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## Original Contributions

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

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**Langmuir, A. D., D. J. Bregman (CDC, Atlanta, GA 30333), L. T. Kurland, N. Nathanson and M. Victor. An epidemiologic and clinical evaluation of Guillain-Barré syndrome reported in association with the administration of swine influenza vaccines. *Am J Epidemiol* 1984;119:841-79.**

**As a result of a court order, computerized summaries of approximately 1,300 cases reported as Guillain-Barré syndrome by state health departments to the Centers for Disease Control during the intensive national surveillance instituted following the swine influenza vaccination program in 1976–1977 became available for further study. Although the data were not uniformly adequate to confirm the diagnosis of Guillain-Barré syndrome, they were sufficient to enable classification according to extent of motor involvement. Vaccinated cases with "extensive" paresis or paralysis occurred in a characteristic epidemiologic pattern closely approximated by a lognormal curve, suggesting a causal relationship between the disease and the vaccine. Cases with "limited" motor involvement showed no such pattern, suggesting that this group included a substantial proportion of cases which were unrelated to the vaccine. The effect attributed to the vaccine lasted for at least six weeks and possibly for eight weeks but not longer. The relative risk of acquiring "extensive" disease over a six-week period following vaccination ranged from 3.96 to 7.75 depending on the particular baseline estimate of expected normal or endemic incidence that was chosen. Correspondingly, the number of cases that could be attributed to**

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Abbreviations: CDC, Centers for Disease Control; GBS, Guillain-Barré syndrome.

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This study was commissioned by the US Department of Justice.

**the vaccine over the six-week period ranged from 211 to 246, or very slightly higher over an eight-week period if the lowest baseline estimate was used. The total rate of Guillain-Barré syndrome cases attributed to prior use of the vaccine was 4.9 to 5.9 per million vaccinees.**

**autoimmune diseases; Guillain-Barré syndrome; polyneuritis; swine influenza vaccine**

In 1976, the Federal Government sponsored the National Influenza Immunization Program which made available to the adult population of the United States immunization with influenza vaccine containing the A/New Jersey/76 strain of influenza virus commonly known as the "swine influenza vaccine." The immunization program began on October 1, 1976, and, by mid-December, 1976, a total of approximately 45 million doses had been administered through a collaborative effort involving all state and territorial health departments coordinated by the Centers for Disease Control in Atlanta, Georgia. (Note—the figure of approximately 45 million doses includes doses administered in the 50 states of the United States as well as those in Puerto Rico, the Virgin Islands, Guam, and the Trust Territories.)

In certain states in late November and early December, cases of Guillain-Barré syndrome were reported among recent vaccinees. Intensive investigations into this temporal association were initiated, first in four states and a few days later in seven additional states. On December 16, the findings of these investigations led to the declaration of a moratorium on further administration of the influenza vaccine. All states were requested to participate in a national surveillance program.

The events of 1976 and early 1977 covering the development of the swine flu vaccine program, the discovery of the Guillain-Barré syndrome cases, and the decisions taken throughout this period, were reported extensively in news releases, committee reports, official statements and current as well as subsequent publications in the scientific and popular literature. (Some of the more relevant documents are listed in references 1–10.)

Following the declaration of the moratorium, claims and suits were filed against the United States Government. Through 1984 (11), over 4,000 claims totaling over 3 billion dollars pertaining to a variety of diagnoses have been submitted. These are in various stages of litigation, negotiation, and resolution.

### *"The Gesell order"*

During the course of recent litigation, criticisms of both the Schonberger et al. (9) and Langmuir (10) papers were made on the grounds that 1) the Schonberger et al. paper did not present the basic data upon which the reported incidence rates, relative risks, and confidence limits were calculated; and 2) the Langmuir paper failed to adjust for the declining population at risk after the sixth week following vaccination and thus reported erroneous estimates for incidence rates and relative risks for the tail end of the epidemic curve. On November 2, 1981, US District Judge Gerhard Gesell issued an order (12) that ". . . plaintiffs . . . shall promptly be afforded access to and permission to copy the statistics and tabulations underlying the studies of Dr. Larry Schonberger and Dr. Alexander Langmuir which were available to the Steering Committee during the pretrial proceedings. . . ." (The Steering Committee refers to the plaintiff's Steering Committee which worked with attorneys of the Department of Jus-

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tice leading to the issuance of a set of "stipulations of facts not in issue.")

Accordingly, the Centers for Disease Control complied fully, within the limits of the Privacy Act, by submitting single sheet computer print-outs of all cases that had been reported as Guillain-Barré syndrome by the state and territorial health departments. The total was approximately 1,300, of which 1,098 consisted of the cases used by Schonberger et al. (9) in the preparation of their report. The additional approximately 100 case reports consisted of patients having onsets of neurologic symptoms prior to October 1, 1976 or subsequent to January 31, 1977. Further commentary on the character of the available data is given in Appendix A.

In addition to these individual sheets, a computer line-listing of the 1,098 cases having onsets from October 1, 1976 to January 31, 1977 was submitted. A computer tape with appropriate code covering most of the specific items on the individual sheets was also released. A tabulation of the estimated number of vaccinations performed each week by states in the National Influenza Immunization Program was also provided. The weekly totals of vaccinations reported to the Centers for Disease Control are shown in Appendix B.

### *The formation of the present panel*

During the winter and spring of 1982, the present special panel was formed. We had all previously consulted with the Department of Justice for varying periods of time regarding swine flu vaccine litigation. The charge of the panel was to prepare, in a form suitable for publication in the scientific literature, a comprehensive, documented and critical evaluation of the data released by the "Gesell order." In as much as this order had emanated from the issue of how long after vaccination any possible causal effect on the occurrence of Guillain-Barré syndrome had continued, this question among many others received specific attention.

### *Restrictions on the panel*

In carrying out its assignment, the panel has operated under rather severe restrictions. We have had access only to the data released by the "Gesell order" and, of course, to such documents, publications, and news releases that were already on the public record. But the basic files at the Centers for Disease Control remained impounded and the personnel involved in the original National Immunization Program and the ensuing Guillain-Barré syndrome surveillance were not interrogated. A limited exception was Mr. Dennis J. Bregman, a member of the panel, who had been recalled to active duty from academic study, to prepare the release of the "Gesell order" data including the single sheet computer printouts, the computer line-listing of the specifically requested data, and the computer tape that were made available. In his participation on the panel, he limited his activities to these specific data.

In view of these restrictions, the panel has been unable to verify records, check apparent inconsistencies, or even investigate apparent typographical errors or possible miscodings. It became imperative, therefore, to undertake a rigorous calibration of the available data, to resolve inconsistencies if logical explanations could be found and to exclude or segregate cases when the data were deemed unsatisfactory.

## MATERIALS AND METHODS OF SURVEILLANCE

The national surveillance program of Guillain-Barré syndrome developed in many phases that will be described and evaluated separately: 1) case ascertainment; 2) case investigation; 3) clinical classification of cases; 4) collection of reports on total vaccinations; 5) verification

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of vaccination of cases; 6) adequacy of surveillance of vaccinated and unvaccinated cases.

### *Case ascertainment*

Schonberger et al. (9) describe in considerable detail the methods employed in case ascertainment and the definitions and criteria adopted by the Centers for Disease Control (CDC) for "acceptance" of a case of Guillain-Barré syndrome (GBS) into the study:

> 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. . . . 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 with 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. (9, pp. 106-7).

