# Risk of Guillain-Barré syndrome after seasonal influenza vaccination and influenza health-care encounters: a self-controlled study

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## Summary

**Background** The possible risk of Guillain-Barré syndrome from influenza vaccines remains a potential obstacle to achieving high vaccination coverage. However, influenza infection might also be associated with Guillain-Barré syndrome. We aimed to assess the risk of Guillain-Barré syndrome after seasonal influenza vaccination and after influenza-coded health-care encounters.

**Methods** We used the self-controlled risk interval design and linked universal health-care system databases from Ontario, Canada, with data obtained between 1993 and 2011. We used physician billing claims for influenza vaccination and influenza-coded health-care encounters to ascertain exposures. Using fixed-effects conditional Poisson regression, we estimated the relative incidence of hospitalisation for primary-coded Guillain-Barré syndrome during the risk interval compared with the control interval.

**Findings** We identified 2831 incident admissions for Guillain-Barré syndrome; 330 received an influenza vaccine and 109 had an influenza-coded health-care encounter within 42 weeks before hospitalisation. The risk of Guillain-Barré syndrome within 6 weeks of vaccination was 52% higher than in the control interval of 9–42 weeks (relative incidence 1·52; 95% CI 1·17–1·99), with the greatest risk during weeks 2–4 after vaccination. The risk of Guillain-Barré syndrome within 6 weeks of an influenza-coded health-care encounter was greater than for vaccination (15·81; 10·28–24·32). The attributable risks were 1·03 Guillain-Barré syndrome admissions per million vaccinations, compared with 17·2 Guillain-Barré syndrome admissions per million influenza-coded health-care encounters.

**Interpretation** The relative and attributable risks of Guillain-Barré syndrome after seasonal influenza vaccination are lower than those after influenza illness. Patients considering immunisation should be fully informed of the risks of Guillain-Barré syndrome from both influenza vaccines and influenza illness.

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## Introduction

Every year, seasonal influenza causes an estimated 3–5 million cases of severe illness and 250 000–500 000 deaths worldwide.[1] Immunisation remains the cornerstone for prevention, and recommendations have expanded toward universal immunisation in many jurisdictions, as well as compulsory immunisation of health-care workers.

However, the possible risk of Guillain-Barré syndrome, an acute inflammatory demyelinating polyneuropathy, from influenza vaccines remains a potential concern for large-scale immunisation programmes. The 1976 swine-origin influenza immunisation programme in the USA was halted because of reports of vaccine-associated Guillain-Barré syndrome and because the outbreak did not progress to an epidemic. This particular vaccine was associated with a four-fold to eight-fold increased risk of Guillain-Barré syndrome within 6 weeks of immunisation, or an attributable risk of one case per 100 000 people vaccinated.[2,3] Subsequent studies of seasonal influenza vaccines have reported relative risk estimates ranging from 0·16 to 1·7.[4–10] These investigations were done in different years (with variation in vaccine and circulating strains) and used various study designs, some of which are susceptible to bias from confounding (eg, cohort and case-control studies). The rarity of Guillain-Barré syndrome results in many studies having limited numbers of cases and low power to study associations.

Most patients need hospitalisation, and around 25% have respiratory failure requiring intensive care.[11] Even with access to supportive medical care, 4% of patients die, and 14% are permanently disabled.[12] Most cases have preceding respiratory or gastrointestinal infections, most commonly *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, and *Mycoplasma pneumoniae*.[13,14] Infectious agents are believed to induce an inflammatory autoimmune response against peripheral nerves. Studies suggest that influenza infection is also strongly associated with Guillain-Barré syndrome.[7,8,15] However, conclusions from these studies have been limited by small sample sizes or study designs susceptible to bias.

We aimed to assess the risk of Guillain-Barré syndrome after exposure to the unadjuvanted, seasonal trivalent inactivated influenza vaccine and after seasonal influenza illness.

## Methods

### Study design and population

We used the self-controlled risk-interval design to explore the temporal association between Guillain-Barré syndrome and influenza vaccination or influenza-coded health-care encounters (proxy for influenza illness).[9,16] Although similar to the self-controlled case series method, which examines the timing of exposure in relation to each case,[17] the risk interval design anchors observation periods to the exposure date.[9] We used only time after exposure to construct our control intervals, since Guillain-Barré syndrome after vaccination is a precaution for future influenza vaccination,[18] and we conditioned on the exposed patient having a hospitalisation in either the risk or control interval.[9] Since vaccination is a self-selected exposure, most observational study designs could be susceptible to biases associated with vaccination. The main advantage of this method compared with case-control and cohort designs is that it requires only cases with a history of both the exposure and the outcome of interest within a defined period. Since each patient is their own control, confounding from comparing groups of vaccinated and unvaccinated individuals is eliminated.

