Priorities for hearing loss prevention and estimates of global cause-specific burdens of hearing loss: a systematic rapid review

Kavita Prasad, Ethan D Borre, Lauren K Dillard, Austin Ayer, Carolina Der, Kathleen E Bainbridge, Catherine M McMahon, Debara L Tucci, Blake S Wilson, Gillian D Sanders Schmidler, James Saunders

Summary

Background Hearing loss affects approximately 1·6 billion individuals worldwide. Many cases are preventable. We aimed to estimate the annual number of new hearing loss cases that could be attributed to meningitis, otitis media, congenital rubella syndrome, cytomegalovirus, and ototoxic medications, specifically aminoglycosides, platinum-based chemotherapeutics, and antimalarials.

Methods We used a targeted and a rapid systematic literature review to calculate yearly global incidences of each cause of hearing loss. We estimated the prevalence of hearing loss for each presumed cause. For each cause, we calculated the global number of yearly hearing loss cases associated with the exposure by multiplying the estimated exposed population by the prevalence of hearing loss associated with the exposure, accounting for mortality when warranted.

Findings An estimated 257·3 million people per year are exposed to these preventable causes of hearing loss, leading to an estimated 33·8 million new cases of hearing loss worldwide per year. Most hearing loss cases were among those with exposure to ototoxic medications (19·6 million [range 12·6 million–27·9 million] from short-course aminoglycoside therapy and 12·3 million from antimalarials). We estimated that 818 000 cases of hearing loss were caused by otitis media, 346 000 by meningitis, 114 000 by cytomegalovirus, and 59 000 by congenital rubella syndrome.

Interpretation The global burden of preventable hearing loss is large. Hearing loss that is attributable to disease sequelae or ototoxic medications contributes substantially to the global burden of hearing loss. Prevention of these conditions should be a global health priority.

Funding The US National Institute on Deafness and Other Communication Disorders and the US National Institute on Aging.

Lancet Glob Health 2024; 12: e217–25

See Comment page e173

Tufts University School of Medicine, Boston, MA, USA (K Prasad BA); **Department of Internal Medicine, Massachusetts General Hospital, Boston, MA, USA** (E D Borre MD); **Department of Otolaryngology-Head and Neck Surgery, Medical University of South Carolina, Charleston, SC, USA** (L K Dillard PhD); **University of California San Diego, San Diego, CA, USA** (A Ayer MD); **Facultad de Medicina Universidad del Desarrollo, Clínica Alemana de Santiago, Santiago, Chile** (C Der MD PhD); **National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD, USA** (Prof D L Tucci MD, K E Bainbridge PhD); **HEAR Centre, Macquarie University, Sydney, NSW, Australia** (Prof C M McMahon PhD); **Department of Head and Neck Surgery and Communication Sciences, Duke University School of Medicine, Durham, NC, USA** (Prof G D S Schmidler PhD); **Duke Global Health Institute, Duke University, Durham, NC, USA** (Prof B S Wilson PhD); **Department of Electrical & Computer Engineering** (Prof B S Wilson), **Department of Biomedical Engineering, Pratt School of Engineering, Duke University, Durham, NC, USA; Duke-Margolis Center for Health Policy, Durham, NC, USA** (Prof G D S Schmidler, Prof J Saunders MD); **Department of Surgery, Geisel School of Medicine, Dartmouth University, Lebanon, NH, USA** (Prof B S Wilson)

Introduction

Hearing loss affects over 1·57 billion people worldwide, is the third most common cause of years lived with disability, and can have serious consequences beyond the health effects.[1] Children with hearing loss can face challenges with literacy, speech and language development, and educational attainment.[2] Adults with hearing loss are more likely to experience increased depressive symptoms, social isolation, and cognitive decline compared with peers without hearing loss.[3] Globally, unaddressed hearing loss costs approximately US$1 trillion annually.[4]

WHO estimate that over 50% of hearing loss in adults worldwide can be prevented through primary prevention measures, or interventions implemented before the health effect occurs.[4] A major cause of preventable hearing loss is noise exposure, but hearing loss can also be secondary to disease-based causes (eg, infections and ototoxic medications). These causes are particularly prevalent in low-income and middle-income countries, making prevention of hearing loss a priority in these settings. Hearing loss is a common sequela of various causes and risk factors experienced throughout the life course.[4] However, the relative contribution of each cause of hearing loss is unknown.[5]

Few studies have attempted to quantify the burden of hearing loss due to preventable causes alone. The Global Burden of Diseases, Injuries, and Risk Factors (GBD) studies stratify hearing loss by meningitis, congenital, otitis media and "age-related or other", where "other" encompasses most preventable causes. Understanding the specific contribution of major preventable causes might help to prioritise and address these conditions at both the national and international level. We aimed to estimate the global caseload of hearing loss due to certain preventable, disease-based causes of hearing loss, specifically, meningitis, otitis media, congenital rubella syndrome, cytomegalovirus, and medication-induced ototoxicity from aminoglycosides, platinum-based chemotherapeutics, and antimalarials. The study was conducted in conjunction with the *Lancet* Commission on Hearing Loss[5] and in recognition that such data could inform policy decisions on how best to allocate resources.

