



Practice of Epidemiology

Guillain-Barré Syndrome During the 2009–2010 H1N1 Influenza Vaccination Campaign: Population-based Surveillance Among 45 Million Americans

Matthew E. Wise*, Melissa Viray, James J. Sejvar, Paige Lewis, Andrew L. Baughman, Walter Connor, Richard Danila, Greg P. Giambrone, Christa Hale, Brenna C. Hogan, James I. Meek, Rendi Murphree, John Y. Oh, Arthur Reingold, Norisse Tellman, Susan M. Conner, James A. Singleton, Peng-Jun Lu, Frank DeStefano, Scott K. Fridkin, Claudia Vellozzi, and Oliver W. Morgan

* Correspondence to: Dr. Matthew E. Wise, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Mailstop A-35, Atlanta, GA 30333 (e-mail: cxx4@cdc.gov).

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Because of widespread distribution of the influenza A (H1N1) 2009 monovalent vaccine (pH1N1 vaccine) and the prior association between Guillain-Barré syndrome (GBS) and the 1976 H1N1 influenza vaccine, enhanced surveillance was implemented to estimate the magnitude of any increased GBS risk following administration of pH1N1 vaccine. The authors conducted active, population-based surveillance for incident cases of GBS among 45 million persons residing at 10 Emerging Infections Program sites during October 2009–May 2010; GBS was defined according to published criteria. The authors determined medical and vaccine history for GBS cases through medical record review and patient interviews. The authors used vaccine coverage data to estimate person-time exposed and unexposed to pH1N1 vaccine and calculated age- and sex-adjusted rate ratios comparing GBS incidence in these groups, as well as age- and sex-adjusted numbers of excess GBS cases. The authors received 411 reports of confirmed or probable GBS. The rate of GBS immediately following pH1N1 vaccination was 57% higher than in person-time unexposed to vaccine (adjusted rate ratio = 1.57, 95% confidence interval: 1.02, 2.21), corresponding to 0.74 excess GBS cases per million pH1N1 vaccine doses (95% confidence interval: 0.04, 1.56). This excess risk was much smaller than that observed during the 1976 vaccine campaign and was comparable to some previous seasonal influenza vaccine risk assessments.

Guillain-Barre syndrome; influenza A virus; influenza A virus, H1N1 subtype; influenza vaccines; population surveillance; safety; vaccines

Abbreviations: BRFSS, Behavioral Risk Factor Surveillance System; CI, confidence interval; EIP, Emerging Infections Program; GBS, Guillain-Barré syndrome; NHFS, National 2009 H1N1 Flu Survey; RR, rate ratio.

Editor's note: An invited commentary on this article appears on page 1129.

Guillain-Barré syndrome (GBS) is an uncommon disorder of the peripheral nerves that classically causes ascending limb paralysis and, in severe cases, respiratory failure and death. Although it is incompletely understood, GBS is thought to be an immune-mediated disorder (1). Most persons

with GBS report having experienced an antigenic challenge during the weeks prior to onset of GBS, such as a gastrointestinal or respiratory illness (1). Rarely, GBS may follow vaccination (1, 2). In 1976, the emergence of a swine-origin influenza virus in Fort Dix, New Jersey (influenza A/New Jersey/76 [Hsw1N1]; influenza A/NJ/76 (H1N1) virus) and subsequent concerns about an influenza pandemic prompted the development of a vaccine and rapid mass vaccination of the US population (3). Subsequent studies found a statistically

significant increase in the incidence of GBS among adult vaccinees up to 6 weeks after vaccination (4, 5), with an excess of 8.8 GBS cases per million persons vaccinated; these findings contributed to the decision to halt the national vaccination campaign (3).

In 2009, spread of the pandemic (H1N1) 2009 influenza virus, which was partially of swine origin, prompted rapid development of inactivated and live attenuated influenza A (H1N1) 2009 monovalent vaccines (hereafter referred to collectively as pH1N1 vaccine) for widespread use in the United States and internationally beginning in October 2009 (6). In light of the previous association between GBS and the 1976 vaccine, we implemented surveillance in the United States during 2009–2010 to rapidly monitor the populace for GBS following vaccination.

MATERIALS AND METHODS

Case-finding and definition

Active, population-based surveillance for GBS cases in persons who had an initial health-care encounter between October 1, 2009, and May 31, 2010, was conducted among 44.9 million residents at the 10 sites of the Emerging Infections Program (EIP): California (3 counties), Colorado (5 counties), Connecticut (statewide), Georgia (8 counties), Maryland (statewide), Minnesota (statewide), New Mexico (statewide), New York (statewide, excluding New York City), Oregon (3 counties), and Tennessee (statewide). The EIP was established in 1995 by the Centers for Disease Control and Prevention (7). Each EIP site established a surveillance network comprised of neurologists and other health-care providers that was queried weekly to stimulate reporting of suspected GBS cases; hospital discharge data were also reviewed (*International Classification of Diseases*, Ninth Revision, code 357.0) to capture additional cases not reported through the provider network. Trained surveillance officers reviewed medical records to gather standardized information on patient characteristics, clinical presentation, and medical history for every suspected GBS case. A telephone questionnaire was administered to persons with suspected GBS (or, in rare instances, a proxy) to gather further information about medical and vaccination history. Dates of receipt of pH1N1 vaccine and 2009–2010 seasonal influenza vaccine (hereafter referred to as seasonal vaccine) were recorded from vaccination cards, vaccine registries, or providers administering the vaccine, or via self-report (as recorded in the medical record or telephone interview) if a documented source was not available.

