Effectiveness of a Mass Immunization Campaign Using Serogroup C Meningococcal Conjugate Vaccine

Philippe De Wals, MD, PhD
Geneviève Deceuninck, MD
Nicole Boulianne, MSc
Gaston De Serres, MD, PhD

Meningococcal polysaccharide vaccines are of limited effectiveness. New protein-polysaccharide conjugate vaccines have yet to be evaluated in field conditions.

Objective
To assess the effectiveness of a serogroup C conjugate meningococcal vaccine in an outbreak setting.

Design, Setting, and Participants
Population-based observational study of cases of invasive serogroup C meningococcal disease from 1996 through 2002 in Quebec identified from the provincial registry of notifiable diseases and from the provincial reference laboratory. In 2001, a mass immunization campaign with a conjugate vaccine was conducted to control an emerging epidemic. The number of vaccinated individuals was extracted from meningococcal immunization registries.

Main Outcome Measures
Incidence of invasive meningococcal disease before and 1 year after the campaign in vaccinated and unvaccinated individuals.

Results
Vaccination coverage of those 2 months to 20 years was 82.1%. After the campaign, the number of cases of serogroup C disease decreased from 58 in 2001 to 27 in 2002, and the incidence from 7.8 per million to 3.6 per million. Vaccine effectiveness was found to be 96.8% (95% confidence interval, 75.0%-99.9%). There was no observed increase in the incidence of the other serogroups.

Conclusion
The new conjugate vaccine was effective in controlling an emerging epidemic of serogroup C meningococcal disease, as well as providing short-term protection across a wide age range.

Context
Meningococcal polysaccharide vaccines are of limited effectiveness. New protein-polysaccharide conjugate vaccines have yet to be evaluated in field conditions.

Effectiveness of a Mass Immunization Campaign Using Serogroup C Meningococcal Conjugate Vaccine

Philippe De Wals, MD, PhD
Geneviève Deceuninck, MD
Nicole Boulianne, MSc
Gaston De Serres, MD, PhD

S E R O G R O U P  C P O L Y S A C C H A R I D E meningococcal vaccines are not effective in young children, and protection is of short duration in older children and adults.1 In contrast, protein-polysaccharide conjugate vaccines elicit a T-cell dependent immunologic response that is present in young infants and characterized by the production of high levels of high-avidity bactericidal antibodies and the induction of immunologic memory.2 The use of bactericidal assays and possibly other functional tests has been proposed as a standard to license new meningococcal conjugate vaccines, as phase 3 randomized trials aiming at assessing vaccine efficacy would be impracticable.3,4(pp371-393) However, carefully conducted observational studies are of paramount importance to evaluate the effectiveness of these new vaccines.

An increase in the incidence of meningococcal disease was identified in the province of Quebec in 1990, caused by a virulent C:2a ET15 clone.5,6 To control the epidemic, a mass immunization campaign was conducted in the winter of 1992-1993, using polysaccharide vaccines and targeting the population between the ages of 6 months and 20 years.7 Disease incidence decreased markedly in the following years. In February of 2001, several outbreaks caused by a parent clone occurred, mainly in the Quebec City area.8 Localized immunization programs using plain polysaccharide vaccines were conducted that targeted secondary school students. However, the epidemic extended to younger age groups and other regions, generating a high level of anxiety in the population and extensive media coverage. A serogroup C oligosaccharide-CRM197 protein conjugate vaccine (Menjugate, Chiron, Emeryville, Calif) was licensed following a fast-track process and a
MENINGOCOCCAL MASS IMMUNIZATION CAMPAIGN

mass immunization campaign was launched in the Quebec City area from May through June 2001. The campaign was extended to other regions during the autumn of 2001, targeting all residents in the province between the ages of 2 months and 20 years. The vaccine was mainly administered through the local public health units in special clinics and education facilities. This intervention provided a unique opportunity to assess the effectiveness of the conjugate vaccine.

METHODS

The population targeted for vaccination encompassed all residents in the province of Quebec born between July 17, 1980, and November 30, 2001. The size of the target population and its age distribution on January 31, 2002, was estimated from projections based on the 1996 census. A meningococcal immunization registry was established in the Quebec City region in the spring of 2001 and a provincial registry was established in the fall of 2001. This enabled the processing of immunization records received from vaccine providers, both nurses and physicians, in public health units and private clinics. Data concerning the number of vaccinated individuals and doses administered were extracted from the 2 registries.

