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The Risk of Meningitis After Cochlear Implantation: A Systematic Review and Meta-Analysis

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Abstract

Objective. This study aims to estimate the rate of postoperative meningitis (both immediate and long-term) in patients following cochlear implants (CIs). It aims to do so through a systematic review and meta-analysis of published studies tracking complications after CIs.

Data Sources. MEDLINE, Embase, and Cochrane Library.

Review Methods. This review was performed in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Studies tracking complications following CIs in patients were included. Exclusion criteria included non-English language studies and case series reporting <10 patients. Bias risk was evaluated using the Newcastle-Ottawa Scale. Meta-analysis was performed through DerSimonian and Laird random-effects models.

Results. A total of 116/1931 studies met the inclusion criteria and were included in the meta-analysis. Overall, there were 112 cases of meningitis in 58,940 patients after CIs. Meta-analysis estimated an overall rate of postoperative meningitis of 0.07% (95% confidence interval [CIs], 0.03%-0.1%; $I^2 = 55\%$). Subgroup meta-analysis showed this rate had 95% CIs crossing 0% in implanted patients who received the pneumococcal vaccine, antibiotic prophylaxis, those with postoperative acute otitis media (AOM), and those implanted less than 5 years.

Conclusion. Meningitis is a rare complication following CIs. Our estimated rates of meningitis after CIs appear lower than prior estimates based on epidemiological studies in the early 2000s. However, the rate still appears higher than the baseline rate in the general population. The risk was very low in implanted patients who received the pneumococcal vaccine, antibiotic prophylaxis, received unilateral or bilateral implantations, developed AOM, those implanted with a round window or cochleostomy techniques, and those under 5 years.

Keywords

antibiotics, cochlear implant, meningitis, otitis media, postoperative complications, postoperative meningitis, vaccination

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Cochlear implants (CIs) involve opening the cochlea and inserting an electrode array close to the auditory nerve, enabling direct stimulation of this nerve.[1] The implantation procedure is generally very safe.[2] However, as with all surgical procedures, there are potential complications associated with CIs. These can be divided into minor complications (eg, temporary taste change), and major complications that often require revision surgery or hospitalization (eg, meningitis).

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An apparent link between meningitis following cochlear implantation came to prominence in 2002, when the US Food and Drug Administration (FDA) received reports of this association, including 9 deaths.[2,3] Following this, a large epidemiological study was commissioned in 2002 and found that children under 6 years of age receiving CIs were at a significantly higher risk of meningitis compared to children from the general population.[4] A finding of additional concern was that risk remained elevated beyond the immediate postoperative period.[5]

In these studies, certain factors were recognized as increasing the risk of postoperative meningitis. These include the use of a "positioner" during implant surgery, which was subsequently withdrawn by the manufacturer.[4] This was a plastic shim that pressed the implanted electrode against the medial wall of the cochlea, closer to the auditory nerve cell bodies in the modiolus. However, in doing so, it was thought to damage the cochlear wall, facilitating infection spread.[6] Since then, further studies have proposed several other risk factors such as young age, postoperative otitis media, and vaccination status against pneumococcus.[7,8] However, there is a lack of published data stratifying risk in those implanted who have these risk factors.

Given the potentially serious consequences of meningitis, it is important for surgeons and patients to fully appreciate the level of this risk following CIs. Complications from meningitis, particularly bacterial meningitis, can be devastating and includes septic shock, organ failure, and death. Even with adequate treatment, 5% to 10% of patients die and complications including brain injury occur in 10% to 20% of survivors.[9]

However, to the best of our knowledge, the literature lacks a comprehensive meta-analysis providing an overall estimate of this risk in patients receiving CIs. Initial estimates from epidemiological studies in the early 2000s only included pediatric cases under 6 years, and do not factor in more recent studies. Some recent studies have reported rates varying greatly from this initial estimate.[10] There is also little published data on risk in those with proposed risk factors.

The overall aim of this systematic review, therefore, is to:

(a) Calculate the overall rate of postoperative meningitis in patients after CIs through meta-analysis of published studies tracking complications.
(b) Perform a subgroup analysis to identify the risk of postoperative meningitis in those with a range of proposed risk factors.

Methods

This study was carried out in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] This review was registered prospectively on PROSPERO (Registration ID: CRD42022309520).

Eligibility Criteria

The inclusion criteria are outlined in **Table 1** using a patient, intervention, comparison, outcome, and time format. The exclusion criteria were non-English language studies, editorials, conference abstracts, and reviews. There were no limits placed on publication year. When reviews were encountered, their references were searched to identify articles matching the eligibility criteria.

Search Strategy and Information Source

The search strategy was designed with a search specialist (I.K.) from the University Medical Library and included variants of the following keywords and index terms: "cochlear implants" and "postoperative complications" including word variants of "meningitis." The full search strategy is included in Supplemental File S1, available online. The search was run on MEDLINE, Embase, and the Cochrane Library in February 2022.

Study Selection

After removing duplicates, each study was screened by 2 independent reviewers (S.G. and A.F.) by reviewing the title and abstract against the eligibility criteria. All relevant articles were then reviewed in full text by 2 independent reviewers (S.G. and A.F.). Disagreements were resolved through another reviewer (D.B.) if a consensus could not be reached.

