Original Contribution

Investigation of the Temporal Association of Guillain-Barré Syndrome With Influenza Vaccine and Influenzalike Illness Using the United Kingdom General Practice Research Database

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In 1976, the national swine influenza vaccination program in the United States was suspended because of an increased risk of Guillain-Barré syndrome. Subsequent studies of seasonal influenza vaccine have given conflicting results. The authors used the self-controlled case series method to investigate the relation of Guillain-Barré syndrome with influenza vaccine and influenzalike illness using cases recorded in the General Practice Research Database from 1990 to 2005 in the United Kingdom. The relative incidence of Guillain-Barré syndrome within 90 days of vaccination was 0.76 (95% confidence interval: 0.41, 1.40). In contrast, the relative incidence of Guillain-Barré syndrome within 90 days of an influenzalike illness was 7.35 (95% confidence interval: 4.36, 12.38), with the greatest relative incidence (16.64, 95% confidence interval: 9.37, 29.54) within 30 days. The relative incidence was similar (0.89, 95% confidence interval: 0.42, 1.89) when the analysis was restricted to a subset of validated cases. The authors found no evidence of an increased risk of Guillain-Barré syndrome after seasonal influenza vaccine. The finding of a greatly increased risk after influenzalike illness is consistent with anecdotal reports of a preceding respiratory illness in Guillain-Barré syndrome and has important implications for the risk/benefit assessment that would be carried out should pandemic vaccines be deployed in the future.

association; Great Britain; Guillain-Barré syndrome; influenza, human; influenza vaccines; safety

Abbreviations: GPRD, General Practice Research Database; HES, Hospital Episode Statistics; VAERS, Vaccine Adverse Event Reporting System.

Guillain-Barré syndrome is an autoimmune disease often preceded by a respiratory or gastrointestinal illness. It is the commonest cause of acute neuromuscular paralysis in the United Kingdom, with an estimated annual incidence of 1.5/100,000 (95% confidence interval: 1.3, 1.8) (1). Clinical features include motor, sensory, and autonomic dysfunction such as limb weakness, severe pain, and sinus arrhythmia. Cases can present in any age group, but incidence increases with age, with an excess in males (2).

In 1976, the national influenza immunization program in the United States was suspended following an increased number of reports of Guillain-Barré syndrome after administration of swine influenza vaccine. A subsequent epidemiologic study showed relative risks of 4.0 and 7.6 for the 6- and 8-week postvaccination periods, respectively, with

an attributable risk of just less than 1 case per 100,000 vaccinations (3). Studies with seasonal influenza vaccines over the period 1978–1988 showed no evidence of an increased risk of Guillain-Barré syndrome in the postvaccine period (4–6). However, following an increase in reports of vaccine-associated Guillain-Barré syndrome to the US national Vaccine Adverse Event Reporting System (VAERS), from 37 in 1992–1993 to 74 in 1993–1994, a further study was conducted (7). This study found no difference in risk between the 2 seasons, although there was an increased relative risk of 1.7 ($P = 0.04$) for the 2 seasons combined. Furthermore, a recent analysis of VAERS data (8) identified 2 features of influenza-vaccine-associated Guillain-Barré syndrome reports that suggested a possible causal association. First, the proportion of VAERS-reported cases with

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a preceding illness was lower than usually reported for non-vaccine-associated cases; second, there was an excess of VAERS cases with onset in the second week after vaccination.

These findings require further research to investigate the temporal association between influenza vaccine and Guillain-Barré syndrome. Cohort and case-control studies have traditionally been used for investigating putative vaccine-associated risks but pose problems when dealing with influenza vaccines. First, influenza vaccine is frequently given to individuals with specific clinical indications, thus raising the possibility of confounding by indication. Second, when the cohort approach is used, comprehensive population-based data are not usually available and person-time denominators inside and outside the risk period have been estimated from vaccination data obtained from small population samples (4, 5, 7). The self-controlled case series method (9) does not have these limitations. Based on a novel cases-only approach, this method automatically controls for individual-level confounders and requires only data on cases with their linked vaccination records.

We used the self-controlled case series method to investigate the temporal relation between influenza vaccine and Guillain-Barré syndrome. We also used this methodology to assess the risk of Guillain-Barré syndrome after influenza-like illness.

