DEAFNESS CAUSED BY OTOTOXICITY IN DEVELOPING COUNTRIES

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This report attempts to review systematically the current literature on deafness caused by ototoxicity in developing countries and make an appraisal of its current status in different regions of the developing world. This involves critically assessing research and accessing routine electronic literature databases.

Deafness Worldwide

Deafness is a worldwide problem. It is estimated that 1:1000 children are born deaf, while 2:1000 children are born hard of hearing.[1] In 2002, the World Health Organization estimated that 250 million people in the world had a disabling hearing impairment and that two-thirds of these people lived in developing countries.[2] Furthermore, Torrigiani in Geneva outlined that avoidable hearing impairment and deafness are an important public health problem, particularly in low-income countries. Although infectious conditions, such as otitis media, account for the largest proportion of conductive hearing loss, damage to sensori-neural hearing caused by ototoxic medication has been increasingly reported from countries in recent years.[3]

Table 1: Grades of Hearing Impairment

Grade of impairment	Corresponding audiometric ISO* value
0 - None	25 dB or better
1 – Slight	26-40 dB
2 – Moderate	41-60 dB
3 - Severe	61-80 dB
4 – Profound	81 dB or greater

*International Organization for Standardization

Grades of Hearing Impairment

Deafness can be expressed as a complete loss in the ability to hear from one or both ears. It can also be described as a hearing threshold of 81dB or greater, averaged at frequencies 0.5, 1, 2, 4 kHz.[2] Table 1 provides the different grades of hearing impairment.[2]

Ototoxicity and its Causes

Ototoxicity refers to the harmful effect of a drug, chemical substance or heavy metal on the organ of hearing or balance, which may lead to a hearing impairment, and/or balance problems. Table 2 displays some of these substances.[3]

Table 2: Causes of Hearing Impairment and/or Balance Problems

Aminoglycosides	Gentamicin, streptomycin, kanamycin, amikacin, tobramycin, neomycin, netilmicin, polymyxin-B	
Macrolides	Erythromycin, azithromycin, clarithromycin	
Loop diuretics	Furosemide, bumetanide, ethacrinic acid	
Salicylates		
Antimalarials	Quinine, chloroquine (high dosage)	
Non-steroid anti-inflammatory drugs	Naproxen, indomethacin (no definite findings)	
Anti-neoplastic drugs	Cisplatin, bleomycin, carboplatinum	
Chelating agents	Desferoxamine	
Topical otological preparations	***Antibiotic solutions:***	Neomycin Aminoglycosides Polymyxin-B Chloramphenicol Fosfomycin
	Anti-inflammatory:	Propylene-glycol, hydrocortisone
	Antiseptic:	Chlorohexidine, povidone-iodine (?)
	Acidifying:	2% acetic acid solution (?)
Chemical agents	***Heavy metals:***	Mercury, lead (Industrial pollution, cosmetics).
	Solvents:	Toluene, styrene
	Others:	Arsenic, cobalt, cyanides, benzene, propylene-glycol, potassium bromide

Ototoxicity tends to be thought of in the context of drug administration leading to damage of the cochlea or vestibular portion of the inner ear, causing transitional or permanent sensorineural hearing loss (SNHL) and/or vertigo. Antibiotics, diuretics and anti-malarial pharmaceuticals have been implicated as potentially toxic to both the auditory and vestibular systems. Kanamycin and neomycin are perhaps the most alarming ototoxic drugs at this time.[4] This report will later discuss and evaluate the current status of ototoxicity due to these substances. This will be accomplished by assessing and reviewing different literature written about the use of these chemicals in various regions of the world, and in particular, the developing world.