Table 1. PICOTS Table for the Systematic Review

Population/intervention	Human individuals of any age and sex receive the cochlear implant(s). This included patients before and after the positioner was discontinued
Comparator	Not applicable
Outcome	Postoperative meningitis
Time course	Postoperative meningitis occurring at any time following the operation (both immediate and long-term)
Study design	Any peer-reviewed study reporting a cohort of patients ($n \geq 10$) undergoing cochlear implantation and tracking complications.

Abbreviation: PICOTS, patient, intervention, comparison, outcome, and time.

Data Items and Extraction

A data extraction form was designed prospectively on Microsoft Excel by S.G., D.B., and M.B. For each study, data were extracted by 2 reviewers independently (S.G. and A.F., or R.D. and R.U., or S.M. and S.S., or J.M. and H.M.). Disagreements were resolved with input from a third reviewer (D.B.). Before data extraction, all reviewers met to go through the finalized data extraction form and to clarify questions on the inclusion requirements for each section. In this meeting, the finalized form was also used to perform data extraction on examples of included studies. These steps were included to promote consistent data extraction.

From each eligible study, the following data items were retrieved: author, year, and country of publication, study design, number of patients implanted, number of bilateral and unilateral implants placed, gender breakdown, mean age at implantation, number of postoperative meningitis cases, time from implantation to the onset of meningitis, and follow-up time.

For each study, data on the following risk factors were collected, if available. The number of postoperative meningitis cases in those with a risk factor was also extracted. The selection of risk factors was determined based on the prior literature and with the advice of senior authors (D.B. and M.L.B.), and included:

(1) The use of prophylactic antibiotics.
(2) Vaccination against (i) *Streptococcus pneumoniae*, (ii) *Hemophilus influenzae*, and/or (iii) *Neisseria meningitides*.
(3) The number of patients implanted under 5 years.
(4) Postoperative acute otitis media (AOM).
(5) Unilateral versus simultaneous bilateral implantation.
(6) Round window (RW) versus cochleostomy (extended RW techniques were grouped under the RW).

Risk of Bias Assessment

The Newcastle-Ottawa Scale for Cohort Studies was used for risk of bias analysis. This quality assessment tool is used to score studies across 3 domains: study selection, comparability between cohorts, and outcome measures including follow-up rate. Risk of bias analysis for each study was performed in the same manner as data extraction (ie, independently by 2 authors).

Statistical Methods

Meta-analyses of the postoperative rates of meningitis, and corresponding 95% confidence intervals (CIs), were performed through a random-effects model of DerSimonian and Laird[12] using arcsine transformation and weighted through the inverse variance method.

Statistical heterogeneity was calculated using the I^2 and t^2 tests.[13] Funnel plots and Egger's test was used to evaluate publication bias.[14,15] Analysis of statistics was performed using R (version 4.2.1, R foundation for Statistical Computing); packages "meta" and "metafor." Statistical significance was defined as $p < .05$.

Results

Study Selection and Characteristics

Our search resulted in 2652 articles; 721 were duplicates and were removed before the screening. The titles and abstracts of the remaining 1931 unique articles were screened, yielding 659 articles. Full-text screening of these studies confirmed that 116 of these articles met the inclusion criteria.[5,16-130] The selection process, including reasons for exclusion, is shown through a PRISMA flowchart in **Figure 1**. The characteristics of the 116 included studies are shown in Table 1 in Supplemental File S2, available online.

The Overall Risk of Meningitis

In 116 studies, a total of 58,940 patients received CIs. There were 112 cases of postoperative meningitis reported. Meta-analysis of all 116 studies estimated a rate of postoperative meningitis of 0.07% (95% CI, 0.03%-0.1%; $I^2 = 55\%$). Due to a large number of studies, the R platform used for statistical analysis was unable to generate a legible Forest plot. Inspection of the funnel plot and Egger's test ($p = .23$) did not suggest significant publication bias (**Figure 2**).

The time from implantation to postoperative meningitis was reported for 67/112 cases of meningitis (**Table 2**). It was recorded that 19 cases occurred ≤1 month after implantation; 21 cases occurred >1 month and ≤12 months; 10 cases occurred >12 months and ≤24 months; and 17 cases occurred >24 months.

The causative bacterium for meningitis was reported for 55/112 cases (**Table 2**). These included *Streptococcus pneumoniae* (n = 39); nontypeable *Haemophilus influenzae* (n = 4); *Acinetobacter baumannii* (n = 3); *Haemophilus influenzae* type b (Hib) (n = 2); *Neisseria meningitidis* (n = 2); *Pseudomonas aeruginosa* (n = 2); *Escherichia coli* (n = 1); *Enterococcus* (n = 1); Group A *Streptococcus* (n = 1). The causative organism for 57 cases was unknown.

