Changing Epidemiology of Bacterial Meningitis Since Introduction of Conjugate Vaccines: 3 Decades of National Meningitis Surveillance in The Netherlands

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Background. The epidemiology of acute bacterial meningitis has changed substantially since the introduction of conjugate vaccines.

Methods. We analyzed nationwide surveillance data of all cerebrospinal fluid isolates received by the Netherlands Reference Laboratory for Bacterial Meningitis. We assessed the impact of conjugate vaccines on incidence (defined as episodes per 100,000 population per year) and for different age groups using incidence rate ratios (IRRs), comparing incidence before and after conjugate vaccine introduction.

Results. We analyzed 17,393 episodes, of which 5960 episodes (34%) occurred in preschool children (aged 3 months to 4 years). Overall, bacterial meningitis incidence decreased from 6.37 to 1.58 between 1989–1993 and 2014–2019 (IRR, 0.25 [95% confidence interval {CI}, 0.23–0.26]; P < .001). This decrease was most pronounced in preschool and school-aged children (5–15 years); IRR, 0.10 [95% CI, 0.09–0.12] and 0.08 [95% CI, 0.06–0.10]; both P < .001. The incidence was highest in young infants (<90 days) due to a high incidence of group B Streptococcus and Escherichia coli meningitis (42.48 and 19.49, respectively). Conjugate vaccines effectively reduced the incidence of Haemophilus influenzae type b, Neisseria meningitidis serogroup C, and 10 pneumococcal serotypes (IRRs, 0.02–0.04; P < .001). At the end of the observed period, Streptococcus pneumoniae caused the majority of meningitis cases (829/1616 [51%]), mostly in older adults (aged 45–64 years) and elderly adults (aged ≥65 years; incidence of 1.06 and 1.54, respectively).

Conclusions. Conjugate vaccines reduced the burden of bacterial meningitis, especially in children. The efforts for new measures to prevent bacterial meningitis should be focused on neonates and elderly, as the residual rate of disease is still high in these age groups.

Keywords. bacterial meningitis; conjugate vaccines; surveillance study; epidemiology.

Bacterial meningitis is associated with high rates of mortality and morbidity [1, 2]. The most common bacteria causing meningitis include Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae [3]. Conjugate vaccines have been developed that target specific serogroups or serotypes of these bacteria that commonly cause bacterial meningitis [3–5]. Over the past 3 decades, these conjugate vaccines have been implemented in routine pediatric immunization programs to lower the burden of disease. In the Netherlands, vaccination against H. influenzae type b (Hib) was initiated in 1993, vaccination against meningococcal serogroup C (MenC) was initiated in 2003, and the first pneumococcal conjugate vaccine (PCV) was implemented in 2006 [6]. The Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) performs nationwide surveillance and monitors the incidence of bacterial meningitis and sepsis and the effect of vaccination. Our aim was to provide a complete overview of the epidemiology of bacterial meningitis over the past 3 decades in the Netherlands.

METHODS

Patient Identification and Data Collection

Nationwide surveillance data were obtained by the NRLBM. The NRLBM receives approximately 90% of cerebrospinal fluid (CSF) isolates of all patients with bacterial meningitis in the Netherlands (±17 million population) [7, 8]. Limited clinical data, including patient age and sex, are provided in the submission template of each bacterial isolate by medical microbiology laboratories. We included all episodes of patients with a positive CSF culture between 1 July 1988 and

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30 June 2019. Episodes with missing patient date of birth were excluded. Episodes with positive blood culture but with negative CSF culture were not included in this study. Meningococcal isolates were serogrouped, and pneumococcal and *H. influenzae* isolates were serotyped by the NRLBM as previously described [9–11]. Population statistics were obtained from Statistics Netherlands with the use of StatLine [12].

**Definitions**

We categorized patients into 6 age groups: neonates and young infants (grouped as “infants” [0–89 days]), preschool children (3 months–4 years), school-aged children (5–15 years), young adults (16–44 years), older adults (45–64 years), and elderly adults (≥65 years). Several conjugate vaccines have been implemented in the Netherlands during the observed period: Hib vaccine (October 1993, first vaccination at age 2 months); MenC vaccine (June–November 2002, single vaccination for all children [1–18 years]; September 2002 included in nationwide immunization program for children >14 months) [13], later replaced by a tetravalent meningococcal vaccine additionally covering serogroups A, W, and Y (May 2018); and pneumococcal vaccination against 7 serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F (PCV7; June 2006, at age 2 months) later replaced by a 10-valent vaccine additionally covering serotypes 1, 5, and 7F (PCV10; May 2011) [14].

