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Chart-Confirmed Guillain-Barré Syndrome After 2009 H1N1 Influenza Vaccination Among the Medicare Population, 2009–2010

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Given the increased risk of Guillain-Barré Syndrome (GBS) found with the 1976 swine influenza vaccine, both active surveillance and end-of-season analyses on chart-confirmed cases were performed across multiple US vaccine safety monitoring systems, including the Medicare system, to evaluate the association of GBS after 2009 monovalent H1N1 influenza vaccination. Medically reviewed cases consisted of H1N1-vaccinated Medicare beneficiaries who were hospitalized for GBS. These cases were then classified by using Brighton Collaboration diagnostic criteria. Thirty-one persons had Brighton level 1, 2, or 3 GBS or Fisher Syndrome, with symptom onset 1–119 days after vaccination. Self-controlled risk interval analyses estimated GBS risk within the 6-week period immediately following H1N1 vaccination compared with a later control period, with additional adjustment for seasonality. Our results showed an elevated risk of GBS with 2009 monovalent H1N1 vaccination (incidence rate ratio = 2.41, 95% confidence interval: 1.14, 5.11; attributable risk = 2.84 per million doses administered, 95% confidence interval: 0.21, 5.48). This observed risk was slightly higher than that seen with previous seasonal influenza vaccines; however, additional results that used a stricter case definition (Brighton level 1 or 2) were not statistically significant, and our ability to account for preceding respiratory/gastrointestinal illness was limited. Furthermore, the observed risk was substantially lower than that seen with the 1976 swine influenza vaccine.

Fisher Syndrome; Guillain-Barré Syndrome; human influenza; vaccination

Abbreviation: GBS, Guillain-Barré Syndrome.

Guillain-Barré Syndrome (GBS) is a peripheral neuropathy characterized by rapid onset of bilateral limb weakness and diminished or absent reflexes. It occurs with an annual incidence in the range of 0.4–4 per 100,000 persons, with average incidence increasing by approximately 20% for every 10-year increase in age (1–4). The disease is thought to be caused by an autoimmune process that results in nerve demyelination, axonal damage, or both (5). It is considered to be postinfectious, triggered by preceding respiratory or gastrointestinal infection in approximately two-thirds of cases (6, 7), and has been occasionally associated, though not necessarily causally linked, with vaccinations (e.g., for influenza, polio, meningococcal disease, rabies) (8–12). The most notable vaccine-associated GBS occurred in 1976 with the influenza A/New Jersey/1976(H1N1) vaccine when the risk of GBS was found to be 7.6 times higher within the 6 weeks following vaccination and approximately 18 times higher 2–3 weeks after vaccination (13–15). Reassessment of this association by using enhanced case ascertainment and a standardized case definition revealed a similar elevated relative risk of 7.1 within the 6 weeks following vaccination (16). Subsequent epidemiologic studies on seasonal influenza vaccines have shown no or smaller increases (approximately 2-fold) in the risk of GBS after vaccination (17–23). The Institute of Medicine (Washington, DC) has since concluded that the evidence is inadequate to accept or reject a causal relationship between GBS and influenza vaccines administered after 1976 and through 2008 (24, 25). However,

the emergence of the novel influenza A(H1N1) virus in April 2009 and the corresponding accelerated development of the monovalent H1N1 influenza vaccines invoked renewed safety concerns in the public (26) and hastened the development of rapid vaccine safety surveillance systems for the new vaccine, including a system to identify increased GBS risk among the Medicare population (27).

The US Food and Drug Administration (Silver Spring, Maryland) and the Centers for Medicare & Medicaid Services (Baltimore, Maryland) conducted weekly analyses of the risk of GBS among Medicare beneficiaries who received both the seasonal and the 2009 monovalent H1N1 influenza vaccines; no safety signals were detected during the vaccination campaign (28). However, the Emerging Infections Program of the Centers for Disease Control and Prevention (Atlanta, Georgia) identified a slight increase in GBS risk among the vaccinees in their population (29). The rarity of GBS and the detection of this signal prompted further examination of potential GBS cases (identified through various health-care databases) through medical chart review among all US vaccine safety surveillance systems to contribute data to a meta-analysis with increased statistical power. Herein, we present the results of medical chart review of hospitalized GBS cases occurring among Medicare beneficiaries receiving the 2009 monovalent H1N1 influenza vaccine during the 2009-2010 influenza season and an evaluation of GBS risk among this H1N1-vaccinated cohort.

MATERIALS AND METHODS

Data sources

Data for this study consisted of administrative files and medical records for the US Medicare population, which includes persons 65 years of age and above and those under age 65 with disability or end-stage renal disease. Among approximately 35 million persons enrolled in fee-for-service Medicare (30), vaccination claims were identified in the Medicare carrier and outpatient files by using the first occurrence of Healthcare Common Procedure Coding System codes G9141 and G9142 for the 2009 monovalent H1N1 influenza vaccine, as well as Current Procedural Terminology codes 90470 and 90663. Medicare beneficiaries who were hospitalized for GBS were identified in data files of inpatient claims by using the *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic code 357.0 as the principal diagnosis or any of 9 possible secondary discharge diagnoses. This project was approved by the Food and Drug Administration's Research Involving Human Subjects Committee. Medicare administrative data were used under a data use agreement with the Centers for Medicare & Medicaid Services and data use was approved by the Centers' privacy board. Medical records were requested from hospitals by the Medicare Quality Improvement Organization Program's Clinical Data Abstraction Center.

Study population and study period

The population of potential incident GBS cases that underwent medical chart review consisted of Medicare beneficiaries enrolled in Parts A and B fee-for-service (excluding Medicare Advantage) who: 1) received 2009 monovalent H1N1 influenza vaccine during the period October 1, 2009–March 26, 2010; 2) were admitted to the hospital for GBS within 126 days after vaccination; and 3) had no prior GBS hospitalization in the 12 months preceding vaccination. Cases were initially identified by the admission date from claims data, and analyses were performed on chart-confirmed cases by using the GBS symptom onset date (determined during abstraction).

Chart abstraction and case definition

For each potential (claims-identified) GBS case, the hospital record with diagnosis code 357.0 was reviewed. If the patient had been transferred to a second hospital for further acute care of the same illness episode and the initial hospitalization was less than 28 days, the second hospital record was also reviewed. Chart abstraction was performed to identify the clinical and diagnostic criteria necessary for classification with the Brighton Collaboration's case definitions for GBS and Fisher Syndrome (31) and to obtain information about preceding illnesses. Classification criteria are delineated in Appendix Table 1. Distinction between Brighton levels 1, 2, and 3 was made as follows: Level-1 cases met all clinical criteria and had documented confirmatory evidence on both cerebrospinal fluid and electrophysiological tests; level-2 cases were confirmed through at least 1 of these tests; and level-3 cases met clinical criteria only. A case was classified as having "insufficient evidence" if a physician's diagnosis of GBS or Fisher Syndrome was made, but evidence was insufficient to classify the patient at any higher level of diagnostic certainty. If a case did not meet the criteria necessary for classification as Brighton level 1, 2, or 3, was not diagnosed with GBS or Fisher Syndrome by a physician, or had a definitive alternate diagnosis documented in the chart, the patient was classified as "not GBS." Cases were designated as "chart-confirmed GBS" if they met criteria for Brighton level 1, 2, or 3 for either GBS or Fisher Syndrome. Additionally, although Fisher Syndrome is a GBS variant with the same diagnostic code, classifications of GBS and Fisher Syndrome were mutually exclusive.

