Complications and Sequelae of Meningococcal Disease in Quebec, Canada, 1990–1994

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To study complications and sequelae of serogroup B and C meningococcal disease, a retrospective survey examined the outcome of all culture-proven cases reported in the province of Quebec, Canada, from January 1990 through December 1994 (serogroup B, 167 cases; serogroup C, 304 cases). Data were collected from medical files, postal questionnaires, and telephone interviews. Age groups having the most cases were the 10–19-year age group for serogroup C and the <1-year age group for serogroup B. Fatality rates were 7% for serogroup B and 14% for serogroup C disease. Only 3% of survivors of serogroup B disease had physical sequelae, compared with 15% of survivors of serogroup C disease (skin scars, 12%; amputations, 5%; hearing loss, 2%; renal problems, 1%; and other sequelae, 4%). These results confirm the gravity of disease caused by serogroup C, serotype 2a Neisseria meningitidis and justify liberal use of vaccination for outbreak control.

An increase in incidence of meningococcal disease began in the province of Quebec, Canada, in 1990 and was associated with the emergence of a virulent strain of serogroup C, serotype 2a Neisseria meningitidis [1]. Similar strains were responsible for outbreaks in other areas in North America [2, 3] and in Europe [4–6].

In 1992, local and regional immunization campaigns were carried out in several regions of the province of Quebec, but outbreaks continued to occur. A mass vaccination program was undertaken in early 1993, reaching 84% of the target population (aged 6 months to 20 years) at a cost of ~$25.5 million CAD [7]. In the first year following the campaign, the incidence of serogroup C meningococcal disease dropped markedly among those vaccinated and also in the unvaccinated fraction of the target population, while it remained unchanged among persons aged >20 years. This observation suggests a slowing down in the transmission of the bacteria, as a result of the immunization campaign. At least 37 cases were prevented during the first year as a result of the direct efficacy of the vaccine, and an estimated 26 additional cases were prevented as a consequence of herd immunity [7]. During the 1990–1994 period, serogroup B meningococcal disease remained endemic.

A thorough analysis of the health impacts of meningococcal disease is required to evaluate actual and potential benefits of immunization and to guide public health policy. This study assesses the rate of complications, deaths, and physical and psychological sequelae in cases of serogroup B and C meningococcal disease reported in the province of Quebec from 1990 through 1994. The quality of life of survivors was also evaluated, by means of both objective and subjective scoring systems.

Study Population and Methods

Meningococcal disease is a notifiable disease in Quebec. Cases diagnosed by clinicians and laboratories are reported to the regional health board, which gathers administrative and epidemiological information, including date of occurrence, laboratory confirmation of the diagnosis, and serogroup of the bacteria. Since 1990, reports have been entered into a provincial registry; since 1993, the information routinely collected has included symptoms, clinical diagnosis, and complications. In a majority of cases diagnosed by bacterial culture, a specimen is sent to the provincial reference laboratory for confirmation and classification of the bacterial strain. When a strain isolated from a patient is received at the reference laboratory, the case is reported to the regional health board concerned.

The provincial central registry was reviewed to identify all confirmed cases of serogroup B and C meningococcal disease occurring between 1 January 1990 and 31 December 1994. Information on identified cases was gathered from the records of the 17 regional health boards and the provincial reference laboratory. Survivors (or their parents or guardians) were contacted by mail to obtain written consent to consult their hospital medical record and to complete a self-administered questionnaire.

Follow-up of nonresponders was done by telephone after 2 weeks and by a further mailing after another week. When necessary, respondents were contacted by telephone to obtain...
additional information on complications and sequelae. After exclusion of refusals, permission was requested to access medical files in the 91 hospitals where patients were treated (consenting survivors, survivors who were not successfully located, and deceased persons).

A case was defined by the culture-proven presence of meningococci in normally sterile sites such as blood, CSF, or synovial fluid. There were no cases in which the diagnosis was made solely on the basis of antigen detection. Cases were classified in different clinical categories on the basis of combined clinical and laboratory data. Meningitis was defined by a CSF culture positive for \textit{N. meningitidis}, by the presence of microscopic or biochemical signs of inflammation in the CSF, or by specific clinical signs of cerebrospinal fluid irritation (e.g., stiff neck, Kernig’s or Brudzinski’s sign, focal neurological deficits, coma, or paralysis).

Septicemia was defined by distinct clinical signs (e.g., shock, extended purpura or petechiae, or disseminated intravascular coagulation). Major complications were defined as disseminated intravascular coagulation, coma, multiple organ failure, cardiorespiratory arrest, respiratory distress syndrome, extensive necrosis or gangrene, pericarditis, and death. Minor complications were defined as anemia, arthritis, temporary neural perturbations, or other minor problems.

