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# Invasive Meningococcal Disease in Scotland, 1994 to 1999, with Emphasis on Group B Meningococcal Disease

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**A review was carried out on 774 invasive meningococcal isolates reported to the active meningococcal surveillance system in Scotland from 1994 to 1999. This showed that serogroups B (51.7%) and C (39.2%) caused the majority of disease. The six common PorB proteins (4, 1, 15, 2B, 12, and 21) and PorA proteins (serosubtypes) (P1.4, P1.15, P1.9, P1.14, P1.7, and P1.16) accounted for 50 and 51% of all group B isolates, respectively, during the study period.**

*Neisseria meningitidis* is the most common cause of bacterial meningitis in the United Kingdom and throughout the world (27). The organism has at least 13 serogroups, 20 serotypes, 10 serosubtypes, and 13 immunotypes (19, 25). Of the five different structural classes of outer membrane proteins (OMPs), class 2 or 3 OMP (PorB) is expressed by all meningococci and defines the serotype (14). Class 1 protein (PorA) is generally present in most meningococci and determines the serosubtype (2).

Worldwide, serogroups A, B, C, Y, and W135 are the most common causes of disease (19), and their distributions differ with age, time, and geographic location (23, 25). Although polysaccharide and conjugate meningococcal vaccines are available for the prevention of serogroup A, C, Y, and W135 disease, there is no effective vaccine against group B meningococcal disease. Since group B polysaccharide is poorly immunogenic and has cross-reactivity with human neonatal neural tissue (13), a vaccine against group B disease has been developed based on OMPs. These vaccines have been shown to be safe and immunogenic in infants (8, 17) and adults (18). Studies have suggested that OMP vaccines need to include multiple OMPs due to the diversity of the prevalence of OMPs in group B strains. Therefore, the identification of the important OMPs associated with group B isolates would aid in selecting appropriate OMPs for vaccine formulation. We herein examine the characteristics of invasive meningococcal isolates and identify the distribution of group B serotypes and serosubtypes reported to the population-based surveillance system in Scotland from 1994 to 1999.

The estimated population under surveillance was 5.1 million in the study period. A case of invasive meningococcal disease (IMD) was defined when *N. meningitidis* was isolated from a normally sterile site such as blood, cerebrospinal fluid, or joint fluid. Serogrouping was performed for all invasive isolates. Latex agglutination and coagglutination tests were used for the serogrouping of *N. meningitidis* (7, 12). Serotyping and serosubtyping were carried out by a whole-cell enzyme-linked immunosorbent assay (1, 14). The full set of meningococcal monoclonal antibodies available from the National Institute of Biological Standards and Control (http://www.nibsc.ac.uk) was used for the immunotyping of the disease strains. The set is the same as that used by the other major meningococcal reference laboratories, including the Meningococcal Reference Unit at Manchester Public Health Laboratory, Manchester, United

TABLE 1. Annual cases of meningococcal disease by age group and serogroup in Scotland, 1994 to 1999

| Age group | No. of cases by serogroup in indicated yr | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1994 | | | 1995 | | | 1996 | | | 1997 | | | 1998 | | | 1999 | | | 1994 to 1999 | | |
| | B | C | Others | B | C | Others | B | C | Others | B | C | Others | B | C | Others | B | C | Others | B | C | Others |
| <1 yr | 19 | 4 | 0 | 15 | 2 | 5 | 22 | 3 | 5 | 20 | 2 | 2 | 23 | 6 | 1 | 21 | 3 | 1 | 120 | 20 | 14 |
| 1 yr | 14 | 7 | 0 | 8 | 2 | 2 | 7 | 1 | 1 | 4 | 5 | 2 | 11 | 3 | 1 | 7 | 8 | 1 | 51 | 26 | 7 |
| 2 to 4 yr | 15 | 5 | 0 | 12 | 3 | 3 | 13 | 4 | 3 | 8 | 7 | 5 | 4 | 6 | 0 | 14 | 9 | 0 | 66 | 34 | 11 |
| 5 to 17 yr | 9 | 8 | 1 | 12 | 13 | 3 | 15 | 11 | 4 | 11 | 14 | 3 | 9 | 36 | 3 | 14 | 24 | 0 | 70 | 106 | 14 |
| 18 to 34 yr | 2 | 1 | 0 | 7 | 3 | 3 | 9 | 11 | 4 | 14 | 15 | 1 | 5 | 10 | 2 | 14 | 25 | 1 | 51 | 65 | 11 |
| 35 to 49 yr | 4 | 1 | 0 | 0 | 2 | 2 | 1 | 6 | 0 | 1 | 5 | 1 | 2 | 3 | 2 | 2 | 4 | 1 | 10 | 21 | 6 |
| 50 to 64 yr | 4 | 0 | 0 | 4 | 4 | 0 | 3 | 2 | 0 | 1 | 2 | 1 | 0 | 3 | 0 | 7 | 2 | 0 | 19 | 13 | 1 |
| ≥65 yr | 1 | 2 | 0 | 2 | 1 | 0 | 3 | 3 | 1 | 0 | 2 | 2 | 0 | 5 | 2 | 7 | 5 | 2 | 13 | 18 | 7 |
| All ages | 68 | 28 | 1 | 60 | 30 | 18 | 73 | 41 | 18 | 59 | 52 | 17 | 54 | 72 | 11 | 86 | 80 | 6 | 400 | 303 | 71 |