Serotypes and serogroups were subcategorized according to the conjugate vaccine groups.

**Statistical Analysis**

Annual incidence rates were calculated as the number of new episodes per 100,000 population per epidemiological year (1 July–30 June, defined as the year on 1 January). We compared mean annual incidences of bacterial meningitis overall, and due to specific pathogens in the first 5 years to the last 6 years of the observed period. To compare incidences of different time periods, we estimated incidence rate ratios (IRRs) using unconditional maximum likelihood estimation (Wald) using the “epitools” package [15]. All statistical tests were 2-sided and were considered statistically significant at a *P* value of ≤ .05. Analyses were performed using R statistical programming language version 3.6.1.

**RESULTS**

We identified a total of 17,428 episodes of bacterial meningitis. We excluded 35 episodes (0.2%) because of missing patient date of birth. The 17,393 included episodes occurred in 17,132 patients (Figure 1). Two hundred twenty-three patients had 2 episodes, 28 had 3 episodes, 5 had 4 episodes, and 5 had ≥5 episodes. A total of 7,796 episodes (45.5%) occurred in females and 8,783 (51.3%) in males (sex was unknown in 814 episodes).

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**Figure 1.** Flowchart baseline characteristics. Abbreviations: CSF, cerebrospinal fluid; *E. coli*, *Escherichia coli*; *H. influenzae*, *Haemophilus influenzae*; *L. monocytogenes*, *Listeria monocytogenes*; *N. meningitidis*, *Neisseria meningitidis*; *S. agalactiae*, *Streptococcus agalactiae*; *S. pneumoniae*, *Streptococcus pneumoniae*. *Only age of onset of the first episode is described here.*
We identified 102 different pathogens (Table 1, Figure 2, and Supplementary Table 1). The median age of patients differed between causative pathogens (Figure 3). *Haemophilus influenzae* and meningococcal meningitis were predominantly seen in preschool children (1560 of 1989–1993 [79.2%] and 2903 of 6817 meningococcal [48.7%] meningitis episodes), whereas most pneumococcal meningitis cases occurred in older and elderly adults (3200 of 5881 episodes [54.4%]). Five hundred forty-two of 644 *Escherichia coli* (84.2%) and 294 of 424 *Streptococcus agalactiae* (69.3%) episodes occurred in infants, together accounting for 63.9% of meningitis cases in this age group. Prior to conjugate vaccine implementation (1989–1993; Figure 4, Table 2, and Supplementary Table 2), *N. meningitidis* was the most common cause of bacterial meningitis (2.9 episodes per 100 000 population per year), followed by *H. influenzae* (1.6 per 100 000) and *S. pneumoniae* (1.1 per 100 000). The incidence of bacterial meningitis was highest in infants (121.5 per 100 000) and preschool children (49.9 per 100 000) in this prevaccination period.

The incidence of bacterial meningitis due to any pathogen decreased from 6.37 in 1989–1993 to 1.58 episodes per 100 000 population per year in 2014–2019 (IRR, 0.25 [95% confidence interval [CI], 0.23–0.26]; P < .001). This decrease was most pronounced in preschool and school-aged children (IRR, 0.10 [95% CI, 0.09–0.12] and 0.08 [95% CI, 0.06–0.10], respectively; both P < .001). The incidence of bacterial meningitis remained highest in infants, mainly due to a high incidence of *S. agalactiae* (42.48 per 100 000 infants) and *E. coli* meningitis (19.49 per 100 000 infants). Pneumococcal meningitis is currently most common, with a mean annual incidence of 0.81 episodes per 100 000 population per year in 2014–2019.