Preceding illness was assessed by noting any documentation in the hospital record (usually in the history of present illness) of signs, symptoms, or confirmed diagnoses occurring within the 6 weeks preceding GBS symptom onset. Respiratory illness was defined as upper respiratory infection, influenza-like illness (fever and cough or sore throat), bronchitis, and/or pneumonia; gastrointestinal illness was defined as diarrhea, nausea and/or vomiting (unless information clearly indicated nausea alone), or *Campylobacter jejuni* isolated in the stool of any patient with gastrointestinal illness prior to GBS symptom onset.

Study design and analysis

We used a self-controlled risk interval design (32–34) to compare the GBS risk in a predefined period immediately following vaccination with that in an unexposed control period occurring later. We included all hospitalized cases of

Brighton level 1, 2, or 3 GBS or Fisher Syndrome occurring among Medicare beneficiaries vaccinated with monovalent H1N1 influenza vaccine during the period October 1, 2009–March 26, 2010 and having GBS symptom onset within 119 days after vaccination. The GBS rate during 1–42 days after vaccination was compared with the rate during 50–119 days after vaccination within the same individual. We included a 1-week "washout period" between the end of the risk period and the start of the comparison period, which is occasionally used to account for some GBS risk that might extend beyond the 6 weeks after vaccination. Incidence rate ratios and 95% confidence intervals were estimated by fitting a conditional Poisson regression model that used data from GBS cases only, unadjusted and adjusted for seasonality, as described below.

Because wild-type influenza infection is possibly associated with GBS (23) and can act as a potential confounder, the analysis was adjusted for influenza seasonality. In self-controlled risk interval analyses, each vaccinee's risk period and comparison period are established on the basis of vaccination date. For each day of the risk period and comparison period, each time-varying covariate is then assigned a value that differs on the basis of a specific reference date. In our analyses, seasonality was designated as a binary covariate with respect to a measure of background incidence of influenza in the population. The "high-incidence" period was the time during which ≥10% of respiratory specimens were positive for influenza (August 8, 2009–December 5, 2009), and the "low-incidence" period was when <10% were positive (December 6, 2009–July 30, 2010) according to the Centers for Disease Control and Prevention's viral influenza isolates data for the 2009-2010 flu season (35). We plotted the weekly proportion of positive influenza isolates against the weekly administration of H1N1 vaccine among our study population to better assess the potential influence of seasonality on our analyses.

Sensitivity analyses included those with the same comparison period and an alternate "higher risk" period of 8–21 days after vaccination, those that estimated risk by using a more specific GBS case definition of Brighton level 1 or 2, and those that excluded cases with respiratory or gastrointestinal illness in the 6 weeks preceding GBS symptom onset. Additional analyses that used a variable-length comparison period (GBS symptom onset between day 43 after vaccination and April 30, 2010) were also performed after medical chart review of cases admitted to the hospital through May 28, 2010; these provided a different, though overlapping, comparison group. All analyses were conducted by using Stata/MP, version 11, software (StataCorp LP, College Station, Texas), SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina), and Microsoft Excel 2007 (Microsoft Corporation, Redmond, Washington).

Attributable risk (per 42 million person-days) was calculated by subtracting the daily rate (total number of cases divided by the total number of person-days that all vaccinees contributed) in the risk period by the daily rate in the comparison period. For comparability to annual incidence rates, estimates were converted into per 100,000 person-years. Estimates per 42 million person-days are equal to estimates for the 6-week risk period per 1 million vaccine doses administered under the assumption that only 1 H1N1 dose was counted for each vaccinee. Corresponding 95% confidence intervals were calculated by using the standard equation for the difference between 2 independent Poisson means.

Temporal scan statistic analyses (36) were performed to identify significant clustering of cases by GBS symptom onset date during the full postvaccination period, assuming uniform and independent distribution under the null hypothesis. We used SaTScan, version 9.1.1, software (37) to analyze the distribution of all chart-confirmed GBS cases and to obtain risk estimates for every time period combination (of variable start date and duration) within the entire 119-day postvaccination period. We identified the time period of greatest GBS risk by using a case definition of Brighton level 1, 2, or 3 and by using the stricter definition of Brighton level 1 or 2.

RESULTS

Case ascertainment and description

From October 1, 2009, through March 26, 2010, a total of 3,436,452 doses of monovalent H1N1 influenza vaccine were administered in the Medicare population, as identified from claims processed through September 17, 2010. Among this H1N1-vaccinated population, a total of 95 potential incident cases of GBS (either principal or secondary diagnosis) were hospitalized within 126 days after vaccination. Of the 95 potential (claims-identified) cases, 44 had GBS listed as the principal diagnosis, and among these, 30 were chart-confirmed (Brighton level 1, 2, or 3) GBS cases (28 GBS and 2 Fisher Syndrome), with the remaining 14 classified as having insufficient evidence or as not GBS (Table 1). Of the 51 claims-identified cases with GBS listed as a secondary diagnosis, 4 were chart confirmed (3 GBS and 1 Fisher Syndrome), with the majority (90%) determined to be not GBS. This resulted in a total of 34 chart-confirmed GBS cases. Of those ultimately determined to be not GBS, a wide variety of diagnoses were identified, including chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, transverse myelitis, lumbar radiculopathy, polymyalgia rheumatica, and drug-induced myopathy. The positive predictive value of the diagnostic code 357.0 for GBS in identifying chart-confirmed GBS cases was 34/95 (35.8%) overall, 30/44 (68.2%) for principal diagnoses, and 4/51 (7.8%) for secondary diagnoses. Demographic variables and other potential confounding characteristics for both claims-identified and chart-confirmed cases are presented in Table 2. Compared with claims-identified cases, chart-confirmed cases consisted of a larger proportion of men, persons of white race, persons 65–74 years of age, and persons with a preceding illness.

Figure 1 shows the process of case ascertainment from the original population of potential (claims-identified) GBS cases ($n = 95$) into the chart-confirmed GBS cases that comprised the final study cohort. Claims-identified cases were reduced to the 34 chart-confirmed cases after exclusion of 61 cases that did not meet criteria for Brighton level 1, 2, or 3 GBS or Fisher Syndrome. An additional 3 cases were

Table 1. Breakdown of Claims-Identified Cases[a] of Guillain-Barré Syndrome and Fisher Syndrome Hospitalized After Monovalent 2009 H1N1 Vaccination Among the US Medicare Population, 2009–2010

Case Classification	Principal Diagnosis ($n = 44$)	Secondary Diagnosis ($n = 51$)
Guillain-Barré Syndrome		
Brighton level 1	9[b]	0
Brighton level 2	16[b]	3
Brighton level 3	3	0
Insufficient evidence	4	1
Fisher Syndrome		
Brighton level 1	0	0
Brighton level 2	1	1
Brighton level 3	1	0
Insufficient evidence	1	0
Not Guillain-Barré Syndrome or Fisher Syndrome	9	46[c]
Past history only	0	14
Alternate diagnosis	3	20
Did not meet criteria	6	3
Miscoded	0	9

[a] Claims-identified Guillain-Barré Syndrome cases are defined as Medicare beneficiaries enrolled in Parts A and B fee-for-service (excluding Medicare Advantage) who were vaccinated with monovalent 2009 H1N1 influenza vaccine October 1, 2009–March 26, 2010, and hospitalized within 126 days after vaccination for a first episode of Guillain-Barré Syndrome in 12 months (as determined by an *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic code of 357.0).