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Kingdom. Data analysis was performed with SPSS version 10 (SPSS INc., Chicago, Ill.).

There were 774 cases of IMD in all: 400 cases (51.7%) were caused by group B strains, 303 cases (39.2%) by group C strains, 11 cases (1.4%) by group Y strains, 7 cases (0.9%) by group W135 strains, 7 cases (0.9%) by other strains (including those of groups Y, Z, 29E, and X), and 46 cases (5.9%) by nongroupable strains. The proportion of cases of IMD due to group C strains increased significantly from 1994 to 1999, but the incidence of group B disease was relatively stable (Table 1). The majority of cases of IMD occurred in patients aged 5 to 17 years and <1 year. There was also an increase in the number of cases of IMD in patients aged 5 to 17 and 18 to 34 years during the study period.

Cases of IMD caused by group B strains were more prevalent in patients aged <1 year (30%), while those caused by group C strains were more prevalent in patients aged 5 to 17 years (35%) and 18 to 34 years (21%). The incidence of both group B IMD and group C IMD was highest in patients aged <1 and 1 year (33.3 and 14.5 cases per 10,000 persons for group B disease and 5.6 and 7.4 cases per 10,000 persons for group C disease, respectively).

The distribution of group B meningococcal serotypes and subtypes was substantially diverse and varied annually (Tables 2 and 3). Of the 212 isolates (53%) with serotype information, serotypes 4, 1, 15, 2B, 14, and 21 (in descending order of prevalence) accounted for 50% of the total isolates from 1994 to 1999. The predominant serotype was 4. The six most prev-

TABLE 2. Annual distribution of PorB group B meningococci, 1994 to 1999

| Yr | Serotype | No. of cases | % |
|---|---|---|---|
| 1994 | 4 | 15 | 22.1 |
| | 15 | 12 | 17.6 |
| | 2B | 11 | 16.2 |
| | 1 | 5 | 7.4 |
| | 21 | 4 | 5.9 |
| | 14 | 3 | 4.4 |
| | 2A | 1 | 1.5 |
| | 4,15 | 1 | 1.5 |
| | 4,21 | 1 | 1.5 |
| | TY[a] | 53 | 77.9 |
| | NT[b] | 15 | 22.1 |
| | All[c] | 68 | 100 |
| 1995 | 4 | 10 | 16.7 |
| | 15 | 9 | 15 |
| | 1 | 3 | 5 |
| | 2B | 3 | 5 |
| | 21 | 2 | 3.3 |
| | 14 | 1 | 1.7 |
| | TY | 28 | 46.7 |
| | NT | 32 | 53.3 |
| | All | 60 | 100 |
| 1996 | 4 | 19 | 26 |
| | 1 | 4 | 5.5 |
| | 14 | 3 | 4.1 |
| | 22 | 3 | 4.1 |
| | 2B | 3 | 4.1 |
| | 2A | 2 | 2.7 |
| | 15 | 2 | 2.7 |
| | TY | 36 | 49.3 |
| | NT | 37 | 50.7 |
| | All | 73 | 100 |
| 1997 | 4 | 17 | 28.8 |
| | 1 | 7 | 11.9 |
| | 15 | 3 | 5.1 |
| | 2B | 1 | 1.7 |
| | 14 | 1 | 1.7 |
| | 21 | 1 | 1.7 |
| | 4,21 | 1 | 1.7 |
| | TY | 31 | 52.5 |
| | NT | 28 | 47.5 |
| | All | 59 | 100 |
| 1998 | 4 | 14 | 25.9 |
| | 1 | 7 | 14 |
| | 15 | 4 | 7.4 |
| | 2A | 1 | 1.9 |
| | 2B | 1 | 1.9 |
| | 21 | 1 | 1.9 |
| | TY | 28 | 51.9 |
| | NT | 26 | 48.1 |
| | All | 54 | 100 |
| 1999 | 4 | 18 | 20.9 |
| | 1 | 10 | 11.6 |
| | 14 | 2 | 2.3 |
| | 15 | 2 | 2.3 |
| | 2A | 1 | 1.2 |
| | 2B | 1 | 1.2 |
| | 21 | 1 | 1.2 |
| | 4,21 | 1 | 1.2 |
| | | | 1.2 |
| | TY | 36 | 41.9 |
| | NT | 50 | 58.1 |
| | All | 86 | 100 |
| 1994 to 1999 | 4 | 93 | 23.3 |
| | 1 | 36 | 9 |
| | 15 | 32 | 8 |
| | 2B | 20 | 5 |
| | 14 | 10 | 2.5 |
| | 21 | 9 | 2.3 |
| | 2A | 5 | 1.3 |
| | 22 | 3 | 0.8 |
| | 4,21 | 3 | 0.8 |
| | 4,15 | 1 | 0.3 |
| | TY | 212 | 53 |
| | NT | 188 | 47 |
| | All | 400 | 100 |

