

# Influenza vaccine and GBS

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Presented to the

Institute of Medicine

Immunization Safety Review

Committee

March 13, 2003



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

The New England Journal of Medicine  
1998  
339 (25): 1797-1802

# Investigators

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# Study Purpose

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- 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.

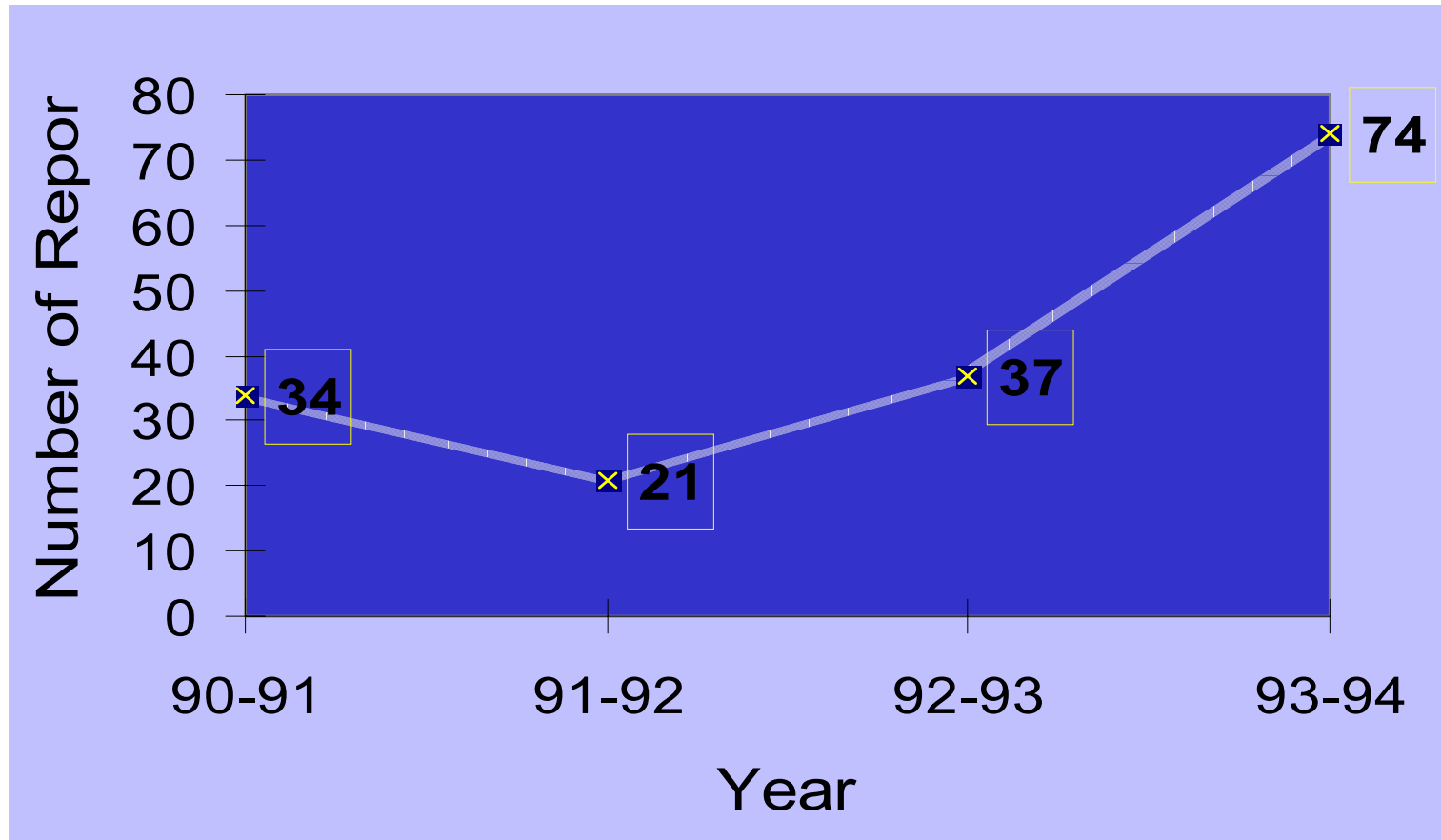
<i>Year</i>	<i>Relative Risks</i>	<i>Authors and years</i>
<i>1976 swine influenza vaccine</i>	4.0-7.6	Schonberger et al., 1976; Marks, 1980; Breman, 1984; Safranek et al., 1991; Langmuir et al., 1984
<i>1978-79, 1979-80 and 1980-81, 1980-88</i>	1.4, .6-1.4, 1.1	Hurwitz et al., 1981; Kaplan et al., 1982; Roscelli et al., 1991
<i>1990-91</i>	3.0 (ages 18-64) .5 (65 and over)	CDC, 1995

# Background

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- Increase in VAERS reports of GBS following influenza vaccinations.

