Influenza vaccine and GBS

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Guillain-Barré Syndrome and the 1992-93 and 1993-94 Influenza Vaccines
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Study Purpose

- To assess whether an increase in reports of Guillain-Barré Syndrome (GBS) after 1993-94 influenza vaccine in the Vaccine Adverse Event Reporting System (VAERS) was due to an increase in vaccine-associated risk.

- To estimate the risk of GBS associated with the 1992-93 and 1993-94 influenza vaccines.
**Background:** Association of GBS with influenza vaccine in the 6-8 week period following vaccination.

<table>
<thead>
<tr>
<th>Year</th>
<th>Relative Risks</th>
<th>Authors and years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976 swine influenza vaccine</td>
<td>4.0-7.6</td>
<td>Schonberger et al., 1976; Marks, 1980; Breman, 1984; Safranek et al., 1991; Langmuir et al., 1984</td>
</tr>
<tr>
<td>1990-91</td>
<td>3.0 (ages 18-64).5 (65 and over)</td>
<td>CDC, 1995</td>
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</table>
Background

- Increase in VAERS reports of GBS following influenza vaccinations.
GBS Reports in VAERS

![Graph showing number of GBS reports in VAERS from 1990-1991 to 1993-1994. The number of reports increased from 34 in 1990-1991 to 74 in 1993-1994.]
Study Design

- Estimate vaccine coverage in denominator population of approximately 21.3 million persons 18 and over in four states
- Ascertain all GBS cases hospitalized in four states during study period
- Ascertain exposure histories (influenza vaccinations) of GBS cases
Study Population

- Persons 18 and over residing in Illinois, Maryland, North Carolina, and Washington State
  - 21.2 million in 1992-93
  - 21.4 million in 1993-94
Study Period

- September 1, 1992 - February 28, 1993
- September 1, 1993 - February 28, 1994
Case Ascertainment

- Obtained hospital discharge databases of 1201 discharges with ICD-9 357.0 during study periods
- Requested hospital charts and received 1109 (92% coverage)
- Reviewed charts and abstract using a standardized data collection form
Categorization of Patients

- Exclude if onset was outside study period
- Exclude if patient was not state resident
- Categorize as definite, probable, possible or non-case
Chart Abstraction

1201 Discharges

1109 Charts Received (92%)

821 patients

288 Repeat Admissions
Chart abstraction - eligibility

- 821 Patients
  - 759 In-state residents
    - 606 Eligible Patients
    - 153 with disease onset outside the study period
  - 62 Out-of-state residents
    - Not eligible
Definite GBS

- Symmetrical progressive paralysis in more than one limb
- Areflexia or hyporeflexia in legs and arms
- Absence of conditions such as:
  - Hexacarbon exposure, abnormal porphyrin metabolism, diphtheria, lead poisoning, polio, botulism, Lyme disease, toxic neuropathy, purely sensory syndrome
- CSF protein > 40 mg/dl
- CSF mononuclear cell count < 10/ml
- Peak of illness within 4 weeks of disease onset
Probable GBS

- As for definites except:
  - CSF missing or CSF mononuclear cell count between 10 and 50
Possible GBS

- Information missing on criteria for categorization
Non-Cases

- Patient does not meet one or more of criteria for Definite or Probable
Chart Abstraction and categorization of 606 patients

- 87 Definites (14.4%)
- 211 Probables (34.8%)
- 123 Possibles (20.3%)
- 185 Non-cases (30.5%)
Distribution of GBS cases over the two study periods
Patient Interviews

180 Patient Interviews (69.5%)

273 Definite and Probable Cases

- 58 not located
- 15 Refusals
- 20 No MD access (Illinois)
Patient Characteristics (interviewed)

- **State of residence**
  - 30.0% Illinois
  - 22.8% Maryland
  - 23.9% North Carolina
  - 23.3% Washington

- **Season of onset**
  - 38.9% 92-93
  - 61.1% 93-94

- **Mean age** 59.0

- **69.4%** Admitted from home
- **41.1%** Discharged to home
- **4.4%** Died in the hospital

- **Mean CSF**
  - protein 110.5 mg/dl
  - 1.23 mononuclear cells/ml

- **57.8%** Received plasmapheresis

- **23.3%** Required ventilator support

- **83.3% White**
- **43.3% Female**
Definitions

- **Vaccine associated cases** – onset of GBS occurred within 6 weeks following influenza vaccination

- **Non-vaccine associated cases** -
  - GBS in patients with no reported influenza vaccinations
  - GBS in patients with onset of GBS outside the six week window following influenza vaccination
Underlying assumption about biology of GBS

