Effectiveness of a Mass Immunization Campaign Against Serogroup C Meningococcal Disease in Quebec

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A gradual increase in the number of cases of meningococcal disease (MCD) reported to the public health authorities was observed in Quebec in the late 1980s.1,2 This was associated with an increased proportion of cases caused by a virulent clone of serogroup C serotype 2a Neisseria meningitidis, an increased proportion of cases in teenagers and young adults, a high case fatality rate, and a high sequelae rate.3,4 In an attempt to control this outbreak, local immunization programs directed at school-aged children and adolescents were initiated in late 1991 and extended in 1992. By the autumn of that year, approximately 300000 doses of polysaccharide vaccine had been administered, but the incidence of serogroup C MCD continued to stay high in the groups that were not vaccinated, and clusters appeared in previously unaffected areas. This generated enormous anxiety in the population, fueled by the media. As a result, local authorities decided to conduct a mass immunization program and to offer the vaccine free to all 1.9 million people living in the province between the ages of 6 months and 20 years. The campaign started in December 1992 and was completed by the end of March 1993.5

The incidence of serogroup C disease decreased after the mass immunization campaign, from 1.4 per 100 000 in 1990-1992 to 0.3 per 100 000 in 1993-1998, and the overall incidence of other serogroups remained stable at 0.7 per 100 000, with a small increase in the proportion of cases caused by serogroup Y (P=.009). Protection from serogroup C MCD was indicated in the first 2 years after vaccine administration (VE, 65%; 95% confidence interval [CI], 20%-84%), but not in the next 3 years (VE, 0%; 95% CI, −5% to 65%). Vaccine effectiveness was strongly related to age at vaccination: 83% (95% CI, 39%-96%) for ages 15 through 20 years, 75% (95% CI, −17% to 93%) for ages 10 through 14 years, and 41% (95% CI, −106% to 79%) for ages 2 through 9 years. There was no evidence of protection in children younger than 2 years; all 8 MCD cases in this age group occurred in vaccinees.

Conclusions Serogroup C polysaccharide vaccine is effective for controlling outbreaks in teenaged individuals but should not be used in children younger than 2 years. The mass campaign did not induce significant serogroup switching.

Context An outbreak of meningococcal disease in Quebec province prompted a mass immunization program. The impact of this campaign on the epidemiology of meningococcal disease has not been studied.

Objectives To study the impact of a mass immunization campaign using polysaccharide vaccine on the epidemiology of meningococcal disease (MCD) and to assess serogroup C vaccine effectiveness (VE).

Design, Setting, and Subjects Analysis of MCD cases reported in Quebec from 1990 to 1998, before and after the mass immunization campaign was conducted during the winter of 1992-1993, when 84% of residents aged 6 months to 20 years (the target population, approximately 1.9 million individuals) were vaccinated.


Results The incidence of serogroup C disease decreased after the mass immunization campaign, from 1.4 per 100 000 in 1990-1992 to 0.3 per 100 000 in 1993-1998, and the overall incidence of other serogroups remained stable at 0.7 per 100 000, with a small increase in the proportion of cases caused by serogroup Y (P=.009). Protection from serogroup C MCD was indicated in the first 2 years after vaccine administration (VE, 65%; 95% confidence interval [CI], 20%-84%), but not in the next 3 years (VE, 0%; 95% CI, −5% to 65%). Vaccine effectiveness was strongly related to age at vaccination: 83% (95% CI, 39%-96%) for ages 15 through 20 years, 75% (95% CI, −17% to 93%) for ages 10 through 14 years, and 41% (95% CI, −106% to 79%) for ages 2 through 9 years. There was no evidence of protection in children younger than 2 years; all 8 MCD cases in this age group occurred in vaccinees.

Conclusions Serogroup C polysaccharide vaccine is effective for controlling outbreaks in teenaged individuals but should not be used in children younger than 2 years. The mass campaign did not induce significant serogroup switching.
ride vaccine according to age at vaccination. This is especially important because immunization is increasingly used for controlling outbreaks or epidemics in different parts of the world and because of the controversy surrounding the induction of anergy to meningococcal C polysaccharide.

