

Influenza vaccine and GBS

Tamar Lasky, PhD

DHHS/NIH/NICHD

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

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Investigators

- University of Maryland, Baltimore
 - Tamar Lasky, PhD
 - Laurence Magder, PhD
 - Carol Lee Koski, MD
 - Paul D. Stolley, MD, MPH
 - Michael Ballesteros, MS
 - Shelley Clark, MS
 - Denis Nash, MPH
- DHHS/CDC/National Immunization Program
 - Robert T. Chen, MD
 - Gina T. Terracciano, DO, MPH
 - Penina Haber, MPH
- DHHS/CDC/National Center for Infectious Disease
 - Laurence Schonberger, MD

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

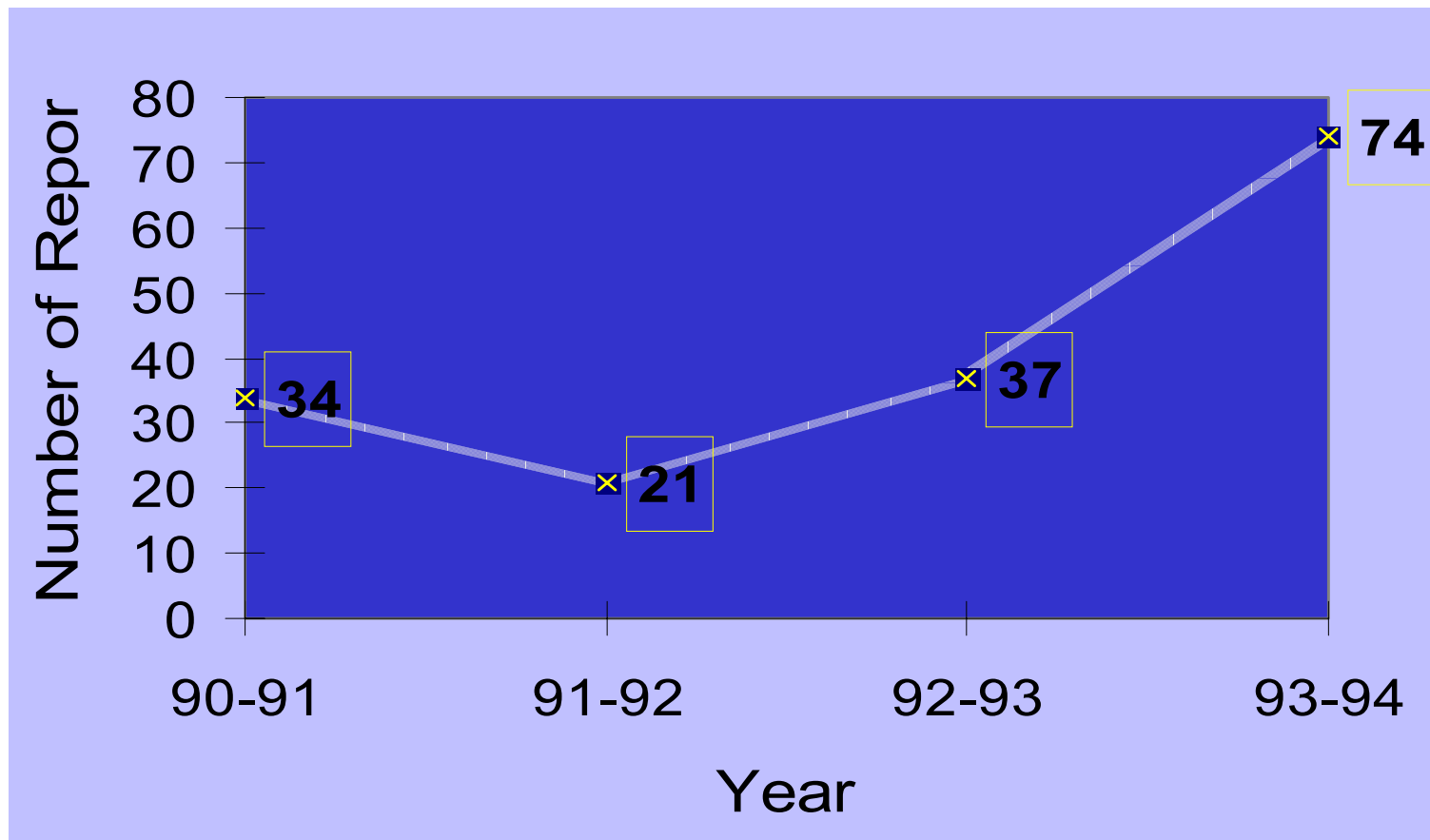
Background: Association of GBS with influenza vaccine in the 6-8 week period following vaccination.