While aminoglycosides have been largely replaced over the last decades by modern antibiotics with fewer side effects, they remain a mainstay in medicine. In fact, they may be the most commonly used antibiotics worldwide, chiefly due to their use in developing countries. Their high efficacy, coupled with extremely low cost, frequently makes aminoglycoside antibiotics the only affordable drugs. Furthermore, since tuberculosis is on the rise worldwide, particularly in low income countries, aminoglycoside use will not be reduced.[5]

Streptomycin and kanamycin are part of the recommended regimen of the World Health Organization against tuberculosis, and their widespread use makes these antibiotics a major cause of preventable hearing loss in the world today.[5] Given that most drug-induced hearing loss is caused by the prescription of ototoxic drugs, one should assume that preventive measures could be taken effectively. Minja makes reference to the preventability of deafness due to ototoxicity, despite its variety of causes.[1] Suggestions will be made regarding methods and strategies for the prevention of ototoxicity in developing countries.

Another report refers to the extensive use and abuse of aminoglycosides and how they are a major concern.[3] It suggests that the most common cause of hearing impairment from ototoxic damage by drugs is due to injectable aminoglycosides. It is also implied that gentamicin is cheaper than newly available alternatives and, hence, is more widely available. Additionally, WHO recognises that the global resurgence of tuberculosis is leading to greater use of streptomycin.[3] For example, in South Africa, streptomycin and kanamycin form part of the drug regimen administered to multidrug resistant tuberculosis (MDR-TB) sufferers.[6] One of the aims of this report is to ascertain the extent to which these antibiotics are being abused.

This report will also consider the many agents within the workplace, particularly within heavy industry, that can potentially bring about chemical trauma to the ear. Examples include xylene, toluene, mercury, tin, lead and carbon monoxide.[4]

The meaning of a developing country is a final point of importance in this introduction. It has been defined by the World Bank Income Groupings, in which the main criterion for classifying economies is gross national income (GNI) per capita. Based on its GNI per capita, every economy is classified as low income, middle income (subdivided into lower middle and upper middle), or high income. Table 3 identifies some of the developing countries that will be discussed in this report, and others that are noteworthy.[7]

Table 3: High Income, Upper Middle Income, Lower Middle Income and Low Income Countries

High Income	Upper Middle Income	Lower Middle Income	Low Income ($765 or less)
Australia	Argentina	Brazil	Bangladesh
France	Barbados	China	Ghana
Germany	Botswana	Colombia	India
Hong Kong	Chile	Indonesia	Kenya
Ireland	Costa Rica	Iran	Malawi
Italy	Czech Republic	Morocco	Nepal
Japan	Latvia	Namibia	Nigeria
Korea	Lebanon	Paraguay	Pakistan
Netherlands	Malaysia	Peru	Sudan
Singapore	Mauritius	Philippines	Tanzania
Switzerland	Mexico	South Africa	Uganda
UK	Oman	Sri Lanka	Zambia
USA	Poland	Thailand	Zimbabwe

To summarise this introduction to ototoxicity-induced deafness, it is important to note that the global magnitude of the problem is not accurately known and that there is a great need for more detailed research on ototoxicity.

Discussion and Results

This report will now analyse and review the literature found. It will discuss the current status of ototoxicity in developing countries by comparing results from clinical studies carried out. It will then assess the disagreements, strengths and weaknesses of various papers. The problems facing people in developing countries will also be considered in depth.

The fact that aminoglycosides and other drugs, such as antimalarials, can produce ototoxicity has been well established in both humans and experimental animals. The ototoxicity can take the form of damage to the auditory system or the vestibular system, or both.[8] In one study, Tange et al showed that malaria patients experienced adverse effects related to ototoxicity induced by quinine: 9 had impaired hearing, 11 tinnitus, 8 had feeling of pressure on the ears and 4 felt giddiness.[9] While malaria may cause deafness, the drugs used in the treatment are potentially ototoxic. Quinine is the drug of choice in the treatment of chloroquine resistant falciparum malaria in the developing world. Minja observed 354 pupils at a School for the Deaf in Dar es Salaam, of which five had become totally deaf following intravenous infusion of quinine.[1] Table 4 displays the distribution of the 354 children according to causes of deafness. Ototoxicity can be seen as a cause in 20 % of cases.[1]

Studies on the ototoxicity of quinine in humans are scarce, however, and there are still some questions about the reversibility of quinine induced hearing loss. Nevertheless, quinine induced ototoxicity in patients and volunteers appears to be largely, if not completely, reversible.[9] The salicylates and diuretics produce

