Lack of Association of Guillain-Barré Syndrome With Vaccinations

Roger Baxter,[1] Nandini Bakshi,[2] Bruce Fireman,[1] Edwin Lewis,[1] Paula Ray,[1] Claudia Vellozzi,[3] and Nicola P. Klein[1]

[1]Kaiser Permanente Vaccine Study Center and [2]The Permanente Medical Group, Oakland, California; and [3]Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, Georgia

(See the Editorial Commentary by Salmon and Halsey on pages 205–7.)

Background. Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy, thought to be an autoimmune process. Although cases of GBS have been reported following a wide range of vaccines, a clear association has only been established with the 1976 H1N1 inactivated influenza vaccine.

Methods. We identified hospitalized GBS cases from Kaiser Permanente Northern California (KPNC) from 1995 through 2006. The medical record of each suspected case was neurologist-reviewed according to the Brighton Collaboration GBS case definition; only confirmed cases were included in the analyses, and cases of Miller Fisher syndrome were excluded. Using a case-centered design, we compared the odds of vaccination in the 6 and 10 weeks prior to onset of GBS to the odds of vaccination during the same time intervals in all vaccinated individuals in the entire KPNC population.

Results. We confirmed 415 incident cases of GBS (including Brighton levels 1, 2, and 3) during the study period (>30 million person-years). Incidence peaked during the winter months. The odds ratio of influenza vaccination within a 6-week interval prior to GBS, compared with the prior 9 months, was 1.1 (95% confidence interval [CI], .4–3.1). The risk in the 6-week interval compared to the prior 12 months for tetanus diphtheria combination, 23-valent pneumococcal polysaccharide, and for all vaccines combined was 1.4 (95% CI, .3–4.5), 0.7 (95% CI, .1–2.9), and 1.3 (95% CI, .8–2.3), respectively.

Conclusions. In this large retrospective study, we did not find evidence of an increased risk of GBS following vaccinations of any kind, including influenza vaccination.

Keywords. Guillaine-Barré syndrome; vaccine; immunizations; influenza; safety.

Guillain-Barré syndrome (GBS) is an acute inflammatory polyradiculoneuropathy affecting primarily motor neurons, which in severe cases can progress to complete paralysis and even death. Estimates of GBS incidence are in the range of 1–2 cases per 100 000 person-years worldwide, and increase with age [1, 2]. Although the causes are unknown, GBS is thought to be an autoimmune process that is triggered by antigenic stimulation [3, 4], resulting in demyelination and destruction of peripheral nerves.

In many cases, the syndrome is temporally associated with an infectious disease; most published case series report that approximately two-thirds of all cases are preceded by a gastrointestinal or respiratory infection within the prior 3 months [1]. *Campylobacter enteritis* is the most common trigger, but influenza [5], cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus (HIV), and *Mycoplasma pneumoniae*, among others, have been implicated as well [4, 6, 7].

The 1976 A/New Jersey swine influenza vaccine was associated with a small but significant increase in the number of GBS cases in the 6 weeks following vaccination [8–10]. Several studies assessing the risk of GBS following seasonal influenza vaccines since 1976 have shown either no risk or a very small attributable risk of

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Correspondence: Roger Baxter, MD, Kaiser Permanente Vaccine Study Center, 1 Kaiser Plaza, 16B, Oakland, CA 94612 (roger.baxter@kp.org).

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approximately 1 case per million doses [9–13]. Recently, studies assessing the risk of GBS following the 2009 H1N1 monovalent influenza vaccines in the United States found an attributable risk ranging from 1 to 5 per million doses [14]. Other than case reports, no conclusive evidence has clearly linked GBS with other vaccines [14, 15–22]. The Advisory Committee on Immunization Practices currently cautions against revaccinating persons who developed GBS within 6 weeks of influenza vaccination [23].

The purpose of this study was to evaluate the possible relationship between GBS and vaccinations, using retrospective data accumulated over multiple years from a large integrated healthcare plan.

