



A meta-analysis and systematic review of the prevalence of mitochondrially encoded 12S RNA in the general population: Is there a role for screening neonates requiring aminoglycosides?

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ABSTRACT

Background: This was a meta-analysis and systematic review to determine the global prevalence of the mitochondrially encoded 12S RNA (MT-RNR1) genetic mutation in order to assess the need for neonatal screening prior to aminoglycoside therapy.

Materials and Methods: A comprehensive search of MEDLINE, EMBASE, Ovid, Database of Abstracts of Reviews of Effect, Cochrane Library, Clinical Evidence and Cochrane Central Register of Trials was performed including cross-referencing independently by 2 assessors. Selections were restricted to human studies in English. Meta-analysis was done with MetaXL 2013. **Results:** Forty-five papers out of 295 met the criteria. Pooled prevalence in the general population for MT-RNR1 gene mutations (A1555G, C1494T, A7445G) was 2% (1–4%) at 99%. **Conclusion:** Routine screening for MT-RNR1 mutations in the general population prior to treatment with aminoglycosides appear desirable but poorly supported by the weak level of evidence available in the literature. Routine screening in high-risk (Chinese and Spanish) populations appear justified.

Key words: Aminoglycoside, mitochondrial genetics, mutation, ribosomal ribonucleic acid, sensorineural hearing loss

INTRODUCTION

The presence of gene variants in mitochondrial encoded MT-RNR1 (12S RNA) genes is associated with aminoglycoside-induced sensorineural hearing loss (SNHL).^[1-7] Global reports have shown variations in the prevalence/incidence of MT-RNR1; however, the A1555G mutation (the first identified homoplasmic variant)^[2] is frequent among families in Africa, Asia, Europe and America.^[6-13] This mutation has a matrilineal inheritance and in one study a reported propensity in more than 50% of those affected to develop SNHL following exposure to aminoglycosides.^[14] Sporadic development of hearing loss in those who carry this mutation without aminoglycoside exposure is rare.^[15]

Despite the risk of ototoxicity, aminoglycosides are widely used. Gentamicin is the most commonly used aminoglycoside in the treatment of neonatal sepsis due to bacterial sensitivity and cost effectiveness compared to other groups of antibiotics. Minimizing the risk of ototoxic hearing loss may require screening of all patients especially newborns for MT-RNR1 mutant genes prior to aminoglycoside therapy if MT-RNR1 mutations are common in the exposed population and if the risk of ototoxicity in the affected patients is significant.

Rapid screening tests with the ability to detect the most common variants are available.^[16,17] The cost effectiveness of such screenings are yet to be done, but would need to consider both the upfront costs associated with screening for the mutation versus the lifetime cost of habilitation of a deaf child, either of which can be significant. Mohr *et al.* in a societal study put the lifetime cost of habilitation of children with severe-to-profound hearing loss at one million dollars USD per individual.^[18]

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The objective of this systematic review was to determine the prevalence/incidence of MT-RNR1 genetic mutations in the general population as a first step toward determining the cost-effectiveness of neonatal screening for MT-RNR1 mutations prior to gentamicin therapy.

MATERIALS AND METHODS

A comprehensive search of MEDLINE (from 1947 to April 2014), EMBASE (from 1974 to April 2014), Publius Ovidius Naso (Ovid), Database of Abstracts of Reviews of Effects and the Cochrane Central Register of Controlled Trials in issue 3, 2014 of the Cochrane Library was performed. The studies were restricted to humans and English language. The search strategy used the exploded Medical Subject Headings term “hearing screening” “hearing loss” combined with the second set obtained using the exploded terms “Genetic screening gene” or “susceptible gene for newborn” or “aminoglycosides” OR “MT-RNR1” OR “A1555G” OR “A7445G” OR “C1494T”. Reference lists and citation indexes of identified manuscripts were cross-referenced to identify further relevant literature. Short-listing of titles and abstracts on the basis of relevancy and subsequent data extraction were undertaken independently by two authors. Differences were resolved by mutual consensus.

Inclusion criteria

1. Studies investigating the prevalence/incidence of MT-RNR1 gene mutations (A1555G, C1494T, A7445G) in the population.
2. Relevant human studies on screening for MT-RNR1.
3. Studies describing the risk of SNHL in MT-RNR1 mutation.