| | Received influenza vaccine (n=330) | Had influenza-coded health-care encounter (n=109) |
|---|---|---|
| **Age group** | | |
| <18 years | 14 (4·2%) | 24 (22·0%) |
| 18–64 years | 124 (37·6%) | 59 (54·1%) |
| ≥65 years | 192 (58·2%) | 26 (23·9%) |
| **Sex** | | |
| Male | 179 (54·2%) | 57 (52·3%) |
| Female | 151 (45·8%) | 52 (47·7%) |
| **Month of exposure*** | | |
| January | 6 (1·8%) | 19 (17·4%) |
| February | ≤5 | 12 (11·0%) |
| March | 0 | 21 (19·3%) |
| April | 0 | 13 (11·9%) |
| May | 0 | ≤5 |
| June | 0 | ≤5 |
| July | 0 | ≤5 |
| August | 0 | 6 (5·5%) |
| September | 7 (2·1%) | ≤5 |
| October | 106 (32·1%) | 8 (7·3%) |
| November | 169 (51·2%) | 13 (11·9%) |
| December | 40 (12·1%) | 6 (5·4%) |

Data are number (%). *Due to a contractual agreement with the data provider, numbers of five or fewer cannot be reported.

*Table 1:* **Baseline characteristics of individuals hospitalised for Guillain-Barré syndrome who received influenza vaccine or had an influenza-coded health-care encounter within the previous 42 weeks**

This analysis was done using health records for all Ontario residents eligible to receive health coverage between April 1, 1993, and March 31, 2011. Ontario is Canada's most populous province (population 13·4 million in 2011) and most residents have universal, publicly funded access to physician services, hospital care, and since 2000, influenza vaccines (for individuals aged ≥6 months).

We ascertained cases of Guillain-Barré syndrome through the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD). We extracted data for hospitalisations for Guillain-Barré syndrome (International Classification of Diseases, 9th Revision [ICD-9] diagnosis code 357·0 and International Statistical Classification of Diseases, 10th Revision [ICD-10] diagnosis code G61·0) as the most responsible (primary) diagnosis. Since distinguishing Guillain-Barré syndrome from the acute onset of chronic inflammatory demyelinating polyneuropathy (CIDP) can be challenging,[19] we excluded patients with either a diagnosis of CIDP (ICD-9: 357·8, 357·9; ICD-10: G61·8, G61·9, G62·8, G62·9) any time during the study period or another primary-coded Guillain-Barré hospitalisation more than 2 months after the initial episode. The validity of the diagnosis of Guillain-Barré syndrome in Ontario's administrative hospitalisation data is uncertain, but in similar settings, positive predictive values (PPVs) of 61·8% (Lombardy Region, northern Italy)[20] and 64·5% (Vaccine Safety Datalink Project)[9] have been reported for hospitalisations coded as Guillain-Barré syndrome. We were unable to ascertain Guillain-Barré subtypes or severity from this database.

Ethics approval was obtained from the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Canada.

### Influenza vaccination and influenza-coded health-care encounters

The Ontario Health Insurance Plan database contains billing claims submitted by around 94% of Ontario physicians for services provided in inpatient and outpatient settings. Using encrypted health-care numbers as unique identifiers, we linked hospitalisations for Guillain-Barré syndrome to the Ontario Health Insurance Plan database to assess admissions in the 42 weeks after exposure to influenza vaccination or influenza illness.

We ascertained receipt of the trivalent inactivated influenza vaccine (live, attenuated influenza vaccine was not available during the study period) using influenza-specific vaccination codes submitted between April 1, 1998, and Oct 26, 2009 (to exclude the adjuvanted monovalent 2009 influenza A H1N1 pandemic vaccines used in Ontario, by contrast with the unadjuvanted trivalent seasonal influenza vaccines). Introduced in 1998, the influenza-specific vaccination codes have a PPV of 92% when using self-reported vaccination as the criterion standard.[21]

Influenza illness was defined as a billing claim with a diagnosis of influenza submitted between April 1, 1993, and March 31, 2009 (to exclude cases of pandemic influenza, because of the epidemiological differences between pandemic and seasonal influenza). Influenza-coded health-care encounters in Ontario have a PPV of 72% (appendix). Multiple influenza-coded health-care encounters within 2 weeks were considered as one episode and given the earliest encounter date.

## Statistical analysis

We analysed the risk of Guillain-Barré syndrome after exposure to influenza vaccination and influenza illness separately. For each analysis, the date of the exposure (vaccination or influenza-coded health-care encounter) closest to admission served as the index date for each patient. Analyses were restricted to individuals who had both an influenza exposure and Guillain-Barré syndrome during the subsequent 42 weeks. The follow-up period was divided into risk and control intervals. We truncated observation time after exposure to 42 weeks to minimise observation time running into the next influenza vaccination campaign or influenza season and to maximise comparability of patients during risk and control intervals, since the self-controlled risk interval method does not control for time-varying confounding.

