Studies of Guillain-Barré syndrome (GBS) after influenza vaccination

Institute of Medicine
Immunization Safety Review Committee
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Immunization Safety Branch
National Immunization Program
• **Studies:**
  - 1976-77 (*Swine influenza*) vaccine
    - Schonberger L et al
    - Safranek T et al
    - Others (Retaliau, Poser, Kurland)
  - 1980-81 vaccine (Hurwitz E et al)
  - 1981-82, 1982-83 vaccines (Kaplan J et al)
  - 1990-91 vaccine (Chen R et al)
  - [1992-93, 1993-94 vaccine (Lasky T et al)]
  - 1993-94, 1994-95 vaccine (McBean M et al)

• **Military paradox?**

• **Hypotheses**
Chronology 1976-77 A/New Jersey “Swine Flu” Vaccinations

- 8/11/76: PL 94-380: US Govt take on liability
- 10/1/76: begin national vaccination campaign
- 10/16-12/14/76 NJ, AL, MN, CO: GBS RR=7.35
- 12/16/76: moratorium; ~45m doses given
- 12/17/76: all states requested to participate in nationwide survey of GBS
- 1/14/77 MMWR: 581 reported cases of GBS from 49 states; GBS RR= 8-14
Schonberger AJE 1979: Methods I

• Case finding:
  – Active surveillance all practicing neurologists
  – New GBS cases dx’ed: 10/1/76-1/31/77
  – GBS case investigation form completed
  – Some states: additional measures

• GBS definition:
  – MD dx (Neurologist dx in IL, MT, OH) +
  – Objective evidence of muscle involvement
Schonberger AJE 1979: Methods II

• Denominator:
  – 7/1/76 Census: civilian pop by state and age
  – CDC: weekly + monthly doses administered

• Analysis:
  – GBS “attack rates” in vaccinated vs. unvaccinated populations
<table>
<thead>
<tr>
<th>Age Grp (years)</th>
<th>Exposed N (AR/10^6 p-m)</th>
<th>Unexposed N (AR/10^6 p-m)</th>
<th>RR (95%CI)</th>
<th>Attrib Risk w/i 6 wks /10^6 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-17</td>
<td>1 (1.1)</td>
<td>86 (0.46)</td>
<td>2.4 (0.4,16.2)</td>
<td>NS</td>
</tr>
<tr>
<td>18-24</td>
<td>23 (3.3)</td>
<td>60 (0.89)</td>
<td>3.7 (2.4,5.8)</td>
<td>3.3</td>
</tr>
<tr>
<td>25-44</td>
<td>146 (9.1)</td>
<td>96 (0.74)</td>
<td>12.2 (10.0,14.9)</td>
<td>11.4</td>
</tr>
<tr>
<td>45-64</td>
<td>118 (7.5)</td>
<td>108 (1.1)</td>
<td>6.8 (5.4-8.5)</td>
<td>8.8</td>
</tr>
<tr>
<td>65+</td>
<td>75 (7.3)</td>
<td>68 (1.4)</td>
<td>5.2 (3.9-7.0)</td>
<td>8.1</td>
</tr>
</tbody>
</table>
Schonberger AJE 1979: Results II

- Lot-specific AR: some nonrandom distribution
- $p = \text{NS}$: whole vs. split virus vaccines; 4 manufacturers

<table>
<thead>
<tr>
<th></th>
<th>Vaccin</th>
<th>Ated</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Fatality Ratio</td>
<td>6.0%</td>
<td>4.7%</td>
<td>$p = \text{NS}$</td>
</tr>
<tr>
<td>Antecedent Illness</td>
<td>32.8%</td>
<td>61.8%</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Neurologist Diagnosis</td>
<td>84%</td>
<td>89%</td>
<td>$p &lt; 0.05$</td>
</tr>
</tbody>
</table>
Schonberger AJE 1979: Evidence supporting causality