Correspondence to:
Prof James Saunders,
Department of Surgery, Geisel
School of Medicine, Dartmouth
University, Lebanon, NH 03756,
USA
james.e.saunders@hitchcock.org

Research in context

Evidence before this study

Hearing loss affects over 1·5 billion people worldwide, with over 50% of cases estimated to be due to preventable causes. Previous studies have identified the incidence of hearing loss due to specific causes; however, we were unable to identify similar scoping reviews that estimated the annual, global number of hearing loss cases associated with disease-based causes of hearing loss. We identified and prioritised the following diseases-based causes of hearing loss according to a previously developed aetiological framework of hearing loss: meningitis, otitis media, congenital rubella syndrome, cytomegalovirus, and medication-induced ototoxicity from aminoglycosides, platinum-based chemotherapeutics, and antimalarials. We used systematic and targeted literature reviews to obtain estimates of the incidence of causes associated with increased risk of hearing loss and, when applicable, the prevalence of permanent hearing loss associated with an exposure. We did a rapid systematic review to estimate the prevalence of hearing loss associated with short-term aminoglycoside use. We searched PubMed using the terms "aminoglycosides" and "ototoxicity" with an "RCT" study type filter. Studies were required to (1) focus on aminoglycosides treatment for fewer than 16 days in humans and (2) report objectively measured hearing loss (via audiometry or otoacoustic emissions) before and after aminoglycoside exposure. We excluded studies that only investigated aminoglycosides with concurrent otoprotectant use. In studies that had an otoprotectant and non-otoprotectant group, we included data from the non-otoprotectant group only. For each disease-based cause, we combined prevalence of hearing loss estimates with incidence estimates to calculate our main study outcome: the number of yearly incident hearing loss cases due to each cause.

Added value of this study

We found that more than 257 million people per year are exposed to preventable causes of hearing loss, leading to an estimated 33·8 million incidence cases of hearing loss worldwide. Medication-induced ototoxicity, particularly from short-course aminoglycoside and antimalarial therapy, accounted for most of these cases.

Implications of all the available evidence

Given the great burden and psychosocial impact that hearing loss can have on an individual, countries around the world must work to address preventable causes of the disease. Overall, there is a paucity of data surrounding the incidence and prevalence of hearing loss associated with each preventable cause. Future efforts should focus on improving data collection and prevention.

Methods

Study overview

We used a published framework[6] to identify the following common, potentially preventable, disease-based causes of hearing loss (appendix 1): meningitis, otitis media, congenital rubella syndrome, cytomegalovirus, and medication-induced ototoxicity from use of aminoglycosides, platinum-based chemotherapeutics, and antimalarials. We used previously published systematic reviews[7–11] to obtain incidence rate estimates for conditions known to increase the risk of hearing loss and, when applicable, the prevalence of permanent hearing loss among those exposed. When prevalence data were not available, we did a rapid systematic literature review, a form of evidence synthesis similar to a traditional systematic review but more limited in scope.[12] We did our own quality assessment, with the RoB 2 (Cochrane, London, UK), a revised tool for assessing risk of bias in randomised trials, when one had not previously been done. We estimated global incidence of hearing loss for each cause, with the exception of otitis media, considering we only had a previously published estimate[7] of prevalence for this eitology. Next, we used these estimates to calculate the annual number of new hearing loss cases for each cause. Global burdens were previously published for exposure to congenital rubella syndrome, multidrug-resistant (MDR) tuberculosis, and platinum-based chemotherapies. Otherwise when published burdens were not available, we compiled country-specific or regional estimates to derive the global estimates (appendix pp 5–6). We describe our methods of estimating the annual global incidence of the selected causes, hearing loss associated with each of those causes, and methods for aggregation to obtain the study outcomes. Analyses were done with TreeAge (TreeAge, Williamstown, MA, USA), to derive the global incidence of hearing loss from otitis media, and Microsoft Excel Data Source (Microsoft, Redmond, WA, USA) for the meta-analysis.

See **Online** for appendix 1

No institutional review board approval was needed for this study.

Meningitis

We derived country-specific incidence of acute meningitis cases and deaths from the GBD 2016 study, which presents the most recent country-specific and age-specific meningitis data available.[8] For countries without GBD data, we applied the average incidence of survived meningitis by WHO region and World Bank income level.

We derived the proportion of meningitis cases resulting in (1) any hearing loss and (2) bilateral hearing loss from a systematic review[13] that defined hearing loss as greater than 25 dB (plus or minus 5 dB) bilaterally (panel 1). We calculated the country-specific proportion of meningitis cases resulting in bilateral hearing loss by applying published region-specific multipliers for disabling sequelae of meningitis.[25] For each country, we calculated the number at risk for hearing loss as the incident cases of survived meningitis (incident cases−deaths). We calculated the country-specific percentage of meningitis cases resulting in bilateral hearing loss as the product of the percentage of meningitis cases with hearing loss (ie, 14·0%), the proportion of that hearing loss that is bilateral (ie, 60·0%), and the region-specific multiplier for major meningitis sequelae (range 0·69–1·92; appendix pp 5–6).[13,25]

Otitis media

We used published estimates[7] on prevalence of permanent (sensorineural or conductive) hearing loss associated with all types of otitis media, defined as hearing loss of greater than 25 dB in the better ear (panel 1), to derive the yearly number of incident cases of permanent hearing loss (appendix p 7). We did not consider transient otitis media-related hearing losses, such as otitis media with effusion. Using the equation prevalence=incidence×duration, and a lifetime duration for permanent hearing loss, we used WHO life tables,[26] with remaining life expectancy as duration, to estimate incident hearing loss associated with otitis media. We validated our estimates via Markov simulation with age-specific life tables to derive prevalence of otitis media by age group. Last, we applied annual age-specific incidence of otitis media-related hearing loss to existing estimates of the number of people alive in each age group to estimate the yearly global incidence of hearing loss due to otitis media.[27]

Congenital rubella syndrome

We adjusted published data[14] modelling the incidence of congenital rubella syndrome in 2010 based on rubella seroprevalence to account for 38 countries that have introduced rubella-containing vaccination as of 2018 according to rates of rubella-containing vaccination coverage and reported effectiveness of the vaccine.[28]

We identified the estimated incidence of hearing loss associated with congenital rubella syndrome from a targeted review (60·0%), which defined hearing loss as hearing loss of at least 30 dB in either or both ears (panel 1).[29]

Cytomegalovirus

We identified a published global annual estimate[9] of incident congenital cytomegalovirus cases. We estimated cytomegalovirus exposure by multiplying the annual incidence of cytomegalovirus cases by the number of annual livebirths.[30]

We used a published estimate[31] of hearing loss prevalence associated with congenital cytomegalovirus infection (12·6%), defined as hearing loss of at least 20 dB in one or both ears (panel 1).