MATERIALS AND METHODS

We identified consultations for Guillain-Barré syndrome from the General Practice Research Database (GPRD), one of the world's largest primary care databases. It holds data on consultations, referrals, prescriptions, and vaccinations for more than 3 million active patients in practices throughout the United Kingdom (5.7% of the population). We selected any patient in the GPRD whose practice record had an ''acceptable'' status and listed an ''up-to-standard'' date earlier than the patient's first or new consultation for Guillain-Barré syndrome in the period 1990–2005. The up-to-standard date reflects when the practice complied with specific quality measures based on completeness, continuity, and plausibility in key areas. Acceptable status is given to a patient when certain data quality conditions have been met, such as no events recoded before the birth date, age less than 115 years, and a completed gender field. Consultations for Guillain-Barré syndrome were identified by using one of the following codes: READ F370000 (Guillian-Barré Syndrome), READ F370.00 (Acute Infective Polyneuritis), OXMIS 354 GB (Syndrome Guillian-Barré), or OXMIS 354 P (Polyneuritis). Influenza and influenzalike illness were identified by using any READ or OXMIS codes that included the terms ''influenza*'' or ''flu'' (a full list is available from the authors).

Two-stage validation of Guillain-Barré syndrome coding was carried out for just those individuals who received at least one dose of vaccine, since they contributed most of the power for looking at vaccine effects. First, the patient profile was reviewed to identify confirmatory clinical symptoms such as limb weakness at the time of diagnosis and to iden-

tify any cases with an earlier date of onset than the first coded diagnosis of Guillain-Barré syndrome. The patient profile is a summary of the whole patient record that includes dates and information on consultations, prescriptions, test results, referrals, and immunizations. Second, anonymized free-text comments were reviewed for 1 week before to 23 weeks after the date of the Guillain-Barré syndrome consultation to verify date of diagnosis and to identify supporting clinical information.

Analysis was carried out on all Guillain-Barré syndrome episodes, and, after review of the patient profile, just those episodes with supporting symptoms, and finally just those with supporting evidence and a confirmed earliest date of symptoms. The date that influenza vaccine was given was identified along with the date of any pneumococcal vaccine, which is recommended for the same age and clinical risk groups as influenza vaccine and, when given, is often administered at the same time as influenza vaccine.

The self-controlled case series method (6) was used to test the hypothesis of an increased risk of Guillain-Barré syndrome in the 3 risk periods of 0–30 days, 31–60 days, and 61–90 days after vaccination or influenzalike illness. Age was controlled for by using the 12 age periods of less than 8 years, 8–15 years, 16–23 years, 24–31 years, 32–39 years, 40–47 years, 48–55 years, 56–63 years, 64–71 years, 72–79 years, 80–87 years, and 88 years or older. Season was also controlled for in the analysis by using calendar month because influenza vaccine is given mainly between October and December. In this paper, relative incidence estimates are reported with 95% confidence intervals. A prevaccination low-risk period of 2 weeks was taken out of the background risk to allow for delayed vaccination because of Guillain-Barré syndrome. Repeat episodes with an interval of at least 6 months were counted as a separate episode.

To validate the recording of Guillain-Barré syndrome in a primary care setting, the GPRD consultation rate was compared with the admission rate from the Hospital Episode Statistics (HES) data set over the same period. HES holds details of discharge diagnoses for all National Health Service hospital admissions in England and, since April 1996, has used the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision, diagnosis codes. Annual HES admissions for the period 1997–2004 were extracted by using code G610 (Guillain-Barré syndrome) in the primary diagnosis field, with an additional admission within 6 months being classified as the same episode. Repeat episodes in the same patient were identified by using the unique identifier HES ID. The overall annual and average age-specific incidence over the period was calculated by using the Office of National Statistics population statistic for England as the denominator. The overall annual and age-specific incidence of GPRD recorded cases was estimated by using episodes recorded between 1997 and 2004 using the GPRD population statistic for each year.

RESULTS

A total of 989 episodes of Guillain-Barré syndrome within the study period were identified in the GPRD.

Seventeen episodes were excluded because the Guillain-Barré syndrome date was unknown, and one individual with 19 episodes of influenzalike illness was also excluded because no other individual experienced more than 3 episodes. Of the remainder, 196 episodes were excluded because they recurred within 6 months of a previous episode, which left 775 episodes for analysis. These 775 episodes occurred in 690 individuals; 372 were male and 318 female. The majority of individuals ($n = 625$, 91%) had only one episode recorded, 52 had 2 episodes, 9 had 3, 2 had 4, one had 5, and one had 6. Of these 775 GBS episodes in the analysis, 692 (89 percent) were coded as GBS and 83 (11 percent) as polyneuritis.

