearing threshold means existed between the control and two experimental groups and the smallest between the two experimental groups. Even tough the differences that existed in the high frequency categories (3 + 4 + 6 kHz) between the three groups were larger than the differences in the low frequency categories (0.5 + 1 + 2 kHz), the possible influence of TB/TB treatment and the related risk profile of these patients could be observed over the whole frequency range. This indicates that the influence of ototoxic medication, age (which was controlled for) or noise can not alone be responsible for the observed deterioration in hearing thresholds between the three groups, but probably the combined influence of these factors together with TB/TB treatment. Possible explanations for this phenomenon is that the intrinsic free radical buffering system of the TB positive subjects had been altered or was inefficient, or that the homeostatic mechanisms of their ears had been altered, causing their cochleas to become much more vulnerable to the effects of noise and age (Balboni et al., 2008; Pouyatos et al., 2007; Duggal and Sarkar, 2007; Sha, 2005). Careful consideration of a statement like this is however necessary, as noise exposure (as seen in the discussion of the second sub-aim), is in reality not a contributing factor to the deterioration of hearing thresholds in the two experimental groups. A compromised immune system and therefore a compromised free radical buffering system could nevertheless leave the cochlea more vulnerable to develop hearing loss.

The only non-significant difference between two groups was found between the single TB treatment and multiple TB treatment groups for the right ears' average high frequency category. This can possibly be explained by the fact that differences between the two experimental groups were in any case small. It has been reported in the literature that the right ear is less vulnerable to develop hearing loss than the left

ear (Sliwinska-Kowalska et al., 2006). The fact that the difference between the two experimental groups was smaller than between the control and two TB groups, might be due to the influence of TB (in combination with continued noise exposure and the related risk profile associated with TB) being more pronounced, than the influence of TB treatment (more specifically - *Streptomycin*) on its own.

6.2.3 Change in mean hearing thresholds across frequency categories over time

The difference in group means (between the first and last audiogram) in all frequency categories was statistically significant ($p < 0.01$) with the smallest shift in hearing threshold values between the first and last audiogram in the control group. The shifts in hearing threshold values were smaller in the low frequency groups (although still significant). This could possibly be explained by the fact that the ANCOVA test indicated (with p values of 0.8 and 0.6), that there was no significance in adjusting for the 'time of exposure between the two audiograms' in the low frequency categories (although adjusting for the 'age at test' and the 'hearing threshold at the first audiogram', were significant). In other words, apart from ongoing noise exposure and age, no other specific factor (that was controlled for) contributed to a shift in the low frequencies of the control group. The slightly larger shift in the low frequency hearing threshold values (from the first to the last audiogram recorded) for the two experimental groups could be due to the influence of TB/TB treatment (in combination with ongoing noise exposure and the related risk profile of this group).

On the other hand, the changes in the hearing threshold values in the high frequency categories between the first and last audiogram, were more pronounced in all the groups - even in the control group. The ANCOVA indicated that adjusting for 'age at test', 'hearing thresholds at the first audiogram' as well as 'time of exposure between the two audiograms' in the high frequency categories was significant, probably due to the fact that high frequency outer hair cells in the cochlea are more vulnerable to the effect of age which is linked to the time of exposure (Nanda & Tripathy, 2007; Morata, 2007). The largest shift in hearing threshold values (from the first to the last audiogram) existed between the control and two experimental groups. Results indicated therefore that TB/TB treatment (possibly combined with ongoing noise exposure and this group's related risk profile), contributed more to the deterioration of high frequency hearing thresholds than ongoing noise exposure alone. The smallest shift in the hearing

threshold values (from the first to the last audiogram) was between the two experimental groups. Therefore a small but significant probability exists that the effect of TB on the hearing status of gold miners is more pronounced than the effect of TB treatment.

It is important however, to realize that there were other confounding factors that were not controlled for in this study, but could have had an effect on aggravating the already existing (noise-induced) hearing loss of the subjects such as: noise exposure beyond the workplace, co-exposure to noise and vibration (e.g. drillers), smoking, alcohol consumption, elevated blood pressure levels, elevated cholesterol levels, cardiovascular events, diabetes mellitus and infection or illness (e.g. HIV) (Fransen et al., 2008; Carlson, 2007; Sliwinska-Kowalska et al., 2006). As discussed previously, the role of immune-suppression, opportunistic infections, tumours, antiretroviral medication and ototoxic medications associated with HIV/AIDS (Dias, Chunderdoojh & Hurkchund, 2006; Khoza & Ross, 2002; Chandrasekhar et al., 2000) on the hearing status of the miners cannot be ignored.

6.2.4 High frequency hearing thresholds (6 and 8 kHz) for the last audiograms

There was a significant difference ($p < 0.001$) between the group means of the hearing threshold values of 6 and 8 kHz (left and right ears respectively), indicating that TB/TB treatment (possibly in association with ongoing noise exposure and this group's related risk profile) contributes to the deterioration of hearing thresholds in the higher frequencies. The distinctive 'notch' (usually seen at 4 kHz and characteristic of NIHL as described by *inter alia* Dobie (2005) and McBride & Williams (2001), has been recorded in this study at 6 kHz and might be due to the type of noise these subjects have been exposed to, or to the combined effect of TB and ongoing noise exposure. This notch in hearing thresholds occurred only in the control and single TB group, but was not present in the multiple TB group. The reason for this might be the influence of ototoxic medication on the higher frequencies (8 kHz) of the cochlea (Sarkar, 2007; Nanda & Tripathey, 2007; Sha, 2005).

The differences between the control and both experimental groups were larger than the difference between the two TB groups, and can be explained by the effect of the TB on the hearing status of gold miners being more pronounced than the effect of treatment

or *Streptomycin*. The reason for the insignificant difference between the hearing threshold values at 6 kHz in the right ear of the single TB treatment and multiple TB treatment groups might be that the differences between the two experimental groups were already smaller than between the control and experimental groups, and with the right ear being less susceptible to developing hearing loss (Nageris et al., 2007; Sliwinska-Kowalska et al., 2006) there existed no significant difference. It may also be attributed to the fact that the deterioration of the 6 kHz hearing threshold value in the single TB treatment group was already larger than the 6 kHz hearing threshold value in the left ear, so the difference between the single TB and multiple TB treatment groups was not significant. In addition left ears may be more susceptible to the influence of TB treatment (ototoxic medication) than right ears, as seen in the multiple TB group.

6.2.5 Percentage loss of hearing (PLH) for the last audiograms

The difference in group means for PLH between the three groups was highly significant ($p < 0.01$) indicating that even without taking the contribution of the high frequencies (6 and 8 kHz) to the hearing status of the subjects into consideration, there still exists a difference in the hearing threshold averages of the groups. This phenomenon can once more be due to TB/TB treatment (in combination with ongoing noise exposure and this group's related risk profile) - causing the immune system of the body to be compromised. This has an influence on the cochlea's anti-buffering system, causing it to become more susceptible to many types of damage and the possible deterioration of hearing thresholds. Once more the difference between the control group and two experimental groups was larger than between the two experimental groups. This may again be an indication that the effect of TB is more pronounced than the effect of TB re-treatment (*Streptomycin*) on the hearing thresholds of gold miners.

It is however also apparent that there exist even larger differences between the average hearing threshold means of the groups when 6 kHz was included (e.g. 3 + 4 + 6 kHz), indicating that it might be necessary to rethink the current classification or weighing systems that is used to calculate a potential hearing loss. PLH (where the weighing is highest for hearing loss at 1 kHz and lowest for hearing loss at 4 kHz) might fail to indicate a high frequency hearing loss, as a lot of consonants and other important sounds (e.g. alarms) are located in this area and contribute to speech

discrimination and overall safety and awareness (ACOEM Evidence-based statement, 2003). It is therefore important to be aware of this phenomenon.