<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

- Increase in VAERS reports of GBS following influenza vaccinations.

GBS Reports in VAERS



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

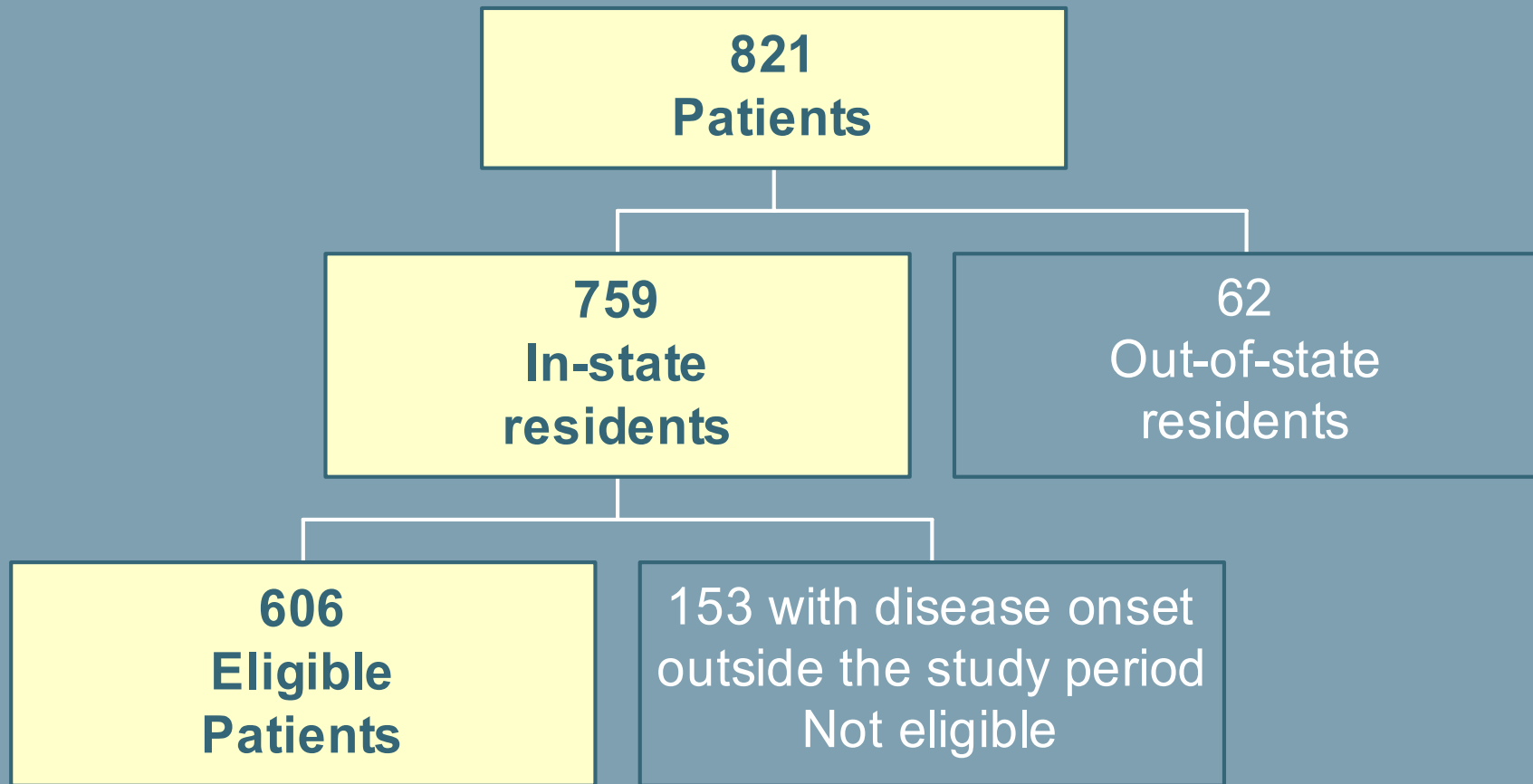
1201 Discharges

**1109 Charts Received
(92%)**

**821
patients**

**288
Repeat Admissions**

Chart abstraction - eligibility



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

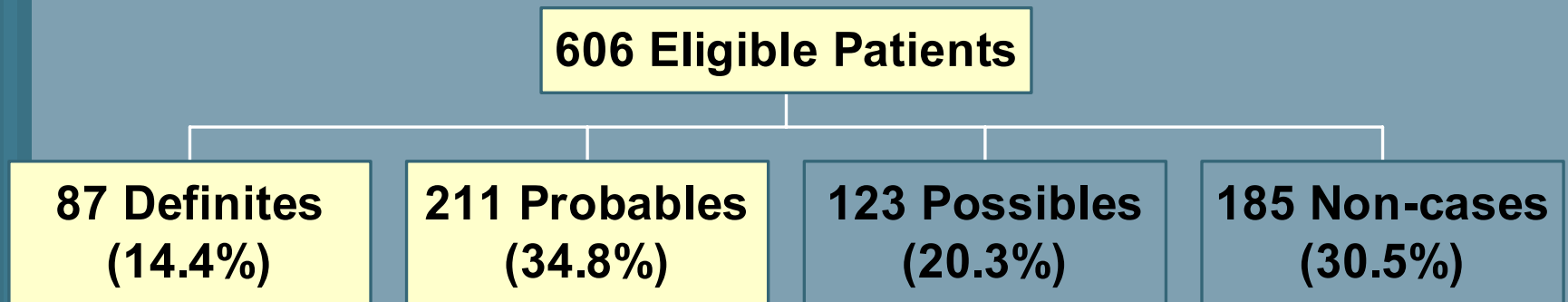
Possible GBS

- Information missing on criteria for categorization