The incidence of *H. influenzae* meningitis declined from 1.57 per 100 000 population in 1989–1993 to 0.14 per 100 000 in 2014–2019 (IRR, 0.09 [95% CI, 0.07–1.10]; Figure 4 and Table 2). *Hib* accounted for 1133 of 1175 (96.4%) of *H. influenzae* meningitis cases before *Hib* vaccination in 1993. Prior to vaccination, the proportion of *H. influenzae* meningitis cases due to type b was significantly lower in adults (≥16 years; 18 of 45 cases [40.0%]) compared to children (<16 years; 1115/1130 cases [98.7%]) (P < .001). The incidence of *Hib* declined from 1.44 per 100 000 population per year prior to vaccination (1991–1993) to 0.04 afterward (2000–2002; IRR, 0.02; P < .001; Supplementary Table 3). The absolute decline in *Hib* incidence was largest in the preschool children, in whom incidence decreased from 22.94 to 0.46 episodes per 100 000 per year. The relative reduction in *Hib* incidence was similar for the nonvaccinated age groups (IRR, 0.02 [95% CI, 0.02–0.04]). Incidence of non–type b typeable *H. influenzae* has increased since *Hib* vaccination (0.002 in 1989–1993 to 0.014 episodes per 100 000 population per year in 2014–2019; IRR, 5.14 [95% CI, 1.17–22.61]; P = .01), mainly due to type f (11 of 14 non–type b typeable *H. influenzae* cases [79%] in 2014–2019). Also, we observed an increase in nontypeable *H. influenzae* meningitis (0.05 in 1989–1993 to 0.08 episodes per 100 000 population per year in 2014–2019 (IRR, 1.49 [95% CI, 1.02–2.17]; P = .04), which was most pronounced in older adults (IRR, 2.23 [95% CI, 1.98–5.10]; P = .05) and elderly adults (IRR, 2.27 [95% CI, 0.86–6.00]; P = .08).

The incidence of *N. meningitidis* meningitis decreased from 2.87 per 100 000 population in 1989–1993 to 0.20 per 100 000 population in 2014–2019 (IRR, 0.07 [95% CI, 0.06–0.08]; Figure 4 and Table 2). Twenty-two percent of this reduction in meningococcal meningitis was attributable to a decline in MenC, which in its peak from July 2001 and June 2002 caused 153 of 377 meningococcal meningitis episodes (41%). A rapid decrease in MenC meningitis followed vaccination in June 2002, from 0.62 to 0.01 between 2000–2002 and 2009–2011 (IRR, 0.02 [95% CI, 0.01–0.04]; P < .001; Supplementary Table 4). This decline was similar in all age categories. Meningitis due to serogroup B, a non-vaccine-targeted serogroup, declined from 2.23 to 0.16 per 100 000 population per year between 1989–1993 and 2014–2019 (IRR, 0.07 [95% CI, 0.06–0.08]; P < .001). This relative decline due to serogroup B was most pronounced in school-aged children, with an IRR of 0.03 (95% CI, 0.02–0.05). Overall, the mean annual incidence of meningococcal meningitis in school-aged

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**Table 1. Bacteria Causing Bacterial Meningitis in The Netherlands, July 1988–June 2019**

| Pathogen                        | No. of Episodes (%) | Patient Age, y, Median (IQR) |
|---------------------------------|---------------------|-------------------------------|
| *Neisseria meningitidis*        | 6817 (39.2)         | 6.3 (1.8–17)                  |
| *Streptococcus pneumoniae*     | 5881 (33.8)         | 50 (4.7–68)                   |
| *Haemophilus influenzae*        | 1970 (11.3)         | 1.7 (0.9–3.7)                 |
| *Streptococcus agalactiae*     | 644 (3.7)           | 15 d (3 d–40 d)               |
| *Escherichia coli*             | 424 (2.4)           | 27 d (9 d–26 y)               |
| *Listeria monocytogenes*       | 379 (2.2)           | 67 (54–75)                    |

A list of all bacteria cultured from the cerebrospinal fluid and received by the National Reference Laboratory for Bacterial Meningitis between July 1988 and June 2019. Data are presented as No. of episodes (%), and the age of patients in whom episodes of the specified pathogen occurred is reported as median (IQR) in years, unless specified otherwise. Only pathogens that are mentioned in the main text are listed here. A full overview is provided in Supplementary Table 1.

Abbreviation: IQR, interquartile range.

