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THE GUILLAIN-BARRÉ SYNDROME AND THE 1992-1993 AND 1993-1994 INFLUENZA VACCINES

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ABSTRACT

Background The number of reports of influenza-vaccine-associated Guillain-Barré syndrome to the national Vaccine Adverse Event Reporting System increased from 37 in 1992-1993 to 74 in 1993-1994, arousing concern about a possible increase in vaccine-associated risk.

Methods Patients given a diagnosis of the Guillain-Barré syndrome in the 1992-1993 and 1993-1994 influenza-vaccination seasons were identified in the hospital-discharge data bases of four states. Vaccination histories were obtained by telephone interviews during 1995-1996 and were confirmed by the vaccine providers. Disease with an onset within six weeks after vaccination was defined as vaccine-associated. Vaccine coverage in the population was measured through a random-digit-dialing telephone survey.

Results We interviewed 180 of 273 adults with the Guillain-Barré syndrome; 15 declined to participate, and the remaining 78 could not be contacted. The vaccine providers confirmed influenza vaccination in the six weeks before the onset of Guillain-Barré syndrome for 19 patients. The relative risk of the Guillain-Barré syndrome associated with vaccination, adjusted for age, sex, and vaccine season, was 1.7 (95 percent confidence interval, 1.0 to 2.8; $P=0.04$). The adjusted relative risks were 2.0 for the 1992-1993 season (95 percent confidence interval, 1.0 to 4.3) and 1.5 for the 1993-1994 season (95 percent confidence interval, 0.8 to 2.9). In 9 of the 19 vaccine-associated cases, the onset was in the second week after vaccination, all between day 9 and day 12.

Conclusions There was no increase in the risk of vaccine-associated Guillain-Barré syndrome from 1992-1993 to 1993-1994. For the two seasons combined, the adjusted relative risk of 1.7 suggests slightly more than one additional case of Guillain-Barré syndrome per million persons vaccinated against influenza. (N Engl J Med 1998;339:1797-802.)

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GUILLAIN-BARRÉ syndrome is characterized by loss of reflexes and symmetric paralysis, usually beginning in the legs, with eventual nearly complete or complete clinical recovery in most cases.^{1,2} It is mediated by an immune response that results in the direct destruction of either the myelin sheath surrounding the peripheral nerves or the axon itself, and it may or may not follow triggering events, including vaccinations.^{3,4} Among the vaccines reported to be associated with the onset of Guillain-Barré syndrome are the swine influenza (A/New Jersey) vaccine in 1976-1977, oral poliovirus vaccine, and tetanus toxoid.⁵ The association with the A/New Jersey swine influenza vaccine was notable for relative risks of Guillain-Barré syndrome ranging from 4.0 to 7.6 for six- or eight-week periods after vaccination.⁶⁻¹⁰ Subsequent studies of Guillain-Barré syndrome and influenza vaccines found low relative risks of 1.4 in 1978-1979, 0.6 to 1.4 in 1979-1980 and 1980-1981, and 1.1 in 1980-1988; these relative risks were not significantly different from 1.¹¹⁻¹³ For the 1990-1991 influenza season, an elevated risk was found among vaccinated persons 18 to 64 years of age (relative risk, 3.0; 95 percent confidence interval, 1.5 to 6.3) but not among persons 65 years old or older.¹⁴

Reports of vaccine-associated Guillain-Barré syndrome are monitored by the Vaccine Adverse Event Reporting System (VAERS) of the Centers for Dis-

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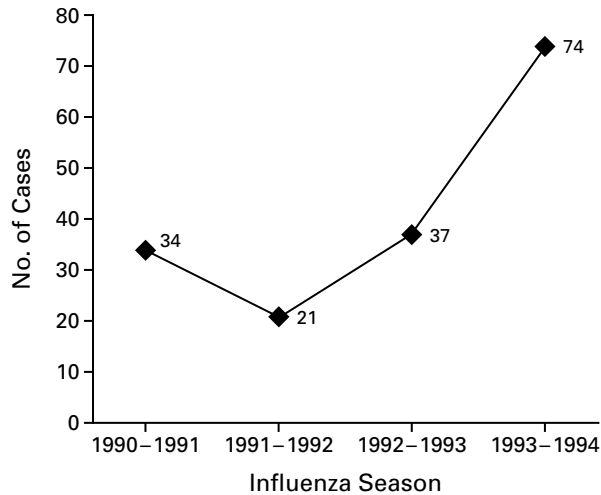


