

# 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.

*Arch Intern Med.* 2006;166:1301-1304

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**F**OLLOWING REPORTS OF AN INCREASED RISK OF Guillain-Barré syndrome (GBS) after immunization with the 1976-1977 A/New Jersey ("swine influenza") vaccine,<sup>1</sup> there has been continued interest in whether other immunizations do increase the risk of GBS. In one study, the reported attributable risk of GBS associated with the swine influenza vaccine was as high as 1 case per 100 000 vaccinations.<sup>1</sup> In one subsequent epidemiological study in the United States, there was a possible increase in risk of 1 case of GBS per 1 million persons who were immunized with the influenza vaccines that were developed subsequently.<sup>2</sup> The relative risk (RR) of GBS associated with influenza vaccine in this later study, after age, sex, and vaccine season were adjusted for, was 1.7 (95% confidence interval [CI], 1.0-2.8).<sup>2</sup> In 2004, an Institute of Medicine review stated that the evidence concerning a relationship between influenza vaccines other than the swine influenza vaccine was inconclu-

sive.<sup>3</sup> We used the General Practice Research Database (GPRD) of the United Kingdom to estimate the incidence of GBS in a large population registered in primary care in the United Kingdom. For each GBS case, we determined whether the date of diagnosis took place within the 6-week period (42 days) of immunization that Lasky et al<sup>2</sup> used to define vaccine-associated GBS.

## METHODS

Data were obtained from the GPRD, whose Scientific and Ethical Advisory Group approved the study protocol. The GPRD is a large database that includes data from several hundred general (family) practices in the United Kingdom. The GPRD data are subject to quality checks, and when the data are of a quality that is high enough to be used in research, they are said to be *up to standard*.<sup>4</sup> We analyzed data for all 253 practices that continuously provided up-to-standard data between January 1, 1992, and

**Table 1. Age- and Sex-Specific and Age-Standardized Incidence Rates of Guillain-Barré Syndrome per 100 000 Population: Data for 1992 to 2000 From 253 General Practices in the United Kingdom**

Age Group, y	Registered Population (Person-Years at Risk)	No. of Cases	Incidence Rate per 100 000 Person-Years (95% Confidence Interval)
<b>Women</b>			
0-14	1 425 487	6	0.42 (0.15-0.92)
15-24	927 393	10	1.08 (0.52-1.98)
25-34	1 261 361	14	1.11 (0.61-1.86)
35-44	1 162 115	15	1.29 (0.72-2.13)
45-54	1 078 998	13	1.21 (0.64-2.06)
55-64	825 851	19	2.30 (1.39-3.23)
65-74	751 444	14	1.86 (1.02-3.13)
75-84	550 431	14	2.54 (1.39-4.27)
85-100	232 651	2	0.86 (0.10-3.11)
Age-standardized rate all ages	...	107	1.22 (0.98-1.46)*
<b>Men</b>			
0-14	1 503 578	7	0.47 (0.19-0.96)
15-24	947 824	6	0.63 (0.23-1.38)
25-34	1 264 460	11	0.87 (0.43-1.56)
35-44	1 201 137	12	1.00 (0.52-1.75)
45-54	1 112 102	22	1.98 (1.24-3.00)
55-64	826 366	26	3.15 (2.05-4.61)
65-74	647 085	25	3.86 (2.50-5.70)
75-84	350 659	10	2.85 (1.37-5.25)
85-100	88 663	2	2.26 (0.27-8.14)
Age-standardized rate all ages	...	121	1.45 (1.19-1.72)*
<b>Total</b>	<b>16 157 605</b>	<b>228</b>	<b>1.33 (1.15-1.50)*</b>

\*European standard population used for reference.

December 31, 2000. The study period was chosen to optimize the number of practices contributing data in each year of the study, as a number of practices withdrew from the database after 2000. For each year of the study, we calculated the number of registered patients by age, sex, and practice as the denominator by summing all person-time at risk. We obtained numerator data by searching the medical records of each registered subject for the medical diagnostic codes for GBS or infective polyneuritis. If a case had a diagnostic code recorded on 1 or more occasions, the date of the first recorded medical code was considered the date of onset. In the GPRD, each recorded medical diagnostic code is allocated a line in the record, and no distinction is made between primary and secondary diagnoses. Numerator and denominator data were aggregated by sex and 5-year age group in order to estimate age- and sex-specific rates, and CIs were estimated from the Poisson distribution.<sup>5</sup> The age-standardized rate for all ages was estimated using the European standard population for reference, and CIs were estimated using the normal approximation method.<sup>5</sup>

