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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

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An increased risk of Guillain-Barré syndrome (GBS) following administration of the 1976 swine influenza vaccine led to a heightened focus on GBS when monovalent vaccines against a novel influenza A (H1N1) virus of swine origin were introduced in 2009. GBS cases following receipt of monovalent inactivated (MIV) and seasonal trivalent inactivated (TIV) influenza vaccines in the Vaccine Safety Datalink Project in 2009–2010 were identified in electronic data and confirmed by medical record review. Within 1–42 days following vaccination, 9 cases were confirmed in MIV recipients (1.48 million doses), and 8 cases were confirmed in TIV-only recipients who did not also receive MIV during 2009–2010 (1.72 million doses). Five cases following MIV and 1 case following TIV-only had an antecedent respiratory infection, a known GBS risk factor; furthermore, unlike TIV, MIV administration was concurrent with heightened influenza activity. In a self-controlled risk interval analysis comparing GBS onset within 1–42 days following MIV with GBS onset 43–127 days following MIV, the risk difference was 5.0 cases per million doses (95% confidence interval: 0.5, 9.5). No statistically significant increased GBS risk was found within 1–42 days following TIV-only vaccination versus 43–84 days following vaccination (risk difference = 1.1 cases per million doses, 95% confidence interval: −3.1, 5.4). Further evaluation to assess GBS risk following both vaccination and respiratory infection is warranted.

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

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; GBS, Guillain-Barré syndrome; ICD-9, *International Classification of Diseases*, Ninth Revision; MIV, monovalent inactivated influenza vaccine; TIV, trivalent inactivated influenza vaccine; VSD, Vaccine Safety Datalink.

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

The United States implemented a swine influenza vaccination program in 1976, in response to concerns that a novel swine-origin influenza A (H1N1) virus would cause substantial morbidity and mortality. Over 49 million persons were vaccinated, mostly from October to December 1976 (1). An excess risk of approximately 1 additional case of Guillain-Barré syndrome (GBS) per 100,000 swine influenza vaccinations was noted, with significantly elevated risk in each of the first 9 weeks following vaccination, peaking in weeks 2 and 3 (2, 3); this contributed to the suspension of the swine influenza vaccination program in December 1976. In contrast, most (4–8) analyses of seasonal influenza vaccines in subsequent years have not demonstrated a significant association with GBS, although an association of approximately

Table 1. Case Definitions for Guillain-Barré Syndrome and Fisher Syndrome (15), as Applied in the Vaccine Safety Datalink Project, 2009–2010

Sign or Laboratory Result	Guillain-Barré Syndrome	Fisher Syndrome
Clinical	Acute onset of bilateral and relatively symmetric flaccid weakness/paralysis of the limbs with or without involvement of respiratory or cranial nerve-innervated muscles *and*	Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes, and ataxia *and*
		Absence of limb weakness *and*
	Decreased or absent deep tendon reflexes, at least in affected limbs, *and*	Monophasic illness pattern and interval between onset and nadir of weakness between 12 hours and 28 days and subsequent clinical plateau *and*
	Monophasic illness pattern, with weakness nadir reached between 12 hours and 28 days, followed by clinical plateau and subsequent improvement, or death *and*	No alterations in consciousness or corticospinal tract signs *and*
	Absence of an alternative diagnosis for weakness	Absence of an identified alternative diagnosis
Electrophysiologic	Abnormal nerve conduction in limbs	Nerve conduction studies are normal, or indicate the involvement of sensory nerves only
CSF	Cytoalbuminologic dissociation (elevation of CSF protein level above laboratory normal value *and* CSF total white blood cell count <50 cells/mm^3)	Cytoalbuminologic dissociation (elevation of CSF protein level above laboratory normal value *and* CSF total white blood cell count <50 cells/mm^3)

Abbreviation: CSF, cerebrospinal fluid.

1 additional GBS case per million vaccinees has been reported (9).

With the introduction of influenza A (H1N1) 2009 monovalent vaccines in response to the emergence of another novel swine-origin influenza A (H1N1) virus in April 2009, multiple vaccine safety surveillance systems, including the Vaccine Safety Datalink (VSD) Project, were utilized. These systems monitored vaccinees for GBS and other potential adverse events following immunization during the 2009–2010 influenza season (10, 11). This report characterizes GBS risk following receipt of monovalent inactivated influenza vaccine (MIV) and seasonal trivalent inactivated influenza vaccine (TIV) in the VSD population during the 2009–2010 influenza season.