6.3 Sub-aim # 2: Hearing threshold parameters across groups, considering noise exposure as co-variable

6.3.1 Mean hearing thresholds across frequency with noise exposure as co-variable

There were no significant differences in hearing threshold means between any of the 'noise exposure' and 'no noise exposure' groups within each of the frequency categories (although there was not controlled for non-occupational noise exposure). The hearing threshold averages of the 'noise exposure' group within the control group were higher than the hearing threshold averages of the 'no noise exposure' group. A possible explanation for this phenomenon is that the effect of noise exposure (and age) on the hearing status of the subjects is evident, without the influence of e.g. TB or TB treatment. The hearing threshold averages for the 'no noise exposure' groups in the two experimental groups were however higher than the hearing threshold averages for the 'noise exposure' groups. This might be due to the fact that the categorization of noise and no noise exposure subjects as used was insufficient to identify the impact of confounding factors. It is furthermore possible that TB/TB treatment (and the related risk profile of this group) has a larger influence on the subjects' hearing status than noise or no noise exposure. The fact that there are significant differences between the hearing threshold means of the three groups (control, single TB treatment and multiple TB treatment) when noise exposure was not considered, serve as a strong confirmation of this supposition. In an attempt to narrow the analysis down and to corroborate the above observation an alternative indicator of noise exposure was also analysed and compared within the three groups i.e. drillers (high levels of noise exposure) vs. admin workers (at present almost no noise exposure at work).

6.3.2 Mean hearing thresholds across frequency categories for two employment groups

There were no significant differences in hearing threshold averages between any of the drillers and admin staff groups within each of the frequency categories. Although the number of subjects in the groups was less, the differences in hearing threshold

averages between the driller vs. admin groups were larger with the thresholds for the driller group more affected than those of the admin group. These differences were not present in the 'noise exposure' vs. 'no noise exposure' groups. This is an indication that with a more discriminatory indication of noise exposure, deterioration of hearing threshold with exposure might be more evident. It is also essential to remember that there was no indication given in this study of the number of years (if any) that the admin staff were exposed to noise before they started work in the admin section. There were however still significant differences between the hearing threshold averages of the three groups (control, single TB treatment and multiple TB treatment) within the frequency categories when occupation (driller vs. admin staff) was not considered, again indicating that the role of TB/TB treatment is significant.

6.3.3 Change in mean hearing thresholds across all frequencies in the noise exposed and unexposed groups

There was no significant difference between the shift in hearing threshold values (from the first to the last audiogram) involving the 'noise exposure' vs. 'no noise exposure' groups in any of the frequencies (0.5 to 8 kHz). In the control group there were nearly always larger differences between hearing threshold means in the 'noise exposure' group than in the 'no noise exposure' group, indicating that noise exposure has an influence on the whole frequency spectrum of hearing thresholds. In the two experimental groups however, there was no constant pattern in the differences involving the 'noise exposure' and 'no noise exposure' groups, indicating that the influence of TB/TB treatment (and this group's related risk profile), is more pronounced than that of noise exposure alone (it must again be considered that the categorization of the noise exposure groups it this way might not allow sufficient discrimination). The shifts in hearing threshold means (between the first and last audiogram) were always larger in the two experimental groups than in the control group – even in the lower frequencies. In some of the frequencies the differences in hearing threshold means from the first to the last audiogram were larger in the 'no noise exposure' groups than in the 'noise exposure' group and vice versa. This indicates that the effect of TB/TB treatment on the deterioration of hearing thresholds is definite, even when no or little noise exposure is involved.

The largest differences between the thresholds of the first and last audiogram consistently occurred in die multiple TB groups, and most frequently in the left ear. The influence of TB/TB treatment and especially its influence over time is confirmed by this phenomenon. Once more the left ear's higher vulnerability to develop hearing loss is evident. In two cases however (multiple TB treatment 6 & 8 kHz), the largest shifts in hearing thresholds were in the right ear. The reason for the hearing threshold shifts in the right ears' noise category at 3, 4 and 6 kHz in the single TB treatment group being larger than in the multiple TB treatment group, is an indication that TB alone has an influence on hearing thresholds of gold miners. In most frequencies in the single TB treatment group, the differences between hearing thresholds in the noise vs. no noise categories were nearly the same, confirming that noise exposure was not the leading contributor to hearing loss. The fact that the shift in hearing thresholds for the 'noise exposure' group was slightly larger than the shift in hearing thresholds for the 'no noise exposure group' in the multiple TB group, is a possible indication that noise exposure and some types of ototoxic medication (*Streptomycin*) might have interacted synergistically (Campo et al., 2009; Mills and Going, 1982) in order to aggravate the effect of the treatment on the hearing status of the gold miners. Aminoglycoside ototoxicity can also progress after discontinuation of the drug (Duggal & Sarkar, 2007). Here the combined effect of TB/TB re-treatment (its related risk profile), ongoing noise exposure and possibly age, is visible again.

6.4 Conclusion

From the results it can be concluded that significant differences exist between the hearing status of gold miners in the control group (not infected with TB) and the hearing status of gold miners in the two experimental groups (single TB treatment and multiple TB treatment). Using different hearing threshold parameters to observe and analyse the hearing status of the three groups, most hearing threshold parameters differed significantly between the groups. The largest differences were observed between the control and multiple TB treatment group, and the smallest differences between the two TB groups. When compared over time, the differences between the groups became even larger, and the deterioration in the high frequency hearing thresholds became more pronounced. Although highly significant differences were present between the three groups at all frequency categories (left average low, right average low, left average high and right average high), the largest differences existed

in the high frequency categories. There were also significant differences observed between the three groups when the high frequency (6 and 8 kHz) parameter and PLH were analysed. It seemed as if the hearing threshold values for the left ears were slightly more affected than for the right ears. No significant differences exist however between the three groups when they were assessed according to noise exposure using two different indicators of noise exposure (‘noise exposure’ vs. ‘no noise exposure’ and drillers vs. admin staff). It appears that TB (and its associated risk profile) has a larger influence in the deterioration of the gold miners’ hearing status, than noise exposure alone.

Chapter 7

Conclusions and recommendations

7.1 Introduction

The main aim of this study was to investigate the hearing status of gold miners with and without tuberculosis. This was done by comparing various hearing threshold parameters of three groups (a control and two experimental groups) with each other. The control group was the TB negative group, while the two experimental groups consisted of a single TB treatment group and a multiple TB treatment group. Adjustments were made for the covariates age, exposure time and hearing thresholds at the first recorded audiogram. The co-variable of noise exposure was also considered in the second sub-aim. The significance of the difference in the various hearing threshold parameters between the three groups served as an indication of the relationship that exists between deterioration in hearing thresholds and the presence of tuberculosis or tuberculosis treatment. The fact that the 95%CI levels were successively higher for each of the three groups (control, single TB treatment and multiple TB treatment) is an indication that above pattern can in all possibility be inferred from the sample to the general population of gold miners.

The aim of this chapter is to draw conclusions from the reported results and to critically review the research process. Implications of the research are presented along with recommendations for further research.

7.2 Conclusions

The research process described in this report was successful in attaining the main aim set for this study, namely to compare the hearing status of gold miners with and without TB. The differences between the hearing threshold values of the three groups were in most instances statistically significant – indicating that TB and TB treatment groups demonstrated greater deterioration in hearing status. The differences between the various noise exposure groups were however not significant, also demonstrating that presenting with TB contributed more to the decline in the hearing thresholds of miners, than noise exposure alone. The following conclusions were drawn from the study findings:

- The largest differences in hearing thresholds throughout this study were between the control group and the multiple TB group while the smallest differences in hearing thresholds were between the two TB groups. This is an indication that the presence of TB (most likely in connection with its related risk profile, ongoing noise exposure and age) had a pronounced influence on the decline of miners' hearing thresholds. The fact that the hearing thresholds of the multiple TB treatment group were more deteriorated than the hearing thresholds of the single TB treatment group, also points to the influence of repeated TB on the subjects' hearing thresholds over time being more pronounced than a single incidence of TB.