Suspected cases of GBS were evaluated by surveillance officers according to criteria established by the Brighton Collaboration (8), an international organization that develops criteria for adverse events following vaccination (see Web Table 1, which appears on the *Journal's* website (<http://aje.oxfordjournals.org/>)). Patients with confirmed (Brighton levels 1 and 2) and probable (Brighton level 3) GBS were included in the analysis. When surveillance officers could not clearly apply components of the Brighton criteria, an initial review was conducted in consultation with Centers for Disease Control and Prevention subject matter experts.

When this review failed to assign case status, a panel of 4 expert neurologists reviewed de-identified patient charts to make a final determination.

Vaccine coverage and calculation of person-time at risk

The proportions of persons vaccinated with pH1N1 or seasonal vaccine in the EIP catchment counties were estimated using telephone survey data from the Behavioral Risk Factor Surveillance System (BRFSS) and the National 2009 H1N1 Flu Survey (NHFS), using previously published methods to combine estimates from the two surveys (9, 10). BRFSS and NHFS data from October 2009 through June 2010 were used to estimate the cumulative proportion of persons vaccinated at the end of each month from October 2009 (August 2009 for seasonal vaccine) through May 2010. Second-dose coverage for seasonal vaccine among children aged 6 months through 9 years was estimated using only the NHFS. The proportion vaccinated was applied to the surveillance population, obtained from age- and sex-stratified US Census data, to estimate the total number of persons vaccinated.

The amount of person-time exposed to vaccine was assumed to be the total number of vaccinated persons multiplied by a 42-day GBS risk period following vaccination (5). Children under age 10 years who received a second dose of vaccine as recommended by the Advisory Committee on Immunization Practices (11, 12) were allocated an additional 28 days of person-time at risk (the Advisory Committee on Immunization Practices recommended that secondary doses be given 4 weeks after the primary dose, resulting in two 42-day exposure intervals overlapping by 14 days). We excluded exposed person-time accumulated before (for seasonal vaccine) or after (for seasonal vaccine and pH1N1 vaccine) the surveillance period by estimating the number of vaccine doses administered each day during the 6 weeks prior to October 1, 2009 (seasonal vaccine only) and the 6 weeks prior to May 31, 2010 (seasonal vaccine and pH1N1 vaccine). Vaccine doses were apportioned to administration dates using the proportions of daily vaccine administrations recorded at a sample of all private outpatient primary care provider offices in the surveillance population (compiled by SDI Health LLC, Plymouth Meeting, Pennsylvania) (Web Appendix 1, Web Figure 1, and Web Figure 2). Vaccines administered immediately before the beginning or end of the surveillance period were assigned exposed person-time only for that portion of the 42-day window that fell within the surveillance period, since inclusion of exposed person-time outside of the surveillance period would negatively bias exposed rate estimates. We calculated person-time unexposed to vaccine as the total person-time under surveillance minus the person-time exposed to vaccine.

Statistical assessment of excess GBS risk

Categorical variables were compared by pH1N1 vaccine and seasonal vaccine status using Fisher's exact test; 2-sided *P* values less than 0.05 were considered statistically significant. A scan statistic (13) was used to test for clustering of the interval between vaccination and GBS onset during an

84-day window following vaccination; 84 days was selected because scan statistics should be applied to a period at least twice that of the assumed risk window. The observed number of GBS cases was compared with the number of expected cases, which we estimated by applying age-specific GBS background rates to the EIP population. We estimated GBS background rates by modeling published population-based GBS rates (14).

For the primary analysis of vaccine-associated GBS risk, GBS incidence rate ratios were calculated by comparing person-time exposed to pH1N1 vaccine and seasonal vaccine with person-time unexposed. The rate in exposed person-time was the number of cases vaccinated during the 42 days prior to GBS onset divided by the cumulative exposed time following vaccination. The rate in person-time unexposed to vaccine was the number of GBS cases not occurring during the 42 days after vaccination divided by the cumulative unexposed person-time. In order to control for confounding by age, we stratified all analyses into age groups (<25 years and ≥25 years). Two age categories were used so that there would be sufficient person-time in each category to allow for stable rate estimates; 25 years was chosen as the cutoff a priori because of higher anticipated vaccine coverage below this age. For statistically significant rate ratios, the number of excess cases per million vaccine doses was calculated by dividing the number of excess cases (the difference between the exposed and unexposed rates, multiplied by person-time exposed to vaccine) by the estimated number of vaccine doses administered.