Table 4: Causes of Deafness in Dar-es-Salaam

Causes of deafness	No. of children
Meningitis	76
Ototoxicity	66
Mumps	53
Congenital	36
Otitis media	28
Measles	13
Febrile convulsions	5
Unknown	77

temporary hearing loss that may be reversible, fully or partially, when the patient is taken off the medication.[4]

Conversely, aminoglycosides, such as streptomycin and kanamycin, cause the destruction of outer hair cells and hearing changes are most likely irreversible.[6] These antibiotics alerted the medical community and the public more than any others with regard to the ototoxic side effects of medications. This is despite the fact that at the time of its introduction, streptomycin was the long-sought cure for tuberculosis.[5] Sixty cases treated with streptoduocin and sixty cases treated with streptomycin were studied clinically and by various tests in Kanpur, India to find their ototoxicity. It was established that 25 % of the patients on streptoduocin (mixture of streptomycin and dihydrostreptomycin) developed ototoxicity compared to 10 percent on streptomycin. Table 5 summarises the findings on the incidence of ototoxicity as a result of streptoduocin and streptomycin administration.[10]

It can be noted that the toxicity of streptomycin is almost exclusively directed against the vestibular system, whereas, dihydrostreptomycin (a derivative which is chemically different in only one position of the molecule) can cause irreversible hearing loss.[5,6,10]

In South Africa, streptomycin and kanamycin form part of the drug regimen administered to MDR-TB sufferers. In the Western Cape, the incidence of ototoxicity varies between 0-20% depending on the type of aminoglycoside.[6] As in most developing countries, acquired causes of deafness and hearing impairment are also common in Tanzania. Minja reports that gentamicin and streptomycin, prescribed for treatment of septicaemia and tuberculosis respectively, was a cause of deafness in 18.6% of cases.[1] Other aminoglycosides show varying ototoxic effects. Gatell et al showed that slight or mild auditory toxicity developed in 42.1% of patients given tobramycin and 35.2 percent of those given amikacin.[11]

Despite the lack of data on deafness in developing countries, the ototoxic effect of drugs such as aminoglycosides is clear to see. However, there are disagreements between reported incidences of ototoxicity-induced deafness. For example, reports on the toxicity of streptoduocin have been contradictory.[10]

The discrepancy between the incidence rates can be attributed to the criteria used to define ototoxicity by different writers. Most studies consider ototoxicity to have occurred if at any time after a base-line audiogram has been obtained, an increase occurs in the auditory threshold of 15dB or more.[8] Yet, one study describes criteria for auditory dysfunction as a hearing loss greater than 10dB [10] and others use a ≥20dB change in threshold.[11,12] It is important to note the different definitions for ototoxicity presented by clinical studies in developing countries.

The disagreements between papers can also be accounted for by referring to the patients used in the studies. Screening by questionnaire, otoscopy and tympanometry has been used,[12] whereas Minja relied on the policy of admission to a deaf school in Dar es Salaam.[1] Another study carried out a loudness balance test and a difference limen test (a test of loudness perception) before recruiting,[10] which may have been insufficient. A gold standard screening process recruited patients with normal hearing from a TB-hospital in the Western Cape, after consent was received, and treated them with streptomycin and kanamycin.[6]

In a number of developing countries, it is reported that sub-standard drugs are readily available. After collecting 96 samples of chloroquine from Nigeria and Thailand, the results indicated that 36.5% were sub-standard.[13] Not only does this imply discrepancies in clinical studies, but this may, in itself, be a cause of ototoxicity in developing countries.

