New Zealand Epidemic of Meningococcal Disease Identified by a Strain with Phenotype B:4:P1.4

Diana R. Martin, Susan J. Walker, Michael G. Baker, and Diana R. Lennon

New Zealand experienced an epidemic of serogroup B meningococcal disease, which has taken the rate of disease from an average of 1.5/100,000 population in the preepidemic years of 1989 and 1990 to 14.0/100,000 in 1996. Sterile-site isolates of Neisseria meningitidis from cases of invasive disease have been phenotypically characterized by serogrouping, serotyping, and serosubtyping, revealing the involvement of a strain with phenotype B:4:P1.4. Macrophor analysis using pulsed-field gel electrophoresis on 667 meningococci isolated from cases during the epidemic has identified the clonal relationship of meningococci expressing the PorA P1.4 antigen. Multilocus enzyme electrophoresis has shown the epidemic strain B:4:P1.4 to belong to lineage III. The recorded characteristics of New Zealand’s epidemic are consistent with previous serogroup B epidemics in other parts of the world.

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clonal populations of meningococci. Most protracted epidemics in Europe and the Americas over the last 30 years have involved the introduction of new clones of serogroup B meningococci. Clones with phenotypes B:2b:P1.2 or B:2a:P1.2 (or both) were associated with peaks of infection in The Netherlands in 1966, in Iceland in 1976–1977, and in England and Wales in 1973–1975 [6]. A strain with phenotype B:15:P1.16 (ET-5 complex), first identified in Norway, subsequently caused outbreaks of disease in Europe and other parts of the world [6, 7]. In the 1980s, strain B:4:P1.15 (ET-5 complex) caused outbreaks in Cuba [7] and Brazil [8], and Chile experienced an outbreak of disease involving B:15:P1.3 [9]. The recent increase in serogroup B disease in the Pacific Northwest of the United States also involved strains of the ET-5 complex [10].

A newly identified clone with phenotype B:4:P1.4, ET-24 (lineage III), was encountered in The Netherlands in the early 1980s [11]. We describe the first 6 years, 1991–1996 (inclusive), of a continuing epidemic of meningococcal disease in New Zealand, which has involved the increased incidence of a strain with phenotype B:4:P1.4 and which belongs to lineage III.

Materials and Methods

Case definitions. A confirmed case was defined as a person with a clinically compatible illness and (1) isolation of Neisseria meningitidis from an otherwise sterile body site; or (2) a finding of gram-negative intracellular diplococci in blood or in cerebrospinal fluid or skin petechiae; or (3) a positive antigen test on cerebrospinal fluid. A probable case was defined as a person with clinical evidence of meningitis or septicaemia in association with either a petechial or purpuric rash or N. meningitidis isolated from the throat [12].

Analysis of case data. We used notified confirmed and probable cases as the basis of our analysis. The years 1989 and 1990, immediately prior to the epidemic, were included as the baseline against which changes were measured.

Isolates. Sterile-site isolates, mostly cerebrospinal fluid and blood, referred for confirmation of identity and for surveillance purposes, provided the meningococci. Referred isolates were retained in glycerol broth at −70°C.


Genetic typing. Macrorestriction analysis of 667 invasive isolates using SfiI and NheI was based on the method of Bygraves and Maiden [5]. Chromosomal DNA (Saccharomyces cerevisiae) was used in gels as a band migration size reference, and restricted DNA from a local isolate was used to control pattern reproducibility. ET [4] on 30 isolates representative of the epidemic was done by D. Caugant (National Institute of Public Health, Oslo).

Definitions. Strains are defined by specific phenotypic or genotypic characteristics. Clones are genetically related isolates that by typing methods are shown to be indistinguishable from each other or are so similar by pattern analysis that they are presumed to be derived from a common parent [13].