Additional information regarding the procedures of case ascertainment is revealed by the two memoranda issued on January 6 and 7, 1977 (13). In the first memorandum, state epidemiologists in 39 states and selected cities were asked by the Centers for Disease Control to adopt a slightly revised version of the comprehensive case investigation form that had been developed in consultation with a group of neurologists in late December and which was already in use in 11 selected states. The second memorandum asked the epidemiologists in these 11 states to adopt the same slight revisions in order to ensure national uniformity in the collection of data. Apparently, prior to January 6, the 39 states had been reporting the cases they had discovered in a simpler fashion through telephone and mail contacts with specified "contact persons" in Atlanta. Originally, each state was requested to discover and report all cases that occurred from September 1, 1976 through January 31, 1977, although the "study period" was later narrowed by one month to begin October 1, 1976, when vaccinations began on a national scale. This explains, in part, the reports of cases which had onsets in September 1976 that were distributed by the Centers for Disease Control in November 1981 but neither included in the computer line-listing, the several news releases issued by the Centers for Disease Control during 1976 and 1977 (6), nor in the papers by Schonberger et al. (9) or Langmuir (10).

Thus, national surveillance began as a truly emergency measure on December 17, 1976 by direct telephone contact between the staffs of the Centers for Disease Control and state health departments. Ef-

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fort was first concentrated on soliciting the cooperation of practicing neurologists who were believed likely to have seen most cases and who were best qualified to make a differential diagnosis. Also, a variety of other sources of case reports was utilized. The methods varied from state to state.

Early on, a two-way flow of information was established between the staffs of the Centers for Disease Control and the state health departments, and the state agencies, in turn, with their local reporting sources. Information on suspect cases from whatever source was promptly exchanged, investigated, verified, and, where pertinent, added to the individual surveillance file maintained in Atlanta. This interchange continued for many months after the formal surveillance period was terminated on January 31, 1977.

### *Case investigation*

As one of its first steps, the panel studied line-listings of each of the 1,098 cases for completeness and consistency of the data. In some instances, essential identifying facts were missing or insufficiently complete to permit further analysis. A total of 33 cases (3.0 per cent) were thus excluded, as shown in table 1. An additional 121 cases were found to be under 18 years of age. Since the vaccine had not been recommended for this age group and only two were reported to have received it, these 121 cases were also set aside. With these two groups excluded,

TABLE 1

*Categorization of Guillain-Barré syndrome (GBS) cases in the United States with onsets from October 1, 1976 through January 31, 1977*

| Categorization | No. |
|---|---|
| I. *Total cases* Accepted by the Centers for Disease Control as GBS with onset of neurologic symptoms between October 1, 1976 and January 31, 1977 | 1098 |
| II. *Exclusions* | |
| 1. Vaccination data insufficient: | |
| Month but no date recorded | (14) |
| Vaccination status unknown | ( 8) |
| 2. Date of onset inadequate | ( 3) |
| 3. Age unknown | ( 3) |
| 4. Vaccinated after December 16, 1976, or prior to October 1, 1976. | ( 5) |
| | 33 |
| III. *Age under 18 years* Subject to separate analysis | 121* |
| IV. *Cases subjected to clinical and epidemiologic review* with particular emphasis on the relation of GBS to swine influenza vaccine | 944† |

* Of these 121 cases, two received the vaccine.

† Of these cases, 504 were vaccinated with one of the vaccines containing the swine influenza virus one or more days prior to onset of neurologic symptoms; 440 were unvaccinated or received swine influenza vaccine on the day of onset or some time later. Persons receiving vaccine containing influenza B virus, or non-swine strains of influenza A only, were classified as "unvaccinated."

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the 1,098 "Gesell order" cases were reduced to a total of 944.

The next step was to study the recorded clinical data on each case to determine the consistency of the findings deemed sufficient to warrant a presumptive diagnosis of Guillain-Barré syndrome and to search for possible groups of cases by severity, extent of motor involvement, or other features that might reveal special characteristics or distinctive classifications within this unique body of cases.

The clinical data available for study are described in Appendix A and included:
1) Extent of motor involvement, a) "1 to 2 extremities," b) "3 to 4 extremities," c) "trunk," d) "cranial," and e) "respiratory impairment."
2) Clinical characteristics, a) "progressive motor weakness and/or paralysis," b) "bilateral involvement," and c) "lower motor neuron" signs.
3) Diagnostic support, a) "lumbar puncture performed," b) "concentration of spinal fluid protein," and c) "diagnosed by a neurologist."
During this clinical review, information regarding vaccination status was deliberately omitted in the process of classifying the cases.

Certain problems and inconsistencies were immediately encountered, reflecting probable misinterpretations by those reporting the data, errors of recording or coding, or simply failure to complete the form. A fundamental defect of the original form concerned the mode used to record the extent of limb involvement as "1 to 2 extremities" or "3 to 4 extremities." In so far as the limb involvement in Guillain-Barré syndrome is invariably bilateral, the use of terms such as "both legs," "both arms," or "all limbs" would have been more appropriate. Some problems raised by the method of recording could be readily resolved. For example, where involvement of 3 or 4 extremities was recorded as positive, the space for 1 to 2 extremity involvement was often ignored and sometimes even recorded as negative; the latter notation is obviously inconsistent with the first and was disregarded. Furthermore, in a few patients with 3 to 4 extremity involvement, bilateral signs were recorded as absent. This inconsistency was studied more carefully. When other findings were compatible with the diagnosis, the case was included, but, if other inconsistencies existed, it was classified as "data insufficient." When only 1 or 2 extremity involvement was recorded as positive, the presence of bilateral paresis was required to accept a case.

During this individual review of clinical data, the panel carefully considered the adoption of stringent diagnostic criteria, including not only consistent clinical findings but a record of spinal fluid protein concentration of 50 mg or higher and a diagnosis made by a neurologist. Such an approach might be considered appropriate in studies with a primary clinical emphasis in order to insure the highest specificity of diagnosis. To do so, however, would have excluded more than 25 per cent of the cases otherwise having clinical features believed to be characteristic, and thus would have introduced a substantial underestimate into an epidemiologic study where the primary objective was to achieve the soundest possible estimates of incidence rates on a nationwide basis.

Furthermore, we recognized that all of the case records had been reviewed at the Centers for Disease Control and by state epidemiologists and "accepted" as Guillain-Barré syndrome. Very possibly, more information was available to those reviewers than was released by the "Gesell order". By long tradition in state-federal surveillance relationships, the certification by the state epidemiologists has been respected. Such cases have been placed "on the record" even when fuller information has required separation or subsequent elimination. The panel chose also to respect this tradition by the inclusion

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of all 1,098 cases in its review, but, in our subsequent classifications, to be described, we have relied on our own evaluation of the limited factual information available to us. Also, by following this policy, the data presented can be compared with the data presented in the Schonberger et al. (9) and Langmuir (10) papers, and thus make it possible to account for differences appearing in the various published documents.

*Clinical classification of the cases*

After a variety of attempts, a relatively simple clinical classification of the cases by extent of motor involvement was adopted. The criteria are summarized in table 2. Group A (32.1 per cent) had "extensive motor involvement" including trunk and/or cranial muscles with respiratory impairment; Group B (29.3 per cent) similarly had "extensive" paresis or paralysis but without recorded respiratory impairment; Group C (18.3 per cent) had motor involvement "limited" to 3 or 4 extremities; Group D (7.3 per cent) had involvement "limited" to 1 to 2 extremities; Group E, comprising 122 cases (12.9 per cent), was made up of cases that had to be classified as "insufficient".

The per cent frequency of positive clinical findings among Groups A–E is shown in table 3 (the actual counts, as coded from the basic records, can be derived from Appendix tables C-1 and C-2). By definition, all cases in Group A had respiratory impairment, and they also exhibited a high proportion of involvement of all muscle groups. The Group B cases had involvement of cranial and/or trunk muscles in addition to involvement of extremities. Group C and D cases, again by definition, had motor involvement limited to the extremities.