Early studies identified the presence of a positioner in CIs as a significant risk factor for postimplantation meningitis, and these models were subsequently removed from the market by the manufacturer in July 2002.[4] Thirty-seven of the 116 studies identified by the systematic review had their full cohort implanted after 2003 and thus did not use positioners (Table 1 in Supplemental File S3, available online). A total of 17,976 patients were implanted from 2003 onward and there were 18 cases of meningitis in this group. A subgroup meta-analysis of these 37 studies estimated a rate of postoperative meningitis of 0.04% (95% CI, 0.006%-0.1%, $I^2 = 36\%$). Egger's test ($p = 0.7$) revealed no evidence of publication

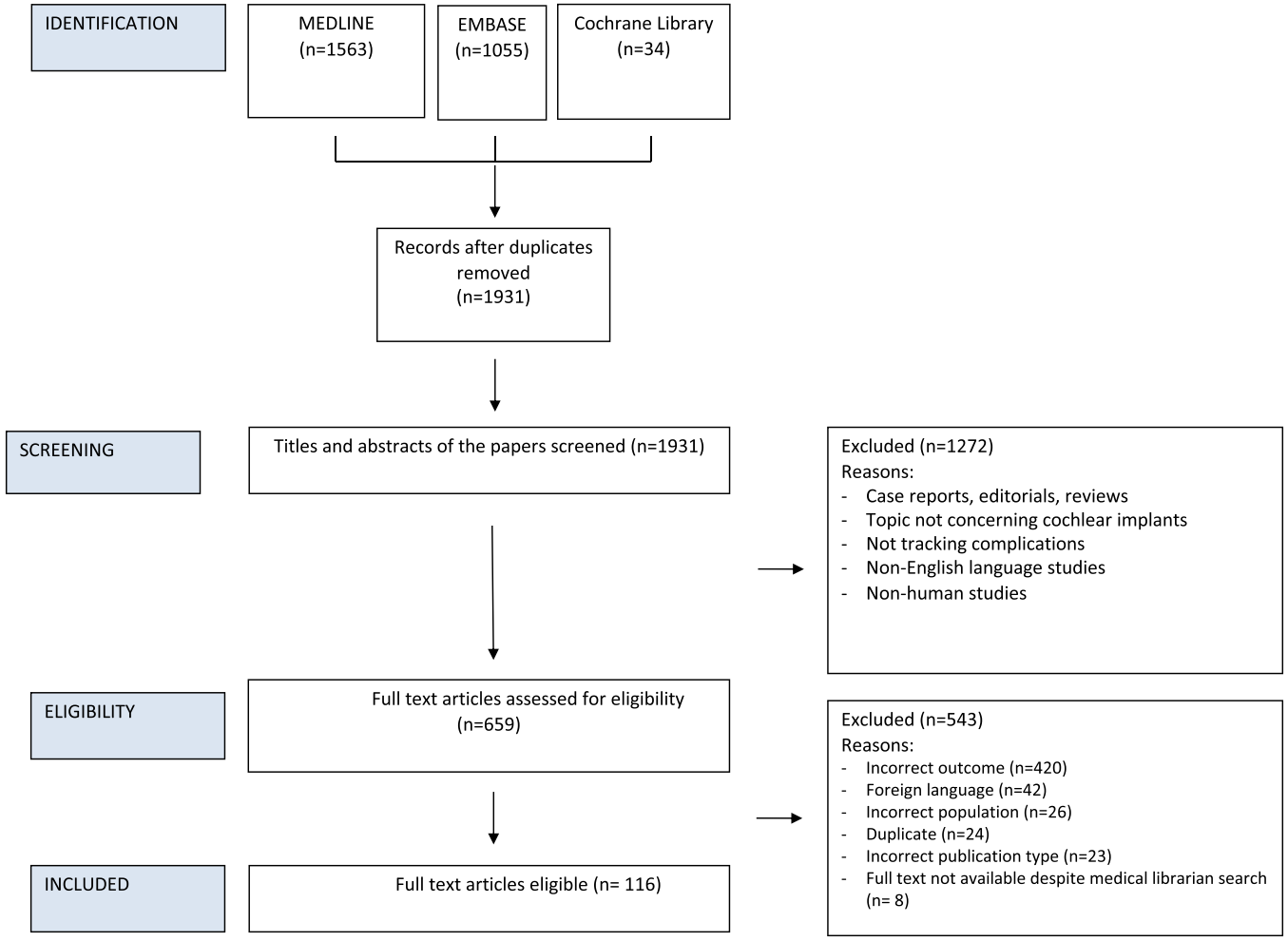

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the search and screening process.

bias; the forest plot for this set is included in Figure 1 in Supplemental File S4, available online.

Other Risk Factors

Antibiotic Prophylaxis. Twenty-four studies reported the use of prophylactic antibiotics in patients receiving CIs. These studies, including the types of antibiotics used, and the time and duration of administration, are highlighted in Table 2 in Supplemental File S3, available online. A total of 6959 patients received prophylactic antibiotics and there were 5 cases of postoperative meningitis in this group. Subgroup meta-analysis of these 24 studies showed a rate of post-operative meningitis of 0.02% (95% CI, 0.0%-0.06%; $I^2 = 0\%$). Egger's test ($p = .8$) revealed no evidence of publication bias; the forest plot for this set is included in Figure 2 in Supplemental File S4, available online.

Only 1 study out of 116 confirmed not using prophylactic antibiotics.[17] They reported 1 case of post-operative meningitis in 371 implanted patients.