- The differences between the three groups were larger in the high frequencies than in the low frequencies, although the differences in the low frequencies were still significant. This phenomenon of high frequency hearing damage preceding low frequency hearing damage is commonly reported in literature and is attributed to high frequency hair cells in the cochlea being more vulnerable to damage (Sha, 2005; Sha, et al., 2001; Henderson & Hamernik, 1995). This includes damage by noise exposure, acoustic trauma, age, ototoxic substances and free radicals (Duggal & Sarkar, 2007; Henderson et al., 2006; Sliwinska-Kowalska et al., 2006; Sha, 2005; Kopke et al., 2002). The fact that the differences between the low frequencies among the three groups, although smaller were also significant, indicate that the effect associated with TB status was evident across the whole frequency range.

- Throughout this study the hearing thresholds of the left ears were predominantly poorer than the hearing thresholds of the right ears. This phenomenon was visible in all three groups and is also reported in literature, indicating that the left ear is somehow more vulnerable to develop hearing loss than the right ear (Sliwinska-Kowalska et al., 2006, Nageris et al., 2007).

- A deterioration of hearing thresholds over time in all three groups was evident indicating that continued noise exposure and age may also contribute to a decline in the hearing status of these gold miners. This phenomenon is also reported in literature (Duggal & Sarkar, 2007; Ologe et al., 2006; Sliwinska-Kowalska et al., 2006) and served as motivation to adjust for age, time of noise exposure and the hearing threshold at the first audiogram. The differences that existed in hearing

threshold shifts (from the first to the last audiogram) between the groups were once more larger between the control and two experimental groups, than between the two experimental groups. This pointed to the fact that TB (and its related risk profile) had a more pronounced influence on the decline in the miners' hearing status than noise exposure, age or ototoxicity by TB medication alone.

- The co-variable of noise exposure was considered in this study since the effect of of noise and acoustic over-stimulation on the cochlea is well documented (Guild et al., 2001; Henderson & Hamernik, 1995). Two indicators of noise exposure were considered namely 1) 'noise exposure' vs. 'no noise exposure' and 2) drillers vs. admin staff. No significant differences between any of the three groups in these two categories were found, indicating that noise was not the single most important contributor to the deterioration of the hearing thresholds of miners. TB's influence (in association with ongoing noise exposure, age and TB's related risk profile) appear to have been more prominent in contributing to a decline in the subject's hearing status. This phenomenon can partially be explained by the suppression of the TB positive subjects' immune system (due to TB or other illnesses), which could have lead to a compromised intrinsic free radical buffering system, leaving the subjects more vulnerable to noise damage, the effects of age, the effect of free radicals and oxidative stress (Pouyatos et al., 2007; Seidmann et al., 2000). Balboni et al. (2008) argued that TB can alter the homeostatic mechanisms of the ear in a way comparable to that seen in age-related hearing loss. This could have contributed to a decline in the subjects' hearing thresholds. The effect of effective hearing protection should however also be considered as a possible explanation for finding no significance between the different noise exposure groups, as information on the type of hearing protection (if any) that the subjects made use of was not available.

- It is clear from the results that the two experimental groups delineated by TB demonstrated a greater deterioration in their hearing thresholds than the control group. It is however not a simple matter of attributing the decline in the subjects' hearing thresholds to TB alone, since TB is often associated with a compromised immune system. Although the effect of HIV/AIDS and ARVs were not accounted for in this study as information on subjects' HIV status was unavailable, it is assumed that 85 to 90 % of the current TB cohort was infected with HIV (WHO 2009;

AngloGold Ashanti Report to Society, 2006). The role of immune-suppression, opportunistic infections, the neurotropic nature of HIV, tumours, antiretroviral medication, ototoxic medications etc. on the hearing status of the miners can therefore not be ignored (WHO, 2009; Bektas et al., 2008; Dias, Chunderdoojh & Hurkchund, 2006; Khoza & Ross, 2002, Chandrasekhar et al., 2000). In a study by Toppila, Pyykkö & Starck (2001) it was found that as the number of confounders increased, the noise exposure was overruled by these factors in the development of hearing loss. It seems appropriate to conclude that noise exposure in this study was also overruled by the confounding factors.

7.3 Implications

From the above conclusions it is clear that TB and the associated risk profile accompanying this diagnosis, contributes more to a decline in the subjects' hearing status than age, noise exposure, TB treatment or ototoxicity alone. This is important in our understanding of the hearing status of gold miners who are infected with TB. The following implications should be considered:

- ***TB's influence on hearing***

Knowing that TB (in the presence of ongoing noise exposure and the related risk profile) has a deteriorating influence on gold miners' hearing status, it may be sensible to temporary remove these gold miners from their work places with high noise levels until their treatment has been completed. The reason for this is that TB infection can compromise the immune system as well as alter the free radical buffering system, leaving the miners more susceptible to develop hearing loss (Pouyatos et al., 2007) even age-related hearing loss (Seidmann et al., 2000). This phenomenon is also to be found when ototoxic substances are used in combination with continued noise exposure (Campo et al., 2009). Although the medication used in the first line of TB treatment has no known ototoxic side effects, research reported single case studies where TB or TB treatment had a deteriorating effect on hearing (Balboni et al., 2008; Vaamonde et al., 2004; Stach et al., 1998). Stach et al. (1998) confirmed this by mentioning that it is difficult to separate the effects of the disease from the effects of the treatment. When *Streptomycin* is used it can persist in the inner ear for as long as six months after administration (Bardien et al., 2009) and do further damage.

Another fact to keep in mind is that the risk of deterioration in hearing thresholds is linked to older age and cumulative dosages of ototoxic medication (Peloquin et al., 2004). The risk to develop TB is also directly linked to increased age in gold miners (Guild et al., 2001) possibly due to more silica exposure. Older gold miners' (infected with TB) hearing status may therefore need to be monitored more frequently.

The role of anti-oxidants in protecting the inner ear against the effects of free radicals due to excessive noise exposure, age, an inefficient immune- and free radical buffering system and ototoxic substances is also important for future investigations. Studies clearly indicated that the inner ear can be protected against the destructive effect of oxidative stress (Henderson et al., 2006; Kopke et al., 2002; Ohinata, Yamasoba, Schacht & Miller, 2000). The efficiency of gold miners' hearing protection (especially TB positive gold miners) should also be carefully considered as they are more susceptible to developing a hearing loss.

- ***HIV/AIDS influence on hearing***

A high percentage of the current TB cohort are also infected with HIV (AngloGold Ashanti Report to Society, 2006), and as HIV/AIDS as well as ARVs has a known influence on hearing, the effect of HIV/AIDS on the hearing of gold miners should also be considered Bektas et al., 2008; Dias et al., 2006). In case studies mentioned by Bektas et al. (2008) it was indicated that older HIV patients who received ARVs were more vulnerable to develop a hearing loss. Simdon et al. (2001) also described three case studies of possible nucleoside analog reverse transcriptase inhibitors (NRTI) associated ototoxicity in HIV-infected patients, all of whom were older than 45 years of age and had a history of noise-induced hearing loss. In a study with inbred mice Bektas et al. (2008) indicated permanent deterioration in the hearing status of the mice who received NRTI treatment while exposed to high levels of noise. Therefore, since there exists a synergistic interaction between noise and ARV (NRTI) treatment, it is important that the hearing status of miners who are HIV positive and who receive ARV treatment should be monitored with more regularity.

- ***Other confounding factors influence on hearing***

In a similar way the possible effect of other factors that can contribute to a decline in hearing thresholds or even cause the miners to become more susceptible to

developing a hearing loss such as noise exposure beyond the workplace, co-exposure to noise and vibration (e.g. drillers), smoking, alcohol consumption, elevated blood pressure levels, elevated cholesterol levels, cardiovascular events and diabetes mellitus (Fransen et al., 2008; Carlson, 2007; Sliwinska-Kowalska et al., 2006) should be considered and handled with circumspection.

