The Changing Epidemiology of Meningococcal Disease in the United States, 1992–1996

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New meningococcal vaccines are undergoing clinical trials, and changes in the epidemiologic features of meningococcal disease will affect their use. Active laboratory-based, population-based US surveillance for meningococcal disease during 1992–1996 was used to project that 2400 cases of meningococcal disease occurred annually. Incidence was highest in infants; however, 32% of cases occurred in persons ⩾30 years of age. Serogroup C caused 35% of cases; serogroup B, 32%; and serogroup Y, 26%. Increasing age (relative risk [RR], 1.01 per year), having an isolate obtained from blood (RR, 4.5), and serogroup C (RR, 1.6) were associated with increased case fatality. Among serogroup B isolates, the most commonly expressed serosubtype was P1.15; 68% of isolates expressed 1 of the 6 most common serosubtypes. Compared with cases occurring in previous years, recent cases are more likely to be caused by serogroup Y and to occur among older age groups. Ongoing surveillance is necessary to determine the stability of serogroup and serosubtype distribution.

Neisseria meningitidis is an important cause of morbidity and mortality worldwide and a leading cause of bacterial meningitis and septicemia in children and young adults in the United States [1]. Since 1991, the frequency of outbreaks of meningococcal disease has increased [2]; however, outbreak-associated cases account for only 2% of cases in the United States each year [3]. Therefore, the majority of meningococcal disease in the United States is endemic. In the 5 years since the last complete description of the epidemiologic features of meningococcal disease in the United States [4], significant changes have occurred in serogroup and age distribution of cases as well as in the progress toward new meningococcal vaccines.

Vaccines against meningococcal disease, based on the polysaccharide capsule, have been used in the US military since the 1970s [5]. The formulation currently available in the United States is a quadrivalent meningococcal vaccine, which consists of the purified polysaccharide capsules of serogroups A, C, W-135, and Y. Because of its relative ineffectiveness in children <2 years of age and its relatively short duration of protection, use of this vaccine among civilians has been limited to control of outbreaks. Widespread use of *Haemophilus influenzae* type b (Hib) conjugate vaccines, in which a carrier protein is conjugated to the polysaccharide to produce a T cell–dependent response, has resulted in near-elimination of Hib in the United States [6]. New serogroup A and C meningococcal conjugate vaccines based on similar principles, with enhanced immunogenicity in infants and toddlers, have undergone clinical trials [7–9]. Information concerning the current trends in meningococcal disease in the United States is essential to aid in decision making about use of these vaccines as they approach licensure.

We report herein the results of laboratory-based surveillance for invasive meningococcal disease, conducted in a large US population from January 1992 through December 1996.

Methods

Active surveillance. Population-based surveillance for invasive disease caused by *N. meningitidis* is part of an ongoing multistate

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active surveillance project coordinated by the Centers for Disease Control and Prevention (CDC) [1, 4]. Between 1992 and 1996, the CDC collaborated on active surveillance with investigators in state and local health departments and universities in up to 7 geographically dispersed areas of the United States. Active surveillance was not conducted continuously in all 7 surveillance areas. In 1992, surveillance for meningococcal disease was conducted in 4 sites (8 counties in metropolitan Atlanta, 3 counties in the San Francisco Bay Area, 4 counties in Tennessee, and the state of Maryland) with an aggregate population of 12.2 million. During 1995, as part of the National Center for Infectious Diseases Emerging Infections Program site activities, the states of Connecticut, Minnesota, and Oregon were added, bringing the aggregate population to 21.8 million. For Connecticut, Minnesota, and Oregon, only cases from 1996, the first complete year of surveillance, are included in this report. This report includes only those cases reported as of June 1997. Surveillance is continuous, but this report focuses on 1992–1996, a 5-year period during which additional laboratory analysis was done for all available isolates.

Because surveillance was not continuous in all areas, analyses comparing annual surveillance and changes in serogroup distribution for 1992–1996 were done only for the 4 surveillance areas (8 counties in metropolitan Atlanta, 3 counties in the San Francisco Bay Area, 4 counties in Tennessee, and the state of Maryland) with continuous surveillance during those 5 years (an aggregate population of 12.2–12.8 million).