To evaluate whether immunization was associated with the onset of GBS, we searched the clinical data of each case for recorded instances of any immunization. This search encompassed all specific active immunizations and vaccinations, including those listed in section 14.4 of the *British National Formulary*,<sup>6</sup> as well as unspecified immunizations, but administration of immunoglobulin was not included. (Details of the codes used are available from the authors.) It has been shown that immunizations in the GPRD may sometimes be recorded more than once, eg, a medical code and a prescription, a few

days apart.<sup>7</sup> We therefore considered all codes recorded within a 7-day period to represent a single immunization, with the date of immunization taken as the earliest recorded code. The same results were obtained if a 3-day interval was used instead of a 7-day interval. We used the self-controlled case series method to estimate the RR from immunization.<sup>8</sup> The method was modified by aggregating separately, for each patient, all time at risk after immunization and all time not at risk after immunization. The study period for each case subject was considered to start January 1, 1992, or at the beginning of the up-to-standard period, whichever was later. The end of the study period was the date of diagnosis of GBS. The diagnosis date was used for censoring because patients who have had GBS may be advised not to have further immunizations. The time at risk was considered to be within 42 days of an immunization, according to the method used by Lasky et al.<sup>2</sup> Each patient's record was then divided into the days at risk after immunization and the days not at risk after immunization. We determined whether the date of diagnosis took place during the time at risk. Poisson regression was used to estimate the RR of diagnosis in the 42 days after immunization compared with diagnosis at any other time by fitting the patient identifier as a random effect using the "xtpoisson" command in Stata version 9.1.<sup>9</sup> Analyses were adjusted for sex and age as a continuous variable.

## RESULTS

Age-specific and age-standardized incidence rates are shown in **Table 1**. The mean number of registered patients was 1.8 million, with 16.2 million person-years at risk during the study period. There were 228 cases of GBS, including 107 women and 121 men.

There were 114 persons who received no immunizations and 114 persons who received a total of 270 immunizations (range, 1-9 per subject) during the study period (**Table 2**). In total, there were 28.78 person-years of time at risk within 42 days of vaccination and 934.65 person years not associated with immunization. Seven of 228 GBS cases had a first diagnostic code that was recorded up to and including 42 days after immunization. The adjusted RR was 1.03 (95% CI, 0.48-2.18;  $P = .94$ ). This estimated RR is consistent with a similar risk of GBS after immunization as compared with other times. However, the CIs are wide and do not exclude a halving or doubling of the risk. If the period at risk after immunization was extended to 84 days, then there were 14 GBS cases with onset during this period, with an adjusted RR of 1.11 (95% CI, 0.65-1.91;  $P = .71$ ).

For the 7 GBS cases in which the onset occurred within 42 days of immunization, the immunizations associated with GBS diagnosis were influenza ( $n = 3$ ), hepatitis A and hepatitis B ( $n = 1$ ), tetanus ( $n = 1$ ), meningococcal disease ( $n = 1$ ), and tetanus, polio, and diphtheria ( $n = 1$ ). Forty-two subjects who were later diagnosed as having GBS had a total of 119 episodes of influenza immunization during the study period, but only 3 episodes took place within 42 days before GBS diagnosis. The adjusted RR of GBS within 42 days after influenza immunization was 0.99 (95% CI, 0.32-3.12;  $P = .99$ ) (Table 2).

## COMMENT

Incidence studies of GBS in the United Kingdom, based on chart review, have calculated a similar incidence for

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

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

\*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.

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.<sup>10</sup> 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).<sup>10,11</sup> 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.<sup>12-18</sup> 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.<sup>19</sup>

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,<sup>20-22</sup> including immunizations.<sup>7,23</sup> 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 al<sup>23</sup> 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.<sup>24</sup> There have been few population-based studies relating GBS incidence to immunization. Lasky et al<sup>2</sup> 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 in-

fluenza 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.<sup>25</sup> In the study of Lasky et al,<sup>2</sup> 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.<sup>2</sup> We acknowledge that our study is too small to confirm or refute the small increase in risk calculated by Lasky et al,<sup>2</sup> 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 Medicine<sup>3</sup> 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.<sup>26,27</sup> 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.<sup>28</sup>

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,<sup>1,2</sup> and different vaccines may be in use in different countries during similar periods.

Accepted for Publication: March 31, 2006.

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Financial Disclosure: None.

Funding/Support: This study was supported by the Guy's and St Thomas' Charity, London, England.

Role of the Sponsor: The funding body played no part in the design, conduct, or analysis of the study.

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