METHODS

Study Population

Kaiser Permanente of Northern California (KPNC) is an integrated healthcare delivery system with a membership of >3 million persons in 2006. KPNC provides services in >15 counties and operates >40 outpatient clinics and 18 hospitals throughout Northern California. The member population is generally representative of the general population in the Northern California region with regard to age, race, and sex, although, as an insured population, it underrepresents persons on the lower end of the economic spectrum [24]. 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. Hospitalizations and emergency department visits that occur outside the health plan are captured in databases covering claims and referrals. Laboratory tests, medications, and most other services are covered by the plan, and provided at Kaiser Permanente facilities. Vaccinations are provided at no additional cost to members, are almost all received within the system [25], and are recorded in a dedicated immunization tracking system. Influenza vaccines in particular are delivered conveniently during the season to boost uptake, and this has the added benefit of ensuring that almost all influenza vaccines are given within the health plan [25].

Case Ascertainment

We identified all individuals from 1994 through October 2006 in KPNC with a first occurrence of GBS using the *International Classification of Diseases, Ninth Revision* (*ICD-9*) code 357.0. After reviewing a sample of outpatient GBS diagnoses, we determined that almost all outpatient visit diagnoses were for follow-up care of GBS and did not indicate an incident case (data not shown). Therefore we limited the study to hospitalized cases.

All identified cases underwent chart review by trained medical records analysts (MRAs) using a chart abstraction form designed to validate the diagnosis and onset date of GBS and to capture information regarding prior infections. Cases were rejected by the MRA if there was no reference to GBS in the chart, or if GBS was clearly ruled out by the providers. Remaining cases were subsequently reviewed by a neurologist and classified as level 1, 2, or 3 according to the Brighton Collaboration case definition criteria for GBS [26]. Level 1 denotes a laboratory-confirmed case, level 2 has partial laboratory data and is considered a probable case, and level 3 meets only clinical criteria and is considered a possible case. To meet any level of the Brighton case definition, the presence of weakness was required; therefore, GBS variants such as Miller Fisher syndrome and pure sensory GBS were excluded.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) presents with signs and symptoms similar to GBS but has a chronic or relapsing course, rather than the monophasic course seen with GBS [27]. Cases that were initially classified as GBS based on acute onset, but eventually identified as CIDP due to a relapsing course, were excluded from the initial data extraction.

Case-Centered Design and Analyses

The case-centered study design is detailed elsewhere, and has been used in other vaccine safety and effectiveness studies [28–30]; we will review here briefly. This method is best suited to outcomes hypothesized to have an acute onset during a transient period of increased risk after exposure, called the "risk interval." The timing of the risk interval is hypothesized from prior studies and biologic plausibility. For our GBS analyses, we chose risk intervals of 6 and 10 weeks after vaccination, based on prior investigations [8, 31]. Case-centered analyses look back from the date of onset of the adverse event and determine whether there is clustering of vaccinations (exposures) in the risk interval prior to onset of the adverse event. We limited the study population to people who received some kind of vaccine in the year prior to the onset of GBS, because the unvaccinated population may be very different, in ways that may not be measured from the vaccinated [32, 33]. For influenza vaccines, we limited the observation time to 9 months to minimize inclusion of the prior year's vaccines. We calculated the observed odds that vaccination of cases occurred within the risk interval prior to GBS onset and compared this to the expected odds derived from the entire Kaiser Permanente population. The expected odds were computed from the proportion of the vaccinated health plan population, matched for age and sex, that was vaccinated with that same vaccine within the same risk interval. Odds ratios and confidence intervals (the odds of vaccination inside vs outside the risk interval) were obtained using a logistic regression model with a case-centered specification [30, 32]. The method adjusts fully for seasonality because each individual case has its own expected proportion in the risk interval, based on its onset date. The relative risk of GBS during the risk