A case of meningococcal disease was defined as the isolation of *N. meningitidis* from a normally sterile site, such as blood or cerebrospinal fluid (CSF), from a resident of the surveillance area between 1 January 1992 and 31 December 1996. Cases were reported to surveillance workers by contacts in each hospital laboratory in the surveillance area. A case report form was completed for each case, including information about the patient's age, sex, race, outcome, and clinical syndrome, as well as the site of isolation, serogroup, and antibiotic sensitivities of the organism. A case of invasive disease was considered to be meningitis if a clinical diagnosis of meningitis had been entered into the patient's medical record or if *N. meningitidis* was isolated from CSF. To evaluate the sensitivity of reporting and to ensure ascertainment of all cases, hospitals were periodically audited by review of microbiology records. Between 1992 and 1996, 96%–98% of cases were detected by surveillance personnel before the audit was done. Cases identified by audit are included in the analysis.

Because race is a likely risk marker for meningococcal disease, data were analyzed by race, and the projected national incidence and annual number of cases based on incidence among surveillance area residents were adjusted for race.

Laboratory methods. All available isolates of *N. meningitidis* were sent to the CDC for further study. Serogrouping was done at hospital microbiology laboratories, at state health departments, and at the CDC; CDC serogroup results were used in the analysis if discrepant serogroup results were obtained in multiple laboratories.

Multilocus enzyme electrophoresis (MEE) with use of 24 constitutive enzymes was done at the CDC on a sample of isolates [10, 11]. Numbers were assigned to enzyme alleles on the basis of enzyme mobilities, and each unique set of alleles was defined as an electrophoretic type (ET). An index of genetic relatedness was determined by weighing the degree of diversity at each of the 24 enzyme loci, and similarities among the ETs were assessed by dendrogram analysis [12]. The isolates tested included all available isolates from 1992–1996 from the 4 sites with continuous surveillance (California, Georgia, Maryland, Tennessee).

Serosubtyping by dot-blotting was done as described elsewhere for serogroup B isolates from the 4 sites with continuous surveillance (California, Georgia, Maryland, Tennessee) as well as for serogroup B isolates collected from Oregon in 1996 [13, 14]. The whole cell suspensions were dotted on nitrocellulose, and strips were blocked for 30 min with 3% bovine serum albumin in PBS. Monoclonal antibodies were pipetted into the blocking buffer at dilutions ranging from 1 : 4000 to 1 : 32,000. After overnight incubation, strips were washed 3 times with PBS and incubated for 2 h with goat anti-mouse IgG conjugated to peroxidase (1 : 4000) (Sigma, St. Louis). Strips were developed with the substrate 3-amino-9-ethyl-carbazole (Sigma) and hydrogen peroxidase. Monoclonal antibodies with specificities for serotypes 2a (5D4-5), 2b (2H10-2), 2c (6-D9-5.6-F3), 4 (5DC4-C8-G8), 5 (7BG5-H2), 11 (9-1-P11), 15 (8-B5-5-B9), and 21 (6B11-C2-F1) and serosubtypes P1.2 (OD6-4), P1.3 (5G8-B2-F9), P1.15 (7A2-11), and P1.16 (OF11-4) were supplied by W. D. Zollinger (Walter Reed Army Medical Center, Washington, DC). Monoclonal antibodies against serotypes 1 (MN3C6B) and 14 (MN5C8C) and serosubtypes P1.1 (MN14C2.3), P1.4 (MN20B9.34), P1.5 (MN22A9.19), P1.6 (MN19D6.13), P1.7 (MN14C11.6), P1.9 (MN5A10.7), P1.10 (MN20F4.17), P1.12 (MN20A7.10), P1.13 (MN25H10.75), and P1.14 (MN21G3.17) were purchased from the National Institute for Biological Standards and Control (Hertfordshire, UK). Monoclonal antibody against serotype 17 (F4-3C1/1A6) was provided by C. T. Sacchi (Institute Adolfo Lutz, São Paolo, Brazil) [15].

Statistical analysis. Cumulative incidences were calculated with use of population data from the US Bureau of the Census for 1992–1996. χ^2 or Fisher's exact test was used to assess statistical significance. Poisson regression was used to estimate rate ratios and confidence intervals. Multivariate, stepwise logistic regression analysis with the SAS software system (version 6.03; SAS Institute, Cary, NC) was done to determine independent risk factors (e.g., case fatality).