[b] Among the claims-identified cases of principal diagnosis of Guillain-Barré Syndrome or Fisher Syndrome, 1 Brighton level–1 case, 1 Brighton level–2 case, and 1 Brighton level–3 case were determined to have symptom onset outside the 1- through 119-day postvaccination period. These cases were not included in final analyses.

[c] Among the claims-identified cases of Guillain-Barré Syndrome or Fisher Syndrome listed as the secondary diagnosis, 2 cases classified as not Guillain-Barré Syndrome or Fisher Syndrome were determined to have symptom onset outside of the 1- through 119-day postvaccination period.

Table 2. Characteristics of Claims-Identified Guillain-Barré Syndrome Cases Versus Chart-Confirmed Guillain-Barré Syndrome Cases[a] Occurring After Monovalent 2009 H1N1 Vaccination Among the US Medicare Population, 2009–2010

Characteristic	Claims-Identified Cases[b] ($n = 95$)		Chart-Confirmed Cases ($n = 34$)	
	No.	%	No.	%
Age				
<65 years	20	21	6	18
65–74 years	35	37	15	44
≥75 years	40	42	13	38
Male sex	54	57	21	62
White race	80	84	30	88
High-incidence seasonality[c]	20	21	6	18
Preceding illness[d]	22	23	15	44
Seasonal influenza vaccine[e]	2	2	2	6

[a] Chart-confirmed Guillain-Barré Syndrome cases are defined as claims-identified Guillain-Barré Syndrome cases hospitalized with Guillain-Barré Syndrome within 126 days after vaccination who met level 1, 2, or 3 of clinical diagnostic criteria established by the Brighton Collaboration for Guillain-Barré Syndrome or Fisher Syndrome. These do not exclude those with Guillain-Barré Syndrome symptom onset outside of the 1–119 days after vaccination.

[b] Based on *International Classification of Diseases, Ninth Revision, Clinical Modification.*

[c] Seasonality was determined by distribution of viral influenza isolates for the 2009-2010 season. High-incidence seasonality for this study period includes the portion of the season with weekly data showing ≥10% of respiratory isolates positive for viral influenza; in the 2009-2010 season, this period was August 8, 2009–December 5, 2009. Low-incidence seasonality for this study period includes the portion of the season with weekly data showing <10% of respiratory isolates positive for viral influenza; in the 2009-2010 season, this period was December 6, 2009–July 30, 2010.

[d] Preceding respiratory or gastrointestinal illness occurring within 42 days prior to GBS symptom onset. Respiratory illness includes upper respiratory infection, influenza-like illness (fever and cough or sore throat), bronchitis, and/or pneumonia. Gastrointestinal illness includes diarrhea, nausea and/or vomiting (unless information clearly indicates nausea alone), or *Campylobacter jejuni* isolated in stool.

[e] Also received seasonal influenza vaccine 1–42 days prior to Guillain-Barré Syndrome symptom onset.

excluded because GBS symptom onset fell outside the 1- through 119-day postvaccination period. Figure 2 displays the distribution of these cases by days to symptom onset. Of the 31 remaining chart-confirmed cases, 2 occurred within the washout period of 43–49 days after vaccination and were not included in the risk analyses. These 2 cases were, however, included in the scan statistic analyses.

The 29 chart-confirmed GBS cases that comprised the primary analytical cohort were assessed for respiratory and/or gastrointestinal illness in the 6 weeks preceding GBS symptom onset; 17 occurred within the risk period and 12 occurred within the comparison period (Table 3). The proportion of cases with either preceding respiratory or gastrointestinal illness was similar between risk and comparison periods, although a greater proportion of cases occurring in the risk period had a preceding respiratory illness, and a smaller proportion had a preceding gastrointestinal illness.

Self-controlled risk interval analyses

In the primary analysis, 17 cases occurred within the risk period and 12 occurred within the comparison period, resulting in an unadjusted incidence rate ratio of 2.36 (95% confidence interval: 1.13, 4.94). Adjustment for seasonality did not appreciably change this estimate (Table 4). The relative risk estimate obtained for the 8- through 21-day risk period