MATERIALS AND METHODS

Study population

The VSD Project (12–14) is a collaboration between the Centers for Disease Control and Prevention (CDC), America's Health Insurance Plans, and participating medical care organizations. The VSD Project collects vaccination and medical care data on enrollees, including age, sex, dates and types of vaccines administered, dates of medical encounters occurring in clinic, emergency department, and hospital settings, and *International Classification of Diseases*, Ninth Revision (ICD-9) diagnosis codes assigned to these medical encounters.

Eight medical care organizations during the 2009–2010 influenza season provided data on over 9 million members: Group Health Cooperative (Washington State); Harvard Vanguard Medical Associates, and Harvard Pilgrim Health Care (Massachusetts); HealthPartners Research Foundation (Minnesota); Kaiser Permanente of Colorado (Colorado); Kaiser Permanente of Northern California (California); Kaiser Permanente of Southern California (California); Marshfield Clinic Research Foundation (Wisconsin); and Kaiser Permanente Northwest (Oregon). Institutional review boards at each VSD site and at CDC approved this study, and an informed consent waiver was issued.

Case-finding and medical record review

Potential GBS cases were identified by searching for ICD-9 code 357.0 (acute infective polyneuritis) in any setting (inpatient, emergency department, or clinic). Cases in electronic data following a first or second dose of MIV or TIV administered between August 2009 and April 2010 were identified. To restrict the data to new-onset events, we excluded cases if they had another GBS diagnosis recorded in electronic data within the prior year.

Medical charts were reviewed for a minimum of 60 days prior to the incident GBS diagnosis and 60 days following the diagnosis, to exclude cases representing a history of GBS or follow-up for GBS without new symptom onset. The chart abstraction instrument was based on the Brighton Collaboration definition (15). Possible new-onset cases underwent final review and adjudication by 2 neurologists (A. A. A. and either D. T. H. or S. I. S.) with expertise in acute neuropathies. Separate criteria were used for GBS and Fisher syndrome (Table 1), and cases were categorized into 4 levels of certainty (Table 2). Descriptive analyses were conducted for confirmed new-onset cases.

Table 2. Information Required in Order to Assign the Level of Diagnostic Certainty for Guillain-Barré Syndrome or Fisher Syndrome (15), Vaccine Safety Datalink Project, 2009–2010

Level of Diagnostic Certainty	Required Data
Brighton Criteria Level 1	Clinical *and* electrophysiologic *and* cerebrospinal fluid
Brighton Criteria Level 2	Clinical *and* either electrophysiologic *or* cerebrospinal fluid
Brighton Criteria Level 3	Clinical
Probable	Reported event of Guillain-Barré syndrome or Fisher syndrome with insufficient evidence to meet the case definition for Brighton Criteria Levels 1–3

Seasonal patterns

To visualize the timing and seasonality of TIV and MIV vaccination, we plotted the weekly administration of these vaccines within the VSD Project for the 2006–2007 to 2009–2010 influenza seasons. Weekly GBS diagnoses in electronic data without regard to vaccination status were plotted for the same period. The national peak of outpatient visits for influenza-like illness was determined from data collected by the US Outpatient Influenza-Like Illness Surveillance Network (16).

Self-controlled risk interval design

A self-controlled risk interval design (17–19) was used to compare the risk of GBS onset in a predefined risk period (1–42 days) following MIV or TIV administration with the risk in a control period (≥43 days). This self-controlled risk interval design diverged from a standard risk interval design (20) in that we conditioned on the individual vaccinee having GBS onset in either the risk period or the control period. The self-controlled risk interval design was more efficient to implement because only vaccinated cases (as opposed to all vaccinees) were informative in the estimation of the relative risk. Furthermore, the conceptual framework used to design the study began with well-defined intervals in relation to vaccination (i.e., exposure). This is in contrast to the self-controlled case series (21, 22) and case-crossover (23) designs, which begin with cases (i.e., outcomes) occurring during an observation period and subsequently examine the timing of vaccination in relation to the outcome.

The control period for both vaccines was originally defined as equal in length to the risk period (43–84 days; i.e., 7–12 weeks), but the control period for MIV was then extended (43–127 days; i.e., 7–18 weeks) for consistency with the July 2010 version of a protocol for a planned Department of Health and Human Services study combining data from multiple vaccine safety surveillance systems. Because the occurrence of GBS within 6 weeks of a prior influenza vaccination is a precaution for receiving future influenza vaccines (24), a control period prior to vaccination was not selected, to avoid underestimating the GBS background rate. The null hypothesis assumed that the risk of GBS onset on a day during the risk period was the same as that on a day during the control period. The relative risk (an incidence rate ratio) of GBS occurring during the risk period versus the control period was estimated by fitting a conditional Poisson regression model using data only from cases (25). A secondary analysis adjusting for month of GBS onset (December to January vs. November, February, or March) yielded similar results (not shown).

