

ORIGINAL ARTICLE

## Risk of Bacterial Meningitis in Children with Cochlear Implants

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### BACKGROUND

In June 2002, the Food and Drug Administration received reports of bacterial meningitis in patients with cochlear implants for treatment of hearing loss. Implants that included a positioner (a wedge inserted next to the implanted electrode to facilitate transmission of the electrical signal by pushing the electrode against the medial wall of the cochlea) were voluntarily recalled in the United States in July 2002.

### METHODS

We identified patients with meningitis and conducted a cohort study and a nested case-control investigation involving 4264 children who had received cochlear implants in the United States between January 1, 1997, and August 6, 2002, and who were less than six years of age when they received the implants. We calculated the incidence of meningitis in the cohort and assessed risk factors for meningitis among patients and among 199 controls, using data from interviews with parents and abstracted from medical records.

### RESULTS

We identified 26 children with bacterial meningitis. The incidence of meningitis caused by *Streptococcus pneumoniae* was 138.2 cases per 100,000 person-years — more than 30 times the incidence in a cohort of the same age in the general U.S. population. Postimplantation bacterial meningitis was strongly associated with the use of an implant with a positioner (odds ratio, 4.5 [95 percent confidence interval, 1.3 to 17.9], with adjustment for medical, surgical, and environmental factors) and with the joint presence of radiographic evidence of a malformation of the inner ear and a cerebrospinal fluid leak (adjusted odds ratio, 9.3 [95 percent confidence interval, 1.2 to 94.5]). The incidence of meningitis among patients who had received an implant with a positioner remained higher than the incidence among those whose implants did not have a positioner for the duration of follow-up (24 months from the time of implantation).

### CONCLUSIONS

Parents and health care providers should ensure that all children who receive cochlear implants are appropriately vaccinated and are then monitored and treated promptly for any bacterial infections after receiving the implant.

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**N**EARLY 10,000 CHILDREN IN THE UNITED States with severe-to-profound hearing loss currently have a cochlear implant, a surgically implanted device that includes an electrode array that is inserted into the cochlea.<sup>1</sup> With the use of cochlear implants, people who have severe-to-profound hearing loss may perceive sounds and learn to speak.<sup>2</sup>

In June 2002, one manufacturer of cochlear implants notified the Food and Drug Administration (FDA) of 15 reports of postimplantation bacterial meningitis in patients of any age who had received its implants. Early speculation implicated a positioner, a component used by one manufacturer in some types of implants.<sup>3</sup> This small Silastic wedge is inserted next to the implanted electrode to facilitate transmission of the electrical signal by pushing the electrode against the medial wall of the cochlea. The implants that included a positioner were voluntarily recalled by the manufacturer in July 2002.<sup>4</sup> Since the initial reports were issued, however, the other two manufacturers of cochlear implants in the United States have notified the FDA of additional cases of meningitis, principally in young children.

Because the magnitude of the problem was unknown, as were the factors, aside from the use of a positioner, that might increase the risk of meningitis among implant recipients, the Centers for Disease Control and Prevention (CDC), the FDA, and the health departments of 36 states, Chicago, New York City, and Washington, D.C., undertook an investigation. The purpose was to establish the incidence of bacterial meningitis among children with cochlear implants and to identify specific types of devices, surgical factors, and patient characteristics that might be associated with an increased risk of bacterial meningitis among recipients of cochlear implants. The focus of the investigation was young children, because they account for the majority of known cases and represent the population that will receive most cochlear implants in the future.

## METHODS

### STUDY DESIGN AND POPULATION

The investigation consisted of two parts: a cohort study to determine the incidence of bacterial meningitis among young children with cochlear implants and a nested case-control study to examine risk factors for meningitis. The study population included all children who had received a cochlear implant in the United States between January 1, 1997,

and August 6, 2002, and who were less than six years old at the time of implantation. All three companies that market cochlear implants in the United States provided warranty lists (estimated to be 95 percent complete) of children who met these criteria. We combined these lists to define a study population of 4264 children.

Nineteen cases of bacterial meningitis were identified from reports to the companies, the Adverse Event Reporting System of the FDA, and the surveillance systems of the CDC and state and local health departments. Seven additional cases were identified by means of a brief questionnaire that was mailed to the families of all children in the study population. The rate of response to the questionnaire was 57.3 percent and did not vary according to the year of implantation. The use of different methods of ascertainment and the attention paid to this issue by the media lead us to believe that our ascertainment of cases was relatively complete.

### DEFINITION AND CONFIRMATION OF CASES

A patient with meningitis was defined as a child in the study population in whom bacterial meningitis developed after the placement of a cochlear implant and before September 15, 2002. The classification of a case of meningitis as definite, probable, or possible was based on an abstraction of the medical records reviewed by two investigators using criteria developed for this study (Table 1).