7.4 Critical evaluation of this study

A critical evaluation of the research process is necessary, in order to interpret the findings within the context of its strengths and limitations. The perceived strengths and limitations of the current study are provided below.

Strengths

Strengths of the current study include the following in terms of data collection methods, data collection material and participants:

- The fact that this study utilized a large sample (n = 2698), assists in providing better estimates of the population's parameters. As mentioned previously, the law of large numbers states that larger samples provide better estimates of a population's parameters than smaller samples (Lohmeier, 2010). Therefore, as the sample sizes increases the variability in sample statistics decreases and there will better estimates of the true population parameters.
- A retrospective cohort design was used where data collected in the past (hearing thresholds) was used to determine the relationship between a set of potential risk factors and an outcome that is measured (DeForge, 2010). An advantage of a retrospective cohort study is that it can be completed faster and more economically because it is based on already existing data (Maxwell & Satake, 2006). The data for this study were collected over years by the occupational health department at the West Wits operation of the AngloGold Ashanti Gold Mine in the Witwatersrand and made available to be used in this study
- The fact that the miners' hearing status was observed and analysed over time, provided the researcher with the opportunity to study the hearing threshold changes (from the first to the last audiogram), allowing to draw more precise conclusions regarding the relationship between TB/TR treatment and hearing loss longitudinally.

- Using a control group (TB negative subjects) vs. two experimental groups (TB positive subjects) gave the researcher the opportunity to clearly analyse the effective of TB (and its associated risk profile) on the subjects' hearing status.
- The fact that there are very little research available on the effect of TB and TB treatment on individuals' hearing status (especially reporting the results of such a large sample), is a definite strength of the current study.

Limitations

Limitations of the current study include the following:

- Limitations in the methodology of the study due to the fact that there were large differences in the hearing threshold values of the subjects (from very high values to very low values), where the effect might have been cancelled out by making use of the median. This also explains the larger values of the standard deviations.
- Although the current occupation of the miners was known to the researcher, a work history specifying the period of time spent in a specific occupation as well as the exact level of noise exposure in that occupation was not available. Also more specific information regarding the type of hearing protection that the miners used was unavailable. This information could have assisted in improved categorization of the miners into noise exposure groups according to their current noise exposure levels as well as previous noise exposure. Results where noise exposure was considered as a co-variable might have been influenced by such improved categorization.
- Even though literature indicates that 85% to 90% of the current TB cohort are also infected with HIV (AngloGold Ashanti Report to Society, 2006), and HIV/AIDS as well as ARVs has a known influence on hearing (Bektas et al., 2008; Dias, Chunderdoojh & Hurkchund, 2006; Khoza & Ross, 2002; Chandrasekhar et al., 2000), the HIV status of the miners in this study was unknown. This is important to consider when reporting these results, as it is difficult to separate the influence of HIV/AIDS and ARV treatment from TB and its associated risk profile's influence on the subjects' hearing status.
- Other confounding contributors to a decline in hearing thresholds e.g. non working related noise-exposure, lifestyle considerations (e.g. smoking and alcohol consumption), prolonged exposure to part- or whole-body acoustic vibration, genetic

factors, different individual levels of susceptibility, elevated blood pressure, elevated cholesterol levels, cardiovascular events, diabetes mellitus and too high/too low body mass index was not recorded in this study and could have had a influence on the results (Fransen et al., 2008; Kurmis & Apps, 2007; Konings et al., 2007; Ologe et al., 2006; Sliwinska-Kowalska et al., 2006; Henderson & Hamernik, 1995).

- Although the frequency of TB seems to differ according to race (based on 2007 CDC data), its influence were not considered in the current study.
- It would have been possible to form a more precise conclusion regarding the influence of TB/TB treatment on the progress of miners' hearing status, if their hearing thresholds were observed, analysed and compared for every single year in the period between the year 2001 to 2009.
- Gold miners (due to particular noise exposure and high levels of silica exposure) are a very specific population, and the results can therefore not necessarily be generalised to all other populations.

7.5 Recommendations for further research

This study provided insight into the effect of TB and TB treatment on the hearing status of gold miners. Using different hearing threshold parameters allowed the researcher to investigate the influence of TB/TB treatment on all frequencies of the audiogram. However, additional research could prove valuable in understanding the phenomenon better, especially considering the influence of HIV/AIDS, ARVs, other health conditions as well as noise exposure. The following recommendations for future research are made:

- Investigate and consider the subjects' work history as well as noise exposure levels and use this information for the categorization of noise exposure groups and correction for number of work years.
- Monitor the shift in hearing thresholds annually over a number of years in order to follow the effect of TB and TB treatment on the hearing statuses of gold miners as a function of time.
- Divide the experimental groups (TB positive) in a HIV positive and HIV negative group. This will allow researchers to distinguish the effect of TB from the effect of HIV/AIDS on miners' hearing statuses.

- Divide the HIV/AIDS sub-group into a group that is receiving ARV treatment and a group not receiving ARV treatment. This will help the researcher to reach more definite conclusions regarding the effect of HIV/AIDS, ARV treatment and TB/TB treatment on the hearing statuses of gold miners.
- Launch a study to investigate the effect of other possible confounding factors e.g. elevated blood pressure, diabetes mellitus and high cholesterol levels on the hearing status of noise exposed individuals.
- Launch the same type of study using a different population e.g. another type of mining population or in a population that is not necessarily exposed to high levels of noise. This will allow for better understanding of the effect of TB on individuals' hearing status as well as allowing for generalisation to other populations.

7.6 Final conclusion

The research project described in this study has been successful in answering the research questions posed in the first three chapters. Previous research has been extensively explored, and shortcomings were identified in order to provide a framework that served to guide the rationale of this study. The experiment provided new information regarding the effect of TB and TB treatment on the hearing status of gold miners, and paved the way for future research in this direction. Results also offered motivation for the careful monitoring of gold miners hearing thresholds once they become infected with TB, and to consider their working conditions and noise exposure levels.

References

ACOEM Noise and Hearing Conservation Committee. (2003). Noise-induced hearing loss. *Journal of Occupational & Environmental Medicine, 45*(6), 579-581.

Amedofu, G. K. (2002). Hearing-impairment among workers in a surface gold mining company in Ghana. *African Journal of Health Sciences, 9*(1-2), 91-97.

Anderson, C. W., & Stevens, M. H. (1981). Synchronous tuberculous involvement of both ears and the larynx in a patient with active pulmonary disease. *Laryngoscope, 91*(6), 906-909.

AngloGold Ashanti. (2006, 2007, 2008). *Annual report, report to society 2006, 2007, 2008.* Retrieved March http://www.anglogold.com/subwebs/InformationForInvestors/Reports06/ReportToSociety06/default.htm

Balboni, A. L., Bergemann, A. D., Reidenberg, J. S., & Laitman, J. T. (2008). Tuberculosis induced changes to the osseous cranial base and its potential effect on hearing. *Anatomical Record, 291*(5), 488-490.

Bardien, S., de Jong, G., Schaaf, H. S., Harris, T., Fagan, J., & Peterson, L. (2009). Aminoglycoside-induced hearing loss: South Africans at risk. *SAMJ, 99*(6).

Bastian, I., Stapeldon, R., & Colebunders, R. (2003). Current thinking on the management of Tuberculosis. *Current Opinion in Pulmonary Medicine, 9*, 186-192.

Begley, A. (2006). *Development of an internet-based mining industry database for audiograms* SIMRAC (Safety in Mines Research Advisory Committee) report nr. SIM 03-09-02.

Bektas, D., Martin, G. K., Stagner, B. B., & Lonsbury-Martin, B. L. (2008). Noise-induced hearing loss in mice treated with antiretroviral drugs. *Hearing Research, 239*(1-2), 69-78.

Bindu, L. H., & Reddy, P. P. (2008). Genetics of Aminoglycocide-induced and prelingual non-syndromic mitochondrial hearing impairment: A review. *International Journal of Audiology, 47*, 702-707.