Of the 690 individuals, 169 had at least one influenza vaccine, 69 at least one pneumococcal vaccine, and 99 at least one influenzalike illness recorded. Although no minimum interval between influenzalike illness was prespecified, no repeat episodes within 4 months were identified. Table 1 shows the number of individuals and Guillain-Barré syndrome episodes according to the number of vaccine doses and influenzalike illness episodes. The ages of the individuals when the 775 separate episodes of Guillain-Barré syndrome occurred peaked in the group 56–63 years, whereas the ages in the subset of 199 with a linked influenza
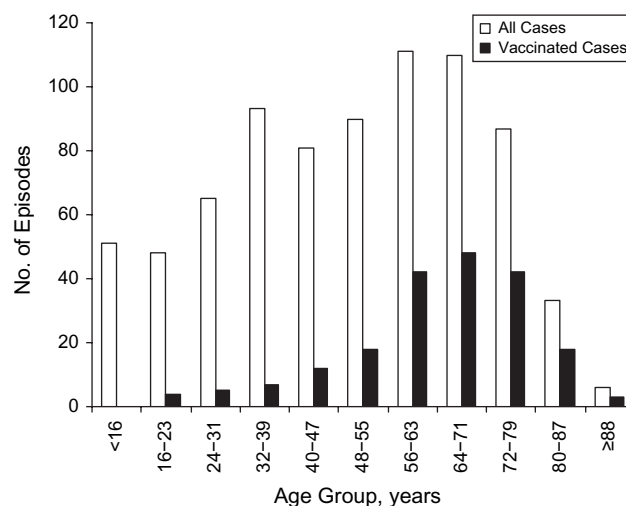
Figure 1. Age groups of individuals at onset of Guillain-Barré syndrome considering all episodes in the analysis ($n = 775$) and the subset with linked influenza or pneumococcal vaccination records ($n = 199$), United Kingdom, 1990–2005.

or pneumococcal vaccine record peaked in the group 64–71 years (Figure 1). The seasonal distribution of cases of Guillain-Barré syndrome showed an increase in January compared with the other months (chi-squared test $P < 0.001$) (Figure 2).

Vaccinations

We found no evidence of an increased risk of Guillain-Barré syndrome after pneumococcal vaccine or influenza vaccine, with relative incidence estimates for the 0–90-day period of 0.61 and 0.76, respectively (Table 2). An additional analysis was performed restricted to only those individuals who received at least one vaccination in case those without a recorded vaccination were missing vaccination
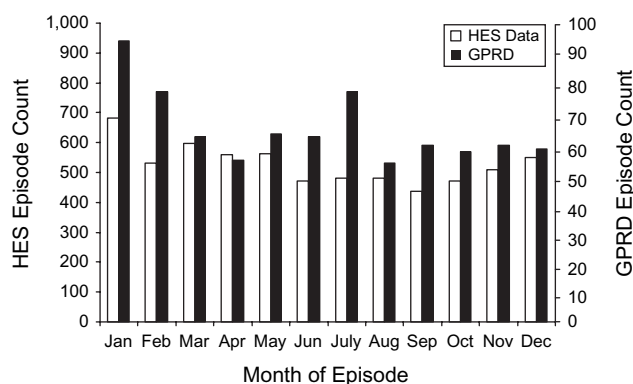
Table 1. Number of Individuals and Guillain-Barré Syndrome Episodes According to Number of Doses of Influenza and Pneumococcal Vaccines Received and Influenzalike Illness Episodes Recorded, United Kingdom, 1990–2005

Risk Factor	No. of Individuals ($n = 690$)	No. of Episodes ($n = 775$)
Influenza vaccination, no. of doses		
0	521	589
1	47	49
2	26	27
3	22	27
4	18	22
5	9	10
6	13	15
7	12	12
8–18	22	24
Pneumococcal vaccination, no. of doses		
0	621	698
1	67	75
2	2	2
Influenzalike illness, no. of episodes		
0	591	662
1	83	97
2	13	13
3	2	2
4	1	1

Figure 2. Number of Guillain-Barré syndrome episodes by month recorded in the General Practice Research Database (GPRD) and Hospital Episode Statistics (HES), United Kingdom, 1997–2004.