### COHORT STUDY

We estimated the incidence of meningitis in the study population using the number of cases of meningitis as the numerator and the number of person-years between implantation and the diagnosis of meningitis or September 15, 2002, as the denominator. We calculated stratified rates using variables that were available for the entire cohort: type of implant, age at implantation, year of implantation, geographic region where implantation was performed, and time since implantation.

### CASE-CONTROL STUDY

The nested case-control study included all children with cases of bacterial meningitis and a random sample of 200 children who did not have postimplantation meningitis. These 200 controls were selected with the use of a stratified approach so that the distributions of the year of implantation and of manufacturers were proportionate to those in the total cohort, but controls were not individually

matched to children with meningitis. Information on risk factors in children with meningitis and controls was obtained from a parental interview that included questions about the causes of the child's hearing loss and medical history; the abstraction of the medical records for the cochlear-implant surgery and hospitalization for meningitis; and data on immunizations and medical history obtained from the primary care provider. All available information on malformations of the inner ear was reviewed, and all such malformations were classified by an otolaryngologist.<sup>5</sup>

#### STATISTICAL ANALYSIS

The cohort data were summarized with the use of the stratum-specific incidence of meningitis. The incidence according to the time since implantation was calculated for recipients of implants with a positioner and recipients of implants without a positioner, in an analysis that was limited to children who received their implants after the devices with a positioner became available in 1999.

In the case-control analysis, we assessed the possible association of postimplantation bacterial meningitis with a number of factors in the medical history: the occurrence of meningitis before implantation, the placement of tympanostomy tubes, the occurrence of otitis media, the placement of a ventriculoperitoneal shunt, other chronic medical conditions that could increase the risk of systemic infections, ossification of the cochlea, the vaccination status for pneumococcal, *Haemophilus influenzae* type b (Hib), and meningococcal vaccines, and radiographic evidence of inner-ear malformations. The demographic variables evaluated included sex, age at implantation, year of implantation, race, and geographic region.

We examined surgery-related factors, including the use of a positioner; the incomplete insertion of the electrode; a requirement for multiple attempts in order to insert the electrode; the presence of a cerebrospinal fluid leak (defined as a preexisting leak or an intraoperative leak or "gusher" resulting in rapid leakage of cerebrospinal fluid during surgery); the use of antibiotics before, during, or after the procedure; more than one implant; and signs of middle-ear inflammation at the time of surgery. Use of a positioner was defined as the use of an implant model that included the electrode positioner as a standard component (AB-5100H and AB-5100H-11, Advanced Bionics) or the use of an implant for which the positioner was optional (AB-5100, Advanced

**Table 1. Case Definitions for Definite, Probable, and Possible Bacterial Meningitis.\***

Diagnosis	Criteria
Definite	Isolation of bacteria from cerebrospinal fluid or isolation of bacteria from blood with abnormal cerebrospinal fluid and symptoms consistent with the presence of bacterial meningitis
Probable	Abnormal cerebrospinal fluid, symptoms consistent with bacterial meningitis, and evidence of bacteria in cerebrospinal fluid (on antigen testing, Gram's staining, or polymerase chain reaction), or histopathological evidence of bacterial meningitis on autopsy
Possible	Abnormal cerebrospinal fluid, symptoms consistent with bacterial meningitis, and no evidence suggesting a nonbacterial cause, or death after an unexplained illness with compatible symptoms

\* Abnormal cerebrospinal fluid was defined by two or more of the following: a cerebrospinal fluid protein level above 55 mg per deciliter, a cerebrospinal fluid white-cell count above 10 per cubic millimeter after adjustment for hemorrhagic cerebrospinal fluid (with allowance for 1 white cell per 8000 red cells), and a cerebrospinal fluid glucose level of 40 mg per deciliter (2.2 mmol per liter) or less. Symptoms consistent with the presence of bacterial meningitis included two or more of the following: fever (temperature  $\geq 38^{\circ}\text{C}$ ), stiff neck or nuchal rigidity, lethargy or altered mental status, and headache.

Bionics) in a child whose operative report indicated that the positioner was used. The postimplantation factors evaluated were the presence of tympanostomy tubes at the time of or after cochlear-implant surgery, the occurrence of otitis media after surgery, attendance at day care, and exposure to smoking in the household.<sup>6,7</sup> Because inner-ear malformations and cerebrospinal fluid leaks were strongly correlated with one another, new combination variables were created. These consisted of both inner-ear malformation and cerebrospinal fluid leak, inner-ear malformation but no cerebrospinal fluid leak, and cerebrospinal fluid leak but no inner-ear malformation.

