No Association Between Immunization and Guillain-Barré Syndrome in the United Kingdom, 1992 to 2000

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Background: Our goal was to determine whether immunization is associated with the incidence of Guillain-Barré syndrome (GBS).

Methods: We analyzed data for all patients registered with 253 general practices in the United Kingdom General Practice Research Database from 1992 to 2000, with a mean of 1.8 million registered patients. We identified new occurrences of GBS and estimated age- and sex-specific and age-standardized incidence rates. We then determined whether the date of diagnosis was made within 42 days of any immunization and estimated the relative risk of diagnosis following immunization after adjusting for age and sex.

Results: There were 228 incident cases of GBS, including 107 women and 121 men. The age-standardized incidence rate per 100 000 person-years was 1.22 (95% confidence interval [CI], 0.98–1.46) in women and 1.45 (95% CI, 1.19–1.72) in men. Age-specific incidence rates per 100 000 person-years were highest in men aged 65 to 74 years (3.86; 95% CI, 2.50–5.70) and women aged 75 to 84 years (2.54; 95% CI, 1.39–4.27). There were 7 cases (3.1%) in which the onset occurred within 42 days of any immunization; 3 of the 7 cases occurred after influenza immunization. There were 221 cases (97.0%) that were not associated with immunization. The adjusted relative risk during the 42 days after immunization was 1.03 (95% CI, 0.48–2.18; P=.94).

Conclusions: There is either minimal or no risk of GBS associated with routine immunization practice in the United Kingdom. Obtaining a precise estimate of any potential risk associated with an individual vaccine would require a study with more GBS cases.
Incidence studies of GBS in the United Kingdom, based on chart review, have calculated a similar incidence for
GBS, which lends credibility to the estimates in this article. Our population-based study in southeast England in 1994 used capture-recapture techniques from multiple sources and identified a crude annual incidence of 1.2 cases per 100,000 population (95% CI, 0.9-1.4) and 1.5 cases per 100,000 (95% CI, 1.3-1.8) after undetected cases were adjusted for.10 In a review of 35 incidence studies until 1997, the median annual incidence was 1.3 cases per 100,000 (range, 0.4-4.0 cases).10,11 Subsequent studies have reported similar figures. For instance, the crude annual incidence based on hospital records in the Netherlands between 1987 and 1996 was 1.18 per 100,000.12-18 In Lombardy, Italy, in 1996, the crude annual incidence of GBS was 1.55 per 100,000, and 5 (4.0%) of the 138 incident patients had received an antecedent vaccination.19

The present data provide estimates drawn from a large population registered with general practices in the United Kingdom. The data were obtained from practices' electronic clinical records and may be affected by the general limitations of this source, including potential problems of misdiagnosis, lack of detail about the precise time of onset, lack of standardization, and possible underascertainment. However, in view of the generally serious nature of GBS, and the relatively specific clinical picture, these problems may have been fewer than usual. Other studies have shown that data from the GPRD provide valid information for diagnoses and therapies,20,21 including immunizations.7,23 We acknowledge that additional validation of information concerning the diagnosis of GBS, as well as the date of the onset of symptoms, is desirable, because the inclusion of cases incorrectly diagnosed as GBS would generally introduce a bias against detecting causal associations. However, it was clear to us that only a very small proportion of included cases were exposed to recent immunization. We acknowledge that there is a potential for the underrecording of vaccinations, but Kaye et al23 reported that the recording of vaccinations in the GPRD was "virtually complete."

In a case-controlled study in England (1983-1984), 6 of 99 patients with GBS and 5 of 99 controls had been immunized during the previous 12 weeks.24 There have been few population-based studies relating GBS incidence to immunization. Lasky et al2 used hospital databases to identify cases of GBS in 4 states in the United States (1992-1993) and identified 273 adult patients with GBS, 180 of whom were contacted and 19 of whom had received influenza vaccine during the previous 6 weeks. Nine of their 19 patients had the onset of disease during the second week after the immunization, a distribution that was argued to be consistent with the vaccine being an immunologic trigger. From 1990 to 2003, the American Vaccine Adverse Event Reporting System received 501 reports of GBS following influenza vaccine, and the most common interval from immunization to the onset of neuropathy was 2 weeks.25 In the study of Lasky et al,2 the best estimate of the attributable risk was 1.1 additional cases of GBS per 1 million vaccinations. Our sample of 228 cases yielded 7 cases associated with immunization, including 3 associated with influenza immunization, much fewer than the 19 of 180 cases of GBS after influenza immunization reported by Lasky et al.2 We acknowledge that our study is too small to confirm or refute the small increase in risk calculated by Lasky et al,2 but our results do suggest that it is generally unlikely that there is an increase in GBS incidence in the short period after any immunization that is greater than twice the background incidence. In view of the very small number of cases found to be associated with immunizations, we can also conclude that our findings would be robust to substantial underrecording of immunizations in the GPRD. In a comprehensive review, the US Institute of Medicine3 concluded that it was not possible to confirm or refute a causal relationship between GBS in adults and influenza vaccines administered after 1976. The present results contribute by narrowing the range of RRs associated with influenza vaccine, at least in the United Kingdom during the period studied.

This evidence does not address the question as to whether immunization after GBS is safe, a question that is raised by a few reports of such occurrences.20,27 According to a patient survey, these events are rare. Of 311 patients who reported being immunized after GBS, 11 developed new symptoms but only 1 had symptoms that were severe enough to cause new disability.28

Our results provide reassurance that the great majority of sporadically occurring cases of GBS in the United Kingdom are not associated with immunization. Caution in interpretation is required because the risk of GBS associated with immunization may vary in different times and places. The distinct influenza vaccines prepared at different times may be associated with varying risks,1,2 and different vaccines may be in use in different countries during similar periods.

Table 2. Association of Guillain-Barré Syndrome With All Immunizations and Influenza Immunization Separately

<table>
<thead>
<tr>
<th>Date of Diagnosis</th>
<th>No. of Cases</th>
<th>Time at Risk (Person-Years)</th>
<th>Adjusted Relative Risk* (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All vaccinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 42 d of any immunization</td>
<td>7</td>
<td>28.78†</td>
<td>1.03 (0.48-2.18)</td>
<td>.94</td>
</tr>
<tr>
<td>Not within 42 d of any immunization</td>
<td>221</td>
<td>934.65‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 42 d of influenza immunization</td>
<td>3</td>
<td>13.31†</td>
<td>0.99 (0.32-3.12)</td>
<td>.99</td>
</tr>
<tr>
<td>Not within 42 d of influenza immunization</td>
<td>225</td>
<td>950.12‡</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age at diagnosis and sex.
†Value includes exposed time after immunization for all cases.
‡Value includes unexposed time not after immunization for all cases.
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REFERENCES