Antigenic Shift and Increased Incidence of Meningococcal Disease

Lee H. Harrison,1,2 Keith A. Jolley,3 Kathleen A. Shutt,2 Jane W. Marsh,2 Mary O'Leary,2 Laurie Thomson Sanza,1 Martin C. J. Maiden,3 and the Maryland Emerging Infections Program

1Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; 2Infectious Diseases Epidemiology Research Unit, Division of Infectious Diseases, University of Pittsburgh Graduate School of Public Health and School of Medicine, Pittsburgh, Pennsylvania; 3Department of Zoology, University of Oxford, Oxford, United Kingdom

Background. The incidence of serogroup C and Y meningococcal disease increased in the United States during the 1990s. The cyclical nature of endemic meningococcal disease remains unexplained. The purpose of this study was to investigate the mechanisms associated with the increase in the incidence of meningococcal disease.

Methods. We characterized an increasing incidence of invasive serogroup C and Y meningococcal disease using population-based surveillance from 1992 through 2001. Isolates were characterized by multilocus sequence typing and antigen sequence typing of 3 outer membrane protein (OMP) genes: porA variable regions (VRs) 1 and 2, porB, and fetA VR.

Results. For both serogroups, OMP antigenic shifts were associated with increased incidence of meningococcal disease. For serogroup Y, antigenic shift occurred through amino acid substitutions at all 3 OMPs—PorA VR 1 and 2, PorB, and FetA VR. For serogroup C, antigenic shift involved amino acid substitutions at FetA VR and, in some cases, deletion of the porA gene. On the basis of deduced amino acid sequences, the antigenic changes likely occurred by horizontal gene transfer.

Conclusions. Antigenic shifts were associated with increased incidence of serogroup C and serogroup Y meningococcal disease. For serogroup Y, the changes involved all OMP genes that were studied. Increases in the incidence of meningococcal disease may be caused, in part, by antigenic shift.
Antigenic Shift and Meningococcal Disease

Figure 1. A, Average annual incidence of serogroup Y infection in Maryland, 1992–2001, by outer membrane protein (OMP) sequence profile. The dark gray area represents infections caused by the early clone (sequence type [ST]–23 complex, 2:P1.5-1,2-2:F.5-8), the light gray area represents infections caused by the late clone (ST-23 complex, 3:P1.5-2,10-1:F.4-1), and the black area represents infections caused by isolates with other OMP sequence profiles. The dotted areas represent the subset of early and late strains with porA deletions.

B, Average annual incidence of serogroup C infection among 15–24-year-olds in Maryland, 1992–2001, by OMP sequence profile. The dark gray area represents infections caused by the early clone (ST-11 complex, 2:P1.5,2:F.1-30), the light gray area represents infections caused by the late clone (ST-11 complex, 2:P1.5,2:F.3-6), and the black area represents infections caused by isolates with other OMP sequence profiles. The dotted areas represent the subset of early and late strains with porA deletions.

MATERIALS AND METHODS

Study isolates and serogroup determination. The study isolates were obtained through active, laboratory-based surveillance from 1 January 1992 through 31 December 2001. This study was performed as part of the Maryland Active Bacterial Core Surveillance component of the multistate Emerging Infections Program Network [18]. The case definition was the isolation of N. meningitidis from a normally sterile body fluid from a Maryland resident [19, 20]. Periodic laboratory audits were conducted to identify unreported cases. Meningococcal serogrouping and serosubtyping were performed as described elsewhere [21].

MLST and OMP gene sequence analysis. Chromosomal DNA extraction was performed by streaking 1–2 colonies onto chocolate agar, incubating them overnight, placing a thick suspension of organisms in 0.5 mL of PBS, and boiling them for 20 min. MLST and antigen gene sequence typing of porA VR1

Antigenic Shift and Meningococcal Disease • JID 2006:193 (1 May) • 1267
and VR2, porB, and fetA VR was performed by use of polymerase chain reaction (PCR) amplification and sequence analysis, as described elsewhere [11, 13, 22–25]. Final DNA sequences were determined using both forward and reverse strands.

