Epidemic Serogroup B Meningococcal Disease in Oregon
The Evolving Epidemiology of the ET-5 Strain

Marion Diermayer, MD
Katrina Hedberg, MD, MPH
Frederick Hoesly, MD, MPH
Marc Fischer, MD
Bradley Perkins, MD
Michael Reeves, PhD
David Fleming, MD

Context In 1993, Oregon’s incidence of serogroup B meningococcal disease began to rise because of a highly clonal group of strains designated enzyme type 5 (ET-5), the first such increase observed in the United States.

Objective To evaluate the impact that the ET-5 strain has had on the epidemiology of meningococcal disease in Oregon.

Design and Setting Epidemiologic analysis of surveillance data on Oregon meningococcal disease cases from 1987 through 1996 and multilocus enzyme electrophoresis typing of serogroup B isolates from June 1993 through April 1995 and from April through June 1996.

Patients A total of 836 persons with invasive meningococcal disease.

Main Outcome Measures Disease frequency and clonality of strains.

Results Serogroup B disease incidence rates more than doubled from the preepidemic period in 1987-1992 (1.0 case per 100 000 population) to the recent epidemic period in 1995-1996 (2.2 cases per 100 000). The age-specific incidence rate of serogroup B disease among those 15 through 19 years old increased 13-fold between the preepidemic period (0.5 case per 100 000) and 1995-1996 (6.4 cases per 100 000). However, the proportion of cases with meningococcemia and the case-fatality rate did not change. Of 99 Neisseria meningitidis isolates obtained from 1993-1995, 88 (89%) belonged to the ET-5 complex. Of these, 69 (78%) were a single clone, designated 301. Of 20 serogroup B isolates from 1996, 18 (90%) belonged to the ET-5 complex; 17 (94%) were the 301 clone.

Conclusion Serogroup B meningococcal disease incidence continues at high levels in Oregon with increasing predominance of the ET-5 clonal strains.
demic to epidemic disease: (1) an increase in the overall number of cases; (2) a shift in the age distribution of cases from predominantly younger than 5 years of age toward older age groups; and (3) the predominance of a single bacterial strain rather than the heterogeneous mix of strains typical of epidemic disease. In this article, we investigate the epidemiological features of Oregon’s recent cases to see if they match the requirements for epidemic disease.

METHODS

Case Definition

A confirmed case of meningococcal disease was defined as an Oregon resident in whom *N meningitidis* was isolated from a normally sterile site (predominantly blood and cerebrospinal fluid), or in whom characteristic clinical signs and symptoms were present and whose blood or cerebrospinal fluid was positive for *N meningitidis* antigens by latex agglutination test. Presumptive cases were defined as those persons in whom gram stain–negative diplococci were visualized in blood or cerebrospinal fluid; suspect cases were those persons who had symptoms diagnosed by physicians as most compatible with meningococcal disease (usually petechial rash, meningismus, or fever), but on whom no latex agglutination test or bacterial culture was done, or if a culture was done, yielded no growth. A case found to be linked to another case was defined as either coprimary (onset of disease in a contact within 24 hours of onset in the primary case) or secondary (onset of disease in a contact more than 24 hours after onset in the primary case).

Data Collection

By law, physicians and laboratories in Oregon are required to report cases or laboratory results indicative of invasive meningococcal disease to the local health department. Demographic and epidemiologic data collected on surveillance forms are sent to the Oregon Health Division Acute and Communicable Disease Program and entered into a computer database.

Serogrouping of all *N meningitidis* isolates is performed by the Oregon Center for Public Health Laboratories using standard methods. Since the early 1980s, laboratories have been required to report cultures that yielded *N meningitidis* isolates from normally sterile sites to local health departments. However, they have only been required to submit isolates as part of routine reporting since December 1994; prior to that time, laboratories submitted isolates voluntarily. At the time of the study, isolates were only available from patients with disease onsets after June 1993.

During the study, the Centers for Disease Control and Prevention, Atlanta, Ga, performed multilocus enzyme electrophoresis on selected isolates. Multilocus enzyme electrophoresis, which is described in previous publications, relies on differences in the electrophoretic mobility of constitutive enzymes to indicate the genetic relatedness of strains. All serogroup B isolates from patients with onset during the period June 1993 through April 1995 were tested to determine clonality of the strains. All serogroup B isolates from patients with onset during the 3-month period from April through June 1996 were tested to confirm the continued presence of the clonal strain.

Data Analysis

We examined the incidence of invasive meningococcal disease cases in Oregon from 1983 through 1996 (Figure 1). However, we chose to analyze case data, including sex, race and age distributions, symptoms and severity of disease, and geographic and seasonal distributions beginning 5 years before the increase in incidence. We compared characteristics of cases over 3 time periods: the preepidemic (1987-1992), the early epidemic (1993-1994), and the recent epidemic period (1995-1996), and compared serogroup B with serogroup C disease. Frequencies and relative risks (RRs) stratified by time period and serogroup were calculated using the Epi Info statistical software program, statistical significance was determined using χ² and χ² for trend tests.