[a] TY, total serotypeable isolates.
[b] NT, nontypeable isolates.
[c] All serotypeable and nonserotypeable isolates.

TABLE 3. Annual distribution of PorA group B meningococci, 1994 to 1999

| Yr | Serosubtype | No. of cases | % |
|---|---|---|---|
| 1994 | P1.7 | 11 | 16.2 |
| | P1.4 | 10 | 14.7 |
| | P1.10 | 8 | 11.8 |
| | P1.15 | 6 | 8.8 |
| | P1.14 | 4 | 5.9 |
| | P1.16 | 4 | 5.9 |
| | P1.2 | 3 | 4.4 |
| | P1.9 | 3 | 4.4 |
| | P1.1,7 | 2 | 2.9 |
| | P1.2,5 | 2 | 2.9 |
| | TY[a] | 53 | 77.9 |
| | NT[b] | 15 | 22.1 |
| | All[c] | 68 | 100 |
| 1995 | P1.4 | 10 | 16.6 |
| | P1.16 | 7 | 11.7 |
| | P1.9 | 6 | 10 |
| | P1.15 | 5 | 8.3 |
| | P1.7 | 5 | 8.3 |
| | P1.10 | 3 | 5 |
| | P1.2 | 3 | 5 |
| | P1.14 | 2 | 3.3 |
| | P1.3 | 1 | 1.7 |
| | P1.6 | 1 | 1.7 |
| | P1.13 | 1 | 1.7 |
| | TY | 44 | 73.3 |
| | NT | 16 | 26.7 |
| | All | 60 | 100 |
| 1996 | P1.4 | 19 | 26 |
| | P1.15 | 7 | 9.6 |
| | P1.14 | 4 | 5.5 |
| | P1.9 | 3 | 4.1 |
| | P1.10 | 3 | 4.1 |
| | P1.3 | 2 | 2.7 |
| | P1.16 | 2 | 2.7 |
| | P1.2,5 | 2 | 2.7 |
| | P1.12 | 1 | 1.4 |
| | P1.13 | 1 | 1.4 |
| | P1.5 | 1 | 1.4 |
| | P1.6 | 1 | 1.4 |
| | TY | 46 | 63 |
| | NT | 27 | 37 |
| | All | 73 | 100 |
| 1997 | P1.4 | 8 | 13.6 |
| | P1.15 | 6 | 10.2 |
| | P1.5 | 4 | 6.8 |
| | P1.14 | 4 | 6.8 |
| | P1.7 | 3 | 5.1 |
| | P1.9 | 2 | 3.4 |
| | P1.16 | 2 | 3.4 |
| | P1.2 | 1 | 1.7 |
| | P1.3 | 1 | 1.7 |
| | P1.10 | 1 | 1.7 |
| | P1.12 | 1 | 1.7 |
| | P1.19 | 1 | 1.7 |
| | TY | 34 | 57.6 |
| | NT | 25 | 42.4 |
| | All | 59 | 100 |
| 1998 | P1.4 | 13 | 24.1 |
| | P1.9 | 5 | 9.3 |
| | P1.15 | 5 | 9.3 |
| | P1.16 | 4 | 7.4 |
| | P1.5 | 3 | 5.6 |
| | P1.14 | 3 | 5.6 |
| | P1.1 | 1 | 1.9 |
| | P1.3 | 1 | 1.9 |
| | TY | 35 | 64.8 |
| | NT | 19 | 35.2 |
| | All | 54 | 100 |
| 1999 | P1.4 | 12 | 14 |
| | P1.9 | 9 | 10.5 |
| | P1.15 | 9 | 10.5 |
| | P1.14 | 8 | 9.3 |
| | P1.3 | 4 | 4.7 |
| | P1.5 | 3 | 3.5 |
| | P1.12 | 1 | 1.2 |
| | P1.13 | 1 | 1.2 |
| | P1.16 | 1 | 1.2 |
| | P1.7,16 | 1 | 1.2 |
| | TY | 49 | 57 |
| | NT | 37 | 43 |
| | All | 86 | 100 |
| 1994 to 1999 | P1.4 | 72 | 18 |
| | P1.15 | 38 | 9.5 |
| | P1.9 | 28 | 7 |
| | P1.14 | 25 | 6.3 |
| | P1.7 | 20 | 5 |
| | P1.16 | 20 | 5 |
| | P1.10 | 15 | 3.8 |
| | P1.5 | 11 | 2.8 |
| | P1.2 | 11 | 2.8 |
| | P1.3 | 9 | 2.3 |
| | P1.1,7 | 3 | 0.7 |
| | P1.13 | 3 | 0.7 |
| | P1.12 | 3 | 0.7 |
| | P1.6 | 2 | 0.5 |
| | P1.19 | 1 | 0.3 |
| | TY | 261 | 65.3 |
| | NT | 139 | 34.7 |
| | All | 400 | 100 |