Several of the clinical characteristics considered essential or strongly supportive of the diagnosis were consistently high in groups A–D. (Note—the National Institutes of Health (14, 15) diagnostic criteria were not published until

TABLE 2

*Clinical evaluation of Guillain-Barré syndrome in the United States and classification of cases by extent of motor involvement (onsets from October 1, 1976 through January 31, 1977)*

| Group | Extent of motor involvement* | No. of cases | % |
|---|---|---|---|
| | *Extensive.* Paresis or paralysis of extremities plus trunk and/or cranial muscles: | | |
| A. | With respiratory impairment | 303 | 32.1 |
| B. | Without respiratory impairment | 277 | 29.3 |
| | *Limited.* Paresis or paralysis of only: | | |
| C. | 3–4 extremities | 173 | 18.3 |
| D. | 1–2 extremities | 69 | 7.3 |
| E. | *Insufficient.* The recorded data were either too limited in extent, or conflicting in character or simply recorded "unknown," thereby precluding any classification by extent of paralysis | 122 | 12.9 |
| | Total | 944 | 100.0 |

* All cases classified into Groups A–D had substantial evidence of the presence of the clinical characteristics: progressive motor weakness, bilateral involvement, and lower motor neuron signs, to justify the presumptive diagnosis of Guillain-Barré syndrome. See text for interpretation of exceptions.

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TABLE 3

*Cases of Guillain-Barré syndrome in the United States: per cent of positive findings of muscle areas affected, clinical characteristics, and other features supportive of diagnosis, by groups according to extent of motor involvement (onsets from October 1, 1976 through January 31, 1977)**

| | Cases grouped by extent of motor involvement† | | | | |
|---|---|---|---|---|---|
| | A $N = 303$ | B $N = 277$ | C $N = 173$ | D $N = 69$ | E $N = 122$ |
| % involvement of motor areas | | | | | |
| Respiratory | 100.0 | | | | 5.7 |
| Cranial | 69.3 | 63.2 | | | 17.2 |
| Trunk | 81.8 | 63.9 | | | 4.9 |
| 3–4 extremities | 95.0 | 85.6 | 100.0 | | 12.3 |
| 1–2 extremities | 66.7 | 69.0 | 59.5 | 100.0 | 21.3 |
| % with clinical characteristics | | | | | |
| Progressive motor weakness | 98.3 | 97.1 | 97.1 | 98.6 | 33.6 |
| Bilateral involvement | 97.4 | 94.2 | 94.8 | 100.0 | 27.0 |
| Lower motor neuron signs | 91.4 | 84.5 | 87.3 | 87.0 | 17.2 |
| % with other features supportive of diagnosis | | | | | |
| Seen by neurologist | 77.6 | 74.0 | 71.1 | 65.2 | 30.3 |
| Lumbar puncture done | 89.8 | 89.5 | 80.9 | 78.3 | 47.5 |
| Lumbar puncture positive‡ | 82.0 | 82.7 | 75.7 | 81.5 | 56.9 |

* See Appendix tables C-1 and C-2 for case counts.

† See table 2 for criteria defining groups A–E.

‡ Positive: cerebrospinal fluid protein ≥50 mg/100 ml.

1978.) Progressive motor weakness was reported in ≥97.1 per cent and bilaterality in ≥94.2 per cent, although lower motor neuron affection, a somewhat more difficult criterion to assess, was positive in ≥84.5 per cent. No tendency toward lower frequencies was observed among Groups C and D, although these two groups had markedly less extensive motor involvement. The following features considered to be strongly supportive of the diagnosis could not be assessed: motor weakness in both lower extremities, areflexia, autonomic dysfunction, absence of fever, and recovery. The panel concludes that in so far as the limited clinical data recorded for Groups A–D permit, these cases conform to generally accepted criteria for the clinical diagnosis of Guillain-Barré syndrome, and the four groups fall into a qualitative gradient from A, the most extensive, to D, the least motor involvement.

Regarding confirmation of diagnosis by a neurologist, there is a slight downward trend in frequency, from 77.6 per cent (Group A) to 65.2 per cent (Group D). Similarly, there is a downward trend, from 89.8 per cent to 78.3 per cent, in the frequency of lumbar punctures. Such slight trends seem wholly understandable in that the patients with less extensive or life threatening illnesses may have been less prone to seek specialist consultation. Interestingly, among those cases in Groups A–D in which lumbar punctures were performed, no downward trend appears in the proportion showing elevated spinal fluid protein concentrations. Therefore, these data, limited though they are, tend to confirm the preceding conclusion that a high proportion of the cases in Groups A–D conform to generally accepted criteria of Guillain-Barré syndrome. This conclusion is the more remarkable because of the distinctive epi-

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demiologic patterns that will be reported in an ensuing section between Groups A and B on the one hand and Groups C and D on the other.

The low frequencies of positive findings for the cases in Group E fully justify the decision to classify them as "insufficient." It is quite possible that some may have been bona fide cases; 4.9 per cent had respiratory impairment and 17.2 per cent had cranial nerve involvement and one fourth had elevated spinal fluid protein concentration in the absence of increased cells, but as can be seen by examining Appendix tables C-1 and C-2, the essential clinical data was recorded as "unknown" or even "negative" in such a high proportion of cases that no logical alternative but exclusion of the cases was open to the panel. One small point deserves mention. Among the 47.5 per cent of cases in Group E in which a lumbar puncture was performed, only 56.9 per cent showed elevated spinal fluid protein concentration, a figure considerably lower than the approximately 80 per cent average for Groups A–D. Therefore, it is reasonable to conclude that Group E includes some and possibly a high proportion of non-specific cases.

### *Vaccination data*

Two distinct sources of numbers of vaccinations performed were available: one was the weekly and monthly reports collected routinely by the National Influenza Immunization Program (NIIP), the other was the Health Interview Survey conducted by the National Center for Health Statistics (16). Schonberger et al. (9) describe the reporting procedures of the former:

> 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. 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. . . . 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. . . . [The] weekly reports of vaccinations were . . . adjusted to reflect the total numbers of reported vaccinations . . . (9, p. 107).

The final adjusted weekly totals of vaccinations reported during the program between October 1 and December 16, 1976 are given in Appendix B.

The weekly report of the National Health Survey describes the methods and definitions used in collecting the data on the vaccinations performed:

> The data . . . are based on information collected in the Health Interview Survey (HIS) . . . Each week a probability sample of households representing the civilian non-institutionalized population of the United States is interviewed by trained personnel of the US Bureau of the Census. Interviewing is done continuously in a weekly sample of about 800 households. . . .
>
> *Flu shot*—Vaccination received for the purpose of preventing any type of influenza including A/Victoria, the A/New Jersey (Swine), and the B/Hong Kong strains (16).

Appendix B compares the data on swine influenza vaccinations collected by this continuing survey with the adjusted reports collected by the National Influenza Immunization Program.

The panel reasoned that there were certain limitations in both sources of data that were intrinsic to their basic methodology. The weekly reports from the states comprised the total counts that had accumulated in the National Influenza Immunization Program centers in each state by the reporting dates. In as much as there were involved a large number of project groups, city and county health officers, hospital directors in some states, as well as practicing physicians, some lag or under-reporting was unavoidable, particularly in the early stages of the program.

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A compensatory over-reporting could be anticipated later in the program as delayed reports came in. The monthly reports were presumably designed in part to pick up this "slack" as well as provide more detailed data. Indeed, Schonberger et al. (9) state that the monthly reports from the states continued for a full six months after the moratorium was initiated. From these late reports an additional number of vaccinations ("about 4 per cent") were added. No data made available to the panel, however, revealed any effort to correct or adjust the weekly reports from the state for the presumed early lag and later compensatory over-reporting.

On the other hand, the National Health Survey was presumably relatively free of this reporting lag because the interviewers were collecting current information each week. A certain small systematic error due to memory loss or other causes of under-registration can be presumed to have occurred.

The total estimated number of "swine flu shots" reported by the National Health Survey from early October to mid-December, 1976 was 40,575,000. The total vaccinations reported by the Centers for Disease Control during the program was 43,327,000. (This number excludes Puerto Rico, the Virgin Islands, Guam, and the Trust Territories.) The figure of 43,327,000 was accepted by the panel as the best available estimate of the total vaccinations performed in the civilian population of the United States during the program.