Figure 1. Reports of Vaccine-Associated Guillain-Barré Syndrome to the Vaccine Adverse Event Reporting System during the 1990-1991, 1991-1992, 1992-1993, and 1993-1994 Influenza Seasons.

case Control and Prevention (CDC) and the Food and Drug Administration.¹⁵ An increase in the number of cases of Guillain-Barré syndrome after the receipt of influenza vaccine was reported to VAERS by week 29 of the 1993-1994 influenza season. The number increased from 21 in 1991-1992 to 37 in 1992-1993 and to 74 in 1993-1994 (Fig. 1).¹⁶ Because reports to the VAERS consist only of data on the number of vaccine-associated cases without showing the number of people at risk, the CDC and the University of Maryland School of Medicine undertook a collaborative investigation to estimate the relative risks associated with vaccination against influenza during the 1992-1993 and 1993-1994 seasons.

METHODS

Data bases on hospital-discharge summaries were used to identify cases of Guillain-Barré syndrome in four states: Illinois, Maryland, North Carolina, and Washington. Hospital charts of patients discharged with code 357.0 of the *International Classification of Diseases, 9th edition* (ICD-9)¹⁷ and with disease onset between September 1, 1992, and February 28, 1993, or between September 1, 1993, and February 28, 1994, were reviewed by abstractors who were unaware of the patients' vaccination histories. A standardized data-collection form based on widely accepted abstraction methods and clinical criteria was used.^{1,9,18} Review procedures for studies involving human subjects were followed, as required by the institutional review boards associated with the University of Maryland at Baltimore, the CDC, and the participating states.

Cases were categorized as definite, probable, or possible, as not Guillain-Barré syndrome (noncases), or as requiring review by a neurologist. In definite cases, other conditions were ruled out and the patients were afebrile on admission (unless they had fever due to an illness other than Guillain-Barré syndrome) and had symmetric, progressive paralysis in more than one limb, areflexia

or hyporeflexia in the legs and arms, a cerebrospinal fluid protein level above 40 mg per deciliter with a mononuclear-cell count of less than 10 per milliliter, and either died or reached the peak of their neurologic illness within four weeks of onset. Patients meeting all of these criteria who did not have a lumbar puncture, the results of whose cerebrospinal fluid tests were missing, or whose cerebrospinal fluid mononuclear-cell count was between 11 and 50 per milliliter were classified as probably having Guillain-Barré syndrome. Patients with missing information for one or more of the required criteria were classified as possibly having the syndrome. Patients whose charts provided definitive information that they did not meet one or more of the required criteria were classified as not having the syndrome. If arm reflexes were normal or information on arm reflexes was missing and if all other criteria were met, the chart was reviewed by the study neurologist and the illness was categorized as a case or noncase. Our algorithm for categorizing cases as definite or probable was adapted from published criteria used by expert neurologists to guide their review of cases. The definite and probable cases differ only with respect to the completeness of cerebrospinal fluid evaluation, which is not a required criterion for diagnosis of Guillain-Barré syndrome. After implementing the computer algorithm, we found that the completeness of cerebrospinal fluid evaluation was not enough to distinguish definite from probable cases, and so we combined the two groups.

Patients' vaccination histories were collected by telephone interviews. Providers were then contacted to obtain the exact dates of vaccination. Vaccine-associated cases were defined a priori as those with onset of Guillain-Barré syndrome within the six-week period after influenza vaccination. Previous researchers used either six- or eight-week periods after vaccination to define vaccine-associated cases; however, the studies that reported an elevated risk also showed that all or almost all of the risk was within the first six weeks after vaccination.⁶⁻¹²

