

BACTERIAL MENINGITIS IN THE UNITED STATES IN 1995

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**ABSTRACT**

**Background** Before the introduction of the conjugate vaccines, *Haemophilus influenzae* type b was the major cause of bacterial meningitis in the United States, and meningitis was primarily a disease of infants and young children. We describe the epidemiologic features of bacterial meningitis five years after the *H. influenzae* type b conjugate vaccines were licensed for routine immunization of infants.

**Methods** Data were collected from active, population-based surveillance for culture-confirmed meningitis and other invasive bacterial disease during 1995 in laboratories serving all the acute care hospitals in 22 counties of four states (total population, more than 10 million). The rates were compared with those for 1986 obtained by similar surveillance.

**Results** On the basis of 248 cases of bacterial meningitis in the surveillance areas, the rates of meningitis (per 100,000) for the major pathogens in 1995 were *Streptococcus pneumoniae*, 1.1; *Neisseria meningitidis*, 0.6; group B streptococcus, 0.3; *Listeria monocytogenes*, 0.2; and *H. influenzae*, 0.2. Group B streptococcus was the predominant pathogen among newborns, *N. meningitidis* among children 2 to 18 years old, and *S. pneumoniae* among adults. Pneumococcal meningitis had the highest case fatality rate (21 percent) and in 36 percent of cases was caused by organisms that were not susceptible to penicillin. From these data, we estimate that 5755 cases of bacterial meningitis were caused by these five pathogens in the United States in 1995, as compared with 12,920 cases in 1986, a reduction of 55 percent. The median age of persons with bacterial meningitis increased greatly, from 15 months in 1986 to 25 years in 1995, largely as a result of a 94 percent reduction in the number of cases of *H. influenzae* meningitis.

**Conclusions** Because of the vaccine-related decline in meningitis due to *H. influenzae* type b, bacterial meningitis in the United States is now a disease predominantly of adults rather than of infants and young children. (N Engl J Med 1997;337:970-6.)

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FEW medical advances in recent decades have affected pediatric infectious diseases as much as conjugate vaccines against *Haemophilus influenzae* type b disease.<sup>1</sup> In the United States, before the advent of conjugate vaccines, *H. influenzae* type b meningitis or invasive disease developed in nearly 1 in 200 children by five years of age,<sup>2</sup> and 70 percent of bacterial meningitis among children under five was attributable to *H. influenzae*.<sup>3</sup> Now, reports of dramatic declines in the disease from several countries after conjugate vaccines entered routine use suggest that the elimination of the disease may be attainable.<sup>4-7</sup>

The near elimination of *H. influenzae* type b disease will radically alter the view of bacterial meningitis as a major health problem of children. Because clinicians typically initiate therapy for meningitis before an etiologic agent is confirmed, the decrease in *H. influenzae* meningitis and the increase in antimicrobial resistance among pneumococci influence choices for empirical management of meningitis.<sup>8</sup> Evaluation of the epidemiology of bacterial meningitis in the era of the *H. influenzae* type b vaccine thus has important implications for both public health planning and clinical management. We report the results of laboratory-based surveillance for bacterial meningitis in 1995, five years after the licensure of conjugate *H. influenzae* type b vaccines for use in infants.

**METHODS**

Surveillance for invasive disease due to *Neisseria meningitidis*, *H. influenzae*, group B streptococcus, *Listeria monocytogenes*, and *Streptococcus pneumoniae* was performed during 1995 in eight counties in Georgia, in five counties in Tennessee, and in six counties in Maryland, and from October 1, 1994, to September 30, 1995, in three counties in California. These 22 counties had a total population of 10,281,746, or 3.9 percent of the U.S. pop-

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\*The members of the Active Surveillance Team are listed in the Appendix.