Vaccination. Twelve studies reported the vaccination status of their implanted cohorts against *Streptococcus pneumoniae*. These studies, including the times of vaccination and the types of vaccines used, are shown in Table 3 in Supplemental File S3, available online. A total of 2475 patients were vaccinated against *Streptococcus pneumoniae* and there were 2 cases of meningitis in this group. Subgroup meta-analysis of these 12 studies showed a rate of postoperative meningitis of 0.02% (95% CI, 0.0%-0.1%; $I^2 = 0\%$). An Egger's test for this was not possible due to the low number of events of meningitis. The forest plot for this set is included in Figure 3 in Supplemental File S4, available online.

Only 1 study specified that their cohort had not received the pneumococcal vaccine.[17] They reported 1 case of meningitis in 371 implanted patients.

Seven studies reported the vaccination status against Hib.[22,27,64,110,111,114,121] A total of 1552 patients received the Hib vaccine and there were 0 cases of meningitis reported in this group, which precluded a meta-analysis. One study confirmed that their cohort had been vaccinated against Neisseria meningitidis in addition to *Streptococcus pneumoniae*; there were 0 cases of postoperative meningitis in 148 vaccinated patients.[56]

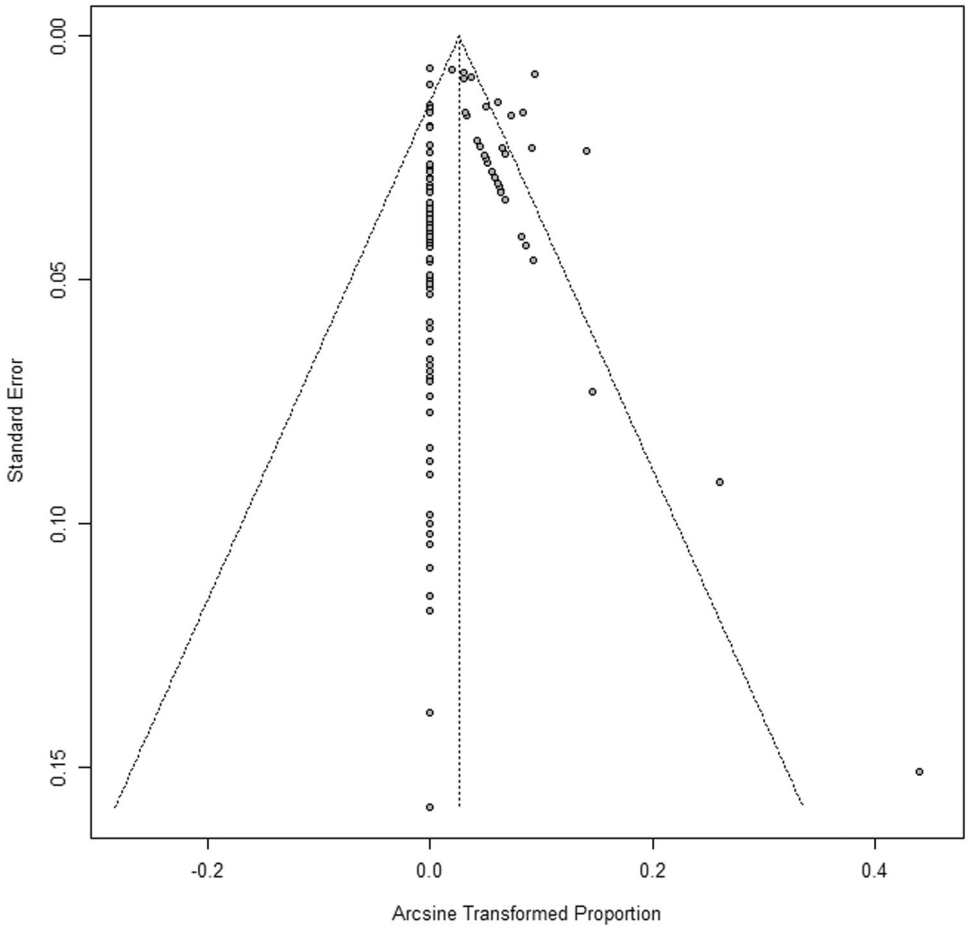

Figure 2. Funnel plot showing all included studies in the overall meta-analysis.

Unilateral Versus Bilateral Implantation. Thirty-eight studies specified the number of unilateral and simultaneous bilateral implantations placed (Table 4 in Supplemental File S3, available online). There were 8 cases of post-operative meningitis in 7793 unilateral implants and 0 cases of postoperative meningitis in 762 bilateral simultaneous implants. Subgroup meta-analysis of these 38 studies showed a rate of postoperative meningitis of 0.02% (95% CI, 0.001%-0.06%; $I^2 = 0\%$) in those with unilateral implants. Egger's test ($p = .6$) revealed no evidence of publication bias.

AOM. Twenty-three studies tracked the number of patients who developed AOM postoperatively (Table 5 in Supplemental File S3, available online). There were 254 cases of postimplant AOM and 2 cases of meningitis in this group. Subgroup meta-analysis of these 23 studies showed a rate of meningitis of 0.2% (95% CI, 0%-1.2%; $I^2 = 0\%$) in those with postoperative AOM. Egger's test ($p = .5$) revealed no evidence of publication bias; the forest plot for this set is included in Figure 4 of Supplemental File S4, available online.