# GBS Reports in VAERS



# Study Design

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- 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

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- 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

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

# Case Ascertainment

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- 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

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

# Chart Abstraction

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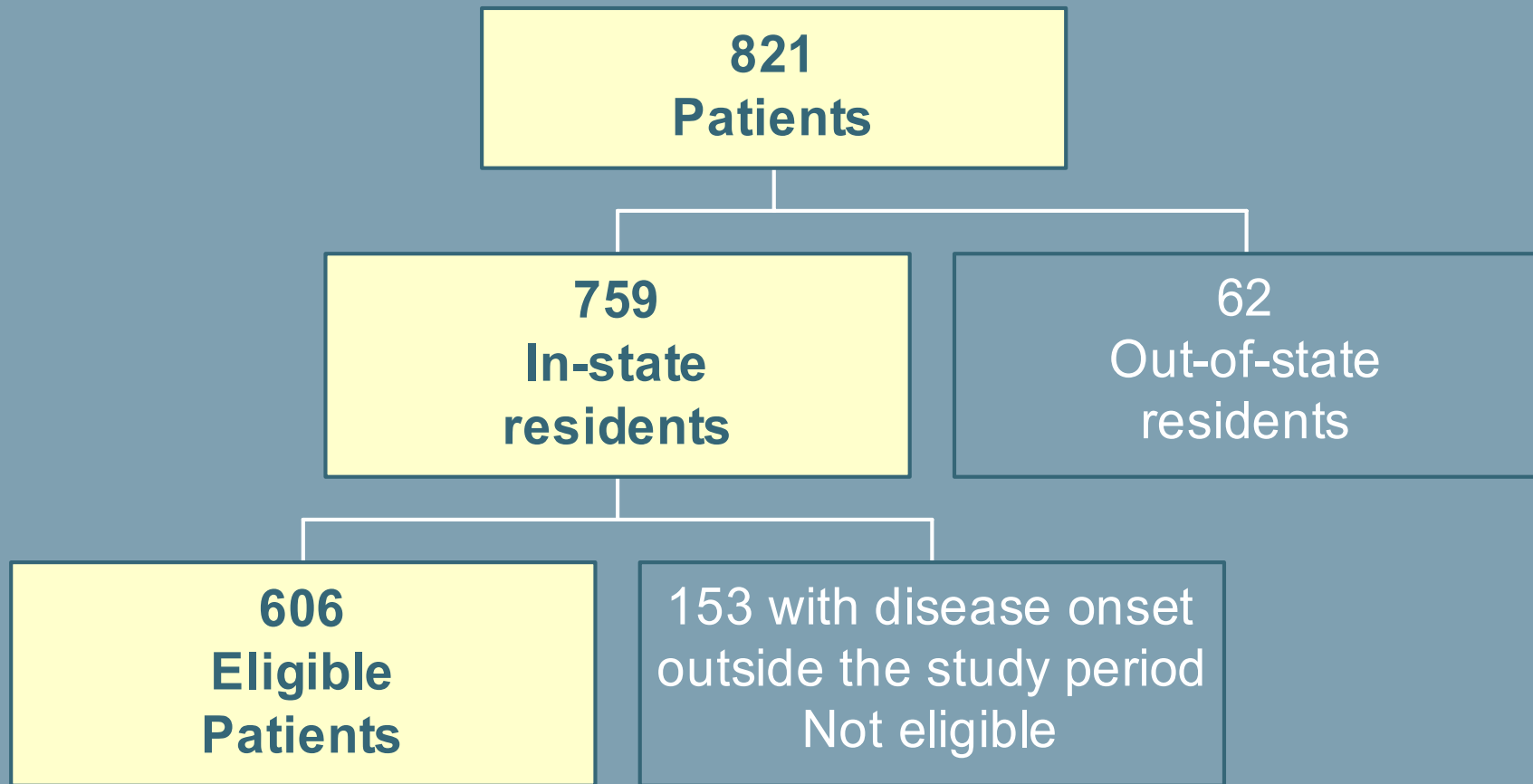
**1201 Discharges**