**Molecular analysis of porA deletions.** Investigation of possible porA deletions was performed by PCR and sequence analysis, with primers A11.2 and A13.2, which flank the porA coding region, on the basis of the published N. meningitidis MC58 genome [26]. Genomic DNA was isolated from each of the 13 suspected serogroup C porA deletion strains and 1 wild-type serogroup C strain, using the DNeasy Mini Kit (QIAGEN). Ten nanograms of purified genomic DNA was amplified by long-range PCR, using the GeneAmp XL PCR Kit rTth (Applied Biosystems). The resulting PCR products were resolved on a 0.8% agarose gel and visualized by ethidium-bromide staining. Sequence analysis of PCR products was performed with the BigDye Terminator Cycle Sequencing Kit 3.1 (Applied Biosystems). The resulting PCR products were analyzed against the published porA genomic region from N. meningitidis MC58, with DNAstar SeqMan and MegAlign software (version 6.0; DNASTar).

**Data analysis.** MLST sequences were assembled with the sequence analysis package of Staden, and the automatic calling of alleles was performed using Sequence Typing Analysis and Retrieval System software (available at: http://neelix.molbiol.ox.ac.uk:8080/userweb/mchan/stars/) [27]. Assignment of STs and porA, porB, and fetA alleles was performed by querying the MLST (http://pubmlst.org/neisseria/) and Neisseria.org (http://neisseria.org/nm/typing/) Web sites. Antigen gene sequence typing results were expressed as porB class, porA VR1 allele and porA VR2 allelafetA allele [28, 29]. The assignment of STs and MLST-based clonal complexes was also performed by querying the MLST Web site. STs are considered to belong to the same ST clonal complex if they share alleles at 4 or more of the 7 MLST loci with the central ST of that complex. The PorA VR1 and VR2, PorB, and FetA VR amino acid sequences were deduced from the DNA sequences obtained for each locus. Deducd amino acid sequences were aligned using the ClustalW method in MegAlign (version 6.0; DNASTar). Single-nucleotide differences were assumed to have occurred by point mutation, whereas multiple nucleotide/multiple amino acid changes were assumed to have occurred by horizontal gene transfer [30].

Minimum spanning trees were constructed to infer evolutionary models, using Bionumercics software (version 3), which incorporates the BURST algorithm (Applied Maths) [31]. The founder ST for each serogroup was defined as the ST that had the greatest number of single-locus variants (SLVs). Temporal trends were assessed in SAS (version 8.2; SAS Institute), using the Cochran-Armitage trend test.

**RESULTS**

There were 360 cases of meningococcal disease that met the surveillance case definition. Of these, 121 (34%) were serogroup Y, of which isolates were available for 106 (88%). There were 104 serogroup C cases (29%), and isolates were available for 97 (93%) of these, including 36 isolates from 15–24-year-olds. In addition, there were 63 cases of serogroup B infection (18%), 13 cases of serogroup W-135 infection (4%), and 2 cases each of serogroup X and serogroup Z (<1% for each) infection. For 14 cases (4%), the isolates could not be serogrouped with standard serogrouping reagents, and the serogroup was unknown for 41 cases (11%) because the isolates were unavailable.

**Serogroup Y.** Of the 106 available serogroup Y isolates, 100 (94%) had STs belonging to the ST-23 complex. When these serogroup Y isolates were classified according to OMP sequence profile, 59 (56%) were 2:P1.5-1,2-2:F.5-8, 37 (35%) were 3:P1.5-2,10-1:F.4-1, and 10 (9%) had other OMP sequence profiles. When examined temporally, 2:P1.5-1,2-2:F.5-8 predominated early in the 1990s and, therefore, was referred to as the early OMP sequence profile. In contrast, 3:P1.5-2,10-1:F.4-1 predominated later in the 1990s and was referred to as the late OMP profile (P < .0001, test for trend) (figure 1A and table 1). All of the early and late OMP profile isolates had STs belonging to the ST-23 complex.

On the basis of the deduced amino acid sequences, the late OMP sequence profile differed from the early OMP sequence profile by 2 aa for PorA VR1, 6 aa for PorA VR2, and 22 aa for FetA, suggesting that the genetic variation between the 2 OMP profiles had occurred through horizontal gene transfer (table 2). All early profile isolates had a class 2 porB gene, whereas the late profile isolates had a class 3 porB gene; the predominant porB alleles for the early and late profiles were 2–55 (90% of early profile isolates) and 3–36 (100% of late profile isolates), respectively. The remaining early profile isolates had porB sequence types with 97.9%–99.9% amino acid homology with the porB 2–55 allele observed in the early profile isolates. Translation of porB DNA sequences revealed minimal amino acid homology at PorB VR loops V and VII between early and late profile isolates (table 2). The genetic variation observed at porB is significant since class 2 PorB proteins differ substantially from class 3 PorB proteins. For example, the protein encoded by porB 2–55 is 323 aa long, whereas the porB 3–36 allele encodes a protein that is 293 aa long.