METHODS
Meningococcal disease is a notifiable disease in Canada and a standard case definition is provided. A confirmed case must have clinically compatible symptoms with the identification of N meningitidis or its antigen from any normally sterile site or from a skin lesion. When a case is confirmed by culture, hospital laboratories are asked to forward the strain to the provincial public health reference laboratory. A clinical case must have symptoms clinically compatible with purpura fulminans even if there is a failure to identify any organism in the blood or cerebrospinal fluid by either isolation or antigen detection. Since 1990, MCD cases reported by physicians and laboratories in Quebec have been entered in a central provincial registry database. When a case of invasive meningococcal infection is reported, an investigation is conducted by the regional public health authority to collect additional information, including the date of occurrence of the disease, the confirmation of the diagnosis, the serogroup of the bacteria, and the vaccination status of the patient. Sources of information include the hospital, the laboratory, and the patient or his/her family. For our study, the case list from the provincial registry of notifiable diseases was matched with the case list from the reference laboratory and additional telephone interviews and verification of the patient’s immunization card were performed for all culture-proven serogroup C cases notified since 1993.

The target population for mass immunization was Quebec residents born between December 4, 1971, and September 30, 1992. The size of the population was estimated from projections based on the 1991 census. In 1993, a central vaccination registry was created by linking the provincial health insurance file with the individual vaccination forms returned by the local health units. This registry contains 174957 records and aggregated data on the distribution of vaccinees by age were obtained. Written permission to administer the vaccine was requested during the mass campaign but not to transmit information. The records in the registry were supplemented with records of immunizations not involving an individual in the health insurance file (n = 2362), of the vaccines administered in 1991-1992 and not registered (n = 435471), and of vaccinations administered by the private sector (n = 12003). A proportional distribution was used for records with missing information on age (n = 14509).

The incidence of MCD in the population was analyzed for the period 1990 to 1998. To assess vaccine effectiveness, incidence of culture-proven serogroup C MCD during the period April 1, 1993, to March 31, 1998, was compared between those vaccinated and those not vaccinated in the target population. In the control group, the estimated age at vaccination was calculated as the difference between June 30 of the year of birth and February 1, 1993, which was the median point of the mass campaign. Vaccine effectiveness (VE) was defined as 1 minus the relative risk of disease (or the odds ratio). Confidence intervals (CIs) of unadjusted or age-adjusted VE were computed using exact P values. Variation of VE was analyzed by a logistic regression model using a maximum-likelihood estimation of parameters and included vaccination status, age at vaccination, and an interaction term as explanatory variables. Confidence boundaries of the VE curve were computed by a Taylor series approximation method (details available on request). The total number of cases prevented in vaccinees was calculated as the sum of the differences between observed and expected numbers in each single year age category.

RESULTS
A total of 899 MCD cases were registered from January 1, 1990, to December 31, 1998: 355 were serogroup C; 332, serogroup B; 36 serogroup Y; 17, other serogroups; and 10, not definable by serogroup. Seventy-one confirmed MCD cases did not receive serogroup identification, and information is not available for the remaining 78 cases. The bimonthly distribution of cases is presented in Figure 1. The incidence of serogroup C disease decreased markedly in April 1993 after the mass immunization campaign and remained low thereafter. After adjustment of rates for cases without serogroup identification, the average annual incidence of serogroup C MCD was 1.4 per 100000 during the 1990-1992 period, and 0.3 per 100000 during the 1993-1998 period. There was no increase in the incidence of cases due to all other serogroups. The average annual incidence of all other serogroups was exactly the same (0.7 per 100000) during the 1990-1992 period and the 1993-1998 period. A small increase in the proportion of cases due to serogroup Y was observed, with an average of 1.0 case per year during the first period, and 5.5 cases per year during the second period (P = .009).