Exclusion criteria

1. Letters to the editor, conference proceedings and editorials.
2. Non-English literature and animal studies.
3. Case reports from which incidence/prevalence data could not be extracted.

Studies that did not meet the inclusion criteria, though considered relevant to the body of evidence were reviewed as appropriate, including review of references to ensure inclusion of all relevant literature.

The 2011 Centre for Evidence Based Medicine Oxford criteria was used to assess/classify the quality designs of studies.^[19]

Results/Meta-analysis

This was performed on all the prevalence recorded globally using the MetaXL 2013 random effect package and method.^[20]

The preliminary search yielded 295 articles. Sixty-nine full text articles were selected following review of the titles and abstracts. Cross-referencing of these articles provided a further 25 studies bringing the cumulative total to 91 of which 45 were found to meet our inclusion criteria [Figure 1], representing cohorts, case-control studies and case series only. All papers were independently reviewed for study design and data extraction by at least two investigators [Table 1].

Forty-two articles^[3,6,7,9-13,16,17,21-36] (the others are as shown in Figure 2) addressed the prevalence/incidence of MT-RNR1 mutation in the populations with SNHL for which a range of 0% in Brazilian^[30] and Argentine^[32] subjects to 100% in 3 Spanish families^[31] with aminoglycoside-induced hearing loss were presented. The modal prevalence was 3.2% and only A1555G and/or C1494T variants were assessed. Fourteen papers^[9,10,16,21,30,32-34] [rest as seen in Figure 2] described prevalence/incidence in the general population/normal controls; these included low birth weight neonates, newborns and neonatal intensive care unit (NICU) patients. A range of 0% to 1.8% was presented. Three papers documented ototoxicity in patients with no observed MT-RNR1 mutations^[9,21,24] while two papers had no hearing impairment among patients with the mutation with or without the gentamicin exposure.^[26,33] Eight papers^[7,17,22,26,29,35-37] recorded a wide phenotypic variance of hearing impairment, age-of-onset and audiometric configurations in patients with the mutation and hearing impairment.

Two articles^[22,31] described the adverse effects/relative risks on hearing following aminoglycoside exposure in patients carrying the mutation. Both articles focused on Spanish populations and reported a relative increase in development of SNHL following aminoglycoside administration among the genetic mutation carriers, as high as 2.3 times greater in one of the studies^[22] compared to those without the mutation.

A noteworthy article^[16] focused on the accuracy and rapidity of a screening test for common MT-RNR1 gene mutations. The screening test was found to be highly accurate (up to 99.8%), and results were rapidly available (within 60 min). Other innovative methods for screening MT-RNR1 include MassArray (Sequenom Inc, USA)(that combines a highly specific

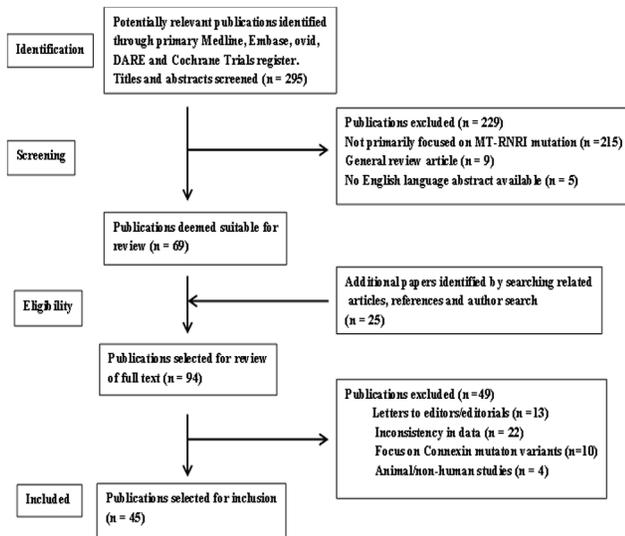


Figure 1: Illustrates the search and selection processes for the articles utilised in the mitochondrially encoded 12S RNA systematic review and meta-analysis

polymerase chain reaction [PCR] and the accuracy of mass spectrometry^[38] and the “on/off switch” that is combined with PCR.^[39] Base quenched probe technique in a PCR assay^[40] and the multiplex primer extension methods^[41] were described as the most appropriate for mass screening of MT-RNR1. The denaturing high-performance liquid chromatography^[42] method was found to be simple, accurate and cost effective whereas, Li *et al.*^[43] also described the Real-time quantitative PCR as suitable for a rapid screening for MT-RNR1 in the deaf population.

