Recurrent Guillain-Barré Syndrome Following Vaccination

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Background. Guillain-Barré syndrome (GBS) is an acute polyradiculopathy, thought to be autoimmune, which has been reported following vaccinations. The Advisory Committee on Immunization Practices recommends not administering influenza vaccine to individuals who have had a history of GBS within 6 weeks of a prior influenza vaccination if they are not at high risk of severe complications from influenza illness.

Methods. We identified GBS cases from the Kaiser Permanente Northern California databases from 1995 into 2006 using hospital discharge codes; each medical record was neurologist-reviewed and only GBS-confirmed cases were included for follow-up. We followed confirmed cases through 2008 for vaccinations and recurrent GBS.

Results. We identified 550 cases of GBS over 33 million person-years. Following their GBS diagnoses, 989 vaccines were given to 279 of these individuals, including 405 trivalent inactivated influenza vaccines (TIV) administered to 107 individuals with a prior diagnosis of GBS. Among the 550 total cases of GBS, 18 initially had onset within 6 weeks of TIV; of these, 2 were revaccinated with TIV without a recurrence of GBS. Only 6 individuals of 550 (1.1%) had a second (recurrent) diagnosis of GBS. Among these 6 individuals, none had any vaccine exposure at all in the 2 months prior to the second onset of GBS.

Conclusions. In our population of over 3 million members, during an 11-year period, risk of GBS recurrence was low. There were no cases of recurrent GBS after influenza vaccination and none within 6 weeks after any vaccine.

Guillain-Barré syndrome (GBS) is an acute, rapidly evolving polyradiculoneuropathy, typically presenting with bilateral muscle weakness and paresthesias, in association with absent or diminished deep tendon reflexes. The severity of weakness in cases of GBS ranges from mild weakness to total paralysis, which can lead to death. The annual average incidence rate of GBS, depending on the population being assessed and the method of surveillance, is between 0.4 and 4 cases per 100,000 population [1–3]. Persons of any age are at risk; however, the incidence is much higher among the elderly [4, 5].

GBS is thought to be an autoimmune disorder; the most widely accepted current hypothesis is that of molecular mimicry in which the immune response to specific antigens (including infectious organisms) is characterized by an attack on cross-reactive epitopes in the host peripheral nervous system, causing inflammation and demyelination [5]. Numerous antecedent events have been temporally associated with subsequent development of GBS, including viral and bacterial infections, and surgery [6–11]. An antecedent illness has been reported in up to two-thirds of patients with GBS [2, 7, 12]. Receipt of vaccines has also been temporally associated with GBS, including rabies [10], combined diphtheria, pertussis and tetanus, rubella, tetanus toxoid [8], hepatitis B, hepatitis A [13], polio [14], influenza [15–17], and meningococcal conjugate vaccines [2, 18, 19].

In most cases, the association of vaccination with subsequent GBS is temporal only, and causality is rarely established [20, 21]. The most accurately characterized relationship between GBS and vaccines is that which was seen following the 1976 swine influenza vaccine [15].
Concerns about the association of GBS with influenza vaccine have resulted in caution regarding revaccination in individuals with a history of GBS [15]. The Advisory Committee on Immunization Practices (ACIP) currently recommends avoiding influenza vaccination in persons who are not at high risk for severe influenza illness complications and who have a history of GBS within 6 weeks after a previous influenza vaccination [22]. While persons with a history of GBS have a greater likelihood of subsequently experiencing GBS (regardless of any potential etiologies, including vaccination) than persons without such a history [23, 24], there is little evidence to support these recommendations. Further, this recommendation may be interpreted to mean avoidance of influenza vaccination for anyone with a history of GBS, not just those who had GBS temporally associated with a previous influenza vaccination; this may also cause avoidance of other vaccines as well. Studies [25, 26] and case reports [27–29] of the recurrence of GBS following immunization suggest that the rate of recurrence is low, but evidence and population-based recommendations regarding vaccinating persons with a history of GBS are needed.

The purpose of this study is to describe the vaccination and GBS recurrence rate in individuals with a history of GBS, and to determine whether they have an increased risk of disease recurrence following vaccination.