- Significantly elevated RR
- Nonrandom distribution of onset intervals
- Lower prevalence of antecedent illness in vaccinated vs. unvaccinated GBS cases suggestive of a “replacement” trigger
Original Contributions

AN EPIDEMIOLOGIC AND CLINICAL EVALUATION OF GUILLAIN-BARRÉ SYNDROME REPORTED IN ASSOCIATION WITH THE ADMINISTRATION OF SWINE INFLUENZA VACCINES

ALEXANDER D. LANGMUIR,¹ DENNIS J. BREGMAN,² LEONARD T. KURLAND,³ NEAL NATHANSON⁴ AND MAURICE VICTOR⁵


As a result of a court order, computerized summaries of approximately 1,300 cases reported as Guillain-Barré syndrome by state health departments to the Centers for Disease Control during the intensive national surveillance instituted following the swine influenza vaccination program in 1976–1977 became available for further study. Although the data were not uniformly adequate to confirm the diagnosis of Guillain-Barré syndrome, they were sufficient to enable classification according to extent of motor involvement. Vaccinated cases with “extensive” paresis or paralysis occurred in a characteristic epidemiologic pattern closely approximated by a lognormal curve, suggesting a causal relationship between the disease and the vaccine. Cases with “limited” motor involvement showed no such pattern, suggesting that this group included a substantial proportion of cases which were unrelated to the vaccine. The effect attributed to the vaccine lasted for at least six weeks and possibly for eight weeks but not longer. The relative risk of acquiring “extensive” disease over a six-week period following vaccination...
Basis for Questioning Causal Relationship between GBS and Swine Flu vaccine

- Case finding by PH w/o clinical training for dx of GBS
- GBS rare, clinicians bias for dx with adverse publicity?
- GBS “cases” based on reports, not medical records.
- 2/1100 reported cases rejected => little CDC screening
- Insufficient F/U to clarify dx in all cases
- Some cases accepted by CDC did not meet GBS criteria
- 1.7 million military & 1 million Dutch vax’ed => no risk
- GBS background rate in Olmstead County 2x CDC rate
Safranek AJE 1991

• Methods:
  – Medical records obtained on all adult GBS patients in MI and MN: 10/1/76-1/31/77
  – Vaccine exposure status blinded
  – Expert neurologist panel review using standard GBS case definition

• Results:
  – 29% of GBS cases discarded: vaxed = unvaxed
  – RR = 7.1 (vs. 7.6 in Schonberger et al)
Article abstract—We compared Guillain-Barré syndrome (GBS) cases reported from cities in the United States in 1976-1977 with spouse or associate controls to detect possible HLA associations. HLA-A11 was somewhat less common among 92 cases than among 100 controls ($p = 0.04$). The 38 patients and 42 controls vaccinated against A/NJ/76 differed slightly in overall distribution of B locus antigens ($p = 0.06$), but the individual HLA-B antigen associations were more easily explained by chance. The 54 unvaccinated cases showed no apparent relation to HLA type. These findings should encourage further immunogenetic study of etiologically related GBS cases.

NEUROLOGY (Cleveland) 1984;34:240-2

Richard A. Kaslow, MD, MPH; John Z. Sullivan-Bolyai, MD; Barry Hafkin, MD; Lawrence B. Schonberger, MD, MPH; Linda Kraus, PhD; Michael J. Moore, MD; Edmund Yunis, MD; and R. Michael Williams, MD, PhD
Original Contributions

ILLNESS AFTER INFLUENZA VACCINATION REPORTED THROUGH A NATIONWIDE SURVEILLANCE SYSTEM, 1976–1977

HENRY F. RETAILLIAU, ARTHUR C. CURTIS, GORDON STORR, GREGORY CAESAR, DONALD L. EDDINS AND MICHAEL A. W. HATTWICK


In 1976, the Center for Disease Control coordinated nationwide surveillance for illnesses after influenza vaccination as part of an effort to vaccinate the nation against influenza A/New Jersey/76. For the 48,161,019 persons vaccinated in 1976, a total of 4733 reports of illness were received which included reports of 223 deaths. When Guillain-Barré syndrome was reported in vaccine recipients, an investigation was begun to examine this possible association. Other than the Guillain-Barré syndrome and rare cases of anaphylaxis, no serious illnesses were causally associated with influenza vaccination by this type of surveillance. Widespread underreporting of illness and death in the passive phase of this surveillance system, however, impaired the ability...