[a] TY, total serotypeable isolates.
[b] NT, nonserotypeable isolates.
[c] All serotypeable and nonserotypeable isolates.

alent serosubtypes expressed by group B were P1.4, P1.15, P1.9, P1.14, P1.7, and P1.16, accounting for 51% of all isolates (Table 3). The predominant serosubtype was P1.4.

Although a shift in the age distribution of group B disease has been detected recently in older children and adults in the United States (20) and Canada (11), we did not observe this in the present study. The incidence of both group B and C disease in infants in Scotland was significantly higher than that in the

United States (20). In many countries, an increase in the prevalence of group B meningococcal disease was reported to parallel the high prevalence of serotype 4 (3), which was associated with the majority of disease in New Zealand from 1991 to 1999 (86% of cases) (16), in Canada from 1987 to 1995 (4, 15), in Spain from 1987 to 1992 (53% of cases) (5), and in other European countries from 1992 to 1995 or 1996 (10). In the United States (13, 14), serotypes 15, 14, 10, 1, and 2a accounted for 67% of all serotypeable isolates between 1992 and 1998 (24). A multivalent PorB vaccine composed of the six most common serotypes in Scotland accounted for 40 to 74% of all serosubtypes (86 to 100% of serotypeable isolates) in the study period.

Studies show that an increased incidence of group B disease has been associated with hypervirulent strains (9, 21). In developed countries, group B was associated with P1.4 in The Netherlands (22) and New Zealand (16) and with P1.7,16 in Norway (26). Surveillance of meningococcal disease in Europe showed that most group B isolates expressed P1.7,16, P1.4, P1.5, P1.2, and P1.2.5 in most European countries (10). We found that 18% of cases were associated with P1.4. The six most prevalent serosubtypes in Scotland were responsible for 42 to 58% of all group B isolates (72 to 86% of serosubtypeable isolates) from 1994 to 1999. In the United States, six serosubtypes (P1.7,16, P1.19,15, P1.7,1, P1.5,2, P1.22a,14, and P1.14) were found in 54% of serosubtypeable group B isolates from 1992 to 1998 (24).

Although the serosubtypes (P1.7,16, P1.5,2, P1.19,15, P1.7, P1.5, and P1.1213) in the current hexavalent PorA OMP vaccine were associated with a majority of group B disease in The Netherlands, these serosubtypes accounted for only 9% of total isolates in Scotland. Wide diversity of PorA proteins and geographic differences in their prevalence pose major challenges to designing an effective group B vaccine for global use. Studies have shown that antibodies directed against immunodominance variable region of OMPs produced a broader protective immune response (6). Therefore, data on the characteristics of variable region in OMPs are needed in Scotland. Continued enhanced surveillance of the distribution of serogroups, serotypes, serosubtypes, the emergence of new clones of virulent meningococci, and the extent of cross-reactivity among the different OMPs could assist control strategies for epidemic outbreaks, the implementation of immunization policies, and the design of a vaccine for the prevention of meningococcal disease.

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