Bootstrapping methods (15) were used to estimate all 95% confidence intervals. GBS cases (numerator) were assumed to follow a Poisson distribution, vaccine coverage estimates (used for denominator calculations) were assumed to follow a normal distribution, and GBS background rates were assumed to follow a *t* distribution. We adjusted rate ratios for age and sex using the Mantel-Haenszel method (16). Sensitivity analyses were conducted for the pH1N1 analysis to assess the impact of 10% relative errors in vaccine coverage, 10% misclassification of exposure status (e.g., due to recall bias), and the use of a 28-day exposure window. We used SaTScan 9.1 (17) to calculate the scan statistic and SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina), for all other statistical analyses.

RESULTS

Descriptive epidemiology

Among 44.9 million persons under surveillance from October 1, 2009, to May 31, 2010, study personnel identified 707 suspected GBS cases; 282 (40%) did not meet the Brighton criteria (the most common reason was lack of bilateral and flaccid weakness of the limbs). Among the remaining 425 patients, a total of 411 GBS cases were included in the analysis (349 confirmed and 62 probable); 14 patients with GBS onset dates prior to October 1, 2009, were excluded. Medical records were reviewed for 100% of the 411 cases; 78% of the patients completed the telephone survey. Eighty-five percent of GBS cases were aged ≥25 years; 52% were male, 68% were white, 15% required mechanical

ventilation, and 3% died (Table 1). The median weekly number of GBS cases by date of onset was 12 (range, 1–19); the numbers of cases were similar across the surveillance period for both age groups (Figure 1).

History of pH1N1 vaccination was ascertained for 408 GBS cases (99%), of whom 67 (16%) received pH1N1 vaccine. Of these 67 patients, pH1N1 vaccine was received during the 42 days prior to GBS onset for 29 (43%), more than 42 days prior to onset for 34 (51%), and after GBS onset for 4 (1%). Fifty-seven patients (85%) received inactivated vaccine, 4 (6%) received live attenuated vaccine, and for 6 (9%) the vaccine type was unknown. pH1N1 vaccination status was ascertained by means of vaccine administration records, state registries, or administering provider documentation for 79% of cases, with the remainder being ascertained by self-report.

History of seasonal vaccination was ascertained for 90% (*n* = 371) of GBS cases, of whom 131 (35%) received seasonal vaccine. Of these 131 patients, seasonal vaccine was received during the 42 days prior to GBS onset for 36 (27%), more than 42 days prior to onset for 90 (69%), and after GBS onset for 5 (4%). Sixty-nine patients (53%) received inactivated vaccine, 1 (1%) received live attenuated vaccine, and vaccine type was unknown for 61 (47%). Seasonal vaccination status was ascertained by means of documented sources for 63% of cases, with the remainder being ascertained by self-report. Five cases received both pH1N1 vaccine and seasonal vaccine during the 42 days prior to GBS onset.

Among GBS cases receiving pH1N1 vaccine 1–84 days prior to GBS onset, the median interval between vaccine receipt and disease onset was 27 days. The most likely cluster identified using the scan statistic was 29 cases occurring during days 1–37, but this cluster was not statistically significant (*P* = 0.13) (Figure 2). For seasonal vaccine, the median interval was 36 days, and no statistically significant cluster was identified.

Generally, demographic characteristics, medical history, and outcomes for GBS cases did not differ by vaccine status (Table 1), although antecedent events were less common among cases who received pH1N1 vaccine during the 42 days prior to onset than among those who did not (59% vs. 79%; *P* = 0.02) (Table 1). Examination of specific types of antecedent events showed that upper respiratory or influenza-like symptoms were the only category of antecedent event that was significantly less common among cases who received pH1N1 vaccine than among those who did not (38% vs. 67%; *P* < 0.01) (Table 1).

Vaccine coverage and person-time at risk

From October 1, 2009, through May 31, 2010, an estimated 28.4% of persons in the EIP catchment area received a primary dose of pH1N1 vaccine; cumulative vaccine coverage increased more quickly in persons under age 25 years than in persons aged ≥25 years, with the younger age group achieving higher cumulative coverage at the end of the surveillance period (36.2% vs. 24.5%) (Figure 3). Cumulative second-dose pH1N1 vaccine coverage was 24.6% among all children under age 10 years during this period. This

Table 1. Characteristics of Confirmed and Probable Cases of Guillain-Barré Syndrome According to pH1N1 and Seasonal Vaccine Status, Emerging Infections Program Catchment Area, October 1, 2009–May 31, 2010