Table 2

*Diagnosis reported as a cause of two or more deaths after vaccination against influenza A/New Jersey/76, United States, October–December 16, 1976*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of cases reported</th>
<th>Rate per 100,000 vaccinees</th>
<th>Crude expected death rate for a two-day period*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>83</td>
<td>0.17</td>
<td>0.786</td>
</tr>
<tr>
<td>with mention of hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic ischemic heart disease</td>
<td>23</td>
<td>0.05</td>
<td>0.585</td>
</tr>
<tr>
<td>without mention of hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>12</td>
<td>0.02</td>
<td>0.037</td>
</tr>
<tr>
<td>Acute cerebrovascular disease</td>
<td>10</td>
<td>0.02</td>
<td>0.153</td>
</tr>
<tr>
<td>without mention of hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction with hypertension</td>
<td>8</td>
<td>0.02</td>
<td>0.079</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>8</td>
<td>0.02</td>
<td>0.026</td>
</tr>
<tr>
<td>Chronic ischemic heart disease</td>
<td>6</td>
<td>0.01</td>
<td>0.845</td>
</tr>
<tr>
<td>with hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecified arrhythmia</td>
<td>5</td>
<td>0.01</td>
<td>0.003</td>
</tr>
<tr>
<td>Generalized arteriosclerosis</td>
<td>5</td>
<td>0.01</td>
<td>0.082</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>5</td>
<td>0.01</td>
<td>0.009</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
<td>0.01</td>
<td>0.062</td>
</tr>
<tr>
<td>Myocardial insufficiency</td>
<td>3</td>
<td>0.01</td>
<td>0.003</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>3</td>
<td>0.01</td>
<td>0.017</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>3</td>
<td>0.01</td>
<td>0.031</td>
</tr>
<tr>
<td>Emphysema</td>
<td>3</td>
<td>0.01</td>
<td>0.052</td>
</tr>
<tr>
<td>Other ischemic heart disease</td>
<td>2</td>
<td>0.004</td>
<td>0.011</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>0.01</td>
<td>0.026</td>
</tr>
</tbody>
</table>
Retailliau AJE 1980: Reported Morbidity in Civilians

- 2860 reports
- 283 different ICD-8 codes illnesses
  - 65% “ill defined/unspecified reactions”
- Associated symptoms:
  - Fever (42%)
  - Headache (36%)
  - Malaise (29%)
  - Myalgia (25%)
  - Allergic: rash (3%); hives (1.5%); anaphyl (N=11)
- Neuro syndromes (N):
  - GBS (61 vs. 532 active surv)
  - Facial paralysis (26)
  - Other neuritis (26)
  - Encephalitis (18)
  - Periph nerve disease (16)
  - Brachial neuritis (9)
  - Optic neuritis (8)
  - Demyelinating disease (5)
  - Labyrinthitis (5)
  - Meningitis (5)
Neurological complications of swine influenza vaccination

CHARLES M. POSER

The emphasis upon the remarkably large number of cases of Guillain-Barre syndrome which resulted from the 1976 National Swine Influenza immunization program in the U.S.A. has obscured the fact that other neurological complications, involving the central nervous system also occurred. The anatomical distribution of lesions is almost identical with that seen following other types of vaccination: involvement of the brain, cerebellum, optic nerve, cranial nerves and spinal cord occurred with approximately the same frequency.