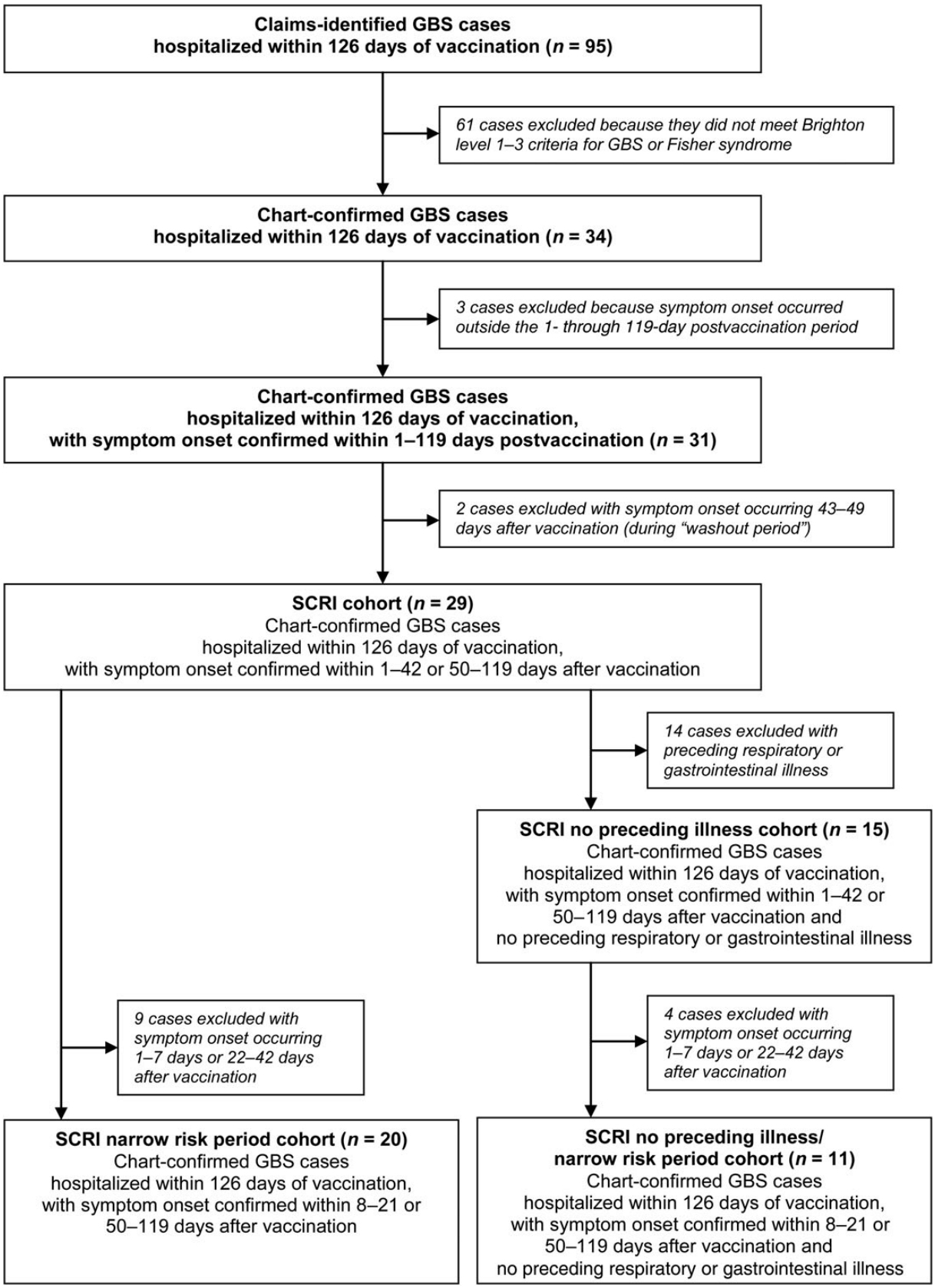

Figure 1. Guillain-Barré Syndrome (GBS) case ascertainment for the self-controlled risk interval (SCRI) cohorts examining GBS risk after 2009 monovalent H1N1 vaccination among the US Medicare population, 2009–2010. GBS cases represent either GBS or Fisher Syndrome.

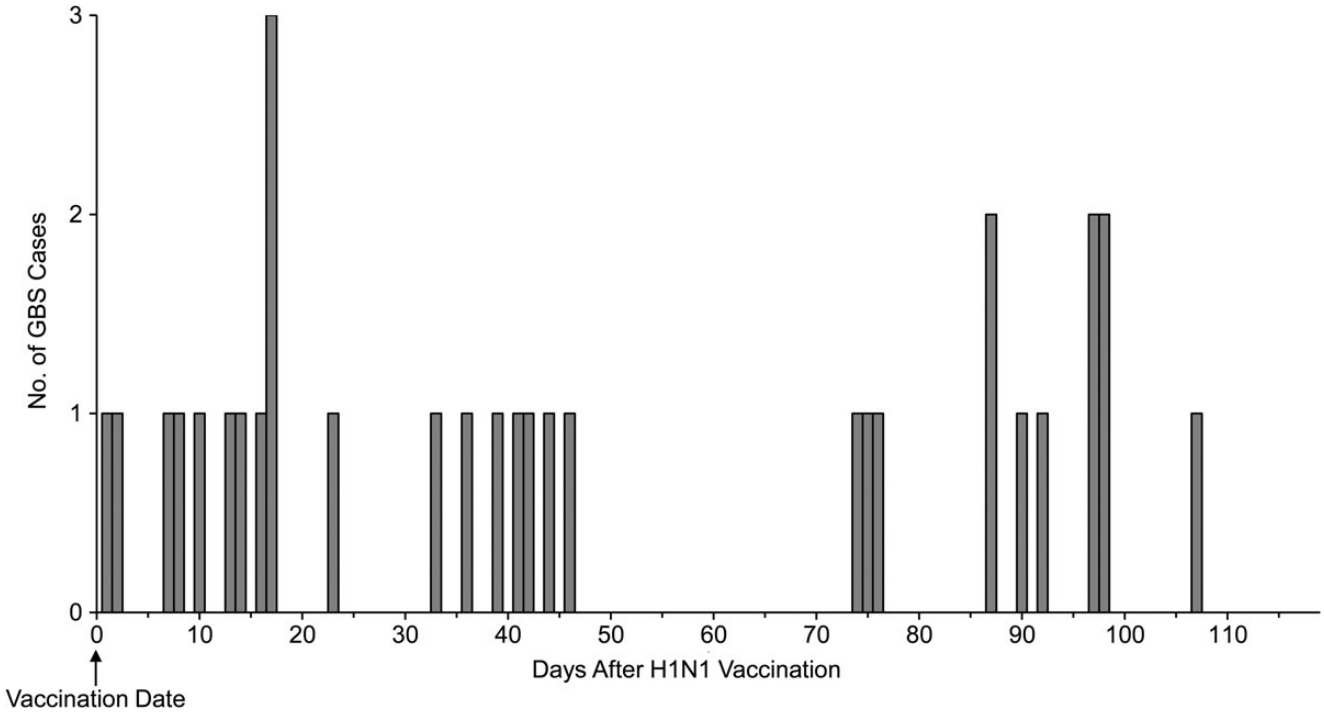

Figure 2. Chart-confirmed (Brighton level 1, 2, or 3) Guillain-Barré Syndrome (GBS) cases ($n = 31$) by days to symptom onset after 2009 monovalent H1N1 vaccination among the US Medicare population, 2009–2010. The study population included Medicare beneficiaries who received the H1N1 vaccination from October 1, 2009, through March 26, 2010, and who were hospitalized within 126 days after vaccination with confirmed GBS symptom onset occurring within 1–119 days after vaccination.

was slightly higher than that for the 1- through 42-day risk period (incidence rate ratio = 3.33, 95% confidence interval: 1.36, 8.15).

The incidence rate of GBS in the risk period was 4.95 per 42 million person-days or 4.30 per 100,000 person-years, and the GBS incidence rate in the comparison period was 2.11 per 42 million person-days or 1.83 per 100,000 person-years. This resulted in an attributable risk of 2.84 per 42 million person-days (95% confidence interval: 0.21, 5.48) or 2.47 per 100,000 person-years (95% confidence interval: 0.18, 4.77).

Table 3. Preceding Illness Within 6 Weeks Prior to Guillain-Barré Syndrome Symptom Onset Among Chart-Confirmed Guillain-Barré Syndrome Cases[a] in Risk Period Versus Comparison Period Following 2009 Monovalent H1N1 Influenza Vaccination Among the US Medicare Population, 2009–2010

Preceding Illness	No. of Cases With Preceding Illness	No. of Cases in Risk Period (1–42 Days After Vaccination)	%	No. of Cases With Preceding Illness	No. of Cases in Comparison Period (50–119 Days After Vaccination)	%
Total respiratory[b] and/or gastrointestinal[c] illness	8[d]	17	47	6[d]	12	50
Respiratory illness	8	17	47	3	12	25
Gastrointestinal illness	2	17	12	4	12	33

[a] Chart-confirmed Guillain-Barré Syndrome cases are defined as claims-identified Guillain-Barré Syndrome cases hospitalized with Guillain-Barré Syndrome within 126 days after vaccination who met level 1, 2, or 3 of clinical diagnostic criteria established by the Brighton Collaboration for Guillain-Barré Syndrome or Fisher Syndrome with confirmed symptom onset within 1–119 days postvaccination.

[b] Respiratory illness is defined as upper respiratory infection, influenza-like illness (fever and cough or sore throat), bronchitis, and/or pneumonia.

[c] Gastrointestinal illness is defined as diarrhea, nausea and/or vomiting (unless information clearly indicates nausea alone), or *Campylobacter jejuni* isolated in stool.

[d] Total number of cases with preceding respiratory and/or gastrointestinal illness may not equal the sum of cases with respiratory and gastrointestinal illness because of cases with multiple symptoms.