In addition to determining the frequency of sequelae, we wanted an index of their relative severity. The Annotated Scale of Bodily Injuries Regulation (a scale used by the Quebec Occupational Health and Safety Commission [OHSC] for work-related injuries) was used to calculate an overall score of permanent mental/physical impairment \cite{8}. The physical impairment score is widely used in the province and is comprehensive, taking account of anatomic and physiologic deficits, disfigurement, and suffering or loss of enjoyment of life resulting from the deficit or disfigurement. The score is expressed as a percentage of physical impairment, which increases with increasing severity of permanent injury.

An impairment score of 100\% normally provides for compensation equivalent to full salary. Because scores for different types of injuries are additive, it is possible for certain individuals with multiple sequelae to have a percentage score greater than 100\%. For certain types of sequelae there is a threshold that must be surpassed to have a physical impairment score greater than zero. For example, hearing losses are evaluated by averaging the thresholds at frequencies of 500 Hz, 1,000 Hz, and 2,000 Hz. Compensation is awarded when this average threshold is >30 dB.

A self-administered postal questionnaire was developed for this study. Revisions were made in consultation with experts, and the questionnaire was administered to individuals of various ages to confirm and improve its comprehension and readability. Parents completed the questionnaire for survivors younger than 14 years of age. Survivors were asked about their use of health care/services, temporary and permanent physical problems, and psychosocial impairment stemming from the disease. Those considering their recovery to be incomplete were asked to note their degree of agreement (on a five-point scale) with 12 statements concerning different aspects of quality of life.

The categories were energy, anxiety, social and leisure activities, quality of family life, physical appearance, ability to learn and solve problems, general satisfaction with life, and, when applicable, capacity to do housework, drive an automobile, work, and study. An overall ad hoc impairment score was then calculated as a percentage of the maximum possible score. This gave an index of the magnitude of reduction of quality of life as noted by the individual in the questionnaire (0\% = no impairment; 100\% = maximum impairment).

Univariate comparisons were conducted with use of the \( \chi^2 \) test for categorical variables and Student’s \( t \)-test for continuous variables. Correlation between the two scoring systems was measured by Pearson’s \( R \) coefficient. This project was approved by the Provincial Commission for Access to Information and the Ethics Committee of the Sherbrooke University Hospital.

### Results

A total of 471 cases were identified, 167 of serogroup B infection and 304 of serogroup C infection. Among serogroup C strains that were characterized at the reference laboratory, 93\% (207 of 233) were of serotype 2a and 89\% (201 of 226) were of electrophoretic type 15. Forty-nine percent of infections with each serogroup were in males. The average age of patients was 13.5 years (median, 2 years) for serogroup B and 17.6 years (median, 14 years) for serogroup C (\( P < .05 \)). The distribution across age groups was different between serogroups B and C. Age groups having the most cases were the 10–19-year age group for serogroup C and the 0–1-year age group for serogroup B (table 1).

#### Table 1. Age distribution of cases of meningococcal disease in Quebec, Canada, 1990–1994.

<table>
<thead>
<tr>
<th>Age group (y)</th>
<th>Serogroup B</th>
<th>Serogroup C</th>
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<tbody>
<tr>
<td>&lt;1</td>
<td>72 (43.1)</td>
<td>26 (8.6)</td>
</tr>
<tr>
<td>1–4</td>
<td>32 (19.1)</td>
<td>57 (18.8)</td>
</tr>
<tr>
<td>5–9</td>
<td>7 (4.2)</td>
<td>32 (10.5)</td>
</tr>
<tr>
<td>10–19</td>
<td>16 (9.6)</td>
<td>101 (33.2)</td>
</tr>
<tr>
<td>20–59</td>
<td>30 (18.0)</td>
<td>74 (24.3)</td>
</tr>
<tr>
<td>≥60</td>
<td>10 (6.0)</td>
<td>14 (4.6)</td>
</tr>
<tr>
<td>Total</td>
<td>167 (100)</td>
<td>304 (100)</td>
</tr>
<tr>
<td>Average age (y)</td>
<td>13.5*</td>
<td>17.6*</td>
</tr>
<tr>
<td>Median age (y)</td>
<td>2</td>
<td>14</td>
</tr>
</tbody>
</table>

\* \( P < .05 \) (Student’s \( t \)-test).
In the study population, 54 persons died of meningococcal infection. Of the 417 survivors, 5 had died of other causes since the onset of the disease and 139 were not successfully retracted because of address changes. Of the individuals contacted, 96% participated in the study and 4% refused to participate or did not respond. On the average, participants completed the questionnaire 38 months after occurrence of the disease (range, 9 to 72 months). The hospital record was reviewed for 91% of the cases (430 of 471). Four rapidly fatal cases and three very mild cases did not involve hospitalization. Permission to review records was not obtained for 33 cases, and the record of another patient was not found by the hospital concerned.