Cases of invasive meningococcal disease were identified from the provincial registry of notifiable diseases. Any case suspected or diagnosed by a physician or a laboratory had to be reported to the regional public health department. An investigation was conducted by the public health department to collect additional information, including the clinical presentation and outcome, the vaccination status of the patient, and the results of diagnostic tests. Cases were classified as clinical or confirmed according to standardized criteria. Hospital laboratories were asked to transmit samples and/or cultures to the Quebec Public Health Laboratory for confirmation of the bacteriological diagnosis and strain characterization. Polymerase chain reaction and additional strain characterization tests were performed by the Health Canada National Reference Laboratory in Winnipeg. The list of cases identified by the Quebec Public Health Laboratory in 1996-2002 was cross-checked against the notifiable diseases file.

Incidence rates for serogroup C disease were calculated as number of cases divided by mid year projections of the population of Quebec based on the 1996 census obtained from the Institut de La Statistique du Quebec. Incidence rates in the total population and target population 2 months to 20 years were compared between the period 1996-2000 (before the mass vaccination campaign), 2001 (during the outbreak), and 2002 (after the campaign). The incidence rates of serogroup B and serogroup Y meningococcal disease were also compared to identify any ecological effect. To assess vaccine effectiveness, the incidence of confirmed serogroup C meningococcal disease during the year 2002 was compared between vaccinated and unvaccinated individuals in the target population. Vaccine effectiveness was defined as 1 minus the relative risk of disease (or the odds ratio). Confidence intervals and P values were computed using StatXact software. P < 0.05 was considered statistically significant. The study was approved by the Quebec Ministry of Health and Social Services.

RESULTS

The population of Quebec was 7399931, while the target population (2 months to 20 years) included 1,919,070 individuals. During the mass campaign, 51,781 doses of plain polysaccharide vaccine were administered, mainly to adolescents in the Quebec City area. A total of 1,606,635 doses of serogroup C conjugate vaccine were administered; 1,524,003 individuals received at least 1 dose. The vast majority of vaccines (94.7%) were given before December 31, 2001, and the vaccines administered in

![Figure 1. Immunization Coverage of Target Population](image)

**Table 1. Cases of Invasive Meningococcal Disease Reported in the Province of Quebec, According to Serogroup, 1996-2002**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>39</td>
<td>39</td>
<td>23</td>
<td>17</td>
<td>22</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>C</td>
<td>12</td>
<td>12</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>58</td>
<td>27</td>
</tr>
<tr>
<td>29E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>W-135</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td></td>
<td>1</td>
<td></td>
<td>9</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Y</td>
<td>1</td>
<td>9</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Z</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not groupable</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Confirmed case, serogroup unknown</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Clinical case</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

*Blank spaces indicate that no cases were reported.*
were mostly second and third doses given to young infants. Vaccination coverage was 82.1%; 81.5% were fully immunized. Vaccine coverage was higher in children aged 6 through 16 years than in younger or older age groups (FIGURE 1).

The number of cases of serogroup C meningococcal disease reported in Quebec from 1996 to 2000 ranged from 3 to 12. In 2001, the number of cases suddenly increased to 58 (TABLE 1). In 2002, the year following the mass campaign, the number of cases of serogroup C decreased to 27 but was still higher than in the endemic period 1996-2000. The incidence rates were 1.04 per million in 1996-2000, 7.84 in 2001 (P<.001), and 3.63 in 2002 (P<.001 comparing 2001 rates; TABLE 2). For the age group targeted for vaccination, the incidence increased from 2.90 per million in 1996-2000 to 21.47 in 2001, then decreased to 3.26 in 2002. In contrast, for those 21 years and older, the incidence was similar between 2001 (3.26) and 2002 (3.77; Table 2).

For serogroup B, the incidence rate in 2002 (4.0 per million) was close to that observed in the period between 1996-2000 (3.8 per million, P=.26). For serogroup Y, the incidence rate in 2002 (0.7 per million) was not significantly different than in the period 1996-2000 (1.2 per million, P=.07). In the Quebec City area (FIGURE 2), the number of cases of serogroup C in the population younger than 21 years decreased markedly after the mass campaign. However, sporadic cases continued to occur in individuals exceeding this age bracket. A similar pattern was observed throughout the entire province (Figure 2). A second wave of the epidemic was expected to occur in the winter 2001-2002 but was not observed.