The meta-analysis result gave a global pooled prevalence 0.02 (confidence interval 0.01; 0.04) at 99% of the global population. This represents approximately 2% (1-4%) of the general global population. The forest plot is as below in Figure 2.

Mutations in the MT-RNR1 gene result in increased susceptibility to ototoxic hearing loss following treatment with aminoglycoside antibiotics. Mutations are globally prevalent across all races^[9,10,16,18-21,24,33,44] with variable susceptibility and penetrance,^[42,45] affecting both sexes and all age groups.^[46] Before now, there is no acceptable global prevalence because of the skewed distribution in the inheritance pattern of this gene. This necessitated the systematic review and metanalysis on all documented prevalences within the general population to give insight into this lacuna. A pooled global prevalence of 0.02 recorded represents 2% of the world’s population, and this suggests that up to 0.14 billion people are at risk of MT-RNR1 mutation.

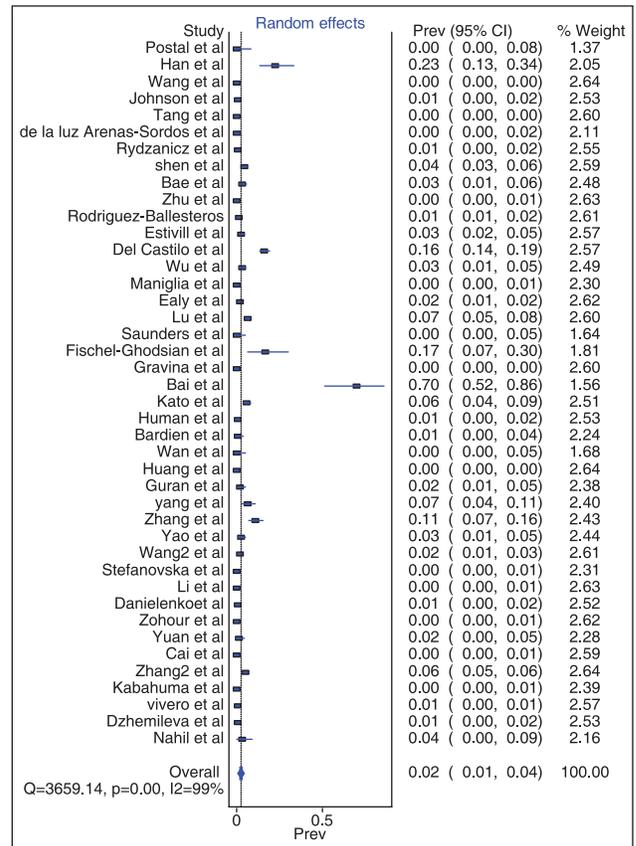


Figure 2: The Forest plot of the meta-analysis of the mitochondrially encoded 12S RNA pooled global prevalence using the MetaXL 2013

DISCUSSION

The prevalence estimates of MT-RNR1 mutations vary widely across different populations, perhaps artificially influenced by the screening method used and the accuracy of available epidemiologic data. In African countries,^[6,9,16] estimated prevalence ranged from 0.9% to 2%, in Asia^[7,16,21,25,28,34-36] 0.09-17%, in the Polish^[28] population 0.4% and in America^[10,12] 1.85%. In a recent report^[13] no patients with the mutation were found among Mexicans whereas prevalence estimates ranged as high as 17% in Chinese and Spanish populations.^[24,29,32,35] A limited comparative study conducted in Iowa (USA) suggested no significant difference in the prevalence of MT-RNR1 mutations between NICU babies and the general population (1.85% vs. 1.83%).^[9] Exposure to aminoglycosides could increase the relative risk of developing SNHL among the mutant gene carriers by 2.3 times.^[31,36] However, this could be confounded by low birth weight^[33] prematurity, variations in duration of drug exposure^[33] and race^[21,34] which were not controlled for in the available limited studies.