Ototoxic medications

Short-course aminoglycoside exposure

We used the WHO defined daily dose (DDD) data (per 1000 inhabitants per day) to estimate the number of

Panel 1: Hearing loss definitions

Meningitis
Bilateral hearing loss of greater than 25 (plus or minus 5 dB).[7]

Otitis media
Hearing loss in the better ear greater than 25 dB. Article did not define which frequencies were used to define hearing loss.[8]

Congenital rubella syndrome
Hearing loss of greater than one threshold shift of 30 dB in one or both ears.[14]

Cytomegalovirus
Hearing loss greater than one threshold shift of 20 dB in one or both ears.[9]

Aminoglycosides (short-course treatment, <16 days)
In four (36%) of 11 studies,[15–18] hearing loss was defined as at least 10 dB audiometric threshold shift at two or more adjacent frequencies of 0·25–8·00 kHz in one or both ears; in six (55%) studies,[11,19–23] hearing loss was defined as at least 15 dB audiometric threshold shift at two or more adjacent frequencies from 0·25–8·00 kHz in one or both ears; and in one (9%) study,[20] the American Speech-Language Hearing Association (ASHA) definition was used, which defines hearing loss as either loss in pure tone threshold of at least 20 dB in at least one frequency, at least 10 dB decrease at two adjacent frequencies, or loss of responses at three consecutive frequencies where responses were previously obtained.

Aminoglycosides (multidrug-resistant tuberculosis)
Definitions of hearing loss varied across studies used in meta-analysis.[24] In 15 (79%) of 19 studies (ASHA), hearing loss was defined as at least 10 dB decrease (audiometric threshold shift) at two adjacent frequencies; in one (5%) study, the Common Terminology Criteria for Adverse Events (CTCAE) was used, defining hearing loss as an audiometric threshold shift or absolute level of hearing loss of greater than 25 dB to 90 dB, averaged at two contiguous test frequencies in at least one ear; and three (16%) studies used other or mixed definitions.

Platinum-based cancer therapy (cisplatin or carboplatin)
Cut points for hearing loss defined by ototoxicity grading scales might vary slightly depending on authors' definitions in studies included in the published meta-analysis.[10] In 18 (21%) of 87 studies (ASHA), hearing loss was defined as at least 10 dB decrease (audiometric threshold shift) at two adjacent frequencies; in seven (8%) studies (CTCAE), hearing loss was defined as audiometric threshold shift or absolute level of hearing loss of greater than 25 dB to 90 dB, averaged at two contiguous test frequencies in at least one ear; in 22 (25%) studies, Brock criteria was used and hearing loss was defined as absolute level of hearing greater than 40 dB at 4·0 kHz and above; in three (3%) studies, the Chang grading system was used, with hearing loss defined as absolute level of hearing of at least 40 dB at 4·0 kHz and above; in six (7%) studies, Muenster classification was used, which defines losses as an absolute level of hearing greater than 4·0 kHz, greater than 20 dB to less than 40 dB; four (5%) studies based their definition of hearing loss on the International Society of Pediatric Oncology, which defines hearing loss as absolute level of hearing greater than 20 dB, at 4·0 kHz and above; in three (3%) studies, the definition of hearing loss was not specified; and 24 (28%) studies used other or mixed definitions.

Antimalarials
In one (25%) of four studies in the published meta-analysis,[11] hearing loss was defined as at least 10 dB audiometric threshold shift; one (25%) study used self-reported hearing difficulties; and in two (50%) studies the definition of hearing loss was not specified.
Audiometric threshold shifts are defined by changes in audiometric thresholds between baseline and follow-up measurements. Absolute levels of hearing loss are defined by measurement at a single point in time (ie, baseline measurements were unavailable).

people exposed to short-course aminoglycoside therapy (<16 days) and scaled estimates to country population estimates.[24,32] When country-specific DDD estimates were unavailable (128 countries), mean DDD of settings within the same region and income level were imputed. Matching regional and income data were unavailable for 22 countries, so the mean DDD for the nearest income level in that region was imputed (appendix p 8). We accounted for aminoglycoside exposure related to MDR tuberculosis treatment (which is considered separately) by converting the number of cases of MDR tuberculosis (estimated by WHO[33]) to DDDs and subtracting this number from the estimates of short-course aminoglycoside exposure. We divided this estimate of population-level DDD by an estimated 10-day mean course length of aminoglycoside treatment, which assumes individuals were exposed to no more than one course of aminoglycosides every year.[34]

Using PubMed, we did a rapid systematic literature review and meta-analysis to estimate the prevalence of aminoglycoside-induced hearing loss associated with short-course (<16 day) aminoglycoside treatment (appendix pp 9–10). In summary, we searched PubMed for randomised controlled trials published from database inception to Dec 20, 2023, using the search terms “aminoglycosides” AND “ototoxicity”. Studies were required to (1) focus on aminoglycosides treatment less than 16 days in humans, and (2) report objectively measured hearing loss (via audiometry or otoacoustic emissions) before and after aminoglycoside exposure. We excluded studies that only investigated aminoglycosides with concurrent otoprotectant use. In studies that had an otoprotectant and non-otoprotectant group, we included data from the non-otoprotectant group only. We used a random effects model to estimate pooled prevalence of hearing loss associated with short-course aminoglycoside exposure from the studies in the review (appendix p 11). We examined heterogeneity and did a subgroup analysis. Two independent reviewers assessed for risk of bias, with conflicts resolved by consensus or a third reviewer (appendix p 12).[35] For all aminoglycosides, study authors defined hearing loss as an audiometric threshold shift or absolute level of hearing loss defined by common ototoxicity grading scales (panel 1). Data extracted from included studies and used for analyses are detailed in the appendix (p 17).