We included in the analyses only the first implant or the first occurrence of meningitis after implantation for children who had received multiple implants or who had had multiple episodes of meningitis. Risk factors that had an association with any of the categories of meningitis with a two-sided P value of less than 0.1 on univariate analysis were included in the multivariate logistic-regression model for all cases of meningitis.

## RESULTS

### IDENTIFICATION OF CASES

A total of 29 episodes of postimplantation bacterial meningitis were identified in 26 children; 3 children

**Table 2. Episodes of Postimplantation Bacterial Meningitis and Predisposing Factors in Children Who Received a Cochlear Implant in the United States between 1997 and 2002.\***

Patient No.	Time from Implantation to Diagnosis	Age at Time of Episode	Sex	Causal Bacteria	Implant Model at Time of Episode	Radiographic Evidence of Inner-Ear Malformation	Cerebrospinal Fluid Leak or Gusher	Previous Meningitis or Ventriculoperitoneal Shunt	History of Recurrent Otitis Media	Otitis Media at Time of Hospitalization for Meningitis	Signs of Acute Otitis Media†
1	1 day	2 yr 1 mo	M	<i>Streptococcus pneumoniae</i>	CI24M	None	Neither	Neither	Yes	No	No
2	4 days	16 mo	M	<i>Acinetobacter baumannii</i>	AB-5100H	Cochlear dysplasia	Gusher	Neither	Yes	No	No
3	4 days	18 mo	M	<i>A. baumannii</i>	AB-5100	Unknown	Perioperative leak	Neither	Yes	Yes	No
4	Episode 1 Episode 2‡	4 days 2 mo	F F	<i>Enterococcus</i> Unknown	CI24M CI24M	Mondini's malformation Mondini's malformation	Gusher Gusher	Neither Meningitis	Yes Yes	Yes Yes	No No
5	10 days	23 mo	F	<i>Escherichia coli</i>	AB-5100H-11	None	Perioperative leak	Neither	Yes	Yes	No
6	13 days	2 yr	F	<i>S. pneumoniae</i>	AB-5100H-11	None	Neither	Neither	No	No	No
7	14 days	5 yr 3 mo	M	<i>S. pneumoniae</i>	AB-5100H-11	Enlarged vestibular aqueduct	Gusher	Neither	Yes	Yes	Unknown
8‡	20 days	2 yr 1 mo	M	<i>S. pneumoniae</i>	CI24RST	None	Neither	Both	Yes	No	No
9	29 days	2 yr 4 mo	F	<i>Haemophilus influenzae</i> type b	CI22M	Mondini's malformation	Preoperative leak	Meningitis	Yes	Yes	No
10	1.5 mo	3 yr	F	<i>S. pneumoniae</i>	AB-5100H-11	Unknown	Neither	Neither	Yes	Yes	No
11	1.5 mo	3 yr 10 mo	M	<i>S. pneumoniae</i>	AB-5100H	None	Neither	Neither	No	No	Yes
12	Episode 1 Episode 2	1.5 mo 9 mo	M M	<i>S. pneumoniae</i> <i>H. influenzae</i> , nontypeable	AB-5100H AB-5100H	Unknown Unknown	Unknown Unknown	Neither Meningitis	Yes Yes	Yes Yes	Yes Yes
13	2 mo	4 yr 3 mo	F	<i>S. pneumoniae</i>	AB-5100H	Common cavity	Neither	Neither	No	No	Yes
14	2 mo	4 yr	M	<i>S. pneumoniae</i>	AB-5100H	None	Neither	Neither	Yes	Yes	Unknown
15	Episode 1 Episode 2	3 mo 15 mo	M M	<i>S. pneumoniae</i> Unknown	AB-5100H AB-5100H	None None	Neither Neither	Neither Meningitis	Yes Yes	No No	Unknown Unknown
16	9 mo	3 yr 6 mo	M	<i>H. influenzae</i> , nontypeable	AB-5100H-11	Unknown	Unknown	Neither	Yes	No	Yes



had 2 episodes of bacterial meningitis each. Of the 29 episodes, 24 met the criteria for definite bacterial meningitis, and 5 met the criteria for possible bacterial meningitis. The cases of possible meningitis were associated with a cerebrospinal fluid white-cell count of 300 to 6115 per cubic millimeter, and in all but one case, there was a predominance of neutrophils. Nine episodes of bacterial meningitis were perioperative (occurring  $\leq 30$  days after surgery); 20 episodes were sporadic (occurring  $> 30$  days after surgery). Of the 20 sporadic episodes, 8 (40 percent) were in patients who had evidence of acute otitis media at presentation. One child died, and three had the implant removed during their hospitalization for meningitis.