Bock, N., & Reichman, L. B. (June 2004). Tuberculosis and HIV/AIDS: Epidemiological and clinical aspects (world perspective). *Seminars in Respiratory and Critical Care Medicine. Tuberculosis and Other Mycobacterial Infections, 25*(3), 337-344.

Bovo, R., Ciorba, A., & Martini, A. (2007). Genetic factors in noise-induced hearing loss. *Audiological Medicine, 5*(1), 25-32.

Breen, R. A. M., Smith, C. J., Bettinson, H., Bannister, B., Johnson, M. A., & Lipman, M. C. (2004). Paradoxical reactions during Tuberculosis treatment in patients with and without HIV co-infection. *Thorax, 59*(8), 704-707.

Brennan-Benson, P., Lyus, R., Harrison, T., Pakiananthan, M., & Macallan, D. (2005). Pharmacokinetic interaction between Efavirenz and Rifampicin in the treatment of HIV and Tuberculosis: One size does not fit all. *AIDS (Research Letters), 19*, 1541-1546.

Bretlau, P., Zou, J., Pyykko, I., Toppila, E. O., N.P., Stephanson, N., Beck, O., et al. (2004). Vibration-induced hearing loss: Comparison of the protective efficacy of antioxidants and neurotrophins. *Audiological Medicine, 3*, 169-173.

Burgess, M., & Williams, W. (2006). Non-noise contributors to occupational hearing loss. *Acoustics Australia, 34*(3), 109-116.

Caminero, J. A. (2005). Management of multidrug-resistant Tuberculosis and patients in retreatment. *Eur Respir J,* 25, 928-936.

Campbell, B. H., Chatton, T. B., Chusid, M. J., & Yale, R. S. (1985). Tuberculous otomatoiditis. *Wisconsin Medical Journal, 84*(10), 22-24.

Campo, P., Maguin, K., Gabriel, S., Möller, A., Nies, E., Gómez, M. D. S., & Toppila, E. (2009). Combined exposure to noise and ototoxic substances. *European Agency for Safety and Health at Work*.

Carlsson, P., Fransen, E., Stenberg, E., & Bondeson, M. (2007). The influence of genetic factors, smoking and cardiovascular diseases on human noise susceptibility. *Audiological Medicine, 5*(2), 82-91.

Carlsson, P., Laer, L. V., Borg, E., Bondeson, M., Thys, M., Fransen, E., et al. (2005). The influence of genetic variation in oxidative stress genes on human noise susceptibility. *Hearing Research, 202*(1), 87-96.

Centre for Disease Control and Prevention [CDC]. (2008). Tuberculosis. Retrieved April, 2008, from www.cdc.gov/tb/

Chamber of Mines of South Africa. *Facts and figures, 2009.* Retrieved November, 2010, from www.bullion.org.za/Publications/Facts&Figures

Chandrasekhar, S. S., Connelly, P. E., Brahmbhatt, S. S., Shah, C. S., Kloser, P. C., & Baredes, S. (2000). Otologic and audiologic evaluation of human immunodeficiency virus-infected patients. *American Journal of Otolaryngology - Head and Neck Medicine and Surgery, 21*(1), 1-9.

ChemIDplus lite (2008). United States, National Library of Medicine, National Institutes of Health. Retrieved April, 2008, from http://0-chem.sis.nlm.nih.gov.innopac.up.ac.za/chemidplus/chemidlite.jsp

Cho, Y., Lee, H., Kim, S., Chung, K., Lee, D., Koh, W., et al. (2006). Tuberculous Otitis Media: A clinical and radiologic analysis of 52 patients. *The Laryngoscope, 116*(6), 921-927.

Corbett, E. L., Churchyard, G. J., Clayton, T., Herselman, P., Williams, B., Hayes, R., et al. (1999). Risk factors for pulmonary mycrobacterial disease in South African gold miners. *American Journal of Respiratory and Critical Care Medicine, 159*(1), 94-99.

Corbett, E. L., Watt, C. J., Walker, N., Maher, D., Williams, B. G., Raviglione, M. C., et al. (2003). The growing burden of Tuberculosis. *Archives of Neurology, 163*(9), 1009-1021.

Corbett, E. L., Charalambous, S., Fielding, K., Clayton, T., Hayes, R. J., De Cock, K. M., et al. (2003). Stable incidence rates of Tuberculosis (TB) among human immunodeficiency virus (HIV)-negative South African gold miners during a decade of epidemic HIV-associated TB. *Journal of Infectious Diseases, 188*(8), 1156-1163.

Cowie, R. L. (1994). The epidemiology of Tuberculosis in gold miners with Silicosis. *American Journal of Respiratory and Critical Care Medicine, 150*(5 I), 1460-1462.

Cummings, C. W., Flint, P. W., Harker, L. P., Haughey, B. H., Richardson, M. A., Robbins, K. T. et al. (Eds.) (2005). *Cummings otolaryngology head & neck surgery* (4th ed.). Philadelphia, Pennsylvania: Elsevier Mosby, Inc.

Curry, F. J. (2008). *Drug-resistant tuberculosis: A survival guide for clinicians* (2nd ed.) CNTC and the Tuberculosis Control Branch of the California Department of Public Health.

Daniel, E. (2007). Noise and hearing loss: A review. *Journal of School Health, 77*(5), 225-231.

Davis, R. R., Newlander, J. K., Ling, X., Cortopassi, G. A., Krieg, E. F. & Erway, L. C. (2001). Genetic basis for susceptibility to noise-induced hearing loss in mice. *Hearing Research, 155*, 82-90.

DeForge, B. R. (2010). *Research design principles. Encyclopedia of Research Design.* SAGE Publications. http://0-www.sage-ereference.com.innopac.up.ac.za/researchdesign/Article_n381.html

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

de Lima, M. L. L. T., Lessa, F., Aguiar-Santos, A. M., & Medeiros, Z. (2006). Hearing impairment in patients with Tuberculosis from Northeast Brazil. *Revista do Instituto De Medicina Tropical De São Paulo, 48*(2), 99-102.

Department of Health. Report on TB, including XDR-TB in South Africa. (16 September 2006). Retrieved 18 November, 2008, from www.doh.gov.za/docs/reports/2006/xdr-tb/index.html

Department of Health. The South African National Tuberculosis Control Programme Practical Guidelines. (2004). *South Africa.*

Department of Labour. Compensation for occupational injuries and diseases act, no. 130 of 1993. The determination of permanent disablement resulting from hearing loss caused by exposure to excessive noise and trauma. Circular Instruction No. 171. *South Africa.*

Department of Minerals and Energy (1996). Mine Health and Safety Act (MHSA, Act 29 of 1996). *South Africa.*

Dias, B., Chunderdoojh, B., & Hurkchund, H. (2006). *Effects of HIV on occupational health and safety* SIMRAC report nr. SIM 03-09-05.

Dobie, R. (2008). The burden of age-ralated and occupational noise-induced hearing loss in the United States. *Ear and Hearing, 29*(4), 565-577.

Dobie, R. A. (2005). Estimating noise-induced permanent threshold shift from audiometric shape: The ISO-1999 model. *Ear and Hearing, 26*(6), 630-635.

Dogru, H., Tüz, M., & Uygur, K. (2003). Correlation between blood group and noise-induced hearing loss. *Acta Oto-Laryngologica, 123*(8), 941-942.

Ducati, R. G., Ruffino-Netto, A., Basso, L. A., & Santos, D. S. (2006). The resumption of consumption – a review on Tuberculosis. *Mem Inst Oswaldo Cruz,* 101(7), 694-714.

Duggal, P., & Sarkar, M. (2007). Audiological monitoring of multi-drug resistant Tuberculosis patients on Aminoglycoside treatment with long term follow-up. *BMC Ear Nose Throat Disord, 7*(5), 1-7.

Durackova, Z. (2010). Some current insights into oxidative stress. *Physiological Research, 59*(4), 459-469.