	Total (n = 411)		Receipt of pH1N1 Vaccine During the 42 Days Prior to Symptom Onset ^a				P for Difference	Receipt of 2009–2010 Seasonal Vaccine During the 42 Days Prior to Symptom Onset ^a				P for Difference
			Yes (n = 29)		No (n = 379)			Yes (n = 36)		No (n = 335)		
	No.	%	No.	%	No.	%		No.	%	No.	%	
GBS case status												
Confirmed (Brighton levels 1 and 2)	349	85	27	93	319	84	0.28	30	83	287	86	0.63
Probable (Brighton level 3)	62	15	2	7	60	16		6	17	48	14	
Sex												
Male	215	52	17	59	197	52	0.57	20	56	171	51	0.73
Female	196	48	12	41	182	48		16	44	164	49	
Age, years												
0–24	61	15	7	24	53	14	0.55	7	19	54	16	0.01
25–49	115	28	7	24	106	28		3	8	99	30	
50–64	129	31	8	28	121	32		10	28	104	31	
≥65	106	26	7	24	99	26		16	44	78	23	
Race/ethnicity												
White	280	68	21	72	257	68	0.84	26	72	228	68	0.86
Black	32	8	1	3	31	8		1	3	27	8	
Asian	10	2	1	3	9	2		1	3	9	3	
Other	14	3	1	3	13	3		1	3	10	3	
Unknown/missing data	75	18	5	17	69	18		7	19	61	18	
Antecedent events occurring during the 42 days prior to onset												
1 or more antecedent events documented	320	78	17	59	300	79	0.02	24	67	270	81	0.08
Specific antecedent events ^b												
Upper respiratory or influenza-like symptoms	267	65	11	38	254	67	<0.01	21	58	235	70	0.18
Fever	122	30	6	21	115	30	0.40	10	28	108	32	0.71
Gastrointestinal symptoms	158	38	9	31	147	39	0.44	11	31	135	40	0.29
Seasonal influenza vaccine	36	9	5	17	31	9	0.16	N/A		N/A		N/A
Noninfluenza vaccination	25	6	1	3	24	6	1.00	5	14	19	6	0.07
Medical history ^b												
Prior episode of GBS	9	2	1	3	8	2	0.49	0	0	9	3	1.00
Diabetes mellitus	53	13	5	17	48	13	0.56	8	22	43	13	0.13
Other immune disorder ^c	72	18	6	21	66	17	0.62	7	19	61	18	0.82
Cancer ^d	27	7	1	3	26	7	0.71	3	8	23	7	0.73
Outcome during the 30 days after GBS onset ^b												
Mechanical ventilation	60	15	5	17	55	15	0.60	4	11	50	15	0.80
Death (from any cause)	11	3	1	3	10	3	0.56	1	3	8	2	0.61

Abbreviations: GBS, Guillain-Barré syndrome; N/A, not applicable.

^a pH1N1 vaccine status was known for 408 of 411 GBS cases, and seasonal vaccine status was known for 371 of 411 GBS cases.^b Categories are not mutually exclusive.^c Includes liver failure/cirrhosis, thyroid disease, systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, human immunodeficiency virus/acquired immunodeficiency syndrome, chemotherapy, neuropathy, and receipt of a transplanted organ.^d Includes solid tumors such as breast, ovarian, and lung cancers, malignant melanoma, and hematologic malignancies.

corresponded to administration of over 14 million pH1N1 vaccine doses and 1.6 million person-years exposed to pH1N1 vaccine in the EIP catchment area during surveillance.

Primary seasonal vaccination coverage increased from 8.3% on October 1, 2009, to 43.6% on May 31, 2010; cumulative coverage at the end of surveillance was similar for