We defined the risk interval as the first 6 weeks after the index date and the control interval as weeks 9–42. We chose 6 weeks since this was the risk interval for Guillain-Barré syndrome indicated by Langmuir and colleagues[2] during the 1976 swine-origin influenza campaign, and to be consistent with previous studies.[4–6,9,10] To identify periods of greatest risk for Guillain-Barré syndrome within the initial 6 weeks, we also considered narrower risk intervals: weeks 1, 2, 3–4, and 5–6. The relative incidence of Guillain-Barré syndrome during the risk interval compared with the control interval was analysed with a fixed-effects conditional Poisson regression model that included exposure and control period terms, and an indicator variable for each patient allowing each individual to serve as his or her own control.

Since an individual could have multiple influenza vaccinations or influenza-coded health-care encounters within 42 weeks of hospital admission, we created a

See Online for appendix

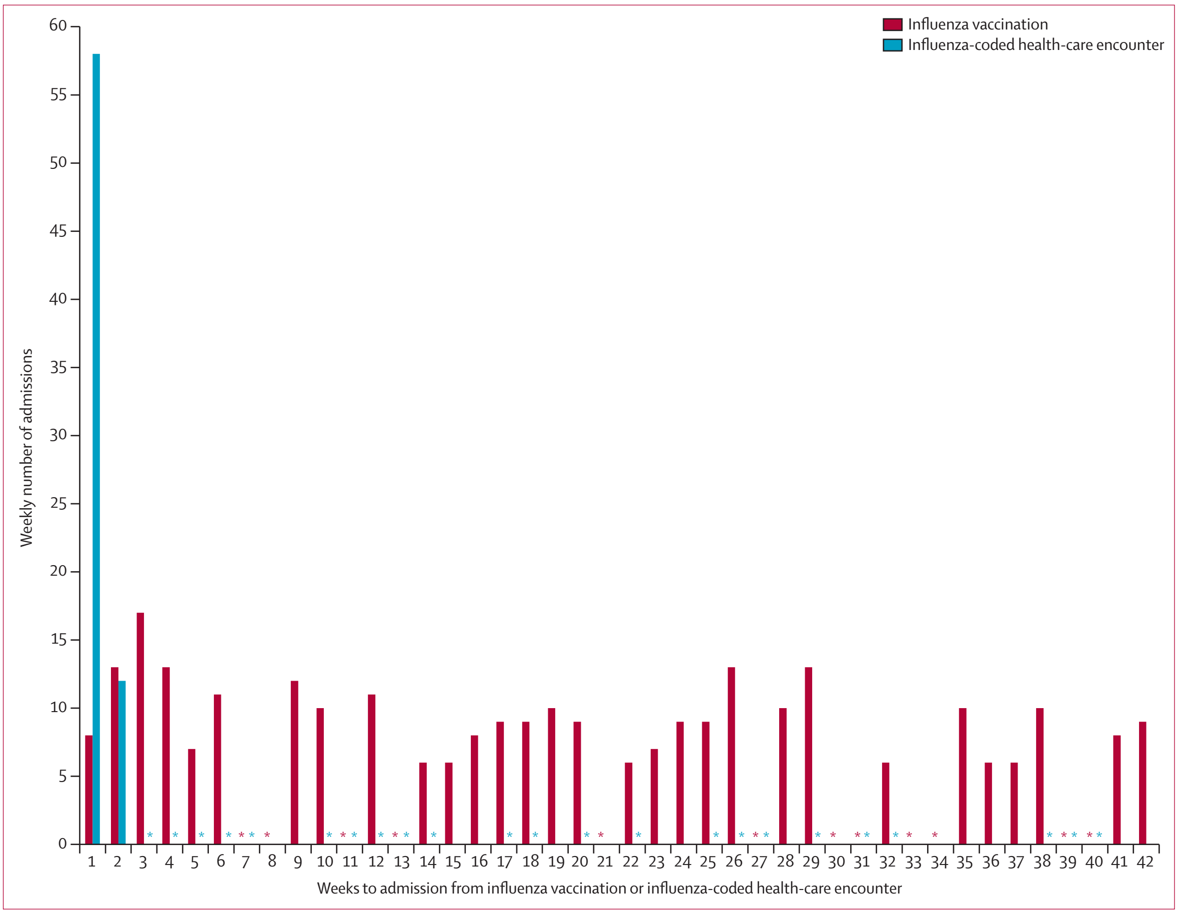


***Figure:* Number of cases of Guillain-Barré syndrome by week after receipt of influenza vaccine and after an influenza-coded health-care encounter**

*Five or fewer admissions for Guillain-Barré syndrome; due to a contractual agreement with the data provider, numbers of five or fewer cannot be reported.