*Streptococcus pneumoniae* accounted for 15 of the 24 episodes of bacterial meningitis with a known cause (62 percent) (Table 2). In 11 of these 15 cases (73 percent), meningitis was associated with bacteremia, and in 1 of these cases, pneumonia was present. Two children (Patient 7, a five-year-old boy, and Patient 10, a three-year-old girl) (Table 2) had received one dose of 7-valent pneumococcal conjugate vaccine (PCV7); the serotypes that caused the illness were unknown. One child (Patient 24, a three-year-old girl) had received two doses of PCV7 and had *S. pneumoniae* meningitis caused by serotype 10A—a type that is not included in PCV7. No patients received a 23-valent pneumococcal polysaccharide vaccine.

Two children had meningitis caused by Hib; it is unknown whether the serotype of these isolates was reconfirmed.<sup>8</sup> One of these children (Patient 21, a three-year-old boy) had no clinically significant medical history and was fully vaccinated against Hib. The second (Patient 9, a two-year-old girl) had received three of four recommended doses of vaccine; this child had six episodes of meningitis before receiving the cochlear implant, two of which were caused by Hib.

#### COHORT ANALYSIS

The median follow-up period for children in the cohort in whom postimplantation meningitis did not develop was 29 months (interquartile range, 15 to 45). The incidence of all cases of meningitis in the cohort was 239.3 per 100,000 person-years (95 percent confidence interval, 156.4 to 350.6). Meningitis caused by *S. pneumoniae* accounted for 138.2 cases per 100,000 person-years (95 percent confidence interval, 77.4 to 227.9). Perioperative meningitis occurred at a rate of 2.1 cases per 1000

procedures. There were differences in the observed rate according to whether the implant type included a positioner, the type of implant, and the year of implantation (Table 3). When the analysis was restricted to children who had received an implant between 1999 and 2002, the observed incidence of bacterial meningitis among children with the AB-5100H or AB-5100H-11 implant was higher for the duration of follow-up than the incidence among those with implant models that did not include a positioner (Table 4 and Supplementary Appendix 1 [available with the full text of this article at <http://www.nejm.org>]), although the 95 percent confidence intervals for the incidence in the two groups overlapped.

#### CASE-CONTROL ANALYSIS

We reviewed the implant-surgery records of 24 of the patients with bacterial meningitis (92 percent) and 186 of 200 controls (93 percent). One control was excluded from the analysis because she was more than six years old at the time of surgery. Interviews were conducted with parents of all 26 patients with meningitis and with parents of 161 of the 199 remaining controls (81 percent). We received information from primary care providers for 20 of the patients with meningitis (77 percent) and 159 of the controls (80 percent).

Univariate analyses showed possible associations between several risk factors and one or more subcategories of meningitis (Table 5). These risk factors included a history of placement of a ventriculo-peritoneal shunt; a history of otitis media before implantation; the presence of inner-ear malformations combined with a cerebrospinal fluid leak and a cerebrospinal fluid leak alone; the use of a positioner; incomplete insertion of the electrode; signs of middle-ear inflammation at the time of implantation; and exposure to smoking in the household. The risk factors for sporadic meningitis were different from those for perioperative meningitis: the use of a positioner was more strongly associated with the occurrence of sporadic meningitis, and incomplete insertion of the electrode and a cerebrospinal fluid leak without an inner-ear malformation were associated with the occurrence of perioperative meningitis but not with the occurrence of sporadic meningitis.

On multivariate modeling, the use of a positioner was significantly associated with the occurrence of meningitis (odds ratio, 4.5; 95 percent confidence interval, 1.3 to 17.9), as was inner-ear malforma-

**Table 3. Incidence of All Cases of Bacterial Meningitis (Sporadic or Perioperative) and of Sporadic Meningitis among Children Who Received a Cochlear Implant.\***