METHODS

Study Population
Kaiser Permanente of Northern California (KPNC) is a large, integrated healthcare delivery system with a membership of over 3.2 million. The KPNC population is diverse with regard to age, sex, race, and socioeconomic status, and is similar to the region’s demographic distribution, except for the extremes of wealth and poverty [30, 31]. Members of the health plan receive almost all medical care at KPNC facilities, and information on all visits is recorded in the electronic medical record. Laboratory tests, medications, and most other services are covered by the plan, and are provided at KP facilities. Hospitalizations and emergency department visits that are not covered by the health plan are captured via claims. Vaccinations are provided at no additional cost to members, and are mostly received and recorded [32] in a unique immunization tracking system. Influenza vaccines in particular are delivered to multiple areas during the season to make vaccination as convenient as possible for members.

Study Design
We identified all persons ≥5 years of age in KPNC databases discharged from the hospital with a first occurrence of the ICD-9 code corresponding to GBS (357.0) during the study period 1995–2006. The study cohort excluded persons <5 years of age to minimize the effect of the multiple vaccination schedule in this younger age group. All identified cases underwent chart review by trained medical records analysts (MRAs). If the record review indicated that the case was diagnosed prior to the visit identified, we searched for earlier diagnoses, and extensively examined the medical record to determine the GBS onset date. We included all cases, including those in which subsequent review determined that the GBS onset date was prior to the study period. An abstraction form was used that was designed to validate the diagnosis of GBS and determine etiologic factors, including vaccination. Cases were rejected by an MRA if there was no reference to GBS in the chart, or if GBS was ruled out. All cases that were not rejected were subsequently reviewed by a neurologist and classified as level 1, 2, or 3 according to the Brighton Collaboration criteria [33]. Level 1 denotes a laboratory-confirmed case, while levels 2 and 3 denote probable cases without all laboratory variables and possible cases with clinical criteria only, respectively.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an illness that presents with signs and symptoms similar to GBS but has a chronic or relapsing course, rather than a monophasic course typical of GBS. CIDP may be difficult to distinguish from GBS in the early stages [34], and may be misclassified as a recurrence of GBS [35]. Cases primarily identified as CIDP by ICD-9 codes were excluded from the initial data extraction. Among cases with the ICD-9 code 357.0 (GBS), subsequent chart review sometimes revealed that the disease was later confirmed as CIDP, and these cases were also excluded. Recurrent GBS was defined as 2 or more episodes of acute monophasic neuropathy followed by near complete recovery between episodes [36].

After identifying the first episode of GBS, we searched inpatient and outpatient databases as well as our immunization databases for vaccination and GBS recurrence through 2008, until the patient died or left the health plan, or until 25 years had elapsed since the first episode of GBS. The neurologist reviewed all cases and determined whether or not a recurrence of GBS had, in fact, occurred. Follow-up time for the study was determined by the total number of person-years in the KPNC cohort ≥5 years of age during the study years. Follow-up time after the onset of GBS was determined by total person-time from the date of GBS diagnosis of all cases to the end of 2008, death, or disenrollment from the health plan.

This study was approved by the KPNC Institutional Review Board.

RESULTS
Out of a total of 896 individual cases of GBS that were identified on the basis of the ICD-9 codes, medical records were available for 892. Of these, 114 (12.8%) were rejected by the MRAs as being inconsistent with GBS. Of the remaining 778 potential
cases, 220 (28.3%) were rejected by the reviewing neurologist due to information in the chart that was incompatible with GBS, and 8 (1.0%) were rejected for insufficient information in the medical record to determine a diagnosis. The remaining 550 (61.4% of the original set identified) were verified as GBS cases, of which 139 were classified as Brighton level 1 (laboratory-confirmed), 360 cases as level 2 (met some but not all laboratory criteria), and 51 cases as level 3 (clinical diagnosis only). The earliest confirmed case was in September 1958 and the latest confirmed case was in February 2008. We included all 550 first-episode cases in our analysis. Of the 550 cases, 91 were determined to have occurred prior to the study period. The 459 remaining cases occurred over 31,305,844 person-years, resulting in an overall incidence of GBS of 1.47 per 100,000 person-years for ages ≥5 years (95% Poisson confidence interval [CI], 1.34–1.61). We assessed vaccines administered to individuals subsequent to their GBS diagnosis and observed that a total of 989 vaccines were given to 279 individuals with a history of GBS (Table 1). There was a wide range of vaccines administered, with the most common being trivalent inactivated (killed) influenza vaccine (405 doses were given to 107 individuals), pneumococcal polysaccharide vaccine (151 doses), and tetanus-diphtheria vaccines (143 doses).