The penetrance of the effects of the MT-RNR1 gene A1555G variant mutation (hearing loss following

Table 1: This contains the summary of the contents of the articles selected for inclusion in this study including the level of evidence, article type, race studied, results and outcome

Paper	Level of evidence	Type of paper	What is the focus	Study population	Race	Drug	Mutation	Outcome
Postal <i>et al.</i> (2009)	Level III	Case control A=HL + A (n=20) B=NH + A (n=20) C=HL - A (n=20)	Incidence	NICU (high-risk)	Latin American (Brazil)	Aminoglycoside	C1494T	No mutation seen
Han <i>et al.</i> (2007)	Level IV	Cross-section	Incidence/ effect	Adults	Chinese	Aminoglycoside (n=2/66) HL (n=13/66)	C1494T	15/66 mutation seen
Wang <i>et al.</i> (2011)	Level III	Cross-section	Prevalence	Neonatal	Chinese	None	12S rRNA, A1555G	18/14913 mutation seen
Johnson <i>et al.</i> (2010)	Level III	Case control	Prevalence/ effect	NICU-LBW	Caucasian (USA)	Gentamicin	T1494C, T961C, T1494C, A1555G	4/436, 1/4 immediate HL post exposure
Tang <i>et al.</i> (2002)	Level III	Cross-section	Prevalence	NICU	Mixed (USA)	None	A1555G	1/1161 (0.09%)
De Moraes (2009)		Case control	Prevalence	NICU (high-risk)-A, B, C	Latin America	Aminoglycoside	A1555G, C1494T, A827G	19/85
Diverse data, unable to have clear outcome		A=HL + A (n=25) B=NH + A (n=25) C=HL - A (n=25) D=HL - A (n=10)		Adults-D	(Argentina)			
Rydzanicz (2009)	Level IV	Cross-section (n=500)	Prevalence	General population	Polish (Caucasians)	None	A827G, T961C, A1555G	A827G (1/500), T961C (1/250), A1555G (1/250)
Shen <i>et al.</i> (2011)	Level III	Case (n=440), control (n=449)	Prevalence	Paediatric subjects with HL	Chinese	None	A1555G, T1494C, T1095>C	Case: A1555G (33/440, 7.5%), T1494C (2/440), T1095c (4/440), no clear control details
Zhu (2009)	Level IV	Cross-section	Prevalence	HL in Chinese	Chinese	Aminoglycoside	C1494T	13/3133
Rodriguez-Ballesteros (2006)	Level III	Case (n=1340) Control (n=894)	Relative risk	General population (1340 + HL), 894 no HL	Caucasian (Spanish)	None	C1494T	Case: 20/1340 Control: 0
Estivill <i>et al.</i> 1998	Level III	Case (n=429 out of which Bil NSHL=214) Control (n=200)	Prevalence Relative risk	General population + NSNL (at risk gp)	Caucasian (Spanish)	Aminoglycoside	A155G	Case: Control: 0 Relative risk postaminogly=X2.3 105/649
Del Castillo <i>et al.</i> (2003)	Level IV	Case (n=649 families with HL)	Prevalence	General population	Caucasian (Spanish)	None	A1555G	
Wu <i>et al.</i> (2007)	Level IV	Cases (n=families 3 15, 620 patient with NSHL)	Prevalence	General population	Hans-Chinese	None	A1555G	10/315 families, penetration depends on mitochondrial haplotype 0 for case and control
Maniglia <i>et al.</i> (2008)	Level IV	Cross-section Case (n=27) Control (n=100)	Prevalence	General population	Latin Americans (Brazil)	Aminoglycoside	A1555G	
Ealy (2001)	Level III	Cases: 703 (NICU) Control: 1473 Total=2176	Prevalence	NICU and general population	USA (Iowa)	None	A1555G, C1494T, T1095C, A827G	NICU 1.85%, general population 1.83% (A827G, most common, next A1555G)
Lu <i>et al.</i> (2010)	Level III	Paed cases: 1642 (HL) Control: 449	Prevalence	Paediatric and general population	Han-Chinese	Aminoglycoside	A1555G, T1494C, T1095C	A1555G 3.9%, T1494C (0.18%), T1095C (0.61%), T 961 (1.7%) Control: no mutation, no details of the effect of aminoglycoside