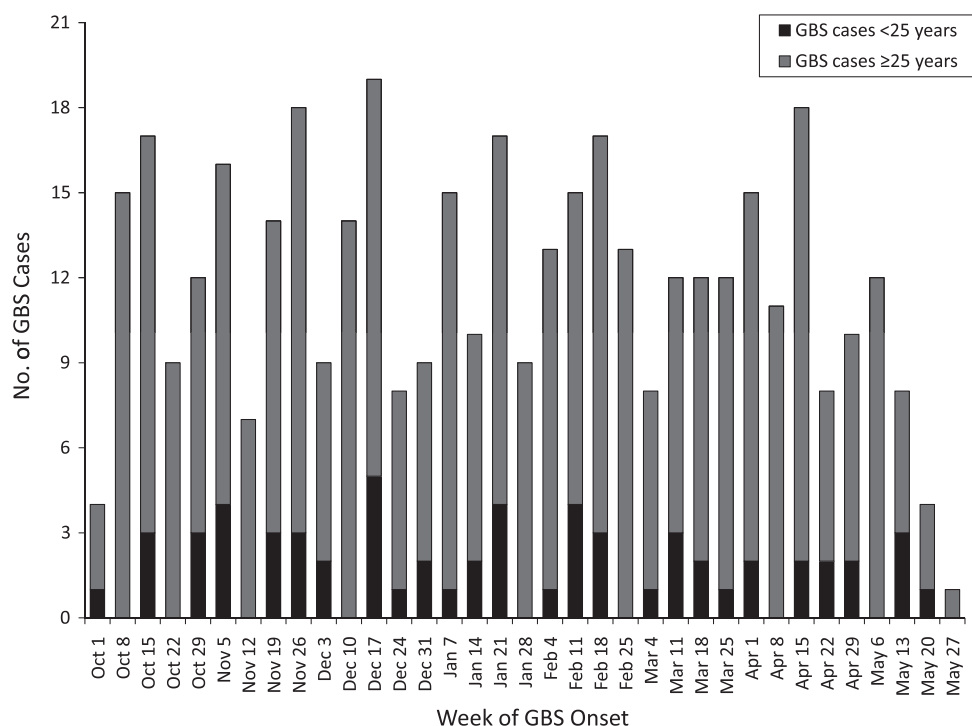


Figure 1. Weekly numbers of confirmed and probable Guillain-Barré syndrome (GBS) cases according to week of symptom onset ($n = 411$) and cumulative pH1N1 vaccine coverage, by age group, Emerging Infections Program catchment area, October 1, 2009–May 31, 2010.

persons aged <25 years and ≥ 25 years. Coverage for second seasonal vaccine doses among children under age 10 years increased from 1.7% to 6.5%. This corresponded to approximately 18 million seasonal vaccine doses administered and 2.0 million person-years of exposure to seasonal vaccine during the surveillance period.

Statistical assessment of excess GBS risk

The total number of observed GBS cases in the EIP catchment area ($n = 411$) was similar to the expected number for the surveillance population (age-adjusted observed/expected ratio = 1.21, 95% confidence interval (CI): 0.78, 1.81), as well as among persons aged <25 years and ≥ 25 years (Table 2). Additional analyses comparing observed and expected cases among vaccine recipients only can be found in Web Appendix 2 and Web Table 2.

Controlling for age and sex, the incidence of GBS was significantly higher during the 42 days following pH1N1 vaccination than during the person-time unexposed to pH1N1 vaccine (rate ratio (RR) = 1.57, 95% CI: 1.02, 2.21) (Table 3). This corresponded to 11 total excess GBS cases during the surveillance period and an estimated 0.74 (95% CI: 0.04, 1.56) excess cases of GBS per million pH1N1 vaccine doses. Sex-adjusted rate ratios were similarly elevated for persons aged <25 years and persons aged ≥ 25 years, although neither was significantly different from the null value (Table 3). GBS incidence was not significantly elevated following receipt of seasonal vaccine (Table 3).

Sensitivity analysis indicated that the magnitude of the association between pH1N1 vaccine and GBS was relatively robust to moderate errors. A relative 10% underestimate in vaccine coverage would have resulted in a lower age- and sex-adjusted rate ratio (RR = 1.42, 95% CI: 0.89, 2.03), while a relative 10% overestimate would have resulted in a higher rate ratio (RR = 1.75, 95% CI: 1.12, 2.49). Similarly, a 10% over- or underestimate of exposure to pH1N1 vaccine during the 42 days prior to GBS onset resulted in rate ratios of 1.35 (95% CI: 0.86, 1.97) and 1.74 (95% CI: 1.13, 2.46), respectively. A simultaneous overestimate of vaccine coverage and underestimate of vaccine exposure among cases resulted in a rate ratio of 1.94 (95% CI: 1.31, 2.72), corresponding to 1.22 excess cases per million doses (95% CI: 0.41, 2.09). Use of a 28-day risk window resulted in a slightly higher rate ratio (RR = 1.83, 95% CI: 1.17, 2.63) but had no effect on estimates of excess GBS cases.

DISCUSSION

Active surveillance among 45 million Americans during the 2009–2010 influenza season indicated that the incidence of GBS during the 42 days following pH1N1 vaccine administration was 57% higher than the rate outside of the 42-day window. The estimated excess occurrence of GBS associated with pH1N1 vaccine—less than 1 case per million pH1N1 doses administered—is similar to that associated with some previous seasonal influenza vaccine formulations