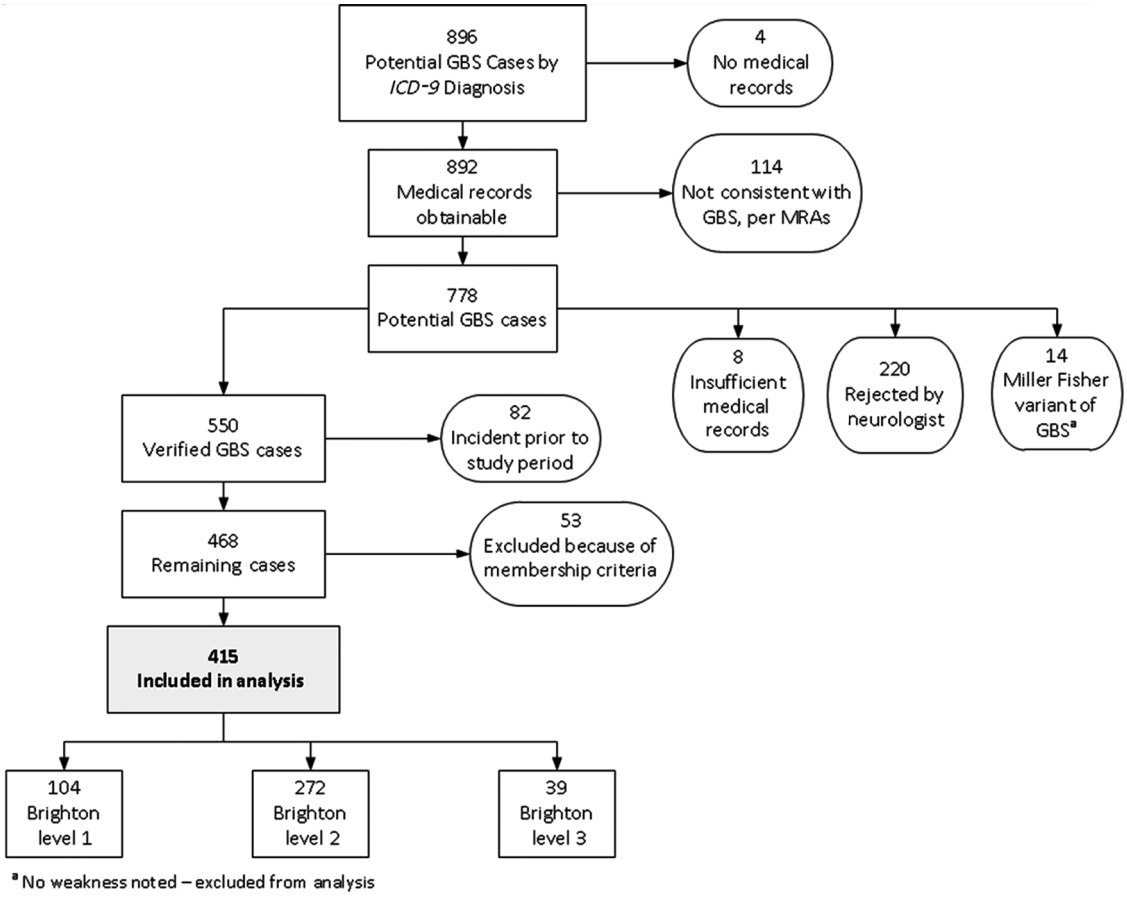

Figure 1. Determination of Guillain-Barré syndrome study cases, Kaiser Permanente Northern California, 1994–2006. Abbreviations: GBS, Guillain-Barré syndrome; *ICD-9, International Classification of Diseases, Ninth Revision*; MRAs, medical records analysts.

interval compared to the rest of the observation period is estimated by the odds ratio of the case-centered logistic regression model. Separate analyses were conducted for each type of vaccine and for "any" vaccine (persons with a vaccine of any type).

Cohort Analysis

In addition to the case-centered analysis, we performed a Poisson regression evaluating the relationship between trivalent inactivated influenza vaccine (TIV) and GBS, adjusting for age in decades, month, year, and sex, using cases from 1994 to 2005 (years for which we had complete ascertainment). Because of the significant differences between vaccinated and unvaccinated individuals, we included only persons vaccinated in the prior 9 months in the analysis. We summarized all vaccinated follow-up time among KPNC members from 1994 to 2006 as vaccinated with TIV within 6 weeks of GBS onset, or vaccinated >6 weeks before GBS onset in the same influenza season (up to 9 months).

