Guillain-Barré Syndrome After Influenza Vaccination in Adults

A Population-Based Study

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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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IN 1976, THE UNITED STATES implemented the National Influenza Immunization Program in anticipation of a swine influenza epidemic that never materialized. This program was discontinued prematurely, in part because of reports of Guillain-Barré syndrome (GBS) among those vaccinated. Subsequent analyses suggested that individuals who received this vaccine were at a 4- to 8-fold risk for developing GBS.1 The threat of an influenza pandemic has again prompted policy makers to consider the possibility of instituting mass influenza vaccination programs as a preventive measure.2 However, uncertainty remains about the potential risk for GBS that may be associated with such initiatives.

In 2000, the province of Ontario, Canada, adopted a universal influenza immunization program, providing influenza vaccinations free every year to all residents aged 6 months or older. Introduction of the program was associated with a marked increase in the percentage of the population vaccinated, particularly those younger than age 65 years (Table 1).3 In this study, we used Ontario health care data to explore the temporal relationship between vaccination and subsequent development of GBS. We also examined whether institution of the mass influenza vaccination campaign was associated with a measurable populationwide increase in hospital admissions because of GBS.

METHODS

DESIGN

We analyzed individual-level health care data for residents of Ontario, Canada, and conducted 2 distinct but related studies.

First, we used the self-matched case-series method, described by Farrington and associates,4,5 to examine the risk for adverse events after immunization and to explore the temporal association between influenza vaccination and the development of GBS. This approach is increasingly used to explore potential adverse sequelae of vaccination and is derived from a...
Poisson cohort by conditioning on a history of exposure (influenza vaccination) and the outcome of interest (subsequent hospital admission because of GBS). The major feature of this design is that it requires only case data, that is, patients who have been vaccinated and subsequently developed GBS. Therefore, it removes the effects of unmeasured confounding between those who are vaccinated and those who are not.6-8 In a second study, time-series analysis was used to determine whether institution of the universal vaccination program in 2000 was associated with a subsequent increase in hospital admissions because of GBS at the population level.

ASSESSMENT OF EXPOSURE AND OUTCOME

Influenza vaccination was identified using the Ontario Health Insurance Plan database, which contains fee-for-service claims data submitted by physicians in Ontario. Because only a minority of influenza immunizations were coded using specific influenza vaccination codes, we used codes for general vaccination that were provided only during October and November, the peak of the influenza vaccination campaign. We restricted our analyses to patients aged 18 years or older to further reduce the possibility of including noninfluenza vaccinations.

Hospital admissions because of GBS were ascertained from the Canadian Institute for Health Information Discharge Abstract Database, which contains a detailed record of all hospitalizations, including diagnostic and procedural information. In the self-matched case-series analysis, incident cases of GBS occurring between April 1, 1993, and March 31, 2004, were identified using International Classification of Diseases, Ninth Edition (ICD-9) code 357.0 or ICD-10 (ICD, 10th Edition) code G61. In this analysis, incident cases were defined as patients with no previous admission for GBS in the preceding 18 months. We also excluded patients with any previous hospital admission because of GBS to avoid misclassification of patients with chronic inflammatory demyelinating polyneuropathy. In the time-series analysis, we identified incident cases occurring between June 1, 1991, and March 31, 2004. In this analysis, incident cases were defined as patients with no admission for GBS in the preceding year.

We linked the vaccination records and hospital admission data for each patient using an encrypted version of the unique 10-digit health card number. The observation period for each subject was defined as the 43 weeks after vaccination, which allowed complete outcome ascertainment for each subject and averted the possibility of repeat influenza vaccination during follow-up.

STATISTICAL ANALYSIS

In the self-matched case series, the date of vaccination served as the index date for each patient. We restricted this analysis to Ontarians who had both an influenza vaccination and an incident diagnosis of GBS during the subsequent 43 weeks of follow-up. For analytical purposes, we divided each individual follow-up period into 8 distinct intervals after the vaccination date: an initial 7-day interval followed by seven 6-week intervals. The initial 7-day interval was not included in the risk period because admissions to the hospital because of GBS during this period are almost certainly not the result of vaccination but could be associated with disease onset that occurred before vaccination. Therefore, the first 6-week period was considered the primary risk interval (Figure 1) and the final four 6-week intervals represented the control interval, when incident GBS cases were deemed as unlikely related to vaccination against influenza. The relative incidence rate of hospitalization because of GBS during the risk period compared with the control period was analyzed using a fixed-effects Poisson regression model that included exposure and control period terms, and an indicator variable for each patient that allowed each individual to serve as his or her own control.5 A 6-week period was selected as the risk interval based on the findings of previous studies that suggested a potential association of GBS and vaccination against influenza.10 These studies found that GBS primarily occurs within 8 weeks of immunization, with most cases occurring within 6 weeks. In addition to our primary analysis, we also conducted 3 sensitivity analyses. In the first analysis, we used an extended risk interval of 8 weeks to address the possibility that GBS may occur later than in the original studies. In the other 2 sensitivity analyses, we used shorter (weeks 32-43) and longer (weeks 20-43) control periods. The control period was varied to reduce the likelihood that chance or seasonal variations in GBS

Table 1. Percentage of Household Population in Ontario Vaccinated Against Influenza in the Past Year, by Age Group*

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<tbody>
<tr>
<td>20-49</td>
<td>8.0</td>
<td>26.6</td>
<td>23.0</td>
</tr>
<tr>
<td>50-64</td>
<td>20.5</td>
<td>41.6</td>
<td>45.5</td>
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<tr>
<td>≥65</td>
<td>59.5</td>
<td>72.5</td>
<td>74.2</td>
</tr>
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*Data adapted from Kwong et al.3

Figure 1. Self-matched case-series design. The observation period for each patient begins with influenza vaccination and continues for 43 weeks. Guillain-Barré syndrome developing during the first week after vaccination (period 1) is deemed unrelated to vaccination. Periods 2 through 8 are each 6 weeks in duration. In the primary analyses, the first of these (period 2) is the risk interval and the final 4 (periods 5-8) compose the control interval.
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, 2000.11 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.12 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.13,14 The autoregressive $R^2$ 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).

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**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.15 Other studies, however, have not shown a similar association.16,17 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).”10(p9)

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.18

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.19 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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