Impact of an Immunization Campaign to Control an Increased Incidence of Serogroup B Meningococcal Disease in One Region of Quebec, Canada

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Background. Invasive meningococcal disease (IMD) incidence increased in Quebec, starting in 2003, and was caused by a serogroup B sequence type 269 clone. The Saguenay-Lac-Saint-Jean (SLSJ) region was particularly affected with a rate of 3.4 per 100,000 person-years in 2006–2013. In May 2014, an immunization campaign was launched in SLSJ, using the 4-component protein-based meningococcal vaccine (MenB-4C). We aimed to evaluate the impact of the campaign 2 years after its initiation.

Methods. Immunization registry data and serogroup B invasive meningococcal disease (B-IMD) cases notified to public health authorities and confirmed by culture or polymerase chain reaction from July 1996 to December 2016 were analyzed, including a multivariate Poisson regression model of incidence rates.

Results. By the end of the campaign, 82% of the 59,000 targeted SLSJ residents between 2 months and 20 years of age had been immunized. Following the initiation of the campaign, no B-IMD case occurred among vaccinees, whereas 2 cases were reported among unvaccinated adult SLSJ residents, and a third case in an unvaccinated child who had stayed in the region during the week prior to disease onset, in 2015. B-IMD incidence decreased in all other regions in the years 2015–2016 but sporadic cases continued to occur. A multivariate analysis showed a significant effect of the campaign in the SLSJ region (relative B-IMD risk: 0.22; P = 0.04).

Conclusions. Results suggest a high level of protection provided by MenB-4C following mass vaccination at regional level. This, along with reassuring safety data, supports the current recommendations for MenB-4C use for controlling outbreaks caused by clones covered by the vaccine.

Keywords. serogroup B meningococcal disease; outbreak; immunization campaign; meningococcal vaccine.

A 4-component protein-based meningococcal vaccine (MenB-4C/Bexsero, Novartis, now a GSK company) was licensed in the United States and Canada in 2015. Both the US Advisory Committee on Immunization Practices and the Canadian National Advisory Committee on Immunization considered that there was insufficient evidence to support the use of MenB-4C in routine infant and adolescent immunization programs but recommended its use to control outbreaks caused by clones expected to be susceptible to the vaccine [1, 2]. In 2003, a virulent serogroup B Neisseria meningitidis sequence type 269 (ST269) clone emerged in the province of Quebec, Canada [3]. The circulation of this clone caused a prolonged increase in the incidence of serogroup B invasive meningococcal disease (B-IMD). The Saguenay-Lac-Saint-Jean (SLSJ) region was particularly affected, with an average incidence rate of 3.4 per 100,000 person-years from 2006 to 2013, 5 times the provincial average (0.7/100,000), and >10 times the Canadian average (0.3/100,000) [4–6]. During this period, 76% (56/74) of B-IMD cases in SLSJ occurred in persons ≤20 years of age (9% in <1-year-olds, 12% in 1- to 4-year-olds, 9% in 5- to 11-year-olds, 18% in 12- to 16-year-olds, and 27% in 17- to 20-year-olds). Genotyping of the ST269 clone circulating in Quebec showed that although there was no exact match with MenB-4C antigens, a high proportion of strains (152/158) possessed genes that encoded for the factor H-binding protein (fHbp) peptide 1.15 variant closely related to the vaccine fHbp peptide 1 [7]. Results of the meningooccal antigen typing system enzyme-linked immunosorbent assay relative potency tests on ST269 strains isolated from 2006 to 2009 in Canada (33/37 from Quebec) predicted that 95% (35/37) would be covered by MenB-4C [8].

To control this prolonged increase in incidence, the Quebec Immunization Committee recommended the implementation of a short-term mass immunization campaign in the SLSJ region [9]. The campaign started on 6 May 2014, targeting individuals...
between 2 months and 20 years of age residing or attending school in the SLSJ region. The recommended immunization schedule was 4 doses for infants 2–5 months of age, 3 doses for those 6–11 months, and 2 doses at age 12 months and older, with a minimum interval of 2 months between doses. Vaccines were offered in schools and dedicated clinics in local public health units. Most of the first doses were given in May–June 2014 and most of the second doses in September–October 2014. Enrollment was terminated on 31 December 2014, although recommended doses were administered after this date. The objective of this study was to assess the impact of this campaign in preventing invasive meningococcal disease among vaccinees and to reduce B-IMD incidence in the SLSJ region.