Table 4. Incidence Rate Ratios for Chart-Confirmed[a] Guillain-Barré Syndrome (Brighton levels 1–3 and Brighton levels 1–2) Among US Medicare Beneficiaries Receiving the Monovalent 2009 H1N1 Influenza Vaccine in Self-Controlled Risk Interval Analyses

Brighton Levels and Exclusion of Cases With Preceding Illness	Study Design	Risk Period, days	Comparison Period, days	No. of Cases in Risk Period	No. of Cases in Comparison Period	IRR	95% CI
1–3 (Not excluding cases with preceding illness[b])	SCRI-unadjusted	1–42	50–119	17	12	2.36	1.13, 4.94
	SCRI-adjusted[c]	1–42	50–119	17	12	2.41	1.14, 5.11
	SCRI-unadjusted	8–21	50–119	8	12	3.33	1.36, 8.15
1–2 (Not excluding cases with preceding illness[b])	SCRI-unadjusted	1–42	50–119	14	12	1.94	0.90, 4.20
	SCRI-adjusted[c]	1–42	50–119	14	12	1.97	0.90, 4.34
	SCRI-unadjusted	8–21	50–119	6	12	2.50	0.94, 6.66
1–3 (Excluding cases with preceding illness[b])	SCRI-unadjusted	1–42	50–119	9	6	2.50	0.89, 7.02
	SCRI-adjusted[c]	1–42	50–119	9	6	2.92	1.03, 8.30
	SCRI-unadjusted	8–21	50–119	5	6	4.17	1.27, 13.65
1–2 (Excluding cases with preceding illness[b])	SCRI-unadjusted	1–42	50–119	8	6	2.22	0.77, 6.40
	SCRI-adjusted[c]	1–42	50–119	8	6	2.62	0.90, 7.64
	SCRI-unadjusted	8–21	50–119	4	6	3.33	0.94, 11.81

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; SCRI, self-controlled risk interval.

[a] Chart-confirmed Guillain-Barré Syndrome cases are defined as patients who received H1N1 vaccination between October 1, 2009, and March 26, 2010, and who were hospitalized with Guillain-Barré Syndrome or Fisher Syndrome symptoms that met levels 1, 2, or 3 of clinical diagnostic criteria established by the Brighton Collaboration for Guillain-Barré Syndrome or Fisher Syndrome.

[b] Preceding respiratory or gastrointestinal illness occurring within 42 days prior to Guillain-Barré Syndrome symptom onset. Respiratory illness includes upper respiratory infection, influenza-like illness (fever and cough or sore throat), bronchitis, and/or pneumonia. Gastrointestinal illness includes diarrhea, nausea and/or vomiting (unless information clearly indicates nausea alone), or *Campylobacter jejuni* isolated in stool.

[c] Adjusted for seasonality, determined by distribution of viral influenza isolates for the 2009-2010 season. High-incidence seasonality for this study period included the portion of the season with weekly data showing ≥10% viral influenza isolates positive. In the 2009-2010 season, this period was August 8, 2009–December 5, 2009. Low-incidence seasonality for this study period included the portion of the season with weekly data showing <10% viral influenza isolates positive. In the 2009–2010 season, this period was December 6, 2009–July 30, 2010.

Sensitivity analyses that used a stricter GBS case definition of Brighton level 1 or 2 resulted in lower relative risk estimates that were no longer significant (Table 4). Relative risk estimates after exclusion of those with preceding illness were slightly higher, but exclusion of nearly half of the cases resulted in much wider confidence intervals (Table 4). Risk estimates obtained by using a self-controlled risk interval design with a variable-length comparison period were similar to those obtained by using a fixed-length comparison period (data not shown).

Temporal scan statistic analyses

We identified clustering of cases classified as Brighton level 1, 2, or 3 in the period 7–17 days after vaccination (Figure 2), but the relative risk was not statistically significant (relative risk = 4.02; $P = 0.17$). Similar analyses for cases classified as Brighton level 1 or 2 identified clustering 16–17 days after vaccination, but it was also not statistically significant (relative risk = 9.75; $P = 0.14$).

DISCUSSION

Analyses of the chart-confirmed cases found a slightly increased statistically significant risk of GBS within the 6-week risk period after 2009 monovalent H1N1 influenza vaccination compared with the postvaccination control period. The attributable risk estimates for this 6-week period indicate that if there is a true association, it is approximately 3 cases per 1 million vaccinated individuals (or doses administered). When analyses were adjusted for seasonality, the risk of GBS after 2009 H1N1 influenza vaccination did not change significantly. This is most likely because peak incidence of influenza virus circulation (predominantly H1N1) occurred early in the season before most Medicare beneficiaries were vaccinated, as displayed in Figure 3. Adjustment for seasonality in this study was an imperfect proxy for wild-type influenza infection. Analyses excluding cases with documented preceding respiratory or gastrointestinal illness better accounted for illness with the potential to cause GBS. These risk estimates, although slightly higher, were more unstable because of the smaller number of cases and decreased power. Given the similar proportion of cases with preceding illness in the risk and comparison periods (Table 3), minimal change in risk is not surprising. The proportion of cases with preceding respiratory illness in the risk period was nearly twice as high as that in the comparison period, but we did not perform separate analyses excluding only those cases because gastrointestinal illness (particularly *Campylobacter* infection) is also a possible precipitant of GBS. Overall, it appears that neither influenza circulation nor documented preceding illness had an appreciable impact on the association between H1N1 vaccination and GBS in this population. This conclusion may be limited by the

