Guillain-Barré Syndrome After Influenza Vaccination in Adults

A Population-Based Study

David N. Juurlink, MD, PhD; Therese A. Stukel, PhD; Jeffrey Kwong, MD, MSc; Alexander Kopp, BA; Allison McGeer, MD, MSc; Ross E. Upshur, MD, MSc; Douglas G. Manuel, MD, MSc; Rahim Moineddin, PhD; Kumanan Wilson, MD, MSc

Background: Whether influenza vaccination is associated with Guillain-Barré syndrome (GBS) remains uncertain.

Methods: We conducted 2 studies using population-based health care data from the province of Ontario, Canada. In the first study, we used the self-matched case-series method to explore the temporal association between probable influenza vaccination (adults vaccinated during October and November) and subsequent hospitalization because of GBS. In the second study, we used time-series analysis to determine whether the institution of a universal influenza immunization program in October 2000 was associated with a subsequent increase in hospital admissions because of GBS at the population level.

Results: From April 1, 1992, to March 31, 2004, we identified 1601 incident hospital admissions because of GBS in Ontario. In 269 patients, GBS was diagnosed within 43 weeks of vaccination against influenza. The estimated relative incidence of GBS during the primary risk interval (weeks 2 through 7) compared with the control interval (weeks 20 through 43) was 1.45 (95% confidence interval, 1.05-1.99; \( P = .02 \)). This association persisted in several sensitivity analyses using risk and control intervals of different durations. However, a separate time-series analysis demonstrated no evidence of seasonality and revealed no statistically significant increase in hospital admissions because of GBS after the introduction of the universal influenza immunization program.

Conclusion: Influenza vaccination is associated with a small but significantly increased risk for hospitalization because of GBS.

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associated with a subsequent increase in hospital admissions

institution of the universal vaccination program in 2000 was

second study, time-series analysis was used to determine whether

have been vaccinated and subsequently developed GBS. There-

ment for GBS in the preceding 18 months. We also excluded pa-

avoid misclassification of patients with chronic inflammatory de-

tients with any previous hospital admission because of GBS to

have been vaccinated and subsequently developed GBS. There-

ment for GBS in the preceding 18 months. We also excluded pa-

The risk interval and the final 4 (periods 5-8) compose the control interval.

The first 7-day interval followed by seven 6-week intervals. The initial 7-day

In the self-matched case series, the date of vaccination served as

Influenza vaccination was identified using the Ontario Health

The total number of vaccination claims in the Ontario Health

Our analysis was restricted to vaccinations given in October and November.

We linked the vaccination records and hospital admission data

during off-peak months (February to August) generally

Influenza vaccination codes, we used codes for general vacci-

The majority of influenza immunizations were coded using specific

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incidence may have falsely lowered or elevated the number of hospital admissions during this period.

For the ecological analysis, we used time-series analysis with autoregressive integrated moving average modeling to compare observed and expected numbers of GBS admissions in Ontario each month before and after the introduction of the universal influenza immunization program, defined as October 1, 2000. The autocorrelation, partial autocorrelation, and inverse autocorrelation functions were assessed for model parameter appropriateness. Seasonality was assessed using the coefficient of determination of the autoregressive regression model, which we have previously shown to be an excellent indicator of seasonality. All P values were 2 sided, and analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC).

### RESULTS

**SELF-MATCHED CASE SERIES**

From April 1, 1993, through March 31, 2004, we identified 1601 patients aged 18 years and older with an incident hospital admission for GBS. In 269 of these patients, GBS was newly diagnosed within 43 weeks of receiving a vaccination in October or November. As illustrated in Figure 2, the vast majority of vaccinations each year among those aged 18 years or older are given during these months, corresponding to Ontario’s influenza vaccination season.

In the primary analysis, the estimated relative incidence of hospitalization because of GBS during the risk interval compared with the control interval was 1.45 (95% confidence interval, 1.05-1.99; P=.02), indicating a 45% increased risk for GBS in the immediate period after vaccination (Table 2). Sensitivity analyses using control intervals of the final three 6-week periods and then the final five 6-week periods revealed consistent findings, as did another analysis using an 8-week period structure (Table 2) and a marginally shorter total observation period.