model that accounted for repeated exposures during follow-up by appropriately segmenting the within-individual data according to each exposure.[22] To examine the independent effects of influenza vaccination and influenza illness, we did an analysis with both influenza vaccination and influenza illness in the same model, again segmenting the within-individual data according to each exposure and restricting to exposures that took place within an assessment window common to both exposure types (April 1, 1998 to March 31, 2009). Using previously described methods for identifying influenza seasons in Ontario,[23] we incorporated a categorical term for influenza season to adjust for potential confounding due to unobserved influenza episodes. We also ran separate models with categorical terms for calendar season (spring, summer, autumn, winter) and month to establish the effect of adjusting for seasonality. To further test the robustness of our findings and facilitate comparisons with similar studies that used different risk intervals, we varied the length of the risk intervals (eg, 4 weeks, 8 weeks) and excluded the first week after vaccination.

We adjusted for potential misclassification of admissions for Guillain-Barré syndrome with the method proposed by Green,[24] which adjusts relative risk estimates that could be subject to error due to misclassification of the outcome status according to the PPV. We used a PPV of 61·8% from a previous study.[20]

We did subgroup analyses by age group (<18 years, 18–64 years, ≥65 years), sex, and month of exposure. For risk of Guillain-Barré syndrome after influenza illness, we repeated analyses using exposure to acute respiratory infections (pneumonia, upper respiratory tract infection, sinusitis, acute bronchitis, and other viral infections), which is a more sensitive but less specific measure of influenza illness.

We repeated the analyses using negative tracers for which no associations with Guillain-Barré syndrome were expected. We considered non-vaccine intramuscular or subcutaneous injections as a negative tracer for influenza vaccination, and dermatitis-coded health-care encounters and periodic health examinations as negative tracers for influenza-coded encounters. Because injections and dermatitis-coded encounters occur frequently, we controlled for repeated exposures.[22]

We used the total number of influenza vaccinations and influenza-coded health-care encounters in Ontario during each respective exposure assessment window (April 1, 1998, to Oct 26, 2009, for influenza vaccines; April 1, 1993, to March 31, 2009, for influenza illness) to determine the attributable risks of each exposure, expressed as the number of cases of Guillain-Barré syndrome per million exposures.[25]

| | Cases during risk interval | Cases during control interval | Relative incidence (95% CI) |
|---|---|---|---|
| Primary analysis (risk interval=6 weeks*) | 69 | 251 | 1·52 (1·17–1·99) |
| Narrower risk intervals | | | |
| Week 1 | 8 | 251 | 0·95 (0·47–1·92) |
| Week 2 | 13 | 251 | 1·76 (1·01–3·08) |
| Week 3 and 4 | 30 | 251 | 2·03 (1·39–2·97) |
| Week 5 and 6 | 18 | 251 | 1·22 (0·76–1·97) |
| Sensitivity analyses | | | |
| Accounting for repeated influenza vaccinations† | 69 | 254 | 1·52 (1·16–1·98) |
| Incorporating influenza vaccine & illness‡ | 67 | 244 | 1·49 (1·13–1·96) |
| Controlling for influenza season | 69 | 251 | 1·57 (1·19–2·06) |
| Controlling for calendar season | 69 | 251 | 1·35 (0·82–2·22) |
| Controlling for calendar month | 69 | 251 | 1·39 (0·82–2·37) |
| Shortening risk interval to 4 weeks | 51 | 251 | 1·67 (1·23–2·25) |
| Lengthening risk interval to 8 weeks | 79 | 251 | 1·31 (1·02–1·69) |
| Excluding first week | 61 | 251 | 1·65 (1·25–2·19) |
| Excluding first week and shortened risk interval | 43 | 251 | 1·94 (1·41–2·68) |
| Adjusted for potential misclassification of Guillain-Barré syndrome | 69 | 251 | 1·84 (1·28–2·60) |
| Subgroup analyses | | | |
| Age <18 years | ≤5§ | 10 | 1·66 (0·46–6·03) |
| Age 18–64 years | 35 | 84 | 2·31 (1·55–3·42) |
| Age ≥65 years | 31 | 157 | 1·09 (0·74–1·61) |
| Male | 38 | 137 | 1·54 (1·07–2·20) |
| Female | 31 | 114 | 1·51 (1·01–2·24) |
| Vaccinated in October | 19 | 82 | 1·28 (0·78–2·11) |
| Vaccinated in November | 37 | 128 | 1·60 (1·11–2·31) |
| Vaccinated in December | 8 | 31 | 1·43 (0·66–3·11) |
| Negative tracers (no association expected) | | | |
| Receipt of non-vaccine injections | 65 | 351 | 1·21 (0·80–1·82) |

*Includes the day of vaccination. †We considered repeated vaccinations during the same influenza season. ‡Influenza illness was defined as an influenza-coded health-care encounter. §Due to a contractual agreement with the data provider, numbers of five or fewer cannot be reported.