**1109 Charts Received  
(92%)**

**821  
patients**

**288  
Repeat Admissions**

# Chart abstraction - eligibility



# 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

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

# Possible GBS

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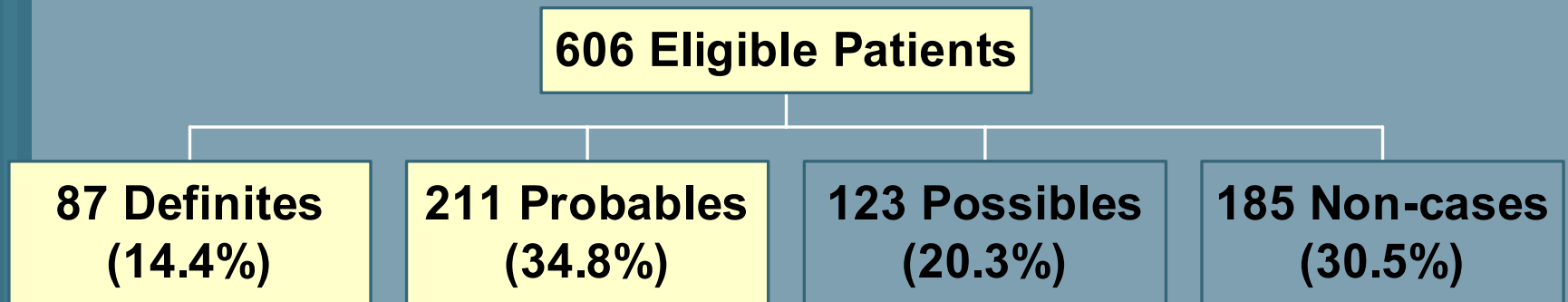
- Information missing on criteria for categorization

# Non-Cases

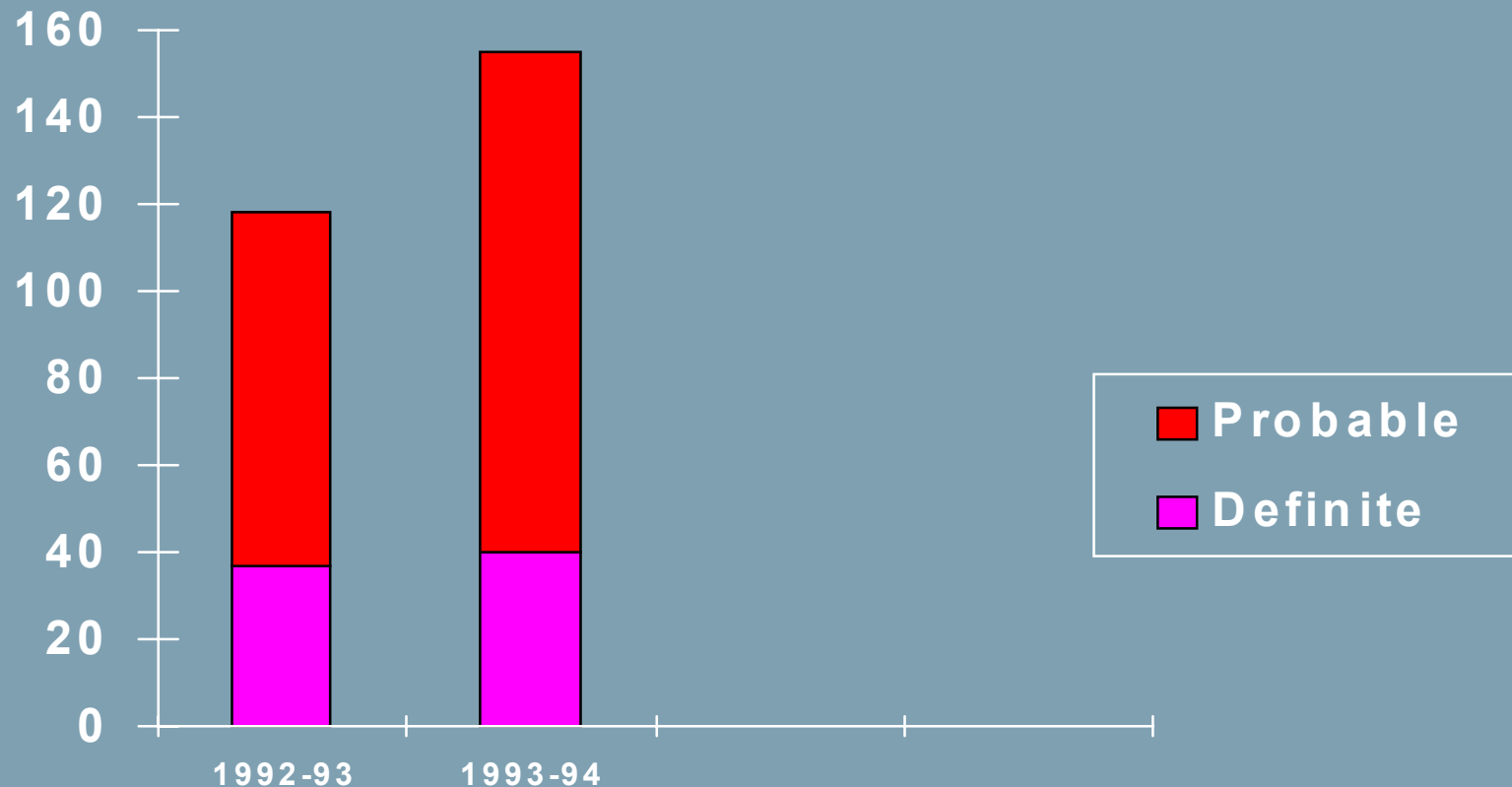
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- Patient does not meet one or more of criteria for Definite or Probable