To calculate the risk difference, the numbers of person-days in the risk and control periods were determined for each vaccinee. Vaccinees receiving 2 doses contributed more person-time than vaccinees receiving 1 dose; vaccinees receiving both MIV and TIV contributed varying amounts of person-time, depending on the interval(s) between vaccine administrations; and the control period for MIV was defined to exclude any portion of the risk period following TIV. The daily rate during the risk period was calculated using the number of confirmed cases in the risk period divided by exposed person-time, and the daily rate during the control period was calculated using the number of confirmed cases in the control period divided by unexposed person-time. Then, the risk difference for the general population of VSD vaccinees during a 42-day follow-up period and its confidence interval were calculated using the standard formula for the difference between 2 independent Poisson means, ignoring the weak within-subject correlation because GBS is rare.

If the self-controlled risk interval analysis suggested statistically significant elevated risk at $\alpha = 0.05$ between a particular vaccine type and GBS, then 2 secondary analyses, described below, were applied.

Case-centered analysis

If both vaccination and GBS exhibited seasonality during the study period, then the self-controlled risk interval analysis can be biased. Because vaccine administration is seasonal, we decided a priori without regard to whether GBS was also seasonal to implement a case-centered analysis to adjust for time-varying covariates (26–28).

Logistic regression was used to model the observed-versus-expected odds that GBS occurred within 1–42 days following vaccination. The data set included only 1 record for each stratum (defined by onset date, age group, sex, and VSD site) in which there was a GBS case. The model included 2 variables: a binary indicator of the outcome (whether GBS was inside or outside of the risk period) and the log of the ''expected'' odds of being in the risk period, specified as an offset. The ''expected'' odds were derived from the proportion of vaccinees in the stratum among the whole population who were still in a postvaccine risk period on the onset day of the GBS case. The intercept yielded the odds ratio estimate. To obtain a corresponding risk difference estimate, a crude risk (r_1) was obtained by dividing the total number of GBS cases with onset during the risk period by the total number of vaccinees. The risk difference was estimated as $r_1 \times (1 - 1/\text{odds ratio})$, and its 95% confidence interval was calculated using empirical percentiles obtained through sampling independent realizations of r_1 from a binomial distribution and independent realizations of log(odds ratio) from a normal distribution. The parameters of the binomial and normal distributions were determined by the corresponding parameter estimates.

The case-centered analysis, which was not self-controlled, had a smaller effective sample size than the self-controlled risk interval analysis. The reason is that for GBS cases occurring early in the vaccination season, the proportion of vaccinees still in the risk period following vaccination was almost 100%, making those GBS cases essentially uninformative (Appendix Table 1).

All analyses described above were conducted using SAS, version 9 (SAS Institute Inc., Cary, North Carolina).

Temporal scan statistic

The presence of temporal clusters of GBS symptom onset following MIV was assessed to identify any periods of elevated risk other than the predefined risk period of 1–42 days. A temporal scan statistic with variable window size was

used, which adjusted for the multiple testing inherent when overlapping time intervals of different length are evaluated (SaTScan, version 9.1; M. K. and Information Management Services, Inc., Silver Spring, Maryland) (29, 30). Confirmed cases with illness onset within 1–84 days following MIV were identified. Under the null hypothesis of no association between vaccination and GBS symptom onset, onset was assumed to be uniformly and independently distributed during the 84 days after vaccination. To identify potential clusters, all time intervals that started and ended within 42 days were evaluated.

RESULTS

TIV administration was concentrated in surveillance weeks 37–44 (i.e., September 13–November 7, 2009), while MIV administration was concentrated later in weeks 43–7 (i.e., October 25, 2009–February 20, 2010) (Figure 1, part A). Although influenza-like illness peaked nationally in surveillance week 42 (16), minimal seasonality in GBS incidence was observed within VSD (Figure 1, part B).

Thirty-one GBS cases were diagnosed within 1–127 days following 1,480,135 MIV doses administered (Figure 2, part A); of MIV doses, 1,121,636 (75.8%) were administered to patients who also received *trivalent* inactivated or live influenza vaccine during the 2009–2010 season. In addition, 39 GBS cases were diagnosed within 1–84 days following 1,724,570 TIV doses administered to patients who did not also receive *monovalent* inactivated or live influenza vaccine in 2009–2010 (i.e., TIV-only recipients). Of 70 total cases, 69 (98.6%) had medical records available for review, and 40 (58.0 %) were not confirmed, for the following reasons: alternative diagnosis ($n = 15$), no documentation of GBS in the medical record ($n = 14$), remote GBS occurrence listed in medical history ($n = 8$), coding error ($n = 2$), and follow-up care for prior GBS diagnosis ($n = 1$). Alternative diagnoses included Charcot-Marie-Tooth disease, conversion disorder, myositis, steroid or toxic myopathy, and chronic inflammatory demyelinating polyneuropathy.