*Table 2:* **Relative incidence of Guillain-Barré syndrome admission after receipt of influenza vaccine**

### Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

We identified 2831 individuals who were hospitalised for Guillain-Barré syndrome and had no diagnosis of CIDP or recurrent episode of Guillain-Barré syndrome during the study period. Of these, 330 cases of Guillain-Barré syndrome were preceded by influenza vaccination and 109 cases were preceded by influenza illness within 42 weeks of admission (table 1). Admission for Guillain-Barré syndrome occurred most frequently during the second and third weeks after vaccination, and during the first week after an influenza-coded health-care encounter (figure).

The relative incidence of Guillain-Barré syndrome after influenza vaccination was 52% higher during the initial 6 weeks (1·52; 95% CI 1·17–1·99), with the greatest risk during week 2 (1·76; 1·01–3·08) and week 3 (2·03; 1·39–2·97) after vaccination (table 2). The risk estimates were unchanged in analyses incorporating both vaccination and influenza illness, and when controlling for influenza season, calendar season, or month, although the confidence intervals were wider in the two latter analyses. Shortening the risk interval and excluding the first week after vaccination increased the relative incidence estimates, as did adjusting for the potential misclassification of Guillain-Barré syndrome in our study (1·84; 1·28–2·60). The relative incidence was higher in those aged 18–64 years (2·31; 1·55–3·42) than in those aged 65 years or older (1·09; 0·74–1·61, p=0·008 for interaction). The other age comparisons did not achieve statistical significance. No differences were noted by sex or month of vaccination. Non-vaccine injections were not associated with an increased risk of Guillain-Barré syndrome.

The relative incidence within 6 weeks of an influenza-coded health-care encounter was greater than that for vaccination (15·81; 95% CI 10·28–24·32; table 3). The risk was highest during the first week after a health-care encounter (61·63; 39·25–96·75) and decreased over time. The relative incidence estimates were not significantly different from the primary analysis when accounting for repeated encounters, incorporating vaccination and influenza illness, and controlling for influenza season, calendar season, or month. Adjusting for potential misclassification of Guillain-Barré syndrome resulted in a larger risk estimate (24·96; 16·02–38·73). Analyses using coded encounters for acute respiratory infections (with or without influenza included) produced lower risk estimates. We noted no differences by age group, sex, or month of illness. Dermatitis-coded encounters and periodic health examinations were not associated with Guillain-Barré syndrome.

We estimated the attributable risks to be 1·03 admissions per million vaccinations (one admission per 971 567 vaccinations), compared with 17·2 admissions per million influenza-coded health-care encounters (one admission per 58 108 influenza encounters).

| | Cases during risk interval | Cases during control interval | Relative incidence (95% CI) |
|---|---|---|---|
| Primary analysis (risk interval=6 weeks*) | 80 | 28 | 15·81 (10·28–24·32) |
| Narrower risk intervals | | | |
| Week 1 | 58 | 28 | 61·63 (39·25–96·75) |
| Week 2 | 12 | 28 | 14·57 (7·41–28·65) |
| Weeks 3 and 4 | 6 | 28 | 3·64 (1·51–8·80) |
| Weeks 5 and 6 | ≤5† | 28 | 2·43 (0·85–6·92) |
| Sensitivity analyses | | | |
| Accounting for repeated health-care encounters‡ | 80 | 37 | 15·17 (9·85–23·37) |
| Incorporating influenza vaccine and illness§ | 44 | 14 | 18·25 (9·96–33·47) |
| Controlling for influenza season | 80 | 28 | 16·69 (10·56–26·39) |
| Controlling for calendar season | 80 | 28 | 15·08 (9·61–23·66) |
| Controlling for calendar month | 80 | 28 | 16·05 (9·97–25·84) |
| Shortening risk interval to 4 weeks | 76 | 28 | 22·28 (14·44–34·36) |
| Lengthening the risk interval to 8 weeks | 81 | 28 | 12·08 (7·86–18·56) |
| Adjusted for potential misclassification of Guillain-Barré syndrome | 80 | 28 | 24·96 (16·02–38·73) |
| Acute respiratory infections¶ | 757 | 356 | 11·77 (10·38–13·35) |
| Acute respiratory infections without influenza | 693 | 339 | 11·31 (9·93–12·88) |
| Subgroup analyses | | | |
| Age <18 years | 16 | 8 | 11·07 (4·74–25·87) |
| Age 18–64 years | 45 | 13 | 19·16 (10·34–35·51) |
| Age ≥65 years | 19 | 7 | 15·02 (6·32–35·74) |
| Male | 43 | 14 | 17·00 (9·30–31·07) |
| Female | 37 | 14 | 14·63 (7·91–27·06) |
| Illness in November | 9 | ≤5 | 12·45 (3·84–40·44) |
| Illness in December | ≤5 | ≤5 | 11·07 (2·03–60·44) |
| Illness in January | 14 | ≤5 | 15·50 (5·58–43·03) |
| Illness in February | 10 | ≤5 | 27·67 (6·06–126·30) |
| Illness in March | 16 | ≤5 | 17·71 (6·49–48·35) |
| Illness in April | 8 | ≤5 | 11·07 (3·33–36·76) |
| Negative tracers (no association expected) | | | |
| Dermatitis-coded health-care encounters | 34 | 153 | 1·25 (0·84–1·86) |
| Periodic health examinations | 44 | 185 | 1·32 (0·95–1·83) |