Seasonality

Prior to the analysis, we hypothesized that GBS might have seasonal variation, and performed a Poisson regression analysis, using the count of events in a month as a function of whether or not they occurred in the winter (December through March), adjusting for the number of days in each month. We also graphed the number of cases per month over the study period.

RESULTS

Case Determination

We identified 896 potential cases of GBS by *ICD-9* discharge diagnosis codes during our 13-year ascertainment period (1994–2006; Figure 1). Of the 892 potential cases for which medical records were available, 114 were rejected by the MRAs, and 242 were rejected by the reviewing neurologist, either as incompatible with GBS or because of not enough information or no weakness found in chart review. Of the 550 confirmed cases, 415 were incident within the study period, and patients were KPNC members at the time of GBS onset, so were eligible for inclusion in the analysis. Of the 415 cases, 104 were classified as Brighton level 1, 272 cases as level 2, and 39 cases as

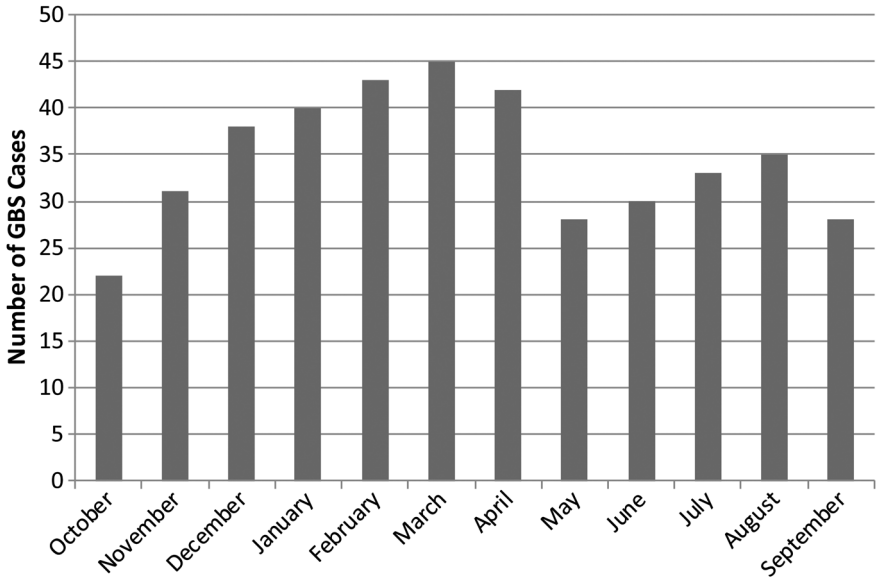

Figure 2. Month of onset of Guillain-Barré syndrome, Kaiser Permanente Northern California, 1994–2006 (N = 415).

level 3. Cases classified into all 3 Brighton levels were included in the analyses.

Characteristics of Confirmed Cases

The 415 confirmed cases of GBS were observed during a follow-up time of 32 734 642 person-years, for a calculated incidence rate of 1.27 cases per 100 000 person-years. A majority of GBS patients were male (58.6%), and the mean age was 48.5 years (range, 5–87 years). In the 90 days preceding the onset of GBS, 277 (66.7%) cases had a respiratory or gastrointestinal illness documented in the medical record; 159 cases (38.3%) had a respiratory illness, 77 cases (18.6%) had a gastrointestinal illness, and 41 cases (9.9%) had both.

There were greater numbers of GBS cases in the winter months (November through April), peaking in March (Figure 2). Our seasonality analysis, using December through March (our prior hypothesis), found that GBS was significantly more likely to occur in the winter, with a relative risk of 1.5, compared to the nonwinter months ($P = .003$).

Vaccination Prior to GBS onset

Among the 415 patients, only 25 had received any vaccine in the 6 weeks prior to GBS onset. Vaccines received included TIV (n = 18), 23-valent polysaccharide pneumococcal vaccine (n = 2), tetanus-diphtheria combination vaccines (n = 3), hepatitis A (n = 2), and hepatitis B (n = 1) (Table 1). The remaining 390 GBS patients received no vaccines in the 6 weeks before onset of disease.

