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Original Contributions

GUILLAIN-BARRE SYNDROME FOLLOWING VACCINATION IN THE NATIONAL INFLUENZA IMMUNIZATION PROGRAM, UNITED STATES, 1976–1977[1]

LAWRENCE B. SCHONBERGER, DENNIS J. BREGMAN, JOHN Z SULLIVAN-BOLYAI, RICHARD A. KEENLYSIDE, DONALD W. ZIEGLER, HENRY F. RETAILLIAU, DONALD L EDDINS AND JOHN A. BRYAN

Schonberger, L. B. (CDC, Atlanta, GA 30333), D. J. Bregman, J. Z. Sullivan-Bolyai, R. A. Keenlyside, D. W. Ziegler, H. F. Retailliau, D. L. Eddins and J. A. Bryan. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. *Am J Epidemiol* 110:105–123, 1979.

Because of an increase in the number of reports of Guillain-Barre syndrome (GBS) following A/New Jersey influenza vaccination, the National Influenza Immunization Program was suspended December 16, 1976 and nationwide surveillance for GBS was begun. This surveillance uncovered a total of 1098 patients with onset of GBS from October 1, 1976, to January 31, 1977, from all 50 states, District of Columbia, and Puerto Rico. A total of 532 patients had recently received an A/New Jersey influenza vaccination prior to their onset of GBS (vaccinated cases), and 15 patients received a vaccination after their onset of GBS. Five hundred forty-three patients had not been recently vaccinated with A/New Jersey influenza vaccine and the vaccination status for 8 was unknown. Epidemiologic evidence indicated that many cases of GBS were related to vaccination. When compared to the unvaccinated population, the vaccinated population had a significantly elevated attack rate in every adult age group. The estimated attributable risk of vaccine-related GBS in the adult population was just under one case per 100,000 vaccinations. The period of increased risk was concentrated primarily within the 5-week period after vaccination, although it lasted for approximately 9 or 10 weeks.

Guillain-Barre syndrome; immunization; influenza; polyradiculitis; vaccination; vaccine

In 1976 the Federal Government sponsored the National Influenza Immunization Program (NIIP) which was designed to provide A/New Jersey influenza vaccine for almost the entire adult population in the United States, as well as for children at high risk of serious illness from influenza virus infection. On October 1, 1976, the vaccination program, which incorporated a nationwide surveil-

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Abbreviations: CCA, chick cell agglutinating; CSF, cerebrospinal fluid; GBS, Guillain-Barre syndrome; NIIP, National Influenza Immunization Program.

[1] From the Viral Diseases Division, Bureau of Epidemiology, Center for Disease Control, Atlanta, GA 30333. (Reprint requests to Dr Schonberger.)

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lance system to evaluate possible adverse vaccine reactions, began. By December 2, when over 35 million doses of vaccine had been administered, two clusters of Guillain-Barre syndrome (GBS) in recent recipients of the vaccine were reported to the Center for Disease Control (CDC) from two states: Minnesota (four cases) and Alabama (three cases). As a result of identification of these two clusters, CDC, with the cooperation of several state health departments, initiated an epidemiologic investigation to evaluate the possibility of a relationship between GBS and vaccination with the A/New Jersey influenza vaccine. By December 15, preliminary data from Alabama, New Jersey, Minnesota, and Colorado suggested that the incidence of GBS among vaccinees was approximately seven-fold greater than the incidence among those who had not received vaccine (1). In addition, case reports from these four states, and from seven other states in which active surveillance for GBS was begun, suggested an association between vaccination and onset of GBS two to three weeks later. These apparent associations led to the suspension of NIIP on December 16 and to the expansion of GBS surveillance nationally in order to determine as quickly as possible whether the influenza vaccinations were, in fact, related to GBS and, if so, to determine the risk. This paper presents an analysis of the national surveillance data received by CDC through March 1978 on cases of GBS with onset between October 1, 1976 and January 31, 1977.

liam Foege, M.D., Philip Brachman, M.D , Donald Millar, M.D., Walter Dowdle, Ph.D , Michael Gregg, M.D., of CDC and the helpful advice received from Alexander Langmuir, M.D., Harvard School of Public Health, Michael Hattwick, M.D., and Richard Kaslow, M D., of CDC. James Marks, M.D , Rick Curtis, Alan Hinman, M.D., Harold Mauldin, William Griggs, CDC, provided both general support and essential information on vaccine utilization. Lyle Conrad, M.D., and Stanley Music, M.D , CDC, helped coordinate assignment of CDC medical epidemiologists to state health departments Ronald Teske, Max Peses, Jack Jones, James Hicks, Larry Brown, and Karl Kappus, Ph.D , CDC, helped coordinate the collection of information at CDC. The authors also acknowledge the technical support of Robert Holman, Betsey Lander, Annabelle Alter, Lois Vernon, Anita Garner, and Jean Heslin, CDC

Methods

Case ascertainment and definition

An active surveillance system for reporting of GBS cases with onset during the study period, October 1, 1976–January 31, 1977, was established in cooperation with state and local health authorities. This surveillance system was initiated in 11 arbitrarily selected states during the period December 3–16, 1976, and subsequently expanded to include the 39 remaining states, Puerto Rico, and District of Columbia on December 17. The surveillance information on the 1098 patients in this report was gathered primarily through investigators' direct telephone and/or letter contact with practicing neurologists and their review of physician and hospital records.

Initially, state health departments were requested to contact as many practicing neurologists as possible in their respective states and to telephone a designated person at CDC with basic information on newly identified cases of GBS each work day. By early January, CDC requested that an individual GBS-case-investigation form be completed on all reported cases. This GBS form was developed at CDC to help insure more uniform collection of epidemiologic data; included were questions about clinical and laboratory findings, antecedent events, and the patient's medical history, as well as space for the more basic information initially reported to CDC by telephone; the patient's name, age, race, sex, county of residence, date of onset of neurologic symptoms, history of A/New Jersey influenza vaccination, the attending physician's name and telephone number, and whether the patient was hospitalized, required ventilatory assistance and/or died.

For those patients who indicated they had received an A/New Jersey influenza vaccine, a copy of a vaccination consent form was generally sought; it included the vaccine type and manufacturer's lot number.

Additional case-finding techniques that were utilized by some states included sending letters to non-neurologist practitioners; surveying hospitals through contacting hospital-based physicians, administrators, and/or infection control officers; and conducting a repeat survey of neurologists after mid-January 1977. Persons who had originally been working on the influenza immunization program in each state, regular state and local health department personnel, CDC medical epidemiologists based in Atlanta and CDC officers assigned to state and city health departments assisted in the GBS surveillance effort.

By definition GBS cases had (a) to have been diagnosed by a physician (Illinois, Montana, and Ohio reported requiring a neurologist's diagnosis) and (b) to have objective evidence of muscle involvement (New York State and City and Texas required slightly stricter clinical criteria). Suspected cases reported to CDC directly by patients or medical personnel were included in this report only if they were accepted as a case by a state health department. Two reported cases in patients with >160 white blood cells per cubic millimeter in their cerebrospinal fluid were excluded from analysis at CDC.