The four study states had a total population of 21.2 million people 18 years of age or older in 1992-1993 and 21.4 million in 1993-1994.^{19,20} Rates of coverage with influenza vaccine for the general population were obtained from a random-digit-dialing telephone survey designed to determine whether respondents received influenza vaccine during the fall and winter of 1992-1993 or 1993-1994.²¹ The survey instrument consisted of 49 items, including the following questions about influenza vaccinations: "Did you get a flu shot during this past fall or winter — that is, for the winter of 1993-1994?" "Approximately when did you receive the flu vaccine shot during the winter of 1993-1994?" Similar questions were asked for 1992-1993, as well as questions about the vaccine provider, factors affecting the decision to be vaccinated, and indications for influenza vaccination. A total of 1015 telephone interviews were conducted with adult residents of the four study states, 19 percent of whom were 65 years of age or older and 58 percent of whom were women. The survey had an 81 percent response rate. A response-validation study of the 1993-1994 data estimated that 90 percent of the positive vaccination reports were correct for the vaccine season. The 1992-1993 reports were validated by comparing the reported change in vaccine coverage between 1992-1993 and 1993-1994 with surveillance data.²²

Ascertainment of cases (vaccine-associated and non-vaccine-associated) and estimation of the population denominators (person-weeks within the six-week period after vaccination and person-weeks outside this period) were used to estimate the relative risk of Guillain-Barré syndrome during the six weeks after influenza vaccination. We used Poisson regression analysis to estimate the effect of the vaccine on risk while controlling for age, vaccine season, and sex. We controlled for age by including dummy variables for the following age groups: 18 to 34, 35 to 44, 45 to 54, 55 to 64, 65 to 74, and 75 or more years. Standard Poisson regression is based on the assumption that the amount of person-time during which the population is exposed and the amount during which it is unexposed are known. However, in our study

we only had estimates of the person-time exposed, because we had to estimate the vaccine-coverage rates. To adjust our inferences to take this limitation into account, we used the method of multiple imputation (described below).²³ This method was also used to adjust for uncertainty in classifying six cases and resulted in somewhat broader confidence intervals than would result from standard analyses (details are available from the authors).

RESULTS

We obtained hospital charts for 1109 of 1201 hospital discharges (92 percent) with ICD-9 code 357.0 during the study periods, including 288 charts referring to multiple admissions. Of the 821 patients whose charts we obtained, 62 (8 percent) resided outside the study states, and another 153 (19 percent) had onset of disease outside the study periods; these patients were excluded from the study. The final distribution of cases for the 606 remaining patients was as follows: 87 definite (14 percent), 211 probable (35 percent), 123 possible (20 percent), and 185 noncases (31 percent). Of the 298 patients with Guillain-Barré syndrome, 273 were 18 years of age or older. In this group there were 37 definite and 81 probable cases in 1992-1993, as compared with 40 definite and 115 probable cases in 1993-1994.

The mean age of the 273 patients at admission was 54 years (range, 18 to 90). The group was predominantly white (84 percent) and male (62 percent). The mean cerebrospinal fluid protein level for the patients was 128.9 mg per deciliter, and the mean mononuclear-cell count was 1.6 per milliliter. While they were hospitalized, 56 percent of patients underwent plasmapheresis, and 22 percent received ventilator support.

We interviewed 180 of the 273 patients (66 percent) by telephone; 15 declined to participate, 58 could not be located, and the permission of the physician to interview the patient was not obtained for 20 patients. Of the 180 patient interviews, 141 (78 percent) were conducted directly with the patient and 39 (22 percent) were conducted with spouses, surviving children, parents, or other proxies. Although the proportion of patients interviewed was lower than we would have wished, the primary reason that some patients were not interviewed was the inability to locate them — a factor unlikely to be associated with vaccine history or recall of vaccinations. In comparing interviewed with noninterviewed patients, we found the two groups to be similar clinically and slightly different demographically; the median age of the noninterviewed patients was 51 years, as compared with 56 years for the interviewed patients ($P=0.03$).