Table 1: (Continued)

Paper	Level of evidence	Type of paper	What is the focus	Study population	Race	Drug	Mutation	Outcome
Saunders et al. (2009)	Level IV	Cases (n=31)	Prevalence	Paediatrics=31	Latin America (Nicaragua)	Aminoglycoside	A1555G, T1494C, T1095C	No mutant detection
Fischel-Chodians et al. (1997)	Level IV	Cases (n=41)	Incidence in high-risk group	General population (NSHL)	Mixed races (USA)	Aminoglycoside	A1555G	17% incidence
Gravina et al. (2007)	Level IV	Blood donors=712 + dried blood spots=330 new born	Prevalence	General population	Latin America (Argentina)	None	A1555G, T1291C	1/1042 for T1291C, none for A1555G
Bai et al. (2008)	Level IV	Pedigree with mutation A1555G	To assess HL and frequency of mutation	Single family pedigree	Chinese	Aminoglycoside	A1555G	19/27 positive for A1555G, 4/27 have normal hearing with mutation (2 nd and 3 rd decade)
Kato et al. (2010)	Level IV	Case series n=373 (SNHL)	Assess accuracy and of screening test (1 h), prevalence	Adult HL	Japanese	None	A1555G, A3243G, A8348G, G1177A	A1555G 11/373 (2.9%), A3243G 9/373 (2.7%), A8348G 1/373, G1177A 1/373. Test was accurate in 99.8%
Human et al. (2010)	Level IV	MDR-TB cases=115 General population n=439 (Africaner 93, black 112, Caucasian 104 and mixed ancestry 130)	Prevalence	Adult TB patients	South Africans (Africaner, Black, Caucasian and mixed ancestry)	Aminoglycoside (Strepto, Kana, Amikacin)	A1555G, A827G, C1494T, T1095C, T1291C	A827G 1/115, no other mutation Control: A1555G 1/112 black, 1/93 Africaner, A827G 1/93 Africaner
Bardien et al. (2009)	Level IV	General population (black 106, mixed ancestry 98)	Prevalence	General population	South Africans	None	A1555G, A827G, C1494T, T1095C, T1291C	A1555G 1/106 black, no other mutation identified
Wan et al. (2013)	Level III	Case control Meniere's disease population (Caucasian 33)	Prevalence	Meniere's disease population	Canadians	None	A1555G, A827G, C1494T	No mutation 0/33
Huang et al. (2013)	Level III	Case control deaf population (Chinese)	Prevalence	Deaf	Chinese	None	A1555G, A827G, C1494T, T1095C, T1291C	6/6000, 0.1%
Guaran et al. (2013)	Level III	Cohort study	Prevalence	Deaf	Italian	None	A1555G	4/169, 2.3%
Zhu et al. (2014)	Level IV	Case series	Penetrance	Single family pedigree	Chinese	Aminoglycoside	A1555G	Penetrance varies=10-52%; risk of deafness= heteroplasmy levels
Liang et al. (2013)	Level III	Case series	Penetrance	Single family pedigree	Chinese	tRNAle	A1555G, A4317G	Penetrance high 66.7% and 81%
Yang et al. (2013)	Level III	Case control	Prevalence	General population	N/W China (Tibet, Tu and Mongolians)	None	A1555G, C1494T	13/189, 6.9%
Zhang et al. (2013)	Level III	Cohort	Prevalence	Deaf	Chinese	None	A1555G, C1494T	25/215, 11.6%
Yao et al. (2013)	Level III	Case control	Prevalence	Deaf and general population	Chinese	None	A1555G, C1494T	Case 6/227=2.64% Control 0/200
Wang et al. (2011)	Level III	Cohort	Prevalence	Deaf	Chinese	None	A1555G, C1494T	29/1448, 1.8%

(Continued)

Table 1: (Continued)