Age. Twenty-six studies reported the number of patients implanted who were aged 5 years or less (Table 6 in Supplemental File S3, available online). There were 3109 children in this age group and 4 cases of postoperative meningitis. Subgroup meta-analysis of these 26 studies showed a rate of meningitis of 0.02% (95% CI, 0%-0.1%; $I^2 = 0\%$) in this group. Egger's test ($p = 1.0$) revealed no evidence of publication bias; the forest plot for this set is included in Figure 5 in Supplemental File S4, available online.

Forty-two studies reported the number of adult patients who were implanted (≥18 years). There were 13,721 adults implanted and 8 cases of postoperative meningitis (Table 7 in Supplemental File S3, available online). Meta-analysis showed a rate of meningitis of 0.02% (95% CI, 0.002%-0.04%; $I^2 = 0\%$) in adults. Egger's test ($p = .5$) revealed no evidence of publication bias; the forest plot for this set is included in Figure 6 in Supplemental File S4, available online.

Nineteen studies reported the number of patients implanted between 5 and 18 years.[17,27,38,46-48,52,58,65,79,83,92,98,108,110,114,116,117,129] There were 745 individuals in this group and 1 case of post-operative meningitis.

RW Versus Cochleostomy. Twenty studies reported the technique used for electrode insertion and specified

Table 2. Details From Studies Reporting Meningitis

Reference	Number of patients implanted	Number of patients with postoperative meningitis	Causative bacteria	Time from implantation to postoperative meningitis
Achiques et al[16]	246	1	Unknown (n = 1)	Not stated
Afsharpaiman et al[17]	371	1	Unknown (n = 1)	Not stated
Ahn et al[18]	11	2	Unknown (n = 2)	Not stated
Ajallouyean et al[20]	262	1	Unknown (n = 1)	Not stated
Biernath et al[5,a]	4265	38	*Streptococcus pneumoniae* (n = 24) *Haemophilus influenzae* type b (n = 2) *Haemophilus influenzae* nontypeable (n = 2) Group A *Streptococcus* (n = 1) *Acinetobacter baumannii* (n = 2) *Enterococcus* (n = 1) *Escherichia coli* (n = 1) Unknown (n = 5)	≤1 mo (n = 9) >1 mo and ≤12 mo (n = 14) >12 mo but ≤24 mo (n = 8) >24 mo (n = 7)
Brito et al[32]	550	1	Unknown (n = 1)	Not stated
Broomfield et al[33]	961	1	Unknown (n = 1)	Not stated
Callanan and Poje[35]	30	2	*Streptococcus pneumoniae* (n = 1) *Haemophilus influenzae* nontypeable (n = 1)	0.4 mo (n = 1), 9 mo (n = 1)
Chweya et al[38]	327	1	*Streptococcus pneumoniae* (n = 1)	36 mo
Cullen et al[40]	47	1	Unknown (n = 1)	12 mo
Dagkiran et al[42]	1357	5	Unknown (n = 5)	Not stated
Daneshi et al[44]	4346	4	*Streptococcus pneumoniae* (n = 1) Unknown (n = 3)	Not stated
Fakurnejad et al[51]	3420	3	Unknown (n = 3)	≤1 mo (n = 3)
Farinetti et al[52]	403	1	*Streptococcus pneumoniae* (n = 1)	3 mo
Güldiken et al[61]	148	1	Unknown (n = 1)	Not stated
Hashemi and Bahrani Fard[67]	275	1	*Streptococcus pneumoniae* (n = 1)	Not stated
Hoffman and Cohen[68]	5308	2	Unknown (n = 2)	Not stated
Hou et al[70]	262	1	Unknown (n = 1)	1 mo
Javia et al[72]	478	4	*Streptococcus pneumoniae* (n = 1) *Acinetobacter baumannii* (n = 1) Unknown (n = 2)	0.1 mo (n = 1) 10 mo (n = 1) 28 mo (n = 1) 32 mo (n = 1)
Johnston et al[76]	224	1	Unknown (n = 1)	Not stated
Kosec et al[81]	491	1	Unknown (n = 1)	Not stated
Kubo et al[82]	964	5	Unknown (n = 5)	Not stated
Loundon et al[90]	434	2	*Streptococcus pneumoniae* (n = 1) Unknown (n = 1)	0.1 mo (n = 1) 48 mo (n = 1)
McJunkin and Jeyakumar[94]	136	1	*Pseudomonas aeruginosa* (n = 1)	12 mo
Ovesen and Johansen[101]	300	1	Nontypeable *Haemophilus influenzae* (n = 1)	Not stated
Petersen et al[104]	1017	1	Unknown (n = 1)	3 mo
Piromchai et al[105]	458	9	Unknown (n = 9)	Not stated

(continued)

Table 2. (continued)