Since the National Health Survey data were believed to better reflect the weekly progress of the program, these data have been adjusted by the factor 1.068 (43,327/40,575) to provide the denominators for calculating weekly rates and person-weeks of observation among both vaccinated and unvaccinated populations (Appendices B and D).

### *Adequacy of surveillance of vaccinated and unvaccinated cases*

The panel was particularly alert to possible variation in the thoroughness and quality of the surveillance in vaccinated compared with unvaccinated cases. Although in their requests to neurologists and other physicians, and in their searches of hospital records, the state epidemiologists were urged to secure reports of *all* cases, the possibility that factors of bias were introduced had to be examined. In view of the multiplicity and diversity of reporting sources and the great public concern about the swine influenza vaccine, more attention might have been focused on patients who had been vaccinated, and more interest might have been directed to those cases with extensive motor involvement than to those with only limited paresis or paralysis. It is possible also that knowledge of recent vaccination and severity of disease might have influenced patients in seeking medical care.

Two quite separate questions regarding this problem were considered: 1) How completely and consistently were *all* cases discovered? And 2), once reported, how adequately were they investigated? The first is a difficult question to answer from the data available to the panel and is best discussed after all the analytic data have been presented (see below). The second question, namely the thoroughness of investigation after reporting, can be approached through an internal comparison of the recorded data. This is summarized in table 4.

The 944 cases comprising this study were divided into 504 vaccinated cases (53.4 per cent) and 440 unvaccinated cases (46.6 per cent). The proportionate distribution of vaccinees among each of the groups A–E varied only within the range of random chance, and there is therefore no evidence to suggest that

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TABLE 4

*Cases of Guillain-Barré syndrome in the United States: per cent of positive findings of muscle areas affected, clinical characteristics and other features supportive of diagnosis, by groups according to extent of motor involvement and vaccination status (onsets from October 1, 1976 through January 31, 1977)**

| | Cases grouped by extent of motor involvement† | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | A | | B | | C | | D | | E | |
| | Vaccinated $N = 158$ | Unvaccinated $N = 145$ | Vaccinated $N = 162$ | Unvaccinated $N = 115$ | Vaccinated $N = 89$ | Unvaccinated $N = 84$ | Vaccinated $N = 32$ | Unvaccinated $N = 37$ | Vaccinated $N = 63$ | Unvaccinated $N = 59$ |
| % of vaccinated | 31.3 | | 32.1 | | 17.7 | | 6.3 | | 12.5 | |
| % of unvaccinated | | 33.0 | | 26.1 | | 19.1 | | 8.4 | | 13.4 |
| % involvement of motor areas | | | | | | | | | | |
| Respiratory | 100.0 | 100.0 | | | | | | | 4.8 | 6.8 |
| Cranial | 75.3 | 62.8 | 68.5 | 55.7 | | | | | 14.3 | 20.3 |
| Trunk | 83.5 | 80.0 | 60.5 | 68.7 | | | | | 6.3 | 3.4 |
| 3–4 extremities | 95.6 | 94.5 | 85.2 | 86.1 | 100.0 | 100.0 | | | 15.9 | 8.5 |
| 1–2 extremities | 73.4 | 59.3 | 70.4 | 67.0 | 57.3 | 61.9 | 100.0 | 100.0 | 19.0 | 23.7 |
| % with clinical characteristics | | | | | | | | | | |
| Progressive motor weakness | 97.5 | 99.3 | 97.5 | 96.5 | 94.4 | 100.0 | 96.9 | 100.0 | 33.3 | 33.9 |
| Bilateral involvement | 98.1 | 96.6 | 91.4 | 98.3 | 97.8 | 91.7 | 100.0 | 100.0 | 22.2 | 32.2 |
| Lower motor neuron signs | 93.0 | 89.7 | 80.9 | 89.6 | 87.6 | 86.9 | 90.6 | 83.8 | 12.7 | 22.0 |
| % with other features supportive of diagnosis | | | | | | | | | | |
| Seen by neurologist | 72.8 | 82.8 | 69.8 | 80.0 | 66.3 | 76.2 | 62.5 | 67.6 | 27.0 | 33.9 |
| Lumbar puncture done | 91.1 | 88.3 | 88.3 | 91.3 | 75.3 | 86.9 | 71.9 | 83.8 | 44.4 | 50.8 |
| Lumbar puncture positive ‡ | 89.6 | 73.4 | 86.0 | 78.1 | 74.6 | 76.7 | 91.3 | 74.2 | 50.0 | 63.3 |

* See Appendix tables C-1 and C-2 for case counts.
† See table 2 for criteria defining groups A–E.
‡ Positive: cerebrospinal fluid protein ≥50 mg/100 ml.

more attention was directed to the investigation of vaccinated cases with more extensive motor involvement. In addition, the consistency of recording clinical data for each of the groups A–D was notable since only minor variations well within the range of random chance were observed here too. No trend of even slightly higher frequencies of recorded positive findings appeared among the vaccinees. The panel concludes that once a case was reported as Guillain-Barré syndrome it was investigated without evident bias due to vaccination status. Therefore, the panel proceeded with increased confidence in the validity of the epidemiologic comparisons it has made.

## RESULTS

### *Incidence of vaccinated cases*

The numbers of vaccinated cases by week of onset and extent of motor involvement are shown in table 5. Few cases occurred during the early weeks of October, when the cumulative numbers of vaccinees remained small, but, as the vaccinated population increased, the incidence of new cases followed upward. The highest numbers of cases occurred during late November and early December, after which the incidence fell rather abruptly, but continued through January.

Table 5 describes the traditional epidemic curve as it unfolded over the cal-

TABLE 5

*Guillain-Barré syndrome in the United States: vaccinated cases by calendar week of onset and extent of motor involvement, October 2, 1976 through January 31, 1977*

| Week ending | | Cumulated vaccinees (person-weeks × $10^6$)* | No. of cases grouped by extent of motor involvement† | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | | | A | B | C | D | E | |
| October | 10‡ | 1.3 | | 1 | | | | 1 |
| | 17 | 3.1 | 1 | | | | | 1 |
| | 24 | 6.5 | 4 | 3 | 1 | | 3 | 11 |
| | 31 | 11.1 | 11 | 4 | 4 | | 1 | 20 |
| November | 7 | 16.2 | 13 | 8 | 3 | 1 | 6 | 31 |
| | 14 | 22.3 | 15 | 10 | 4 | 3 | 3 | 35 |
| | 21 | 28.5 | 15 | 21 | 9 | 1 | 2 | 48 |
| | 28 | 33.3 | 20 | 22 | 6 | 4 | 9 | 61 |
| December | 5 | 37.5 | 21 | 14 | 13 | 1 | 4 | 53 |
| | 12 | 40.9 | 17 | 29 | 14 | 5 | 6 | 71 |
| | 19§ | 43.0 | 11 | 23 | 9 | 4 | 14 | 61 |
| | 26 | 43.3 | 6 | 9 | 7 | 2 | 3 | 27 |
| January | 2 | 43.3 | 9 | 6 | 7 | 2 | 1 | 25 |
| | 9 | 43.3 | 6 | 8 | 2 | 4 | 4 | 24 |
| | 16 | 43.3 | 4 | 2 | 5 | 2 | 3 | 16 |
| | 23 | 43.3 | 3 | 1 | 3 | 2 | 1 | 10 |
| | 31‡ | 49.5 | 2 | 1 | 2 | 1 | 3 | 9 |
| Total | | 509.7 | 158 | 162 | 89 | 32 | 63 | 504 |

* See Appendix D for computation of cumulative vaccinees.

† See table 2 for criteria defining Groups A–E.

‡ October 2–10 = 9-day interval; January 24–31 = 8-day interval; cases occurring on October 1 classed as unvaccinated.