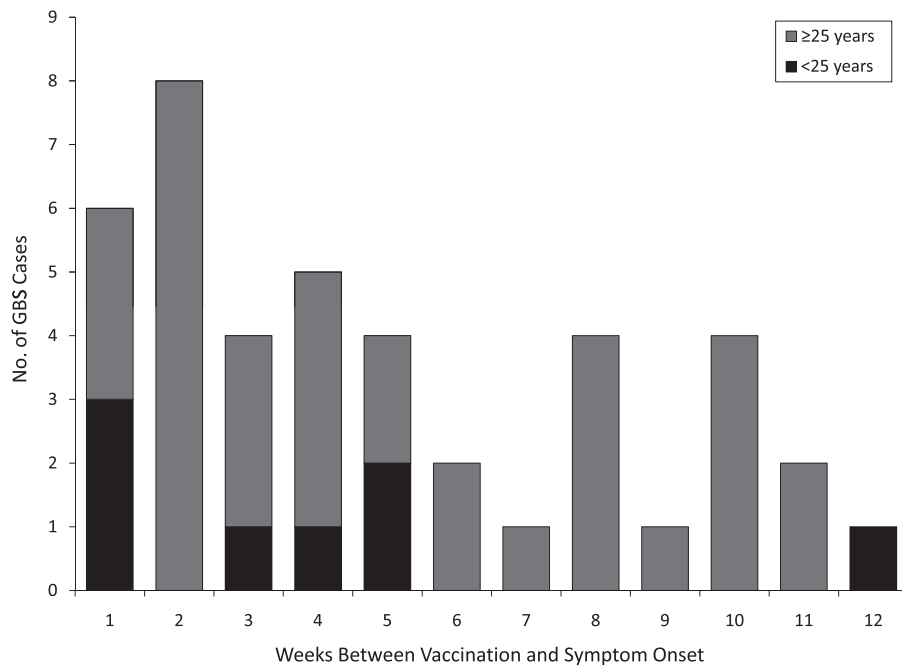


Figure 2. Interval between receipt of pH1N1 vaccine and onset of Guillain-Barré syndrome (GBS) in weeks ($n = 42$), by age group, Emerging Infections Program catchment area, October 1, 2009–May 31, 2010. The chart is limited to cases with an interval of 1–84 days; 4 additional cases developed GBS prior to receiving pH1N1 vaccine, and 21 cases developed GBS more than 84 days after receiving pH1N1 vaccine.

(18, 19) and is 10-fold lower than the excess risk associated with the 1976 vaccine. The estimated number of excess cases was higher in the EIP catchment area than that reported from

a large pH1N1 vaccine safety monitoring program in China (20), although this difference may be related to the passive case-finding approach used in that system. While findings

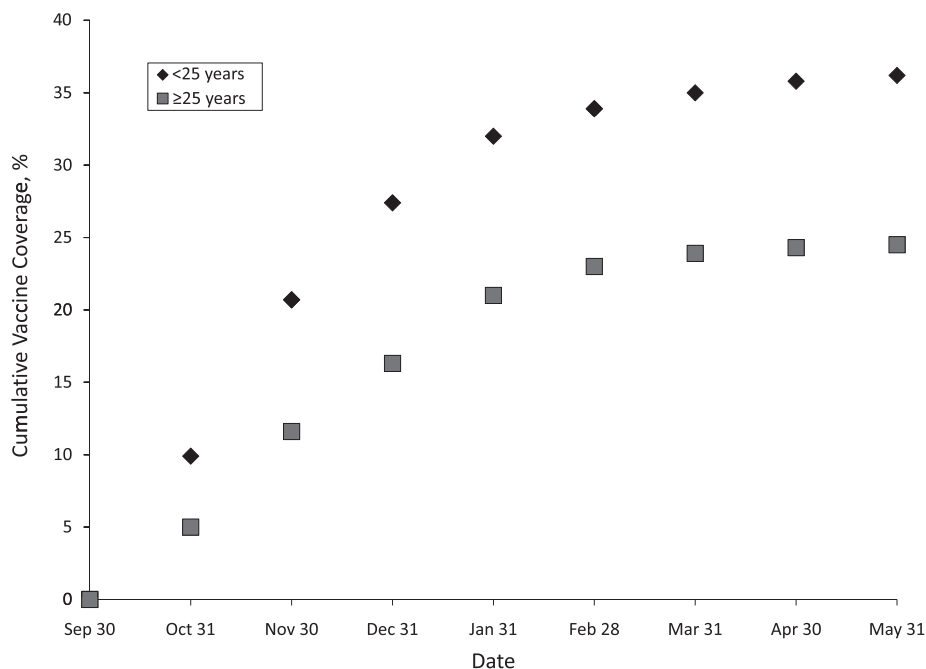


Figure 3. Monthly cumulative pH1N1 vaccine coverage in the Emerging Infections Program catchment area, by age group, October 2009–May 2010.

Table 2. Age-Specific Observed and Expected Numbers of Cases of Guillain-Barré Syndrome in the Emerging Infections Program Catchment Area, October 1, 2009–May 31, 2010

Age, years	Observed No. of Cases	PY in EIP Population	Observed Rate per 100,000 PY	Background Rate Per 100,000 PY ^a	Expected No. of Cases	Observed/Expected Ratio	95% Confidence Interval ^b
<25	61	9,920,000	0.61	0.71	70.1	0.87	0.63, 1.19
≥25	350	19,934,000	1.76	1.36	270.8	1.29	0.77, 2.20
Total	411	29,854,000	1.38	1.14	340.9	1.21 ^c	0.78, 1.81

Abbreviations: EIP, Emerging Infections Program; PY, person-years.