Largely because there was a relatively sharp decrease nationally in reported cases with onset after the week ending December 18 (the week in which NIIP was suspended), state epidemiologists were sent a brief questionnaire in late April 1977 to help assess possible differences in case ascertainment before and after December 18. As indicated in some analyses in this report, data were omitted from nine states that reported more than a slight decrease in case ascertainment in the latter period.

Size of vaccinated and unvaccinated populations—weekly and monthly assessments

To evaluate the possible association of cases of GBS to receipt of A/New Jersey vaccine, we attempted to develop rates of GBS in the civilian population of the United States who had received vaccine and for those who had not received vaccine prior to onset of GBS. We obtained estimates of the civilian population, by state and age, as of July 1, 1976, from the Bureau of the Census (2). We obtained the number of A/New Jersey vaccinations administered in the United States from the CDC-NIIP Surveillance and Assessment Center. This Center had sent guidelines for gathering and reporting this information to all state and local health departments prior to the national immunization campaign (3). For each state, two sets of data on vaccine administration were available, weekly reports of total vaccinations administered and monthly reports of vaccinations administered, by age group and type of vaccine (monovalent A/New Jersey/76 or bivalent A/New Jersey/76 and A/Victoria/75). The weekly reports were collected only during the national immunization campaign, October–December 1976; the monthly reports were collected October 1976 through June 1977. The vaccinations reported January–June 1977 (about 4 per cent of the total) were, in fact, administered almost entirely in 1976. In this paper, the age-specific monthly reports of vaccinations, by state, in 1976 were adjusted proportionally to include the late reports. Also, the weekly reports of vaccinations were similarly adjusted to reflect the total numbers of reported vaccinations administered to the adult target population—those over 17 years of age; about 98 per cent of the officially reported civilian total of 45.65 million vaccinations were administered to this target population.

Because both the size of the populations and the period in which they were ob-

served influenced the likelihood of detecting cases, attack rates in this paper are expressed in terms of cases per size of population per period of observation. For some analyses, where indicated, data are omitted from three states which had unusually large discrepancies between reported overall totals of vaccinations administered in their weekly and monthly reports and from four other states for which the monthly data were combined in a single overall report that could not be separated into its monthly components.

National survey and sex- and race-specific ratios

In order to determine whether the occurrence of GBS was related to sex or race, we compared the estimated number of vaccinated and unvaccinated persons in the population over 17 years of age in the continental United States in January 1977, by sex and race, with the number of comparable GBS cases reported in the study period. The estimates of the population sizes were derived from a national survey conducted by the Opinion Research Corporation, January 1977 (4). It was assumed that the sex- and race-specific ratios of reported GBS cases to size of population in January 1977 reflected the relative size of the sex- or race-specific attack rates within a vaccinated or within an unvaccinated population. At the time of onset of GBS for most of the reported cases, the size of the vaccinated population was smaller and the size of the unvaccinated population was larger than in January 1977; thus the sex- and race-specific ratios were not used to estimate relative risks of GBS for a vaccinated population compared with an unvaccinated population.

Vaccine inventories and manufacturer- and lot-specific attack rates

As part of NIIP, civilian health departments received over 100 million doses of influenza vaccine produced by four manufacturers; approximately 66 million doses (0.5 ml each) of monovalent vaccine containing 200 chick cell agglutinating (CCA) units of A/New Jersey/76 antigen and 35.5 million doses (0.5 ml each) of bivalent vaccine containing 200 CCA units each of A/New Jersey/76 and A/Victoria/75 antigens. All four manufacturers produced inactivated vaccine. Two manufacturers (A and B), whose final products contained whole virus antigen, produced about 93 per cent of the monovalent and 14 per cent of the bivalent vaccine. The remaining doses were produced by the other two manufacturers (C and D) whose final products contained split virus or subvirion antigens. Civilian health departments used vaccine from a total 141 different bulk lots: 60, 27, 34, and 20 bulk lots from manufacturers A, B, C, and D, respectively. In order to evaluate the possibility that the number of cases of GBS that occurred in vaccinated persons might be related to the vaccine from a single manufacturer or to a specific lot of vaccine, we attempted to develop crude attack rates of GBS, by manufacturer and lot number. Based on the difference between the amount of each manufacturer's vaccine distributed and an inventory in 1977 of the monovalent and bivalent vaccine on hand in each state, by manufacturer, we estimated the proportion of each type of vaccine administered in each state. These proportions and the monthly reports of vaccine administered enabled estimation of manufacturer-specific denominators. Based on a lot-specific inventory completed in 1978 after vaccine was placed in centralized storage facilities, the net national distribution of vaccine was calculated by subtracting inventory data for each lot from the total doses of each lot distributed. Although these net distributions included numbers of doses lost in shipment, wasted, or otherwise unaccounted for, they provided rough, but the best available, estimates of the number of doses of each lot of vaccine administered.

The numerators for the lot-specific attack rates were derived from the 80.6 per cent of cases with known onset of GBS in the six-week period after vaccination for which the vaccine lot numbers were reported. The six-week period was chosen in this and other analyses to equalize the period of observation of all vaccinees; a longer period was not selected because intensified surveillance for GBS ended about 6½ weeks after suspension of NIIP.

Results

Distribution of cases by vaccination status and week of onset

A total of 1098 patients with onset of GBS from October 1, 1976, through January 31, 1977, were reported to CDC from all 50 states, District of Columbia, and Puerto Rico. Five hundred thirty-two received an A/New Jersey/76 influenza vaccine from NIIP prior to their onset of GBS (vaccinated cases) and 15 patients received the vaccine after their onset. Five hundred forty-three did not receive an A/New Jersey/76 influenza vaccine, and the vaccination status of eight was unknown. Unless otherwise indicated, the 15 patients vaccinated after their onset of GBS were included in analyses of nonrecipients (unvaccinated cases).

The first case of GBS in a person who had been vaccinated occurred in the first week of October. The number of cases rose sharply between mid-October and mid-December, peaking in the week ending December 18, when 73 cases were reported. A precipitous drop-off in cases was observed thereafter, which in part may be attributed to a decreased case ascertainment in many states following their initial surveillance efforts (figure 1).

In contrast to the sharply rising incidence of GBS observed among vaccinees, the number of unvaccinated cases each week from October 1 through December 18 was relatively stable. Even among the unvaccinated population, there was a drop-off in reported cases after December 18 (figure 1).

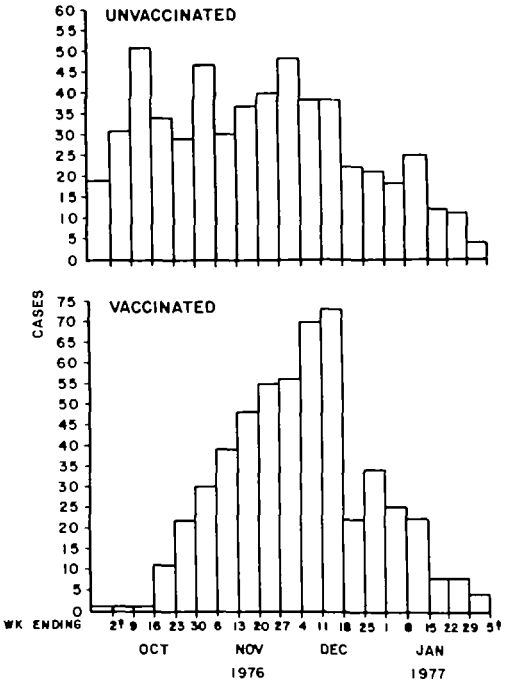

FIGURE 1 Reported cases of Guillain-Barre syndrome, by week of onset and A/New Jersey influenza vaccination status, United States (including Puerto Rico), Oct. 1, 1976–Jan. 31, 1977 The symbol ‡ indicates partial week.