The remaining 13 cases following MIV (Figure 2, part B) and 16 cases following TIV-only were confirmed, indicating an overall positive predictive value of 42.0% (29/69) for ICD-9 code 357.0. The positive predictive value for initial GBS diagnoses in the inpatient setting (20/31 = 64.5%) was higher than the positive predictive values in the clinic (8/30 = 26.7%) and emergency department (1/8 = 12.5%) settings. Although 31.0% of patients with GBS were initially diagnosed as outpatients, 93.1% were ultimately hospitalized, for a median hospital stay of 10 days (range, 2–144 days). Five patients (17.2%) required intubation, 26 (89.7%) were treated with intravenous immune globulin, and 7 (24.1%) received plasmapheresis. There was 1 death (3.4%), although available medical records were insufficient to determine whether it was attributable to GBS. The median number of days between illness onset and the date of last follow-up in the medical record was 142 (range, 21–286 days).

Based on onset date (Figure 2, part C), 9 GBS patients had illness onset during the 1- to 42-day risk period following MIV, of whom 2 cases had also received a dose of seasonal influenza vaccine in the 1–42 days prior to onset. Most met Brighton Criteria Level 1 or 2 for GBS ($n = 5$; 55.6%) or Fisher syndrome ($n = 1$; 11.1%), while 1 (11.1%) had only clinical evidence of GBS (i.e., Brighton Criteria Level 3), and 2 (22.2%) were probable cases with insufficient evidence to meet Brighton Criteria Levels 1–3. Of these 9 cases, 6 (66.7%) were female, and the median age was 51 years (range, 1–71 years). Patients had medical histories notable for prior neurologic disease ($n = 2$; 22.2%), including cranial nerve palsies (i.e., Bell's and abducens nerve; $n = 2$), and peripheral nervous system disorders/cervical spinal stenosis/radiculopathy ($n = 1$). Family histories were notable for neurologic disease ($n = 3$; 33.3%) and autoimmune disease ($n = 2$; 22.2%). Five patients (55.6%; all Brighton Criteria Level 1 or 2) had had an upper respiratory infection within 1 month prior to GBS onset, and none had a recorded recent gastrointestinal illness.

Among TIV-only vaccinees, 8 patients had illness onset during the 1- to 42-day risk period following TIV. Half met Brighton Criteria Level 2 for GBS ($n = 4$; 50.0%), 1 (12.5%) had only clinical evidence of GBS (i.e., Brighton Criteria Level 3), and 3 (37.5%) were probable cases with insufficient evidence to meet Brighton Criteria Levels 1–3. Of these 8 patients, 5 (62.5%) were female, and the median age was 52 years (range, 2–83 years). Patients had medical histories of prior autoimmune disease ($n = 1$; 12.5%) and neurologic disease ($n = 5$; 62.5%), including peripheral neuropathy ($n = 4$), and reflex sympathetic dystrophy ($n = 1$). Two patients (25.0%) had a family history of autoimmune disease. One (12.5%) had had an upper respiratory infection and 1 (12.5%) had had a gastrointestinal illness within 1 month prior to GBS onset.

Self-controlled risk interval design

The risk of confirmed GBS was increased following receipt of MIV (relative risk = 4.4 (95% confidence interval (CI): 1.3, 14.2); risk difference = 5.0 per million MIV doses (95% CI: 0.5, 9.5)) but not following receipt of TIV-only (relative risk = 1.3 (95% CI: 0.5, 3.8); risk difference = 1.1 per million doses (95% CI: −3.1, 5.4)). The results were similar after restriction of the data to the subset of confirmed cases classified as Brighton Criteria Levels 1–3 (Table 3). Of the patients who had GBS following receipt of MIV, 2 of 9 whose onset occurred during the risk period and 0 of 4 whose onset occurred during the comparison period had also received a dose of seasonal influenza vaccine 1–42 days prior to onset.

Because the relative risk for the association between GBS and vaccination was statistically significant for MIV but not for TIV-only, secondary analyses were performed only for cases following MIV.