Global estimates of the number of individuals treated for MDR-tuberculosis with aminoglycosides in 2019 have been published.[33] We incorporated published estimates of the prevalence of hearing loss associated with MDR-tuberculosis treatment and the global number of related cases of hearing loss. Hearing loss was defined as an audiometric threshold shift, defined by changes in audiometric thresholds between baseline and follow-up measurements, or absolute level of hearing loss, defined by thresholds measured at a single point in time (ie, when baseline measurements were unavailable), as defined by common ototoxicity grading scales or by the authors of the studies (panel 1).[33]

Cisplatin or carboplatin exposure for cancer treatment

The estimated global numbers of individuals exposed to cisplatin or carboplatin for cancer treatment for 2020 have been published.[10] We used published estimates of the prevalence of hearing loss and the global number of cases of hearing loss associated with cisplatin or carboplatin exposure. Study authors defined hearing loss as an audiometric threshold shift or absolute level of hearing loss defined by common ototoxicity grading scales (panel 1).[10]

Antimalarial exposure for malarial treatment

We estimated the global population exposed to antimalarials by using WHO estimates of malaria incidence, treatment, and mortality. We calculated the proportion of cases treated with country-specific data from the WHO Malaria Indicator Survey and Demographic and Health Survey. [36] We used data from 57 countries with estimates for (1) incident malaria cases and (2) the number of cases treated with a first-line treatment to calculate the proportion of incident cases that received treatment. [36] We accounted for mortality by subtracting estimates of the proportion of deaths (deaths/cases) from WHO data.

We identified a systematic review[11] on ototoxicity associated with antimalarial (quinine and derivatives and artemisinin-based combination therapies) exposure. In the review, hearing loss was defined as an audiometric threshold shift or absolute level of hearing loss defined by common ototoxicity grading scales or by authors of included studies (panel 1). We estimated pooled prevalence and corresponding 95% CIs of permanent hearing loss associated with antimalarial exposure via a random effects model (four studies).

Data synthesis

For each cause, we calculated the global number of yearly hearing loss cases associated with the exposure by multiplying the estimated exposed population by the prevalence of hearing loss associated with the exposure, accounting for mortality when warranted. We did sensitivity analyses as described in the appendix (p 13).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The estimated number of meningitis cases in 2016 was 2 831 000 (table). Combined with the prevalence of hearing loss per case of meningitis (14·0% [95% CI 5·4–19·6]), an estimated 346 000 individuals worldwide developed hearing loss as a sequela of meningitis in 2016

	Global exposures (per year)	Prevalence, hearing loss associated with exposure (95% CI)	Global hearing loss cases (per year)	Global hearing loss cases per year, from the sensitivity analysis (range)
Disease				
Meningitis	2 831 000	14·0% (5·4–19·6)	346 000	153 000–555 000
Otitis media	*	*	818 000	*
Congenital Rubella Syndrome	99 000	60·0% (50·5–69·3)	59 000	50 000–69 000
Cytomegalovirus	896 000	12·6% (10·2–16·5)	114 000	91 000–147 000
Ototoxicity				
Aminoglycosides (short-course treatment, <16 days)	118 676 000	16·6% (10·6–23·5)	19 641 000	12 580 000–27 889 000
Aminoglycosides (multidrug-resistant tuberculosis†)	135 000†	40·6% (32·8–66·6)	55 000	44 000–90 000
Platinum-based chemotherapy (cisplatin or carboplatin)	1 022 000	43·2% (37·9-48·6)	441 000	387 000–497 000
Antimalarials	133 736 000	9·2% (7·1–11·6)	12 276 000	9 495 000–15 513 000
Total	257 395 000	..	33 750 000	..

*Incidence of hearing loss for otitis media was derived from previously published estimates of the global incidence of otitis media-related hearing loss cases (our primary outcome), and therefore we did not need to calculate global exposures and average prevalence of hearing loss after exposure. †Exposure estimates were updated from a published systematic review[24] to account for mortality to remain consistent with presentation of exposure estimates for other causes.

***Table:* Global estimates of hearing loss cases per year attributable to preventable causes**

(table; appendix p 14). The estimated annual number of new permanent hearing loss cases attributed to otitis media was 818 000 (table; appendix p 14). The global incidence estimate of new cases of congenital rubella syndrome in 2010 was 105 000.[27] Based on changes in the proportion of rubella cases per million between 2010 (1·8%) and 2018 (1·7%), the estimated number of congenital rubella syndrome cases in 2018 was 99 000 (table).[37] The estimated prevalence of hearing loss after congenital rubella syndrome was 60·0% (50·5–69·3). The estimated number of hearing loss cases from congenital rubella syndrome was 59 000 cases per year (table; appendix p 14).[14] The incidence rate of congenital cytomegalovirus per year was 0·64%.[9] Combined with the number of global livebirths, an estimated 896 000 infants are born with cytomegalovirus annually. The prevalence of hearing loss associated with congenital cytomegalovirus was 12·6% (10·2–16·5), producing an estimated 114 000 annual cases of hearing loss attributed to cytomegalovirus (table; appendix p 14).[31]

The estimated number of individuals exposed to short-course aminoglycoside therapy in 2020 for each WHO region is given in the appendix (p 16). Hearing loss definitions varied widely across included studies (panel 1). After accounting for the exposures related to MDR-tuberculosis treatment, the estimated number of exposures was 118 676 000 (table; appendix p 14).