The attack rates, by week, in the vaccinated and unvaccinated adult target populations revealed significantly higher attack rates among vaccinees throughout October, November, and December. In early December, the weekly attack rates in the vaccinated population began to fall sharply. By late January, it had decreased to approximately the level of the unvaccinated population (figure 2).

Distribution of cases by age, sex, and vaccination status

Analysis of GBS cases, by five-year age groups and A/New Jersey influenza vaccination status, revealed differing age distributions for cases in vaccinated persons and unvaccinated persons. In vaccinated persons, the cases ranged in age from 11 to 85 years (median 46 years), and the plurality of cases, 80, occurred in persons 35–39 years old. Only 3 per cent

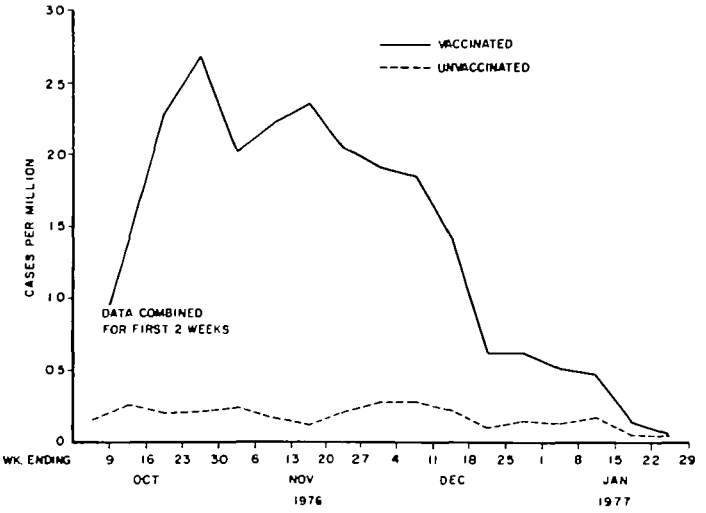

FIGURE 2. Guillain-Barre syndrome attack rates in vaccinated and unvaccinated persons over 17 years of age, by week of onset, United States, Oct 3, 1976–Jan. 29, 1977, excluding 12 states: Arkansas, California, Connecticut, Delaware, Florida, Georgia, Missouri, North Carolina, New Jersey, New York, Texas, and Washington.

of the vaccinated persons with GBS were under 20 years of age. In contrast, GBS occurred in unvaccinated persons ranging in age from one to 93 years (median 34.5 years), and the plurality of these cases, 67, occurred in the 15–19-year age group. Approximately 26.1 per cent of the unvaccinated persons with GBS were under 20 years of age (figure 3). Males comprised about 46.5 per cent of those with GBS who had been vaccinated and 55.2 per cent of those who had not been vaccinated.

Sex- and race-specific ratios

Though the sex and race of vaccine recipients were not routinely recorded, a survey of the population over 17 years of age in the continental United States estimated that in January 1977, 29 per cent of males, 32 per cent of females, 33 per cent of whites, and 14 per cent of blacks had received an A/New Jersey influenza vaccination (4). These percentages enabled estimation of sex- and race-specific ratios of the number of reported GBS cases in adults to size of population in January 1977; these ratios were expressed in terms of cases to one million population (table 1). For the unvaccinated population, the sex-specific ratio for males (4.9 cases to one million population) was 38 per cent higher than for females (3.6). For the vaccinated population, this ratio for males (12.0) was only 9 per cent higher than for females (11.0). For the unvaccinated population, the ratio for whites (4.1) was 54 per cent higher than for blacks (2.6) and for the vaccinated population, over 140 per cent higher than for blacks (10.4 compared to 4.3); the ratios for blacks were based on much smaller populations than for whites and many fewer cases.

Distribution of cases by interval between onset of GBS and vaccination

There was a striking nonrandom distribution of intervals between influenza vaccination and onset of GBS. Seventy-one per cent of the vaccinated cases with known intervals became ill within the first four weeks after vaccination and 52 per cent in the second and third weeks after vaccination (figure 4). By two-day intervals between vaccination and onset, the largest percentage of cases (10 per

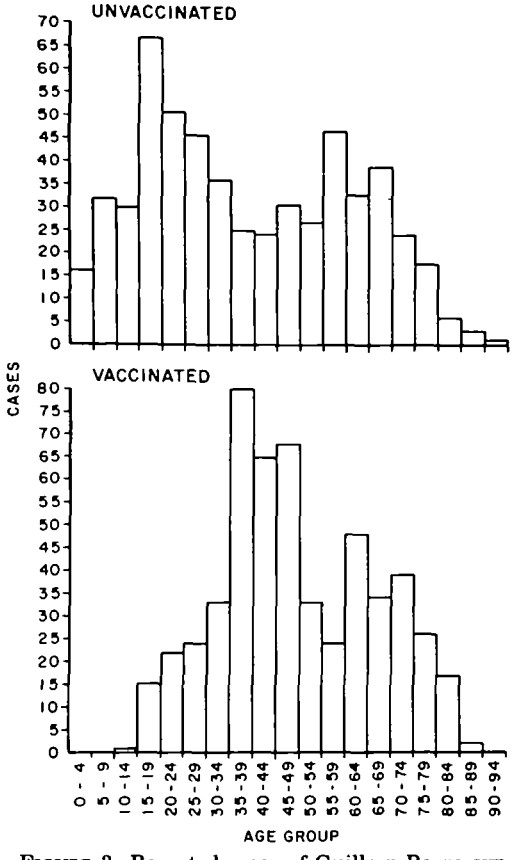

FIGURE 3 Reported cases of Guillain-Barre syndrome, by five-year age group, and A/New Jersey influenza vaccination status, United States (including Puerto Rico), Oct. 1, 1976–Jan. 31, 1977

cent) occurred on the 16th and 17th days after vaccination (figure 5).

Attack rates by week interval between onset of GBS and vaccination

Using the reports of vaccinations administered by week, attack rates were determined for the population over 17 years of age, by week of onset after their influenza vaccination (figure 6). Several states were analyzed only for the period October 3 through December 18, 1976, when their reported case ascertainment was maximal. The expected GBS attack rate based on the average attack rate for those over 17 years of age who did not receive an A/New Jersey influenza vaccination prior to onset was 0.22 cases per million persons per week (figure 6). The weekly attack rates for the vaccinees were considerably above this level, especially in weeks 2 and 3 after vaccination. The area of the curve above the expected level provided an estimate of the risk each week attributable to vaccination. For the first 10 weeks, the attributable risk for the population over 17 years of age was approximately 9.5 cases per million vaccinees or just under one case per 100,000 vaccinations. Based on figure 6, one could

TABLE 1

Guillain-Barre syndrome cases and population over 17 years of age, by sex, race, and A/New Jersey influenza vaccination status, continental United States, Oct. 1, 1976–Jan 31, 1977

Group	Estimated January 1977 population‡ (in millions)	GBS cases†	Ratio cases to 1 million estimated January 1977 population
Vaccinated			
Male	20.1	241	12 0
Female	24.9	275	11 0
White	42.9	446	10.4
Black	2.1	9	4 3
Unvaccinated			
Male	49.2	243*	4.9
Female	52.9	189*	3.6
White	87.1	354*	4.1
Black	12 9	34*	2 6

* Includes cases vaccinated after onset of GBS.