**MATERIALS AND METHODS**

The study population included residents in Quebec observed from 1 July 1996 to 31 December 2016. The size of the population targeted for immunization in the SLSJ region and of the reference population in the province of Quebec was estimated from census and birth statistics provided by the Institut de la Statistique du Québec. In 2014, the estimated population in Quebec was 8,223,857 and 278,308 in the SLSJ region. Data concerning the number of vaccinated individuals were extracted from the MenB-4C immunization registry initiated at the start of the campaign and maintained by the Institut national de santé publique du Québec. During the campaign, all MenB-4C doses were administered by registered nurses and recorded in the electronic database.

Cases of invasive meningococcal disease were identified from the provincial registry of notifiable diseases. According to the Quebec law, any suspected or confirmed IMD case has to be reported to the regional public health department by physicians and laboratories. An investigation of every IMD case is conducted by the public health department to collect additional information, including the clinical presentation and outcome, the vaccination status of the patient, and results of diagnostic tests. All public hospital laboratories in the province (n = 95, 6 of which are in the SLSJ region) are invited to transmit samples and/or cultures to the Quebec Public Health Laboratory for confirmation of the bacteriological diagnosis and strain characterization, including polymerase chain reaction tests and serogrouping. Additional genotyping and phenotyping tests were performed by the National Microbiology Laboratory in Winnipeg. Details on the techniques have been reported by Law and coworkers [3, 7].

IMD rates were compared assuming a Poisson distribution with a threshold of statistical significance set at 0.05 for a bilateral test, using the exact option when there was no case in one stratum (SAS software version 9.3, SAS Institute, Cary, North Carolina). To assess the overall impact of the campaign in SLSJ on B-IMD risk, a multivariate Poisson regression analysis was performed, using the following predictors: region (SLSJ vs all other regions), season (4 categories), age (5 categories), years (10 categories), and the pre- and postimmunization periods in SLSJ (January 1996–June 2014 vs July 2014–December 2016) (see Supplementary Table 1).

The study was performed under a legal mandate of the Quebec Ministry of Health and Social Services (Ministère de la Santé et des Services sociaux du Québec) and accordingly, the study protocol was not submitted for approval to a research ethics committee.

**RESULTS**

MenB-4C uptake in the SLSJ target population is shown in Table 1. The overall rate (≥1 dose) was 82%, with highest values in primary and junior high schoolchildren and lowest in senior high school and college ages. Not everyone received the age-specific recommended number of doses.

During the study period, 1 July 1996 to 31 December 2016, a total of 1287 IMD cases were recorded in the provincial registry of notifiable diseases, 860 of them (67%) belonging to serogroup B, 210 (16%) serogroup C, 93 (7%) serogroup Y, 36 (3%) serogroup W, 21 (2%) other serogroups, and 67 (5%) of unknown serogroup. No trend was observed in the proportion of unidentified serotypes over time. B-IMD rates in the province of Quebec, in the SLSJ, and other regions are shown in Figure 1. In the province, the emergence of the ST269 clone in 2003 was followed by a gradual and prolonged increase in incidence rate during the 2006–2013 period (peak at 0.9 per 100,000 person-years) followed by a decrease. The same pattern was seen in the SLSJ region but with much higher rates (peak at 6.2 per 100,000 person-years) and more variation caused by small numbers. Following the mass immunization campaign in the second half of 2014, the rate decreased sharply in SLSJ and no case was reported during the 2015–2016 season.