§ Moratorium declared on December 16 and nationwide surveillance initiated.

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endar weeks, but incidence rates have not been calculated because they are difficult to interpret due to the changing population exposed to risk. Internal comparisons among the five groups by extent of motor involvement, however, are valid and helpful in the future analysis. Groups A and B rise and fall together. Variations between them from week to week do not exceed random chance. This close similarity justifies combining the two groups into a single group to be termed the "extensive" cases.

Superficially, Groups C and D appear to rise and fall in an approximately similar fashion to Groups A and B. The total numbers of cases are appreciably smaller, so that wider chance fluctuations can be expected. On more careful scrutiny, however, there is a clear if only slight trend for a proportionately higher frequency of cases in January. This trend will be brought out more clearly in later analyses. As with Groups A and B, the two curves for Groups C and D are sufficiently synchronous to combine them into a single group to be termed the "limited" cases.

The incidence of cases in Group E, "insufficient" over the four-month period seems similar to the curves for Groups C and D.

A more meaningful presentation of the incidence of vaccinated cases is shown in table 6, in which the onsets of cases are grouped according to intervals following

TABLE 6

*Guillain-Barré syndrome in the United States: vaccinated cases by 7-day intervals following vaccination and extent of motor involvement (onsets from October 2, 1976 through January 31, 1977)*

| Interval from vaccination | | Vaccinees (person-weeks × $10^6$)* | No. of cases grouped by extent of motor involvement† | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| 7-day interval | Days | | A | B | C | D | E | |
| 1 | 1–7 | 43.3 | 10 | 12 | 16 | 3 | 12 | 53 |
| 2 | 8–14 | 43.3 | 57 | 50 | 10 | 4 | 14 | 135 |
| 3 | 15–21 | 43.3 | 42 | 49 | 17 | 3 | 14 | 125 |
| 4 | 22–28 | 43.3 | 15 | 14 | 10 | 5 | 5 | 49 |
| 5 | 29–35 | 43.3 | 7 | 14 | 9 | 4 | 3 | 37 |
| 6 | 36–42 | 43.3 | 7 | 5 | 8 | 1 | 2 | 23 |
| 7 | 43–49 | 43.1 | 6 | 5 | 3 | 3 | 3 | 20 |
| 8 | 50–56 | 41.3 | 4 | 6 | 3 | 3 | 4 | 20 |
| 9 | 57–63 | 38.1 | 1 | 3 | 6 | 1 | 2 | 13 |
| 10 | 64–70 | 33.9 | 4 | | 2 | 1 | 1 | 8 |
| 11 | 71–77 | 29.3 | 1 | 2 | 2 | 1 | 2 | 8 |
| 12 | 78–84 | 23.3 | 1 | 1 | 2 | | | 4 |
| 13 | 85–91 | 17.0 | 1 | | | 2 | 1 | 4 |
| 14 | 92–98 | 11.8 | | | | | | 0 |
| 15 | 99–105 | 7.1 | 1 | 1 | 1 | 1 | | 4 |
| 16 | 106–112 | 3.4 | 1 | | | | | 1 |
| 17 | 113–119 | 1.3 | | | | | | 0 |
| 18 | 120–122‡ | 0.2 | | | | | | 0 |
| Total | | | 158 | 162 | 89 | 32 | 63 | 504 |
| Intervals 9–18 | | 165.4 | 10 | 7 | 13 | 6 | 6 | 42 |

* See Appendix E for computation of person-weeks × $10^6$ of vaccinees at risk.

† See table 2 for criteria defining Groups A–E.

‡ 3-day period.

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vaccination. This table shows a distribution of onsets similar to that of incubation periods following simultaneous exposure of a defined population to a single exposure or common source. Note that the total population of vaccinees, 43.3 million, is exposed to risk for the first six 7-day periods, after which the numbers of vaccinees at risk declines progressively to extinction by the 18th interval. The reason for this decline is simply that the surveillance program terminated on January 31, 1977, and the last vaccinations were performed on the day the moratorium was declared—December 16. Therefore, those vaccinated on that last day were followed for only 47 days or 6.7 weeks. Those who were vaccinated earlier were under observation for longer periods of time but only those vaccinated in October were observed for as much as 13 weeks or longer. The computation of the numbers of vaccinees exposed to risk for each 7-day period following vaccination is shown in Appendix E.

Again, as in table 5, the frequencies of cases in Groups A and B, the "extensive" cases, are closely synchronous throughout the observation period. Counts are low during the first 7-day interval, rise rapidly to a peak during the second period, begin to fall during the third period, and then drop progressively to a low level by the end of the eighth 7-day period.

Although the total number of cases in Group C is only 89, considerably less than the number in either Group A or B, the incidence in Group C during the first 7-day interval is 16, higher than the 10 and 12 cases observed in Groups A and B, respectively. No peaking of cases in the second and third 7-day intervals occurred, but by the fifth interval a slow decline begins and continues out to the twelfth interval.

The total number of cases in Group D, 32, is so small as to make analysis of changes from interval to interval precarious. Only three cases were recorded in the first 7-day interval, a flat incidence continued through the first nine intervals, with an average of only three cases per week. As we discussed, the frequencies of cases in Groups C and D seem sufficiently similar to justify combining them into a single "limited" case group for a somewhat more stable statistical analysis.

The incidence rates per million person-weeks by 7-day intervals from vaccination among the "extensive" (A + B) and "limited" (C + D) motor involvement groups as well as the "insufficient" (E) group are shown in table 7 and figure 1. The sharpness of the peak incidence for the "extensive" cases during the second 7-day interval and the rapid decline in the fourth 7-day interval is apparent. Equally notable is the absence of a discernible peak in incidence for the "limited" cases, as already noted. The curve for the "insufficient" cases is slightly elevated during the first three 7-day intervals, without indication of a peak, then the curve declines to a steady low level.

The panel believes that the sharp peak observed in the second and third 7-day interval for the "extensive" cases and the absence of such a peak for the "limited" cases is the most important new finding in this study. Its significance will be discussed after further data are presented.

### *Incidence of unvaccinated cases*

The numbers of unvaccinated cases by extent of motor involvement are shown in table 8 according to onset of neurologic symptoms in calendar weeks from October 1, 1976 to January 31, 1977. Computation of the estimated population of unvaccinated persons at risk is given in Appendix table E. When the vaccination program got underway in early October, the beginning population was 151.2 million unvaccinated persons, 18 years of age and older. The population of unvaccinated persons progressively declined with the increase in vaccinees and reached the

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TABLE 7

*Guillain-Barré syndrome in the United States: incidence rates in 7-day intervals following vaccination in groups according to extent of motor involvement (onsets from October 2, 1976 through January 31, 1977)*

| Interval from vaccination | | Incidence rates (person-weeks × $10^6$), by extent of motor involvement* | | |
|---|---|---|---|---|
| 7-day interval | Days | "Extensive" | "Limited" | "Insufficient" |
| 1 | 1–7 | 0.51 | 0.44 | 0.28 |
| 2 | 8–14 | 2.47 | 0.32 | 0.32 |
| 3 | 15–21 | 2.10 | 0.46 | 0.32 |
| 4 | 22–28 | 0.67 | 0.35 | 0.12 |
| 5 | 29–35 | 0.48 | 0.30 | 0.07 |
| 6 | 36–42 | 0.28 | 0.21 | 0.05 |
| 7 | 43–49 | 0.26 | 0.14 | 0.07 |
| 8 | 50–56 | 0.24 | 0.15 | 0.10 |
| Intervals 9–18 | 57–122 | 0.10 | 0.11 | 0.04 |

* "Extensive" combines Groups A and B; "limited" combines Groups C and D; "insufficient" consists of Group E; see table 2.

level of 107.9 million persons by mid-December.

