Risk of Guillain-Barré Syndrome following Serogroup C Meningococcal Conjugate Vaccine in Quebec, Canada

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To assess the risk of Guillain-Barré syndrome (GBS) following administration of meningococcal serogroup C-CRM197 conjugate vaccine, provincial immunization records were linked with hospital discharge records, and medical charts were reviewed. In the cohort of 1.9 million individuals (age, 2 months to 20 years), observed postvaccination frequencies of GBS were not higher than expected.

Guillain-Barré syndrome (GBS) is an acute autoimmune inflammatory demyelinating neuropathy affecting peripheral motor and/or sensory nerves [1, 2]. In children, adolescents, and young adults, the reported incidence is 1–2 cases per 100,000 person-years, and the prognosis is usually good [3]. In 1976–1977, an increased risk of GBS was identified following the administration of inactivated “swine” influenza vaccines [4]. Recently, a possible association between GBS and receipt of a quadrivalent meningococcal conjugate vaccine was reported in the United States [5]. In the province of Quebec, Canada, a mass immunization campaign using a meningococcal serogroup C conjugate vaccine (C-MCV) was implemented in 2001 [6]. The Quebec Meningococcal Vaccine Safety Database was created by linking several provincial administrative databases to evaluate the effectiveness and safety of the newly licensed vaccine. At the request of the Quebec Ministry of Health, an investigation was performed to assess the risk of GBS following the administration of C-MCV.

Methods. The investigation was performed in accordance with the Quebec Law on Public Health [7], and approval from an ethical committee was not requested. Nominative information from provincial databases was available, and hospital records could be reviewed without the patients’ consent. The study population encompassed all residents in the province of Quebec born between 17 July 1980 and 30 November 2001 (age range, 2 months to 20 years, at the time of the mass immunization campaign), and its size was estimated from projections based on the 1996 census (n = 1,909,734). During the 2001 mass immunization campaign, a Provincial Meningococcal Vaccine Registry was established that contains information on 1,428,463 individuals who received at least 1 dose of C-MCV. From other sources, it was estimated that ∼1,524,002 persons in the target population were vaccinated using C-MCV. A small fraction of vaccinees did not provide written consent for registration, and a small percentage of vaccination forms were not transmitted centrally.

Using the provincial health insurance number, immunization records were linked with hospital discharge records, which contain up to 16 diagnoses coded according to The International Classification of Diseases, Ninth Revision (ICD-9). Patients in the target population with a diagnosis code compatible with GBS (ICD-9: 357.0) were identified, and copies of medical records were obtained and reviewed by one of the authors (R.M.B.) without knowledge of the immunization status. The clinical classification of GBS proposed by Hughes and Cornblath [2] was applied, and cases were categorized on the basis of the provisional Brighton GBS Working Group’s criteria as of 7 March 2007 (confirmed, level 1a; possible, level 1b, 2a, 2b or 3; or probable, other) (J. J. Sejvar, personal communication). On the basis of the experience with the “swine” vaccine [4], 2 risk periods were defined as 6 or 8 weeks following the administration of a first C-MCV dose (95.6% of registered individuals received only 1 dose). Month- and age-adjusted observed-to-expected GBS incidence ratios were calculated using the entire study population investigated between 1 November 2000 and 31 December 31 2002; risk periods were excluded to compute expected rates. Ninety-five percent CIs were estimated by an exact method available in StatXact-6 (Cytel Software).

Results. A total of 46 hospitalization records with a code compatible with GBS were identified, concerning 40 patients admitted in 23 acute care hospitals. Six patients were excluded because the final diagnosis was a neurological condition other than GBS. We also excluded 1 recurrence of GBS in a patient who had received a meningococcal polysaccharide vaccine after the recurrence. Finally, 33 GBS cases were included in the anal-
ysis, from a total of 4,075,465 person-years of observation, representing a crude annual incidence rate of 0.8 cases per 100,000 persons (95% CI, 0.56–1.14 per 100,000 person-years).

Acute inflammatory demyelinating polyradiculopathy was the most frequent clinical GBS presentation (27 cases), and there were 2 cases of acute motor axonal neuropathy, 1 case of acute motor and sensory axonal neuropathy, and 1 case of acute sensory neuropathy with pandysautonomia. In 2 other cases, a precise classification could not be made because of a lack of details. The GBS was considered to be confirmed in 13 cases, probable in 14 cases, and possible in the remaining 6 cases.