Vaccine providers confirmed that 19 patients had received influenza vaccine within six weeks before the onset of Guillain-Barré syndrome. One hundred forty-eight cases were categorized as non-vaccine-associated (116 of the patients reported receiving no influenza vaccine, and 32 were vaccinated

outside the six-week period preceding the onset of Guillain-Barré syndrome). Six patients who reported receiving influenza vaccine did not give us permission to contact their providers. Thus, we could not confirm whether they were vaccinated within six weeks before the onset of disease. Since it is likely that a proportion of these cases were vaccine-associated, excluding these patients would have introduced bias into the analysis. To retain these cases in the analysis, we used the approach of multiple imputation. We based our multiple imputations on the proportion of vaccine-associated cases among those for which the date of vaccination could be confirmed. The approach appropriately inflates the confidence intervals to adjust for the uncertainty about the true status of the six cases. An additional seven patients reported being vaccinated, but the vaccination could not be independently confirmed from the provider's records. All seven were excluded from subsequent analysis. Two of these patients provided credible accounts of influenza vaccinations that might have occurred in the six weeks preceding the onset of Guillain-Barré syndrome. Including these patients in the analysis (and categorizing two cases as vaccine-associated) did not result in a changed point estimate but did result in slightly narrower confidence intervals (1.1 to 2.8).

The distribution of vaccine-associated cases according to the date of onset of disease showed a peak in the second week after vaccination (Fig. 2). Of the 19 vaccine-associated cases, 9 had onset in the second week after vaccination, all between day 9 and day 12. The probability of observing a distribution over the six weeks with at least this degree of imbalance by chance alone was low ($P=0.009$, on the basis of a simulation of 5000 data sets). Accord-

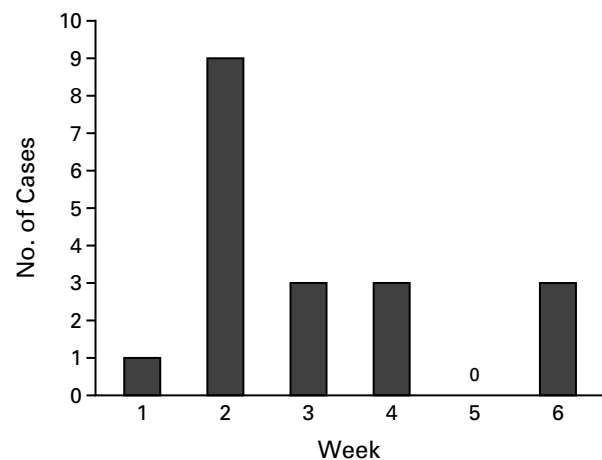


Figure 2. Distribution of Vaccine-Associated Cases of Guillain-Barré Syndrome in the Six Weeks after Influenza Vaccination.

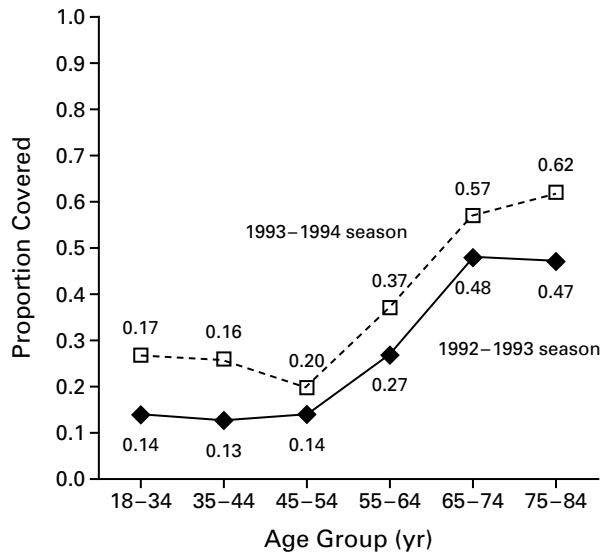


Figure 3. Influenza Vaccine Coverage in the Four Study States in the 1992-1993 and 1993-1994 Influenza Seasons, According to Age Groups.

TABLE 1. OVERALL AND ADJUSTED RELATIVE RISKS OF GUILLAIN-BARRÉ SYNDROME ASSOCIATED WITH INFLUENZA VACCINE ACCORDING TO SEASON, AGE GROUP, AND SEX.