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**Figure 2.** Number of episodes of bacterial meningitis. Histogram showing the number of isolates received per pathogen per epidemiological year (1 July–30 June) from July 1988 to June 2019.
children dropped from 5.95 per 100,000 children in 1989–1993 to 0.19 per 100,000 in 2014–2019 (Supplementary Table 2). From 2015 onward, there was an increase in the number of serogroup W meningitis episodes from 0 in 2015 to 9 in 2018. Thirteen of 25 of the serogroup W meningococcal meningitis cases identified between 2015 and 2019 occurred in preschool and school-aged children.

The incidence of pneumococcal meningitis increased from 1.10 to 1.48 episodes per 100,000 per year between 1989–1993 and 2004–2006 (IRR, 1.34 [95% CI, 1.22–1.48]; P < .001; Figure 4, Table 2, and Supplementary Table 5). This increase was most evident shortly following the reduction of Hib, and there was significant negative correlation between the incidence of pneumococcal meningitis and *H. influenzae* meningitis (r = −0.94; P < .001). Before the implementation of PCVs, 2177 of 3785 pneumococcal meningitis cases (57.5%) were due to serotypes included in PCV10. This proportion was significantly higher in children (aged <16 years; 974/1379 [70.6%]) compared to adults (aged ≥16 years; 1203/2406 [50.0%]; P < .001). Pneumococcal meningitis due to serotypes targeted by PCV7 vaccination diminished from 0.76 to 0.03 episodes per 100,000 per year between 2004–2006 and 2018–2019 (IRR, 0.03 [95% CI, 0.02–0.07]; P < .001), followed by a reduction of the 3 serotypes additionally targeted by PCV10 from 0.17 to 0.01 per 100,000 between 2010–2011 and 2018–2019 (IRR, 0.07 [95% CI, 0.02–0.18]; P < .001; Supplementary Table 5). Since the introduction of vaccination, there has been an increase in non-PCV serotypes from 0.56 to 0.77 episodes per 100,000 per year between 2004–2006 and 2018–2019 (IRR, 1.36 [95% CI, 1.15–1.61]; P < .001). The incidence of meningitis due to pneumococcal serotype 19A increased from 0.04 to 0.08 (IRR, 1.92 [95% CI, 1.07–3.41]; P = .03). The overall decline in pneumococcal meningitis over the past 3 decades was most pronounced in preschool and school-aged children (IRR, 0.39 [95% CI,
Figure 4. Incidence of bacterial meningitis and the impact of vaccination. A, Incidence of bacterial meningitis due to *Haemophilus influenzae* (blue), *Neisseria meningitidis* (green), and *Streptococcus pneumoniae* (red) between June 1988 and July 2019. Lines represent the number of new episodes per 100,000 population per year. The black vertical lines represent the timing of implementation of each vaccine. The dotted lines represent the incidence of the serogroups or serotypes targeted by the implemented vaccines, type b for *H. influenzae* (dotted blue line), serogroup C for *N. meningitidis* (dotted green line), the 10 serotypes targeted by 10-valent pneumococcal conjugate vaccine (PCV) (dotted-dashed red line) and, below, the 7 serotypes targeted by 7-valent PCV (dotted red line) for *S. pneumoniae*. B–G, Incidence of bacterial meningitis due to *H. influenzae* (blue), *N. meningitidis* (green), and *S. pneumoniae* (red) per epidemiological year (symbols) with the fitted loess regression and the corresponding 95% confidence intervals for infants (aged <90 days; B), preschool children (aged 3 months–4 years; C), school-aged children (aged 5–15 years; D), young adults (aged 16–44 years; E), older adults (aged 45–64 years; F), and elderly adults (aged ≥65 years; G). Abbreviations: Hib, *Haemophilus influenzae* vaccine against serotype b; MenACWY, vaccine against serogroups A, C, W, and Y meningococci; MenC, vaccine against serogroup C meningococci; PCV7, 7-valent pneumococcal vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F); PCV10, 10-valent pneumococcal vaccine (additional serotypes 1, 5, 7F).
incidence, are common in alternating periods of high incidence followed by periods of low natural fluctuation. Natural fluctuations, characterized by alternating periods of high and low incidence, are common in meningococcal meningitis due to meningococcal genotypes expressing a certain set of antigens [8, 25, 26]. These genotypes disappear when herd immunity has been developed, which provides opportunity to new genotypes with a different set of expressed antigens [25, 26].