Results

In the years 1992–1996, 807 cases of meningococcal disease were detected in the 7 surveillance areas, for an average annual incidence of 1.1/100,000 population during this period. On the basis of this rate and adjustments for differences in racial distribution between the populations of the surveillance areas and of the US population, an estimated 2454 cases of invasive meningococcal disease occurred annually in the United States during this time period. If Oregon, which was having a serogroup B outbreak in 1996 with an incidence of 3.4/100,000 (figure 1) is excluded, the average incidence was 1.0/100,000. Because the incidence in Oregon was higher than that in the other states, we excluded Oregon and used race-adjusted rates to project to the other 49 states, none of which reported serogroup B outbreaks. We then added the cases that would occur in Oregon

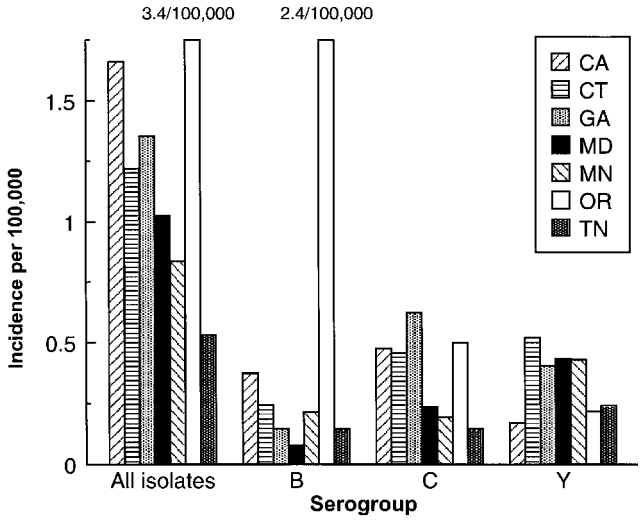

Figure 1. Rates of meningococcal disease by serogroup and area (California, CA; Georgia, GA; Maryland, MD; Tennessee, TN; Connecticut, CT; Minnesota, MN; Oregon, OR), 1996.

and estimated that 2363 cases of meningococcal disease occurred annually in the United States between 1992 and 1996. By use of data from the 4 sites in which surveillance was continuous during the study period and with adjustment for race, the incidence was 0.8 in 1992, 0.9 in 1993, 0.8 in 1994, 1.0 in 1995, and 1.0 in 1996 (χ^2 for linear trend, $P = .006$). Seasonal variation occurred, with the highest proportion of cases occurring in January and December and the lowest in September (figure 2). Of the 769 cases for which outcome information was available, 79 persons died, for an overall case-fatality ratio (CFR) of 10%.

The highest age-specific incidence of meningococcal disease occurred in infants <1 year of age, with a peak incidence of 15.9/100,000 population in infants 4–5 months of age (figure 3). Seventeen percent of case-patients were infants <1 year of age, 22% were children <2 years of age, and 32% were persons ⩾30 years of age. Males accounted for 52% of case-patients, with an incidence among males of 1.2/100,000 compared with 1.0/100,000 among females (relative risk [RR], 1.2; 95% confidence interval [CI], 0.9–1.6; $P = .2$). Female case-patients were significantly older than male case-patients (median, 19 vs. 15 years; Kruskal-Wallis χ^2, $P = .0001$). The difference was in part attributable to persons ⩾55 years of age, among whom the rate of meningococcal disease in women was 1.0/100,000 versus 0.4/100,000 among men ($P = .0001$; figure 3). The incidence of meningococcal disease was higher in blacks (1.4/100,000) than in nonblacks (0.9/100,000; RR, 1.5; 95% CI, 1.1–2.2; $P = .02$). Hispanic ethnicity was reported by 10% of case-patients.

N. meningitidis was isolated from blood in 625 cases (77%), CSF in 284 (35%), joint fluid in 14 (2%), and peritoneal and pericardial fluid in 1 (0.1%) each. In 118 cases (15%), *N. meningitidis* was isolated from both the blood and CSF. Meningitis occurred in 377 cases (47%). Other syndromes were much less common, with pneumonia reported in 48 cases (6%), arthritis in 17 (2%), otitis media in 7 (1%), epiglottitis in 2 (0.3%), and pericarditis in 1 (0.1%). For some case-patients (0.9%), >1 clinical syndrome was reported. Three hundred forty-nine case-patients (43%) had primary bacteremia without another clinical syndrome. Patients with pneumonia were older than patients without pneumonia (median, 57 vs. 16 years; $P < .001$).