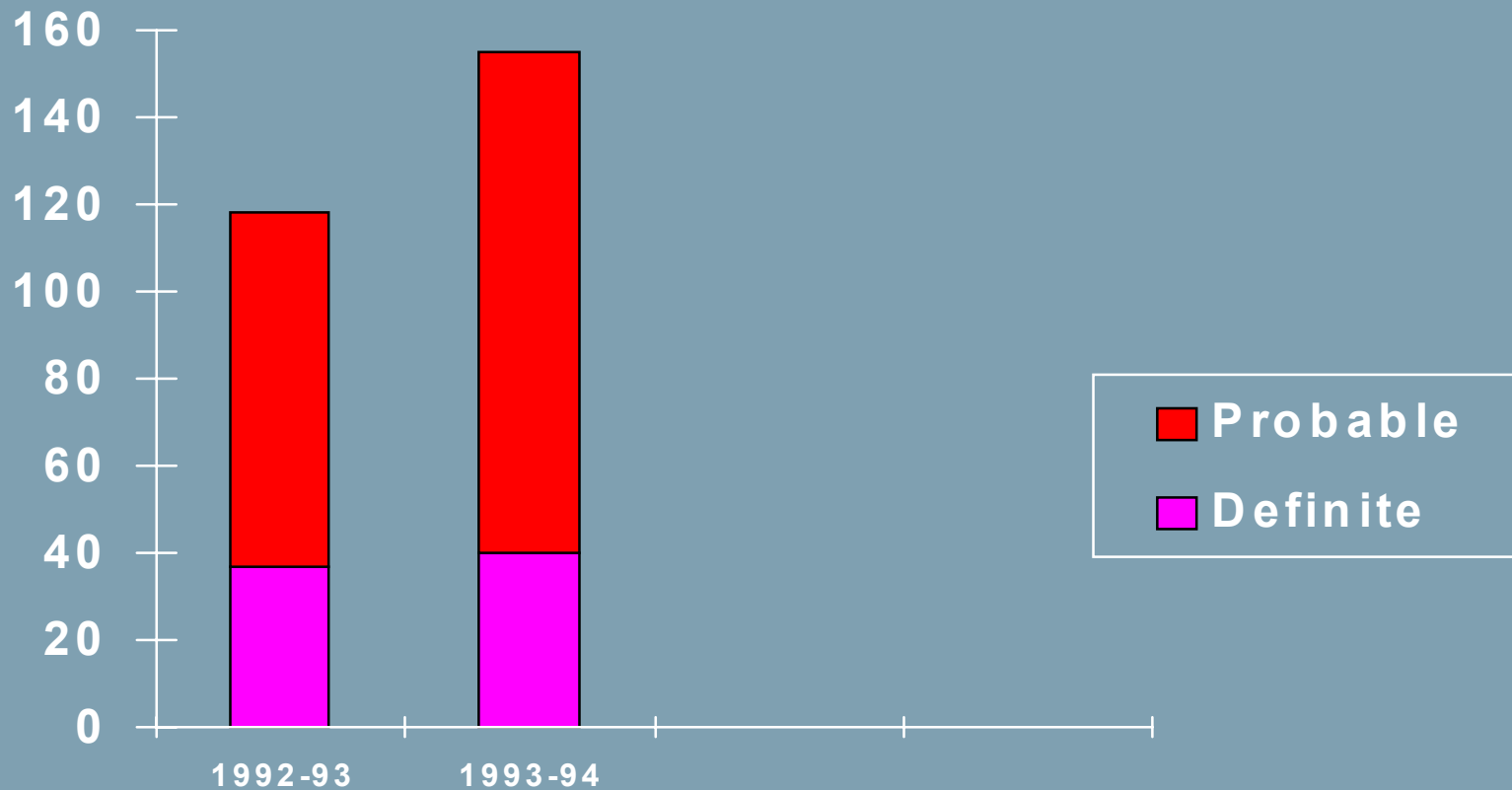
Non-Cases

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

Chart Abstraction and categorization of 606 patients



Distribution of GBS cases over the two study periods



Patient Interviews

273
Definite and Probable Cases

180 Patient Interviews
(69.5%)

58
not located

15
Refusals

20
No MD access
(Illinois)

Patient Characteristics (interviewed)

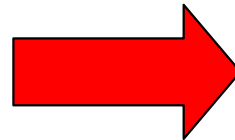
- **State of residence**
 - 30.0% Illinois
 - 22.8% Maryland
 - 23.9% North Carolina