Following the industrial revolution, new health hazards appeared, and industrial solvents, chemicals and pollutants became a new category of environmental factors causing hearing loss.[5] For example, in Colombia, environmental causation was found to be a cause of deafness in 33.8% of cases.[14] Most notable among these chemicals, and of concern today, are solvents such as organotoxins or toluene, but also carbon monoxide and a number of lesser-used chemicals which can adversely affect the hearing and balance functions of the inner ear.[5] It is now known that certain organic solvents in industry are ototoxic when inhaled in excess. They may produce brain damage involving the vestibular pathways and the inner ear directly. One must keep in mind agents within the workplace, as well as medications prescribed by health professionals. There is one further area which may be a much greater cause of ototoxic hearing loss than has been recognised up to now - the synergistic action of noise exposure and inhaled volatile organic substances.

As with occupational noise, many developing countries have little or no legislation to prevent critical exposure to toxic substances. Regulations that do exist are poorly enforced and implemented, and many workers remain ignorant of such problems.[4]

A large proportion of hearing impairment related to ototoxic drugs results from their inappropriate or indiscriminate use by health care providers.[3] In Cambodia,

Table 5 : Ototoxicity after Streptoduocin and Streptomycin Treatment

Group	Total number of patients	Auditory toxicity	Vestibular toxicity	Auditory and vestibular toxicity	Total
Streptoduocin	60	10	-	5	15 (25%)
Streptomycin	60	-	6	-	6 (10%)

as in other developing countries, there is a disturbing tendency for misuse of antibiotics by certain practitioners - for example, the use of antibiotics to prevent infections rather than treat established disease, treatment of untreatable infections, treatment of infections of undetermined origin, without adequate biological knowledge, and frequently improper dosage. Not only does this malpractice encourage increased microbial resistance, but it also raises the potential for ototoxic effects from those drugs that are dangerous to the ear.[3,4] In Tanzania, however, these drugs are controlled and strictly available on prescription only, although one study notes that situations arise when the use of drugs (gentamicin and streptomycin) is required in the absence of any substitute.[1]

Health care professionals are not only to blame. Health authorities, in general, can also be put to shame. To date, out of 122 institutions in the Western Cape, South Africa, where aminoglycoside treatment is provided to TB sufferers, ototoxicity monitoring takes place at only one.[6] The injudicious use of drugs with ototoxic side-effects can also be attributed to self-diagnosis and self-medication. The easy availability of these drugs 'over the counter' and without a physician's prescription favours self-medication with potentially harmful drugs.[3]

The ototoxic potential of drugs should be stressed during training of staff, with regular refresher courses to update relevant knowledge.[3] This approach is already demonstrated in Dar es Salaam where all health workers are taught about the potential hazard of using these drugs during pregnancy and in treating trivial infections.[1]

It is well known that the use of aminoglycoside antibiotics carries a risk of damage to the cochlea. In spite of the introduction of new classes of antibiotics, the aminoglycosides still remain primary agents of choice in treating serious gram-negative infections.[12] Gatell et al also refer to the fact that despite the introduction of new cephalosporins and penicillins, aminoglycosides still have their place amongst treatment options.[11] Their low-cost to developing countries is the reason for this. Along with their effectiveness against gram-negative bacteria, this advantage has led to the persistence of aminoglycoside use, especially in countries like South Africa.[6] In some developing countries, the government infrastructure is grossly deficient, unable to provide the high quality, high volume health care services which can cope with the many ototoxicity-related health problems.[4]

Hearing loss due to ototoxicity is generally irreversible but avoidable in most instances, given proper preventive action through controlled use of drugs in the health care system and by consumers.[3] Minja's findings indicate that most (75.8%) of the causes of acquired deafness are preventable through immunisation, early diagnosis and proper treatment of ear infections and avoidance of prescribing ototoxic drugs.[1] The World Health Organization reports that there are no restrictions in most developing countries limiting the availability of drugs causing ototoxicity.[3]

In one study, deafness due to ototoxicity is substantial, yet preventable at primary and secondary levels of health care. The alarming rate of deafness due to the use of ototoxic drugs calls for a deliberate policy to create awareness among prescribers and the public to avoid these drugs as much as possible.[1] In China, aminoglycosides are available with or without prescription; in India, there are strict rules for their delivery, but regulations are not enforced.[3] Legislation should be introduced in countries where it does not yet exist, and, where legislation exists, it should be strictly enforced.