**Table 1. Uptake of 4-Component Protein-Based Meningococcal Vaccine in the Saguenay-Lac-Saint-Jean Region of Quebec, Canada, According to Age and Number of Doses**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Target No.</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>≥1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns</td>
<td>2168</td>
<td>7%</td>
<td>2%</td>
<td>2%</td>
<td>7%</td>
<td>82%</td>
<td>93%</td>
</tr>
<tr>
<td>Residents</td>
<td>57,205</td>
<td>18%</td>
<td>6%</td>
<td>73%</td>
<td>2%</td>
<td>1%</td>
<td>82%</td>
</tr>
<tr>
<td>2–5 mo</td>
<td>831</td>
<td>6%</td>
<td>2%</td>
<td>4%</td>
<td>23%</td>
<td>65%</td>
<td>94%</td>
</tr>
<tr>
<td>6–11 mo</td>
<td>1,277</td>
<td>8%</td>
<td>2%</td>
<td>2%</td>
<td>22%</td>
<td>47%</td>
<td>3%</td>
</tr>
<tr>
<td>1–4 y</td>
<td>11,024</td>
<td>14%</td>
<td>6%</td>
<td>80%</td>
<td>8%</td>
<td>92%</td>
<td>5%</td>
</tr>
<tr>
<td>5–11 y</td>
<td>18,919</td>
<td>7%</td>
<td>3%</td>
<td>91%</td>
<td>9%</td>
<td>93%</td>
<td>5%</td>
</tr>
<tr>
<td>12–16 y</td>
<td>12,997</td>
<td>8%</td>
<td>6%</td>
<td>86%</td>
<td>8%</td>
<td>92%</td>
<td>5%</td>
</tr>
<tr>
<td>17–20 y</td>
<td>12,157</td>
<td>53%</td>
<td>14%</td>
<td>34%</td>
<td>4%</td>
<td>92%</td>
<td>5%</td>
</tr>
<tr>
<td>All ages</td>
<td>59,373</td>
<td>18%</td>
<td>6%</td>
<td>70%</td>
<td>2%</td>
<td>4%</td>
<td>82%</td>
</tr>
</tbody>
</table>

*For 6 May 2014.

*Born 6 May through 31 December 2014.

*Born 6 May 1993 through 5 March 2014.
The monthly distribution of B-IMD cases in SLSJ and other regions of Quebec is shown in Figure 2. No B-IMD cases were reported in the age group targeted by the mass immunization program in SLSJ from the beginning of the campaign in May 2014 and up to the end of the study period on 31 December 2016. In this region, 2 cases occurred among unvaccinated adults in March–April 2015. A first ST269 B-IMD case was a 44-year-old female resident of the SLSJ region who had stayed in an ice-fishing shelter camp during the week prior to disease onset. A second unrelated B-IMD adult case (ST11386/ST269 clonal complex [CC]) was an unvaccinated 64-year-old female resident of another village in the SLSJ region. Another B-IMD case (without enough DNA to determine ST/CC 269) was linked to the first SLSJ adult case and occurred within a 1-day interval in an unvaccinated 13-year-old girl residing outside the SLSJ region who went on holiday to the same camp. In the other regions of Quebec, B-IMD cases remained sporadic in all age groups up to the end of the observation period.
B-IMD rates during the period of high incidence of the ST269 clone and before the start of the mass immunization campaign in the SLSJ (July 1996–June 2014) and the postcampaign period (July 2014–December 2016) are shown in Table 2. In the other regions, the B-IMD rate decreased by 53%, 51% in the age group ≤20 years and 53% in those >20 years. In SLSJ, decreases were, respectively 92%, 100%, and 67%. Assuming the same reduction in incidence in SLSJ as observed in the other regions (−53%), 11 B-IMD cases would have been expected during the postimmunization period (8 in persons aged ≤20 years and 3 in persons >20 years). Only 2 cases were actually observed, all among older adults (P = .001).

Results of the multivariate Poisson regression analysis are presented in Supplementary Table 1. The region, season, age, and year were significant independent predictors of the B-IMD risk in Quebec during the period 1996–2016. Adjusting for these variables, the campaign in the SLSJ region was associated with a statistically significant decrease in disease risk (relative risk, 0.22; 95% confidence interval [CI], .05–.92; P = .04).

**DISCUSSION**

This is the first assessment of the effectiveness of MenB-4C used in a mass immunization campaign to control an increased incidence of B-IMB at a regional level. More than 2 years after the start of the campaign, no IMD case was observed among approximately 49000 vaccinees in SLSJ. As no case was observed both in vaccinated and unvaccinated persons in the target population, it was impossible to calculate a vaccine effectiveness rate by traditional methods [10]. Although the B-IMD rate decreased in all other regions during the period 2014–2016, the decrease was more pronounced in SLSJ and this was statistically significant using a multivariate Poisson regression analysis.

In 2013–2014, MenB-4C was also used to control an outbreak caused by a serogroup B clone (ST740; CC41/44/lineage 3) at a university campus in the United States, and no further B-IMD case was reported among the 5502 vaccinated students and staff members or on the campus in the year following the campaign [11]. In addition, no vaccine failure was observed following MenB-4C vaccination in 2 other US university campuses: 9825 vaccinees in Santa Barbara and 9652 vaccinees in Santa Clara [12, 13]. Preliminary results of the routine 2 + 1 MenB-4C immunization schedule in the United Kingdom suggest an 83% (95% CI, 24%–95%) vaccine effectiveness after 2 doses against all serogroup B strains [14]. These observations as well as our own add confidence to high level of the short-term protection provided by this new vaccine, which was licensed on the basis of immunogenicity data [1, 2].