**TIME-SERIES ANALYSIS**

From June 1, 1991, through March 31, 2004, we identified 2173 incident hospital admissions because of GBS in Ontario, equivalent to about 170 new cases per year or approximately 14 cases per million person-years, consistent with estimates from other jurisdictions. The autoregressive R² was 0.17, indicating no evidence of seasonality. The intervention model showed no statistically significant increase in admissions because of GBS after institution of the universal influenza immunization program in 2000 (Figure 3).

**COMMENT**

Our analysis of patient-level data from Ontario identified a statistically significant temporal association between receiving an influenza vaccination and subsequent hospital admission because of GBS. However, we also identified no noticeable increase in the incidence of GBS at the population level after the introduction of a mass public influenza vaccination program in Ontario. The relative risk of 1.45 observed in our study is consistent with that from an analysis of the 1992-1993 and 1993-1994 influenza seasons in the United States, which identified a 1.7-fold adjusted relative risk for GBS associated with vaccination. Other studies, however, have not shown a similar association. In 2003, the US Institute of Medicine reviewed published and unpublished studies performed between 1976 and 2002 and concluded that "the evidence is inadequate to accept or reject a causal relationship between GBS in adults and influenza vaccines administered after 1976 (that is, subsequent to the swine influenza vaccine program)." After this review, a study of the US Vaccine Adverse Event Reporting System database noted that, while reports of GBS after influenza vaccination appeared to be decreasing in frequency, the reports had features suggestive of a causal association.

Certain limitations of our study merit emphasis. First, it is possible that a small percentage of the vaccinations we examined may have been against diseases other than influenza. However, because we restricted exposures to those occurring during October and November in Ontario residents aged 18 years or older, the overwhelming majority likely represented influenza vaccinations (Figure 2). Moreover, any misclassification would likely attenuate our observed risk estimates. Second, while the validity of hospital discharge coding for GBS has not been established in Ontario, a sensitivity exceeding 90% has been reported elsewhere. The specificity of the discharge coding is less certain. However, GBS is a condition with unique properties, clear criteria for diagnosis, and a specific diagnosis code in the ICD coding scheme. We also did not include patients with previous admissions because of GBS to eliminate the possibility that chronic inflammatory demyelinating polyneuropathy might be misclassified as GBS. Third,
other confounding factors may have coincided with the administration of the influenza vaccine to yield a spurious temporal association. The lack of seasonality with GBS in Ontario makes this unlikely, but a seasonal confounding factor cannot be excluded outright. Finally, our study was not adequately powered to examine the variability in the association between the influenza vaccine and GBS from year to year. Other analyses have suggested such variability.15

Our research has several notable strengths. We used population-based hospital records in a jurisdiction with the largest mass influenza vaccination program in the world, and the number of incidences of GBS in vaccinated individuals we examined is among the highest in all studies looking into this question. In addition, the case-series design is ideally suited to study this question, given the temporal association between exposure and outcome, and is particularly powerful, given its ability to eliminate confounding by using the individual as his or her own control.4 In particular, other methodologies, such as case-control or cohort study designs, would be susceptible to selection bias and unmeasured confounders. These potential sources of systematic error are greatly reduced by the case-series design method.

Our results must be interpreted carefully. The increase in relative risk we observed corresponds to a very low absolute risk for GBS, given the low baseline incidence of the disease (approximately 1 in 100 000 population). Furthermore, the lack of association on a population health level is consistent with the prevalent impression that influenza vaccine is only one of many potential causes of GBS. Because of the low absolute risk for GBS, we suggest that the decision to recommend vaccination against influenza should primarily be guided by evidence of its benefit.20 However, individuals who receive the influenza vaccine should be advised of the potential risk for GBS, particularly in light of the serious consequences of the illness. Our findings also suggest that it would be prudent to implement active surveillance for GBS as an essential component of any mass vaccination program that is instituted against pandemic influenza.
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REFERENCES