Conclusion

The conclusion to this report considers future problems facing people in low-income countries and summarises what needs to be done to resolve them. It refers to the limitations and controversies in some of the studies carried out in developing countries.

The global magnitude of the problem of hearing impairment or deafness due to ototoxicity is not accurately known, but it is probably responsible for 3-4% of all deafness in children in developing countries.[3] Childhood deafness has two serious consequences; delayed speech and language development, leading to the need for special education. These problems are worse in low-income countries where economic difficulty, human and material resources to enable early diagnosis and appropriate rehabilitation are lacking.[1]

Thus, we need to explore more efficient ways of monitoring, in order to do more with limited resources. Only then will ototoxicity be detected early and the negative side-effects avoided or alleviated.[6] Encouragingly, Schacht and Hawkins believe there is real hope that ototoxicity can be conquered. Simple over-the-counter supplements and medications will become part of an inexpensive pharmacological protection to render drug-induced hearing loss a medical concern of the past.[5]

The lack of general knowledge, however, about the risk of ototoxic damage and insufficient public education on ototoxicity is a great obstacle to preventive action. The aim of public education should be to provide individuals with information about the use of medicines in an appropriate way.[3]

In reading ototoxicity-related scientific papers, the existence of limitations and controversies has become apparent. For example, one study reports that for the first 10 courses of aminoglycosides, the therapeutic benefit could be considered to outweigh the risk of cochleotoxicity.[12] The result of this high-dose therapy is contradictory and not in keeping with many other studies.

One particular drawback is the general lack of concern or ignorance towards ototoxicity-induced deafness in developing countries. Small doses of quinine, for example, can cause tinnitus in susceptible persons. However, because of the lack of clinical significance, the interest in the ototoxicity of quinine has been subdued.[9]

In summary, it is important to realise that this report and the studies cited represent only a fraction of the true extent of deafness caused by ototoxicity in developing countries. More research is needed to find out if there is any substance that could reduce damage from ototoxic drugs during their administration. More importantly, national surveillance systems are needed in most developing countries to set up a monitoring system for ototoxic damage.[3]

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SOLVENT EXPOSURE AT THE WORKPLACE: WORKERS' HEARING IN JEOPARDY

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Modern industry no doubt brings enormous benefits to our society. New industrial techniques accelerate and improve production. New machinery improves the efficiency of manufacture, often creating better quality products, at a better price for consumers. In developed countries, the use of high technology machinery, as well as the introduction of less toxic raw materials, has allowed workers to have less contact with hazardous chemicals. However, in developing countries newer technology is not always available and non-toxic chemicals are not always used, due to economic factors.

Since the start of the industrial revolution, many raw materials have been identified as dangerous for human health. Organic solvents fall within this category. It has been widely demonstrated that solvents may adversely affect the central and peripheral nervous system and other body structures. More recently, the ototoxic properties of solvents have also been uncovered by a number of different research groups.[1,2] Despite this new scientific knowledge, audiologists, industrial hygienists and occupational safety and health professionals have been focused on noise as the main agent capable of inducing hearing loss in the workplace. In developed and some developing countries, workers exposed to solvents receive epidemiological surveillance programmes focused on the effects of these chemicals on the central nervous system. Currently, in most countries not much attention is paid to the ototoxic properties of solvents. This is surprising, considering the diverse range of solvents in daily use.

Solvents and Their Effects

Solvents are now widely used in industrial processes such as in automotive and aviation fuels, plastics industries, as a thinner for paints, lacquers, coatings, and dyes - in the manufacture of artificial leather, detergents, medicines, perfumes, fabric and paper coatings, photogravure inks, spray surface coatings and insect repellents (Table 1). In many occupational settings, workers are often exposed to a combination of solvents and other hazardous agents such as noise.[3]

Focusing on the ototoxic properties of solvents, studies have demonstrated that solvents such as toluene, styrene, and xylene may induce damage on the peripheral auditory system (the cochlea). This means that these chemicals may

A factory in Vietnam

Photo: Adrian Fuente