In 2002, 7 serogroup C cases were reported among unvaccinated individuals from the target population, and 2 cases of vaccine failure were documented. The first reported case was a 19-year-old man with meningococcal meningitis, confirmed by blood culture. He had received a first dose of polysaccharide vaccine in 1993 and a second dose in 2001. The second reported case was a 16-year-old girl with meningitis, confirmed by a polymerase chain reaction test in a blood speci-

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 mo</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Population</td>
<td>14 601</td>
<td>13 739</td>
<td>12 834</td>
<td>12 305</td>
<td>12 158</td>
<td>65 637</td>
<td>12 291</td>
<td>12 249</td>
</tr>
<tr>
<td>Incidence density per million</td>
<td>0.00</td>
<td>72.78</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>15.24</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mo to 20 y</td>
<td>8</td>
<td>10</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>28</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>Population</td>
<td>1 966 296</td>
<td>1 952 729</td>
<td>1 932 763</td>
<td>1 911 591</td>
<td>1 887 771</td>
<td>9 651 149</td>
<td>1 863 019</td>
<td>1 839 728</td>
</tr>
<tr>
<td>Incidence density per million</td>
<td>4.07</td>
<td>5.12</td>
<td>0.52</td>
<td>2.09</td>
<td>2.65</td>
<td>2.90</td>
<td>21.47</td>
<td>3.26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≥21 y</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>9</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Population</td>
<td>5 293 007</td>
<td>5 336 082</td>
<td>5 377 397</td>
<td>5 421 499</td>
<td>5 471 836</td>
<td>26 899 911</td>
<td>5 524 622</td>
<td>5 576 033</td>
</tr>
<tr>
<td>Incidence density per million</td>
<td>0.76</td>
<td>0.19</td>
<td>0.37</td>
<td>0.37</td>
<td>0.00</td>
<td>0.33</td>
<td>3.26</td>
<td>3.77</td>
</tr>
</tbody>
</table>

Total cases for all ages | 38 | 58 | 27 |
Population | 36 616 697 | 7 399 931 | 7 428 010 |
Rate per million person-years | 1.04 | 7.84 | 3.63 |

Figure 2. Monthly Number of Cases of Serogroup C Meningococcal Disease in the Quebec City Area and the Province of Quebec, 2001-2002
men. She had been treated for an astrocytoma 2 years previously and had received the conjugate vaccine in 2001. Overall, the effectiveness of the conjugate vaccine was 96.8% (95% confidence interval, 75.0%-99.9%).

**COMMENT**

In Quebec, a mass immunization campaign relying primarily on a serogroup C conjugate vaccine was successful in controlling an emerging epidemic, and a high level of protection was provided over a wide age range of individuals. The 96.8% effectiveness rate measured in the present study is close to the 88% to 96% short-term effectiveness rates observed in the United Kingdom, where 3 different conjugate vaccines have been used for a routine infant immunization program with a catch-up program for older individuals.13,14 In the year following the first mass immunization campaign in Quebec in 1993, the age-adjusted effectiveness rate of the serogroup C polysaccharide vaccine was 74.3% (95% confidence interval, 9.5%-91.6%).1

In industrialized countries, meningococcal diseases are infrequent, even during outbreaks, and confidence intervals for estimates of vaccine effectiveness from observational studies are likely to be wide, even when conducted in large populations. This proved to be a major limitation of our study.

Although selection bias is always possible, in recent years, the increasing use of polymerase chain reaction tests has improved the diagnosis of cases of invasive meningococcal disease.15,16 This technique is now widely used in Quebec and is included in the case-definition.8 The completeness of reporting of meningococcal disease to public health authorities has been estimated to be 94% in the Montreal, Quebec, area, using hospital records as a reference.15 Similarly, confounding bias is unlikely. Following the 1992-1993 mass immunization campaign in Quebec, polysaccharide vaccine effectiveness was measured in a case-control study, and vaccine effectiveness estimates did not change markedly when potential confounders such as socioeconomic variables were included in the analysis.16 Finally, only short-term protection was assessed. More studies are needed to assess long-term protection, especially for individuals vaccinated before the age of 1 year in whom immunity may wane, as observed in the United Kingdom.17

**REFERENCES**