 - 23.3% Washington
- **Season of onset**
 - 38.9% 92-93
 - 61.1% 93-94
- **Mean age 59.0**
- **83.3% White**
- **43.3% Female**
- **69.4% Admitted from home**
- **41.1% Discharged to home**
- **4.4% Died in the hospital**
- **Mean CSF**
 - protein 110.5 mg/dl
 - 1.23 mononuclear cells/ml
- **57.8% Received plasmapheresis**
- **23.3% Required ventilator support**

Definitions

- 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

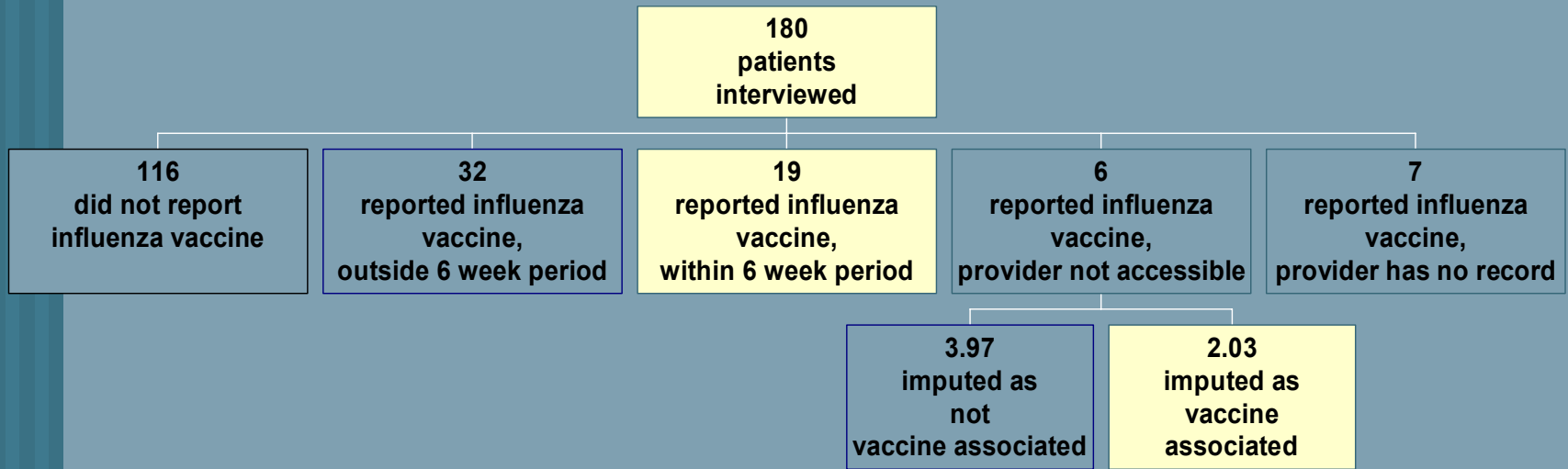
**I n f l u e n z a
V a c c i n a t i o n**