**TABLE 1.** CAUSES OF 248 CASES OF BACTERIAL MENINGITIS IN 1995 AND OVERALL CASE FATALITY RATE ACCORDING TO ORGANISM.

ORGANISM	NO. OF CASES REPORTED	PERCENTAGE OF TOTAL*	INCIDENCE†	CASE FATALITY RATE (%)‡
<i>Haemophilus influenzae</i>	18	7	0.2	6
<i>Streptococcus pneumoniae</i>	117	47	1.1	21
<i>Neisseria meningitidis</i>	62	25	0.6	3
Group B streptococcus	31	12	0.3	7
<i>Listeria monocytogenes</i>	20	8	0.2	15

\*Because of rounding, the percentages do not total 100.

†The incidence is the number of cases per 100,000 population.

‡Outcome data were missing for 11 cases of meningitis (4 percent). The case fatality rates are based on cases with known outcomes.

ulation. Blacks represented 24 percent of the surveillance population, as compared with 12 percent of the U.S. population.

Invasive disease was defined as disease in which an organism had been isolated from a sterile site (such as blood or cerebrospinal fluid) in a resident of the surveillance area. A case of invasive disease was considered to be meningitis if a clinical diagnosis of meningitis had been entered in the patient's medical record.

In each surveillance area, project personnel communicated every two weeks with contacts in all microbiology laboratories serving acute care hospitals and completed standardized case-report forms. Clinical isolates were sent to the Centers for Disease Control and Prevention (CDC) in Atlanta for serogrouping (*N. meningitidis*) and serotyping (*L. monocytogenes* and *H. influenzae*). *S. pneumoniae* isolates were tested for antimicrobial susceptibility at either the CDC or the University of Texas Health Science Center at San Antonio by the broth-dilution method.<sup>9</sup>

The sensitivity of surveillance, determined by audits of all laboratories, was defined as the proportion of all cases identified by laboratory audit that were also identified by initial surveillance.

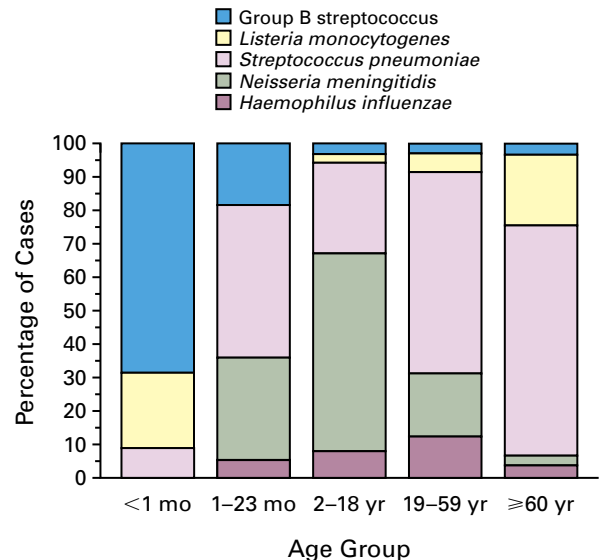
Rates for 1995 were calculated from U.S. Census Bureau population estimates for 1992, the most recent year for which relevant data at the county level were available. Rates for 1986 were obtained from previous surveillance.<sup>3</sup> For national projections of cases, we applied race- and age-specific rates of disease from the total surveillance area to the U.S. population. Race was handled as a dichotomous variable (black or nonblack) for these analyses.

Statistical analysis was performed with SAS for Windows (version 6.12, SAS Institute, Cary, N.C.) and EpiInfo (version 6.02) software. The chi-square test was used to compare proportions. Relative risks were determined with the Statacalc feature of EpiInfo.

RESULTS

Bacterial meningitis due to *N. meningitidis*, *H. influenzae*, group B streptococcus, *L. monocytogenes*, and *S. pneumoniae* was identified in 248 residents of the surveillance areas during 1995. Nine of these cases were identified by laboratory audit, yielding a sensitivity of 96 percent for surveillance of meningitis (range, 92 to 100 percent, according to area).