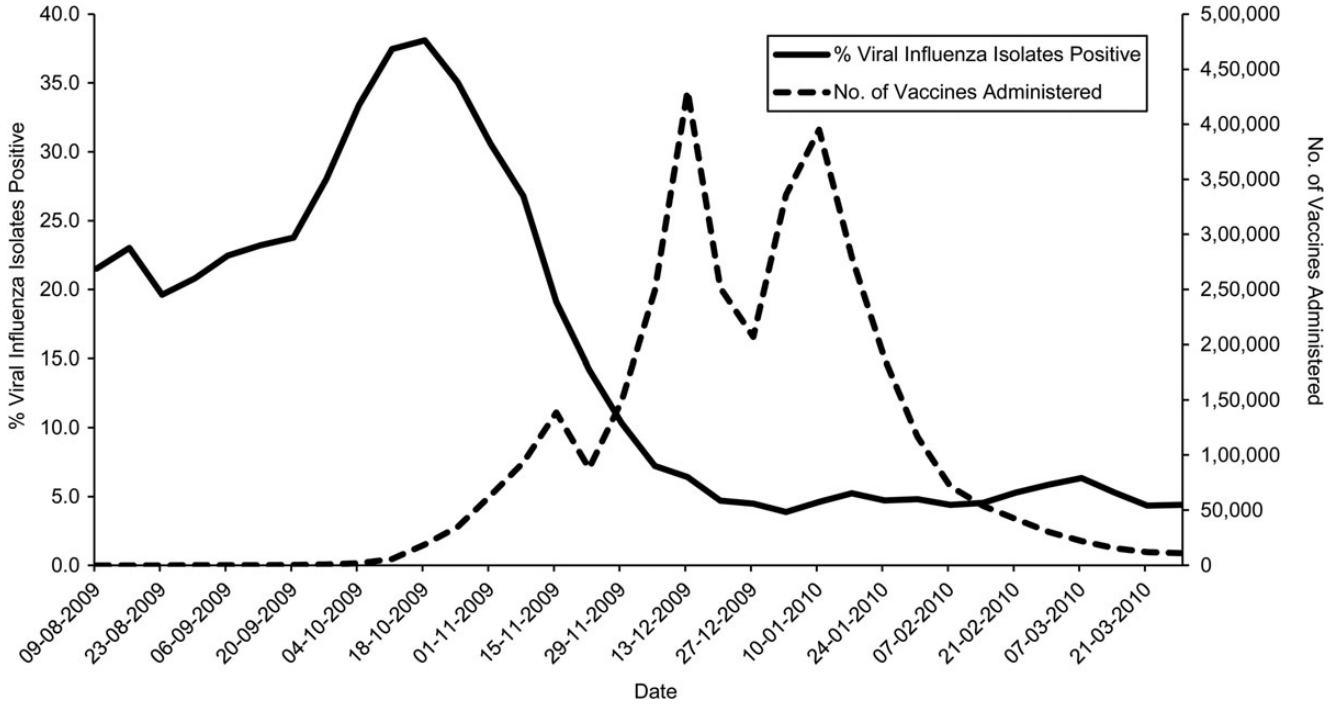

Figure 3. Weekly data on viral influenza isolates and number of vaccines administered among the US Medicare population, 2009–2010. Collection of data on viral influenza isolates began on August 9, 2009, whereas collection of data on the number of vaccines administered began on August 8, 2009; however, both data series are plotted on the weekly start date of the viral influenza isolates data for comparability.

accuracy of detecting all cases with preceding infections, as well as the generalizability of national influenza circulation data among a population of mostly elderly persons.

Our results are similar to those of studies examining the association between the 2009 monovalent H1N1 vaccination and Brighton levels 1, 2, and 3 GBS among other populations in the United States (Table 5) (38–41). Risk estimates among the Medicare population were slightly higher than those seen in the Emerging Infections Program's active surveillance study, in which ascertainment of potential cases and vaccinated and unvaccinated person-time relied on multiple unlinked data sources, and the comparison incidence rates were estimated by modeling published population-based GBS rates (41). Our estimates were slightly lower than those of the other 3 studies that used self-controlled risk interval analyses (38–40). Possible explanations for these differences include size of the study population and corresponding differences in statistical power, a larger proportion of cases in the risk period with preceding infection compared with our study population (39), potential differences in case ascertainment and chart abstraction, and differences in statistical analyses (such as our use of a 10-week comparison period and washout period).

Similar to the findings with the initial swine flu vaccine, GBS risk was higher 8–21 days after vaccination than during the overall 1- through 42-day postvaccination period. However, the relative risk in this shorter period was approximately 5 times lower than that observed in the same period in 1976 (14). Although risk was higher in this preselected period, no statistically significant temporal clustering of cases was identified across the entire study period, likely because of the overall rarity of the disease, but also possibly because of the lack of a strong association with vaccination.

This study relied on medical record review for more accurate ascertainment and classification of GBS cases. As expected, fewer GBS and Fisher Syndrome cases were confirmed by chart review than were identified by claims data alone. The positive predictive value improved when GBS was listed as the principal diagnosis. This use of principal diagnosis in case identification occurs in near real-time, claims-based analyses of GBS risk after influenza vaccination in the Medicare population (28). Chart confirmation of GBS cases versus claims identification alone can result in improved specificity, thus reducing the potential for nondifferential misclassification (in claims identification) that could bias the association between vaccination and GBS toward the null (42). This potential misclassification in claims-based surveillance, coupled with the small number of cases and variance of the case confirmation rate, might explain the absence of a signal in active surveillance despite the statistically significant risk observed in this end-of-season analysis of the same population of Medicare vaccinees. The difference in comparison groups could also contribute if the historical comparison group used in the claims-based surveillance differed from H1N1-vaccinated persons on unmeasured predisposing factors for GBS. Application of the Brighton criteria

Table 5. Comparison of US Studies Evaluating the Risk of Brighton Level 1, 2, or 3 Guillain-Barré Syndrome Following Monovalent 2009 H1N1 Influenza Vaccination During the 2009-2010 Season

System	Analysis	Relative Risk	95% CI	Attributable Risk[a]	95% CI
Medicare population end-of-season analysis	Self-controlled	2.41[b]	1.14, 5.11	2.84	0.21, 5.48
Centers for Disease Control and Prevention Emerging Infections Program active surveillance (41)	Vaccinated vs. unvaccinated	1.57[c]	1.02, 2.21	0.74	0.04, 1.56
Centers for Disease Control and Prevention Emerging Infections Program end-of-season analysis (38)	Self-controlled	3.0	1.4, 6.4	2.8	0.6, 7.4
Post-licensure Rapid Immunization Safety Monitoring System (40)	Self-controlled	2.50	0.42, 15.0	2–3	Not assessed
Vaccine Safety Datalink (39)	Self-controlled	4.7	1.2, 18.3	3.9	0.0, 7.9

Abbreviation: CI, confidence interval.
[a] Per 1 million doses administered.
[b] Adjusted for seasonality.
[c] Adjusted for age and sex.

further standardizes case classification, allowing for improved comparison of postvaccination risk across populations, even with variation in the GBS case definition (i.e., Brighton level 1 or 2 vs. 1, 2, or 3). Sensitivity analyses that use a narrower GBS case definition (Brighton level 1 or 2) resulted in risk estimates that were not significant, likely due to the exclusion of additional cases and corresponding decrease in power.

Our study was unique in that it examined GBS risk following monovalent H1N1 vaccination among a population consisting of mostly elderly persons. This population carries a higher risk of GBS due to age, which we were able to control for with the self-controlled design. To verify that this study design did not appreciably affect risk estimates, we calculated attributable risk by using an age-specific comparison rate obtained by inserting the mean age of our study cohort (73 years) into a regression equation modeled from published GBS rates (4). The comparison rate when using this method was 2.14 per 100,000 person-years, resulting in an attributable risk of 2.16 per 100,000 person-years.

The strengths of the Medicare database in assessing vaccine safety include a large cohort of nearly all elderly Americans with individually linked data containing demographic, diagnostic, and vaccination information. The study design controlled for age, sex, and other time-constant, patient-specific characteristics, such as comorbidities, and the specific parameters (e.g., a longer comparison period) allowed for greater statistical power in the analyses.

Limitations of this study included the inability to fully adjust for some potential confounders, including the receipt of seasonal influenza vaccination, as well as preceding infections within the 6 weeks prior to GBS onset. Both factors can be difficult to accurately and completely assess; administration of the influenza vaccine can be ascertained only if a claim is submitted to Medicare, and information about preceding infections is limited by factors such as whether a physician inquires about them, whether a patient recalls them, and whether they are completely recorded. Additionally, the Brighton criteria can be difficult to operationalize in a retrospective study because medical charts may not always contain the information necessary to accurately classify cases. Strict clinical criteria (e.g., nadir date within exactly 28 days of symptom onset) may increase specificity at the expense of sensitivity, possibly resulting in missing some true cases. Underascertainment of H1N1 vaccination may have occurred, although Medicare allows vaccination billing from nontraditional providers (e.g., community pharmacies, public health clinics) (43), which would decrease the likelihood of this. Our study examined only those for whom an H1N1 vaccination claim was submitted. Whether vaccinees who were not captured by using claims data differed from the study population with regard to GBS incidence is unknown, and thus, the potential bias is unknown. Underascertainment of GBS is unlikely, because GBS is a well-defined disease with serious clinical sequelae that usually require hospitalization. It is possible that some GBS cases might have been miscoded as other conditions, although miscodes in general are likely nondifferential, resulting in little, if any, effect on our risk estimates. A few GBS cases might have been missed because of the criteria used for medical record review. We collected data for all cases with GBS admission dates within 126 days of H1N1 vaccination. We then used a comparison period that examined GBS symptom onset up to 119 days after vaccination. This allowed for a maximum of 7 days between GBS onset and GBS admission date for cases with GBS onset on the latest day of the comparison period (day 119). Our data indicate that 75% of cases had a GBS admission date within 7 days of GBS onset. Thus, we might have missed GBS cases with symptom onset closer to the end of this comparison period who were hospitalized more than 7 days after symptom onset, and this might have slightly overestimated the risk. Finally, our results are for a predominantly elderly population. Host-vaccine interactions hypothetically

could produce differing safety profiles by age group and could thus affect generalizability.