^a Background rates are based on 13 studies of age-specific rates from North America and Europe (14). The background rate used for the "Total" row was calculated by standardizing the age-specific expected rates to the age distribution in the EIP catchment area.

^b Background rate standard errors were incorporated into all confidence intervals by means of bootstrapping methods.

^c Adjusted for age.

for seasonal vaccine demonstrated a rate ratio point estimate similar to that for pH1N1 vaccine, the association between seasonal vaccine and GBS was not statistically significant.

Other antecedent events associated with GBS were present in over half of GBS patients who received pH1N1 vaccine during the 42 days prior to disease onset, although these events occurred less frequently than among GBS cases who did not receive pH1N1 vaccine during the 42-day window. The reason for the lower frequency of antecedent events among pH1N1-vaccinated GBS cases is uncertain, but it may be related to lower incidence of pH1N1 influenza infection following vaccination or to other conditions that might be contraindications for vaccination and related to GBS risk.

Following vaccination with the 1976 H1N1 influenza vaccine, the overall excess risk of GBS among adult vaccinees was 8.8 cases per million doses. Evidence supporting a causal relation included substantial elevation in GBS risk during the 2–3 weeks after vaccination and a low percentage of vaccinated GBS cases reporting other potential causes for GBS prior to onset (5). Despite research on this topic, no specific biologic mechanism has been identified for the as-

sociation between the 1976 vaccine and GBS; results from subsequent studies of GBS and seasonal influenza vaccine have not consistently found an increased risk. Among controlled studies that assessed this risk between 1977 and 2009 (18, 19, 21, 22), two (18, 19) suggested an increase in GBS risk similar to that observed for pH1N1 vaccine; neither increase was of similar magnitude to the association observed for the 1976 vaccine.

Despite the significantly elevated rate ratio for pH1N1 vaccine in our analysis, evidence of a strong relation between GBS and pH1N1 vaccine is limited. First, the rate of GBS during person-time exposed to vaccine, although higher than the rate in the unexposed, was low, especially compared with the rate following administration of the 1976 vaccine. Second, the analysis of GBS case data alone using a scan statistic did not show evidence of temporal clustering on a day-by-day basis following vaccination. Third, over half of GBS cases who received pH1N1 vaccine during the 42 days before GBS onset also reported other exposures that may be linked to GBS. Fourth, although pH1N1 vaccination was initially targeted at younger age groups, GBS cases in persons under 25 years of age did not disproportionately

Table 3. Age-Specific Incidence Rates and Rate Ratios for Confirmed and Probable Cases of Guillain-Barré Syndrome per 100,000 Person-Years for pH1N1 and Seasonal Vaccine, Emerging Infections Program Catchment Area, October 1, 2009–May 31, 2010

Vaccine and Age Group, years	Primary Vaccine Coverage, %	Exposed to Vaccine Within 42 Days			Unexposed to Vaccine Within 42 Days			Rate Ratio ^a	95% Confidence Interval ^b
		No. of Cases	No. of Person-Years ^c	Crude Rate	No. of Cases	No. of Person-Years	Crude Rate		
pH1N1 vaccine									
<25	36.2	7	725,000	0.97	53	9,194,534	0.58	1.67	0.58, 3.22
≥25	24.5	22	839,000	2.62	326	19,095,004	1.71	1.54	0.90, 2.25
Total	28.4	29	1,564,000	1.85	379	28,289,538	1.34	1.57	1.02, 2.21
Seasonal vaccine									
<25	41.1	7	671,000	1.04	54	9,248,914	0.58	1.78	0.59, 3.48
≥25	44.8	29	1,408,000	2.06	281	18,525,876	1.52	1.36	0.84, 1.91
Total	43.6	36	2,079,000	1.73	335	27,774,790	1.21	1.43	0.94, 1.89

^a Age-specific rate ratios were adjusted for sex. Total rate ratios were adjusted for age and sex.

^b Vaccine coverage standard errors were incorporated into all 95% confidence intervals by means of bootstrapping methods.

^c Includes 24.6% second-dose coverage among children under age 10 years for pH1N1 vaccine and 6.5% second-dose coverage among children under age 10 years for seasonal vaccine.

occur early in the surveillance period. For these reasons, any relation between pH1N1 vaccine and GBS during the 2009–2010 influenza season was probably weak.