5 instances of the very rare subacute or chronic, progressive, post-vaccinal encephalopathy are described, a situation which is identical to the subacute and chronic forms of polyradiculoneuropathy. In a number of cases, in particular the myelopathies, a subclinical involvement of peripheral nerves was demonstrated by means of electrodiagnostic studies, illus-
Table 2a. Involvement of the nervous system after swine influenza vaccination (published cases)

<table>
<thead>
<tr>
<th>No.</th>
<th>Author(s)</th>
<th>Year</th>
<th>Case no.</th>
<th>Age/ Sex</th>
<th>Days from vaccination</th>
<th>Brain</th>
<th>Optic nerve</th>
<th>Cranial nerves</th>
<th>Cerebellum</th>
<th>Spinal cord</th>
<th>Brachial plexus</th>
<th>Peripheral nerve</th>
<th>Highest CSF protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bienfang et al.</td>
<td>1977</td>
<td>1</td>
<td>27 M</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Cherington</td>
<td>1977</td>
<td>1</td>
<td>25 M</td>
<td>18</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Furlow</td>
<td>1977</td>
<td>2</td>
<td>41 F</td>
<td>10</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Weintraub &amp; Chia</td>
<td>1977</td>
<td>1</td>
<td>57 M</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Gens &amp; Beecham</td>
<td>1978</td>
<td>1</td>
<td>66 F</td>
<td>4</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>–</td>
<td>1978</td>
<td>2</td>
<td>44 M</td>
<td>3</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>–</td>
<td>1978</td>
<td>3</td>
<td>53 F</td>
<td>1</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>–</td>
<td>1978</td>
<td>4</td>
<td>28 M</td>
<td>2</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>Poser et al.</td>
<td>1978</td>
<td>2</td>
<td>17 M</td>
<td>18</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>215</td>
</tr>
<tr>
<td>10</td>
<td>Cangemi &amp; Bergen</td>
<td>1980</td>
<td>1</td>
<td>38 M</td>
<td>14</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1978-81* (3) Flu Seasons: Methods

• Case finding via National GBS surveillance:
  – Am Acad Neurology members contacted by mail/phone each season (Sept. 1-Mar. 31)
  – Submit case report for each new GBS case
    • objective evidence of muscle involvement
    • Asbury criteria whenever questions arose

• Denominator estimated by National Immunization Survey

## 1978-81* Flu Seasons: Results

<table>
<thead>
<tr>
<th>Flu Season</th>
<th>Vaccinated N (IR/10^6 p-wk)</th>
<th>Unvax'ed N (IR/10^6 p-wk)</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978-79</td>
<td>13 (0.13)</td>
<td>510 (0.10)</td>
<td>1.4 (0.7-2.7)</td>
</tr>
<tr>
<td>1979-80</td>
<td>7 (0.06)</td>
<td>412 (0.09)</td>
<td>0.6 (0.5-1.3)</td>
</tr>
<tr>
<td>1980-81</td>
<td>12 (0.11)</td>
<td>347 (0.07)</td>
<td>1.4 (0.8-1.8)</td>
</tr>
<tr>
<td>F/U phone survey</td>
<td>4</td>
<td>350</td>
<td>&lt;1.4</td>
</tr>
</tbody>
</table>

1978-81* Flu Seasons: Distribution of Onset Intervals

1978-81* Flu Seasons:

• Antecedent Illness 1978-79: vax’ed (33%) vs. unvaxed (69%), p<0.05 (confounding by C/I?)

• “Results..suggest that the epidemiologic association between GBS and influenza vaccinated documented in 1976 was unique and that the causative “trigger agent” in the swine influenza vaccine has not been present in subsequent vaccine preparations.”