Isolates were available for serogrouping at the CDC for 608 (75%) of the 807 cases; serogroup information was collected locally and recorded on the case report form for 468 (58%). Serogroup data were available from either or both sources for 681 (84%). For 395 isolates, serogroup information was available from both sources; the sources agreed in 354 cases (90%).

Serogroup C organisms accounted for 35%, serogroup B organisms for 32%, and serogroup Y organisms for 26% of isolates for which serogroup information was available. W-135, Z, and nongroupable serogroups accounted for 4%, 3%, and 0.3% of isolates, respectively. Two isolates were reported to be serogroup A, but viable isolates were not submitted to the CDC for confirmation. If Oregon, which has been experiencing an epidemic of serogroup B meningococcal disease, was excluded, serogroup B, serogroup C, and serogroup Y accounted for 25%, 38%, and 29%, respectively.

By use of data from the 4 sites from which continuous data were available (California, Georgia, Maryland, and Tennessee), the estimated serogroup-specific incidences, adjusted for race, for serogroups B and C remained stable over the 5-year period at an average rate of 0.2 and 0.3/100,000, respectively (figure 4). However, the incidence of serogroup Y meningococcal disease increased during the study period from 0.1/100,000 in 1992 to 0.2/100,000 in 1996 (RR, 2.4; 95% CI, 1.3–4.6).

The incidence of serogroup-specific disease varied by sur-

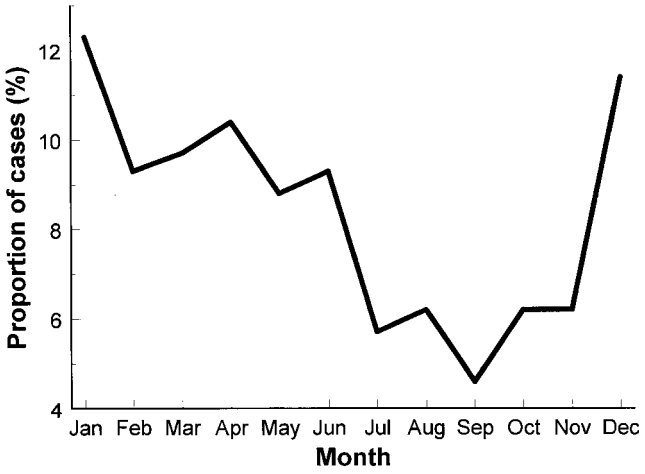

Figure 2. Seasonal variation in cases of meningococcal disease in California, Georgia, Maryland, Tennessee, Connecticut, Minnesota, and Oregon, 1992–1996.

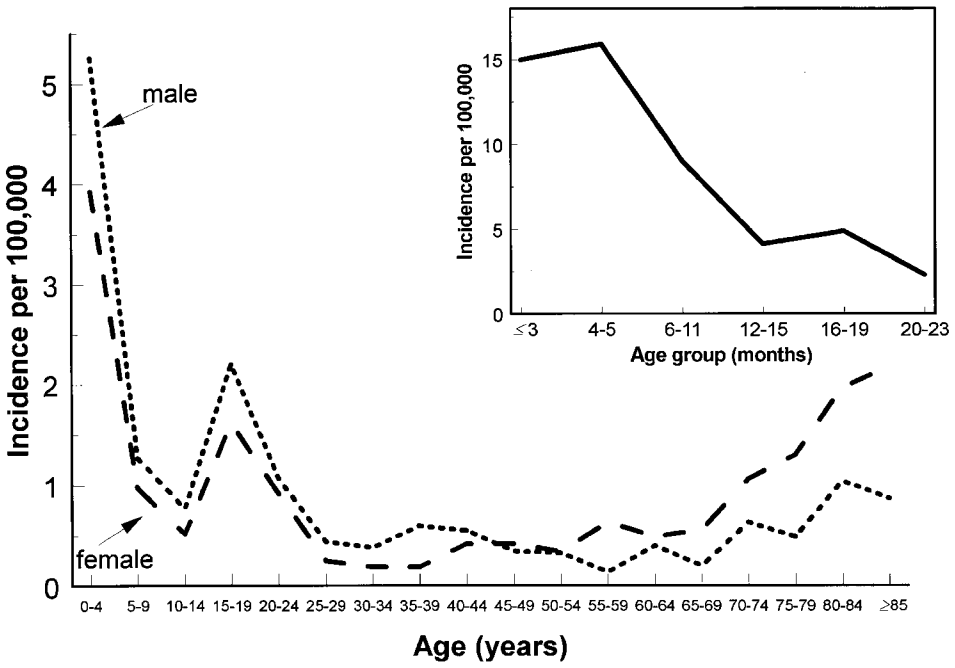

Figure 3. Race-adjusted rates of meningococcal disease by age group and sex in California, Georgia, Maryland, Tennessee, Connecticut, Minnesota, and Oregon, 1992–1996.

veillance area (figure 1). In 1996, the rate of serogroup B disease in Oregon was 2.4/100,000, substantially higher than in any of the other surveillance areas ($P < .005$).