Although the Institute of Medicine has concluded that the evidence through 2008 has been inadequate to accept or reject a causal relationship between GBS and influenza vaccines administered after 1976, we found a statistically significant increased risk of GBS among Medicare beneficiaries after the 2009 monovalent H1N1 influenza vaccination, with and without adjustment for seasonality and exclusion of cases with preceding illness. This observed risk was slightly higher than that seen with previous seasonal influenza vaccines (17–23), and it was similar to or slightly lower than that found in other studies examining GBS risk with this vaccine (38–41). However, additional results that used a stricter case definition were not statistically significant, and our ability to account for preceding illness was limited. Furthermore, the observed risk was substantially lower than that seen with the 1976 swine flu vaccine.

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REFERENCES

1. Hughes RA, Rees JH. Clinical and epidemiologic features of Guillain-Barré Syndrome. *J Infect Dis*. 1997;176(2 suppl): 92S–98S.
2. Rees JH, Thompson RD, Smeeton NC, et al. Epidemiological study of Guillain-Barré Syndrome in south east England. *J Neurol Neurosurg Psychiatry*. 1998;64(1):74–77.
3. Govoni V, Granieri E. Epidemiology of the Guillain-Barré Syndrome. *Curr Opin Neurol*. 2001;14(5):605–613.
4. Sejvar JJ, Baughman AL, Wise M, et al. Population incidence of Guillain-Barré Syndrome: a systematic review and meta-analysis. *Neuroepidemiology*. 2011;36(2):123–133.
5. Hughes RA, Hadden RD, Gregson NA, et al. Pathogenesis of Guillain-Barré Syndrome. *J Neuroimmunol*. 1999;100(1-2): 74–97.
6. Winer JB, Hughes RA, Anderson MJ, et al. A prospective study of acute idiopathic neuropathy. II. Antecedent events. *J Neurol Neurosurg Psychiatry*. 1988;51(5): 613–618.
7. Guillain-Barré Syndrome Study Group. Guillain-Barré Syndrome: an Italian multicentre case-control study. *Neurol Sci*. 2000;21(4):229–234.
8. Israeli E, Agmon-Levin N, Blank M, et al. Guillain-Barré Syndrome—a classical autoimmune disease triggered by infection or vaccination. *Clin Rev Allergy Immunol*. 2012; 42(2):121–130.
9. Kinnunen E, Junttila O, Haukka J, et al. Nationwide oral poliovirus vaccination campaign and the incidence of Guillain-Barré Syndrome. *Am J Epidemiol*. 1998;147(1):69–73.
10. Liu GF, Wu ZL, Wu HS, et al. A case-control study on children with Guillain-Barré Syndrome in North China. *Biomed Environ Sci*. 2003;16(2):105–111.
11. Centers for Disease Control and Prevention. Update: Guillain-Barré Syndrome among recipients of Menactra meningococcal conjugate vaccine—United States, June 2005–September 2006. *MMWR Morb Mortal Wkly Rep*. 2006;55(41): 1120–1124.
12. Hemachudha T, Griffin DE, Chen WW, et al. Immunologic studies of rabies vaccination–induced Guillain-Barré Syndrome. *Neurology*. 1988;38(3):375–378.
13. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barré Syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. *Am J Epidemiol*. 1979;110(2):105–123.
14. Langmuir AD. Guillain-Barré Syndrome: the swine influenza virus vaccine incident in the United States of America, 1976–77: preliminary communication. *J R Soc Med*. 1979; 72(9):660–669.
15. Langmuir AD, Bregman DJ, Kurland LT, et al. An epidemiologic and clinical evaluation of Guillain-Barré Syndrome reported in association with the administration of swine influenza vaccines. *Am J Epidemiol*. 1984;119(6):841–879.
16. Safranek TJ, Lawrence DN, Kurland LT, et al. Reassessment of the association between Guillain-Barré Syndrome and receipt of swine influenza vaccine in 1976–1977: results of a two-state study. Expert Neurology Group. *Am J Epidemiol*. 1991;133(9):940–951.
17. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré Syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *N Engl J Med*. 1998;339(25):1797–1802.
18. Burwen DR, Ball R, Bryan WW, et al. Evaluation of Guillain-Barré Syndrome among recipients of influenza vaccine in 2000 and 2001. *Am J Prev Med*. 2010;39(4): 296–304.
19. Juurlink DN, Stukel TA, Kwong J, et al. Guillain-Barré Syndrome after influenza vaccination in adults: a population-based study. *Arch Intern Med*. 2006;166(20): 2217–2221.
20. Hurwitz ES, Schonberger LB, Nelson DB, et al. Guillain-Barré Syndrome and the 1978-1979 influenza vaccine. *N Engl J Med*. 1981;304(26):1557–1561.
21. Kaplan JE, Katona P, Hurwitz ES, et al. Guillain-Barré Syndrome in the United States, 1979–1980 and 1980–1981. Lack of an association with influenza vaccination. *JAMA*. 1982;248(6):698–700.
22. Roscelli JD, Bass JW, Pang L. Guillain-Barré Syndrome and influenza vaccination in the US Army, 1980–1988. *Am J Epidemiol*. 1991;133(9):952–955.
23. Stowe J, Andrews N, Wise L, et al. Investigation of the temporal association of Guillain-Barré Syndrome with