The agent most commonly associated with bacterial meningitis was *S. pneumoniae* (47 percent of cases), followed by *N. meningitidis* (25 percent) and group B streptococcus (12 percent) (Table 1). The case fatality rate of meningitis varied significantly according to organism (P=0.02) (Table 1). The me-



**Figure 1.** Pathogenic Agents of Bacterial Meningitis According to Age Group.

Meningitis due to *Escherichia coli* or other enteric pathogens among infants less than one month of age was not included in the surveillance.

dian age of the patients with bacterial meningitis was 25 years.

The predominant agents associated with meningitis varied according to age group (Fig. 1 and Table 2). The main pathogen causing meningitis in the neonatal period was group B streptococcus. In infants 1 to 23 months of age, *S. pneumoniae* (45 percent) and *N. meningitidis* (31 percent) together caused three quarters of cases of meningitis. Among those 2 to 18 years of age, *N. meningitidis* caused the majority of cases (59 percent). *S. pneumoniae* caused 62 percent of meningitis cases in persons 19 years of age or older.

**TABLE 2.** AGE-SPECIFIC INCIDENCE IN 1995 OF BACTERIAL MENINGITIS AND OF ALL INVASIVE BACTERIAL DISEASE.

AGE GROUP	HAEMOPHILUS INFLUENZAE	STREPTOCOCCUS PNEUMONIAE	NEISSERIA MENINGITIDIS	GROUP B STREPTOCOCCUS	LISTERIA MONOCYTOGENES
cases per 100,000 population					
Meningitis					
<1 mo	0	15.7	0	125.0	39.2
1-23 mo	0.7	6.6	4.5	2.8	0
2-29 yr	0.1	0.5	1.1	0.1	0.04
30-59 yr	0.2	1.0	0.3	0.05	0.1
≥60 yr	0.07	1.9	0.1	0.1	0.6
Total invasive disease					
<1 mo	78.4	94.1	0	1984.0	39.2
1-23 mo	2.4	183.0	11.1	18.4	0
2-29 yr	0.5	8.6	1.5	0.6	0.1
30-59 yr	1.2	18.9	0.6	4.2	0.4
≥60 yr	5.6	55.9	1.3	18.3	1.8

Only about one third (31 percent) of bacterial meningitis cases due to these pathogens occurred in children under five years of age.

The rates of meningitis due to *S. pneumoniae*, *N. meningitidis*, and group B streptococcus were significantly higher among blacks, with relative risks ranging from 2.1 to 2.6. The rates of meningitis due to *H. influenzae* did not differ according to race.

The age- and race-specific rates of disease in the

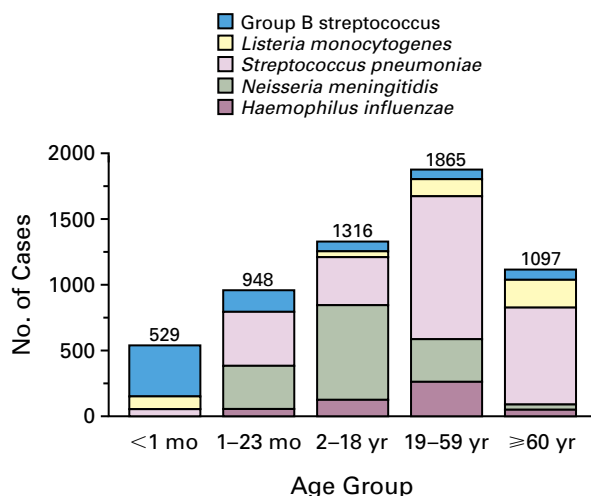
surveillance population were used to estimate the total number of cases of bacterial meningitis due to the five pathogens in the United States in 1995 (Fig. 2).

**Haemophilus influenzae**

*H. influenzae* was associated with meningitis in 18 of the 181 *H. influenzae* infections (10 percent). Of the 12 cases of meningitis for which the serotype was determined, serotype b was identified in 4. Three cases of meningitis occurred among children under five years old, two of whom had serotype b disease. None of the three was reported to have received *H. influenzae* type b vaccine. Ampicillin susceptibility was reported for 12 cases of *H. influenzae* meningitis. Isolates were reported as susceptible in nine cases of *H. influenzae* meningitis, intermediate in two, and resistant to ampicillin in one. Invasive *H. influenzae* disease due to other capsular serotypes was identified in 15 cases (serotype f, 11 cases; serotype a, 2 cases; and serotype e, 2 cases). Only 1 of these 15 cases occurred in a person under five years of age.