*Includes the day of an influenza-coded health-care encounter.†Due to a contractual agreement with the data provider, numbers of five or fewer cannot be reported. ‡We considered repeated health-care encounters during the same influenza season.§Influenza illness was defined as an influenza-coded health-care encounter. ¶Acute respiratory infection represents health-care encounters for: nasopharyngitis/common cold, sinusitis, bronchitis, pneumonia, influenza, and unspecified viral illness.

***Table 3*: Relative incidence of Guillain-Barré syndrome admission after an influenza-coded health-care encounter**

## Discussion

Influenza-coded health-care encounters (as a proxy for seasonal influenza illness) were associated with greater relative and attributable risks of Guillain-Barré syndrome admission than those associated with influenza vaccines. After vaccination, the risk of Guillain-Barré syndrome is highest during weeks 2–4, whereas for influenza illness, the risk is greatest within the first week after a health-care encounter, and remains high for up to 4 weeks. Numerous secondary analyses showed the robustness of our results. Both influenza vaccines and influenza illness are associated with small attributable risks, although the risk associated with influenza infection is larger than that associated with vaccination.

Our estimate of the small risk of Guillain-Barré syndrome after influenza vaccination is similar to that in previous studies (panel; table 4).[4–10] However, those studies were insufficiently powered to generate risk estimates for short risk intervals; the larger sample in our study allowed the identification of a more precise risk period of weeks 2–4. This finding is similar to the peak risk period of weeks 2–3 identified for the 1976 swine-origin influenza vaccine.[2]

We noted that adjusting for seasonality made little difference to the risk estimate, serving only to reduce the effective sample size. Our subgroup analyses revealed

***Panel:* Research in context**

**Systematic review**

We searched PubMed with the search terms "guillain barre syndrome and influenza vaccination" and "guillain barre syndrome and influenza illness". Since our study focused on determining risk estimates for seasonal influenza vaccination and illness, we excluded those studies concentrating on the pandemic influenza A H1N1 monovalent vaccine or pandemic influenza illness. We also excluded descriptive surveillance studies which did not include any measures of association (eg, relative risk, relative incidence, odds ratio). Observational studies (table 4) investigating the association between Guillain-Barré syndrome and seasonal influenza vaccine or illness varied in their study design, some of which might be susceptible to bias from confounding. Due to the rarity of Guillain-Barré syndrome in the population, many studies had a small number of cases and low power to study associations.

**Interpretation**

The present study found Guillain-Barré syndrome to be significantly associated with exposure to both seasonal influenza vaccine and influenza illness. However, the relative and attributable risks of Guillain-Barré syndrome after seasonal influenza vaccination are lower than the risks after influenza illness. Patients' and providers' decision making regarding influenza immunisation should place the risk for Guillain-Barré syndrome associated with vaccination in context with the risk associated with influenza infection. Further investigation is needed to determine whether influenza vaccination is associated with a net increase or decrease in risk of Guillain-Barré syndrome after accounting for the anticipated reductions in the risk of influenza infection in vaccinated people and the possible indirect benefits of mass immunisation (eg, herd immunity).

| | Influenza seasons | Age groups | Study design | Risk period | Estimate of relative risk (95% CI) |
|---|---|---|---|---|---|
| **Influenza vaccination** | | | | | |
| Lasky et al, 1998[6] | 1992–1994 | ≥18 years | Cohort | 42 days | 1·7 (1·0–2·8) |
| Juurlink et al, 2006[5] | 1992–2004 | ≥18 years | SCCS | Weeks 2–7 | 1·45 (1·05–1·99) |
| Hughes et al, 2006[4] | 1992–2000 | All ages | SCCS | 42 days | 0·99 (0·32–3·12) |
| Tam et al, 2007[8] | 1991–2001 | All ages | Case-control | 60 days | 0·16 (0·02–1·25) |
| Stowe et al, 2009[7] | 1990–2005 | All ages | SCCS | 90 days | 0·76 (0·41–1·40) |
| Greene et al, 2012[9] | 2009–10 | All ages | SCRI | 42 days | 1·3 (0·5–3·8) |
| Wise et al, 2012[10] | 2009–10 | All ages | Cohort | 42 days | 1·43 (0·94–1·89) |
| Present study | 1998–2009 | All ages | SCRI | 42 days | 1·52 (1·17–1·99) |
| **Influenza illness** | | | | | |
| Tam et al, 2007[8] | 1991–2001 | All ages | Case-control | 60 days | 18·64 (7·49–46·37) |
| Stowe et al, 2009[7] | 1990–2005 | All ages | SCCS | 30 days | 16·64 (9·37–29·54) |
| Present study | 1993–2009 | All ages | SCRI | 42 days | 15·81 (10·28–24·32) |

SCCS=self-controlled case series. SCRI=self-controlled risk interval.