Variable	All Cases of Meningitis		Sporadic Meningitis	
	No. of Cases	Incidence/100,000 Person-Yr (95% CI)	No. of Cases	Incidence/100,000 Person-Yr (95% CI)
All children	26	239.3 (156.4–350.6)	17	161.8 (94.2–259.0)
Implant with a positioner				
No	10	103.6 (49.7–190.3)	5	53.3 (17.3–124.4)
Yes†	16	1332.7 (762.0–2163.6)	12	1060.3 (547.9–1851.5)
Implant model‡				
AB-5100H-11	7	1687.4 (678.6–3474.1)	4	1062.6 (289.6–2719.0)
AB-5100H	9	1146.2 (524.3–2175.0)	8	1059.7 (457.6–2087.2)
AB-5100	2	66.2 (8.0–239.5)	1	33.8 (0.8–188.9)
CI22M	2	159.5 (19.3–575.9)	1	81.0 (2.0–451.4)
CI24M	3	82.3 (17.0–240.6)	1	28.1 (0.7–156.6)
CI24RST	2	2072.5 (251.0–7469.9)	1	1102.9 (28.0–6132.2)
C40+HS	1	2660.8 (67.3–14,749.8)	1	2771.4 (70.2–15,359.8)
Geographic region				
Northeast	4	191.3 (52.1–489.7)	2	98.8 (12.0–356.5)
Midwest	8	264.6 (114.2–521.3)	5	188.0 (75.6–387.4)
South	11	285.6 (142.6–511.0)	7	214.9 (92.8–423.4)
West	3	163.9 (33.8–479.2)	3	169.8 (35.0–496.1)
Year of implantation§				
1997–1998	3	59.9 (12.4–174.8)	1	20.3 (0.5–113.2)
1999–2000	11	252.6 (126.1–451.8)	8	189.6 (81.8–373.4)
2001–2002	12	802.2 (414.6–1401.0)	8	585.7 (253.0–1153.9)
Age at implantation				
1 yr	8	335.4 (144.8–660.7)	5	217.8 (70.7–508.3)
2 yr	8	262.3 (113.3–516.8)	4	135.4 (36.8–346.6)
3 yr	5	209.9 (68.2–489.8)	4	173.3 (47.2–443.6)
4 yr	1	61.8 (1.6–344.3)	1	63.8 (1.6–355.3)
5 yr	4	299.0 (81.5–765.5)	3	231.2 (47.6–675.7)

\* Perioperative meningitis was defined as meningitis with an onset within 30 days after surgery, and sporadic meningitis as that with an onset more than 30 days after surgery. CI denotes confidence interval.

† Data are for models AB-5100H and AB-5100H-11 (Advanced Bionics); data on children who received model 5100H (Advanced Bionics), for which the use of a positioner was optional, were included in the group without a positioner, because information on the use or nonuse of the positioner was not available for children who were not included in the case-control investigation.

‡ No cases were reported among children who received implant models CI24R(CS), who accounted for 1300 person-years, C40+H, who accounted for 301 person-years, or C40+HGB, who accounted for 10 person-years.

§ A test for trend showed a significant increase over time: chi-square statistic for trend=19.9, with 1 df;  $P<0.001$ .

**Table 4. Incidence of Bacterial Meningitis among Children Who Received Implant Models Including a Positioner as Compared with Those Who Received Other Models, 1999–2002.\***

Months of Follow-up	Implant Models with a Positioner†		Other Implant Models		Incidence-Rate Ratio (95% CI)
	No. of Cases	Incidence/100,000 Person-Yr (95% CI)	No. of Cases	Incidence/100,000 Person-Yr (95% CI)	
≤1.0	4	5818 (1580–14,841)	3	1528 (316–4472)	3.8 (0.6–25.9)
1.1–3.0	5	3676 (1194–8579)	0	0 (0–948)	Undefined (2.6–infinity)‡
3.1–6.0	1	526 (13–2932)	0	0 (0–673)	Undefined (0.1–infinity)‡
6.1–12.0	3	922 (190–2697)	2	205 (25–739)	4.5 (0.5–54.0)
12.1–18.0	2	870 (106–3140)	1	121 (3–675)	7.2 (0.4–423.8)
18.1–24.0	1	701 (18–3896)	1	150 (4–837)	4.7 (0.1–365.6)

\* This analysis was limited to children who received an implant after the devices including a positioner became available in 1999; three children in the cohort who had meningitis in 1997 or 1998 were excluded from the analysis. Confidence intervals for incidence rates and incidence-rate ratios were calculated according to the exact method under the assumption that the number of cases is a Poisson random variable.

† Data are for models AB-5100H and AB-5100H-11 (Advanced Bionics); data on children who received model 5100H (Advanced Bionics), for which the use of a positioner was optional, were included in the group without a positioner, because information on the use or nonuse of the positioner was not available for children who were not included in the case-control investigation.

‡ In instances in which the incidence-rate ratio was undefined, the lower limit for the 95 percent confidence interval was calculated according to exact methods.

tion with a cerebrospinal fluid leak (odds ratio, 9.3; 95 percent confidence interval, 1.2 to 94.5). Other factors were associated with similar adjusted and crude odds ratios, suggesting that they might be independently associated with the occurrence of bacterial meningitis; however, the 95 percent confidence intervals for these odds ratios were wide. When the analysis was limited to implants that were placed between 1999 and 2002, the adjusted odds ratio for meningitis associated with the use of a positioner increased to 5.6 (95 percent confidence interval, 1.3 to 33.5). When the analysis was limited to patients with definite cases of meningitis, the adjusted odds ratio for meningitis associated with the use of a positioner was 5.3 (95 percent confidence interval, 1.4 to 25.1).