† Excludes cases unclassifiable due to unreported information.

‡ Based on National Survey of Public Attitudes Towards A/New Jersey/76 Influenza Vaccination—Report No 6, January 1977.

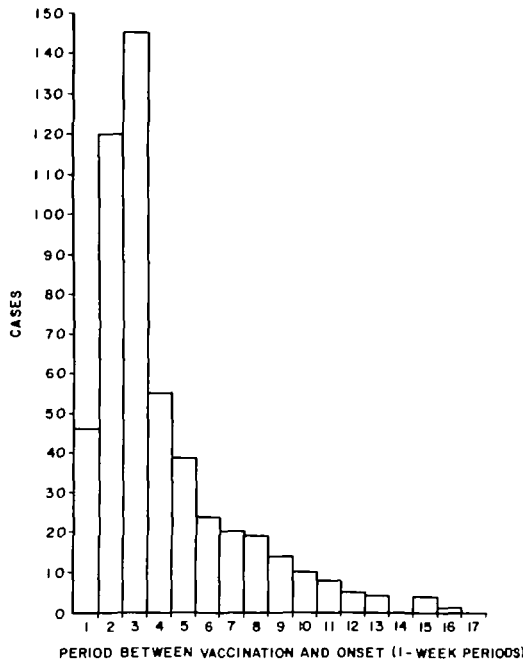

FIGURE 4. Reported cases of Guillain-Barre syndrome, by period between A/New Jersey influenza vaccination and onset of illness, United States (including Puerto Rico), Oct 1, 1976–Jan. 31, 1977.

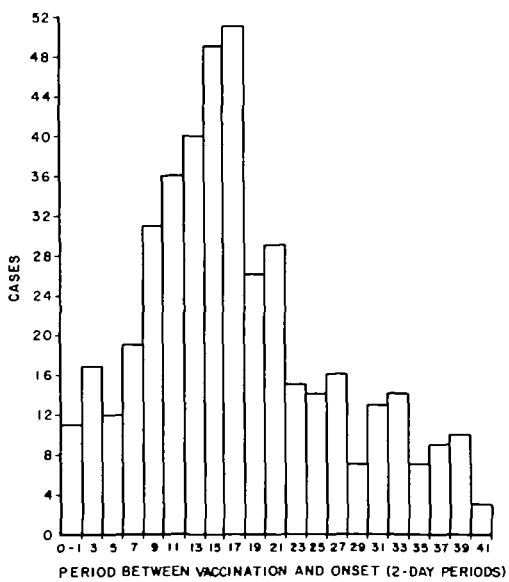

FIGURE 5. Reported cases of Guillain-Barre syndrome, by two-day periods between A/New Jersey influenza vaccination and onset of illness, United States (including Puerto Rico), Oct. 1, 1976–Jan 31, 1977. Day zero indicates day of vaccination.

visualize that the attributable risk would not change very markedly even if the height of the expected attack rate were doubled.

Based on the attack rates, by week after vaccination, in figure 6, the relative risks of GBS (the ratios of attack rates in the vaccinated and unvaccinated populations) were determined (figure 7). The peak relative risks, which exceeded 12, occurred in weeks 2 and 3 after vaccination, and prior to the 10th week after vaccination all relative risks were significantly greater than 1, $p < .05$ (5). From the 10th week on, the relative risks no longer remained significantly different from 1.

Age- and vaccine-specific attack rates

Using the monthly data of vaccinations administered, the age-specific attack rates, by type of A/New Jersey influenza vaccine received (monovalent versus bivalent vaccine), the relative risks and the attributable risks (the difference in attack rates between the vaccinated and unvaccinated populations) were determined (table 2). The attack rates for all vaccinees were based on the six-week period following vaccination. Within each age group the attack rates for recipients of monovalent and bivalent vaccines were not significantly different. Among vaccinees, the overall attack rate in each of the three oldest age groups varied from 7.3 to 9.1 cases per million persons per month. Though these rates were not significantly different from each other, each was significantly greater than the attack rates in the two youngest age groups, at least at the $p < .05$ level. The data for children were less definitive because of the relatively small number of cases and vaccinations in children.

Among nonrecipients of A/New Jersey influenza vaccine, the age-specific attack rates ranged from 0.46 cases per million persons per month in those under 18 years of age to 1.40 cases per million persons per month in those 65 years of age

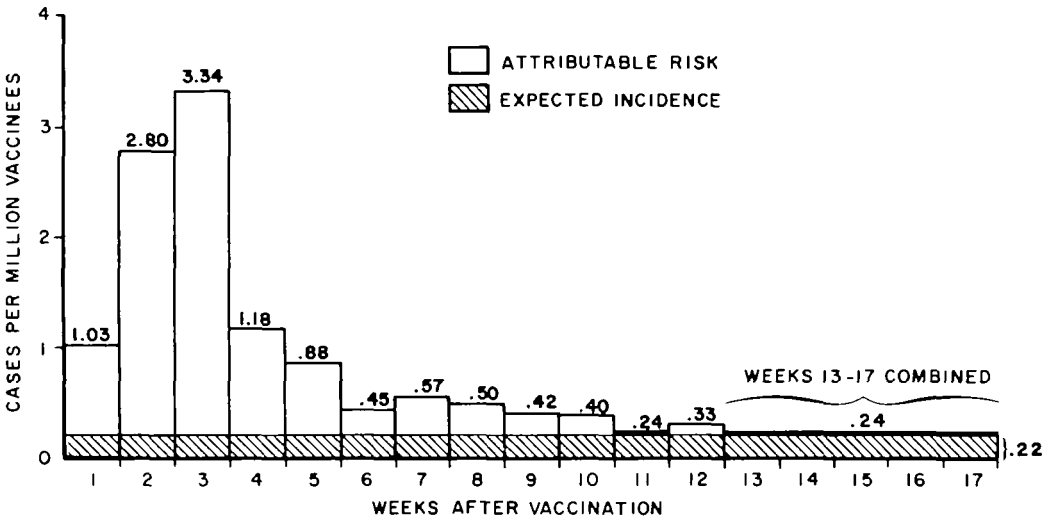

FIGURE 6. Guillain-Barre syndrome attack rates for population over 17 years of age, by week of onset after A/New Jersey influenza vaccination, United States, Oct 3, 1976–Jan. 29, 1977, excluding Arkansas, Connecticut, Delaware, and Washington. Data for California, Florida, Georgia, Missouri, North Carolina, New Jersey, New York, and Texas included for Oct. 3–Dec 18, 1976 only.