Dworkin, M. S., Adams, M. R., Cohn, D. L., Davidson, A. J., Buskin, S., Horwitch, C., et al. (2005). Factors that complicate the treatment of Tuberculosis in HIV-infected patients. *Journal of Acquired Immune Deficiency Syndromes, 39*(4), 464-470.

Eisler, R. (2003). Health risks of gold miners: A synoptic review. *Environmental Geochemistry and Health, 25*(3), 325-345.

Farmer, P. (1997). Social scientists and the new Tuberculosis. *Social Science & Medicine, 44*(3), 347-358.

Fechter, L. D. (2005). Oxidative stress: A potential basis for potentiation of noise-induced hearing loss. *Environmental Toxicology and Pharmacology, 19*(3), 543-546.

Ferrite, S., & Santana, V. (2005). Joint effects of smoking, noise exposure and age on hearing loss. *Occupational Medicine, 55*(1), 48-53.

Fransen, E., Topsakal, V., Hendrickx, J., Van Laer, L., Huyghe, J. R., Van Eyken, E., et al. (2008). Occupational noise, smoking, and a high body mass index are risk factors for age-related hearing impairment and moderate alcohol consumption is protective: An European population-based multicenter study. *Journal of the Association for Research in Otolaryngology: JARO, 9*(3), 264.

Frisina, R. D. (2001). Possible neurochemical and neuroanatomical bases of age-related hearing loss - presbyacusis. *Seminars in Hearing, 22*(3), 213-225.

Fuente, A., Slade, M. D., Taylor, T., Morata, T. C., Keith, R. W., Sparer, J. C. I. H., et al. (2009). Peripheral and central auditory dysfunction induced by occupational exposure to organic solvents. *Journal of Occupational & Environmental Medicine, 51*(10), 1202-1211.

Furin, J. J., Mitnick, C. D., Shin, S. S., Bayona, j., Becerra, M. C., Singler, J. M., et al. (2001). Occurence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant Tuberculosis. *Int J Tuberc Lung Dis, 5*(7), 648-655.

Gates, G. A., Schmid, P., Kujawa, S. G., Nam, B., D'Agostino, R. (2000). Longitudinal threshold changes in older men with audiometric notches. *Hearing Research,* 141(1-2), 220-229*.*

Gazzard, B. (2001). Tuberculosis, HIV and the developing world. *Clinical Medicine JRCPL, 1*, 62-68.

Girard, S. A., Picard, M., Davis, A. C., Simard, M., Laroque, R., Leroux, T., et al. (2009). Multiple work-related accidents: Tracing the role of hearing status and noise exposure. *Occup.Environ.Med., 66*(319), 324.

Glynn, J. R., Yats, M. D., Crampin, A. C., Ngwira, B. M., Mwaungulu, F. D., Black, G. F., et al. (2004). DNA fingerprint changes in Tuberculosis: Re-infection, evolution or a laboratory error. *Journal of Infectious Diseases, 190*, 1158-1166.

Gooze, L. & Daley, C. L. (2003). Tuberculosis and HIV. United States, Department of Veterans Affairs. http://www.hiv.va.gov

Guild, R., Ehrich, R. I., Johnston, J. R., & Ross, M. H. (Eds.). (2001). *SIMRAC handbook of occupational health practice in the South African mining industry* (1st ed.). Braamfontein, South Africa: The Safety in Mines Research Advisory Committee.

Hall, J. W., & Mueller, H. G. (1997). Pure tone audiometry. *Audiologists' desk reference, vol I* (first ed., pp. 77-112). San Diego, London: Singular Publishing Group, Inc.

Haney, P. E., Raymond, B. A., Hernandez, J. M., Seeman, S., & Berry, A. J. (1996). Tuberculosis makes a comeback. *AORN Journal, 63*(4), 705.

Hausler, H., Dr. (2000, October). *Tuberculosis, HIV and AIDS, clinical guidelines* National Department of Health, TB/HIV Policy task group.

Heinrich, U. R., & Feltens, R. (2006). Mechanisms underlying noise-induced hearing loss. *Drug Discovery Today: Disease Mechanisms, 3*(1), 131-135.

Henderson, D., & Hamernik, R. P. (1995). *The biological basis of noise-induced hearing loss*. Hearing Research Laboratory, Dept of Communicative Disorders and Science, State University of New York at Buffalo; Audiology Research Laboratory, State University of New York at Plattsburgh:

Henderson, D., Bielefeld, E. C., Harris, K. C., & Hu, B. H. (2006). The role of oxidative stress in noise-induced hearing loss. *Ear and Hearing, 27*(1), 1-19.

Henderson, D., Steinman, H., & Kopke, R. (1997). Pharmacological intervention with noise-induced hearing loss. *Acoustical Society of America 133rd Meeting Lay Language Papers,* (133), 8 January 2010.

Hercline, T., & Amorosa, J. K. (2009). *Tuberculosis.* Retrieved April, 2009, from http://emedicine.medscape.com

Hershfield, E. (1999). Tuberculosis: Treatment. *Candian Medical Association Journal, 161*(4), 405.

Holden, N. E. (2001). History of the origin of the chemical elements and their discoveries. *41st IUPAC Gneral Assembly.* Brisbane.

Hopewell, P. C., Pai, M., Maher, D., Uplekar, M., & Ravigliance, M. C. (2006). International standards for Tuberculosis care. *The Lancet Infectious Diseases,* 6(11), 710-735.

Jabado, N., & Gros, P. (2005). Tuberculosis: The genetics of vulnerability. *Nature, 434*, 709-711.

Jack, C. I., & Jackson, M. J. (1994). Circulatry markers of free radical activity in patients with pulmonary Tuberculosis. *Int J Tuberc Lung Dis, 75*(2), 132-137.

Joint United Nations Programme on HIV/AIDS (UNAIDS) (2010). UNAIDS report on the global AIDS epidemic 2010. http://www.unaids.org/globalreport/Global_report.htm

Joint United Nations Programme on HIV/AIDS (UNAIDS) (2008). UNAIDS report on the global AIDS epidemic 2008. http://www.unaids.org/globalreport/Global_report.htm

Jones, C. M. (1996). ABC of work related disorders: Occupational hearing loss and vibration induced disorders. *BMJ, 313*, 223-226.

Jones, S.M., & Mock, B.E. (2007). Responsible conduct of research in audiology. *Seminars in Hearing, 28*(3), 206-215.

Konings, A., Van Laer, L., Pawelczyk, M., Carlsson, P., Bondeson, M., Rajkowska, E., et al. (2007). Association between variations in CAT and noise-induced hearing loss in two independent noise-exposed populations. *Human Molecular Genetics, 16*(15), 1872-1883.

Kopke, R. D., Coleman, J. K. M., Liu, J., Campbell, K. C. M., & Riffenburgh, R. H. (2002). Enhancing intrinsic cochlear stress defenses to reduce noise-induced hearing loss. *The Laryngoscope, 112*(September), 1515-1532.

Kuan, C., Kaga, K., & Tsuzuku, T. (2007). Tuberculous meningitis-induced unilateral sensorineural hearing loss: A temporal bone study. *Acta Oto-Laryngologica, 127*(5), 553-557.

Kurmis, A. P., & Apps, S. A. (2007). Occupationally-acquired noise-induced hearing loss: A senseless workplace hazard. *International Journal of Occupational Medicine and Environmental Health, 20*(2), 127-136.

Le Prell, C. G., Yamashita, D., Minami, S. B., Yamasoba, T., & Miller, J. M. (2007). Mechanisms of noise-induced hearing loss indicate multiple methods of prevention. *Hearing Research, 226*(1-2), 22-43.