Paper	Level of evidence	Type of paper	What is the Study population focus	Race	Drug	Mutation	Outcome
Stefanovska <i>et al.</i> (2012)	Level III	Cohort	Deaf	Macedonia	Aminoglycoside	A1555G, C1494T	0/130, 0%
Damilenko <i>et al.</i> (2012)	Level III	Case control	General	Belarius	None	A1555G, C1494T	2/391, 0.55%
Zohour <i>et al.</i> (2012)	Level III	Cohort	Prelingual deaf	Iranian	None	A1555G, C1494T, A7445G	8/2000, 0.4%
Cai <i>et al.</i>	Level III	Cohort	General neonantal	China	None	A1555G	2/1000, 0.2%
Zhong <i>et al.</i> (2013)	Level III	Cohort	General neonantal	China	None	A1555G, C1494T, A7445G	3225/58, 97, 5.52%
Nahil <i>et al.</i> (2010)	Level III	Case control	General	Morocco	None	A1555G	6/164, 3.6%

TB: Tuberculosis; HL: Hearing loss; NICU: Neonatal intensive care unit; LBW: Low birth weight; NSHL: Nonsyndromic hearing loss; MDR: Multi drug resistant; SNHL: Sensorineural hearing loss

aminoglycoside exposure) among Koreans^[26] was estimated between 28.6% and 75%, with an average of 60.8%. This is similar to that recorded for a large Arab-Israeli population (65.4%)^[47] and compares with the Spanish population (54.1%).^[25] It differs significantly in the Chinese population with a relatively low penetrance ranging from 4% to 18%,^[23,37,48,49] a factor to consider when deciding on the merits of population screening. Other factors worthy of consideration that may explain variations in clinical expression include the total dose of the aminoglycoside administered, other potentiating medications given simultaneously as well as the age of the patient. Extremes of ages appear to be more vulnerable.^[26]

Mitochondrially encoded 12S RNA gene mutation on its own is insufficient to produce significant hearing loss and, therefore, aminoglycoside exposure is necessary for full expression of the mutation and for hearing loss to occur.^[7,49-52]

Globally, it is estimated that 10-20% of patients with aminoglycoside-induced ototoxicity carry the MT-RNR1 mutation.^[35,53] This suggests that a significant percentage of non-MT-RNR1 gene carriers may also develop SNHL resulting from aminoglycoside ototoxicity. Some studies showed no correlation between aminoglycoside blood levels and development of ototoxicity^[54-58] in contrast to an earlier finding that high serum levels of amikacin were significantly associated with the development of cochlear toxicity.^[59] In addition, some idiosyncratic reactions (resulting in profound hearing losses) following exposure to an otherwise “low-dose” of an aminoglycoside in some individuals have been reported.^[56] Under-reporting of MT-RNR1 genes due to non-screening or incomplete assessment of the patients for all variations of mutations of the MT-RNR1 genes may be responsible. However, 38.5% of the documentations on prevalence of MT-RNR1 in our study recorded 0 (0%) prevalence [Figure 2], which hypothetically support the notion that the occurrence, spectrum and distribution of the gene are narrow. Hence, there is a need for the identification of susceptible populations for the genetic screening rather than the general population.

Mechanism of action

The exact biochemical mechanism of ototoxicity related to the various MT-RNR1 mutations is unclear. There is evidence to suggest the most common mutations (A1555G and C1494T) tend to reduce the accuracy of the translation in the mitochondria to render the ribosome decoding site hyper-susceptible to aminoglycoside.^[60,61] The mutations locate to

the penultimate helix of the 12S rRNA, which is a component of the aminoacyl-tRNA necessary for the decoding of the mRNA acceptor site (the A-site). The A-site is the target site of the aminoglycoside in bacteria.^[15] Therefore, a defect in this mitochondrial site in humans is thought to result in defective metabolism and elimination of the aminoglycosides and/or their by-products resulting in the exaggerated concentration of metabolites within the system and hence toxicity to susceptible organs.