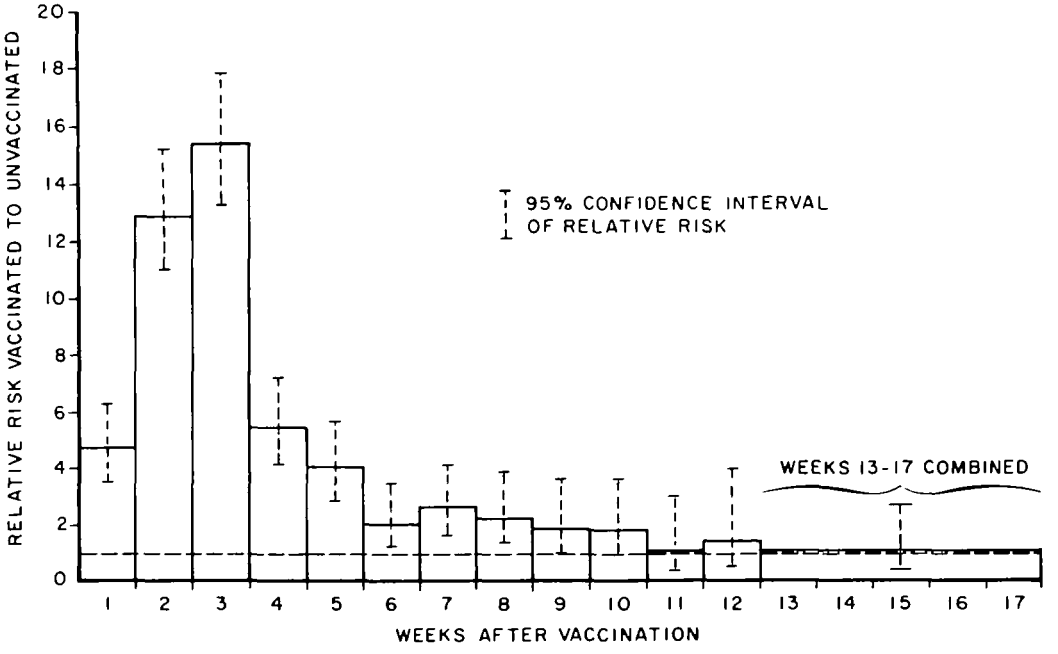

FIGURE 7. Guillain-Barre syndrome relative risks for population over 17 years of age, by week of onset after A/New Jersey influenza vaccination, United States, Oct. 3, 1976–Jan. 29, 1977, excluding Arkansas, Connecticut, Delaware, and Washington. Data for California, Florida, Georgia, Missouri, North Carolina, New Jersey, New York, and Texas included for Oct. 3–Dec. 18, 1976 only.

TABLE 2

Guillain-Barre syndrome attack rates, relative risks (RR) and attributable risks, by age group and type of A/New Jersey influenza vaccine administered, United States§, Oct. 1, 1976–Jan. 31, 1977

Age group, vaccine type	Cases within 6 weeks after vaccination	Attack rate†	Cases not vaccinated with A/New Jersey influenza vaccine‡	Attack rate†	RR	95% confidence interval on RR	Attributable risk within 6 weeks after vaccination¶
0–17							
Monovalent	0	0			0		
Bivalent	1	1.8			3.9		
Total	1	1 1	86	0.46	2.4	(0.4–16 2)	NS¶
18–24							
Monovalent	20	3.2			3.6		
Bivalent	2	3.0			3.4		
Total	23*	3.3	60	0.89	3.7	(2.4–5.8)	3.3
25–44							
Monovalent	125	9.0			12 1		
Bivalent	12	5.4			7.3		
Total	146*	9.1	96	0 74	12 2	(10.0–14.9)	11.4
45–64							
Monovalent	62	7.1			6.4		
Bivalent	45	6.4			5.8		
Total	118*	7.5	108	1 10	6.8	(5 4–8.5)	8.8
65+							
Monovalent	2	6 3			4 5		
Bivalent	71	7 1			5 1		
Total	75*	7 3	68	1.40	5.2	(3 9–7.0)	8.1
All ages							
Monovalent	209	7.0			8.9		
Bivalent	131	6.4			8.1		
Total	363*	7 2	419	0.79	9 2	(8.2–10.3)	8.8
18+							
Monovalent	209	7 2			7.4		
Bivalent	130	6.6			6.8		
Total	362*	7 4	332	0.97	7.6	(6.7–8.6)	8.8

* Includes cases with unknown vaccine type.

† Attack rates given as cases per million people (either vaccinees or unvaccinated persons as appropriate) per month

‡ Includes cases with onset of GBS before vaccination and one case with unknown age.

§ Not including Arkansas, Delaware, New Jersey, and Washington and vaccinees reported in December from California, Florida, Georgia, Missouri, New York, North Carolina, and Texas. Only data on vaccinees included from Massachusetts, Pennsylvania, and West Virginia.

¶ Attributable risks given as cases per million vaccinees

ç Not significant.

and older. Statistically, the attack rates in the 45- to 64-year-olds and in the oldest age group were not significantly different from each other, but both of these older groups had significantly higher attack rates than observed in the 25- to 44-year-old age group, $p < .01$. When the age-specific attack rates for the vaccinated and unvaccinated populations were compared, the vaccinated population had a significantly elevated attack rate in every adult age group. The relative risks in the adult population overall for the six weeks following vaccination was 7.6 (table 2).

The age-specific attributable risks for the six-week period after vaccination in the adult population varied from 3.3 cases per million vaccinations in the 18- to 24-

year-old age group to 11.4 cases per million vaccinations in the 25- to 44-year-old age group. These attributable risks could be derived from data in table 2 by multiplying the difference in average monthly attack rates for the vaccinated and unvaccinated persons by 1.37 (rounded number), the ratio of six weeks to the length of the average month in the study period. Overall the attributable risk in the six-week period after vaccination was 8.8 cases per million vaccinations (table 2).

Occurrence of GBS by region of the United States and period of vaccination

The data in table 2 were analyzed by the four major geographic regions of the United States, Northeast, North Central, South and West (6). For either vaccine recipients or nonrecipients, the distribution of the reported number of GBS cases among these regions was not significantly different from what was expected based on both the national attack rate in any age category and the number of people, by region, in that category and their period of risk. Thus, the relative risk of GBS for vaccine recipients during the six-week period after vaccination compared to nonrecipients was similar in the four geographic regions of the United States. For those over 17 years of age, this relative risk was 7.1 in the South, 7.7 in the Northeast, 7.8 in the North Central and 8.1 in the West. Further analysis of the data used in table 2 also revealed no significant difference in attack rate during the six-week period after vaccination in the three cohorts of adult vaccinees defined by the October, November, and December reports of vaccinations. The ratio of the attack rate of each of these three cohorts to the overall attack rate in adult vaccinees was 0.92, 1.09, and 0.88, respectively.