A higher proportion of serogroup B disease occurred in younger age groups (table 1), with 30% of serogroup B disease occurring in persons <1 year of age, compared with 14% of cases due to other serogroups ($P = .001$). The median age was 6 years for patients with serogroup B, 17 for patients with serogroup C, 24 for patients with serogroup Y, and 33 for patients with serogroup W-135.

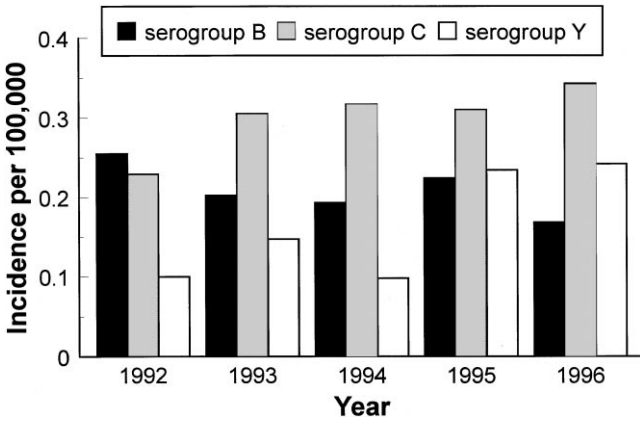

Figure 4. Rates of meningococcal disease by serogroup and year, adjusted for race, at 4 sites with continuous surveillance (California, Georgia, Maryland, and Tennessee), 1992–1996.

After age was adjusted for, a higher proportion of patients with serogroup Y disease than of patients with serogroups B and C disease had pneumonia (14% vs. 2%; $P < .001$). Similarly, after adjustment for age, a higher proportion of patients with serogroup W-135 disease than of patients with serogroups B and C disease reported pneumonia (26% vs. 2%; $P < .001$). The proportions of meningitic and nonmeningitic disease caused by serogroups B and C were similar.

A higher proportion of serogroup Y disease than of disease due to other serogroups occurred among blacks (50% vs. 23%; $P = .001$). Case-patients with serogroup Y disease were more likely to be female than were those with disease due to other serogroups (55% vs. 46%; $P = .03$). Female case-patients with serogroup Y disease were significantly older than were male case-patients with serogroup Y disease (median, 42 vs. 18 years; Kruskal-Wallis χ^2, $P = .0001$). In a multivariate model including only patients with known serogroup, patients with serogroup Y were more likely to be black than white (RR, 1.9; $P < .00001$), to have pneumonia (RR, 1.6; $P < .0002$), and to be older (age >17 years; RR, 1.4; $P = .0002$).

Ten (9%) of the 108 isolates for which sensitivity to sulfonamides was reported were reported to be resistant. Resistance to sulfonamides did not vary by serogroup. The results of rifampin sensitivity testing were reported for 99 isolates. One (1%) of these was reported to be resistant. Although penicillin resistance was reported from local laboratories for only 1 of these isolates, testing among active surveillance isolates from 1 July 1997 to 31 December 1997 as part of a separate study

Table 1. Annual incidence and estimated number of cases of meningococcal disease by serogroup and age group, adjusted for race—United States, 1992–1996.

Age group, years	Cases/100,000 population/year			Estimated no. of cases		
	Group B	Group C	Group Y	Group B	Group C	Group Y
<1	4.5	2.3	2.1	186	87	84
1–2	1.7	0.9	0.4	68	35	16
2–5	0.4	0.7	0.1	79	109	8
6–1	0.1	0.4	0.1	37	96	20
12–17	0.2	0.5	0.3	46	110	62
18–29	0.2	0.3	0.2	92	140	79
⩾30	0.1	0.2	0.2	124	215	216
All ages	0.2	0.3	0.2	633	792	485

NOTE. Rates were calculated excluding Oregon and were adjusted for differences in racial distribution to project to the other 49 states. Cases from Oregon were then added to estimate cases in the United States.

found that 3 of the 90 isolates tested had penicillin MICs ⩾0.12 μg/mL [16].