SUBGROUP	VARIABLE CONTROLLED FOR	RR (95% CI)*	P VALUE
All patients	None	2.4 (1.5-3.8)	<0.001
All patients	Age group, season, sex	1.7 (1.0-2.8)	0.04
1992-1993 season	Age group, sex	2.0 (1.0-4.3)	0.07
1993-1994 season	Age group, sex	1.5 (0.8-2.9)	0.20
Age, 18-64 yr	Season, sex	1.8 (1.0-3.5)	0.07
Age, ≥65 yr	Season, sex	1.5 (0.7-3.3)	0.28
Male subjects	Age group, season	1.9 (1.0-3.7)	0.07
Female subjects	Age group, season	1.5 (0.7-3.1)	0.27

*RR denotes relative risk, and CI confidence interval.

ing to hospital charts, evidence of antecedent gastrointestinal illness, respiratory illness, Epstein-Barr virus infection, cytomegalovirus infection, or surgery was less frequent for patients with vaccine-associated Guillain-Barré syndrome than for patients with non-vaccine-associated cases (33 percent vs. 57 percent, $P=0.06$). The mean age of patients with vaccine-associated Guillain-Barré syndrome was higher than that of patients with the non-vaccine-associated cases (66 vs. 55 years, $P<0.001$). The proportions of patients who received mechanical ventilation (21 percent and 24 percent, respectively) and who died in the hospital (6 percent and 4 percent, respectively) were similar in the vaccine-associated and non-

vaccine-associated groups. Three of the 19 vaccine-associated cases involved complete cerebrospinal fluid evaluation and were definite, and 13 involved incomplete evaluation and were probable.

Vaccine coverage in the four study states increased in all age groups between 1992-1993 and 1993-1994, from 2.8 million to 3.6 million people 18 to 64 years of age and from 1.7 million to 2.1 million people 65 years of age or older (Fig. 3). During the two six-month study seasons, there were 61 million person-weeks of exposure (when people were within the six-week period after influenza vaccination) and 1048 million person-weeks of nonexposure (when people were outside the six-week period after vaccination, including person-weeks for those who were not vaccinated at all, as well as person-weeks outside the six-week exposure period for those who received influenza vaccinations).

The overall relative risk of Guillain-Barré syndrome in the six weeks after influenza vaccination was 2.4 (95 percent confidence interval, 1.5 to 3.8; $P<0.001$) (Table 1). After adjustment for age group, sex, and influenza season, the relative risk was 1.7 (95 percent confidence interval, 1.0 to 2.8; $P=0.04$). (Preliminary estimates of a relative risk of 1.8 and a 95 percent confidence interval of 1.2 to 3.0 were disseminated in influenza-vaccine package inserts for 1998-1999.) There was no significant difference in the effect of vaccine between seasons ($P=0.56$), broad age groups ($P=0.71$), or sexes ($P=0.65$). Point estimates for the relative risks associated with vaccination within 10-year age groups were as follows: 2.1 (95 percent confidence interval, 0.3 to 15.4) for persons 45 to 54 years old, 2.2 (95 percent confidence interval, 0.8 to 6.0) for those 55 to 64, 1.9 (95 percent confidence interval, 0.8 to 4.5) for those 65 to 74, and 1.8 (95 percent confidence interval, 0.7 to 4.9) for those 75 or older. No vaccine-associated cases were observed among the 4 million vaccine recipients who were under 45 years of age, resulting in an estimated effect of 0 in that age group.

DISCUSSION

We estimate that after age, sex, and season have been controlled for, the risk of the Guillain-Barré syndrome is increased by a factor of 1.7 in the six weeks after influenza vaccination. This is only slightly higher than the relative risks reported in earlier studies of influenza vaccine and Guillain-Barré syndrome, except for the much higher risks associated with the swine influenza vaccine.⁶⁻¹⁴ Although a variety of events are associated with the Guillain-Barré syndrome, including vaccinations, infection with *Campylobacter jejuni*, and viral infections, the immunologic events leading to the Guillain-Barré syndrome have not been fully described.^{24,25}

We observed an average incidence of non-vaccine-associated Guillain-Barré syndrome among adults

of 0.145 case per million persons per week, or a background incidence of 0.87 case per million persons per six-week period. The age-, sex-, and season-adjusted relative risk in the six-week period after vaccination was 1.7. Thus, the calculated risk attributable to the vaccine in the six-week period after vaccination was 0.61 case per million vaccinations. This estimate of the vaccine-attributable risk is conservative because of four factors: we received 92 percent of hospital charts, we did not include patients hospitalized out of state, our base-line rate did not include patients who were not interviewed, and our base-line rate did not include those with possible cases of Guillain-Barré syndrome. After adjustment for the first three factors, the best estimate of the attributable risk would be 1.1 cases per million vaccinations. Thus, the adjusted relative risk of 1.7 suggests that just over one additional case of Guillain-Barré syndrome occurred per million vaccinations. Adjusting for all four factors would increase the best estimate of attributable risk to a maximum (if all were definite cases) of 1.6 cases per million vaccinations.