RESULTS

From January 1987 through December 1996, 836 cases of invasive meningococcal disease were reported to the Oregon Health Division. Of these, 725 (87%) were confirmed (range, 75%-96% annually), 35 (4%) were presumptive, and 76 (9%) were suspect cases.

On average, 57 cases (range, 31-75) were reported annually during the years 1987-1992, corresponding to an incidence rate of 2.0 cases per 100,000 population per year. The incidence rate increased to 4.0 in the early epidemic period (1993-1994) and remained high at 3.9 in the recent epidemic period (1995-1996).
Serogrouping

Serogrouping was performed on 623 (86%) of the 725 confirmed cases during the 10-year period studied (range, 64% in 1987 to 95% in 1995). Of these, 408 (65%) were serogroup B, 179 (29%) were serogroup C, and 36 (6%) belonged to other serogroups. Serogroup B predominated throughout the entire study period. The incidence rate of both serogroups B and C disease doubled from the preepidemic period to the early epidemic period (1.0 to 1.9 case per 100,000 population for serogroup B disease and 0.5 to 1.1 for serogroup C disease; Figure 1). The incidence rate of serogroup B disease increased to 2.2 in 1995-1996. However, the rate of serogroup C disease declined to 0.6 during this time, returning to baseline.

Multilocus Enzyme Electrophoresis

Multilocus enzyme electrophoresis was performed on all 99 viable serogroup B isolates (of 107 total) available from June 1993 through April 1995. Of the serogroup B isolates tested, 88 (89%) belonged to the enzyme type 5 (ET-5) complex. Multilocus enzyme electrophoresis can further separate enzyme types such as ET-5 into specific clones. Such analysis revealed that 69 (78%) of the 88 ET-5 isolates from 1993-1995 belonged to a single clone, designated 301. Testing of all 20 serogroup B isolates from April through June 1996 confirmed the continued presence of this clone; 18 (90%) of 20 isolates belonged to the ET-5 complex, and of these, 17 (94%) were clone 301.

Sex, Racial/Ethnic, and Age Distributions

The sex and racial/ethnic distributions of serogroup B cases remained stable throughout the study period (Table). However, the age distribution of cases changed considerably (Figure 2). In the preepidemic period, 96 (64%) of 150 serogroup B disease cases occurred in children younger than 5 years of age; during the early epidemic years of 1993-1994, a progressive shift toward disease in older age groups took place, most notably among 15- through 19-year-olds. Age-specific incidence rates in this group went from 0.5 per 100,000 population in the preepidemic period to 4.1 in the early epidemic period and reached 6.4 by 1995-1996, a 13-fold increase overall. In contrast, the incidence of disease in children younger than 5 years of age only increased from 7.9 to 11.6.

Increases in serogroup C cases in 1993-1994 were also accompanied by a shift in age distribution. The age-specific incidence rate in 15- through 19-year-olds increased from 0.5 during the preepidemic period to 2.7 in 1993-1994, but declined to 0.9 as the overall number of serogroup C cases returned to baseline.

Clinical Syndrome, Hospitalizations, and Deaths

Among serogroup B cases for whom the clinical syndrome was known, the proportion of cases diagnosed with meningococcemia alone decreased somewhat between the preepidemic period (46% [66/144]), the early epidemic period (41% [45/109]), and the recent epidemic period (35% [40/113]), although the change was not significant ($\chi^2$ for trend, $P = .09$; Table). The proportion of cases hospitalized and the case-fatality rates...
remained stable during the 3 periods (Table).

Secondary Transmission
Secondary transmission was uncommon during the entire 10-year period studied. Among serogroup B cases, only 9 cases were linked to others; all were designated secondary cases. Of these, 4 cases occurred in school settings, all before 1994. At least 3 of the secondary cases occurred among individuals for whom prophylactic antibiotics had been prescribed but who were noncompliant. Two additional cases occurred in people who had contact with cases but were not considered at risk when prophylaxis was prescribed. No information is available on the other cases. Secondary transmission was no more common among serogroup C cases than serogroup B cases.

Serogroup B cases occurred predominantly during the fall, winter, and spring months, as did serogroup C cases. This seasonal distribution did not vary by time period.

Geographic Distribution
Throughout the study period, the majority of serogroup B cases, as well as the highest incidence rates, occurred in the western part of the state, particularly the northwestern region. In fact, individuals living in the western third of the state were 3.3 times more likely (95% confidence interval [CI], 2.1-5.3) to develop serogroup B meningococcal disease than those living in the eastern portion of the state. This relationship proved consistent over the 3 time periods. In contrast, serogroup C cases occurred at the same rate east and west of the mountains (RR, 1.4; 95% CI, 0.9-2.4). Serogroup B cases occurred at the same rate as serogroup C cases in the east but were more common than serogroup C cases in the west (RR, 1.4; 95% CI, 1.0-1.9).