The CFR varied by serogroup and was higher for serogroup W135 (21%) and serogroup C (14%) than for serogroup Y (9%) and serogroup B (6%). The CFR was higher among blacks than whites (14% vs. 9%; $P = .04$). The CFR was lower among those who had a CSF isolate only than among those with an isolate from another source (2% vs. 12%; $P = .001$). The median age of those who died was older than that of those who survived (32 vs. 16 years). Case-fatality did not differ significantly by surveillance area. In a multivariate model, age (RR, 1.01 per year; 95% CI, 1.00–1.02), having a blood isolate (regardless of whether *N. meningitidis* was also isolated from another site; RR, 4.5; 95% CI, 1.63–12.44), and serogroup C (RR, 1.6; 95% CI, 1.04–2.55) were associated with increased case-fatality.

Of 462 *N. meningitidis* isolates available from the 4 sites with continuous data, MEE was done on 399 (86%). The proportion of total isolates from those 4 sites that were typed by MEE varied by year as follows: 60% in 1992, 55% in 1993, 75% in 1994, 69% in 1995, and 64% in 1996.

Of the 154 serogroup C isolates for which MEE results were available (78% of the total), 138 (90%) were of a closely related enzyme type, the ET-37 complex, and 52 (34%) were ET-24, a single enzyme type in the ET-37 complex. The proportion of serogroup C isolates of the ET-24 complex varied over the 5-year period, although not linearly (36% in 1992, 9% in 1993, 15% in 1994, 49% in 1995, and 50% in 1996). Race, sex, and median age did not vary significantly by enzyme type. In a multivariate model adjusting for age and for having a blood isolate ($P = .02$), ET-24 was not associated with an increased CFR (RR, 1.0; $P = .2$).

Of the 110 serogroup B isolates for which MEE results were available (87% of the total), 24 (22%) were ET-5. Among patients with serogroup B isolates, the CFR did not differ significantly among those with ET-5 and those with other enzyme types (8% vs. 4%; $P = .4$). Patients with ET-5 isolates were marginally more likely to have a blood isolate (88% vs. 69%; $P = .07$). Among the 101 serogroup Y isolates for which MEE results were available (84% of the total), 2 major enzyme type complexes could be distinguished by a difference in peptidase mobility. One (ET-501/508) accounted for 51 isolates (50%) and the other (ET-516) for 33 isolates (33%). Patients with ET-501 or ET-508 isolates were more likely to be black than were patients with ET-516 isolates (74% vs. 47%; $P < .005$).

Serotyping and serosubtyping were done for 107 of the 112 serogroup B isolates available from the 4 sites with continuous data, with 84% (107/127) of the total cases from those sites due to serogroup B. Of the 107 isolates, 36 could not be serotyped and 10 could not be serosubtyped. The most common serotype was 4, and the most commonly expressed serosubtype was P1.15 (table 2, table 3). Overall, 68% of isolates expressed 1 of the 6 most common serosubtypes, specifically P1.15; P1.14; P1.5,2; P1.7,16; P1.7,1; and P1.7,13. Of the 107 isolates, 9 (8%) were 15:P1.7,16 and 8 (7%) were 4:P1.7,1. All other serotype/serosubtype combinations accounted for <5% of isolates. Of 76 cases of serogroup B meningococcal disease reported from Oregon in 1996, 72 isolates (95%) were available for testing. Fifty-one (71%) of these isolates were serotype 15, and 59 (82%) were serosubtype P1.7,16.

Discussion

The cumulative incidence of meningococcal disease in the United States increased from 0.8/100,000 in 1992 to 1.0/100,000 in 1996. An earlier study found that between 1989 and 1991, the rate of meningococcal disease decreased from 1.3 to 0.9/100,000 [4]. In 1997 and 1998, the projected rates of meningococcal disease based on the same 4 surveillance areas decreased to 0.8 and 0.7/100,000 (CDC, unpublished data), consistent with natural fluctuations in incidence. However, although the overall incidence of meningococcal disease decreased in 1997 and 1998, the incidence of serogroup Y disease remained elevated at 0.2/100,000 (CDC, unpublished data).