**Streptococcus pneumoniae**

Meningitis occurred in 117 of the 2679 invasive infections due to *S. pneumoniae* (4 percent). Although meningitis was rare in all age groups, the clinical presentations of meningitis due to other pathogens varied according to age. Overall, bacteremic pneumonia accounted for 1230 of the cases of invasive pneumococcal disease (46 percent), and bacteremia with no other focus accounted for 1176 of such cases (44 percent). Most cases (374 of 537, or 70 percent) of invasive pneumococcal disease among children under 5 years old presented as bacteremia without a focus of infection, whereas the



**Figure 2.** Projected Number of Cases of Bacterial Meningitis in the United States in 1995, According to Pathogenic Agent and Age Group.

Race-specific rates from a multistate population of 10.2 million were projected to the racial distribution of the United States to obtain these totals.

majority of cases (1078 of 1901, or 57 percent) of invasive disease in persons over 18 years of age presented as bacteremic pneumonia. The case fatality rate for pneumococcal meningitis was 21 percent (23 of 112 patients), significantly higher than the case fatality rate of 13 percent associated with invasive pneumococcal pneumonia (151 of 1200 patients) or the case fatality rate of 8 percent (95 of 1132 patients) in bacteremia without a focus.

The case fatality rate also varied according to age. Invasive cases among persons 60 years of age or older were three times as likely to be fatal (20 percent vs. 7 percent; relative risk, 3.0; 95 percent confidence interval, 2.4 to 3.8;  $P < 0.001$ ). Only 1 percent of cases of invasive pneumococcal disease among children under the age of two years were fatal. Isolates from 84 of 117 cases of pneumococcal meningitis were tested for susceptibility to penicillin. Fifty-four isolates (64 percent) were susceptible to penicillin (minimal inhibitory concentration [MIC] of penicillin, 0.06  $\mu\text{g}$  per milliliter or less); 18 isolates (21 percent) had intermediate susceptibility (MIC, 0.12 to 1.00  $\mu\text{g}$  per milliliter), and 12 isolates (14 percent) were resistant to penicillin (MIC, 2.00  $\mu\text{g}$  per milliliter or more). The proportion of isolates from cases of pneumococcal meningitis that were susceptible to penicillin differed significantly among the four areas ( $P = 0.007$ ). In San Francisco 15 of 18 isolates (83 percent) were susceptible to penicillin; in Tennessee only 4 of 14 isolates (29 percent) were susceptible.

#### ***Neisseria meningitidis***

Meningitis was diagnosed in 62 of 130 cases of invasive disease due to *N. meningitidis* (48 percent). Other clinical syndromes associated with *N. meningitidis* were bacteremia (62 cases; 48 percent) and bacteremic pneumonia (4 cases; 3 percent). The case fatality rate was 11 percent (14 of 124 cases) for all invasive disease, but it was significantly higher for meningococcal bacteremia (17 percent) than for meningococcal meningitis (3 percent,  $P < 0.05$ ). Most cases of invasive disease due to *N. meningitidis* occurred in children and young adults; 56 percent of meningococcal cases occurred in persons 18 years of age or younger, and 67 percent occurred among persons under 30. Of 130 cases of invasive meningococcal disease, 96 isolates (74 percent) were serogrouped. Serogroup C was the most common isolate in three areas, accounting for 39 percent of all isolates that were serogrouped. In Maryland, serogroup Y was the most common serogroup, accounting for 32 percent of all isolates that were serogrouped.