In order to interpret the data in table 8 quantitatively, weekly incidence rates per million person-weeks were calculated. To minimize fluctuations due to random variation, combined data are shown for bi-weekly periods and Groups A + B and C + D. The incidence rates are shown in table 9 and graphed in figure 2. From the

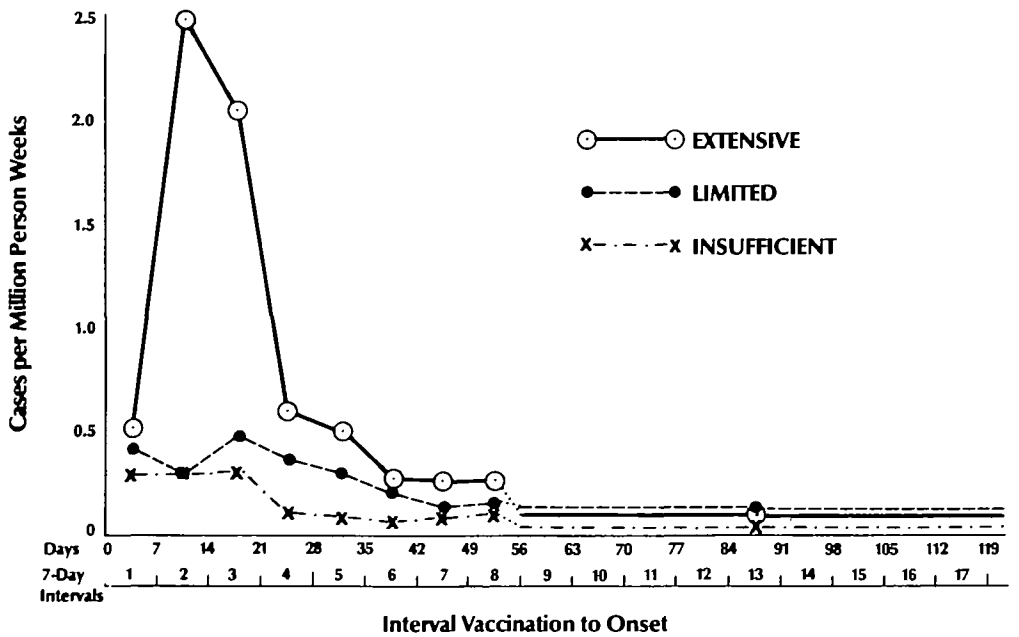


FIGURE 1. Guillain-Barré syndrome in the United States: incidence rates (person-weeks × $10^6$) among vaccinated cases by 7-day interval following vaccination and extent of motor involvement (onsets from October 2, 1976 through January 31, 1977).

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TABLE 8

*Guillain-Barré syndrome in the United States: unvaccinated cases by week of onset of neurologic symptoms and extent of motor involvement, October 1, 1976 through January 31, 1977*

| Onset week ending | Estimated population (person-weeks × $10^6$) | No. of cases grouped by extent of motor involvement* | | | | | Total |
|---|---|---|---|---|---|---|---|
| | | A | B | C | D | E | |
| October 10† | 214.7 | 15 | 17 | 7 | 6 | 8 | 53 |
| 17 | 148.1 | 9 | 10 | 7 | 3 | 5 | 34 |
| 24 | 144.7 | 8 | 4 | 10 | 2 | 7 | 31 |
| 31 | 140.1 | 11 | 11 | 5 | 2 | 1 | 30 |
| November 7 | 134.9 | 8 | 12 | 7 | 3 | 4 | 34 |
| 14 | 128.9 | 12 | 7 | 5 | 1 | 3 | 28 |
| 21 | 122.7 | 13 | 6 | 6 | 1 | 4 | 30 |
| 28 | 117.8 | 11 | 10 | 6 | 1 | 6 | 34 |
| December 5 | 113.6 | 11 | 10 | 7 | 3 | 7 | 38 |
| 12 | 110.2 | 6 | 9 | 6 | 3 | 4 | 28 |
| 19 | 108.2 | 8 | 5 | 10 | 2 | 2 | 27 |
| 26 | 107.9 | 8 | 1 | 1 | 1 | 2 | 13 |
| January 2 | 107.9 | 12 | 1 | 1 | 2 | 3 | 19 |
| 9 | 107.9 | 5 | 3 | 1 | 1 | 1 | 11 |
| 16 | 107.9 | 2 | 6 | 1 | 3 | 1 | 13 |
| 23 | 107.9 | 2 | 1 | 3 | 2 | | 8 |
| 31† | 123.3 | 4 | 2 | 1 | 1 | 1 | 9 |
| Total | | 145 | 115 | 84 | 37 | 59 | 440 |
| Oct. 1–Dec. 19 | 1483.9 | 112 | 101 | 76 | 27 | 51 | 367 |

* See table 2 for criteria defining Groups A–E.

† October 1–10 = 10 days; January 24–31 = 8 days.

beginning of October through mid-December, the rates for "extensive" cases (A + B) fluctuate in the narrow range from 0.11 to 0.18, after which the rates drop progressively to the low point of 0.04 during the last two weeks of January. The incidence rates for the "limited" cases (C + D) fluctuate from 0.05 to 0.10 from October to mid-December, after which they drop to the level of 0.03 through the last half of December and all of January.

One of the remarkable features of the data in table 9 and figure 2 is the essential constancy of the observed rates over the period from October 1 to December 19, for both the "extensive" and "limited" groups. The mean rates, 0.14 and 0.07, respectively, for this slightly more than 11-week period are shown in figure 2. Although there may be a suggestion of slight upward trends, the variations over this period are not statistically significant.

Equally remarkable are the sharp declines in incidence during the last two weeks of December and all of January. These are highly significant statistically. They are so abrupt and marked to require special attention. They are believed to be artifacts resulting from progressive under-reporting, as will be discussed in later sections of this paper.

### *The search for baseline data*

Studies of the epidemiology of Guillain-Barré syndrome have been rather limited in scope. Most reports consist of a collection of cases observed by one or a group of neurologists in which the clinical features may be accurately described but the population from which the cases have been drawn is unknown. The general

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TABLE 9

*Guillain-Barré syndrome in the United States: unvaccinated cases, biweekly incidence rates in groups with "extensive" and "limited" paralysis, October 1, 1976 through January 31, 1977*

| Two-week periods ending | Population at risk (person-weeks × $10^6$) | Incidence rates (person-weeks × $10^6$), by extent of motor involvement* | |
|---|---|---|---|
| | | A + B "Extensive" | C + D "Limited" |
| October 10† | 214.7 | 0.15 | 0.06 |
| 24 | 292.8 | 0.11 | 0.08 |
| November 7 | 275.0 | 0.15 | 0.06 |
| 21 | 251.6 | 0.15 | 0.05 |
| December 5 | 231.4 | 0.18 | 0.07 |
| 19 | 218.4 | 0.13 | 0.10 |
| January 2 | 215.8 | 0.10 | 0.02 |
| 16 | 215.8 | 0.07 | 0.03 |
| 31‡ | 231.2 | 0.04 | 0.03 |
| Oct. 1–Jan. 31 | 2146.7 | 0.12 | 0.06 |
| Oct. 1–Dec. 19 | 1483.9 | 0.14 | 0.07 |

* See table 2 for criteria defining groups A + B and C + D.
† 10-day period.
‡ 15-day period.

impression from such studies is that this syndrome is an uncommon but widespread disease, showing no clear seasonal or geographic variation but a moderately increased prevalence among adults compared with children and adolescents. Schonberger et al. (17) have reviewed its epidemiology and have found eight population-based studies, including the present study, in which some semblance of incidence rates could be made. Only four of these were based on 40 or more