Comparison of the GBS illness and clinical background for the vaccinated and unvaccinated patients

The comparability of the GBS illness and clinical background reported in the vaccinated and unvaccinated patients enabled evaluation of possible biases in case ascertainment. Case-fatality ratios were one measure of the comparability of the GBS illnesses; these ratios were not significantly different for the vaccinated and unvaccinated patients and were almost identical for those over 17 years of age, 6.0 per cent among the vaccinated and 5.7 per cent among the unvaccinated (table 3). In total, 58 fatalities were reported, for an overall case fatality ratio of 5.3 per cent. Among all reported GBS patients, the case-fatality ratios ranged from 0.8 per cent in those under 18 years of age to

TABLE 3

Reported fatal and nonfatal cases of Guillain-Barre syndrome, by age group and A/New Jersey vaccination status, United States, Oct 1, 1976–Jan. 31, 1977

Age group	Vaccinated			Unvaccinated†			Total		
	Cases	Deaths	Ratio	Cases	Deaths	Ratio	Cases	Deaths	Ratio
0–17	2	0	0%	120	1	0 8%	122	1	0.8%
18–24	36	1	2.8%	76	3	3.9%	114*	4	3.5%
25–44	202	4	2.0%	131	4	3.1%	333	8	2.4%
45–64	173	12	6.9%	138	6	4.3%	314*	18	5.7%
65+	118	15	12.7%	91	12	13 2%	212*	27	12.7%
Unknown	1	0	0%	2	0	0%	3	0	0%
Total	532	32	6.0%	558	26	4.7%	1098*	58	5.3%
18+	529	32	6.0%	436	25	5.7%	973*	57	5.9%

* Includes one or more cases with unknown vaccination status.

† Includes cases with onset of Guillain-Barre syndrome before vaccination.

12.7 per cent among those 65 years of age and older.

Information on the cerebrospinal fluid (CSF) protein concentration was reported for 423 (80.0 per cent) of the vaccinated and 364 (83.5 per cent) of the unvaccinated GBS cases over 17 years of age. Of these, a significantly higher proportion of the vaccinated cases (82.3 per cent) than unvaccinated cases (74.7 per cent) had a documented CSF protein elevation (>50 mg/dl or reported as elevated).

The comparability of the reported vaccinated and unvaccinated patients with GBS over 17 years of age was further evaluated based on parameters shown in table 4. It is noteworthy that information was available on the same average proportion (83 per cent) of the patients in each group. Of these, approximately 84 per cent of the vaccinated and 89 per cent of unvaccinated patients with GBS were diagnosed by neurologists, a small but statistically significant difference. There were remarkable similarities between vaccinated and unvaccinated patients in the high frequency of reported progressive weakness and/or paralysis, bilateral neurologic signs, and lower motor neuron signs. Though sensory symptoms were reported in the vast majority of cases, these were reported significantly more often in those who had received vaccine, 89.5 per cent versus 79.9 per cent. A total of 36.2 per cent of the vaccinated and 38.7 per cent of the unvaccinated patients had respiratory impairment, and 20.3 per cent of the vaccinated and 24.7 per cent of the unvaccinated patients required mechanical respiratory assistance. The vaccinated group had a significantly higher percentage of cranial nerve involvement, 53.3 per cent compared to 45.1 per cent.

Though there were no reported differences in recent toxin exposure, history of allergy in the patient or in his family, or in the history of an acute illness among household contacts, a total of 45.1 per cent of the vaccinated patients had a chronic illness as compared to 35.6 per cent of the unvaccinated patients. This difference was expected because vaccinations were particularly encouraged for people with chronic disease. The unvaccinated patients had a significantly greater frequency of reported acute illness in the four weeks prior to onset, 61.8 per cent as compared to 32.8 per cent for the vaccinated patients.

Vaccine evaluation

Manufacturer-specific attack rates

Based on an inventory of vaccine conducted by each state, in early 1977, including Washington, DC, the proportions of monovalent and bivalent vaccine, by manufacturer, that were received but not on hand for inventory were determined. For the states included in table 2, manufacturers A, B, C, and D accounted for 34.2, 63.1, 1.4, and 1.3 per cent, respectively, of the monovalent vaccine that was received but not on hand and 6.7, 9.0, 66.5, and 17.8 per cent, respectively, of the bivalent vaccine. In order to estimate rates of GBS, by manufacturer, the proportions derived above were applied to the denominator for the "all ages" category of table 2. This assumed that for each type of vaccine the amount received, but not in the 1977 inventory, reflected equally well the amount of each manufacturer's vaccine that was administered. As illustrated in table 5, the vaccine of all four manufacturers was similarly associated with cases of GBS. No single manufacturer's vaccine had a significantly different rate of GBS than the other manufacturers combined. However, manufacturer C did approach having a statistically significant lower rate and the rates associated with the bivalent vaccines of manufacturer C and D differed significantly, $p < .05$. The monovalent split-product vaccines combined, vaccines which were recommended primarily for children, had a significantly lower attack rate than the monovalent whole-product vaccines combined, but

TABLE 4

Guillain-Barre syndrome in population over 17 years of age, by history of A/New Jersey influenza vaccination and clinical status, United States, Oct. 1, 1976–Jan. 31, 1977

	Vaccinated with A/New Jersey vaccine prior to onset		All other cases		Ratio of % positive vaccinated to all other cases	Statistical significance
	No.	%	No	%		
Seen by neurologist	403	83.9	359	89.1	.94	$p < .05$
Characterization:						
Progressive weakness and/or paralysis	489	96.5	405	97.5	.99	NS*
Associated sensory symptoms	475	89.5	388	79.9	1.12	$p < .001$
Bilaterial neurologic signs	472	96 8	394	97.2	1.00	NS
Lower motor neuron signs	460	89.6	380	91.6	.98	NS
Severity:						
3–4 extremities involved	476	86.3	382	84.8	1.02	NS
Trunk involved	431	56.6	363	54.5	1.04	NS
Cranial nerves involved	445	53.3	375	45.1	1.18	$p < .005$
Respiratory impairment	458	36.2	380	38.7	.94	NS
Placed on respirator	479	20.3	401	24.7	.82	NS
Clinical background:						
Acute illness in past 4 weeks	460	32.8	377	61.8	53	$p < .001$
Recent toxin exposure	391	12.5	323	15.5	.81	NS
Chronic illness	472	45 1	382	35.6	1.27	$p < .01$
Allergy	441	21 3	351	17.4	1.22	NS
Family history of allergy	330	15.5	253	11.1	1.40	NS
Acute illness among household	368	9.8	294	11 2	88	NS

* Not significant.

TABLE 5

Guillain-Barre syndrome attack rates and relative risks (RR), by manufacturer and type of vaccine administered, United States, Oct 1, 1976–Jan. 31, 1977§

Manufacturer; type of vaccine	Cases within 6 weeks after vaccination	Attack rate‡	Unvaccinated cases†	Attack rate‡	RR, vaccinated to unvaccinated	95% confidence interval on RR
Whole products						
Manufacturer A						
Monovalent	60	5.9				
Bivalent	7	5.1				
Total	67	5.8	419	0.79	7.4	(5.9–9 2)
Manufacturer B						
Monovalent	131	7.0				
Bivalent	11	6.0				
Total	142	6 9	419	0.79	8.7	(7 5–10.2)
Split products						
Manufacturer C						
Monovalent	0	0				
Bivalent	71	5 2				
Total	71	5.1	419	0.79	6 4	(5.1–8.0)
Manufacturer D						
Monovalent	0	0				
Bivalent	31	8.5				
Total	31	7 7	419	0.79	9.7	(7 2–13.1)
All manufacturers						
Monovalent	209*	7.0				
Bivalent	131*	6 4				
Total	363*	7.2	419	0.79	9.2	(8.2–10.3)

* Includes cases with unknown vaccine type and/or manufacturer

† Includes cases with onset of Guillain-Barre syndrome before vaccination.