We estimated the overall incidence of recurrent GBS by identifying and confirming individuals with recurrent GBS. Out of the 896 cases initially suspected as having GBS, 37 individuals initially appeared in the electronic database as having multiple episodes of GBS. Chart review and further neurologist adjudication determined that 11 (29.7%) of these were eventually diagnosed as CIDP, and 20 (54.1%) were either not recurrent (ie, the diagnosis was documented later, but turned out to be referring to the history of the earlier episode) or not confirmed to be GBS. The remaining 6 individuals (1.1% of the group of 550 confirmed cases) were confirmed as having recurrent GBS; these 6 individuals each had only 1 episode of recurrent GBS. There were 3974 person-years of follow-up in the 550 GBS patients after the confirmed diagnosis of GBS. The calculated rate of recurrence of GBS was 1.5 per 1000 person-years (95% Poisson CI, .6–3.3). Table 2 shows time to recurrence for the recurrent cases. Among the 6 individuals with confirmed GBS recurrence, only 1 had any vaccine exposure within the year prior to the recurrent GBS episode. The vaccine exposure was a single dose of measles-mumps-rubella administered 4 months prior to the onset of the recurrent GBS episode.

Of the 550 cases of GBS, 18 (3.3%) had the initial onset within 6 weeks of TIV. This is the group for which the ACIP recommends caution for influenza revaccination. These 18 people were less likely to have received further influenza vaccines than those who developed GBS with no temporal association with TIV (2 [11%] of the 18 received subsequent influenza vaccines vs 105 of 1053 [20%] of those who developed GBS not in relation to TIV), but the difference was not significant (P = .6 by Fisher exact test). None of the GBS cases followed receipt of live intranasal influenza vaccine.

Among the 107 individuals with a previous diagnosis of GBS who received a total of 405 doses of TIV, there were no cases of recurrent GBS within the year following TIV (95% binomial CI, 0–.91 per 100 doses). None of the 18 GBS cases which originally followed TIV, including the 2 with subsequent TIV administration, had a recurrence of GBS.

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**Table 1. Vaccines Given to People After the Diagnosis of Guillain-Barré Syndrome (GBS), Northern California Kaiser, 1995–2006 (Total Number of GBS Cases N = 550)**

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>N</th>
<th>Percent</th>
<th>Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trivalent injectable influenza</td>
<td>405</td>
<td>41.0</td>
<td>107</td>
</tr>
<tr>
<td>Pneumovax</td>
<td>151</td>
<td>15.3</td>
<td>132</td>
</tr>
<tr>
<td>Tetanus diphtheria</td>
<td>136</td>
<td>13.8</td>
<td>126</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>78</td>
<td>7.9</td>
<td>53</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>42</td>
<td>4.3</td>
<td>30</td>
</tr>
<tr>
<td>Combined MMR</td>
<td>19</td>
<td>1.9</td>
<td>18</td>
</tr>
<tr>
<td>Injectable polio</td>
<td>17</td>
<td>1.7</td>
<td>16</td>
</tr>
<tr>
<td>Tetanus, reduced diphtheria, reduced acellular pertussis</td>
<td>43</td>
<td>4.4</td>
<td>43</td>
</tr>
<tr>
<td>Diphtheria, tetanus, acellular pertussis</td>
<td>11</td>
<td>1.1</td>
<td>11</td>
</tr>
<tr>
<td>Zoster</td>
<td>10</td>
<td>1.0</td>
<td>10</td>
</tr>
<tr>
<td>Injectable typhoid</td>
<td>10</td>
<td>1.0</td>
<td>9</td>
</tr>
<tr>
<td>Meningococcal conjugate</td>
<td>7</td>
<td>0.7</td>
<td>7</td>
</tr>
<tr>
<td>Meningococcal polysaccharide</td>
<td>8</td>
<td>0.8</td>
<td>6</td>
</tr>
<tr>
<td>Other*</td>
<td>52</td>
<td>5.3</td>
<td>36</td>
</tr>
<tr>
<td>Any vaccine</td>
<td>989</td>
<td>100</td>
<td>279</td>
</tr>
</tbody>
</table>