In our targeted, rapid literature search, we identified 71 citations detailing hearing loss prevalence associated with short-course intravenous aminoglycoside therapy (gentamicin, netilmicin, amikacin, or tobramycin; figure). Fifteen records were excluded due to duplicate results. After review for relevancy, we used 11 studies (17 articles, including 851 individuals) to estimate hearing loss prevalence (figure; appendix p 17).[15,16,18–22,39] Our assessment of the risk of bias found all studies to be low to moderate risk in all categories, except for missing outcome data, which was high in most studies because of patient illness severity that precluded audiometry (appendix p 12). Although this limitation might lead to an overestimate of hearing loss, we were unable to exclude these studies from meta-analysis as almost all studies were missing data.

The pooled prevalence of hearing loss associated with short-course aminoglycoside therapy was 16·6% (95% CI 10·6–23·5; table; appendix p 15). The estimated global incidence of ototoxic hearing loss after short-course aminoglycoside therapy was 19 641 000 cases per year (table; appendix p 14).

In 2019, an estimated 135 000 individuals worldwide were treated for MDR-tuberculosis with aminoglycoside antibiotics after accounting for deaths and treatment with other medications (table). The pooled prevalence of ototoxic hearing loss associated with MDR-tuberculosis treatment was 40·6% (95% CI 32·8–66·6; table; appendix 10). The estimated number of individuals who developed hearing loss from exposure to MDR-tuberculosis treatment was 55 000 (table; appendix p 14).[33]

In 2020, an estimated 1 022 000 individuals with cancer were exposed to treatment with cisplatin or carboplatin. The pooled prevalence estimate of ototoxic hearing loss attributable to cisplatin or carboplatin treatment was 43·2% (95% CI 37·9–48·6; table; appendix p 15). The estimated number of hearing loss cases attributable to cisplatin or carboplatin treatment was 441 000 cases per year (table; appendix p 14).[10]

In 2019, there were an estimated 229 million global incident cases of malaria. After accounting for treatment rates and estimated deaths, an estimated 133 736 000 (58·4%) individuals worldwide received treatment with potentially ototoxic antimalarials (table; appendix p 14). The pooled prevalence of likely permanent ototoxic

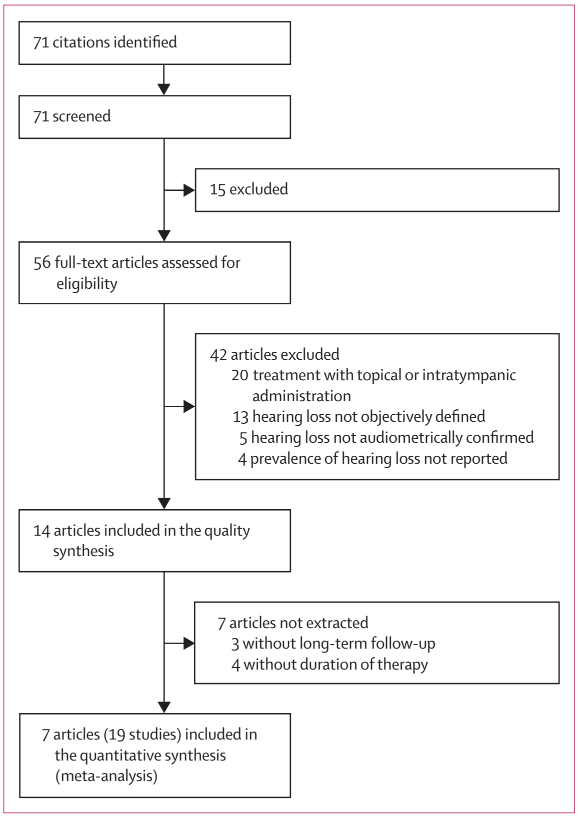

***Figure:* Study selection process for the short-course aminoglycoside systematic rapid review**
This flowchart depicts the study selection process for the short-course aminoglycoside systematic rapid review.

hearing loss attributable to antimalarial treatment was 9·2% (95% CI 7·1–11·6; table; appendix p 15).[11] Therefore, the estimated number of ototoxic hearing loss cases attributable to antimalarial treatment was 12 276 000 (table).

There were an estimated 33·8 million cases of hearing loss each year attributable to exposure to meningitis, otitis media, congenital rubella syndrome, cytomegalovirus, and ototoxic medications (table). Congenital rubella syndrome had the highest prevalence of hearing loss associated with exposure (60·0%; appendix p 15). Antimalarials accounted for the greatest estimated number of exposures, and short-course aminoglycoside therapy produced the highest estimated number of cases of hearing loss (appendix p 14).

The results of our sensitivity analysis are described and depicted in the appendix (p 19-20). The ranges of our estimates for each cause were 50 000–69 000 for congenital rubella syndrome, 91 000–147 000 for cytomegalovirus, 153 000–555 000 for meningitis, 12·6 million–27·9 million for short-course aminoglycosides, 44 000–90 000 for aminoglycosides for MDR tuberculosis treatment, 387 000–497 000 for platinum-based therapy, and 10 million–16 million for antimalarials.