The proportion of meningococcal cases due to serogroup Y increased during the study period from 10.6% in 1992 to 32.6% in 1996. In the period 1989–1991, serogroup Y accounted for

Table 2. Serotyping of serogroup B *Neisseria meningitis* isolates, 1992–1996, from 4 sites with continuous surveillance (California, Georgia, Maryland, Tennessee).

Serotype	Cases (n = 107)
1	5 (5)
2A	4 (4)
2B	2 (2)
4	32 (30)
14	9 (8)
15	15 (14)
17	2 (2)
21	2 (2)
Nontypable	36 (34)

NOTE. Data are no. (%).

Table 3. Serosubtype data, *Neisseria meningitidis* isolates, 1992–1996, from 4 sites with continuous surveillance (California, Georgia, Maryland, Tennessee).

Serosubtype	Cases (n = 107)
P1.15	15 (14)
P1.14	14 (13)
P1.5,2	13 (12)
P1.7,16	13 (12)
P1.7,1	12 (11)
P1.7,13	5 (5)
P1.5	3 (3)
P1.6	3 (3)
P1.7,4	3 (3)
P1.5,10	2 (2)
P1.7	2 (2)
P1.9	2 (2)
P1.10	2 (2)
P1.10,14	2 (2)
P1.1	1 (1)
P1.3,6	1 (1)
P1.7,3,6	1 (1)
P1.12	1 (1)
P1.12,13	1 (1)
P1.16	1 (1)
Nontypable	10 (9)

NOTE. Data are no. (%).

2% of endemic disease [4], whereas in the time period 1978–1981, serogroup Y caused 7% of cases reported through nationwide surveillance [17]. The majority of the serogroup Y isolates we studied were of 2 major enzyme type complexes, 1 of which (ET501/508) was found in only 1 of 39 military and civilian isolates characterized during 1970–1975, when serogroup Y accounted for 18% of isolates submitted to the CDC [18]. One possible explanation for both the increased rate of serogroup Y disease and the elevated median age of patients is waning population immunity. However, the increase may also reflect the emergence of a distinct clone, as characterized by MEE. To distinguish between these explanations and predict whether this shift in serogroup distribution will continue requires additional investigation of the stability of clonal groups in populations over time and of the association between changes in enzyme type and pathogenicity.

Patients with serogroup Y meningococcal disease were more likely to have pneumonia than were patients with disease due to other serogroups, as has been reported in other studies [19, 20]. Meningococcal pneumonia may be underdiagnosed, because of the difficulty in distinguishing persons who are meningococcal carriers from those with meningococcal pneumonia through isolation of the organism from the sputum and because physicians may not consider *N. meningitidis* as a possible cause of pneumonia. As a result, meningococcal infections that occur in the absence of meningitis or bacteremia may be underreported in the current surveillance system, which requires culture confirmation from a normally sterile site.

Consistent with earlier studies, infants continue to have the highest age-specific attack rates of meningococcal disease, but 54% of patients were between 2 and 29 years, a higher proportion than in earlier studies [4]. The elevated incidence among 15- to 19-year-olds may reflect enhanced risk factors for meningococcal transmission and invasion, such as crowding, active or passive smoking, exposure to oral secretions, or increased mixing of this population through such factors as college attendance [21–25]. Outbreaks of meningococcal disease have been associated with a shift toward disease in school-age children and young adults and may be caused by exposure among these age groups to new strains of *N. meningitidis* to which they were not exposed in earlier childhood [2]. If the increase in endemic disease among this age group is also due to introduction of new strains, age-specific rates of meningococcal disease should vary by strain, as defined by enzyme typing. We were unable to document these differences within our study population, suggesting that increased disease among young adults may instead be due to such risk factors as active and passive smoking and college attendance [23, 26]. The increased rate of meningococcal disease among older adults may be attributable to age-related declines in humoral immunity [27], but the increased proportion of disease among older women may be due to sex-specific differences in risk factors, such as crowding, socioeconomic status, underlying illnesses, or exposure to children, or to selective survival of a healthier male cohort [28].

Changes in the age and serogroup distribution of meningococcal disease will influence decision making about use of new conjugate meningococcal vaccines for control of endemic disease. Unlike Hib disease, rates of meningococcal disease remain elevated through adulthood, so effective vaccines must either provide long-lasting protection or be readministered during childhood and adolescence. Initial efforts have focused on conjugating the serogroup C and serogroup A polysaccharides to carrier proteins in an effort to duplicate the remarkable success of conjugated Hib vaccines, and these vaccines have completed or are already in phase II clinical trials. Although it is difficult to predict whether the high proportion of disease due to serogroup Y will persist, currently a combined conjugate vaccine that protects against serogroups C and Y would be superior to a monovalent conjugate serogroup C vaccine.