Secondary analyses

The case-centered analysis used the same 13 cases as the self-controlled risk interval analysis but had a smaller effective sample size (Appendix Table 1) and lower statistical power. The odds ratio for having illness onset inside of the 42-day risk period versus outside of that period was 2.0 (95% CI: 0.5, 8.1). The risk difference was 3.4 per million MIV doses (95% CI: −6.4, 7.6).

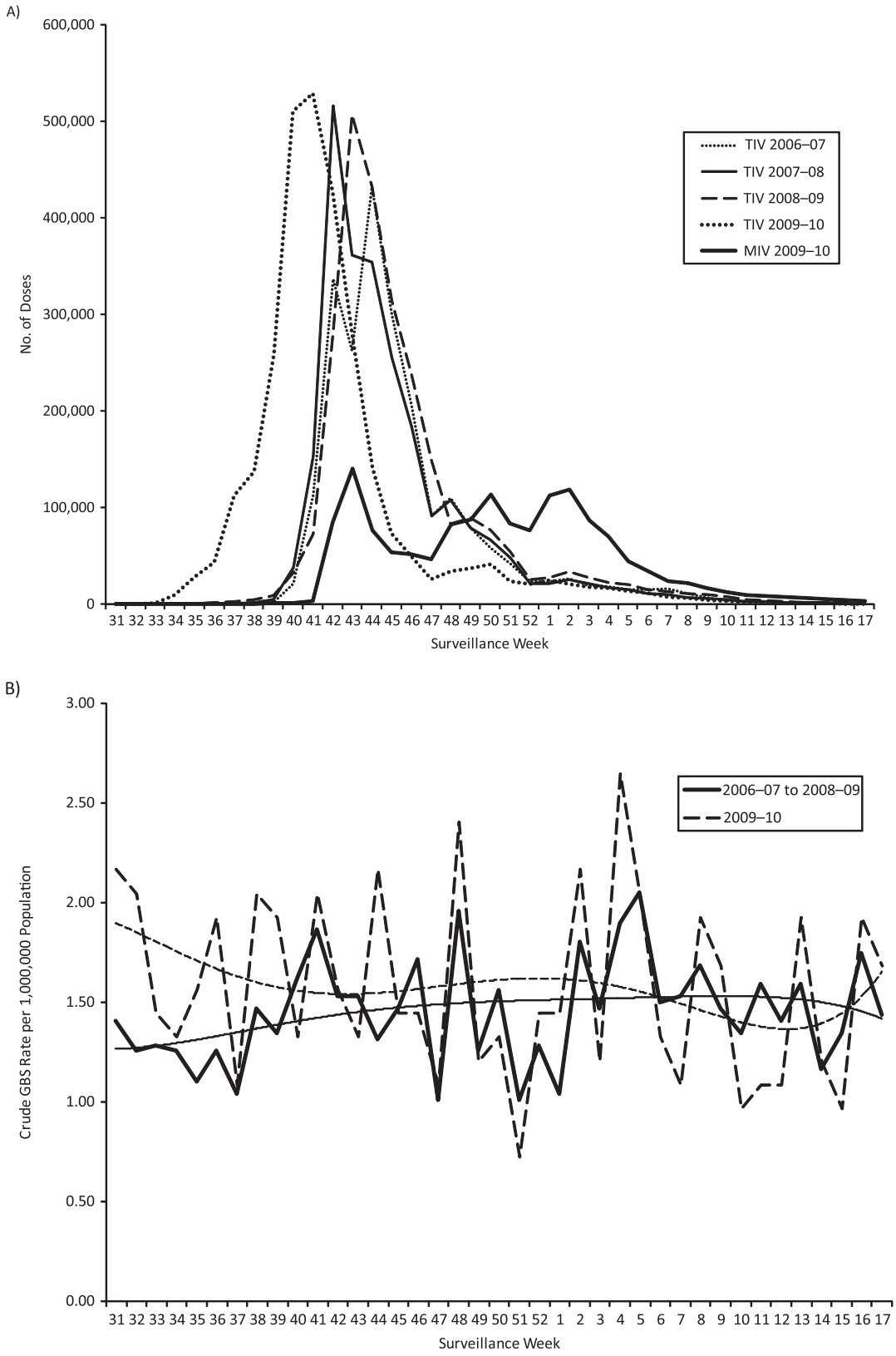

Figure 1. Seasonality of influenza vaccination and Guillain-Barré syndrome (GBS) in the Vaccine Safety Datalink Project. A) Administration of seasonal trivalent inactivated (TIV) and monovalent inactivated (MIV) influenza vaccines during the 2006–2007 to 2009–2010 influenza seasons. B) Rate of first-in-1-year GBS diagnosis without regard to vaccination status during the 2006–2007 to 2008–2009 (averaged) and 2009–2010 influenza seasons.