The average vaccination rate was 84%, and coverage was slightly lower in young children and markedly lower in those aged 17 years or older (Table). Between April 1, 1993, and March 31, 1998, 53 serogroup C cases were observed in the cohort targeted for immunization, including 14 cases among unvaccinated and 39 among vaccinated individuals. In the latter group, 3 persons received the vaccine at the beginning of 1992 and the others during the mass campaign. Among cases of vaccine failure, the shortest interval between vaccine administration and disease onset was 46 days. There were also 59 cases of serogroup B; 8, serogroup Y; and 1 not definable by serogroup. For 16 cases, there was no information available.

Inspection of cumulative incidence rate shows that risk of serogroup C disease was greatest in the first 2 years of the study, and during that period, the risk was higher in unvaccinated than in vaccinated persons, but in years 3
through 5, the risk decreased in both groups (FIGURE 2). Among individuals not vaccinated, serogroup C incidence rate was 1.78 per 100,000 person-years (95% CI, 0.89–3.19) during the first 2 years of follow-up and was 0.32 (95% CI, 0.07–0.95) during years 3 through 5. Among those vaccinated, the incidence rate was 0.62 per 100,000 person-years (95% CI, 0.38–0.95) during the first 2 years and 0.39 (95% CI, 0.24–0.61) thereafter. The unadjusted VE over 5 years was 47% (95% CI, −6% to 72%), which was 65% (95% CI, 20%–84%) during the first 2 years, and was 0% (95% CI, −5% to 65%) during years 3 through 5.

Results of the logistic regression model indicated a significant interaction (P<.05) between vaccination status and age at vaccination in predicting the risk of disease and VE (Log [1 – VE] = 10.0137 – 0.00103 age in years – 0.2286 vaccination status + 0.1033 age in years × vaccination status). The predicted VE curve and its 95% CI boundaries are shown in FIGURE 3. In children younger than 2 years, 8 serogroup C cases occurred among those vaccinated and none among those not vaccinated (P = .38). In this group, estimates of serogroup C VE are negative, but CIs are large and encompass positive values, with limits ranging from −844% to 83% in infants younger than 1 year. There was evidence of protection in children older than 2 years, which increased with age. Age-adjusted VE was 41% (95% CI, −106% to 79%) in the group aged 2 through 9 years, 75% (95% CI, −17% to 93%) in the group aged 10 through 14 years, and 83% (95% CI, 39%–96%) in the group aged 15 through 20. Vaccine effectiveness was significant only in those aged 15 through 20 years, probably because of the small numbers in the age groups. Overall, an estimated 48 MCD cases were prevented during the 5-year period following the mass immunization campaign (1 case per 34,000 doses).

COMMENT

This is the first study to assess the medium-term impact of a mass immunization campaign against serogroup C MCD in a large, well-defined population. However, the decrease in the incidence of serogroup C cases observed in the whole population following the mass immunization campaign limits the power of the analyses. There are reasons to believe that a high level of ascertainment of MCD cases was achieved during the study period. This outbreak provoked a high degree of awareness in the medical profession, and clinicians tended to report very quickly any suspected case to public health departments, which are in charge of tracing high-risk contacts and prescribing chemoprophylaxis. In laboratories, reporting is a routine systematic process. Completeness of reporting has been estimated to be 94% in the Montreal area, based on hospital records.17

Sociodemographic and behavioral factors affecting MCD risk include age, sex, income, and passive smoking.18 Age is the most important determinant of disease risk and was controlled for in this study. Individual data were not available for the other variables, but their effect on disease risk is modest and
Table. Vaccination Coverage and Incidence of Serogroup C Meningococcal Disease During the 5-Year Period After Mass Immunization*

<table>
<thead>
<tr>
<th>Age at Vaccination, y</th>
<th>Population, No.</th>
<th>Vaccination Rate, %</th>
<th>Cases of Meningococcal Disease, Vaccinated/Not Vaccinated*</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Year 1 Year 2 Year 3 Year 4 Year 5 Total</td>
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<tr>
<td>&lt;1</td>
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*Study period is April 1, 1993, to March 31, 1998.