Investigation of GBS and 1990-91 Influenza Vaccine Index Cases

- 12/3/90, 2 GBS in flu vaccinees from same HMO in CO:
  - 53 y.o. female, onset interval 2 weeks
  - 68 y.o. female, onset interval 5 weeks

- 28,700 doses administered by HMO during annual campaign

- \( \frac{2}{(28,700 \times 6 \text{ weeks risk})} = 11.6 /\text{million person-weeks} \)
  - 40x > background rate = 0.25/\text{million person-weeks}

- 12/17/90 preliminary search of neurology referral centers
  - in Colorado, Oregon, Minnesota, New York City, Washington
  - 8 flu vaccinated GBS cases vs. 2.3-4.5 expected
Investigation of GBS and Influenza Vaccination 1990-91
Methods - Study Sites

- Primary:
  - Colorado
  - 2 California HMOs
  - 10 HCFA/Medicare Flu Vaccine Demonstration Sites

- Secondary:
  - Louisiana
  - Washington
Investigation of GBS and Influenza Vaccination 1990-91
Methods - Case Definitions

- First used by neurology panel for swine flu validation study

- Criteria for diagnosing GBS developed by:
  - American Academy of Neurology
  - American Neurological Association

- Modified to permit categorization of cases as:
  - "definite"
  - "probable"
  - "possible"
  - "rejected"
Investigation of GBS and Influenza Vaccination 1990-91 Methods - Active Surveillance I

- Case Finding of all GBS cases via:
  - Practicing neurologists <= secondary sites only
  - Plasmapheresis centers
  - Hospital medical discharge records ICD-9 357.0

- Study Inclusion Criteria
  - Residence in study site at onset of GBS
  - Onset of GBS >7/1/90
  - Age at onset >18 years of age
Investigation of GBS and Influenza Vaccination 1990-91
Methods - Active Surveillance II

- Vaccination Status Ascertainment
  - Patient interview
  - Validation with vaccine provider

- Questionnaire on each suspect GBS case
  - Completed from all sources by medical epidemiologists
  - Classified using case definition
Investigation of GBS and Influenza Vaccination 1990-91
Methods - Case Classification Validation

- First 180 questionnaires masked for:
  - personal identifiers
  - vaccination status
  - antecedent illnesses
  - medical epidemiologist classification

- Panel of 4 experienced neurologists
  - each case independently reviewed by 2 neurologists
  - cases with discrepant classifications
    - reviewed independently by other 2 neurologists
    - all 4 neurologist discuss to reach consensus

- All cases judged "definite", "probable", or "possible" included in analysis.
Investigation of GBS and Influenza Vaccination 1990-91
Methods - Doses of Vaccine Administered

- 18-64 years:
  - computer assisted telephone interview survey
  - random digit dialing
  - July + August 1991
  - reported vax status accepted, not validated

- >65 years:
  - Medicare areas:
    - HCFA-funded vaccine coverage survey
    - combined phone, mail, and field interviews
  - Other sites:
    - extrapolated from Medicare areas
    - pending 1991 National Health Interview Survey
Investigation of GBS and Influenza Vaccination 1990-91
Results - Estimates of Flu Vaccine Coverage
by Study Site and Age Group

<table>
<thead>
<tr>
<th>Site</th>
<th>18-64 years</th>
<th>&gt; 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare</td>
<td>12%</td>
<td>53%</td>
</tr>
<tr>
<td>CO</td>
<td>15%</td>
<td>53%*</td>
</tr>
<tr>
<td>CA HMOs</td>
<td>8%</td>
<td>53%*</td>
</tr>
<tr>
<td>WA + LA</td>
<td>10%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>11%</strong></td>
<td><strong>48%</strong></td>
</tr>
</tbody>
</table>

* Extrapolated from Medicare survey pending results
of 1991 National Health Interview Survey
### Investigation of GBS and 1990-91 Influenza Vaccine Results - Relative Risk (RR) Within 6 weeks of Vaccination by Age Group and Study Site