Table 2. Relative Incidence, 95% Confidence Interval, and Number of Episodes of Guillain-Barré Syndrome in Specified Intervals After Influenza and Pneumococcal Vaccines and a Consultation for Influenzalike Illness, United Kingdom, 1990–2005

Factor and Risk Period (Days)	RI[a]	95% CI	No. of Events
Influenza vaccination			
0–30	0.58	0.18, 1.86	3
31–60	0.39	0.10, 1.60	2
61–90	1.25	0.57, 2.73	7
0–90	0.76	0.41, 1.40	12
Pneumococcal vaccination			
0–90	0.61	0.08, 4.42	1
Influenzalike illness			
0–30	16.64	9.37, 29.54	15
31–60	4.70	1.70, 13.0	4
61–90	0		0
0–90	7.35	4.36, 12.38	19

Abbreviations: CI, confidence interval; RI, relative incidence.
[a] Adjusted for age and calendar month.

Figure 3. Distribution of Guillain-Barré syndrome episodes in 90-day intervals around the date of influenzalike illness, United Kingdom, 1990–2005.
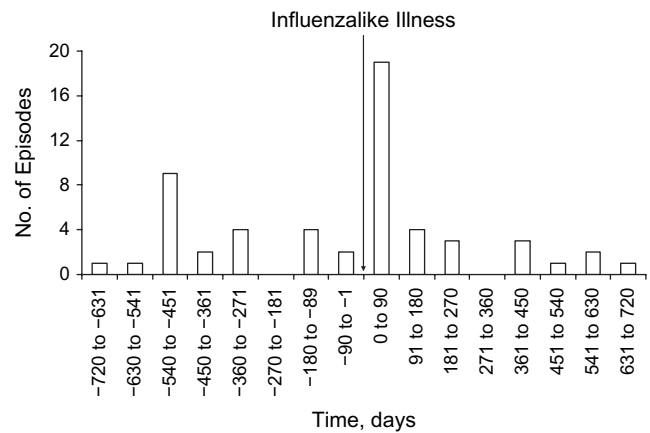
information. In this analysis, the relative incidence in the 90 days after influenza vaccination was 0.81, with a 95% confidence interval of 0.44, 1.48. To further investigate the low relative incidence in the 90-day period and hence a possible protective effect, the postvaccination period was extended to 180 days. Doing so resulted in a relative incidence of 0.80 and a 95% confidence interval of 0.51, 1.27.

Influenzalike illness

An increased risk was seen following a consultation for influenzalike illness, with 19 events in the 0–90-day period and a relative incidence of 7.35 (95% confidence interval: 4.36, 12.38) (Table 2, Figure 3). Fifteen of the 19 episodes occurred in the 0–30-day period, with a relative incidence of 16.64 (95% confidence interval: 9.37, 29.54), with no episodes in the 61–90-day period. The number of Guillain-Barré syndrome events attributable to influenzalike illness was calculated to be 17.2, with an attributable fraction of 2.2%, assuming all influenzalike illness events were captured. An alternative calculation of the excess due to influenzalike illness is to compare the number of cases in January and February with the average from the other 10 months and attribute the excess to influenzalike illness. This comparison gives an estimated excess of 58.2, which is an attributable fraction of 7.5% of all cases.

Validation

After reviewing the patient profiles, 107 of the 199 episodes in individuals with a linked influenza vaccine record had information supporting the diagnosis of Guillain-Barré syndrome, such as leg weakness, a feeling of "pins and needles," leg pain, or referral to the hospital. Of these 107, 47 had a date of first symptoms, for which 39 episodes had the symptom recorded prior to the Guillain-Barré syndrome date (23 within 30 days, 9 within 31–60 days, and 7 within more than 60 days). The relative incidence in the 90-day period when the analysis was restricted to the 107 cases with supporting evidence was 0.77 (95% confidence interval: 0.35, 1.69). When the analysis was restricted further to the 47 cases with a first recorded symptom, the relative incidence was 0.89 (95% confidence interval: 0.42, 1.89). This estimate is similar to the overall relative incidence of 0.76 (95% confidence interval: 0.41, 1.40) based on all episodes of Guillain-Barré syndrome.

Comparison with HES

A total of 6,340 admissions were found in the HES data set, which gave an overall incidence of 1.61/100,000 population, with a peak in admissions in January similar to that seen in the GPRD data set (Figure 2). There were 481 GPRD consultations over the same period, giving an overall incidence rate of 2.05/100,000 population. Age-specific incidence in HES and GPRD followed a similar pattern, with a peak in the age group 64–71 years (Figure 4).