‡ Attack rates given as cases per million people per month. Manufacturer-specific denominators estimated using vaccine inventory, April 1, 1977

§ Not including Arkansas, Delaware, New Jersey, and Washington and vaccinees reported in December from California, Florida, Georgia, Missouri, New York, North Carolina, and Texas. Only data on vaccinees included from Massachusetts, Pennsylvania, and West Virginia

there was no significant difference in the GBS attack rates between whole and split virus vaccines overall.

Lot-specific data

Based on the lot-specific inventory completed in June 1978, the net distributions of each of the total 141 lots, that is, the difference between the quantity of each lot originally distributed and the amount counted in the inventory, varied from 2640 to 1,094,000 doses, median 365,300 (figure 8). For all lots combined, the net distribution based on this inventory was 55.85 million doses, 10.2 million doses more than was reported to have been administered. The 10.2 million doses constituted the best estimate of the amount of vaccine lost, spoiled, broken, discarded, or just not returned for inventory. On the average, net distribution overestimated the reported doses of bivalent vaccine administered by more than it overestimated the reported doses of monovalent vaccine administered, 27.6 per cent overestimation versus 18.8 per cent, respectively.

One hundred seven (76 per cent) of the total 141 lots were known to be associated with at least one case of GBS within the

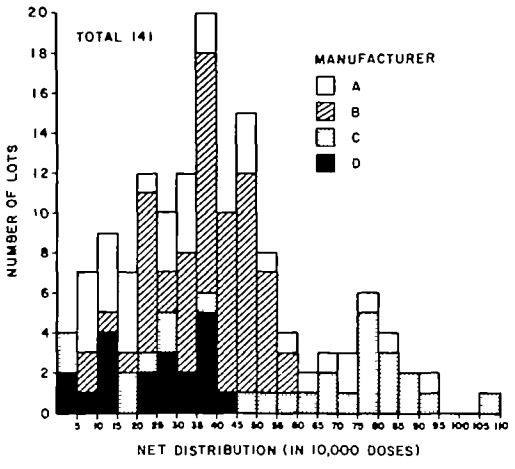

FIGURE 8 Bulk lots of A/New Jersey influenza vaccine, by net distribution of doses, United States, 1976–1977 The net distribution is the total distribution to civilian centers minus storage inventory, June 1978.

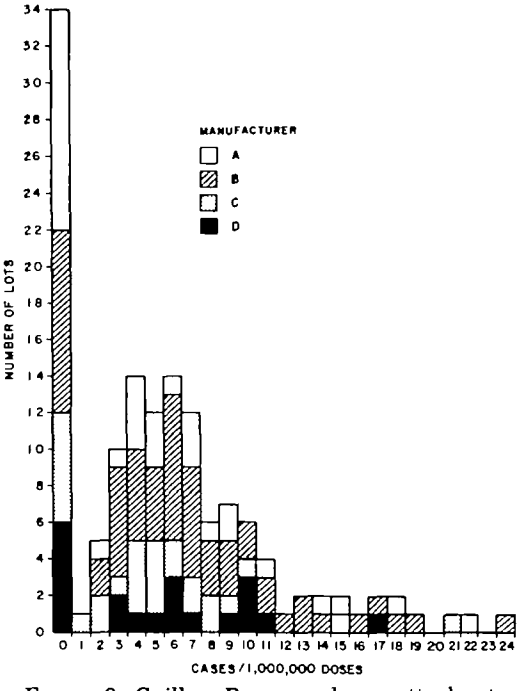

FIGURE 9 Guillain-Barre syndrome attack rates by bulk lots of A/New Jersey influenza vaccine, United States, Oct. 1, 1976–Jan 31, 1977. The attack rates are given as cases within six weeks after vaccination per million doses net distribution (See figure 8 legend for definition of net distribution.)

six-week period after vaccination. Of these, 91 per cent were associated with between one and six cases. The maximal number of cases associated with any single lot within the period was 11. It is noteworthy that the distribution of the observed number of cases associated with lots grouped by 100,000 dose sizes was not significantly different from what would be expected based on the number of doses in each group and the rate of cases for all lots combined, $.10 > p > .05$. Nevertheless, the pattern of the individual lot-specific attack rates for the six-week period after vaccination indicated some nonrandom variation; the lot-specific attack rates greater than zero closely fit a negative binomial distribution. The rates ranged from 0 to 23.7 cases per million doses net distribution, mean 6.2 cases per million doses (figure 9).

When the rate of each of the 141 lots was compared statistically to the rate of the remaining lots combined, each of three lots among those with the highest attack rate differed from all the remaining lots with a relatively high degree of statistical significance ($\chi^2 > 7.92$). The probability of testing 141 pairs of data and finding this degree of statistical significance in three of the pairs by chance alone would be unlikely, $p < .0006$.

On the other hand, no lot had a statistically significant lower attack rate than the other 140 lots combined. Based on their net distributions and the attack rate for all lots combined, the highest expected number of cases in any of the 34 lots associated with no cases was 3.07. For 26 of these lots the expected number of cases was less than two and for 15 lots less than one case.

Review of the lot that statistically had the most significantly elevated attack rate (χ^2 9.52) revealed that all nine of the associated cases within the six-week period after vaccination were reported from Ohio; only a total of 3.1 associated cases would have been expected based on the lot's net distribution and the attack rate

for all lots combined. Since 197,850 doses of the total 496,750 doses net distribution of this lot were reported from outside Ohio, there was an unexplained statistically significant lower attack rate associated with this lot's distribution outside Ohio when compared to the attack rate inside Ohio ($p < .05$). It is noteworthy that 99 per cent of the net distribution of this lot was from four geographic areas where only one reported case with an unknown lot number could possibly have been associated with the lot.

When information provided by the Bureau of Biologics was used, the lot-specific attack rates were found not to correlate significantly with the results of the following laboratory tests on each lot: thimerosal concentration, protein concentration, formaldehyde concentration, potency, and endotoxin levels.

Discussion

The epidemiologic data presented here are the results of a large cooperative surveillance effort in which health personnel from CDC and state and local health departments actively sought from collaborating neurologists and other practicing physicians all their diagnosed cases of GBS within a several-month period. The markedly increased attack rates observed among recipients of A/New Jersey vaccine provided strong support for the hypothesis that vaccination was etiologically linked to GBS. Though undoubtedly some cases of GBS with onset in the study period were not diagnosed, or if diagnosed not reported, the large numbers of reported cases provided relatively stable estimates of GBS attack rates in the vaccinated and unvaccinated populations. The order of magnitude of these GBS attack rates based on the final surveillance data in this report was remarkably similar to that estimated from preliminary data collected prior to the initial publicity about GBS after influenza vaccination (1).