Results

Notifiable disease analysis. Total numbers of cases have increased from an average of 51 during 1989 and 1990 to 473 in 1996. New Zealand has a population of ~3.4 million people (1991 census). The average incidence of meningococcal disease during the immediate preepidemic years, 1989 and 1990, was 1.5/100,000 population. In 1996, a rate of 14.0/100,000 population was reached. Highest rates of disease, in 1996, occurred in children <5 years with rates of 142/100,000 in those <1 year of age and 72.9/100,000 in children 1–4 years old (table 1). A second small peak in incidence occurred in young adults, aged 15–19 years. However, rates for all age groups were significantly elevated compared with those for the 1989–1990 period. Ethnic differences in rates were most pronounced in those <1 year with rates, in 1996, of 549.6/100,000 in Pacific Islands infants, 150.1/100,000 in Maori infants, and 73.7/100,000 in European infants. Annually, a winter-spring seasonal peak in case numbers occurred. The case-fatality rate has remained at ~5%.

Most disease has been confirmed by the isolation of N. meningitidis from a normally sterile site, but since 1994, the number of cases diagnosed on clinical evidence alone increased from ~20% to 36.8% in 1996. Culture of samples from patients treated with antibiotics prior to hospital admission in 1995 yielded meningococcal isolates in 34.0% of instances compared with 64.7% for patients not receiving antibiotics (relative risk, 0.40; 95% confidence interval, 0.40–0.73).

Phenotypic characterization. The numbers of cases involving serogroup B is shown in figure 1 and represents a change in proportion of serogroup B disease from 41% in 1989 to 79% in 1996. Numbers of serogroup C isolates also increased between 1990 and 1993, but since 1993, any increase has been almost exclusively confined to serogroup B (figure 1). No serogroup A strains have been isolated since 1992. Few serogroup Y and W135 isolates have been found.

The increase in disease rates from 1991 was accompanied by an increase in serogroup B meningococci with phenotype B:4:P1.4, identified only three times prior to 1991. During 1991, 14 isolates with phenotype B:4:P1.4 were identified, 13 in the second half of the year. Subsequently, B:4:P1.4 has predominated. In 1996, it represented 72.9% of all serogroup B isolates identified. Each year, some isolates have not been serotypeable although they have expressed the PorA P1.4 antigen. In 1995 and 1996, these accounted for about 12% of serogroup B isolates. Annually a few isolates (~3%) with subtype P1.4 have been associated with serotype 14. The overall contribution to disease by meningococci with the P1.4 antigen is illustrated in figure 1. By 1996, isolates with this P1.4 antigen represented 89% of all serogroup B meningococci associated with cases.
Table 1. Age-specific rates (cases per 100,000 population) of meningococcal disease, 1989–1996, in New Zealand.

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<td>35.9</td>
<td>53.0</td>
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<td>4.8</td>
<td>10.1</td>
<td>18.8</td>
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<td>52.3</td>
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<td>5–9</td>
<td>1.8</td>
<td>2.0</td>
<td>7.2</td>
<td>6.0</td>
<td>8.4</td>
<td>25.5</td>
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<tr>
<td>10–14</td>
<td>2.0</td>
<td>1.6</td>
<td>3.1</td>
<td>5.9</td>
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<td>15.3</td>
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<td>15–19</td>
<td>2.1</td>
<td>4.2</td>
<td>11.3</td>
<td>10.2</td>
<td>8.5</td>
<td>16.9</td>
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<tr>
<td>20–29</td>
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<td>4.1</td>
<td>5.0</td>
<td>5.0</td>
<td>5.4</td>
<td>7.4</td>
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<tr>
<td>30–39</td>
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<td>1.2</td>
<td>1.0</td>
<td>1.6</td>
<td>1.9</td>
<td>2.1</td>
<td>3.3</td>
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<tr>
<td>≥40</td>
<td>0.3</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
<td>1.1</td>
<td>1.9</td>
<td>2.4</td>
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<tr>
<td>Total population</td>
<td>1.5</td>
<td>2.3</td>
<td>4.6</td>
<td>6.0</td>
<td>6.2</td>
<td>11.7</td>
<td>14.0</td>
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* Rates averaged for 1989–1990 as baseline for comparison.

**Genotypic characterization.** Three restriction fragment length polymorphism analysis (RFLP) patterns, designated types 1, 3, and 4, varying only in size and therefore position of one or two of the fragments, represented 63%, 14%, and 12%, respectively, of all serogroup B meningococci with the P1.4 subtype. Isolates with alternative subtypes or of other serogroups had quite distinct profiles. Meningococci of phenotype B:4:P1.4 from Australia and The Netherlands had restriction profiles that were indistinguishable from those of our epidemic strain, B:4:P1.4. The clonal relationship among isolates with phenotypes B:4:P1.4, B:14:P1.4, and B:NT:P1.4 was further demonstrated by multilocus enzyme electrophoresis. ET revealed that they belonged to lineage III.