Noninformative Cases

One hundred five patients had received TIV within the preceding 9 months, 13 of whom had received the vaccine between late April and early September. These 13 cases did not contribute to the case-centered analysis of influenza vaccines, because the odds of vaccination during these summer months were effectively zero. There was 1 case within 9 months of live attenuated influenza vaccine and 1 case within 1 year of Japanese encephalitis vaccine. both of which were similarly noninformative in either risk period, because no similar KPNC members had received the same vaccine in the time frame.

Case-Centered Analyses

Case-centered analyses of vaccine–GBS associations are shown in Table 2. There was no significant association between TIV, 23-valent polysaccharide pneumococcal, tetanus/diphtheria, inactivated polio, hepatitis A, or hepatitis B vaccines, or "any" vaccine (all vaccines combined) and onset of GBS using either a 6- or 10-week risk interval. Using the 10-week interval, the odds ratio estimate for injectable typhoid was elevated (OR = 10.75; 95% confidence interval [CI], 1.14–285.04; $P =$ 0/038). Only vaccines that had at least 1 case during the risk interval are presented in the table. For vaccines given mainly in childhood, there were no GBS cases in the risk interval following vaccination, despite the doses given: oral polio (1.2 million doses); measles-mumps-rubella (1.6 million); conjugated pneumococcal (1.3 million); live attenuated influenza (69 000); diphtheria-tetanus-acellular pertussis (1.9 million); varicella (764 000),

Table 1. Vaccines Given Within 6 Weeks Prior to Guillain-Barré Syndrome Onset, Kaiser Permanente Northern California, 1994–2006 (n = 25)

Vaccine(s)	Days Between Vaccine and Onset of GBS	Age, y	Sex
PPV-23	1	52	M
TIV	1	28	M
TIV	3	65	F
Td	8	36	M
I-typhoid, hepatitis A	9	81	M
Td, TIV	12	62	F
PPV-23, TIV/IPV, JE	14/18	68	F
TIV	14	65	M
TIV	14	65	M
TIV	15	80	M
TIV	18	87	M
Hepatitis A	18	10	M
TIV	21	57	M
TIV	21	37	F
TIV	23	61	M
TIV	24	60	M
TIV	24	59	M
TIV	25	74	M
Tdap	25	61	F
TIV	29	62	M
TIV	31	59	M
TIV	35	76	F
Hepatitis B	35	52	M
TIV	36	66	M
Td	41	57	M

Abbreviations: GBS, Guillain-Barré syndrome; IPV, inactivated (killed) polio vaccine; I-typhoid, injectable (killed) typhoid vaccine; JE, Japanese encephalitis; PPV-23, 23-valent pneumococcal polysaccharide vaccine; Td, combination tetanus and reduced diphtheria vaccine; Tdap, tetanus, reduced diphtheria, and acellular pertussis vaccine; TIV, trivalent inactivated influenza vaccine.

Haemophilus-diphtheria-tetanus-pertussis (525 000); and *Haemophilus* B vaccines (1.2 million). For rabies vaccine (13 000 doses), there was 1 case of GBS, 7.5 weeks after vaccination.

Cohort Analysis of GBS and TIV

The secondary cohort analysis found no significant difference in the GBS incidence rate in people vaccinated 6 weeks prior to GBS onset compared with >6 weeks to 9 months prior to GBS onset (Table 3).

DISCUSSION

In this study spanning 13 years and >30 million person-years, using a case-centered method to control for seasonality and other time-varying confounders, we found no evidence of an increased risk of GBS following any vaccination, as well as all vaccinations combined. Only 25 patients with GBS had received any vaccine within the prior 6 weeks. We found no cases of GBS following childhood vaccines.

We identified 18 cases of GBS within 6 weeks of TIV, during which time we administered 6 841 901 TIV immunizations. Of these, 13 had an antecedent respiratory or gastrointestinal illness, known risk factors for GBS [4, 6]. If we were to attribute causation of all 5 cases having no antecedent illness to TIV, using the upper limit of the 95% CI, we can rule out >1 excess case of GBS per 585 000 TIV doses. For other vaccinations (non-TIV), there were 7 cases within 6 weeks of a vaccine, of which only 1 patient had no prior illness. Using the above logic, we are able to rule out >1 excess case of GBS in 3.8 million non-TIV vaccine doses.