Nineteen of the 33 patients with GBS received a C-MCV. Five patients were immunized after the occurrence of the disease, and 14 received a first dose of vaccine prior to the disease (intervals between first vaccine and GBS onset, 9, 46, 76, 111, 132, 227, 240, 295, 339, 381, 382, 400, 405 and 425 days). Thus, there were 2 cases with GBS onset ≤8 weeks following vaccine administration. The first case was an acute motor axonal neuropathy (possible) in an 8-year-old child who was hospitalized 9 days after vaccine administration. All viral and bacteriologic test results were negative, and the case was reported in the passive surveillance system of adverse events associated with vaccines. The second case was an acute inflammatory demyelinating polyradiculopathy (probable) occurring 46 days after C-MCV administration in a 2-year-old child. Only a bacterial culture of CSF was performed, and the result was negative. This second case was not reported in the surveillance system.

The observed and expected numbers of GBS cases among vaccinees, sorted according to different diagnostic categories and definitions of the risk period, are shown in table 1. In all comparisons, observed numbers were lower than expected, and all 95% CIs of ratios encompassed the value of 1.

**Discussion.** The results of this study do not suggest the existence of an increased risk of GBS associated with the administration of C-MCV. In the mass immunization campaign in Quebec, a vaccine containing the serogroup C meningococcal polysaccharide conjugated to CRM197 protein derived from the diphtheria toxin was mainly used (Menjugate; Chiron Vaccines [now Novartis Vaccines]), whereas the alert in the United States concerned a vaccine containing 4 polysaccharides (A, C, Y, and W135) conjugated to diphtheria toxoid (Menactra; Sanofi Pasteur) [5].

In this study, the whole target population observed before, during, and after the mass immunization campaign was selected as a reference for computing the expected number of GBS cases among vaccinees to minimize selection biases associated with either the avoidance or the report of vaccination of individuals at increased risk of developing GBS [8]. This bias is amplified in comparisons restricted to vaccinees [9]. In our cohort, there were 15 unvaccinated individuals who received a diagnosis of GBS before the end of the mass immunization campaign, and only 6 (40%) of them were ultimately vaccinated. By comparison, ~80% of the whole target population was vaccinated [6].

The main limitation of our study is in its limited power to identify an increased risk of small magnitude. Given the sample size (219,025 person-years exposed and 3,856,440 person-years unexposed), the power was 81% to detect a risk ratio of 5 during the 8-week post-vaccination period, but only 11% for a risk ratio of 2, corresponding to an absolute risk close to 1 additional GBS case per million C-MCV doses.

In Quebec, the accessibility of hospital services is very good and the recommended practice is to admit any person with suspected GBS. Thus, underascertainment in our study is unlikely. However, the results confirm the limitation of passive surveillance systems to identify adverse events possibly associated with vaccination. Only 1 of the 2 GBS cases occurring during the 8-week post-vaccination period was reported to the passive surveillance system. In the United States, the sensitivity of passive surveillance systems was found to be 72% for poliomyelitis after the oral poliovirus vaccine to <1% for rash and thrombocytopenia after the measles, mumps, rubella and varicella vaccine [10].

### Table 1. Observed and expected numbers of Guillain-Barré syndrome cases following the administration of a first dose of serogroup C meningococcal conjugate vaccine in the province of Quebec, Canada.

<table>
<thead>
<tr>
<th>Diagnostic confirmationa</th>
<th>No. of cases observed/no. of cases expected</th>
<th>Ratio (95% CI)</th>
<th>No. of cases observed/no. of cases expected</th>
<th>Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed, probable, and possible cases</td>
<td>2/3.1</td>
<td>0.65 (0.01–2.41)</td>
<td>1/2.5</td>
<td>0.40 (0.02–2.21)</td>
</tr>
<tr>
<td>Confirmed and probable cases</td>
<td>1/2.8</td>
<td>0.36 (0.02–2.07)</td>
<td>0/2.2</td>
<td>0.00 (0.00–1.56)</td>
</tr>
</tbody>
</table>

*a Confirmed, level 1a, typical clinical features with positive electromyogram and positive spinal tab; probable, level 1b, 2a, 2b or 3, typical clinical features and no alternative diagnosis (positive electromyogram or positive spinal tab may be present); possible, incomplete typical clinical features and no alternative diagnosis.

b One probable and 1 possible.
c One possible.
d One probable.
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References