# Chart Abstraction and categorization of 606 patients



# Distribution of GBS cases over the two study periods



# Patient Interviews

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**273**  
**Definite and Probable Cases**

**180 Patient Interviews**  
**(69.5%)**

**58**  
**not located**

**15**  
**Refusals**

**20**  
**No MD access**  
**(Illinois)**

# Patient Characteristics (interviewed)

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

# Definitions

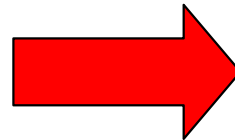
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- Vaccine associated cases – onset of GBS occurred within 6 weeks following influenza vaccination
- Non-vaccine associated cases-
  - GBS in patients with no reported influenza vaccinations
  - GBS in patients with onset of GBS outside the six week window following influenza vaccination

# Underlying assumption about biology of GBS

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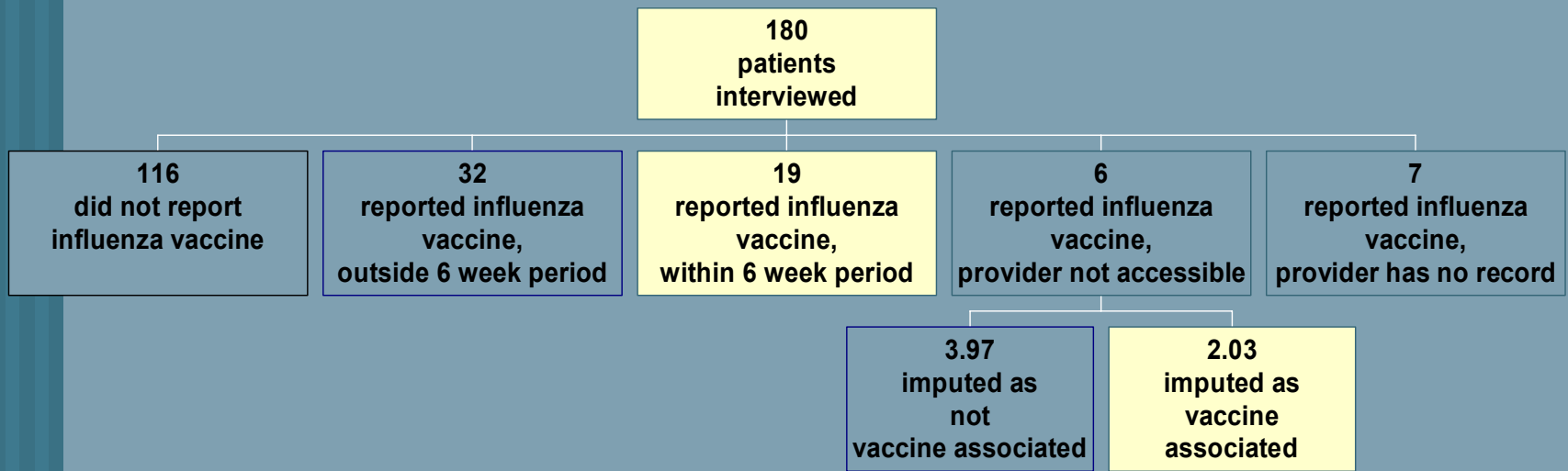
**I n f l u e n z a  
V a c c i n a t i o n**