Previously reported incidence rates of GBS were limited and based on relatively few cases identified over many years. The previously reported average annual incidence rates ranged between 6 and 19 cases per million population per year for an average of between 0.5 and 1.6 cases per million people per month (7–12). The 40 cases in the largest of these population based studies showed, by date of onset, an even distribution throughout all seasons (12). The average incidence rate among unvaccinated persons in the present study, 0.79 cases per million people per month, fell within the previously reported range. In contrast, the average GBS attack rate among vaccine recipients based on the six-week period after vaccination was many fold greater than the upper limit of this range.

Although the comparability of the GBS attack rates in unvaccinated persons in this study to previously reported rates suggested reasonably good ascertainment of unvaccinated persons with GBS, strong evidence existed, independent of the lower attack rate in unvaccinated persons, that A/New Jersey influenza vaccination incited the onset of GBS in many adult vaccinees. This evidence was the strikingly nonrandom distribution of intervals between vaccination and the onset of GBS, specifically the clustering of cases in the first four weeks after vaccination and particularly in the second and third weeks after vaccination. This nonrandom distribution was noted early in the investigation and was an important factor in the decision to suspend NIIP, December 16, 1976.

Another type of evidence for the etiologic relationship of influenza vaccination and GBS included the markedly lower proportion of vaccinated compared to unvaccinated cases with a history of a recent acute illness within four weeks before onset, 32.8 per cent versus 61.8 per cent, respectively. This evidence derived its strength chiefly from the only two studies in the literature comparing the

incidence of a disorder among patients with GBS with the incidence among a control group (12, 13). Relative to controls, GBS patients in these studies had a higher incidence of either a respiratory or a gastrointestinal illness within four weeks of onset; both studies demonstrated that the overall proportion of GBS patients with an acute illness within four weeks of onset was ≥60 per cent (28 of 40 patients and 31 of 52 patients, excluding one with a smallpox vaccination). The significantly lower incidence of acute illness among vaccinated cases in the present series might be attributed, at least in part, to recommendations that acutely ill persons avoid vaccination. Nevertheless, the fact that there was an increased number of GBS cases among vaccinees without the high incidence of antecedent acute illness suggested that vaccine replaced acute illness as a trigger of GBS.

The comparability of the cases reported in the vaccinated and unvaccinated populations was particularly important because the exact clinical boundaries of GBS were not precisely defined and there were no known diagnostic laboratory tests or pathognomonic clinical findings. Clearly, if only the most classical or most severe cases in the unvaccinated population were reported in contrast to much more atypical and mild cases in the vaccinated population, comparison of attack rates based on the number of cases in these two groups could be misleading. GBS, however, was a well-recognized entity, particularly among neurologists, and neurologists diagnosed an estimated 80 per cent or more of the cases in this series. Furthermore, most of the differences observed between vaccinated and unvaccinated cases in this study were relatively small in comparison to the observed differences in attack rates. Evidence that the severity of the disease in both groups was comparable included the similar total and age-specific case-fatality ratios, the similar proportion of each group with respiratory impairment, and the similar proportions who required treatment with a respirator. It is also noteworthy that the reported overall case-fatality ratio, 5.3 per cent, and the overall proportion of cases placed on a respirator, 22.2 per cent, were consistent with figures reported in the literature (14, 15).

The higher incidence of chronic disease in vaccinated persons than unvaccinated persons was expected because bivalent vaccine was directed towards persons with chronic diseases who were at increased risk of serious illness if infected with influenza A/Victoria/75 (16). However, the similar GBS attack rate in recipients of the monovalent and bivalent vaccines suggested that a history of chronic disease in general was not a very important risk factor in developing GBS.

The age distribution of the unvaccinated patients in the present series was strikingly similar to the age distribution of the 176 patients with GBS in the New York-New Jersey metropolitan area 1967–1976 (14). In both series, increased numbers of cases were seen in young adults and a second lesser peak between ages 45 and 64. Age-specific attack rates in the present series, however, demonstrated that rather than a marked predilection for GBS to occur in young adults, the risk of GBS in the unvaccinated populations was significantly higher in those over 45 years of age. In the vaccinated population, the attack rates in the three oldest age groups over 24 years were not significantly different from each other, but each group had a significantly greater attack rate than did those between 18 and 24 years of age. Thus, the present study confirmed the importance of age as a risk factor for GBS and suggested that the influence of this risk factor might vary for GBS cases associated with different agents, i.e., A/New Jersey influenza vaccine and different viral infections.

The present series also strongly suggested that unvaccinated males were at

greater risk of GBS than unvaccinated females and that the risk for both sexes rose to relatively similar levels after vaccination. It also suggested that there was a lesser risk of GBS for the black population than for the white population, which was more evident among the vaccinated than among the unvaccinated. A probable increased susceptibility of males to GBS was reported previously (11, 15).

Though some nonrandom variation in lot-specific attack rates was detected in the present study, there was little evidence that this was due to factors intrinsic to the lots themselves. The comparable attack rates, by geographic region of the United States, period of vaccination, type of vaccine and manufacturer, and the minimum of 76 per cent of lots that were associated with at least one case of GBS within a six-week period after vaccination, indicated that the increased occurrence of GBS after receipt of A/New Jersey influenza vaccine was more a generic than a lot-specific problem.

The epidemiologic data suggesting that A/New Jersey influenza vaccine caused GBS raise the question of biologic feasibility. Though historically some investigators have proposed that GBS is due to a primary viral infection, the more recent prevailing hypothesis is that GBS represents an immunopathologic reaction, triggered by recent exposure to an exogenous agent (17, 18). This immunopathologic reaction leads to certain cellular changes eventuating in attack on nerve rootlets and peripheral nerves (17, 18). Though heretofore the only potential etiologic agents shown to be associated significantly with GBS cases compared to controls were those causing nonspecific acute infections, the possibility that many different antecedent events, including vaccination, might trigger GBS has been suggested (19). In addition, experimental allergic neuritis, which has many features in common with GBS, is elicited by intradermal injections of peripheral nerve and complete Freund's adjuvant, and there is a clear association in humans between allergic encephalomyelitis and polyneuritis and inoculation with killed rabies vaccine produced in nervous tissue (20, 21). It is also noteworthy that the latent period for both experimental allergic neuritis and allergic encephalomyelitis is similar to the latent period between A/New Jersey influenza vaccination and GBS in the present series (20, 21).

The number of articles linking either GBS or a similar neurologic disorder specifically to influenza vaccination was sparse prior to NIIP; only two were found (19, 22). In the first, only one case associated with influenza vaccination was reported among 1100 cases of GBS collected from reports from the French, English, and American literature, 1949–1966. In the second, two cases of polyneuropathy, two cases of transverse myelopathy, and one case of radiculopathy were noted in patients from the United Kingdom and West Germany who had received influenza vaccine with an oil adjuvant.

The present study demonstrated the value of both a passive and active surveillance system for detecting an unanticipated serious vaccine reaction. Though the association of GBS with A/New Jersey influenza vaccination was rare, its discovery and analysis were greatly facilitated by the unusually massive administration of vaccine over a short period of time and the unusual availability of information quantitating these vaccinations. Equally important were the commitments of health authorities to investigate a potentially serious vaccine reaction and the willingness of private physicians and others in the private medical community to actively cooperate in a national surveillance effort.

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