The only ST common to both OMP sequence profiles was ST-23 (figure 2A). Of 59 early profile isolates, 14 (23.7%) were ST-23. The other most common STs among the early profile isolates were ST-1622 (23 isolates [39.0%]) and ST-1625 (17 isolates [28.8%]), which are funC SLVs of ST-23. There was 1 other SLV of ST-23 (ST-1448), at pilhC, which accounted for 1 early profile isolate. Two-thirds (25 isolates) of the 37 late profile
isolates were ST-23. The other most common ST among late profile isolates was ST-1621 (9 isolates [24.3%]). There were 3 other late profile SLVs: 1 of ST-23 and 2 of ST-1621.

There were 10 meningococcal isolates that did not belong to either the early or the late OMP sequence profile. All of these isolates had at least 2 antigens in common with either the early or the late profile or both, but none had all antigens in common with either of the profiles (data not shown).

**Serogroup C.** Of the 97 available serogroup C isolates, 89 (92%) had STs belonging to the ST-11 complex. Of the ST-11 complex isolates, 13 (14.6% of ST-11 complex isolates and 13% of all available serogroup C isolates) could not be porA typed, despite the use of alternative primers. Serosubtyping data were available for 12 of these isolates, and all were nontypeable serogroup C control isolate generated either an ∼4.0-kb band (early profile) or an ∼0.5-kb band (late profile) (figure 2B). ST-11 accounted for 90% of both the early (28/31 isolates) and the late (35/29 isolates) OMP sequence profiles. ST-1988 was represented by 2 isolates (3%): 1 with the early profile and 1 with the late profile. All of the non–ST-11 isolates were SLVs of ST-11, and, other than ST-1988, all of the other STs were represented by a single isolate.

There were 19 ST-11 complex serogroup C isolates (21%) that did not belong to either the early or the late profile (data not shown). All of these isolates had at least 1 OMP antigen in common with either the early or the late profile or both, whereas no other late profile isolates accounted for 21 isolates (68%) and 21 isolates (54%), respectively. There were 3 small serogroup C outbreaks in Maryland during the study period, accounting for a total of 7 cases (7%) [6, 10]. All of these isolates belonged to the late OMP sequence profile.

The early and late profile ST-11 complex isolates comprised 7 STs (figure 2B). ST-11 accounted for 90% of both the early (28/31 isolates) and the late (35/29 isolates) OMP sequence profiles. The early and late clone ST-11 isolates for FetA; early and late clone–deduced FetA VR sequences differed by 23 aa (table 2). PorB 2-2 was the predominant allele for both early and late profile isolates, accounting for 21 isolates (68%) and 21 isolates (54%), respectively. There were 3 small serogroup C outbreaks in Maryland during the study period, accounting for a total of 7 cases (7%) [6, 10]. All of these isolates belonged to the late OMP sequence profile.

PCR analysis of the 13 isolates that were porA nontypeable indicated that the porA gene was entirely deleted. A porA typeable serogroup C control isolate generated an ∼4.0-kb band, whereas the porA nontypeable isolates generated either an ∼1.1-kb band (early profile) or an ∼0.5-kb band (late profile) (figure 3). Sequence analysis of the 4.0-kb PCR product detected the porA gene, whereas no porA gene sequence could be detected in either the early or the late clone PCR product from these 13 isolates.

### Table 1. Isolates with early vs. late outer membrane protein sequence profiles, by serogroup and 2-year period, 1992–2001.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Isolates, no. (%)</th>
<th>P value for trenda</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serogroup Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>12 (92)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Late</td>
<td>1 (8)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Total</td>
<td>13 (100)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Serogroup C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>3 (75)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Late</td>
<td>0 (0)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (25)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Total</td>
<td>4 (100)</td>
<td>6 (100)</td>
</tr>
</tbody>
</table>

**NOTE.** For serogroup Y, all age groups were included. The serogroup Y early isolates were sequence type (ST)–23 complex, 2:P1.5,2:F.5-8, and the serogroup Y late profile isolates were ST-23 complex, 3:P1.5,2,10-1:F.4-1. For serogroup C, 15–24-year-olds were included.