The distribution of times of onset after vaccination showed a peak in the second week, suggesting a relation between vaccination and the onset of disease. These findings differ from the finding that the swine influenza vaccine was associated with a peak of cases in the second and third weeks after vaccination (with more cases occurring in the third week).⁶ However, Winer and colleagues, in discussing the onset of Guillain-Barré syndrome after respiratory infections (another possible trigger), noted that the greatest relative risk of Guillain-Barré syndrome was seen in the first two weeks after infection.²⁶ Although the differences were not significant, the lower percentage of other antecedent events recorded in the hospital charts of patients with vaccine-associated cases as compared with other patients is also consistent with the hypothesis that influenza vaccine triggered some of these cases.⁶

An increase in reports to the VAERS may be due to an increase in the efficiency of reporting, vaccine coverage, the background rate of an illness or event, or the risk associated with a vaccine. Only the last constitutes a true positive signal of a problem with vaccine safety.²⁷ Our study suggests that the increase in reports of vaccine-associated Guillain-Barré syndrome in 1993-1994 was probably due to an increase in both influenza vaccine coverage and the base-line incidence of Guillain-Barré syndrome, but not to an increase in vaccine-specific risk. The absence of major publicity about vaccine-associated Guillain-Barré syndrome during the study period argues against changes in reporting efficiency as an explanation of changes in the number of reports. This study highlights the difficulty of relying on passive surveillance (such as VAERS) alone for identifying true issues of concern regarding vaccine safety.²⁸

In February 1997, preliminary findings of this study were presented to the Advisory Committee on Immunization Practices of the U.S. Public Health Service for use in developing their recommendations on the prevention and control of influenza, and results were reviewed again in October 1997.²⁹ The recommendations noted,

Among persons who received the swine influenza vaccine in 1976, the rate of Guillain-Barré syndrome that exceeded the background rate was slightly less than 10 cases per million vaccinated. Even if Guillain-Barré syndrome were a true side effect in subsequent years, the estimated risk for Guillain-Barré syndrome of 1 to 2 cases per million persons vaccinated is substantially less than that for severe influenza, which could be prevented by vaccination in all age groups, especially persons aged ≥ 65 years and those who have medical indications for influenza vaccination. . . . During influenza epidemics from 1969-70 through 1993-94, the estimated number of influenza-associated hospitalizations has ranged from approximately 20,000 to >300,000 per epidemic with an average of approximately 130,000 to 170,000 per epidemic. . . . An estimated >20,000 influenza-associated deaths occurred during each of 11 different U.S. epidemics from 1972-73 through 1994-95, and 40,000 influenza-associated deaths occurred during each of 6 of these 11 epidemics.²⁹

Our data, therefore, do not suggest an increased risk associated with the influenza vaccine of 1993-1994 as compared with 1992-1993, as was first suggested by the increase in cases reported to the VAERS. Rather, our findings support the hypothesis that a small risk of Guillain-Barré syndrome was associated with the influenza vaccines in both 1992-1993 and 1993-1994.

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REFERENCES

1. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barre syndrome. *Ann Neurol* 1990;27:Suppl:S21-S24.
2. Asbury A. Diagnostic considerations in Guillain-Barre syndrome. *Ann Neurol* 1981;9:Suppl:1-5.
3. Koski CL. Humoral mechanisms in immune neuropathies. *Neurol Clin* 1992;10:629-49.
4. *Idem*. Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy: pathogenesis and treatment. *Semin Neurol* 1994;14:123-30.
5. Stratton KR, Howe CJ, Johnston RB Jr, eds. Adverse events associated with childhood vaccines: evidence bearing on causality. Washington, D.C.: National Academy Press, 1994:464.
6. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976-1977. *Am J Epidemiol* 1979;110:105-23.
7. Marks JS, Halpin TJ. Guillain-Barre syndrome in recipients of A/New Jersey influenza vaccine. *JAMA* 1980;243:2490-4.
8. Langmuir AD, Bregman DJ, Kurland LT, Nathanson N, Victor M. An epidemiologic and clinical evaluation of Guillain-Barre syndrome reported in association with the administration of swine influenza vaccines. *Am J Epidemiol* 1984;119:841-79.