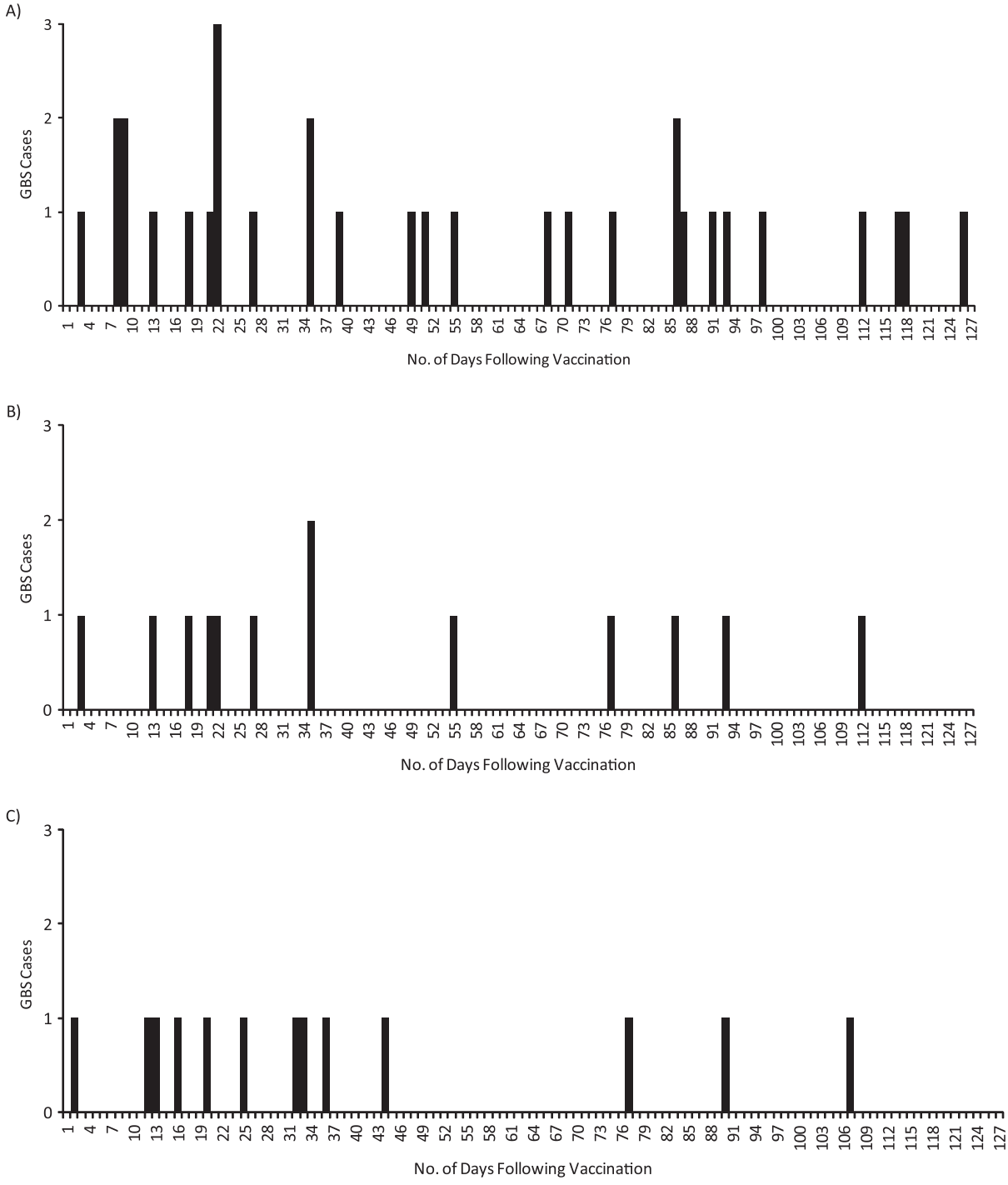

Figure 2. Timing of the occurrence of Guillain-Barré syndrome (GBS) 1–127 days following receipt of monovalent inactivated influenza vaccine, Vaccine Safety Datalink Project, 2009–2010. The graphs show timing according to A) *International Classification of Diseases,* Ninth Revision (ICD-9) code diagnosis date ($n = 31$), B) ICD-9 diagnosis date for confirmed cases ($n = 13$), and C) onset date for confirmed cases ($n = 13$).

Of the 9 cases with illness onset 1–42 days following MIV (Figure 2C), 8 had illness onset within 12–36 days following MIV, but this temporal cluster was not statistically significant ($P = 0.12$).