In the United States, pH1N1 vaccine safety was monitored using the Vaccine Adverse Event Reporting System (23), the Vaccine Safety Datalink Project (24), and several other systems (25). However, the unique strength of the EIP surveillance system was its design for near real-time GBS surveillance throughout the 2009–2010 pH1N1 vaccination program. Key features of this system included 1) a defined surveillance period including only the vaccination program, 2) a large surveillance population in which to monitor real-time changes in GBS incidence (a rare event), 3) active case-finding and classification based on clinical criteria rather than administrative codes alone (26), 4) retrospective review of *International Classification of Diseases*, Ninth Revision, discharge codes to identify suspected GBS cases not otherwise captured, 5) patient interviews for assessment of antecedent events, 6) assessment of vaccine history using multiple data sources, and 7) monthly telephone survey estimates of vaccine coverage that captured all vaccinations administered, regardless of setting.

These findings are subject to several limitations. First, misclassification of GBS might have biased rate ratio estimates, particularly because diagnosis of GBS among children is challenging. Such bias was minimized by using the standardized Brighton Collaboration criteria, conducting rigorous and ongoing training for surveillance officers, and having independent expert neurologists review the most difficult-to-categorize cases. Second, some vaccination dates might have been recorded inaccurately, causing misclassification of whether vaccinations occurred within the 42-day risk window. The small number of GBS patients receiving vaccine during the 42-day risk window could have compounded this issue, as misclassification of only a few cases could have substantially altered rate ratio estimates. This bias was minimized by using multiple vaccine history data sources; three-quarters of pH1N1-vaccinated GBS cases had a vaccine history documented from a state registry, an administration record, or the administering provider. Sensitivity analyses indicated that neither exposure misclassification among GBS cases nor use of a different risk window substantially altered rate ratio estimates. Third, calculation of the rate ratio relied on BRFSS/NHFS vaccine coverage estimates, which may have suffered from nonresponse and self-report biases. Studies indicate that BRFSS can overestimate influenza vaccine coverage, including the 2009–2010 seasonal vaccine (9, 27, 28), potentially underestimating the rate ratio. This was addressed by including vaccine coverage standard errors in 95% confidence intervals to reflect this additional uncertainty and by conducting sensitivity analyses showing that rate ratio estimates were insensitive to moderate errors in vaccine coverage. Fourth, ascertainment and reporting biases might have occurred, despite the use of systematic case-finding methods during the surveillance period. However, the observed overall GBS rates (Table 2) were similar to population-based rates reported in other studies using similar methods (14), suggesting that these biases may be small. Fifth, despite adjustment for age and sex, rate ratio estimates could have been biased because of

residual confounding by factors such as antecedent illnesses or risk groups specified in vaccination recommendations, which could be associated with both GBS and vaccination.

Numerous studies have demonstrated the effectiveness of pH1N1 vaccine in preventing pandemic influenza A (H1N1) 2009 infections (29–32); the Centers for Disease Control and Prevention has estimated that the use of pH1N1 vaccine prevented 713,000–1.5 million cases, 3,900–10,400 hospitalizations, and 200–520 deaths in the United States (33). We estimate that there was less than 1 excess GBS case per million doses of pH1N1 vaccine administered, far less than that observed for the 1976 vaccine. Given the magnitude of morbidity and mortality associated with influenza infection (34–37), these findings provide reassurance that the excess risk of GBS following receipt of the pH1N1 vaccine was small compared with the morbidity and mortality prevented through the widespread use of the vaccine.

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Author affiliations: Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia (Matthew E. Wise, Melissa Viray, Paige Lewis, Frank DeStefano, Scott K. Fridkin, Claudia Vellozzi); Epidemic Intelligence Service, CDC, Atlanta, Georgia (Matthew E. Wise, Christa Hale, Rendi Murphree, John Y. Oh); Division of High-Consequence Pathogens and Pathology, CDC, Atlanta, Georgia (James J. Sejvar); Division of Global HIV/AIDS, CDC, Atlanta, Georgia (Andrew L. Baughman, Oliver W. Morgan); New Mexico Department of Health, Santa Fe, New Mexico (Walter Connor); Minnesota Department of Health, St. Paul, Minnesota (Richard Danila); Emerging Infections Program, New York State Department of Health, Albany, New York (Greg P. Giambrone); Colorado Department of Public Health and Environment, Denver, Colorado (Christa Hale); Maryland Department of Health and Mental Hygiene, Baltimore, Maryland (Brenna C. Hogan); Connecticut Emerging Infections Program, Yale University School of Public Health, New Haven, Connecticut (James I. Meek); Tennessee Department of Health, Nashville, Tennessee (Rendi Murphree); Office of Disease Prevention and Epidemiology, Oregon Public Health Division, Portland, Oregon (John Y. Oh); California Emerging Infections Program, Oakland, California (Arthur Reingold); Georgia Emerging Infections Program, Atlanta, Georgia (Norisse Tellman); Atlanta VA Medical Center, Atlanta, Georgia (Norisse Tellman); Division of Preparedness and Emerging Infections, CDC, Atlanta, Georgia (Susan M. Conner); and Immunization Services Division, CDC, Atlanta, Georgia (James A. Singleton, Peng-Jun Lu).

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Dr. Matthew Wise had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. 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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