***Table 4:* Relative risk estimates of Guillain-Barré syndrome after seasonal influenza vaccination and influenza illness from selected studies**

that the association between influenza vaccination and Guillain-Barré syndrome is stronger for individuals aged 18–64 years than for older adults. Previous influenza vaccine safety studies have similarly shown lower reporting rates of vaccine-associated Guillain-Barré syndrome cases in older adults,[6,26] possibly relating to reduced antibody responses to influenza vaccines in elderly patients.[27]

Our estimate of the risk of Guillain-Barré syndrome after influenza-coded health-care encounters is also similar to results from previous studies that assessed risk associated with clinically defined influenza-like illness.[7,8] Once again, the large number of admissions for Guillain-Barré syndrome in our study permitted the identification of the first week after a health-care encounter being associated with the greatest risk. However, what is unknown from our study is the period of risk for Guillain-Barré syndrome after influenza infection. Influenza symptoms begin 1–4 days after exposure to the virus,[28] and the median interval from symptom onset to physician encounter is 2 days.[29] Therefore, although the risk of Guillain-Barré syndrome is highest 1 week after an influenza-coded health-care encounter, the peak risk interval after influenza exposure is longer due to the interval between infection and health-care encounter.

Our study had some notable strengths. First, the self-controlled risk-interval design eliminates non-time-varying confounding by variables associated with both Guillain-Barré syndrome and vaccine uptake,[9] and mitigates the effect of underascertainment of both exposures and outcomes by needing only cases who have had both an exposure and the outcome. These results are therefore not biased by low sensitivities for the exposure and outcome measures. Second, we used routinely collected population-based administrative data, thereby avoiding the biases arising from passive reporting. Third, we studied a large population over 18 years, leading to a large study sample drawn from several influenza seasons.

The main limitation of this study relates to the uncertain validity of the diagnostic codes used to identify both Guillain-Barré syndrome admissions and influenza illness. Although the diagnostic codes for Guillain-Barré syndrome have never been validated in Ontario, the PPV is reasonably high in similar settings.[9,20] Furthermore, we did a sensitivity analysis to adjust for potential misclassification of cases in our hospital records and determined that our primary analyses might have underestimated the risk estimates for both exposures, although not substantially. Similarly, although influenza-coded health-care encounters represent a fraction of influenza infections occurring in a population, they have a high PPV in this setting, at least for patients tested for influenza. However, whether milder or asymptomatic influenza infections carry the same risk of Guillain-Barré syndrome as illnesses leading to health-care encounters is unknown. A second limitation is that we did not have dates of symptom onset for either Guillain-Barré syndrome cases or influenza infection. Due to the interval from influenza infection to health-care encounter,[28,29] the risk of Guillain-Barré syndrome after an influenza-coded health-care encounter might not represent the risk of Guillain-Barré syndrome after influenza infection. Third, we were only able to include influenza vaccinations given in physician offices with influenza-vaccine-specific billing codes. We do not know if people

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who receive vaccines from such physicians are systematically different from individuals vaccinated in other settings, and if any underlying differences between the two populations are also associated with Guillain-Barré syndrome. Fourth, in the model accounting for both influenza vaccination and influenza-coded health-care encounters, the effect of exposure misclassification due to individuals vaccinated outside of physician offices and infected individuals who are asymptomatic, do not seek medical care, or are not coded as influenza (ie, false negatives in both cases), is uncertain. Finally, our study does not provide data for live, attenuated, or adjuvanted influenza vaccines.

The results of this study can facilitate patients' decision making regarding influenza immunisation, but a formal competing-risk analysis that simultaneously balances the attributable risks of both influenza vaccines and infection is needed. Such an analysis should account for anticipated reductions in the risk of influenza infection from immunisation as well as possible indirect benefits of mass immunisation (ie, herd immunity). The small risk of Guillain-Barré syndrome associated with influenza vaccines of roughly one admission per million vaccinations should be placed in the context of the risk of Guillain-Barré syndrome associated with influenza infection. In view of the strong observed association between influenza-coded health-care encounters and Guillain-Barré syndrome, we speculate that the trigger for the disorder after influenza vaccination might be the influenza antigens contained in the vaccine. Patients considering immunisation should be fully informed of the risks of Guillain-Barré syndrome from both influenza vaccines and influenza illness, as well as the more substantial direct and indirect benefits from immunisation in terms of preventing morbidity and mortality.[30]

#### Contributors

All authors were responsible for the study concept and design, the analysis and interpretation of data, and the critical revision of the manuscript. MAC acquired the data and did the statistical analysis. JCK, PPV, and MAC drafted the manuscript. JCK obtained funding, provided administrative, technical, or material support, and supervised the study.