#### DISCUSSION

The incidence of bacterial meningitis caused by *S. pneumoniae* in our study population of children who received cochlear implants when they were less than six years of age was more than 30 times the incidence of pneumococcal meningitis among children in that age group in the general U.S. popula-

tion in 2000 covered by the Active Bacterial Core Surveillance program of the CDC<sup>9</sup> (4.0 cases per 100,000 children [unpublished data]). Even among children who received an implant without a positioner, the incidence of *S. pneumoniae* meningitis was 16 times as high as the background rate in the general population for this age group. Therefore, the higher incidence of meningitis in this cohort was not fully explained by the use of positioners. Our study was not designed to determine the incidence of meningitis among children with severe-to-profound hearing loss who had not received a cochlear implant, and no data on this incidence are available. The incidence might be higher than that among children in the same age group in the general population because of underlying risk factors in such children. For example, among the controls in our study, 8.5 percent had radiographic evidence of inner-ear malformations, 3 percent had a cerebrospinal fluid leak, and 10.1 percent had a history of meningitis.

The observed incidence of meningitis increased over the six-year study period. Although this finding could reflect underascertainment in earlier years, it is also possible that there has been a true increase

**Table 5. Risk Factors for Meningitis.\***

Variable	All Meningitis		Univariate Analysis		
	Multivariate Analysis (N=26)	Univariate Analysis (N=26)	Perioperative Meningitis (N=9)	Sporadic Meningitis (N=17)	<i>S. pneumoniae</i> Meningitis (N=15)
	<i>odds ratio (95 percent confidence interval)</i>				
Implant with a positioner	4.5 (1.3–17.9)	5.6 (2.4–13.4)†	2.4 (0.5–11.4)	9.7 (3.0–31.1)†	6.0 (1.7–23.1)
Inner-ear malformation and cerebrospinal fluid leak					
Both	9.3 (1.2–94.5)	18.4 (3.4–120.3)	39.2 (4.8–320.2)	8.9 (0.7–84.3)	14.7 (1.7–119.8)
Malformation only	2.0 (0.1–15.2)	1.0 (0.1–4.8)	—‡	1.8 (0.2–9.4)	1.8 (0.2–9.4)
Leak only	6.2 (0.4–79.5)	4.9 (0.4–44.9)	14.0 (1.0–138.5)	—§	—§
Incomplete insertion of electrode	3.2 (0.5–19.7)	3.2 (0.8–10.7)	7.2 (1.0–40.9)	1.7 (0.2–8.8)	3.0 (0.5–13.1)
History of ventriculoperitoneal-shunt placement	7.1 (0.3–126.1)	3.9 (0.3–28.8)	5.9 (0.1–68.2)	2.9 (0.1–31.9)	7.2 (0.6–55.1)
Exposure to smoking in household	2.2 (0.6–7.8)	2.2 (0.9–5.2)†	3.8 (0.8–19.8)	1.7 (0.5–5.2)	2.0 (0.6–6.8)
Otitis media before implantation	2.7 (0.3–127.1)	3.7 (0.8–16.3)	—¶	2.3 (0.5–21.5)	—¶
Signs of middle-ear inflammation at implantation	1.4 (0.2–8.4)	2.3 (0.6–7.3)	4.9 (0.7–27.0)	1.3 (0.1–6.2)	3.3 (0.7–12.7)

\* Perioperative meningitis was defined as meningitis with an onset within 30 days after surgery, and sporadic meningitis as that with an onset more than 30 days after surgery. There were 199 controls included in all analyses. Univariate results included in this table are limited to those that were associated with any subcategory of meningitis with a two-sided P value of less than 0.1.

† Fisher's exact methods were not used, because the expected numbers in the contingency tables were greater than 5.

‡ There were no patients with a malformation only.

§ There were no patients with a leak only.

¶ All patients had otitis media before implantation.

in the number of cases in recent years. In part, such an increase might be attributable to the introduction of the device with the positioner in 1999. In addition, there has been a trend toward earlier placement of implants, because improved development of speech and language is associated with earlier implantation,<sup>10–12</sup> and younger children are at higher risk for meningitis.<sup>9</sup>

The company that marketed cochlear implants with a positioner voluntarily recalled those products in July 2002.<sup>4</sup> In our analysis in the cohort study, the use of the implant models with a positioner was implicated as an important risk factor for meningitis. In the case-control study, the presence of a positioner was significantly associated with the risk of sporadic meningitis but not with the risk of perioperative meningitis. The attributable fraction<sup>13</sup> of all cases of meningitis was 50.9 percent (60.7 percent for cases in children who received their implant between 1999 and 2002), suggesting that about half the cases of bacterial meningitis in implant recipients might be attributable to the use of the positioner, if a causal relation is assumed.