Screening methods: Feasibility and cost-effectiveness

The universal application of aminoglycosides in the management of neonatal sepsis/childhood infections emphasises the clinical relevance of knowledge of the prevalence of these mutations. In the USA alone, over 5 million patients are treated with aminoglycoside antibiotics annually.^[51,53] The worldwide re-emergence of tuberculosis (TB) and the growing incidence of the multi- and extreme-drug resistant (MDR & XDR) TB that are only amenable to aminoglycosides (kanamycin and amikacin) are further cause for concern.

At least five different methods are employed in the (PCR) screening for the MT-RNR1 mutation. These include: Allele specific PCR testing, DNA sequencing, PCR-restriction fragment chain length polymorphism (PCR-RFLP) analysis and allele specific oligonucleotide hybridisation and SNaPshot analysis technique. The SNaPshot analysis technique developed at the Stellenbosch University of Cape Town (2009) possesses the advantage of multiplexing and, therefore, is capable of screening for all five common genetic variants. The quoted costs per screening an individual sample including the cost of DNA extraction is USD \$16 for SNaPshot compared to USD \$30 for PCR methods.^[16]

With over 5 million patients in the USA treated with aminoglycoside antibiotics annually and with the cost of screening using the SNaPshot technique at \$16 each, an estimated \$80 million would be incurred in screening all patients receiving aminoglycoside therapy in the USA annually. Assuming the prevalence rate of 1.85% in the USA for the MT-RNR1 mutant gene, an estimated 92,500 patients are at risk of developing ototoxic hearing loss each year. If the cost of habilitation of a severe-to-profound prelingually deaf child is truly one million dollars screening for MT-RNR1 mutations warrants further consideration, including prospective consecutive cohorts screened for the prevalence of

a relevant mutation and followed prospectively for development of aminoglycoside-induced hearing loss. This would allow better estimates of cost-effectiveness of screening programs.

Hypothetically, the cost of screening the entire world population will be about \$22.4 Billion USD against the cost of full habilitation of the potential 0.14 billion at risk that is estimated at about \$140 trillion USD. The above are quantifiable costs and exclude the non-quantifiable costs. It is true that the above figures for just MT-RNR1 may be unrealistic considering the world's limited resources chasing several global health concerns and disasters; however, it makes economic sense to prevent possible complications that might emanate from this genetic anomaly. On the other hand, effort toward reducing this occurrence appear achievable through the screening of all patients before receiving the first dose of aminoglycosides and/or the screening of every newborn within the at risk population group.

LIMITATIONS

At the onset of the study, the quality and number of the available studies for review evidence were suboptimal and hence the delay in the reporting 2 years after first presentation at the American Academy of Otorhinolaryngology Head and Neck Surgery Conference in Boston USA. This delay was necessary to enable us recruit more papers. No studies identified were felt to offer level 1 evidence (local and current random sample surveys [or censuses]). Our systematic review represents an attempt at obtaining level 2 evidence (systemic reviews and meta-analysis of surveys that allow matching to local circumstances). Many identified studies suffered poor design/sample selection and or ambiguous eligibility criteria for inclusion/exclusion of patients.

In conclusion, the global pooled prevalence of MT-RNR1 mutations in the general population appears significant with a racial bias in Chinese and Spanish populations. Patients with MT-RNR1 mutations are susceptible to aminoglycoside-induced ototoxicity, but with variable penetrance. Routine screening for MT-RNR1 mutations in the general population prior to treatment with aminoglycosides appear desirable, but currently poorly supported by the weak level of evidence available in the literature, but warrants further consideration as more data become available. Routine screening in high-risk (Chinese and Spanish populations) appear justified.

ACKNOWLEDGMENTS

The Librarian of the Children's Hospital Library of the University of British Columbia Vancouver for assisting with paper searches and retrievals.

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Cite this article as: Ibekwe TS, Bhimrao SK, Westerberg BD, Kozak FK. A meta-analysis and systematic review of the prevalence of mitochondrially encoded 12S RNA in the general population: Is there a role for screening neonates requiring aminoglycosides?. *Afr J Paediatr Surg* 2015;12:105-13.

Source of Support: The Global Surgery Foundation of the University of British Columbia supported with training grant during this study and a travel grant to the AAO-HNSF annual meeting where the paper was first presented in 2012. **Conflict of Interest:** None declared.