*S. pneumoniae* has become the most common pathogen to cause meningococcal meningitis in the Netherlands. Interventions to prevent pneumococcal meningitis have not been as effective as the interventions implemented in *H. influenzae* meningitis. The decline in pneumococcal meningitis was relatively small when compared to the (partially natural) decline seen in meningococcal meningitis. The implementation of PCV7 and PCV10 has effectively reduced the rate of pneumococcal meningitis due to vaccine serotypes. However, the overall impact of these conjugate vaccines for pneumococcal meningitis was limited. The proportion of pneumococcal meningitis cases caused by vaccine serotypes prior to vaccination was relatively small, especially in adults in whom only half of pneumococcal meningitis cases were due to vaccine serotypes. In addition, there was evidence of serotype replacement following the eradication of PCV serotypes, with a subsequent increase of 35% in pneumococcal meningitis caused by nonvaccine serotypes. Though we also identified an increase in non-vaccine-targeted *H. influenzae* serotypes, this has had a small impact as the proportion of cases caused by non-type b capsulated and nontypeable *H. influenzae* strains was low.

Both *H. influenzae* and *S. pneumoniae* are colonizers of the human nasopharynx. We observed an increase in incidence of pneumococcal meningitis following the eradication of *H. influenzae* meningitis. We hypothesize this may be related to natural competition in colonization, similar to that of the mechanisms behind serotype replacement [27, 28]. Increased pneumococcal carriage in preschool children may have served as a reservoir for increased adult pneumococcal disease, while nasopharyngeal carriage of Hib in preschool children was not clearly associated with invasive disease in adults (a limited proportion of *H. influenzae* meningitis in adults was due to type b). Almost all nonvaccinated healthy adults have protective immunoglobulin G antibody levels against Hib capsular polysaccharide, probably from nasopharyngeal Hib carriage in childhood [29].

Due to herd protection, conjugate vaccines have also led to a decline in the incidence of meningitis in the nonvaccinated population, including in older adults and elderly. MenC meningitis has almost completely been eradicated in adults and elderly following the immunization of children. Herd protection occurred promptly following the implementation of MenC vaccine. The catch-up campaign may have facilitated the eradication of MenC from the target population and may thereby have accelerated herd protection [30].