Lohmeier, J. H. (2010). Law of large numbers. *Encyclopedia of Research Design.* SAGE Publications. http://0-www.sage-ereference.com.innopac.up.ac.za/researchdesign/Article_n215.html

Lyos, A. T. *Ototoxicity.* Retrieved 22 October, 2008, from www.bcm.edu/oto/grand/82092.html

Marks, S. (2006). The silent scourge? Silicosis, respiratory disease and gold-mining in South Africa. *Journal of Ethnic & Migration Studies, 32*(4), 569-589.

Martin, F. N., & Clark, J. G. (Eds.). (2006). *Introduction to audiology* (9th ed.). United States of America: Pearson Education, Inc.

Mathema, B., Kurepina, N. E., Bifani, P. J., & Kreiswirth, B. N. (2006). Molecular Epidemiology of Tuberculosis: Current Insights. *Clinical Microbiology Reviews, 19(4),* 658-685.

Maxwell, D. L., & Satake, E. (Eds.). (2006). *Research and statistical methods in communication sciences and disorders* (First edition). Canada: Thomson Delmar Learning.

McBride, D., & Williams, S. (2001). Audiometric notch as a sign of noise induced hearing loss. *Occupational and Environmental Medicine, 58*, 46-51.

McBride, D. I. (2004). Noise-induced hearing loss and hearing conservation in mining. *Occupational Medicine, 54*(5), 290-296.

McInerney, P. A., Nicholas, P. K., Wantland, D., Corless, I. B., Ncama, B., Bhengu, B., et al. (2007). Characteristics of anti-tuberculosis medication adherence in South Africa. *Applied Nursing Research: ANR, 20*(4), 164-170.

McMillan, J. H., & Schumacher, S. (Eds.). (2001). *Research in education evidence-based inquiry* (Sixth ed.). United States of America: Pearson Education, Inc.

McReynolds, M. C. (2005). Noise-induced hearing loss. *Air Medical Journal, 24*(2), 73-78.

Miller, M. H., & Schein, J. D. (2005). Selected complex auditory disorders. *Journal of Rehabilitation Research and Development, 42*(4), 1-8.

Mills, J. H., & Going, J. A. (1982). Review of environmental factors affecting hearing. *Environmental Health Perspectives, Vol. 44*, 119-127.

Miura, Y., & Endo, T. (2010). Survival responses to oxidative stress and aging. *Geriatr Gerontol Int, Suppl. 1*, S1-S9.

Moazzez, A. H., & Alvi, A. (1998). Head and neck manifestations of AIDS in adults. *American Family Physician, 57*(8), 1813-1822.

Morata, T. C. (2003). Chemical exposure as a risk factor for hearing loss. *J Occup Environ Med, 45*, 676-682.

Morita, Y., Hirokawa, S., Kikkawa, Y., Nomura, T., Yonekawa, H., Shiroishi, T., et al. (2007). Fine mapping of Ahl3 affecting both age-related and noise-induced hearing loss. *Biochemical & Biophysical Research Communications, 355*(1), 117-121.

Muller, J., & Voztech, D. (2010). Using sigmoid functions for modeling South African gold production. *Geoscience Engineering, LVI*(2), 44-58.

Munro, S. A., Lewin, S. A., Smith, H. J., Engel, M. E., Fretheim, A., & Volmink, J. (2007). Patient adherence to Tuberculosis treatment: A systematic review of qualitative research. *Plos Medicine, 4*(7), e238-e238.

Nageris, B. I., Raveh, E., Zilberberg, M., & Attias, J. (2007). Asymmetry in noise-induced hearing loss: Relevance of acoustic reflex and left or right handedness. *Otology & Neurotology: Official Publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology, 28*(4), 434-437.

Nelson, D. I., Nelson, R. Y., Concha-Barrientos, M., & Fingerhut, M. (2005). The global burden of occupational noise-induced hearing loss. *American Journal of Industrial Medicine, 48*(6), 446-458.

Nelson, G., Girdler-Brown, B., Ndlovu, N., & Murray, J. (2010). Three decades of Silicosis: Disease trends at autopsy in South African gold miners. *Environmental Health Perspectives, 118*(3), 421-426.

Ohinata, Y., Yamasoba, T., Schacht, J., & Miller, J. M. (2000). Glutathione limits noise-induced hearing loss. *Hearing Research, 146*(1-2), 28-34.

Ologe, F. E., Akande, T. M., & Olajide, T. G. (2006). Occupational noise exposure and sensorineural hearing loss among workers of a steel rolling mill. *European Archives of Oto-Rhino-Laryngology, 263*(7), 618-621.

The Oxford encyclopedia of economic history. Retrieved 21 Desember, 2009, from www.mywire.com

Ozcelik, T., Ataman, M., & Gedikoglu, G. (1995). An unusual presentation: Primary Tuberculosis of the middle ear cleft. *Tubercle and Lung Disease, 76*(2), 178-179.

Pai, M., Kalantri, S., & Dheda, K. (2006). New tools and emerging technologies for the diagnosis of Tuberculosis: part II. *Expert Rev Mol Diagn,* 6(3), 423-432.

Palmer, K. T., Griffin, M. J., Syddal, H. E., Pannett, B., Cooper, C., & Coggan, D. (2002). Raynauds's phenomenon, vibration induced white finger, and difficulties in hearing. *Occup.Environ.Med., 59*, 640-642.

Patel, A., Patel, K., Patel, J., Shah, N., Patel, B., & Rani, S. (2004, September). Safety and antiretroviral effectiveness of concominant use of Rifampicin and Efavirenz for antiretroviral-naive patients in India who are coinfected with Tuberculosis and HIV-1. *J.Acquir.Immune Defic.Syndr., 37*(1), 1166-1169.

Peloquin, C. A., Berning, S. E., Nitta, A. T., Simone, P. M., Goble, M., Huitt, G. A., et al. (2004). Aminoglycoside toxicity: Daily versus thrice-weekly dosing for treatment of mycobacterial diseases. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 38*(11), 1538-1544.

Perkins, M.D., & Cunningham, J. (2007). Facing the crisis: improving the diagnosis of Tuberculosis in the HIV era. *J Infect Dis,* 196 S15-S27.

Phillips, J. I., Heyns, P. S., & Nelson, G. (2007). Rock drills used in South African mines: A comparative study of noise and vibration levels. *The Annals of Occupational Hygiene, 51*(3), 305-310.

Philp, C. (2007). Occupational noise, the silent terminator. *Welding Journal (Miami, Fla), 86*(3), 71-72.

Picard, M., Girard, S. A., Simard, M., Larocque, R., Leroux, T., & Turcotte, F. (2008). Association of work-related accidents with noise exposure in the workplace and noise-induced hearing loss based on the experience of some 240,000 person-years of observation. *Accident Analysis and Prevention, 40*, 1644-1652.

Pouyatos, B., Gearhart, C., Fulton, A., & Fechter, L. (2007). Oxidative stress pathways in the protestation of noise-induced hearing loss by Acylonitrile. *Hearing Research, 224*, 61-74.

Prasad, K. N., Cole, W. C., & Haase, G. M. (2008). The case for using multiple antioxidants in hearing diorders. *TechTopic,* (June), 48-55.

Qiaoyan, H., Shi, Z. & Yang, J. (2010). *Confidence intervals. Encyclopedia of Research Design.* Retrieved September, 2010, from http://0-www.sage-ereference.com.innopac.up.ac.za/researchdesign/Article_n68.html>

Rabinowitz, P. M., Galusha, D., Slade, M. S., Dixon-Ernst, C., Sircar, K. D., & Dobie, R. A. (2006). Audiogram notches in noise-exposed workers. *Ear and Hearing,* 27(6), 742-750.

Reddy, Y. N., Murthy, S. V., Krishna, D. R., & Prabhakar, M. C. (2004). Role of free radicals and antioxidants in Tuberculosis patients. *Indian Journal of Tuberculosis, 51*, 213-218.

Rees, D., & Murray, J. (2007). Silica, Silicosis and Tuberculosis. *Int J Tuberc Lung Dis, 11*(5), 474-484.

Ross, M. H., & Murray, J. (2004). Occupational respiratory disease in mining. *Occupational Medicine (Oxford, England), 54*(5), 304-310.