An outbreak of ET-5 serogroup B meningococcal disease, occurring since 1994, has not spread beyond the Pacific Northwest [29]. Although rates of serogroup B meningococcal disease in Oregon in 1996 were 2.4/100,000, 1997 data suggest that the outbreak there may be subsiding, a pattern that is consistent with outbreaks in other countries [30, 31] (P.C., unpublished data). Prevention of serogroup B meningococcal disease has been hindered by the absence of a vaccine licensed for use in the United States. Because of apparent immune tolerance to a self-antigen, the purified serogroup B capsular polysaccharide is not immunogenic in humans [32]. Strategies to develop serogroup B meningococcal vaccines have focused on the use of noncapsular antigens to elicit protective immunity [30]. In large

clinical trials, 3 vaccines based on the outer membrane proteins of epidemic serogroup B strains were found to be safe, immunogenic, and protective in older children and adults [33–36]. However, there is considerable antigenic diversity among the outer membrane proteins of serogroup B strains that cause endemic disease, and their ability to elicit cross-protection against strains other than those used to produce the vaccine as well as strains of other serogroups that share the same serosubtype has not been established. Analysis of serogroup B strains from endemic disease in the United States, excluding strains from Oregon, demonstrates that a multivalent vaccine against 6 common serosubtypes may provide protection against only 68% of disease caused by serogroup B strains. In contrast, in 1996, because of the ongoing outbreak, 82% of cases of serogroup B disease in Oregon were due to a single serosubtype (P1.7,16). The predominant serosubtype also varies between countries. In 1996, 30% of serogroup B cases reported from Europe were due to P1.4, which accounted for only 1% of isolates in this study [37]. Ongoing surveillance for all serogroups is necessary both to determine the stability of serosubtypes in the United States over a longer time period and to determine the representativeness of this sample.

Since 1991, the frequency of serogroup C meningococcal disease outbreaks has increased, with many outbreaks due to a clone identified by MEE as ET-24 [2] (CDC, unpublished data). Although outbreaks are usually caused by closely related strains, ET-24 or the ET-37 complex strains are also a common cause of endemic disease, making their presence alone not a sufficient criterion to distinguish an outbreak [38]. The high proportion of endemic serogroup C disease due to these clones suggests that the appearance of this strain may be the result of waning population immunity and that, on exposure, a person is more likely to develop invasive disease as opposed to colonization [24]. Furthermore, patients who have meningococcal disease due to ET-24 may be more likely to die, because ET-24 is associated with having a blood isolate, a likely correlate of the pathogenicity of the strain.

Mortality from meningococcal disease is likely related to both strain and host characteristics. Although infection with the ET-24 clone was not itself associated with a worse outcome, it was associated with finding *N. meningitidis* in the bloodstream. The CFR differed dramatically between those with a blood isolate (12%) and those without (2%). Proliferation of bacteria in vivo is associated with release of endotoxin, which initiates an inflammatory cascade leading to altered immune response, disseminated intravascular coagulopathy, and circulatory collapse. The concentration of endotoxin has been correlated with severity of disease [39]. Rapid clearance of the organism from the blood may be able to interrupt this cascade, resulting in a better outcome. Disease due to infection with serogroup C was also associated with an increased CFR, suggesting that outcome is also affected by the characteristics of the organism, including the polysaccharide capsule, outer membrane proteins, and lipopolysaccharides.

The overall CFR for meningococcal disease in the United States is similar to that found in many other developed countries [37]. New Zealand, currently experiencing a serogroup B epidemic, has a lower CFR of 5% [40], consistent with the 6% CFR of serogroup B disease in the United States [4]. Nevertheless, patients with meningococcal disease, especially those with meningococcemia, continue to die, even with optimal medical care. Although prompt antibiotic therapy is considered to be very important, clinical data conclusively linking early antimicrobial treatment to improved outcome are lacking [41]. Although research in the optimal use of antibiotics and other experimental therapies should continue, development of better meningococcal vaccines and utilization of such vaccines among high-risk groups, including infants and toddlers, will be the most effective means of preventing the morbidity and mortality associated with meningococcal disease.

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