DISCUSSION

In the VSD population, we found evidence for a small elevated risk of confirmed GBS occurring within 1–42 days

Table 3. Risk of Guillain-Barré Syndrome Following Receipt of Monovalent Inactivated and Seasonal Trivalent Inactivated Influenza Vaccines (Self-Controlled Risk Interval Analysis), Vaccine Safety Datalink Project, 2009–2010

Vaccine and Brighton Criteria Level	No. of Cases in Risk Period 1–42 Days Following Vaccination	No. of Person-Days for Cases in Risk Period	No. of Cases in Control Period[a]	No. of Person-Days for Cases in Control Period	Relative Risk	95% CI	Risk Difference Per Million Doses	95% CI
MIV[b]								
Levels 1–3 and probable	9	588	4	1,110	4.4	1.3, 14.2	5.0	0.5, 9.5
Levels 1–3 only	7	420	3	850	4.7	1.2, 18.3	3.9	0.0, 7.9
TIV-only[c]								
Levels 1–3 and probable	8	605	6	588	1.3	0.5, 3.8	1.1	−3.1, 5.4
Levels 1–3 only	5	420	5	420	1.0	0.3, 3.5	0.0	−3.6, 3.6

Abbreviations: CI, confidence interval; MIV, monovalent inactivated influenza vaccine; TIV, trivalent inactivated influenza vaccine.

[a] The control period was defined as 43–127 days following MIV and as 43–84 days following TIV-only.

[b] MIV was defined without regard to whether patients also received trivalent inactivated or live vaccine during the 2009–2010 influenza season.

[c] TIV was defined as restricted to patients who did not also receive monovalent inactivated or live vaccine at any time during the influenza season.

following MIV, but not following TIV-only, during the 2009–2010 influenza season. Statistically significant increases in GBS risk following receipt of MIV were suggested by the self-controlled risk interval analysis (relative risk = 4.4 (95% CI: 1.3, 14.2); risk difference = 5.0 per million MIV doses (95% CI: 0.5, 9.5)). This association cannot be explained by seasonality of GBS (Figure 1B), but it is notable that 5 of 9 GBS cases with onset during the 6 weeks following MIV vaccination had an antecedent respiratory infection, a known risk factor for GBS (31), as compared with 1 of 8 GBS cases following TIV-only vaccination in the same influenza season. Potential explanations for this include: 1) MIV was administered concurrently with the national peak of influenza-like illness activity (16), while most TIV doses were administered earlier (Figure 1A); 2) there was an interaction effect between MIV and infection that caused GBS; and/or 3) recent or concurrent infection influenced the probability or timing of vaccination, creating a potential bias. One would need to know the population-based risk of confirmed GBS following infection without vaccination in order to tease apart these associations. Furthermore, elevated but not statistically significant increases in risk were suggested by a case-centered analysis that adjusted for time-varying confounders. The case-centered analysis, however, was not self-controlled and had lower power. Within the 1- to 42-day risk period, there was no statistically significant temporal cluster of illness onset. The true excess GBS risk attributable to vaccination may be difficult to ascertain using observational data, because of the rarity of GBS, the time-limited nature of influenza vaccination and delays in MIV administration during the 2009–2010 season, and the potential role of respiratory infection.

The self-controlled risk interval analysis ruled out a risk difference greater than 9.5 GBS cases per million MIV doses, which was lower than the risk associated with the 1976 swine influenza vaccine (10 cases per million doses). However, the observed increased risk was slightly higher than that reported from other concurrent surveillance systems. Preliminary analyses of data from the CDC's Emerging Infections Program suggested an age-adjusted rate ratio of 1.77 among GBS patients who received the 2009 H1N1 vaccine versus those who did not receive it, corresponding to 0.8 excess GBS cases per 1 million vaccinations (10). Passive surveillance systems in the United States and in China received <2 reports (32) and 0.1 reports (33) of GBS, respectively, per million 2009 H1N1 doses administered. In a French case-control study drawing controls from a registry of patients provided by general practitioners, Grimaldi-Bensouda et al. (34) identified 1 and 5 GBS cases during the 6 weeks following administration of influenza A (H1N1) vaccine and following seasonal influenza vaccine, respectively, from October 2009 to March 2010; GBS was not associated with influenza vaccine but was statistically significantly associated with influenza or influenza-like symptoms in the prior 2 months. Subsequently, the VSD Project's preliminary evaluation of the 2010–2011 formulation of TIV (which included the novel H1N1 antigen but was administered earlier in the winter respiratory season than was MIV in 2009–2010) showed no statistically significant elevation in GBS risk on the basis of electronic data: As of January 29, 2011, with 2.83 million TIV doses administered, 26 cases had been observed, with 22.6 cases being expected historically (unpublished data).