**O n s e t o f G B S  
s y m p t o m s**

← **S I X W E E K P E R I O D** →

# Patient Reports of Influenza Vaccinations



# Characteristics of Vaccine Associated Cases

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## ■ 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

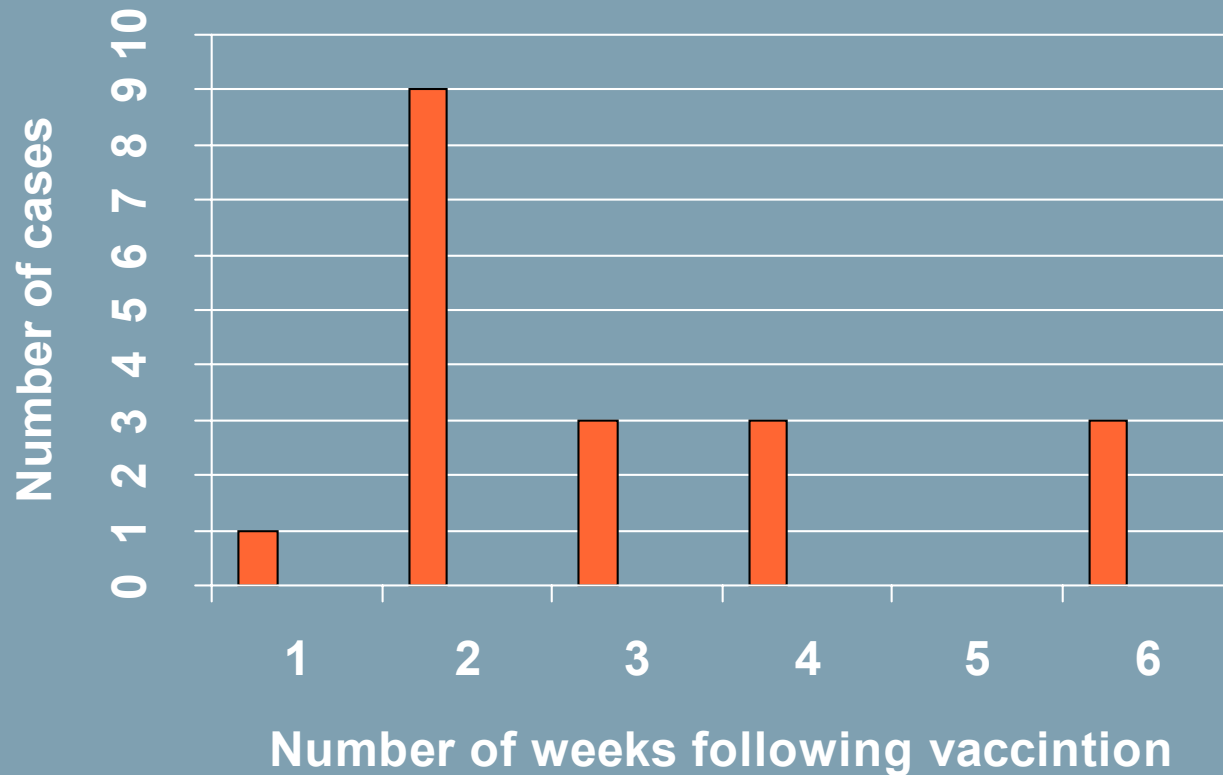
## ■ 94.7% White

## ■ 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

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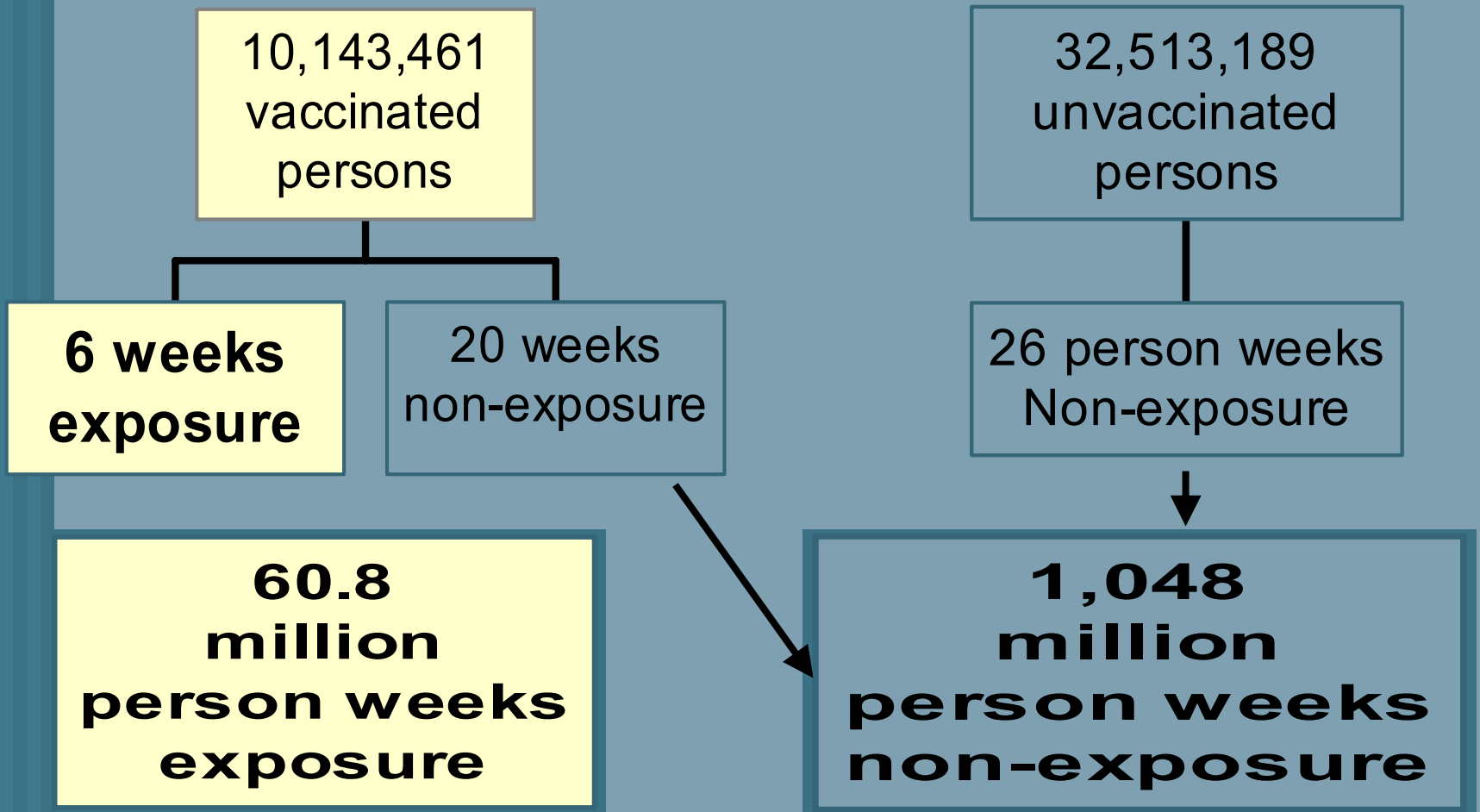


# Calculation of person weeks exposed or un-exposed

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- 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



# Calculation of Relative Incidence Density

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**Number of vaccine associated GBS cases/Number of weeks of exposure (weeks in the six week period following vaccination)**

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**Number of non-vaccine associated GBS cases/ 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

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

# Other supporting data

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- 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

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- 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.

# Effect of vaccine season

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- 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

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- 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

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- 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

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- 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

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- 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.