The peaks with high incidence are caused by meningococcal genotypes expressing a certain set of antigens [8, 25, 26]. These genotypes disappear when herd immunity has been developed, which provides opportunity to new genotypes with a different set of expressed antigens [25, 26].
| Age Group and Pathogen | 1969–1993 (Baseline) Incidence | 1994–1998 Incidence | 1999–2003 Incidence | 2004–2008 Incidence | 2009–2013 Incidence | 2014–2019 Incidence | IRR (95% CI) Baseline vs 2014–2019 |
|------------------------|--------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------------------|
| All pathogens          |                                |                     |                     |                     |                     |                     |                                 |
| All ages               | 4786                           | 6.37                | 3901                | 5.03                | 3420                | 4.28                | 2,250                           | 2.76                             | 1,420                            | 1.71                             | 1,616                            | 1.58                             | 0.25 (0.23–0.26)                  |
| Neonates (0–89 d)      | 293                            | 121.53              | 286                 | 118.65              | 223                 | 87.88               | 178                             | 75.19                           | 130                              | 57.44                           | 198                              | 77.17                           | 0.63 (0.53–0.76)                  |
| Preschool-aged (3 mo–4 y) | 2236                         | 49.91               | 1431                | 30.76               | 1160                | 24.45               | 609                             | 12.97                           | 269                              | 6.14                            | 255                              | 5.09                             | 0.10 (0.09–12)                    |
| School-aged (5–15 y)   | 719                            | 723                 | 658                 | 6.41               | 475                 | 4.40                | 178                             | 1.62                            | 71                               | 0.65                            | 71                              | 0.56                             | 0.08 (0.06–0.10)                  |
| Adults (16–64 y)       | 800                            | 2.23                | 681                 | 1.94                | 609                 | 1.77                | 338                             | 1.01                            | 200                              | 0.62                            | 218                             | 0.57                             | 0.26 (0.22–0.30)                  |
| Elderly (≥65 y)        | 357                            | 3.70                | 419                 | 4.07               | 428                 | 3.93                | 471                             | 4.04                            | 347                              | 2.64                            | 434                             | 2.32                             | 0.63 (0.55–0.72)                  |
| *Haemophilus influenzae* | 1178                          | 1.57                | 320                 | 0.41               | 117                 | 0.15                | 139                             | 0.17                            | 75                               | 0.09                            | 141                             | 0.14                             | 0.09 (0.07–0.10)                  |
| Type b                 | 1133                           | 1.51                | 261                 | 0.34               | 37                  | 0.05                | 60                              | 0.07                            | 28                               | 0.03                            | 46                              | 0.04                             | 0.03 (0.02–0.04)                  |
| Neisseria meningitidis | 2157                           | 2.87                | 2003                | 2.59               | 1681                | 2.10                | 535                             | 0.66                            | 234                              | 0.28                            | 207                             | 0.20                             | 0.07 (0.06–0.08)                  |
| Serogroup C            | 419                            | 0.56                | 220                 | 0.28               | 386                 | 0.48                | 30                              | 0.04                            | 9                                | 0.01                            | 8                               | 0.01                             | 0.01 (0.01–0.03)                  |
| Streptococcus pneumoniae | 826                           | 1.10                | 1055                | 1.36               | 1182                | 1.48                | 1170                            | 1.43                            | 819                              | 0.98                            | 829                             | 0.81                             | 0.74 (0.67–0.81)                  |
| PCV7 serotypesa        | 371                            | 0.49                | 491                 | 0.63               | 581                 | 0.73                | 544                             | 0.67                            | 115                              | 0.14                            | 37                              | 0.04                             | 0.07 (0.05–0.10)                  |
| PCV10–7 serotypesb     | 87                             | 0.12                | 96                  | 0.12               | 104                 | 0.13                | 152                             | 0.19                            | 128                              | 0.15                            | 35                              | 0.03                             | 0.30 (0.20–0.44)                  |
| Listeria monocytogenes | 73                             | 0.10                | 68                  | 0.09               | 72                  | 0.09                | 51                              | 0.06                            | 35                               | 0.04                            | 48                              | 0.05                             | 0.48 (0.34–0.69)                  |
| Streptococcus agalactiae | 102                           | 0.14                | 102                 | 0.13               | 110                 | 0.14                | 108                             | 0.13                            | 90                               | 0.11                            | 132                             | 0.13                             | 0.95 (0.73–1.23)                  |
| Escherichia coli       | 103                            | 0.14                | 89                  | 0.11               | 65                  | 0.08                | 56                              | 0.07                            | 43                               | 0.05                            | 68                              | 0.07                             | 0.48 (0.36–0.66)                  |

Overview of bacterial meningitis episodes in the Netherlands between July 1988 and June 2019 per 5-year period (6 years for last observation period), subcategorized per age group and the 6 most common pathogens, with the vaccine targeted serotype/serogroup if applicable.

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; PCV7, 7-valent pneumococcal conjugate vaccine; PCV10, 10-valent pneumococcal conjugate vaccine.

*aPCV7 serotypes: Number of cases/incidence of pneumococcal meningitis caused by serotypes within PCV7 (serotype 4, 6B, 9V, 14, 18C, 19F, and 23F).

*bPCV10–7 serotypes: Number of cases/incidence of pneumococcal meningitis caused by serotypes additionally covered by PCV10 (serotypes 1, 5, and 79).
In conclusion, the epidemiology of bacterial meningitis in the Netherlands has changed over the past 3 decades. The impact of conjugate vaccines has varied per pathogen and per age group because of the different proportions covered by the vaccine. In addition, replacement of disease, either due to serotypes not included in vaccines or the increase of other pathogens due to changes in nasopharyngeal carriage, has partly limited conjugate vaccine impact. The efforts for preventive measures for bacterial meningitis warrant a shift from preschool children toward neonates and the elderly given the residual high rate of disease in these age groups.

Supplementary Data
Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes
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Our study has several limitations. Over the past 3 decades, changes in clinical practices in performing a lumbar puncture and the rate of negative CSF cultures due to more timely administration of antibiotics may have affected the number of isolates received. Also, there may have been variation in the submission rate of isolates from medical microbiology laboratories to the NRLBM.
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