#### **Group B Streptococcus**

Meningitis accounted for 4 percent of all cases of invasive disease due to group B streptococcus. Six percent of cases of group B streptococcal disease

among newborns were diagnosed as meningitis, as compared with less than 1 percent of cases among persons 60 years of age or older. Of the pathogens under surveillance, group B streptococcus was the dominant cause both of meningitis and of all invasive disease among newborns. Fifty-two percent (16 of 31) of all cases of group B streptococcal meningitis occurred during the first month of life. Sixty-one percent (508 of 829) of all cases of invasive disease due to group B streptococcus occurred in persons 19 years of age or older. The case fatality rate was similar for meningitis and for other group B streptococcal invasive syndromes (7 percent vs. 10 percent,  $P$  not significant). The case fatality rate for all group B streptococcal invasive disease was higher among persons 60 years of age or older (18 percent) than in those under 60 (6 percent).

#### ***Listeria monocytogenes***

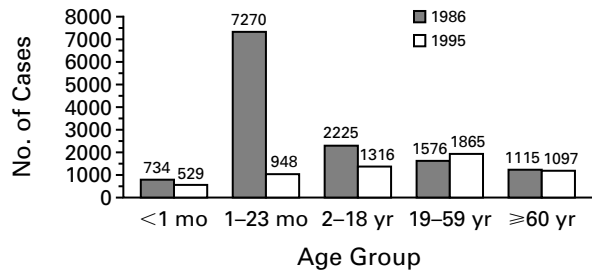
Meningitis occurred in 36 percent of all cases of invasive listeriosis. All five listerial infections in newborns were associated with meningitis, as compared with 30 percent of the listerial infections in older persons ( $P = 0.004$  by Fisher's exact test). Forty-five percent of cases of invasive disease due to *L. monocytogenes* occurred in persons 60 years of age or older. Serotype data were available for 41 invasive cases (75 percent). Serotypes 4b and 1/2b each caused 39 percent of the cases.

### DISCUSSION

Until recently, bacterial meningitis was a greatly feared infectious disease because it struck and killed rapidly, many of its victims were children, and as many as 25 percent of survivors had sequelae such as permanent brain damage, mental retardation, or hearing loss. There were once 10,000 to 20,000 cases each year in the United States,<sup>3</sup> but there have been major efforts to improve treatment<sup>8</sup> and prevent bacterial meningitis.

Over a period of just nine years, the median age of patients with meningitis due to the five pathogens surveyed in this study has shifted remarkably: from 15 months in 1986 to 25 years in 1995. In 1986, two thirds of patients with bacterial meningitis were between one month and five years of age. By 1995, meningitis in this age group had dropped by 87 percent, resulting in a decline of 55 percent for all cases of bacterial meningitis. This achievement highlights the ultimate advantage of prevention over improvements in therapy and suggests the tremendous benefits for children throughout the world if access to the vaccine could be expanded.

Population-based studies from the 1970s and 1980s demonstrated that five pathogens — *H. influenzae* type b, *S. pneumoniae*, *N. meningitidis*, group B streptococcus, and *L. monocytogenes*<sup>3,10-12</sup> — caused at least 80 percent of all cases of bacterial



**Figure 3.** Number of Cases of Bacterial Meningitis Due to Five Major Pathogens in the United States in 1986 and 1995 According to Age Group.

Race-specific rates from a multistate population of 34 million in 1986 and 10.2 million in 1995 were projected to the racial distribution of the United States to obtain these totals. The five pathogens were *N. meningitidis*, *H. influenzae*, *L. monocytogenes*, group B streptococcus, and *S. pneumoniae*.

meningitis. These studies, as well as the current one, clearly showed that the relative importance of these pathogens differs according to age. Treatment and prevention programs have been designed to address these age-specific patterns.

There were efforts to improve antibiotic therapy for bacterial meningitis<sup>8</sup> and to reduce neurologic sequelae by administering corticosteroids to acutely ill children. Although slight declines were noted in mortality due to meningitis caused by each of the three main agents during the 1980s,<sup>13</sup> major improvements in survival and reduction of long-term morbidity did not occur over the past several decades, and antibiotic resistance in *H. influenzae* type b<sup>14,15</sup> and *S. pneumoniae*<sup>16</sup> began to appear in the United States during the late 1970s and early 1990s, respectively, complicating efforts to improve clinical outcome through treatment regimens.