9. Safranek TJ, Lawrence DN, Kurland LT, et al. Reassessment of the association between Guillain-Barre syndrome and receipt of swine influenza vaccine in 1976-1977: results of a two-state study: Expert Neurology Group. *Am J Epidemiol* 1991;133:940-51.
10. Breman JG, Hayner NS. Guillain-Barre syndrome and its relationship to swine influenza vaccination in Michigan, 1976-1977. *Am J Epidemiol* 1984;119:880-9.
11. Hurwitz ES, Schonberger LB, Nelson DB, Holman RC. Guillain-Barre syndrome and the 1978-1979 influenza vaccine. *N Engl J Med* 1981;304:1557-61.
12. Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain-Barre syndrome in the United States, 1979-1980 and 1980-1981: lack of an association with influenza vaccination. *JAMA* 1982;248:698-700.
13. Roscelli JD, Bass JW, Pang L. Guillain-Barre syndrome and influenza vaccination in the US Army, 1980-1988. *Am J Epidemiol* 1991;133:952-5.
14. Chen R, Kent J, Rhodes P, Simon P, Schonberger L. Investigation of a possible association between influenza vaccination and Guillain-Barre syndrome in the United States, 1990-91. *Post Mark Surveill* 1992;6:5-6. abstract.
15. Chen RT, Rastogi SC, Mullen JR, et al. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994;12:542-50.
16. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 1995;44(RR-3):1-21.
17. Department of Health and Human Services. The international classification of diseases, 9th rev., clinical modification: ICD-9-CM. Vol. 1. Diseases: tabular list. Washington, D.C.: Government Printing Office, 1980. (DHHS publication no. (PHS) 80-1260.)
18. Koobatian TJ, Birkhead GS, Schramm MM, Vogt RL. The use of hospital discharge data for public health surveillance of Guillain-Barre syndrome. *Ann Neurol* 1991;30:618-21.
19. Bureau of the Census. RPotU, regions, and states by selected age groups and sex: population estimate and population distribution branches. Washington, D.C.: Government Printing Office, 1992.
20. *Idem*. RPotU, regions, and states by selected age groups and sex: population estimate and population distribution branches. Washington, D.C.: Government Printing Office, 1993.
21. Macro International. Final report: rapid assessment of influenza vaccination in the United States. Calverton, Md.: Macro International, 1995.
22. Pneumococcal and influenza vaccination levels among adults aged 65 and over — United States, 1995. *MMWR Morb Mortal Wkly Rep* 1997;46:913-9. [Erratum, *MMWR Morb Mortal Wkly Rep* 1997;46:974.]
23. Rubin DB, Schenker N. Multiple imputation for interval estimation from simple random samples with ignorable nonresponse. *J Am Stat Assoc* 1986;81:366-74.
24. Hughes RAC, Rees JH. Clinical and epidemiologic features of Guillain-Barre syndrome. *J Infect Dis* 1997;176:Suppl 2:S92-S98.
25. Ropper AH, Wijdicks EFM, Truax BT. Guillain-Barre syndrome. Philadelphia: F.A. Davis, 1991.
26. Winer JB, Hughes RAC, Anderson MJ, Jones DM, Kangro H, Watkins RPE. A prospective study of acute idiopathic neuropathy. II. Antecedent events. *J Neurol Neurosurg Psychiatry* 1988;51:613-8.
27. Chen RT. Special methodological issues in pharmacoepidemiology studies of vaccine safety. In: Strom BL, ed. *Pharmacoepidemiology*. 2nd ed. Chichester, England: John Wiley, 1994:581-94.
28. Chen RT, Glasser JW, Rhodes PH, et al. Vaccine Safety Datalink project: a new tool for improving vaccine safety monitoring in the United States. *Pediatrics* 1997;99:765-73.
29. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 1998;47(RR-6):1-26.