Reference	Number of patients implanted	Number of patients with postoperative meningitis	Causative bacteria	Time from implantation to postoperative meningitis
Sokolov et al[112]	118	1	*Neisseria meningitidis* (n = 1)	1 mo
Summerfield et al[116]	3630	5	*Streptococcus pneumoniae* (n = 3) Unknown (n = 2)	47 mo (n = 1) 14 mo (n = 1) 128 mo (n = 1) 63 mo (n = 1) 72 mo (n = 1)
Tarkan et al[118]	475	2	Unknown (n = 2)	1 mo (n = 1) 30 mo (n = 1)
Theunisse et al[119]	1222	3	*Pseudomonas aeruginosa* (n = 1) *Streptococcus pneumoniae* (n = 2)	0 mo (n = 1) 13 mo (n = 1) 26 mo (n = 1)
Vila et al[123]	421	1	*Streptococcus pneumoniae* (n = 1)	10 mo
Webb et al[124]	250	1	Unknown (n = 1)	Not stated
Wilson-Clark et al[126]	1024	7	*Streptococcus pneumoniae* (n = 2) *Neisseria meningitidis* (n = 1) Unknown (n = 4)	Not stated

The causative bacteria and time from implantation to postoperative meningitis are also included.
[a]Information on "causative organisms" and "time to meningitis" was also taken from Reefhuis et al[4] which was an older study using an identical population. Three patients had recurrent episodes of meningitis. For these, only data from the first episode is included.

whether a cochleostomy or RW approach was used (Table 8 in Supplemental File S3, available online). A cochleostomy was used in 1557 patients and there was 1 case of meningitis reported. An RW approach was used in 584 patients and there were 0 cases of meningitis reported.

Risk of Bias Analysis

The quality of included studies was assessed using the Newcastle-Ottawa Scale for Cohort Studies and is included in Table 2 in Supplemental File S2, available online. The mean score was 4.6 with a standard deviation of 1.1.

Discussion

Synopsis of Findings

Our meta-analysis highlights that meningitis is a rare complication following cochlear implantation with a postoperative rate of 0.07% (95% CI, 0.03%-0.1%). While there was no evidence of publication bias, moderate heterogeneity was present ($I^2 = 55\%$, 95% CI [44%-63%]). The risk of meningitis is influenced by the *combination* of risk factors a patient has. Many studies reported the presence of one particular risk factor but it was not clear if other risk factors were also present in these patients. For example, the risk of meningitis in a patient <5 years of age could have been increased by the presence of other risk factors such as prior meningitis. This could have contributed to the moderate heterogeneity of the meta-analysis because some studies with higher rates of postoperative meningitis could have had a patient population with a larger number of cumulative risk factors, which were unreported.

Baseline Meningitis Risk in the General Population

A global incidence of bacterial meningitis has been estimated to be around 20 cases in 100,000 people (0.02%) but varies greatly depending on factors such as country and age.[131,132] While our meta-analysis of postimplantation meningitis risk contains data from many countries, most data were derived from developed countries (Table 1 in Supplemental File S2, available online), where the risk in the general population is much lower. For instance, epidemiological studies from The Netherlands and the United States have calculated significantly lower rates of bacterial meningitis in the general population (<0.002%).[133,134]

Causative Organisms

The causative bacteria were recorded for 55/112 cases of meningitis (**Table 2**). Of those recorded, the most common agent was *Streptococcus pneumoniae* (n = 39). Other causes including Hib (n = 2) and *Neisseria meningitidis* (n = 2) were far less common. However, it should be noted that the causative organism for the majority of cases (n = 57; 51%) was not specified by studies. As these studies did not report standardized criteria for the identification of the organism type (ie, bacterial, viral, or fungal), it is possible that these

could have had nonbacterial causes. However, we did not come across any case that specifically reported a viral or fungal cause, and prior studies have only suggested an increased risk of bacterial meningitis.[3,4]

Comparison to Other Studies

A large epidemiological study by Reefhuis et al in 2002 investigated the incidence of postoperative meningitis in patients implanted ≤6 years.[4] They calculated an incidence of 239.3 cases per 100,000 person-years (95% CI, 156.4-350.6). They reported that meningitis occurred after implantation in 26 out of 4264 children, giving a rate of 0.6% (95% CI not provided).

In our meta-analysis of a similarly-aged group (<5 years), we estimate a much lower rate of 0.02% (95% CI, 0%-0.1%). We chose this cutoff for data collection, rather than <6 years, due to prior publication standards. Most studies did not collect data separately for <6 years to allow a robust meta-analysis but did so for <5 years.

There are many possible reasons for the lower rate that we calculated compared to Reefhuis et al. The majority of studies included in our <5 subgroup analysis had their cohorts partly or wholly implanted after 2003 (Table 6 in Supplemental File S3, available online). These patients would not have received models with a positioner—a significant risk factor—as this was recalled in July 2002. These patients would have also been implanted after the link with postoperative meningitis received significant attention in 2002, and after preventative recommendations such as pneumococcal vaccination were strongly put forth by organizations such as the CDC.[135] Of the 26 studies reporting the number of children under 5 years implanted, 12 studies reported that all implantations occurred from 2003 onward[20,39,43,49,59,66,100,109-111,129,130] (Table 6 in Supplemental File S3, available online). We identified 1307 children in this age group implanted after this time (ie, without a positioner) and only 1 case of postoperative meningitis. Some studies reported that a part of their cohort of under 5s was implanted after 2003, but did not specify how many, and so could not be included in this analysis (Table 6 in Supplemental File S3, available online). Nevertheless, these findings suggest that implants without positioners are associated with low meningitis rates.