The reasons for the association between the use of the positioner and the occurrence of meningitis

are unclear. Possible explanations include the larger cochleostomy required for the insertion of both the electrode and the positioner, the presence of an additional foreign body in the inner ear, trauma to the fragile anatomy of the inner ear caused by the wedging of the positioner into place,<sup>14</sup> deficient formation of a fibrous-tissue seal at the site of the cochleostomy,<sup>3</sup> and a combination of these factors. A further complication for the comparison of types of implants is that the choice of a particular implant could be based on certain characteristics of the patient. For example, product labeling for the implants with positioners states that their use is contraindicated in people with ossification of the cochlea.

Overall, the risk of meningitis decreased rapidly after the perioperative period. The incidence of meningitis among children with an implant that included a positioner remained higher than that among children with other types of implants for the duration of follow-up. However, only a few cases were identified during each period, and such small numbers result in imprecise estimates; continued follow-up is needed in order to estimate the incidence of meningitis more than 24 months after implantation.

In the case-control study, the combination of radiographic evidence of an inner-ear malformation and a cerebrospinal fluid leak was associated with an increased risk of all subtypes of meningitis, and the presence of a cerebrospinal fluid leak alone was associated with an increased risk of perioperative meningitis. Children with cerebrospinal fluid leaks have been targeted for pneumococcal vaccination, because such leaks represent a known risk factor for pneumococcal meningitis.<sup>15,16</sup> Our analysis did not identify inner-ear malformations alone as a risk factor for meningitis, although case reports have noted such an association, particularly with Mondini's malformation.<sup>17-21</sup>

Our ability to assess the protective effect of pneumococcal vaccinations was limited because of the small number of vaccinated children; pneumococcal conjugate vaccine, now universally recommended for children less than two years of age, was not licensed until 2000 — late in our study period. Assessment of Hib vaccination was limited by the fact that almost all children were vaccinated before receiving a cochlear implant, as is universally recommended.<sup>22</sup>

We found that risk factors and infecting species of bacteria in cases of perioperative meningitis differed somewhat from those in cases of sporadic meningitis. Although it was difficult to interpret these differences because of the small numbers, they suggest a difference in the pathophysiology of infection. In perioperative cases, bacteria may be introduced at the time of the surgery. In sporadic cases, because of the association with cerebrospinal fluid leaks and inner-ear malformations, because 40 percent of the patients with sporadic cases had signs of otitis media at presentation, and because the main pathogens (*S. pneumoniae* and *H. influenzae*, with *Neisseria meningitidis* notably absent) are consistent with those that cause otitis media,<sup>23,24</sup> we suspect that bacteria often entered through the middle and inner ear.

The investigation included cases of meningitis occurring before September 15, 2002; we have subsequently received reports of postimplantation meningitis after this date in six children in the study population. The cases in these six children occurred from 6 to 41 months after implantation, and the causative pathogen in all six was *S. pneumoniae*. Five of these children received cochlear implants that included a positioner (AB-5100H in two and AB-5100H-11 in three), and one received a model C40+HGB implant (MED-EL).

Our findings have important implications for the prevention of meningitis in children with all types of cochlear implants. Providers should review the vaccination records of their patients who have received or are candidates for receiving cochlear implants in order to ensure that they have received pneumococcal vaccinations according to the age-appropriate schedules for high-risk children<sup>25</sup> (see Supplementary Appendix 2, available with the full text of this article at <http://www.nejm.org>) and that they have received age-appropriate Hib vaccinations. Parents should contact their child's health care provider to ensure that all recommended vaccines have been received.<sup>22</sup> Children should receive vaccinations two or more weeks before surgery.

Both parents and health care providers should remain vigilant during the months after surgery for possible signs and symptoms of meningitis. Surgeons who place cochlear implants should inform the child's health care provider and parents about any inner-ear malformations or other findings during surgery (e.g., cerebrospinal fluid leak or incomplete insertion) that could increase the risk of meningitis. Prompt diagnosis and treatment of acute otitis media might prevent the spread of infection through any possible weakness of the fibrous-tissue seal at the cochleostomy site.