Ryan, A. F., Harris, J. P., & Keithley, E. M. (2002) Immune-mediated hearing loss: basic mechanisms and options for therapy. *Acta Oto-Laryngolocica,* 122(5), 38-43.

SANS 10182:2006. The measurement and assessment of acoustic environments for audiometric tests. *Pretoria: Standards South Africa.*

SANS 10083:2004. The measurement and assessment of occupational noise for hearing conservation purposes. *Pretoria: Standards South Africa.*

Santana, V. S., & Barberino, J. L. (1995). Occupational noise exposure and hypertension. [Exposicao ocupacional ao ruido e hipertensao arterial] *Revista De Saude Publica, Sao Paulo, 29*(6), 478-487.

Seidel, H. (1993). Selected health risks caused by long-term, whole-body vibration. *American Journal of Industrial Medicine, 23*(4), 589-604.

Seidman, M. D., Khan, M. J., Bai, U., Shirwany, N., & Quirk, W. S. (2000). Biologic activity of mitochondrial metabolites on aging and age-related hearing loss. *American Journal of Otology, 21*(2), 161167.

Selvaraj, P. (2004). Host genetics and Tuberculosis susceptibility. *Current Science, 26*(1), 115-121.

Sha, S., Talor, R., Forge, A., & Schacht, J. (2001). Differential vulnerability of basal and apical hair cells is based on intrinsic susceptibility to free radicals. *Hearing Research, 155*(1-2), 1-8.

Sha, S. H. (2005). Physiological and molecular pathology of Aminoglycoside ototoxicity. *Volta Review, 105*(3), 325-334.

Skolnik, P. R., Nadol, J. B.,Jr, & Baker, A. S. (1986). Tuberculosis of the middle ear: Review of the literature with an instructive case report. *Clinical Infectious Diseases, 8*(3), 403-410.

Śliwińska-Kowalska, M., Dudarewicz, A., Kotyło, P., Zamysłowska-Szmytke, E., Pawlaczyk-Łuszczyńska, M., & Gajda-Szadkowska, A. (2006). Individual susceptibility to noise-induced hearing loss: Choosing an optimal method of retrospective classification of workers into noise-susceptible and noise-resistant groups. *International Journal of Occupational Medicine and Environmental Health, 19*(4), 235-245.

Soer, M. M., Pottas, L., & Edwards, A. L. (2002). Characteristics of noise-induced hearing loss in gold miners. *Health SA Gesondheid, 7*(2), 78-88.

Sonnenberg, P., Glynn, J. R., Fielding, K., Murray, J., Godfrey-Fausselt, P., & Shearer, S. (2005). How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. *Journal of Infectious Diseases, 191*(2), 150-158.

Sonnenberg, P., Glynn, J. R., Fielding, K., Murray, J., Godfrey-Faussett, P., & Shearer, S. (2004). HIV and pulmonary Tuberculosis: The impact goes beyond those infected with HIV. *AIDS, 18*(4), 657-662.

Soucek, S., & Michaels, L. (1996). The ear in the acquired immunodeficiency syndrome: II. Clinical and audiological investigation. *The American Journal of Otology, 17*, 35-39.

Stach, B. A., Westerberg, B. D., & Roberson Jr., J. B. (1998). Auditory disorder in central nervous system miliary Tuberculosis: Case report. *Journal of the American Academy of Audiology, 9*(4), 305-310.

Starck, J., Pyykkoe, I., & Toppila, E. (1997). In Das B., Karwowski W. (Eds.), *Effects of individual risk factors in the development of noise-induced hearing loss*. IOS Press Amsterdam.

Stead, W. W. (1992). Genetics and resistance to Tuberculosis. *Annals Internal Medicine,* 116(11), 937-941.

Stoltz, A. (2008). Runaway TB epidemic. *S.Afr.Med.J., 98*(9)

Sutinen, P., Zou, J., Hunter, L. L., Toppila, E., & Pyykko, I. (2007). Vibration-induced hearing loss: Mechanical and physiological aspects. *Otology & Neurotology: Official Publication of*

the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology, 28(2), 171-177.

Szanto, C., & Stoica, L. (1999). Correlation between vibration induced white finger and hearing loss in miners. *J Occup Health, 41*, 232-237.

TeWaterNaude, J. M., Ehrlich, R. I., Churchyard, G. J., Pemba, L., Dekker, K., Vermeis, M., et al. (2006). Tuberculosis and Silica exposure in South African gold miners. *Occup.Environ.Med., 63*, 187-192.

Toeruen, T., Guengoer, G., Oezmen, I., Boeluekbasi, Y., Maden, E., Bicakci, B., et al. (2005). Side effects associated with the treatment of multidrug-resistant Tuberculosis. *International Journal of Tuberculosis and Lung Disease, 9*(12), 1373-1377.

Toppila, E., Pyykkö, I., & Starck, J. (2001). Age and noise-induced hearing loss. *Scandinavian Audiology, 30*(4), 236-244.

Torun, T., Gunger, G., Ogmen, I., Bolukbasi, Y., Maden, E., Bicakci, B., et al. (2005). Side effects associated with the treatment of multi-drug resistant TB. *Int J Tuberc Lung Dis, 9*(12), 1373-1377.

Trochim, W. M. K. (2006). *The research methods knowledge base.* Retrieved 31 March, 2008, from http://www.socialresearchmethods.net/kb/

Tse, G. M. K., Ma, T. K. F., Chan, A. B. W., Ho, F. N. Y., King, A. D., Fung, K. S. C., et al. (2003). Tuberculosis of the Nasopharynx: A rare entity revisited. *The Laryngoscope, 113*(4), 737-740.

Uchida, Y., Nakashima, T., Ando, F., Niino, N., & Shimokata, H. (2005). Is there a relevant effect of noise and smoking on hearing? A population-based aging study. *International Journal of Audiology, 44*(2), 86-91.

Vaamonde, P., Castro, C., García-Soto, N., Labella, T., & Lozano, A. (2004). Tuberculous Otitis Media: A significant diagnostic challenge. *Otolaryngology - Head and Neck Surgery, 130*(6), 759-766.

Walsh, T., Demkowicz, L. & Charles, R. (2004). Boundary element modeling of the external human auditory system. *J. Acoust. Soc. Am,* 115(3), 1033-1043.

Wang, Y., Hirose, K. & Liberman, M.L. (2002). Dynamics of noise-induced cellular injury and repair in the mouse cochlea. *Journal of Association for Research in Otolaryngology,* 03, 248-268.

Waskito, H. (2008). The effect of hypertension and other risk factors to the development of sensory-neural hearing loss to workers who are exposed to noise and chemical hazards in oil companies. Society of Petroleum Engineers - 9th International Conference on Health, Safety and Environment in Oil and Gas Exploration and Production 2008*, 1* 126-145.

Wilson, L. G. (2005). Commentary: Medicine, population and Tuberculosis. *International Journal of Epidemiology, 34*, 521-524.

World Health Organization. (2008). *TB Factsheet.* (Centre for Disease Control). Retrieved April 2008, from http://0-www.who.int.innopac.up.ac.za/mediacentre/factsheets/fs104/en/

World Health Organization (2009). *TB/HIV Factsheet.* Retrieved November 2010, from http://www.who.int/tb/challenges/hiv/factsheet_hivtb_2009update.pdf

World Health Organization (2004). MediaCentre. Retrieved April 2008, from http://www.who.int/mediacentre/news/releases/2004/pr66/en

Yamasoba, T., Nuttall, A. L., Harris, C., Raphael, Y., & Miller, J. M. (1998). Role of glutathione in protection against noise-induced hearing loss. *Brain Research, 784*(1-2), 82-90.

Yerdelen, D., & Tan, M. (2008). Ototoxicity probably due to *Isoniazid* in a patient undergoing hemodialysis. *Journal of Neurological Sciences, 25*(1), 51-54.