Data represent a 5-year period after mass immunization, in the cohort of persons aged 6 months to 20 years.

only a very strong association with vaccination status could bias estimates of VE significantly.

The results of the study indicate a strong effect of age at vaccination on VE. Polysaccharides are thymus-independent antigens, inducing an immune response characterized by postnatal maturation, restriction to specific subclasses of humoral antibodies with low affinity, and absence of memory. Bacterialidal serum antibodies are the best marker of clinical protection against MCD. The magnitude of the response to serogroup C polysaccharide vaccine has been shown to be low in young infants and increases monotonously up to age 20 years. This is in agreement with the results of our study.

In several immunogenicity studies, hyporesponsiveness to a second dose of serogroup C polysaccharide vaccine given months after the first dose has been observed in young children and adults. In the absence of protective serum antibodies, anergy to capsular polysaccharide could theoretically increase the risk of invasive disease following nasopharyngeal infection. In our study, VE was negative in children younger than 2 years, but CIs are large and encompass positive values. The absence of any case in unvaccinated children younger than 2 years is likely due to chance. In a randomized trial in Brazil, VE was 12% (95% CI, −33% to 62%) in children aged 6 to 23 months and followed up for more than an 18-month period and was 55% (95% CI, −4% to 72%) in children aged 24 to 36 months. It seems prudent therefore not to administer serogroup C polysaccharide vaccine to those younger than 2 years. Conjugate vaccines inducing a thymus-dependent antigenic response are a promising alternative. An interesting finding is that vaccine-induced immunologic hyporesponsiveness to C polysaccharide can be overcome with the new conjugate vaccine. In our study, estimates of polysaccharide VE were positive in children older than 2 years and increased with age. Protection was excellent in persons aged 15 years or older, with a value close to the 89.5% observed in short-term trials in military recruits. Clinical protection was seen during the first 2 years after vaccine administration. During the last 3 years of the study, the overall number of cases was small and no firm conclusion can be drawn. However, decline in VE with time can be suspected. In a follow-up study of children between the ages of 6 and 8 years who had received 1 dose of group C polysaccharide vaccine, the mean decline from peak
antibody concentration was 74% after 4 years.20

Specific mucosal IgA and IgG antibodies can be detected in saliva 1 month after immunization with meningococcal serogroup C polysaccharide vaccine.20 Prospective studies in military recruits have shown that immunization with serogroup C polysaccharide decreased the incidence of nasopharyngeal colonization by a serogroup C strain.31-33 Rapid serogroup switching from C to B has been demonstrated with \textit{N meningitidis},34 and this capacity aroused concern about the induction of herd immunity by mass vaccination programs in which capsular antigens are used. Indeed, a variant of the epidemic electrophotochrome type ET-15 clone expressing the serogroup B capsular polysaccharide has been isolated in a few cases in Quebec since 1993.35 However, no increase in the overall incidence of MCD due to serogroup B was observed following the mass immunization campaign. The small increase in the proportion of cases due to serogroup Y seems to be an unrelated phenomenon, also observed in the United States.36

In conclusion, mass immunization is effective for controlling outbreaks or epidemics of serogroup C MCD among teenagers and young adults, but there is no evidence of protection in young children. Protection is seen during the first 2 years after vaccination. Ultimately, cost-effectiveness should be the criterion for deciding which of the polysaccharide or conjugate vaccines should be recommended for different age groups. Results of randomized trials and epidemiologic studies on conjugate vaccines are urgently needed for comparison purposes.

**Author Contributions:** Dr De Wals participated in the study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript; provided critical revision of the manuscript for important intellectual content, statistical expertise, and administrative, technical, or material support; obtained funding; and supervised conduct of the study. Dr De Serres participated in the study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript; provided critical revision of the manuscript for important intellectual content; and obtained funding for the study. Dr Nyonsenga participated in analysis and interpretation of data and provided critical revision of the manuscript for important intellectual content and statistical expertise.

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**REFERENCES**


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