Classification of cases in different clinical categories was possible for 452 cases (96%) (table 2). Fifteen cases met neither the criteria for septicemia nor those for meningitis; two of them were only septic arthritis. The 13 remaining cases were of bacteremia with nonspecific symptoms of infection. Septicemia with or without meningitis represented 79% of serogroup B and 88% of serogroup C cases ($P < .05$). There was no significant variation in the proportion of septicemic patients according to age for both serogroups B and C.

The fatality rate was 7% (12 of 167 cases) for serogroup B and 14% (42 of 304 cases) for serogroup C disease. Including deaths, 12% of serogroup B cases and 30% of serogroup C cases involved major complications. When minor complications are included, 37% of serogroup B cases vs. 59% of serogroup C cases had at least one complication. These differences are statistically significant ($P < .05$).

The effect of age on mortality and complications can also be analyzed by stratifying the study population into age groups (figure 1). Although numbers in certain age groups are small, some patterns are evident. For serogroup C cases, the maximum mortality and morbidity are seen in the 20–59-year age group, while a U-shaped distribution is observed for serogroup B cases, with maximum mortality and morbidity at the upper and lower extremes of the age scale.

There was enough information to objectively assess sequelae in 420 survivors. Three percent of serogroup B cases (5 of 158) and 15% of serogroup C cases (40 of 262) were affected ($P < .05$). The types of sequelae detected are indicated in table 3. Most are complications of septicemia. For survivors of serogroup C disease, skin scars and amputations were the most frequent problems observed.

Table 2. Diagnostic classification of cases of meningococcal disease occurring in Quebec, Canada, 1990–1994.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Serogroup B</th>
<th>Serogroup C</th>
</tr>
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<tbody>
<tr>
<td>Septicemia only</td>
<td>62 (38.8)</td>
<td>109 (37.4)</td>
</tr>
<tr>
<td>Meningitis only</td>
<td>28 (17.5)</td>
<td>24 (8.2)</td>
</tr>
<tr>
<td>Septicemia and meningitis</td>
<td>65 (40.6)</td>
<td>149 (51.0)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (3.1)</td>
<td>10 (3.4)</td>
</tr>
<tr>
<td>Total</td>
<td>160 (100)</td>
<td>292 (100)</td>
</tr>
</tbody>
</table>

NOTE. For serogroup B vs. serogroup C, $P < .05$ ($\chi^2$ test; DF = 3).

To assess hearing loss, overall decibel thresholds (the average of thresholds obtained at 500, 1,000 and 2,000 Hz) were calculated from results of audiometric tests. One serogroup B survivor had significant bilateral impairment (70 dB right; 30 dB left), necessitating use of a hearing aid. One serogroup C survivor had significant unilateral impairment (70 dB right). The remaining six cases for both serogroups involved only minor (<45-dB) unilateral hearing impairment. All cases with hearing loss met our criteria for the diagnosis of meningitis.

Three survivors of serogroup C disease had permanent knee damage following septic arthritis causing mild reduction in mobility. Three survivors of serogroup B disease (of whom two also had hearing loss) and three survivors of serogroup C disease (none of whom had hearing loss) had speech problems.

Among those with sequelae, the average physical impairment score was 39% for serogroup B cases (range, 2%–128%) and 55% for serogroup C cases (range, 1%–413%). The worst case involved amputation of two legs (below the knee) and one forearm, as well as scarring over 70% of the body. For serogroup C cases, amputations contributed to 53% of the total of physical impairment scores, compared with 30% for skin scars and only 1% for hearing loss.

Among the 231 persons who completed the questionnaire, 23% (21% of serogroup B–infected patients and 24% of serogroup C–infected ones) noted a reduction in their quality of life due to meningococcal disease. Reduced energy, increased anxiety, reduction of leisure activities, and reduced ability to work were the most common complaints. For individuals reporting psychosocial sequelae, the average reduction in the quality of life score was 20% (of maximum) for serogroup B and 31% for serogroup C cases.

There is a weak correlation between the objective OHSC impairment score and the subjective score of quality of life ($R = 0.25$). This is not surprising, as the two scores measure very different dimensions of health status [9]. Sixty-three per-
cent of survivors of serogroup C disease who reported a reduction of their quality of life in the questionnaire also had physical sequelae. This figure was only 16% for survivors of serogroup B disease. Among those who had no physical sequelae, 19% (38 of 197) mentioned adverse psychosocial consequences (20% in serogroup B cases and 19% in serogroup C cases).