Influenza Vaccination → Onset of GBS Symptoms

Six Week Period
Patient Reports of Influenza Vaccinations

180 patients interviewed

116 did not report influenza vaccine

32 reported influenza vaccine, outside 6 week period

19 reported influenza vaccine, within 6 week period

6 reported influenza vaccine, provider not accessible

7 reported influenza vaccine, provider has no record

3.97 imputed as not vaccine associated

2.03 imputed as vaccine associated
Characteristics of Vaccine Associated Cases

- **State of Residence**
  - 2 Illinois
  - 6 Maryland
  - 2 North Carolina
  - 9 Washington

- **Season of Onset**
  - 8  92-93
  - 11  93-94

- **Mean Age** 66.2
- **94.7% White**
- **47.4% Female**

- **22.2% (3) Discharged to home**
- **5.6% (1) Died in hospital**
- **73.7% (12) Admitted from home**

- **mean CSF**
  - protein 81.5 mg/dl
  - mononuclear cells .5/ml

- **73.7% Received plasmapheresis**

- **21.1% (4) Required ventilator support**
Disease onset relative to influenza vaccination

Number of weeks following vaccination

Number of cases

1 2 3 4 5 6 7 8 9 10
Calculation of person weeks exposed or un-exposed

- Person time denominator population exposed or not-exposed in each 26 week observation period
  - Number of people receiving influenza vaccinations multiplied by 6 weeks
  - Number of people receiving influenza vaccinations multiplied by 20 weeks
  - PLUS number of people not vaccinated multiplied by 26 weeks
Calculation of person weeks of exposure and non-exposure

- 10,143,461 vaccinated persons
  - 6 weeks exposure
  - 60.8 million person weeks exposure
  - 20 weeks non-exposure

- 32,513,189 unvaccinated persons
  - 26 person weeks Non-exposure
  - 1,048 million person weeks non-exposure
Calculation of Relative Incidence Density

\[
\frac{\text{Number of vaccine associated GBS cases}}{\text{Number of weeks of exposure (weeks in the six week period following vaccination)}}
\]

\[
\frac{\text{Number of non-vaccine associated GBS cases}}{\text{Number of person weeks non-exposure (weeks not in the six week period following vaccination)}}
\]
Estimates of RR of GBS within 6 weeks following influenza vaccination compared to risk at other times

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Variables controlled for</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>All patients</td>
<td>None</td>
<td>2.4 (1.5-3.8)</td>
</tr>
<tr>
<td>All patients</td>
<td>Age group, season, sex</td>
<td>1.7 (1.0-2.8)</td>
</tr>
<tr>
<td>1992-93 season</td>
<td>Age group, sex</td>
<td>2.0 (1.0-4.3)</td>
</tr>
<tr>
<td>1993-94 season</td>
<td>Age group, sex</td>
<td>1.5 (0.8-2.9)</td>
</tr>
<tr>
<td>Age 18-64</td>
<td>Season, sex</td>
<td>1.8 (1.0-3.5)</td>
</tr>
<tr>
<td>Age 65 and over</td>
<td>Season, sex</td>
<td>1.5 (0.7-3.3)</td>
</tr>
<tr>
<td>Males</td>
<td>Age group, season</td>
<td>1.9 (1.0-3.7)</td>
</tr>
<tr>
<td>Females</td>
<td>Age group, season</td>
<td>1.5 (0.7-3.1)</td>
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Other supporting data

- The distribution of case onset dates in the six weeks following vaccination shows a peak in the second week, suggesting a consistent interval between vaccination and onset of GBS.
Overall effect

- The relative risk of Guillain-Barre Syndrome associated with influenza vaccine was 1.7 (95% CI=1.0-2.8) after controlling for age group, sex and year.
- This is similar to the risk observed in earlier years, except for 1976.
The relative risks of GBS associated with influenza vaccine were similar in both study years, and, if anything, decreased during the time period.

The increase in cases reported to VAERS may have resulted from independent increases in the denominator (increased vaccine coverage) and in GBS incidence.
Possible sources of underestimate of GBS incidence

- In-state residents who were hospitalized out of state
  - perhaps 1.4 vaccine associated, 22.5 not vaccine associated

- Possible GBS cases
  - perhaps 3.8 vaccine associated, 59.2 not vaccine associated

- Patients reporting no influenza vaccine - false negatives?
Possible explanations for increase in VAERS GBS reports

- Increase in GBS incidence from 118 to 155 cases between the two study years.
- Increase in influenza vaccine coverage from 20.9% to 26.6% over the two study years - an increase of 27.2%
- Study shows no apparent increase in relative risk by study year
Conclusions

- Although the absolute number of VAERS influenza vaccine associated GBS increased over the two study seasons, our data showed a slight decrease in the relative risk over the two seasons. The 1993-94 influenza vaccine does not appear to be associated with a greater risk than the 1992-93 influenza vaccine.
Conclusions

- The relative risk of GBS associated with influenza vaccine was 1.7 (95% CI=1.0-2.8) after adjusting for age group, sex and influenza season.
- This translates into an additional 1-2 GBS cases per one million vaccinated persons per year.