DISCUSSION

This study found no evidence of an association between influenza vaccination and Guillain-Barré syndrome, with an upper end of the 95% confidence intervals excluding a relative incidence of 1.5. An increased risk of Guillain-Barré syndrome was seen in the period shortly after influenzalike illness, consistent with observations that Guillain-Barré syndrome is often preceded by a respiratory illness. A recent case-control study using the GPRD and restricted to cases of Guillain-Barré syndrome occurring between 1990 and 2001 also found evidence of an increased risk in the 2 months after an influenzalike illness (odds ratio = 18.64, 95% confidence interval: 7.49, 46.37) (10). The association with
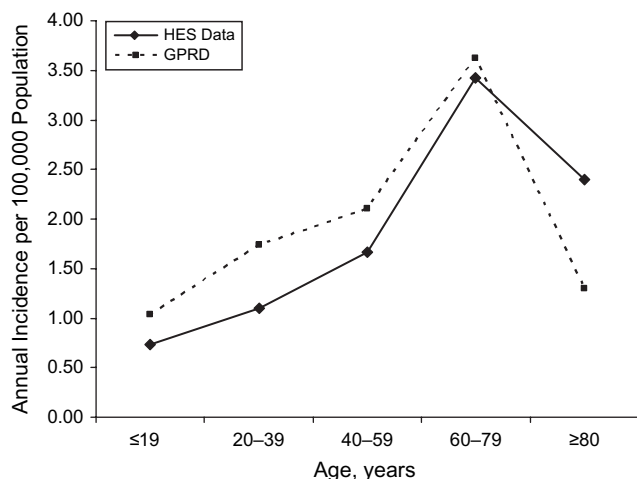
Figure 4. Average age-specific incidence of episodes of Guillain-Barré syndrome over the period 1997–2004 recorded in Hospital Episodes Statistics (HES) and the General Practice Research Database (GPRD), United Kingdom.

influenzalike illness may explain the seasonal pattern of Guillain-Barré syndrome, with an increase in cases during the influenza season that was evident in both the GPRD and HES data sets. Whether this association is specific to influenza virus infection or more generically with other respiratory pathogens that can present as influenzalike illness is difficult to discern since other respiratory infections also peak in the winter.

A time-series analysis investigating the short-term correlations between weekly laboratory-confirmed reports of putative triggering pathogens found a positive association between number of influenza reports in any week and hospital admissions for Guillain-Barré syndrome in the same week (11). The authors of this analysis suggested that absence of a lag period was consistent with a causal association with influenza vaccine rather than influenza infection, since the vaccine is usually administered some weeks before the influenza season begins. However, the correlation with other respiratory pathogens such as respiratory syncytial virus was not investigated. Since the winter peak of respiratory syncytial virus often precedes that of influenza (12), a causal relation between respiratory syncytial virus and Guillain-Barré syndrome is a plausible alternative explanation. Further work to explore the temporal relation between Guillain-Barré syndrome and the viruses known to contribute to the syndrome of influenzalike illness is in progress. The use of a clinical case definition of influenzalike illness as an indicator that influenza incidence has been studied extensively, and corresponding increases in viral positivity rates and general practice consultation rates, have been illustrated (13).

The increased risk of Guillain-Barré syndrome after influenzalike illness, if specific to infection with influenza virus, together with the absence of a causal association with influenza vaccine suggests that influenza vaccine should

protect against Guillain-Barré syndrome. While the relative incidence in the 180 days after vaccination was 0.80, the 95% confidence interval spanned 1, so a significant protective effect was not demonstrated. However, a reduction of 20% is plausible given that the efficacy of seasonal influenza vaccine against influenzalike illness is approximately 15%–30% depending on the match between the vaccine and circulating strain (14). Tam et al. (10), using the case-control approach, reported an odds ratio of 0.16 for the risk of Guillain-Barré syndrome within 2 months of influenza vaccine. However, this reduction was not significant and the analysis was based on a total of 18 cases, only one of which occurred in the risk period. Furthermore, a protective effect of this magnitude against the nonspecific disease endpoint of influenzalike illness is not plausible.

The relation among Guillain-Barré syndrome, influenza vaccine, and influenza infection is relevant to the debate about the safety of pandemic influenza vaccines, for which Guillain-Barré syndrome has been identified as a potential adverse effect that requires enhanced surveillance. If such vaccines are protective against the pandemic strain, then, even if they are associated with a small risk of Guillain-Barré syndrome, the overall risk-benefit analysis for this outcome may be favorable. Clearly, in addition to establishing rapid systems for evaluating the risk of vaccine-associated adverse events such as Guillain-Barré syndrome, it will be equally important to evaluate the risk of such events from pandemic influenza and the degree of protection afforded by the vaccine in order to make an overall risk-benefit assessment.