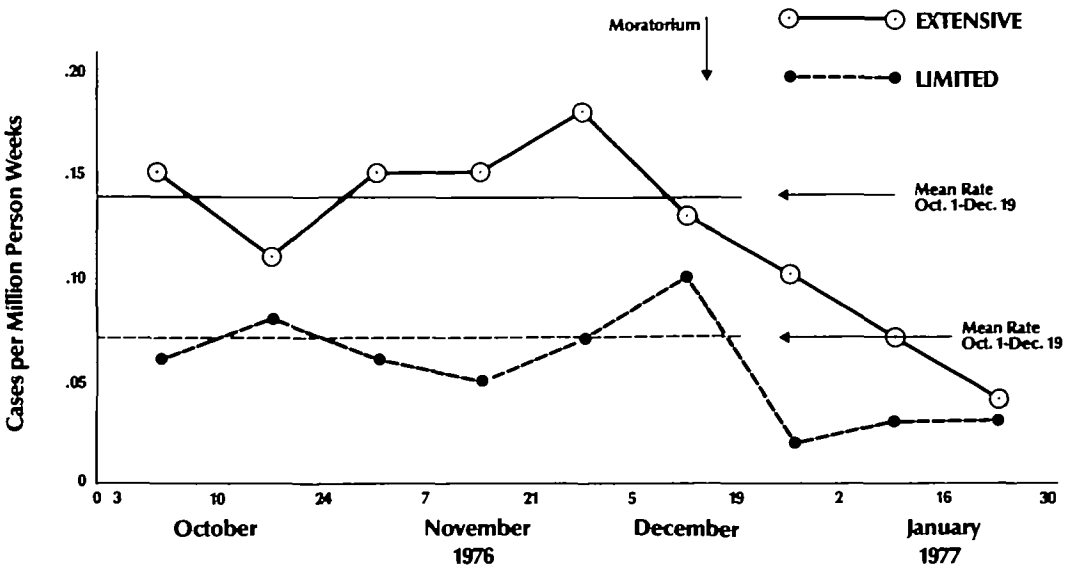


FIGURE 2. Guillain-Barré syndrome in the United States: bi-weekly incidence rates (person-weeks × $10^6$) among unvaccinated cases with onsets from October 1, 1976 through January 31, 1977.

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cases. The average annual incidence rates ranged from 0.75 to 1.7 per 100,000 population. These rates transform to 0.14 and 0.33 per million person-weeks. All of these studies presumably included whole populations of widely varying characteristics. The rates were not corrected for adults 18 years of age or over and the cases were not classified into "extensive" and "limited" motor involvement. Therefore, none of these studies without further modification can be considered comparable to the present problem.

The Olmsted County, Minnesota, study (18–20) seemed the most applicable because of the superb and consistent clinical diagnostic criteria used by the Mayo Clinic staff throughout the study and because the county consisted of a reasonably stable and presumably representative population. Dr. Kurland and his staff were kind enough to add an additional five years of experience to their data, to adjust their cases and population estimates to adults 18 years of age and over, and to classify them by extent of motor involvement according to the criteria developed in the present study (21). These efforts produced incidence rates per million person-weeks of 0.28 for "extensive" cases and 0.16 for "limited" cases. In spite of the small total numbers involved and the long time span over which the study was conducted, the panel believes these corrected figures to be among the best available for comparative studies.

Another population-based study believed to be particularly applicable to the present comparison was conducted in Michigan by Breman and Hayner (22). They made an intensive retrospective and continuing search for reports throughout Michigan among all reasonable sources. The population "at risk" 18 years of age and over was estimated at slightly more than six million persons. The period of the study spanned 10 months: three months—July–September 1976—preceding the vaccination program; four months—October 1976–January 1977—embracing the period of the active vaccination program and the ensuing national surveillance; and three more months—February–April 1977—following the termination of active national surveillance. The rate per million person-weeks for "extensive" cases was 0.27 and that for "limited" cases 0.10. No seasonal variation in incidence was found. A summary of the Michigan data analyzed by us by extent of motor involvement is presented in Appendix F.

The results of the Olmsted County, Minnesota, and Michigan studies are compared in table 10 with the data for unvaccinated cases in the present study. For "extensive" cases, the Olmsted County and Michigan rates are approximately equal—0.28 and 0.27, respectively. Both rates are essentially double the rate of 0.14 observed in the present study from October 1 to December 19, 1976. For the "limited" cases, the rates are as follows: Olmsted County, 0.16; Michigan, 0.10; and the present study, 0.07.

The similarities of the Olmsted County and Michigan rates reinforce each other. The rates for "extensive" cases are nearly identical and the difference in rates for "limited" cases is not statistically significant. Therefore, it seems reasonable to combine the data from these two small but searching studies to obtain one set of estimates for baseline rates, to be termed the "higher" estimates. These become 0.275 for "extensive" cases and 0.13 for "limited" cases.

The data for the unvaccinated cases in the present study are distinctly lower by a factor of approximately 50 per cent. They are based on considerably larger numbers of cases and therefore have more statistical stability, but the data were derived from voluntary reports in an emergency nationwide surveillance and cannot be considered nearly as adequate from the point of view of thoroughness of

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TABLE 10

*Guillain-Barré syndrome in the United States: incidence rates (person-weeks × $10^6$) in population-based studies according to extent of motor involvement*

| Study | No. of cases by extent of motor involvement* | | Incidence rates (person-weeks × $10^6$)* | |
|---|---|---|---|---|
| | "Extensive" | "Limited" | "Extensive" | "Limited" |
| Olmsted County, Minnesota, 1935–1980† | 35 | 19 | 0.28 | 0.16 |
| Michigan, July 1, 1976–April 30, 1977‡ | 58 | 21 | 0.27 | 0.10 |
| Total or mean rate | 93 | 40 | 0.275 | 0.13 |
| United States unvaccinated cases (present study), October 1–December 19, 1976 | 213 | 103 | 0.14 | 0.07 |

* Based on cases and population 18 years of age and older.

† Source: references 19–21.

‡ Source: reference 23. See Appendix F for analysis of Michigan data.

case ascertainment and clinical evaluation. In as much as the methods of surveillance for these cases were apparently quite similar to those for the vaccinated cases in the present study, an intrinsic comparability is implied. Thus, these unvaccinated rates (0.14 for "extensive" and 0.07 for "limited" cases) may be considered as another set of baselines to be termed the "lower" estimates.

### *The lognormal distribution*

The incidence curve for the "extensive" paresis group (figure 1) is skewed to the right in a form similar to the distribution of incubation periods in many if not all point source epidemics. Sartwell (23) has shown that such curves are quite accurately described mathematically by the lognormal distribution. In fact, he has fitted such a curve to the preliminary Guillain-Barré syndrome data published in the *Morbidity Mortality Weekly Report* of February 11, 1977 (24).

A lognormal curve has been fitted to the present data for the "extensive" cases and is shown in figure 3. (See Appendix G.) In calculating the theoretical curve, the assumption was made that the observed incidence rates represented a composite of two factors, one the average background endemic incidence plus the additional effect that could be attributed to the swine influenza vaccine. In choosing which background rate to use, the mean rate for unvaccinated cases from October 1 to December 19, 0.14, was selected as reasonable and conservative. The theoretical curve has been calculated in 3.5-day intervals to provide greater smoothness.

The resulting theoretical curve starts near 0 during the first 3.5-day period after vaccination, rises sharply to a peak in the last half of the second 7-day interval and then falls in a rapidly declining smooth curve becoming indistinguishable from 0 by the end of the eighth 7-day interval.