#### Conflicts of interest

AJMcG reports investigator-initiated research funding from Sanofi Pasteur and GlaxoSmithKline, participation as an investigator in clinical trials sponsored by GlaxoSmithKline, and participation in advisory boards and receipt of honoraria for speaking engagements from Sanofi Pasteur, GlaxoSmithKline, and Novartis Pharmaceuticals. The other authors declare that they have no conflicts of interest.

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# Association between vaccination and Guillain-Barré syndrome

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Guillain-Barré syndrome is a serious neurological autoimmune disorder characterised by inflammatory demyelination of peripheral nerves.[1] Up to 25% of patients experience respiratory failure,[2] and 4% die within the first year from disease complications.[3] The disorder can be triggered by viral infections and bacterial and viral vaccinations.[1,4] After the 1976 influenza vaccine campaign in the USA, an increase in the rate of Guillain-Barré syndrome resulted in the suspension of the vaccination programme.[5] Since then, the disorder has been reported in association with other vaccines, the period between vaccination and disease manifestation ranging from as short as a few days to up to 9 months.[1]

In *The Lancet Infectious Diseases*, a study by Jeffery Kwong and colleagues[6] assessed the risks of Guillain-Barré syndrome after influenza vaccination and exposure to influenza illness. The primary risk period was defined as 0–6 weeks after exposure to influenza illness or influenza vaccine, and the control period defined as 9–42 weeks. Kwong and colleagues identified 2831 cases of Guillain-Barré syndrome, 330 of whom were vaccinated and 109 of whom had an influenza-coded health-care encounter within 42 weeks of hospitalisation. The relative risk of Guillain-Barré syndrome within 6 weeks of vaccination was 52% higher than during the control interval (9–42 weeks); however, the relative risk within 6 weeks of influenza was greater than that for vaccination.

Although self-controlled interval studies are widely used in assessing vaccine risks, the variable selection of risk and control intervals can make the interpretation of the results somewhat vague. An interval of 6 weeks between exposure and outcome is often used as evidence of a plausible causal association;[7–9] however, autoimmune events can have substantially longer latency periods (months or years after vaccination).[10,11] Since 1982, evidence from epidemiological, clinical, and animal research has shown that Guillain-Barre syndrome and other demyelinating neuropathies (such as acute disseminated encephalomyelitis) can occur 4–10 months after vaccination.[11] In such cases, the disease would first manifest with vague symptoms (arthralgia, myalgia, paraesthesia, or weakness), which were frequently deemed insignificant and thus ignored. These symptoms, otherwise known as the bridging symptoms and consistent with a mild subclinical disease, would progress slowly until exposure to a secondary immune stimulus, which would then trigger the rapid and acute clinical manifestation of the disease.[11]

The ramifications of the anamnestic response caused by the secondary immune challenge could depend on the genetic immune make-up of the host and the immunological similarity between vaccine antigens and those previously encountered.[11,12] In particular, in individuals who have already been pre-sensitised from previous exposure to influenza or similar viruses, subsequent vaccinations or infections can trigger pathological anamnestic responses leading to advanced Guillain-Barré syndrome.[11] Nonetheless, compared with infections, vaccines induce potentiated immunological responses, owing to the presence of adjuvants[13] or multiple antigens (ie, trivalent seasonal inactivated influenza vaccines). Moreover, vaccines are often administered over fairly short periods. Thus, the full ramifications of vaccinations could be far more detrimental to the recipient than the infections.[11]

Restricting the risk interval to 6 weeks after vaccine exposure could potentially introduce a type-2 error bias. Since Kwong identified three times more cases of Guillain-Barré syndrome in the influenza vaccine group than in the influenza illness group, perhaps an alternative explanation to the study results is warranted, particularly because such research could have significant effects on future influenza vaccination policies. Indeed, in view of the severity of Guillain-Barré syndrome and the prevailing trends worldwide towards mandatory vaccinations, perhaps we need to let go of current beliefs concerning acceptable timeframes for vaccination-related adverse outcomes. More than 30 years ago, Poser and Behan noted that the documentation for patients with a delayed-onset Guillain-Barré syndrome was rare “due to the rigidly held idea that an incubation period of 1-month or less is the rule”.[11] In the light of this statement, our aim is to encourage a shift in vaccine safety evaluations. Namely, a shift which would take into account the pertinent details of already established research that highlights the fact that some post-vaccination events, particularly those of autoimmune nature, can have significantly longer latency periods than currently assumed.[10,11]

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