Cases of disease caused by the outbreak strain, B:4:P1.4, have occurred sporadically throughout New Zealand, with no obvious geographic focus. Secondary cases among all age groups have been recorded. Additionally, a small number of clusters involving teenage and young adult groups, particularly associated with educational facilities, has been documented. During the epidemic, a phenotypically distinct, sulfonamide-resistant, serogroup B strain with phenotype B:15:P1.7,16 and of the ET-5 complex, also caused a cluster of cases among university students in 1992 [12]. Among the serogroup C meningococci, serotype 2b has predominated. Isolates with phenotype C:2b:P1.(5),2 have been involved in geographically localized clusters of infection, mostly involving preschool children.

**Discussion**

Apart from the outbreak of serogroup A disease, New Zealand had experienced relatively low rates of meningococcal disease prior to 1991 [12]. The background incidence during 1989–1990 was similar to that reported in other “westernized” countries and showed the same characteristics, with a higher disease incidence in preschool children and a dominance of serogroup B disease. Since 1990, rates have been markedly higher than those of other industrialized countries, including our closest neighbor, Australia, where incidence rates of 1.6–2.2/100,000 were recorded in 1991–1994 [14].

![Figure 1. Serogroup distribution of meningococci from cases, 1989–1996, showing proportion of serogroup B isolates that were subtype P1.4.](image-url)
Our data show that a growing proportion of cases is being treated with antibiotics before hospital admission, possibly influencing the number of cases diagnosed on clinical grounds alone. For cases that are not culture-proven, it is impossible to determine how many have been caused by the epidemic strain. New Zealand’s elevated rate of disease has been associated with the sudden and continuing increase in a clonal population of meningococci, the majority of which have the phenotype B:4:P1.4. The recorded characteristics of New Zealand’s epidemic are consistent with serogroup B epidemics experienced in other parts of the world [8, 9, 15], as shown by the steady rise in the epidemic curve, the sporadic distribution of most cases, correlation of case numbers with socioeconomic status, and peak incidence in winter and early spring.

Some clustering of cases involving meningococci of B:4:P1.4 has occurred among students indirectly linked through educational facilities [12]. The sulfonamide-resistant strain, B:15:P1.7,16, which caused a cluster of infections in 1992, belonged to a clone of the same phenotype, which spread globally, having originally caused problems in Norway [6].

Serogroup B epidemics have been linked with the introduction of new strains belonging to clones characterized by their homogeneity with respect to their surface characteristics. Clones that have been prevalent in a population for a long period often undergo modifications in their surface characteristics, due to mutations or recombinations of genes encoding surface markers, and are reflected by increased heterogeneity with respect to phenotype. In the first 6 years of the epidemic, our strain with phenotype B:4:P1.4 has shown considerable stability. The PorA P1.4 antigen in particular has provided a constant marker for the epidemic clone and, although there has been a small increase in numbers of nonserotypeable serogroup B subtype P1.4 meningococci, the majority also express the PorB serotype 4 antigen.

Macrorestriction analyses revealed that the RFLP profiles of isolates with the P1.4 antigen (B:4:P1.4, B:14:P1.4, and B:NT:P1.4) clustered around a common pattern, indicating likely derivation from a common parentage. In addition, genetic typing showed that the New Zealand strain belongs to the clonal lineage III and is indistinguishable from isolates representative of the strain that caused increased disease in The Netherlands. This lineage was first documented in The Netherlands in the 1980s [11].

Serologic and genetic typing have been of pivotal importance in defining the epidemic that began in New Zealand in 1991. No one factor or geographic focus has been identified to explain the overall increase in meningococcal disease. The factors that contributed to the appearance and sudden increase of the strain B:4:P1.4 may never be known. Whether the epidemic in New Zealand has as yet peaked remains to be recorded; if it follows the trend demonstrated in other countries, we are likely to experience a sustained period of high incidence. There is an urgent need for serogroup B vaccines to be developed and made available for either the prevention or interruption of similar protracted epidemics of serogroup B disease.

Acknowledgments

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References