For serogroup Y, all age groups were included. The serogroup Y early isolates were sequence type (ST)–23 complex, 2:P1.5,2:F.5-8, and the serogroup Y late profile isolates were ST-23 complex, 3:P1.5,2,10-1:F.4-1. For serogroup C, 15–24-year-olds were included.

There were 19 ST-11 complex serogroup C isolates (21%) that did not belong to either the early or the late profile (data not shown). All of these isolates had at least 1 OMP antigen in common with either the early or the late profile or both, whereas no other late profile isolates accounted for 21 isolates (68%) and 21 isolates (54%), respectively. There were 3 small serogroup C outbreaks in Maryland during the study period, accounting for a total of 7 cases (7%) [6, 10]. All of these isolates belonged to the late OMP sequence profile.

The early and late profile ST-11 complex isolates comprised 7 STs (figure 2B). ST-11 accounted for 90% of both the early (28/31 isolates) and the late (35/29 isolates) OMP sequence profiles. The early and late clone ST-11 isolates for FetA; early and late clone–deduced FetA VR sequences differed by 23 aa (table 2). PorB 2-2 was the predominant allele for both early and late profile isolates, accounting for 21 isolates (68%) and 21 isolates (54%), respectively. There were 3 small serogroup C outbreaks in Maryland during the study period, accounting for a total of 7 cases (7%) [6, 10]. All of these isolates belonged to the late OMP sequence profile.

The early and late profile ST-11 complex isolates comprised 7 STs (figure 2B). ST-11 accounted for 90% of both the early (28/31 isolates) and the late (35/29 isolates) OMP sequence profiles. ST-1988 was represented by 2 isolates (3%): 1 with the early profile and 1 with the late profile. All of the non–ST-11 isolates were SLVs of ST-11, and, other than ST-1988, all of the other STs were represented by a single isolate.

There were 19 ST-11 complex serogroup C isolates (21%) that did not belong to either the early or the late profile (data not shown). All of these isolates had at least 1 OMP antigen in common with either the early or the late OMP profile or both, whereas no other late profile isolates accounted for 21 isolates (68%) and 21 isolates (54%), respectively. There were 3 small serogroup C outbreaks in Maryland during the study period, accounting for a total of 7 cases (7%) [6, 10]. All of these isolates belonged to the late OMP sequence profile.

**PCR analysis of the 13 isolates that were porA nontypeable indicated that the porA gene was entirely deleted. A porA typeable serogroup C control isolate generated an ∼4.0-kb band, whereas the porA nontypeable isolates generated either an ∼1.1-kb band (early profile) or an ∼0.5-kb band (late profile) (figure 3). Sequence analysis of the 4.0-kb PCR product detected the porA gene, whereas no porA gene sequence could be detected in either the early or the late clone PCR product from these 13 isolates.**
Table 2. Aligned deduced peptide sequences for PorA variable region (VR) 1 and VR2, FetA VR, and PorB loops V and VII, sequence type (ST)–23 complex serogroup Y, and ST-11 complex serogroup C meningococcal isolates, Maryland, 1992–2001.

<table>
<thead>
<tr>
<th>Strain</th>
<th>PorA VR1</th>
<th>PorA VR2</th>
<th>PorB Loop V</th>
<th>PorB Loop VII</th>
<th>FetA VR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allele</td>
<td>Deduced sequence</td>
<td>Allele</td>
<td>Deduced sequence</td>
<td>Allele</td>
</tr>
<tr>
<td>Serogroup Y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>5-1</td>
<td>PLQNIQQPQVTKR</td>
<td>2-2</td>
<td>HFVQQTTPQSQPTLVP</td>
<td>2-55</td>
</tr>
<tr>
<td>Late</td>
<td>5-2</td>
<td>PLQNIQQPQVTKR</td>
<td>10-1</td>
<td>HFVQKNQMQPPTLVP</td>
<td>3-36</td>
</tr>
<tr>
<td>Serogroup C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>5</td>
<td>PLQNIQQPQVTKR</td>
<td>2</td>
<td>HFVQQTTPKQSPTLVP</td>
<td>2-2</td>
</tr>
<tr>
<td>Late</td>
<td>5</td>
<td>PLQNIQQPQVTKR</td>
<td>2</td>
<td>HFVQQTTPKQSPTLVP</td>
<td>2-2</td>
</tr>
</tbody>
</table>