Our calculated GBS incidence of 1.3 per 100 000 person-years is comparable to prior studies that have shown rates from 1 to 4 per 100 000 person-years [34]. The predominance of males and rate of prior illness (67%) are also consistent with prior reports on GBS [6, 34]. We found a seasonal pattern, with a higher incidence in late winter months, consistent with some, but not all, prior studies [1, 35].

Concerns about the association of GBS with vaccines have flourished since an increased risk was found following the 1976 swine influenza vaccine campaign [8, 31]. Since that time, multiple studies failed to show an increased rate of GBS with vaccination [11–13, 36–38], and a recent Institute of Medicine (IOM) review of 21 influenza studies concluded that there was insufficient evidence to determine a causal link between influenza vaccines and GBS [19]. However, 2 studies showed a slight increase in relative risk (both statistically significant) for GBS following influenza vaccines, and both noted a potential attributable risk of approximately 1 per million vaccinations [9, 13]. More recently, Greene et al [21], while finding no increased risk following receipt of TIV, noted a relative risk of 4.4 (95% CI, 1.3–14.2) following the 2009 monovalent H1N1 vaccination. Cases of GBS have been noted following receipt of multiple vaccines, including tetanus [16], rabies [6], polio, and hepatitis B [17], but to date there has been insufficient evidence to show that these cases were causally related to the immunizations. In 2005–2006, data from the Vaccine Adverse Event Reporting System, a US passive reporting system, identified a possible increased risk of GBS in teenagers following a new meningococcal vaccine [39]; subsequent well-designed epidemiologic studies have not found an association [40]. The IOM review concluded that there was also inadequate evidence of an association between GBS and measles, mumps, rubella, varicella, hepatitis A or B, human papillomavirus, and diphtheria toxoid, tetanus toxoid, or acellular pertussis–containing vaccines [19]; our study provides evidence against an association of GBS with

Table 2. Odds Ratio of Vaccination in a 6- or 10-Week Risk Interval Before Onset of Guillain-Barré Syndrome, Using a Case-Centered Analysis Design

Risk Interval	Vaccine	Cases Vaccinated Within Observation Period	Cases Vaccinated Within Risk Interval	Expected No. of Cases Within Risk Interval	Odds Ratio of Vaccination in Risk Interval	95% CI	*P* Value
6 wk	IPV	2	1	0.24	7.19	(.18–281.03)	.245
	Tdap	1	1	0.25	. . .	(.16 to NE)	.249
	PPV-23	18	2	2.63	0.72	(.11–2.87)	.722
	I-typhoid	4	1	0.43	2.78	(.11–26.11)	.425
	Hepatitis A	8	2	1.05	2.22	(.30–10.63)	.36
	Hepatitis B	12	1	2.08	0.43	(.02–2.56)	.455
	Td	20	3	2.22	1.43	(.33–4.56)	.558
	TIV	92	18	17.6	1.11	(.39–3.08)	.83
	Any[a]	153	25	21.31	1.34	(.77–2.27)	.285
10 wk	IPV	2	1	0.39	4.15	(.11–163.38)	.39
	Tdap	1	1	0.38	. . .	(.09 to NE)	.377
	PPV-23	18	2	3.88	0.44	(.07–1.72)	.281
	I-Typhoid	4	3	0.88	10.75	(1.14–285.04)	.038
	Hepatitis A	8	3	1.86	2	(.39–8.74)	.366
	Hepatitis B	12	1	3.19	0.24	(.01–1.46)	.15
	Td	20	4	3.6	1.14	(.32–3.29)	.783
	TIV	99	29	29.03	0.99	(.33–2.70)	.991
	Any[a]	153	37	35.47	1.1	(.66–1.79)	.688

Only vaccines with at least 1 case in the risk interval are presented, 1994–2006 (N = 415).