influenza vaccine and influenzalike illness using the United Kingdom General Practice Research Database. *Am J Epidemiol*. 2009;169(3):382–388.
24. Stratton K, Alamario D, Wizemann T, et al, eds., *Immunization Safety Review: Influenza Vaccines and Neurological Complications*. Immunization Safety Review Committee, Institute of Medicine. Washington, DC: The National Academies Press; 2004.
25. Stratton K, Ford A, Rush E, et al, eds., *Adverse Effects of Vaccines: Evidence and Causality.* Committee to Review Adverse Effects of Vaccines, Institute of Medicine. Washington, DC: National Academies Press; 2011.
26. Maurer J, Uscher-Pines L, Harris KM. Perceived seriousness of seasonal and A (H1N1) influenzas, attitudes toward vaccination, and vaccine uptake among U.S. adults: does the source of information matter? *Prev Med*. 2010;51(2):185–187.
27. Salmon DA, Akhtar A, Mergler MJ, et al. Immunization-safety monitoring systems for the 2009 H1N1 monovalent influenza vaccination program. *Pediatrics*. 2011;127(1 suppl): 78S–86S.
28. Burwen DR, Sandhu SK, MaCurdy TE, et al. Surveillance for Guillain-Barré Syndrome after influenza vaccination among the Medicare population, 2009–2010. *Am J Public Health*. 2012;102(10):1921–1927.
29. Centers for Disease Control and Prevention. Preliminary results: surveillance for Guillain-Barré Syndrome after receipt of influenza A (H1N1) 2009 monovalent vaccine—United States, 2009–2010. *MMWR Morb Mortal Wkly Rep*. 2010; 59(21):657–661.
30. Centers for Medicare & Medicaid Services. US Department of Health and Human Services. Table 2.1. Medicare enrollment: hospital insurance and/or supplementary medical insurance programs for total, fee-for-service and managed care enrollees as of July 1, 2009: selected calendar years 1966–2009. Baltimore, MD: Centers for Medicare & Medicaid Services; 2012. (http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/MedicareMedicaidStatSupp/2010.html). (Accessed July 3, 2012).
31. Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barré Syndrome and Fisher Syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine*. 2011;29(3):599–612.
32. Lee GM, Greene SK, Weintraub ES, et al. H1N1 and seasonal influenza vaccine safety in the Vaccine Safety Datalink Project. *Am J Prev Med*. 2011;41(2):121–128.
33. Greene SK, Kulldorff M, Lewis EM, et al. Near real-time surveillance for influenza vaccine safety: proof-of-concept in the Vaccine Safety Datalink Project. *Am J Epidemiol*. 2010;171(2):177–188.
34. Klein NP, Hansen J, Lewis E, et al. Post-marketing safety evaluation of a tetanus toxoid, reduced diphtheria toxoid and 3-component acellular pertussis vaccine administered to a cohort of adolescents in a United States health maintenance organization. *Pediatr Infect Dis J*. 2010; 29(7):613–617.
35. Centers for Disease Control and Prevention. US Department of Health and Human Services. Seasonal Influenza. Past weekly influenza surveillance reports. Atlanta, GA: Centers for Disease Control and Prevention; 2012. (http://www.cdc.gov/flu/weekly/pastreports.htm). (Accessed February 2, 2012).
36. McClure DL, Xu S, Weintraub E, et al. An efficient statistical algorithm for a temporal scan statistic applied to vaccine safety analyses. *Vaccine*. 2012;30(27):3986–3991.
37. Kulldorff M. *SaTScan User Guide for Version 9.0*. Boston, MA: Information Management Services, Inc; 2010. (http://www.satscan.org). (Accessed May 25, 2012).
38. Tokars JI, Lewis P, DeStefano F, et al. The risk of Guillain-Barré Syndrome associated with influenza A (H1N1) 2009 monovalent vaccine and 2009–2010 seasonal influenza vaccines: results from self-controlled analyses. *Pharmacoepidemiol Drug Saf*. 2012;21(5):546–552.
39. Greene SK, Rett M, Weintraub ES, et al. Risk of confirmed Guillain-Barré Syndrome following receipt of monovalent inactivated influenza A (H1N1) and seasonal influenza vaccines in the Vaccine Safety Datalink Project, 2009–2010. *Am J Epidemiol*. 2012;175(11):1100–1109.
40. Yih WK, Lee GM, Lieu TA, et al. Surveillance for adverse events following receipt of pandemic 2009 H1N1 vaccine in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, 2009–2010. *Am J Epidemiol*. 2012; 175(11):1120–1128.
41. Wise ME, Viray M, Sejvar JJ, et al. Guillain-Barré Syndrome during the 2009-2010 H1N1 influenza vaccination campaign: population-based surveillance among 45 million Americans. *Am J Epidemiol*. 2012;175(11):1110–1119.
42. Copeland KT, Checkoway H, McMichael AJ, et al. Bias due to misclassification in the estimation of relative risk. *Am J Epidemiol*. 1977;105(5):488–495.
43. Centers for Medicare & Medicaid Services, US Department of Health and Human Services. Medicare preventive services quick reference information: Medicare immunization billing. Baltimore, MD: Centers for Medicare & Medicaid Services; 2012. (http://www.cms.gov/MLNProducts/downloads/qr_immun_bill.pdf). (Accessed June 6, 2012).

(Appendix follows)

Appendix Table 1. Clinical Case Definitions for Guillain-Barré Syndrome and Fisher Syndrome[a] Used to Classify Medically Reviewed Cases Occurring After Monovalent 2009 H1N1 Vaccination Among the US Medicare Population, 2009–2010

Syndrome	Diagnostic Criterion[b]	Brighton Level 1 Diagnostic Certainty	Brighton Level 2 Diagnostic Certainty	Brighton Level 3 Diagnostic Certainty
Guillain-Barré Syndrome				
	Flaccidity	Bilateral *and* flaccid paresis of the limbs	Bilateral *and* flaccid paresis of the limbs	Bilateral *and* flaccid paresis of the limbs
	Reflexes	Decreased or absent deep tendon reflexes in affected limbs	Decreased or absent deep tendon reflexes in affected limbs	Decreased or absent deep tendon reflexes in affected limbs
	Monophasic illness	Monophasic illness pattern *and* interval between onset and nadir of weakness between 12 hours and 28 days *and* subsequent clinical plateau	Monophasic illness pattern *and* interval between onset and nadir of weakness between 12 hours and 28 days *and* subsequent clinical plateau	Monophasic illness pattern *and* interval between onset and nadir of weakness between 12 hours and 28 days *and* subsequent clinical plateau
	Diagnostic studies	Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above the laboratory normal value *and* CSF total white blood cell count <50 cells/mm^3)	CSF total white blood cell count <50 cells/mm^3 (with or without CSF protein level above the laboratory normal value) *or* if CSF not collected or results not available, electrophysiological studies consistent with GBS	
		Electrophysiological findings consistent with GBS		
	Alternative diagnoses	Absence of an identified alternative diagnosis for weakness	Absence of identified alternative diagnosis for weakness	Absence of identified alternative diagnosis for weakness
Fisher Syndrome				
	Ophthalmoparesis, hyporeflexia, and ataxia	Bilateral ophthalmoparesis *and* bilateral reduced or absent tendon reflexes *and* ataxia	Bilateral ophthalmoparesis *and* bilateral reduced or absent tendon reflexes *and* ataxia	Bilateral ophthalmoparesis *and* bilateral reduced or absent tendon reflexes *and* ataxia
	Limb weakness	Absence of limb weakness	Absence of limb weakness	Absence of limb weakness
	Monophasic illness	Monophasic illness pattern *and* interval between onset and nadir of weakness between 12 hours and 28 days *and* subsequent clinical plateau	Monophasic illness pattern *and* interval between onset and nadir of weakness between 12 hours and 28 days *and* subsequent clinical plateau	Monophasic illness pattern *and* interval between onset and nadir of weakness between 12 hours and 28 days *and* subsequent clinical plateau
	Diagnostic studies	Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above the laboratory normal *and* total CSF white blood cell count <50 cells/mm^3)	CSF total white blood cell count <50 cells/mm^3 (with or without CSF protein level above the laboratory normal value) *or* nerve conduction studies are normal or indicate involvement of sensory nerves only	
		Nerve conduction studies are normal or indicate involvement of sensory nerves only		
	Altered consciousness or corticospinal tract signs	No alterations in consciousness or corticospinal tract signs	No alterations in consciousness or corticospinal tract signs	No alterations in consciousness or corticospinal tract signs
	Alternative diagnoses	Absence of identified alternative diagnosis	Absence of identified alternative diagnosis	Absence of identified alternative diagnosis