Our finding of an increased risk of Guillain-Barré syndrome after influenzalike illness is also relevant to evaluating the robustness of the prior studies suggesting an increased risk after swine influenza or seasonal influenza vaccines. Any risk from influenzalike illness (or *Campylobacter*) would be a potential confounder in ecologic approaches as carried out with US Army data, where no increase in Guillain-Barré syndrome was seen after vaccination (6). A marginally significant increased relative risk of 1.7 (95% confidence interval: 1.0, 2.8) was reported with the seasonal vaccine by Lasky et al. (7) based on cases occurring in the 1992/1993 and 1993/1994 influenza seasons combined. These periods were chosen because passive reports to VAERS had shown a substantial rise in 1993/1994 compared with 1992/1993. However, when data were analyzed by individual season, the relative risk was not significantly different from 1 in the 1993/1994 season, with only the 1992/1993 season giving a signal (relative risk = 1.5, 95% confidence interval: 1.0, 4.3). This study used a cohort design in which person-time denominators were estimated from a population sample and did not take account of the effect of influenzalike illness.

Passive reporting systems such as VAERS also have major limitations when trying to assess causal associations. Evidence cited by Haber et al. (8) in support of a possible causal association with seasonal influenza vaccines was the lower-than-expected proportion of Guillain-Barré syndrome cases reported to VAERS who had a preceding illness. However, suspicion that a case of Guillain-Barré syndrome may be vaccine attributable is likely to be greater for those with

no other suspected cause, so this reasoning is not convincing. Neither is the apparent excess of VAERS reported cases with onset within the second week after vaccination, since it may also be affected by reporters' judgments regarding the likely interval for a causal association.

The advantage of the self-controlled case series method for assessing causal associations is that it should be free of the individual-level confounding that may affect cohort and case-control studies (9). An earlier study by Juurlink et al. (15) also used the self-controlled case series method to investigate the relation between seasonal influenza vaccine and Guillain-Barré syndrome, and it found a marginally increased relative incidence of 1.45 (95% confidence interval: 1.05, 1.99; $P = 0.02$) in the period 2–7 weeks after administration of influenza vaccine. However, information on the type of vaccine given was not available, and the analysis was restricted to adults who received a vaccine in October or November on the assumption that the majority of vaccines given in these months would be for influenza. Apart from the inherent uncertainty in this assumption, it did not incorporate seasonality, nor did it include influenzalike illness as a potential confounder. The results of this analysis should therefore be treated with caution.

Although our self-controlled case series analysis was not subject to these limitations, there may still be limitations in the GPRD data set that we used for this analysis. The date on which the first Guillain-Barré syndrome consultation is recorded may not be accurate and may reflect the date on which the patient was admitted or discharged from the hospital with the diagnosis. Thus, there may be a time lag between the onset of symptoms and recorded diagnosis. In addition, the coding of Guillain-Barré syndrome in the GPRD may not be accurate. Both these factors would lead to a reduced relative risk estimate. To assess this possibility, an analysis was performed on a vaccinated subset with additional supporting information on the date of onset and accuracy of diagnosis. Although only a relatively low proportion were validated, no significant difference in relative incidence was seen in this subset compared with that found by using all Guillain-Barré syndrome episodes. This finding suggests that a vaccine-attributable effect has not been missed. The finding of a 17-fold increased risk of Guillain-Barré syndrome in the month after an influenzalike illness provides further evidence that the GPRD data are suitable for detecting a vaccine-attributable effect. Further reassurance was provided by the similarity between the GPRD and HES data with respect to the age-specific and monthly incidence.

A further potential criticism of the GPRD data set is that not all influenza vaccine is given by general practitioners; a proportion is administered by occupational health practitioners, for example, to health care workers. However, loss of these data should not affect our results because the self-controlled case series method was also run confined to just those individuals with an influenza vaccine recorded, with similar results.

In conclusion, our study provides robust evidence that seasonal influenza vaccination does not cause Guillain-Barré syndrome. It also shows that patients presenting with influenzalike illness in general practice have a greatly increased risk of developing Guillain-Barré syndrome in the subsequent month. Our findings have implications for the risk assessment process that will need to be put in place to evaluate the utility of pandemic influenza vaccines. They also call into question the robustness of earlier studies that suggest a causal association of swine influenza and seasonal influenza vaccines with Guillain-Barré syndrome. Our study provides further evidence of the power of the self-controlled case series method for evaluating putative causal associations.

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