Abbreviations: CI, confidence interval; IPV, inactivated (killed) polio vaccine; I-typhoid, injectable (killed) typhoid vaccine; NE, not estimable; PPV-23, 23-valent pneumococcal polysaccharide vaccine; Td, combination tetanus and reduced diphtheria vaccine; Tdap, tetanus, reduced diphtheria, and acellular pertussis vaccine; TIV, trivalent inactivated influenza vaccine.

[a] Any is any person with a vaccine of any kind.

these vaccines. We were unable to evaluate the risk of GBS following the 2009 H1N1 vaccines as our study period ended prior to 2009.

Selecting the appropriate risk interval can be challenging: Because GBS occurred up to 10 weeks following the 1976 swine flu vaccine, there were concerns that the shorter (6-week) interval might not be as sensitive, and may misclassify some cases. However, shorter risk intervals have greater power to detect an association if there is one that is concentrated in the short interval [26, 36, 41]. When we used the 10-week interval, injectable typhoid vaccine resulted in a statistically significant increased risk of GBS, with a *P* value of .04. However, using the

Table 3. Number of Guillain-Barré Syndrome Cases and Crude Rates per 100 000 Person-Years

	Crude Rates			Adjusted Rates: Poisson Regression, Comparing GBS Within 6 wk of Vaccine to 6 wk–9 mo		
TIV Vaccination Status	Cases/Person-Years	Rate of GBS per 100 000 Person-Years	95% CI	Relative Rate	95% CI	*P* Value
GBS within 6 wk of vaccination	18/656 443	2.74	1.63–4.33	1.3	.75–2.26	.35
GBS onset 6 wk to 9 mo after vaccination	86/3 561 122	2.41	1.93–2.98			

Cohort analysis of Guillain-Barré syndrome after trivalent inactivated influenza vaccine: Poisson regression results, adjusting for age in decades, month, year, and sex. Kaiser Permanente Northern California population, 1994–2006 (N = 415).

Abbreviations: CI, confidence interval; GBS, Guillain-Barré Syndrome; TIV, trivalent inactivated influenza vaccine.

6-week interval, there was no significant increase in risk. There were 4 GBS cases with injectable typhoid in the prior year: 1 at 9 days, 2 at about 9 weeks, and 1 at nearly 1 year. The onset of both cases that occurred at 9 weeks (ie, >6 and <10 weeks) was subsequent to travel (India and the Philippines), and both persons had been ill during their trips; in these cases it is probably more likely that GBS was due to infections acquired in travel rather than to the receipt of vaccines. This hypothesis is strengthened by the slight increases in RRs for other travel vaccines, hepatitis A, and injectable polio.

The cohort analysis for assessing an association of GBS following TIV showed a slight increase in the relative risk point estimate of GBS, although this was not statistically significant. This type of analysis does not control as well for time-varying confounders as does the case-centered method, but was provided as a comparison analysis, and also provides estimates of incidence rates. We believe this highlights the benefit of the case- centered analysis, where seasonality is especially well controlled. Our analysis showed that seasonality is an issue with studies of GBS.

Our study has several limitations. Despite many years of review of a very large captured population, we are unable to exclude any possible association between vaccines and GBS. In addition, our reviewer, although not privy to the vaccine history in each case, was aware of the hypothesis, and was able to see if medical providers thought the GBS was caused by a vaccine. This could have influenced the reviewer in some way, though we followed strict Brighton criteria for diagnosis.

In summary, this study did not find any association between influenza vaccine or any other vaccine and development of GBS within 6 weeks following vaccination. Although we had limited power to fully assess the risk of GBS following vaccination due to the rarity of the outcome, the low numbers of GBS cases that were temporally associated with vaccination, coupled with our results, provide reassurance that the risk of GBS following any vaccine, including influenza vaccines, is extremely low.

Notes

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Author contributions. R. B.: study concept, design, supervision, interpretation, and drafting of manuscript. N. B.: review of cases, interpretation of findings, and critical revision of manuscript. B. F.: study design, interpretation of results, critical review of manuscript. E. L.: statistical analyses, study design, data acquisition, review of manuscript. P. R.: supervision of chart review and data acquisition, coordination of chart reviews, oversight of records review forms, manuscript review. C. V.: study design, critical review of manuscript. N. P. K.: supervision, design, critical review of manuscript.

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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.

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