Panel 2: Key hearing loss prevention recommendations

Meningitis
Incorporate pneumococcal, haemophilus influenzae type B, and meningococcal vaccines into routine immunisation programmes.

Otitis media
Incorporate pneumococcal vaccines into routine immunisation programmes and promote early detection, screening, and treatment.

Congenital rubella syndrome
Incorporate rubella-containing vaccines into routine immunisation programmes.

Cytomegalovirus
Implement effective screening programmes and increase availability to affordable treatments.

Aminoglycosides (short-course treatment, <16 days)
Use alternative pharmaceuticals or otoprotectant agents (when possible) and reduce clinical and community-based irrational aminoglycoside use.

Aminoglycosides (multidrug-resistant tuberculosis)
Follow updated WHO guidelines for multidrug-resistant tuberculosis to avoid aminoglycoside exposure.

Platinum-based chemotherapy (cisplatin or carboplatin)
Prioritise research on otoprotectant agents and prioritise bringing otoprotectant agents to market and increasing global availability.

Antimalarials
Promote primary prevention of malaria, such as bed nets, and prioritise research of mechanisms of ototoxicity and the ototoxic effects of antimalarials.

The purpose of the sensitivity analyses was to highlight the wide range of uncertainty associated with these estimates due to the lack of available, standardised data.

Discussion

We estimate that approximately 257 million individuals worldwide are exposed to preventable causes of hearing loss including meningitis, congenital rubella syndrome, cytomegalovirus, and ototoxic medications (aminoglycosides, platinum-based chemotherapy, and antimalarials) per year. We estimate these disease-based exposures account for 33·8 million new cases of permanent hearing loss per year with a wide range of severities. Our estimates capture causes occurring throughout the life course and worldwide, highlighting the need to prioritise global hearing loss prevention.

The greatest contributor to preventable cases of hearing loss in this study was exposure to ototoxic medications, approaching an estimated 32·4 million cases annually. Exposure to short -course aminoglycoside treatment and antimalarials accounted for the highest global estimates of exposure and, therefore, the greatest number of annual cases of ototoxic hearing loss. The prevalence of ototoxic hearing loss associated with treatment for MDR tuberculosis and platinum-based chemotherapy was high (>40%), but fewer exposed individuals received these treatments for MDR tuberculosis or cancer.[10,33] Our sensitivity analysis showed a high degree of uncertainty in these estimates, largely due to variations in definitions of ototoxic hearing loss, the timing of audiometric monitoring, and drug dosing regimens.

From our results, several key recommendations for primary, secondary, and tertiary prevention of hearing loss arise that might inform policy discussions concerning resource allocation. Ototoxic medications play a major role in preventable hearing loss. Primary prevention priorities (interventions implemented before the health effect occurs) for ototoxic hearing loss include (1) promoting appropriate drug use; (2) developing and prescribing alternative, less toxic pharmaceuticals; (3) administrating concomitant otoprotectant agents; and (4) preventing diseases commonly treated with ototoxic medications (panel 2).[40] Secondary and tertiary prevention strategies, or reduction of the effects of disease and early treatment of the disease to reduce lasting effects, include hearing screening to detect hearing loss early, followed by appropriate treatment. Inappropriate drug use is most common in low-income and middle-income countries, where antibiotics are often available over the counter.[41] Inappropriate drug use can be mitigated through education of patients and professionals and through policies that regulate these medications.[42] When feasible, access to alternative non-ototoxic pharmaceuticals will decrease hearing loss cases.[43,44] For example, WHO MDR-tuberculosis guidelines recommend the use of bedaquiline, rather than aminoglycosides.[45] Non-ototoxic aminoglycosides exist but have not been approved or marketed for human use. Otoprotectants (eg, sodium thiosulfate and amifostine) that are co-administered with platinum-based chemotherapy have shown protective effects in clinical trials, but are not widely available in low-income or middle-income countries.[40] Concomitant aspirin has been shown to be protective against aminoglycoside ototoxicity.[46] However, safety protocols for this treatment have not been established in children. There is a need to further invest in the development and access to alternative antibiotics and otoprotectants.

Our estimates show the high global burden of hearing loss associated with exposure to causes affecting children. Given the effects of hearing loss are often exacerbated for children,[2] comprehensive prevention strategies must be implemented. For congenital rubella syndrome, meningitis, and otitis media, efforts might focus on widespread use of effective vaccination programmes (table 3). Otitis media-related hearing loss can be reduced by addressing environmental risk factors (primary prevention) and through earlier detection and appropriate treatment to mitigate the risk of permanent hearing loss. The burden of cytomegalovirus-related hearing loss could potentially be reduced through patient education (eg, caregiver hand washing), early detection with highly sensitive screening tests, and possibly with antiviral treatments.[47]

There are several limitations to this study. The greatest limitation was lack of thorough, consistent data on burden of hearing loss due to each cause. Limitations from previously published work have been presented.[10,11,13,25,27,33,37] Importantly, studies that we used to identify pooled prevalence estimates of ototoxic hearing loss used different definitions of hearing loss (panel 1). Our pooled prevalence estimate of hearing loss associated with exposure to short-course aminoglycosides is limited by only having included studies using intravenously administered aminoglycosides, although our exposure estimates (DDD data) reflect intramuscular, inhaled, and intravenously administered treatments.[24] Because of insufficient data for some countries, we extrapolated data from countries with the same income level and WHO region, which assumes that certain regions have similar disease profiles. Estimates related to antimalarials are limited by the low number of studies in the meta-analysis and inconsistent estimates of associations between antimalarial exposure and hearing loss.[11] Congenital rubella syndrome and cytomegalovirus estimates were limited by insufficient global case reporting, requiring us to build estimates from mathematical modelling and global incidence. We tried to use the most recent data available, but our estimates come from different years. Finally, our estimates do not account for comorbidities such as ageing, noise exposure, cardiovascular health, metabolic health, perinatal health, or demographic factors.