Discussion

This study has provided valuable information regarding the frequency of complications and sequelae of meningococcal disease. It is the first study to examine the impact of the disease on survivors by an objective physical injury scale as well as a subjective psychosocial function score. The results allow comparison of serogroup B with serogroup C meningococcal disease.

The study included culture-proven cases of meningococcal disease reported in the province of Quebec during the years 1990–1994. During this period of recrudescence, physicians were especially attentive to notification. In addition, any isolates recovered by laboratories were reported; therefore, the level of case-finding is probably quite high. Studies on the completeness of surveillance of meningococcal disease in Belgium [10] and in the State of New York [11] revealed that the sensitivity of this type of surveillance system is ~90%.

The main weakness of the present study is its retrospective and cross-sectional design. Medical files were consulted in 91 different hospitals, in which there was a large variation in diagnostic tests used and the quality and completeness of medical records. It was therefore difficult to apply rigid, uniform criteria to define complications and sequelae, and assessment was often based on results of nonstandardized tests and notes in medical files.

The results of this study confirm the severity of serogroup C serotype 2a meningococcal disease. In developed countries, fatality rates associated with meningococcal disease are generally from 7% to 10% [12]. We observed a fatality rate of 7% for serogroup B and 14% for serogroup C disease. This agrees with the findings of other studies of serogroup C disease [2, 4, 6, 13].

The pathogenic potential of a meningococcal strain is related to certain surface organelles and secretions [14]. The capsular
polysaccharides, pili, outer membrane vesicles containing lipopolysaccharides (the “endotoxin”), and outer membrane proteins including IgA-protease certainly play a role in the invasion of the human host, multiplication of the bacteria, and induction of tissue damage. The reason for the high virulence of this particular strain of \textit{N. meningitidis} is unknown, but the strain is associated with a high frequency of septicemia (87% of cases in the present series).

The risk of complications of meningococcal disease is usually high in the very young and the very old [15]. In the present study, this was indeed the pattern observed in serogroup B cases. However, serogroup C disease produced high rates of complications in adolescents and young adults.

The most striking finding of this study is the high frequency and exceptional gravity of sequelae in survivors of serogroup C serotype 2a infection. Fifteen percent of survivors had confirmed physical sequelae (mostly postnecrotic scarring and amputations), and the average physical impairment score was 55%. In addition, 19% of survivors who had no physical sequelae indicated a reduction of their quality of life.

There have been few studies of sequelae of meningococcal infection, and comparisons are difficult because of differences in populations studied, selection of cases, length of follow-up after disease, outcomes measured, and diagnostic tests used. In studies of serogroup B disease, rates of clinically significant sequelae were between 6% and 10%, and problems were principally neurological in nature; sensorineural hearing loss was the most common category of sequelae [16–18]. When a battery of very sensitive diagnostic tests are used, the percentage of survivors presenting an anomaly can be as high as 29% [19, 20].

The relatively low percentage of survivors of meningitis with hearing loss (about 3%) is perhaps surprising when compared with those reported in the literature [21]. In a recent prospective study of 124 survivors of bacterial meningitis (74% meningococcal) only 2.4% (three patients) had permanent hearing loss despite extensive audiological testing [22]. Changes in epidemiology, such as the reduction in number of cases of \textit{Haemophilus influenzae} meningitis, are one of many factors that could account for these results.

In a situation of localized outbreak or widespread epidemic, decisions regarding the use of meningococcal polysaccharide vaccines should be based on more than simply incidence of disease. Outbreaks generally involve a change in age distribution and an increase in the case-fatality ratio [23, 24]. In Quebec, the mass immunization of the population younger than 20 years of age was justified less by the number of cases than by their gravity. When the recrudescence occurred, the only information available was the high fatality rate and anecdotal reports of severe complications and sequelae.

Our study shows that for a specific strain of \textit{N. meningitidis}, there is a positive correlation between the rates of complications, fatality, and sequelae. For the surveillance of meningococcal disease, data should be routinely collected on the outcome of reported cases, including deaths and type of sequelae at hospital discharge. The exceptional virulence of the serogroup C serotype 2a \textit{N. meningitidis} supports a liberal use of vaccination for control of disease outbreaks and epidemics. We are currently conducting a cost-effectiveness study to estimate the incremental cost per quality-adjusted life year gained by the mass vaccination campaign carried out in Quebec in 1993.

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References

4. Albertoni F, Chierchini P, Ippolito G, Perucci C, Occhionero M, Manstran F. Study of 124 survivors of bacterial meningitis (74% meningococcal) only 2.4% (three patients) had permanent hearing loss. Changes in epidemiology, such as the reduction in number of cases of \textit{Haemophilus influenzae} meningitis. Scand J Infect Dis 1993; 25:331–9.