<table>
<thead>
<tr>
<th>Study Sites</th>
<th>Age Group</th>
<th>Vaccinated Cases</th>
<th>Rate</th>
<th>Unvaccinated Cases</th>
<th>Rate</th>
<th>RR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>18-64</td>
<td>7</td>
<td>0.93</td>
<td>120</td>
<td>0.28</td>
<td>3.0</td>
<td>(1.4-6.4)</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td>2</td>
<td>0.25</td>
<td>54</td>
<td>0.80</td>
<td>0.3</td>
<td>(0.1-1.3)</td>
</tr>
<tr>
<td></td>
<td>&gt;18</td>
<td>9</td>
<td>0.58</td>
<td>174</td>
<td>0.36</td>
<td>1.1</td>
<td>(0.5-2.1)</td>
</tr>
<tr>
<td>Secondary</td>
<td>18-64</td>
<td>2</td>
<td>0.73</td>
<td>17</td>
<td>0.11</td>
<td>5.9</td>
<td>(1.5-28.2)</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td>1</td>
<td>0.47</td>
<td>7</td>
<td>0.26</td>
<td>1.8</td>
<td>(0.2-14.7)</td>
</tr>
<tr>
<td></td>
<td>&gt;18</td>
<td>3</td>
<td>0.61</td>
<td>24</td>
<td>0.13</td>
<td>3.5</td>
<td>(1.4-15.2)</td>
</tr>
<tr>
<td>Both</td>
<td>18-64</td>
<td>9</td>
<td>0.88</td>
<td>137</td>
<td>0.24</td>
<td>3.3</td>
<td>(1.7-6.5)</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td>3</td>
<td>0.29</td>
<td>61</td>
<td>0.64</td>
<td>0.5</td>
<td>(0.1-1.5)</td>
</tr>
<tr>
<td></td>
<td>&gt;18</td>
<td>12</td>
<td>0.59</td>
<td>198</td>
<td>0.30</td>
<td>1.3</td>
<td>(0.7-2.4)</td>
</tr>
</tbody>
</table>

* Controlled for age (18-44, 45-64, 65+) when appropriate
### Investigation of GBS and Influenza Vaccination 1990-91
Results - Prevalence of Antecedent Acute Illness

<table>
<thead>
<tr>
<th>Season</th>
<th>Vaccinated</th>
<th>Unvaccinated</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>1976-77</td>
<td>460</td>
<td>33%</td>
<td>377</td>
</tr>
<tr>
<td>1990-91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-64</td>
<td>8</td>
<td>88%</td>
<td>145</td>
</tr>
<tr>
<td>65+</td>
<td>4</td>
<td>25%</td>
<td>56</td>
</tr>
<tr>
<td>18+</td>
<td>12</td>
<td>73%</td>
<td>201</td>
</tr>
</tbody>
</table>
> 65 y.o.: No excess risk of GBS associated with recent receipt of 1990-91 influenza vaccine.

18-64 y.o.: Potentially elevated risk, but supporting evidence equivocal.
The Occurrence of Guillain-Barre Syndrome (GBS) in Elderly Medicare Beneficiaries Following Influenza Vaccination, 1993-1994 and 1994-1995

Institute of Medicine, Vaccine Safety Review

University of Minnesota School of Public Health
Methods - Identification of vaccinated cohorts

• Annual “Influenza Immunization” files created by Medicare -- all claims for 9/1/9X through 12/31/9X

• Selected only those identified through Physician/Supplier Part B bills -- the most likely to be correct
  – 94.4% (9,876,152 of 10,354,708 claims in 1993
  – 95.5% (11,013,030 of 11,523,625 claims in 1994
Methods: Identification of Post-Immunization Hospitalizations