In summary, policies and guidelines should focus on primary ototoxicity prevention via use of alternative pharmaceuticals (when possible), reducing inappropriate drug use, and bringing otoprotectant agents to market to improve access. Uniformity is needed regarding the reporting of hearing loss for various causes. Cost-effective vaccination programmes should be prioritised and expanded. For infants and children, efforts should focus on improved early detection and treatment of infectious causes of hearing loss. Finally, further research is needed to assess the global burden of other important, preventable causes (eg, noise exposure and environmental toxins) and comorbidities.

In conclusion, hearing loss that is attributable to disease sequelae or ototoxic medications contributes substantially to the global burden of hearing loss. Prevention of these conditions should be a global health priority.

Contributors

KP and EDB contributed to study conceptualisation, methodology, formal analysis, investigation, writing the original draft, manuscript

review and editing, and data visualisation. LKD contributed to conceptualisation, methodology, formal analysis, investigation, writing the original draft, and manuscript review and editing. AA contributed to formal analysis, investigation, and manuscript review and editing. CD, KEB, CMM, DLT, BSW, and GDSS contributed to conceptualisation, methodology, and manuscript review and editing. JS contributed to conceptualisation, methodology, manuscript review and editing, and supervision. All authors had access to the data in the study and had final responsibility for the decision to submit for publication. KP and EDB accessed and verified the data.

Declaration of interests

We declare no competing interests.

Data sharing

No new data were collected for this study. Any relevant documentation and protocols used for this study can be made available upon reasonable request to the corresponding author.

Acknowledgments

The US National Institute on Deafness and Other Communication Disorders and the US National Institute on Aging (3UL1-TR002553-03S3 to GDSS and F30 DC019846 to EDB) funded this study. All aspects of the study were conducted solely by the authors and there was no substantial government involvement in the design or analysis. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

References

1 Haile LM, Kamenov K, Briant PS, et al. Hearing loss prevalence and years lived with disability, 1990–2019: findings from the Global Burden of Disease Study 2019. *Lancet* 2021; **397:** 996–1009.

2 Olusanya BO, Newton VE. Global burden of childhood hearing impairment and disease control priorities for developing countries. *Lancet* 2007; **369:** 1314–17.

3 Davis A, McMahon CM, Pichora-Fuller KM, et al. Aging and hearing health: the life-course approach. *Gerontologist* 2016; **56** (suppl 2): S256–67.

4 WHO. World report on hearing. Geneva: World Health Organization, 2021.

5 Wilson BS, Tucci DL, O'Donoghue GM, Merson MH, Frankish H. A *Lancet* Commission to address the global burden of hearing loss. *Lancet* 2019; **393:** 2106–08.

6 Borre ED, Myers ER, Dubno JR, et al. Development and validation of DeciBHAL-US: a novel microsimulation model of hearing loss across the lifespan in the United States. *EClinicalMedicine* 2022; **44:** 101268.

7 Monasta L, Ronfani L, Marchetti F, et al. Burden of disease caused by otitis media: systematic review and global estimates. *PLoS One* 2012; **7:** e36226.

8 Zunt JR, Kassebaum NJ, Blake N, et al. Global, regional, and national burden of meningitis, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2018; **17:** 1061–82.

9 Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol* 2007; **17:** 253–76.

10 Dillard LK, Lopez-Perez L, Martinez RX, Fullerton AM, Chadha S, McMahon CM. Global burden of ototoxic hearing loss associated with platinum-based cancer treatment: a systematic review and meta-analysis. *Cancer Epidemiol* 2022; **79:** 102203.

11 Dillard LK, Fullerton AM, McMahon CM. Ototoxic hearing loss from antimalarials: a systematic narrative review. *Travel Med Infect Dis* 2021; **43:** 102117.

12 Ganann R, Ciliska D, Thomas H. Expediting systematic reviews: methods and implications of rapid reviews. *Implement Sci* 2010; **5:** 56.

13 Rodenburg-Vlot MB, Ruytjens L, Oostenbrink R, Goedegebure A, van der Schroeff MP. Systematic review: incidence and course of hearing loss caused by bacterial meningitis: in search of an optimal timed audiological follow-up. *Otol Neurotol* 2016; **37:** 1–8.

14 Patel MK, Antoni S, Danovaro-Holliday MC, et al. The epidemiology of rubella, 2007–18: an ecological analysis of surveillance data. *Lancet Glob Health* 2020; **8:** e1399–407.

15 Kharkheli E, Kevanishvili Z, Maglakelidze T, Davitashvili O, Schacht J. Does vitamin E prevent gentamicin-induced ototoxicity? *Georgian Med News* 2007; **146:** 14–17.

16 Moore RD, Smith CR, Lietman PS. Risk factors for the development of auditory toxicity in patients receiving aminoglycosides. *J Infect Dis* 1984; **149:** 23–30.

17 Prins JM, Büller HR, Kuijper EJ, Tange RA, Speelman P. Once versus thrice daily gentamicin in patients with serious infections. *Lancet* 1993; **341:** 335–39.

18 Sánchez-Alcaraz A, Vargas A, Quintana MB, et al. Therapeutic drug monitoring of tobramycin: once-daily versus twice-daily dosage schedules. *J Clin Pharm Ther* 1998; **23:** 367–73.