In parallel with advances in therapy, vaccine development was aggressively pursued.<sup>17-19</sup> The first vaccines for *H. influenzae* type b, *S. pneumoniae*, and *N. meningitidis* became available in the 1960s and 1970s. Based on the polysaccharide capsules of their respective organisms, these vaccines could induce protective responses in older children and adults, but their effectiveness in young infants was variable. Conjugation to a carrier protein was used to convert *H. influenzae* type b polysaccharide into a T-cell-dependent antigen that could induce immune responses in young infants. After licensure and the recommendation that *H. influenzae* type b conjugate vaccines be used routinely for two-year-old children, and then, in 1990, for two-month-old infants, the incidence of *H. influenzae* type b meningitis and invasive disease dropped dramatically,<sup>4</sup> partly because of the unexpected impact of vaccines on nasopharyngeal carriage.<sup>20-22</sup> In our surveillance areas, serotype b has not been replaced by other types of *H. influenzae*. Thus, our data confirm that the introduction of *H. influenzae* type b vaccines produced a major change in the epidemiology of bacterial meningitis in the United States (Fig. 3 and Table 3).

Vaccines against other causes of meningitis raise the hope of further progress in the prevention of meningitis, but these other pathogens present more complicated challenges. Meningococci, unlike the other encapsulated bacteria, sometimes cause epidemics. Recent outbreaks of serogroup C meningococcal disease in North America led to the immunization of millions of children with the polysaccharide vaccine.<sup>23,24</sup> Meningococci are now the principal cause of bacterial meningitis among persons 2 to 18 years of age. Although the total number of cases of invasive disease caused by meningococci in children and young adults is far lower than the number caused by

**TABLE 3.** INCIDENCE IN 1986 AND 1995 OF BACTERIAL MENINGITIS AND TOTAL INVASIVE DISEASE.

PATHOGEN	BACTERIAL MENINGITIS			TOTAL INVASIVE DISEASE		
	1986*	1995	PERCENT CHANGE	1986*	1995	PERCENT CHANGE
	cases per 100,000 population			cases per 100,000 population		
<i>Haemophilus influenzae</i>	2.9	0.2	-94	5.6	1.8	-68
<i>Streptococcus pneumoniae</i>	1.1	1.1	+4	15.0	26.1	+74
<i>Neisseria meningitidis</i>	0.9	0.6	-33	1.3	1.3	0
Group B streptococcus	0.4	0.3	-25	3.7	8.1	+119
<i>Listeria monocytogenes</i>	0.2	0.2	-5	0.7	0.5	-24

\*Data are from Wenger et al.<sup>3</sup> During 1986, laboratory audits for invasive disease due to *S. pneumoniae* and group B streptococcus were limited to certain areas.<sup>3</sup>

pneumococci, the numbers of deaths in this age group due to the two pathogens are similar. Further, meningococcal disease places a burden on the public health system, since each case requires local public health personnel to ensure that chemoprophylaxis is administered to household and other close contacts.<sup>25</sup>

Several difficult hurdles must be cleared before prevention of meningococcal disease through routine immunization can become a reality. The risk of contracting meningococcal disease extends from infancy through early adulthood, so effective vaccines must either provide long-term protection or be administered repeatedly during childhood and adolescence. Meningococcal vaccines must protect against multiple capsular groups. New serogroup A and C meningococcal conjugate vaccines with enhanced immunogenicity in children are now undergoing clinical trials. The serogroup B capsule is not immunogenic in humans, so immunization strategies have focused primarily on noncapsular antigens,<sup>26</sup> and several vaccines of moderate efficacy in older children and adults have been developed from specific strains of serogroup B meningococci.<sup>27,28</sup> However, strain-specific differences in expression of these antigens suggest that these vaccines may not provide protection against all serogroup B meningococci. In addition, efficacy in young children has not been demonstrated.<sup>29</sup>