- Used MedPAR files for 1993, 1994 and 1995 -- one record per hospitalization
- Chart requested if ICD-9-CM code 357.0 in any of the 10 diagnosis positions
- All hospitalizations that occurred prior to immunization eliminated
- All “prevalent cases” of GBS removed
- Chart abstraction using standardized instruments.
- Cases classified per Lasky algorithm
Figure 1. Distribution of Cases of Guillain-Barre Syndrome Occurring Within 16 Weeks of Receipt of Influenza Vaccine, 1993-1994 and 1994-1995
Table 3. Rate of Hospitalization for Definite and Probable cases of Guillain-Barre Syndrome (GBS) after Influenza Immunization among Medicare beneficiaries 65 years of age and older, 1993-1994

<table>
<thead>
<tr>
<th></th>
<th>Within 6 weeks of vaccination</th>
<th>Between 7 and 16 weeks of vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>Number of weeks</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Weekly denominator</td>
<td>9,876,152</td>
<td>9,876,152</td>
</tr>
<tr>
<td>Cases/million/week (cpmpw)</td>
<td>0.321</td>
<td>0.273</td>
</tr>
</tbody>
</table>

Relative risk (within 6 weeks vs. 7-16 weeks) = 1.18;
95% C.I. = 0.78 to 1.55, p = 0.59.
### GBS in active duty personnel, 1976-77*

<table>
<thead>
<tr>
<th></th>
<th>Mean GBS/4 months</th>
<th>Observed 10/1/76-1/31/77</th>
<th>N Expected RR=3.96</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Army</td>
<td>6.3</td>
<td>5</td>
<td>11.94</td>
<td>0.021</td>
</tr>
<tr>
<td>Navy/Marines</td>
<td>6.1</td>
<td>6</td>
<td>10.26</td>
<td>0.115</td>
</tr>
<tr>
<td>Air Force</td>
<td>4.7</td>
<td>2</td>
<td>8.41</td>
<td>0.01</td>
</tr>
<tr>
<td>Total</td>
<td>17.1</td>
<td>13</td>
<td>30.61</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

A BRIEF ORIGINAL CONTRIBUTION


John D. Roscelli,1 James W. Bass,1 and Lorrin Pang2

An increased incidence of Guillain-Barré syndrome (polyradiculoneuritis) occurred in individuals who received the A/New Jersey (swine) influenza vaccine in 1976–1977. A retrospective study encompassing the years 1980–1988 was conducted to determine if the US Army's mass influenza vaccination program has been associated with an increased incidence of Guillain-Barré syndrome in active duty soldiers during the study years. No temporally related increase in Guillain-Barré syndrome was found during the study years. Am J Epidemiol 1991;133:952–5.
FIGURE 1. The number of active duty US Army soldiers admitted with Guillain-Barré syndrome, by cumulative month of the 9-year (1980–1988) study period. This is also an incidence of Guillain-Barré syndrome since 7.02 million soldiers were at risk of developing the syndrome each cumulative month (780,000 active duty population × 9 years) of the study period. 95 percent confidence intervals for this incidence are shown as error bars.
Rate of GBS/100,000 person-years

<table>
<thead>
<tr>
<th></th>
<th>CDC 76-77</th>
<th>CDC 78-79</th>
<th>CDC 79-80</th>
<th>CDC 90-91</th>
<th>Olm 35-80</th>
<th>Army 71-76</th>
<th>Army 80-88</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>1.16</td>
<td>0.46</td>
<td>0.48</td>
<td>1.8</td>
<td>2.51</td>
<td>3.09</td>
<td>4.08</td>
</tr>
</tbody>
</table>

- Army appears to have higher baseline rate of GBS than civilian populations
- The military have increased risk for infectious diseases, some may be triggers for GBS
- Lack of flu vaccine association due to depletion of GBS susceptibles in military?
Hypothesis

• GBS shown to be caused by Campylobacter
• Campylobacter infects chicken
• Influenza vaccine made in chicken eggs
• GBS after influenza vaccination really due to Campylobacter Ag in vaccine?
• Variability of this “contamination” explain variability in GBS among flu vaccines?