The primary and secondary analyses had contrasting strengths and limitations. The self-controlled risk interval design controlled for confounders that did not vary over the observation period, such as potential comorbid conditions, but did not adjust for time-varying confounders, such as the seasonal effects of respiratory infection concurrent with vaccination. In contrast, the case-centered analysis adjusted for time-varying confounders that were independent of vaccination timing, but it had less power to detect an association and was not self-controlled. The difference in the point estimates between the self-controlled risk interval and case-centered analyses was at least partially due to the difference in effective sample sizes, although different confounder adjustments may also have contributed.

There were several additional potential limitations. First, doses administered to VSD enrollees outside of their physicians' offices may not have been included (35, 36). This may have decreased the statistical power to detect an association, but it is unlikely to have biased the analyses, which were restricted to cases with recorded vaccinations. Second, any differential follow-up for cases between risk and control periods could have resulted in ascertainment bias. Third, of the 5 confirmed cases occurring during the risk period for MIV and TIV with insufficient evidence to meet Brighton Criteria Levels 1–3, 2 lacked complete medical record documentation. Fourth, the crude GBS rate following TIV should not be calculated from the numbers presented, which exclude from the denominator TIV doses (not associated with GBS) that were given to patients who also received monovalent vaccine at any point during the 2009–2010 influenza season. Fifth, even with over 9 million people under surveillance, there was limited power to detect an increased risk of a very rare outcome. Pooling VSD data with data from other surveillance systems could increase power and more precisely define risk.

Despite the limitations of observational data, vaccine safety monitoring is a critical component of public health immunization efforts. For influenza vaccines, postmarket surveillance is particularly important. Premarket trials usually have insufficient power to identify elevated risks of rare adverse events like GBS, and new formulations are rapidly developed and approved for use on an annual basis, making large clinical trials impractical. Strengths of this study include active surveillance and medical record review in a large, well-defined population. Two neurologists with expertise in acute neuropathies adjudicated records and achieved consensus, thus minimizing variability in Brighton Criteria Level case classification. Furthermore, secondary analyses were conducted to overcome potential biases of the primary analysis (18).

In conclusion, there was a relatively small elevated risk of GBS following receipt of MIV, but not receipt of TIV-only, during the 2009–2010 influenza season. Interpretation of this increase should be conducted within the context of the known benefits of influenza vaccination in reducing morbidity and mortality (37) and with the recognition that the independent contribution of antecedent respiratory infection could not be fully assessed. The VSD Project continues to conduct population-based surveillance for GBS following TIV, which included the novel H1N1 antigen in the 2010–2011 and 2011–2012 formulations.

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(Appendix follows)

Appendix Table 1. Data Included in a Case-Centered Analysis of Guillain-Barré Syndrome Following Receipt of Monovalent Inactivated Influenza Vaccine, Vaccine Safety Datalink Project, 2009–2010[a]

Case No.	Was Case Vaccinated 1–42 Days Prior to Illness Onset?	All Vaccinees of the Same Age Group, Sex, and Vaccine Safety Datalink Site, Used in Offset Term			
		No. Vaccinated 1–42 Days Prior to Case's Onset Date	No. Vaccinated 43–127 Days Prior to Case's Onset Date	% Vaccinated 1–42 days Prior to Case's Onset Date	% Vaccinated 43–127 Days Prior to Case's Onset Date
1	Yes	3,123	18,048	14.8	
2	Yes	665	1,302	33.8	
3	Yes	4,854	9,481	33.9	
4	Yes	9,711	16,140	37.6	
5	Yes	7,504	9,523	44.1	
6	Yes	8,230	2,707	75.2	
7	Yes	1,073	139	88.5	
8	Yes	1,786	24	98.7	
9	Yes	818	1	99.9	
10	No	508	162		24.2
11	No	9,926	5,014		33.6
12	No	12,349	6,716		35.2
13	No	2,986	13,833		82.2

[a] Cases 1–9 received monovalent inactivated influenza vaccine during the 1–42 days prior to onset of Guillain-Barré syndrome. Of these, cases 8 and 9 were almost uninformative because nearly all vaccinees in their strata were also vaccinated in the prior 1–42 days. That is, the probability of these GBS cases occurring when they did in relation to vaccination was nearly 100%, and removing them from the analysis would not have meaningfully changed the point estimate or the 95% confidence interval. Cases 6, 7, and 13 were slightly more informative.