Pneumococci pose a similar prevention problem not only for adults, for whom they are the primary cause of both pneumonia and meningitis, but also for children under five years old. Our data show that, in the absence of *H. influenzae* type b, pneumococci are now the principal cause of invasive bacterial disease in this group. Although polysaccharide vaccines are available for use in children older than 2 years and in adults at risk, coverage among adults over 65 years of age was recently estimated to be only 28 to 30 percent.<sup>30</sup> Additional efforts to use the available vaccines could further reduce the incidence of bacterial meningitis in adults but would probably have little effect on the remaining incidence in children. Conjugate pneumococcal vaccines are now undergoing clinical trials, although the large number of capsular serotypes needed for a useful pneumococcal vaccine makes the task complex and costly. The primary motivation for the development of these vaccines is to prevent disease in children, but they may also be more effective in adults.

In neonates, group B streptococcus is the most common pathogen associated with meningitis, and *L. monocytogenes* also causes disease. Vaccines are not yet available for the prevention of neonatal meningitis, but other prevention strategies are being promoted. Consensus recommendations for the administration of antibiotics during labor to women at risk for transmitting group B streptococcus to their newborns have recently been issued.<sup>31-33</sup> Appropriate im-

plementation of these recommendations could reduce neonatal group B streptococcal disease by more than 60 percent. Further disease control may result from the use of group B streptococcal conjugate vaccines, which are undergoing clinical trials.<sup>34</sup> Enhanced efforts to reduce the contamination of processed foods by *L. monocytogenes* and dietary recommendations for persons at risk may have contributed to a recent decrease in disease due to *L. monocytogenes*.<sup>35,36</sup>

Our data can be used to assess the burden of disease and thus set priorities for vaccine development and use. However, certain limitations should be noted. Our surveillance system did not record cases of clinical meningitis without positive cultures of cerebrospinal fluid or blood and may have underestimated the real burden caused by these infections. We did not determine whether there has been a reduction in the use of lumbar punctures for suspected meningitis, which could reduce the sensitivity of our surveillance method. We did not assess disease caused by pathogens other than the five major agents identified in earlier studies, although enteric pathogens are an important cause of neonatal meningitis. As a component of community-acquired bacterial meningitis, however, such pathogens are not likely to constitute a major burden of disease.

Widespread use of *H. influenzae* type b conjugate vaccines has drastically reduced the threat of bacterial meningitis in children from one month to five years of age. Prevention programs for group B streptococcal infections and for listeriosis may further reduce the disease burden, even without the introduction of new vaccines. We need continued evaluation of the epidemiology of the disease to identify appropriate targets for immunization or other preventive strategies. Surveillance linked to laboratory characterization of isolates is critical to the development of appropriate vaccines, as illustrated by the recent emergence of serogroup Y meningococci,<sup>37</sup> serotype V group B streptococcus,<sup>38</sup> and antibiotic-resistant pneumococci.<sup>39</sup> The development of effective vaccines for the meningococcus, the pneumococcus, and group B streptococcus raises the hope of making bacterial meningitis largely a problem of the past.

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#### APPENDIX

The members of the Active Surveillance Team are as follows: California Emerging Infections Program, Berkeley — G. Rothrock, N. Mukerjee, P. Daily, L. Gelling, and D. Vugia; Vanderbilt Medical Center, Nashville — B. Barnes and C. Gilmore; Veterans Affairs Medical Services and Emory University School of Medicine, Atlanta — W. Baughman, S. Whitfield, and M. Bardsley; Johns Hopkins University, Baltimore — L. Billmann; Maryland Department of Health and Mental Hygiene, Baltimore — D. Dwyer; University of Texas Health Science Center at San Antonio — J. Jorgensen, S. Crawford, and L. McElmeel; and Centers for Disease Control and Prevention, Atlanta — G. Ajello, M. Cetron, J. Churchill, J. Elliott, R. Facklam, R. Franklin, P.S. Hayes, M. Kolczak, N. Pigott, T. Thompson, and C. Wright.

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