**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

■ State of Residence

- 2 Illinois
- 6 Maryland
- 2 North Carolina
- 9 Washington

■ Season of Onset

- 8 92-93
- 11 93-94

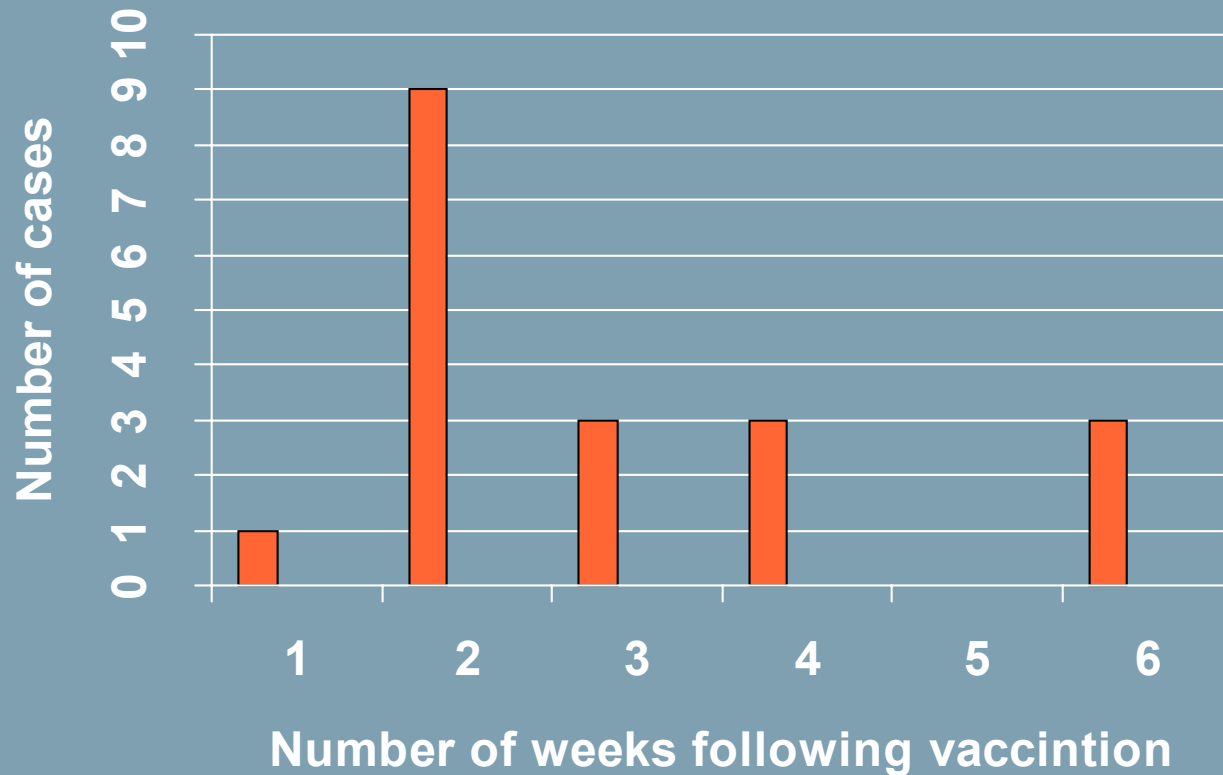
■ Mean Age 66.2

■ 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

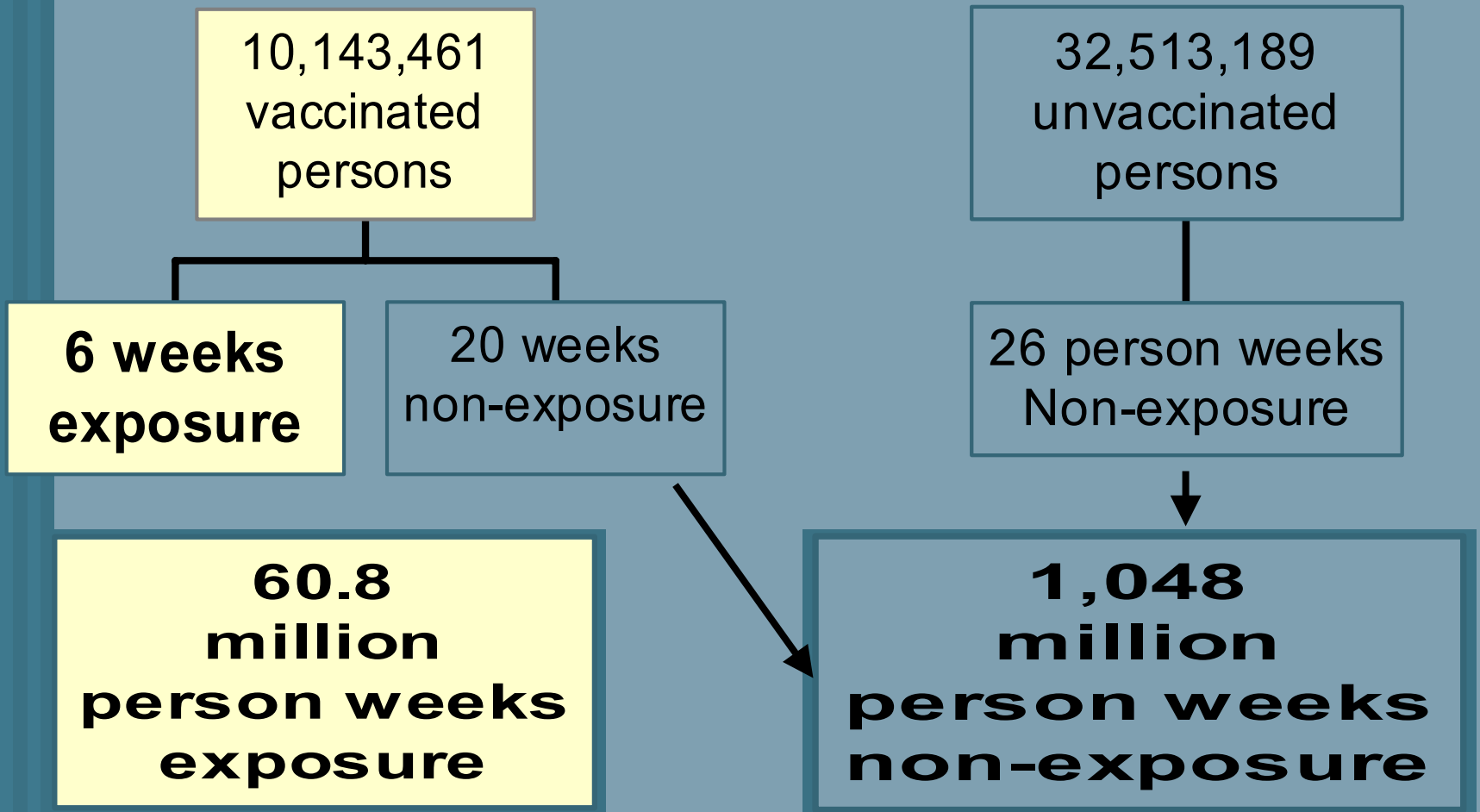
Disease onset relative to influenza vaccination



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



Calculation of Relative Incidence Density

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

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

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

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.

Effect of vaccine season

- 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.