**NOTE.** Some of the early and late serogroup C isolates were *PorA* nontypeable. For *PorB*, the predominant alleles are shown. Amino acid differences are shown in boldface type.
Figure 2.  A, Minimum spanning tree analysis of 96 serogroup Y sequence type (ST)–23 complex isolates with early (2:P1.5-1,2-2:F.5-8) and late (3: P1.5-2,10-1:F.4-1) outer membrane protein (OMP) sequence profiles. There were 14 and 25 early and late clone ST-23 (founder ST) isolates, respectively.  
B, Minimum spanning tree analysis of 70 serogroup C ST-11 complex isolates with early (2:P1.5,2:F.1-30) and late (2:P1.5,2:F.3-6) OMP sequence profiles. There were 28 and 35 early and late clone ST-11 (founder ST) isolates, respectively. For both panels, the large number within each oval represents the ST, and the no. in parentheses represents the no. of isolates. The lines connect single locus variants, and the text along the lines indicates the multilocus sequence typing locus and allele for the ST distal to the founder ST. White ovals indicate STs that are common to both the early and the late clones, gray ovals indicate STs that are unique to the early clone, and black ovals indicate STs that are unique to the late clone.

**DISCUSSION**

In the present study, *N. meningitidis* strains of the same genetic lineage (i.e., the same ST complex) underwent major antigenic shifts, as measured by changes in OMP profiles. For serogroup Y, most cases in the early 1990s were caused by isolates with the same OMP sequence profile. However, in the late 1990s, the incidence of disease caused by these strains decreased sharply. At the same time, there was an increase in the incidence of infection caused by a group of isolates with an entirely different OMP profile. All of the other serogroup Y strains had some, but not all, of the OMP antigens in common with the early and late profiles. However, none of these serogroup Y strains was a major cause of invasive meningococcal disease.
but of a different fetA OMP allele, emerged and eventually decreased. The beginning of the increase in the late profile and the decrease in the early clone were associated with porA deletions. All of the serogroup C ST-11 complex isolates that did not belong to either the early or the late OMP profile had at least 1 antigen, but not all, in common with the 2 main clones. In contrast, none of the non-ST-11 serogroup C isolates had antigens in common with either the early or the late OMP clone.

For serogroup Y, we speculate that the antigenic shift observed in OMPs permitted the early profile clone to escape the population immunity that had developed in response to exposure to this clone. Antigenic shift resulted in significant amino acid substitutions at all 3 OMPs, suggesting that these changes occurred primarily by horizontal gene transfer [33]. porA, porB, and fetA are distant from each other on the N. meningitidis chromosome, indicating that this observed antigenic shift likely occurred by at least 3 horizontal gene transfer events. We also observed hybrid strains that contained a mixture of OMP alleles from the 2 profiles.

Antigenic shift at the capsular level, also known as capsular switching, has been described and shown to both initiate and sustain outbreaks of meningococcal disease [34, 35]. To our knowledge, the present study is the first to demonstrate antigenic shift at the noncapsular level in association with increased incidence of endemic meningococcal disease. We hypothesize that meningococcal antigenic shift of OMPs permitted clonal emergence in an immunologically naive population, which led to an increased incidence of meningococcal disease. A single amino acid substitution in porA has been associated with an increase in serogroup B infection, suggesting that even antigenic drift is sufficient to cause changes in population immunity [36]. Alternative explanations for the findings of the present study include acquisition of unmeasured virulence factors and changes in other antigens that we did not study.

The findings for serogroup Y are supported by models of meningococcal epidemiology. According to Gupta et al. [37], a relative lack of population immunity to the late profile allowed it to emerge in the face of decreasing incidence of early profile infections. The major change in antigenic profile is consistent with strong immune selection acting on 3 genes located on different parts of the genome. The nonoverlapping nature of the antigenic profiles likely occurred because strains that share immunologic variants were at a disadvantage because of bactericidal antibodies. The frequency of meningococcal hybrid strains bearing a mixture of OMP alleles was likely limited because of immunologic cross-protection provided by circulation in the population of isolates bearing early and late OMP profiles. This model was based on the PorA protein [37], but the results of the present study suggest that the model can be extended to PorB and FetA.