19 Bernstein JM, Gorse GJ, Linzmayer MI, et al. Relative efficacy and toxicity of netilmicin and tobramycin in oncology patients. *Arch Intern Med* 1986; **146:** 2329–34.

20 Feldman L, Efrati S, Eviatar E, et al. Gentamicin-induced ototoxicity in hemodialysis patients is ameliorated by N-acetylcysteine. *Kidney Int* 2007; **72:** 359–63.

21 Gorse GJ, Bernstein JM, Cronin RE, Etzell PS. A comparison of netilmicin and tobramycin therapy in patients with renal impairment. *Scand J Infect Dis* 1992; **24:** 503–14.

22 Herting RL, Lorber RR, Miller M, Danzig MR. Multicenter comparative evaluation of netilmicin and gentamicin in adult patients. Efficacy and safety. *Arzneimittelforschung* 1981; **31:** 366–70.

23 Prins JM, Büller HR, Kuijper EJ, Tange RA, Speelman P. Once-daily gentamicin versus once-daily netilmicin in patients with serious infections—a randomized clinical trial. *J Antimicrob Chemother* 1994; **33:** 823–35.

24 WHO. WHO report on surveillance of antibiotic consumption: 2016–18 early implementation. Geneva: World Health Organization, 2018.

25 Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10:** 317–28.

26 WHO. Life tables by WHO region. World Health Organization. https://www.who.int/data/gho/data/indicators/indicator-details/GHO/gho-ghe-life-tables-by-country (accessed Dec 1, 2021).

27 Vynnycky E, Adams EJ, Cutts FT, et al. Using seroprevalence and immunisation coverage data to estimate the global burden of congenital rubella syndrome, 1996–2010: a systematic review. *PLoS One* 2016; **11:** e0149160.

28 Zimmerman LA, Knapp JK, Antoni S, Grant GB, Reef SE. Progress toward rubella and congenital rubella syndrome control and elimination—worldwide, 2012–2020. *MMWR Morb Mortal Wkly Rep* 2022; **71:** 196–201.

29 Reef SE, Plotkin S, Cordero JF, et al. Preparing for elimination of congenital Rubella syndrome (CRS): summary of a workshop on CRS elimination in the United States. *Clin Infect Dis* 2000; **31:** 85–95.

30 Wang H, Abbas KM, Abbasifard M, et al. Global age-sex-specific fertility, mortality, healthy life expectancy (HALE), and population estimates in 204 countries and territories, 1950–2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396:** 1160–203.

31 Goderis J, De Leenheer E, Smets K, Van Hoecke H, Keymeulen A, Dhooge I. Hearing loss and congenital CMV infection: a systematic review. *Pediatrics* 2014; **134:** 972–82.

32 World Bank. Population, total world development indicators. The World Bank Group, 2020. https://data.worldbank.org/indicator/SP.POP.TOTL (accessed Dec 1, 2021).

33 Dillard LK, Martinez RX, Perez LL, Fullerton AM, Chadha S, McMahon CM. Prevalence of aminoglycoside-induced hearing loss in drug-resistant tuberculosis patients: a systematic review. *J Infect* 2021; **83:** 27–36.

34 Paterson DL, Robson JM, Wagener MM. Risk factors for toxicity in elderly patients given aminoglycosides once daily. *J Gen Intern Med* 1998; **13:** 735–39.

35 Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366:** l4898.

36 WHO. World malaria report 2020: 20 years of global progress and challenges. Geneva: World Health Organization, 2020.

37 Simons EA, Reef SE, Cooper LZ, Zimmerman L, Thompson KM. Systematic review of the manifestations of congenital rubella syndrome in infants and characterization of disability-adjusted life years (DALYs). *Risk Anal* 2016; **36:** 1332–56

38 Sha SH, Qiu JH, Schacht J. Aspirin to prevent gentamicin-induced hearing loss. *N Engl J Med* 2006; **354:** 1856–57.

39 Tange RA, Dreschler WA, Prins JM, Büller HR, Kuijper EJ, Speelman P. Ototoxicity and nephrotoxicity of gentamicin vs netilmicin in patients with serious infections. A randomized clinical trial. *Clin Otolaryngol Allied Sci* 1995; **20:** 118–23.

40 Waissbluth S. Clinical trials evaluating transtympanic otoprotectants for cisplatin-induced ototoxicity: what do we know so far? *Eur Arch Otorhinolaryngol* 2020; **277:** 2413–22.

41 Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: a systematic review. *Lancet Infect Dis* 2011; **11:** 692–701.

42 WHO. Guidelines for the regulatory assessment of medicinal products for use in self-medication. Geneva: World Health Organization, 2000.

43 Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline-pretomanid-linezolid regimens for drug-resistant tuberculosis. *N Engl J Med* 2022; **387:** 810–23.

44 Centers for Disease Control and Prevention. Provisional CDC guidance for the use of pretomanid as part of a regimen (bedaquiline, pretomanid, and linezolid [BPaL]) to treat drug-resistant tuberculosis disease. Atlanta: Centers for Disease Control and Prevention, 2022.

45 WHO. WHO consolidated guidelines on tuberculosis. Module 4: treatment-drug-resistant tuberculosis treatment. Geneva: World Health Organization, 2020.

46 Kyle ME, Wang JC, Shin JJ. Ubiquitous aspirin: a systematic review of its impact on sensorineural hearing loss. *Otolaryngol Head Neck Surg* 2015; **152:** 23–41.

47 Huang Y, Wang H, Li T, et al. Comparison of detection strategies for screening and confirming congenital cytomegalovirus infection in newborns in a highly seroprevalent population: a mother-child cohort study. *Lancet Reg Health West Pac* 2021; **12:** 100182.