We were unable to perform a further meta-analysis of this subgroup (<5 years) by factors such as vaccination status due to the low number of studies reporting this in children under 5 years. However, given the robust evidence between pneumococcal vaccination and meningitis risk reduction, vaccination likely played an additional important role in contributing to our low calculated rate.[136]

Risk Factors

Positioner

The presence of a positioner was an important risk factor for postimplant meningitis identified by epidemiological studies.[4] This model was removed from the market in July 2002.[4] Only a few studies specifically reported the presence/absence of a positioner, which was insufficient to perform a meta-analysis. Alternatively, we used studies that implanted their cohort from 2003 onward (Table 1 in Supplemental File S3, available online) as a proxy for those implanted without a positioner. Subgroup meta-analysis of this group revealed a rate of postoperative meningitis of 0.04% (95% CI, 0.006%-0.1%, $I^2 = 36\%$). This included all ages. Our findings suggest implants without positioners are linked with low postoperative meningitis rates.

Prophylactic Antibiotics

Many health regulatory bodies recommend antibiotic prophylaxis in those receiving CIs.[137,138] A recommendation by the FDA was put forth in 2003 following the spike in postoperative meningitis cases reported in North America. While there is a lack of randomized controlled trials evidencing this practice,[137,139] this recommendation remains in place to prevent the potentially serious and expensive sequelae of infectious complications, including death and re-implantation.

Our meta-analysis highlights that the risk of meningitis in those receiving prophylactic antibiotics is negligible. Other systematic reviews, including Cochrane reviews, have highlighted that there is little evidence that prophylactic antibiotics reduce postoperative infections in otologic surgery.[139,140] However, in this study, there was insufficient data reporting meningitis risk in those *not* receiving prophylactic antibiotics to compare risk between these groups.

Vaccination

Our meta-analysis indicates that the rate of postoperative meningitis in implanted patients who received the pneumococcal vaccine is negligible, with low levels of heterogeneity (0.02% [95% CI, 0.0%-0.1%; $I^2 = 0\%$]).

Only 1 study provided data from an unvaccinated cohort, which was insufficient to perform an odds ratio meta-analysis to compare risk between those vaccinated and unvaccinated. However, there is robust evidence that pneumococcal vaccination significantly reduces the incidence of *Pneumococcal meningitis* as well as hospitalizations and deaths from this condition in the general population.[136,141] It is likely that pneumococcal vaccination played an important role in the low meningitis rate we calculated in the vaccinated implanted cohort.

Due to the evidence underlying efficacy, pneumococcal vaccinations form a part of routine childhood immunizations in many countries. Many national health organizations, including the CDC, have identified CI recipients as a high-risk group, and have recommended up-to-date vaccinations prior to implantation, as well as an additional 23-valent pneumococcal polysaccharide vaccine (PPSV23) in those over 2 years.[142] Recently in 2022, the CDC

updated their guidelines to include the use of a single conjugate vaccine (PCV20) in unvaccinated adults receiving CIs.[142] If the PCV15 conjugate vaccine is used in this group, it is still recommended that this is followed by a dose of PPSV23.

In Britain, the PCV15 and PCV20 vaccines are not included in the national immunization framework. For CI recipients, the UK Government and National Institute for Health and Care Excellence recommend an additional dose of PPSV23 in those over 2 years following routine childhood immunization with PCV13. In unvaccinated or incompletely unvaccinated recipients less than 10 years, an additional dose of PCV13 is also recommended.[143,144] In recipients over 10 years, no further PCV13 vaccination is required irrespective of PCV vaccination history, and a single dose of PPSV23 is advised.

There were no cases of meningitis encountered in the small number of studies that confirmed vaccination against Hib and *Neisseria meningitidis*. While there is no evidence that patients with CIs are more likely to get meningitis from these organisms compared to people without implants, these vaccines are typically featured in routine immunizations to prevent potentially serious consequences from this baseline risk, including death.

AOM

Some authors have proposed that AOM might be a risk factor for postimplant meningitis.[4,8] Bacteria from the infected middle ear could contribute to meningitis by passing through to the inner ear, where the electrode can act as a nidus for infection. Our meta-analysis suggests that the risk of meningitis in those who develop postoperative AOM remains negligible. Strategies to reduce this risk in postoperative AOM include early treatment with antibiotics.[8] However, most studies did not specify whether the cases of postoperative AOM encountered were treated. This is important to note as the low rate could be a consequence of AOM being successfully treated; the rate in untreated AOM might be potentially higher.

Age

A large number of children receive CIs before 5 years of age, and an increasing number are receiving implants before 12 months.[145] Our meta-analysis suggests that the rate of meningitis in children implanted 5 years or younger is negligible. Another systematic review reporting complications in children implanted under 12 months also reported a negligible rate of meningitis.[10] A large number of adults also receive CIs,[146] and our meta-analysis also highlights low rates in this group.