*Each with fewer than 10 (1%) total.

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**Table 2. Characteristics of Recurrent Guillain-Barré Syndrome, Northern California Kaiser, 1995–2006**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Years to Recurrence</th>
<th>1st Episode</th>
<th>2nd Episode</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age</td>
<td>Illness</td>
<td>Age</td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>11.0</td>
<td>Respiratory</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>1.8</td>
<td>Respiratory</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>13.2</td>
<td>Respiratory</td>
<td>66</td>
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<tr>
<td>4</td>
<td>F</td>
<td>40.0</td>
<td>None</td>
<td>66</td>
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<tr>
<td>5</td>
<td>F</td>
<td>2.9</td>
<td>GI</td>
<td>28</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>2.9</td>
<td>Respiratory</td>
<td>52</td>
</tr>
</tbody>
</table>

Abbreviation: GI, gastrointestinal.
DISCUSSION

The ACIP strives to make vaccine recommendations based on available evidence. In the absence of evidence, the ACIP has chosen to be cautious in their recommendations to not vaccinate persons with a history of GBS following previous influenza vaccination who are also at low risk of influenza illness complications. Contributing to the knowledge of the risk of GBS recurrence after revaccination will support the work of advisory committees such as ACIP. In our series, the overall incidence rate of GBS of 1.47 per 100 000 person-years was consistent with rates of 0.4–4 per 100 000 person-years found worldwide, and confirms tighter estimates in European studies of 1.2–1.9 per 100 000 person-years [4, 5]. We found that patients diagnosed with GBS subsequently received multiple vaccines of various types, including influenza vaccines. With over 30 million person-years of follow-up over the study period and nearly 1000 vaccines administered after a diagnosis of GBS (including over 400 influenza vaccinations), we did not observe a single recurrent case of GBS that could be considered associated with vaccination. Based on this observation, it appears that vaccination does not increase the risk of recurrent GBS, although our insufficient sample size detracts from the complete confidence we have for this conclusion. Because recurrent GBS is so rare and our study was small in size, we were only able to rule out a recurrence risk of GBS greater than about 1 per 100 doses of TIV (our upper CI limit was .91 per 100).

We identified only 18 cases (3.3% of the total) that would potentially be considered at higher risk of recurrence because they originally experienced onset of GBS within 6 weeks of TIV. The paucity of data does not allow us to evaluate the ACIP recommendation that GBS patients who developed the condition within 6 weeks of an influenza vaccine should not be revaccinated unless they have a compelling need.

Limitations of our study included reliance on inpatient diagnoses to identify GBS cases. It is possible that we could have detected more cases if we had used the outpatient databases as well. However, we think it would be unusual in our practice setting for GBS to be treated solely as an outpatient, particularly since patients often receive plasmapheresis, which is generally done as an inpatient procedure. Another limitation is the possibility that members received vaccines outside of KPNC. However, for the reasons cited above, we think that the vast majority of vaccines of all types are captured by our immunization tracking system.

In conclusion, we found no evidence that vaccination is associated with recurrent GBS. We also did not observe any recurrent GBS in the 18 GBS cases that initially occurred within 6 weeks following receipt of influenza vaccine; however, we did not have enough power to evaluate an association of repeat influenza vaccination and recurrent GBS. It may not be possible to obtain the power to rule out this association, based on the rarity of both the disease and revaccination in GBS cases.

Notes

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Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