Data From Neighboring States
While the annual incidence of meningococcal disease in Washington State between 1987 and 1995 (1.5-2.3 cases per 100 000 population) has been consistently lower than that in Oregon, rates have increased over the past 4 years and are currently at their highest since 1953. Serogroup B cases have been making up an increasing proportion of these cases. The rate of serogroup B disease in Clark County, Washington, which borders on Oregon near metropolitan Portland, increased 5-fold, from 1.4 in 1987 (3 cases) to 7.1 in 1994 (20 cases). Clark County rates decreased to 4.8 in 1995 (14 cases; Karen Steingart, MD, Southwest Washington Health District, Vancouver, Wash, oral communication, January 6, 1999).

In 1995, a cluster of 6 ET-5 serogroup B cases occurred among students at a Seattle middle school. California’s overall meningococcal disease rates have not increased. However, 2 clusters and several sporadic cases of ET-5 serogroup B disease in 1993 and 1995 have been identified (S. B. Werner, MD, California Department of Health Services, Berkeley, oral communication, January 5, 1999).

COMMENT
Oregon has sustained an annual incidence of meningococcal disease 4 times the national rate since the increase in number of serogroup B cases was first noted in 1993. The increase in the number of cases, the shift in the age distribution of cases, and the clonality of the isolates indicate that Oregon is experiencing an epidemic of serogroup B meningococcal disease due to an ET-5 strain specified as the 301 clone. Early in the epidemic (1993-1994), both serogroup B and serogroup C disease contributed to the rise in cases. However, where the incidence of serogroup C disease in Oregon has returned to baseline, the incidence of serogroup B disease remains elevated because of the persistent presence of the ET-5 complex that now constitutes 90% of the serogroup B isolates.

The ET-5 strains of N meningitidis were first identified in 1974 as the cause of a serogroup B epidemic in northern Norway that spread to the rest of the country and persisted through 1991. The ET-5 complex of strains caused epidemics in other parts of northern Europe in the late 1970s, Cuba in 1980, Chile in 1985, and Brazil in 1987. While the increase in serogroup C cases is paralleled in other parts of the United States and Canada, the serogroup B ET-5 complex has not previously been described as the cause of an epidemic in the United States. However, sporadic cases in the United States have been reported among immigrants from Latin America, without transmission to the surrounding community. An ongoing population-based survey of laboratory isolates from 5 US sites (California, Oklahoma, Georgia, Maryland, and Tennessee) conducted by the Centers for Disease Control and Prevention showed that 14% of US endemic strains belonged to the ET-5 complex in 1994, predominantly from the San Francisco surveillance site (currently the California Emerging Infections Program; unpublished data, Childhood and Respiratory Disease Branch, Centers for Disease Control and Prevention, January 1999). None of the sites, including the San Francisco Bay Area, have as yet experienced an increase in disease; however, the increasing presence of the ET-5 complex in Washington and California is noteworthy. Why the ET-5 strain has gained a foothold in the Pacific Northwest at this particular time is unclear, but based on experience with the disease in Scandinavia and South America, the possibility of geographic spread is real.

Endemic meningococcal disease occurs most commonly in children younger than 5 years of age. The progressive shift toward older age groups has proved an early and reliable predictor of the transition from endemic to epidemic meningococcal disease in other parts of the world. The reason for this remains unknown, although lack of immunity in the group—that is, exposure to a meningococcal strain not previously encountered by the age cohort—combined with risk factors that may be inherent in the age group (eg, crowding and close contact with others through school, sports, and social events that facilitate transmission of the bacteria) provide plausible mechanisms.
Whereas the overall increase in numbers of serogroup B cases, the shift in age distribution of cases, and the clonality of isolates are clearly consistent with an epidemic, clinical features of the Oregon ET-5 epidemic (eg, mortality, proportion of cases of meningococemia, and rate of hospitalization) do not differ markedly from endemic disease. Our experience contrasts with that in Norway and Cuba, where ET-5 caused both a high proportion of cases of meningococemia and a high case-fatality rate.12,13 

Controlling the spread of the ET-5 clonal complex represents a formidable challenge—a high index of suspicion, early diagnosis and treatment of the disease, rapid reporting of cases to local and state public health officials, and careful administration of chemoprophylaxis to contacts constitute the basics of control. In Oregon, heightened surveillance and physician and public awareness have been the primary responses to the epidemic. Conditions that lead to the disruption of nasopharyngeal mucosa, such as antecedent respiratory tract infection17-20 and exposure to tobacco smoke,21,22 have been cited as risk factors for invasive disease. In a case-control study we conducted using 1994 Oregon and southwest Washington cases, we found that exposure to tobacco smoke was the single strongest modifiable risk factor for developing meningococcal disease.23 Although the public health impact is unknown, avoiding tobacco smoke may decrease one’s risk of developing meningococcal disease. 

These data underscore the need for an efficacious serogroup B vaccine. Several serogroup B vaccines are currently under development,24-27 but none are yet licensed for use in the United States. Even if an effective vaccine were available, with an incidence of 2.2 cases per 100 000 population, it is unclear that widespread vaccine administration would be a cost-effective intervention. Because ET-5 appears to be linked predominantly to serogroup B disease, serogrouping of meningococcal bacterial isolates should be strongly encouraged by state health departments. Increases in serogroup B disease should be noted as an indicator of possible spread of the ET-5 clone.

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