RW Versus Cochleostomy

The 2 main methods of electrode insertion are the RW approach and cochleostomy. A variant of the RW approach involves extending the edges of the RW prior to electrode insertion (extended RW technique). While the traditional RW technique was initially commonplace, the cochleostomy regained popularity in the 2000s as the early multichannel electrodes were found to buckle and cause cochlear trauma with RW insertion.[147] However, recent evidence suggests no difference in cochlear trauma risk between these techniques, and improved speech perception using the RW approach.[148] A recent international survey suggests that most surgeons now use the RW insertion approach, and this technique is predominantly used in our center.[149] The role of the extended RW technique has been limited and has played a more minor role in our experience.

Prior studies have reported a low risk of postoperative complications with both main techniques and no significant difference between them.[60] In our study, the pooled rate of meningitis was negligible for both RW (1 case in 1557 patients) and cochleostomy (0 cases in 584 patients). We did not separate classical and extended RW approaches and both were grouped under the RW.

Strengths and Limitations

Our review systematically appraises the literature to report the overall rate of postoperative meningitis in patients following cochlear implantation. It includes a large number of patients (≈60,000), greatly exceeding numbers reported by prior epidemiological studies.[4] It also incorporates recent studies and patient groups (eg, >6 years) not included in initial estimates, and stratifies rate by factors such as vaccination and antibiotic prophylaxis.

However, our review also has limitations. It only included peer-reviewed publications, and there may well be cases that were not reported. Adverse events databases, such as the FDA adverse events reporting system and the Manufacturer User Facility and Distributor Experience databases were not specifically searched. While these databases might provide the numerator (cases of meningitis), they do not provide the denominator (number of patients implanted) to calculate incidence and rate.[150,151] Additional issues with these databases include underreporting and cases in other countries being missed.

We could not calculate the odds ratio for developing postoperative meningitis for each risk factor. This was due to low numbers of meningitis encountered and a lack of papers reporting data for critical sections of the odds ratio formula (eg, while there were many studies reporting risk in those vaccinated, there was only 1 reporting risk in those *unvaccinated*). Our ability to stratify rates by risk factor was also limited by the lack of information provided by individual studies. The risk of meningitis is influenced by the *combination* of risk factors a patient has. Many studies reported patients having 1 risk factor (eg, young age) but it was not clear if other risk factors were also present (eg, otitis media). This makes it difficult to calculate the risk of meningitis for each individual risk

factor on its own and is a limitation brought on by the nature of the data in the current literature.

The majority of the studies were deemed as having intermediate to high risk of bias using the Newcastle-Ottawa Scale (Table 2 in Supplemental File S2, available online). Most were observational cohorts without control (Table 1 in Supplemental File S2, available online), and thus, were scored as "N/A" for the categories "selection of the non-exposed cohort" and "comparability of cohorts on the basis of the design or analysis." In addition, many studies were scored as "N/A" in the "adequacy of follow-up of cohorts" category. We defined an adequate follow-up to be a minimum of 12 months, as some studies have found a risk to be elevated beyond the immediate postoperative period.[5] Although many studies did state an average follow-up time longer than this period, it was often not possible to determine exactly what proportion of the cohort had been followed-up for at least 12 months.

Conclusion

The overall estimated risk of postoperative meningitis (both immediate and long-term) following cochlear implantation is low at 0.07% (95% CI, 0.03%-0.1%). However, this is still higher than the baseline risk of meningitis in the general population. The risk in those implanted who received the pneumococcal vaccine, antibiotic prophylaxis, received unilateral or bilateral implantations, developed postoperative otitis media, implanted under 5 years of age, and with RW and cochleostomy techniques is very low.

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Author Contributions

Shravan V. Gowrishankar, formulating the search strategy, screening papers, designing the data extraction form and doing data extraction, risk of bias assessment, creating tables and figures, writing manuscript, the reviewed final version of the manuscript; **Alex Fleet**, contributed to the design of inclusion/exclusion criteria, screening papers, data extraction and analysis, risk of bias assessment, contributed to the writing of manuscript and creation of manuscript figures, reviewed the final version of the manuscript; **Michele Tomasoni**, data analysis and interpretation, manuscript revision; **Rory Durham**, data extraction and analysis, risk of bias assessment, manuscript revision; **Rishi Umeria**, data extraction and analysis, risk of bias assessment, manuscript revision; **Serena A. Merchant**, data extraction and analysis, risk of bias assessment, manuscript revision; **Syed F.H. Shah**, data extraction and analysis, risk of bias assessment, manuscript revision; **Jameel Muzaffar**, data extraction and analysis, risk of bias assessment, manuscript revision; **Hassan Mohammed**, data extraction and analysis, risk of bias assessment, manuscript revision; **Isla Kuhn**, developing the search strategy, carrying out the searches, sourcing the papers for inclusion; **James Tysome**, formulating study question, manuscript revision; **Matthew E. Smith**, formulating study question, manuscript revision; **Neil Donnelly**, formulating study question, manuscript revision; **Patrick Axon**, formulating study question, manuscript revision; **Manohar Bance**, formulating study question, formulating search strategy, formulating data extraction form, manuscript revision; **Daniele Borsetto**, formulating study question, formulating search strategy, formulating data extraction form, data analysis, manuscript revision.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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