Removal of an existing implant containing a positioner might not be beneficial. Because the mechanism by which the positioner increases the risk of meningitis is unknown, it is unclear whether explantation of the device would lower the risk of meningitis; in addition, explantation would place the child at risk for operative complications, including perioperative meningitis. Parents and health care providers should also consider the benefits that cochlear implants provide for children with severe-to-profound hearing loss. We hope that with appropriate use of pneumococcal vaccines and no further use of implants with a positioner, the incidence of bacterial meningitis among children with cochlear implants will decrease. However, the continued occurrence of bacterial meningitis underscores the need for parents and health care providers of all children with any type of cochlear implant to take appropriate precautions.

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## REFERENCES

1. Cochlear implants. Bethesda, Md.: National Institute on Deafness and Other Communication Disorders, 2003. (Accessed July 1, 2003, at <http://www.nidcd.nih.gov/health/hearing/coch.asp>.)
2. NIH Consensus Conference. Cochlear implants in adults and children. *JAMA* 1995; 274:1955-61.
3. Arnold W, Bredberg G, Gstottner W, et al. Meningitis following cochlear implantation: pathomechanisms, clinical symptoms, conservative and surgical treatments. *ORL J Otorhinolaryngol Relat Spec* 2002;64:382-9.
4. Advanced Bionics Corporation. Electrode positioner. (Accessed July 8, 2003, at [http://www.bionicear.com/vaccine/menin\\_implants2.html](http://www.bionicear.com/vaccine/menin_implants2.html).)
5. Jackler RK, Luxford WM, House WF. Congenital malformations of the inner ear: a classification based on embryogenesis. *Laryngoscope* 1987;97:Suppl 40:2-14.
6. Iles K, Poplawski NK, Couper RT. Passive exposure to tobacco smoke and bacterial meningitis in children. *J Paediatr Child Health* 2001;37:388-91.
7. Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. *N Engl J Med* 2000;342:681-9.
8. Serotyping discrepancies in *Haemophilus influenzae* type b disease—United States, 1998–1999. *MMWR Morb Mortal Wkly Rep* 2002;51:706-7.
9. Schuchat A, Robinson K, Wenger JD, et al. Bacterial meningitis in the United States in 1995. *N Engl J Med* 1997;337:970-6.
10. Hammes DM, Novak MA, Rotz LA, Willis M, Edmondson DM, Thomas JF. Early identification and cochlear implantation: critical factors for spoken language development. *Ann Otol Rhinol Laryngol Suppl* 2002;189:74-8.
11. Govaerts PJ, De Beukelaer C, Daemers K, et al. Outcome of cochlear implantation at different ages from 0 to 6 years. *Otol Neurotol* 2002;23:885-90.
12. Sharma A, Dorman ME, Spahr AJ. A sensitive period for the development of the central auditory system in children with cochlear implants: implications for age of implantation. *Ear Hear* 2002;23:532-9.
13. Greenland S. Attributable fraction estimation. In: Rothman KJ, Greenland S, eds. *Modern epidemiology*. 2nd ed. Philadelphia: Lippincott-Raven, 1998:295-7.
14. Richter B, Aschendorff A, Lohnstein P, Husstedt H, Nagursky H, Laszig R. Clarion 1.2 standard electrode array with partial space-filling positioner: radiological and histological evaluation in human temporal bones. *J Laryngol Otol* 2002;116:507-13.
15. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2000;49 (RR-9):1-35.
16. Kline MW. Review of recurrent bacterial meningitis. *Pediatr Infect Dis J* 1989;8: 630-4.
17. Ohlms LA, Edwards MS, Mason EO, Igarashi M, Alford BR, Smith RJ. Recurrent meningitis and Mondini dysplasia. *Arch Otolaryngol Head Neck Surg* 1990;116:608-12.
18. Herther C, Schindler RA. Mondini's dysplasia with recurrent meningitis. *Laryngoscope* 1985;95:655-8.
19. Hayashi N, Kino M, Nobori U, et al. Recurrent bacterial meningitis: secondary to malformation of the inner ear. *Clin Pediatr (Phila)* 1989;28:139-41.
20. Phelps PD, King A, Michaels L. Cochlear dysplasia and meningitis. *Am J Otol* 1994;15: 551-7.
21. Valmari P, Palva A. Recurrent meningitis due to pneumococci and non-typable *Haemophilus influenzae* in a child with a Mondini malformation. *Infection* 1986;14:36-7.
22. Recommended childhood and adolescent immunization schedule: United States, 2003. *MMWR Morb Mortal Wkly Rep* 2003; 52:Q1-Q4. [Erratum, *MMWR Morb Mortal Wkly Rep* 2003;52:191.]
23. Berman S. Otitis media in children. *N Engl J Med* 1995;332:1560-5.
24. Klein JO. Otitis media. *Clin Infect Dis* 1994;19:823-33.
25. Pneumococcal vaccination for cochlear implant recipients. *MMWR Morb Mortal Wkly Rep* 2002;51:931.

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