During the 2-year period following the initiation of the immunization campaign in SLSJ, no IMD case was recorded among the approximately 10000 persons targeted but not vaccinated in the population of SLSJ and among the approximately 2700 infants born in 2015 and not vaccinated. At the end of the winter of 2014–2015, 2 B-IMD cases occurred among unvaccinated adults in addition to another case in an unvaccinated 13-year-old visitor. This suggests the persistence of the circulation of the virulent clone among adults in the region during the first year. However, no other case was reported in the SLSJ population during the second year. In a randomized trial among university students in the United Kingdom, a modest and non–statistically significant reduction in *N. meningitidis* carriage acquisition was observed in the MenB-4C group in comparison with the control group (22% reduction for all *N. meningitidis* and 29% for serogroup B) [15]. More information from mass campaigns would be needed to properly assess any herd effect induced by this vaccine when used among adolescents and young adults.

**Table 2. Incidence Rate of Serogroup B Meningococcal Disease in the Province of Quebec, in Saguenay-Lac-Saint-Jean and Other Regions, July 2006–December 2016, According to Period and Age Group**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Region</th>
<th>Cases</th>
<th>IR/100 000</th>
<th>Cases</th>
<th>IR/100 000</th>
<th>Rate Difference</th>
<th>% Change</th>
<th>Rate Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>Province</td>
<td>447</td>
<td>0.7</td>
<td>59</td>
<td>0.2</td>
<td>−0.5</td>
<td>−67%</td>
<td>0.33</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>SLSJ</td>
<td>75</td>
<td>3.4</td>
<td>2</td>
<td>0.3</td>
<td>−3.1</td>
<td>−92%</td>
<td>0.08</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Other regions</td>
<td>372</td>
<td>0.6</td>
<td></td>
<td>57</td>
<td>0.3</td>
<td>−0.3</td>
<td>−53%</td>
<td>0.47</td>
</tr>
<tr>
<td>≤20 y</td>
<td>Province</td>
<td>293</td>
<td>2.0</td>
<td>36</td>
<td>0.8</td>
<td>−1.2</td>
<td>−61%</td>
<td>0.39</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>SLSJ</td>
<td>56</td>
<td>11.4</td>
<td>0</td>
<td>0.0</td>
<td>−11.4</td>
<td>−100%</td>
<td>0.00</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Other regions</td>
<td>237</td>
<td>1.7</td>
<td></td>
<td>36</td>
<td>0.8</td>
<td>−0.9</td>
<td>−51%</td>
<td>0.49</td>
</tr>
<tr>
<td>&gt;20 y</td>
<td>Province</td>
<td>154</td>
<td>0.3</td>
<td>23</td>
<td>0.1</td>
<td>−0.2</td>
<td>−55%</td>
<td>0.45</td>
<td>.0001</td>
</tr>
<tr>
<td></td>
<td>SLSJ</td>
<td>19</td>
<td>1.1</td>
<td>2</td>
<td>0.4</td>
<td>−0.7</td>
<td>−67%</td>
<td>0.33</td>
<td>.13</td>
</tr>
<tr>
<td></td>
<td>Other regions</td>
<td>135</td>
<td>0.3</td>
<td></td>
<td>21</td>
<td>0.1</td>
<td>−0.2</td>
<td>−53%</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Abbreviations: IR, incidence rate; SLSJ, Saguenay-Lac-Saint-Jean.
Adverse events reported among vaccines have been described in other publications [16, 17]. To summarize, fever was reported in 12% of vaccinees in Quebec and was more frequent in young children. Antipyretic prophylaxis (acetaminophen mainly) was 50% effective in preventing the occurrence of fever in children <5 years of age but not in the older age group. There was no death and no major adverse event with or without sequelae associated with vaccination.

To conclude, results of our study suggest a high level of protection in the first year following the administration of MenB-4C. Coupled with the relative safety of this new vaccine, these results support current recommendations for MenB-4C use to control outbreaks caused by clones covered by the vaccine.

**Supplementary Data**

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

**Notes**

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