Our findings are consistent with the observation that the population of serogroup C strains is highly clonal [38]. Although we did find a major shift in fetA alleles, there was complete homology between amino acid sequences encoded by the porA and porB alleles, except for the isolates with the porA deletions.

Deletion of porA through homologous recombination has been reported for serogroup C isolates [39, 40]. We propose that deletion of porA in our isolates may have permitted continued infection by the early OMP profile clone before it disappeared as a cause of invasive disease in the late 1990s. In addition, deletion of porA may have contributed to the initial increase in the incidence of infection caused by the serogroup C late OMP profile. These data suggest that the deletion of porA is another mechanism by which N. meningitidis evades host immunity. We suspect that the major change in fetA and the porA deletions both contributed to the increase in incidence of serogroup C infection. The finding that all 3 Maryland outbreaks were caused by strains bearing the late OMP profile also suggests that these

![Figure 3. Long-range polymerase chain reaction results for porA-positive (Pos.) control isolate (lane 2), early outer membrane protein (OMP) sequence profile clone isolates (lanes 3–6), and late OMP sequence profile clone isolates (lanes 7–15).](image-url)
strains acquired a selective advantage that predisposed an immunologically naive population to a meningococcal outbreak. Whether this propensity was directly related to the antigenic shift in the FetA protein remains to be determined.

Several clinical and public-health implications can be drawn from the present study. First, our findings provide a credible hypothesis to explain the increase in meningococcal cases and outbreaks that were so troublesome in Maryland and elsewhere in the United States during the 1990s. Second, the finding of antigenic shift at the noncapsular level has important implications for meningococcal vaccine development, particularly for serogroup B. Antibodies against serogroup B polysaccharide cross-react with human neural tissue, and, therefore, serogroup B polysaccharide is recognized as a self-antigen and is poorly immunogenic in humans [41–43]. Serogroup B vaccines, therefore, rely on OMPs as the principal vaccine components [44]. It is conceivable that, if OMP-based serogroup B vaccines were introduced into the United States, an OMP antigenic shift similar to what we observed in the present study could occur, allowing the organism to evade vaccine-induced immunity. An efficacious serogroup B vaccine would need to either include conserved, immunogenic, noncapsular antigens or be polyvalent [44–47]. However, the ability of N. meningitidis to change multiple OMPs, as demonstrated in the present study, suggests that even a polyvalent serogroup B vaccine could be problematic. The finding that 13% of the serogroup C isolates that caused invasive disease in Maryland had a porB deletion supports the notion that vaccines directed primarily against PorA epitopes would have limited efficacy [39].

In summary, antigenic shift involving multiple OMP genes may have contributed to the increase in the incidence of serogroup Y infection observed in Maryland during the 1990s. Antigenic shift was also associated with an increase in the incidence of serogroup C infection in this population. The finding that antigenic shift was associated with both serogroups supports the hypothesis that this phenomenon could have been causally related to the observed increased incidence. Additional studies are needed to determine the frequency of noncapsular antigenic shift and its association with increases in the incidence of meningococcal disease.

Acknowledgments

We thank the participating hospital infection-control practitioners and microbiology-laboratory personnel in Maryland hospitals for identifying the meningococcal cases and providing the bacterial isolates: Nancy Rosenstein and the Active Bacterial Core Surveillance personnel (Centers for Disease Control and Prevention [CDC]), for overall support and contributions to meningococcal surveillance in Maryland; Yvonne Deane-Hibbert and Jackie Hunter (both of Johns Hopkins University), for assistance in conducting surveillance; Althea Glenn (Laboratories Administration, Maryland Department of Health and Mental Hygiene), for processing the isolates; Maria Lúcia Tondella (CDC), for the serotype data; Rachel Urwin, Roisin Ure, Julia Bennett, and Ana Belén Ibarz Pavón (all of University of Oxford), for general assistance in the laboratory; and Rachel Urwin and Samantha Miller (Hampton High School), for assistance with the porB genotyping.

References