The close approximation of the observed rates during the first six 7-day intervals is notable. During the seventh and eighth 7-day intervals, the observed rates plateau at a level of 0.26–0.27, after which the numbers of cases become so small and the numbers of person-weeks of vaccinees exposed to risk dwindle so rapidly that the data for the ninth to seventeenth 7-day intervals must be combined. The resulting rate for the total of 17 "extensive" cases that occurred during this

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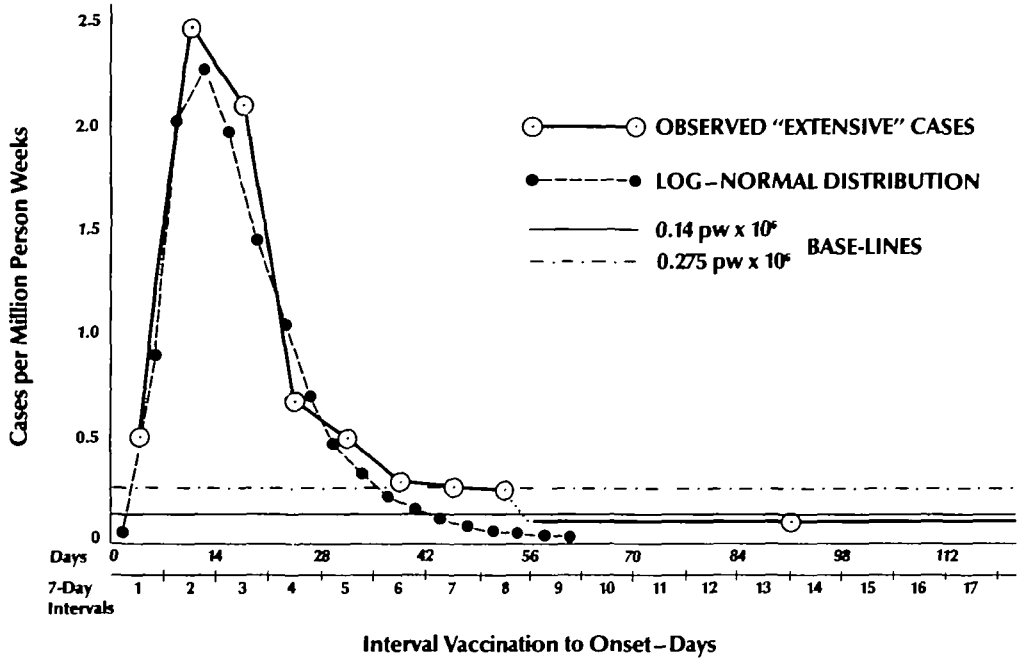


FIGURE 3. Guillain-Barré syndrome in the United States: incidence rates (person-weeks × $10^6$) among cases with "extensive" motor involvement by 7-day intervals following vaccination compared with a log-normal distribution (onsets from October 2, 1976 through January 31, 1977).

tail of the curve is 0.10, slightly but not significantly below the baseline of 0.14.

### *Cohort analysis*

So far in this report, the data on vaccinated cases have been merged together according to interval after vaccination, regardless of date of vaccination. The question may be asked whether the adequacy of reporting of vaccinated cases remained constant throughout this period. The full surveillance network was not established until December 17, and it continued with varying degrees of intensity for a period of at least six months (9). It seems possible that the completeness of case ascertainment might have varied over the period of the study, October 1, 1976–January 31, 1977.

This question, which was raised earlier, can now be approached by means of a cohort analysis, as shown in Appendix tables H-1 and H-2. The vaccinees have been grouped into individual cohorts by week of vaccination, and the "incubation period" curves in 7-day intervals are thus shown separately. For some of the early weeks in October and the last weeks of the program in December, the number of vaccinees is so small as to yield only a few cases. Nevertheless, the cases with "extensive" motor involvement (Groups A + B) consistently concentrate in the second and third 7-day interval. To obtain sufficient numbers of cases to calculate incidence rates having some stability, these weekly cohorts have been combined into three groups, *early* (October 1–31), *middle* (November 1–21), and *late* (November 22–December 16). The *early* cohort was under observation completely for 13 weeks and partially for an additional 4.4 weeks; the *middle* cohort was under complete observation for 10.0 weeks and partially for 4.0 weeks more; the *late* cohort was observed completely for 6.0 weeks and partially for 4.3 weeks more. The denominator data for each co-

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TABLE 11

*Guillain-Barré syndrome in the United States: numbers of cases and incidence rates (person-weeks × $10^6$) among groups of cohorts immunized during early, middle and late periods of the National Influenza Immunization Program, by extent of motor involvement (onsets from October 2, 1976 through January 31, 1977)*

| Vaccination to onset | | No. of cases, by extent of motor involvement* | | | | | | Incidence rates (person-weeks × $10^6$), by extent of motor involvement* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | "Extensive" (A + B) cohorts | | | "Limited" (C + D) cohorts | | | "Extensive" (A + B) cohorts | | | "Limited" (C + D) cohorts | | |
| 7-day | Days | I | II | III | I | II | III | I | II | III | I | II | III |
| 1 | 1–7 | 8 | 6 | 8 | 4 | 4 | 11 | 0.59 | 0.34 | 0.66 | 0.29 | 0.23 | 0.91 |
| 2 | 8–14 | 31 | 44 | 32 | 3 | 5 | 6 | 2.28 | 2.49 | 2.64 | 0.22 | 0.28 | 0.50 |
| 3 | 15–21 | 28 | 37 | 26 | 8 | 9 | 3 | 2.06 | 2.09 | 2.15 | 0.59 | 0.51 | 0.25 |
| 4 | 22–28 | 12 | 14 | 3 | 3 | 5 | 7 | 0.88 | 0.79 | 0.25 | 0.22 | 0.28 | 0.58 |
| 5 | 29–35 | 6 | 8 | 7 | 6 | 4 | 3 | 0.44 | 0.45 | 0.58 | 0.44 | 0.23 | 0.25 |
| 6 | 36–42 | 1 | 5 | 6 | 3 | 4 | 2 | 0.07 | 0.28 | 0.50 | 0.22 | 0.23 | 0.17 |
| 7 | 43–49 | 8 | 1 | 2 | 2 | 2 | 2 | 0.59 | 0.06 | | 0.15 | 0.11 | |
| 8 | 50–56 | 5 | 4 | 1 | 4 | 0 | 2 | 0.37 | 0.23 | 0.09 | 0.29 | 0.00 | 0.13 |
| 9 | 57–63 | 3 | 1 | 0 | 5 | 2 | 0 | 0.22 | | | 0.37 | | |
| 10 | 64–70 | 2 | 2 | 0 | 1 | 2 | 0 | 0.15 | 0.06 | | 0.07 | 0.08 | |
| 11 | 71–77 | 2 | 1 | 0 | 3 | 0 | 0 | 0.15 | | | 0.22 | | |
| 12 | 78–84 | 2 | 0 | | 1 | 1 | | 0.15 | | | 0.07 | | |
| 13 | 85–91 | 1 | 0 | | 2 | 0 | | | | | | | |
| 14 | 92–98 | 0 | 0 | | 0 | 0 | | | | | 0.11 | | |
| 15 | 99–105 | 2 | | | 2 | | | 0.11 | | | | | |
| 16 | 106–112 | 1 | | | 0 | | | | | | | | |
| 17 | 113–119 | 0 | | | 0 | | | | | | | | |
| 18 | 120–122 | 0 | | | 0 | | | | | | | | |
| | Total | 112 | 123 | 85 | 47 | 38 | 36 | | | | | | |

* See table 2 for criteria defining groups A + B and C + D. Numbers of vaccinees and inclusive dates of vaccinations of each cohort: *early*, I—13.6 × $10^6$ person-weeks, October 1–31; *middle*, II—17.7 × $10^6$ person-weeks, November 1–21; *late*, III—12.1 × $10^6$ person-weeks, November 22–December 16.

hort is shown in Appendix table E, and the combined numbers of cases and incidence rates are shown in table 11. The incubation curves for the "extensive" cases in the three cohorts are shown in comparison with the lognormal curve for the total experience in figures 4–6. At the bottom of each figure is given the calendar weeks of the program. Each curve is placed in general relation to the time of occurrence of cases by charting the curves beginning in the median week of the cohort. Although not precise, the characterization of *early, middle,* and *late* is believed validly descriptive.

When comparing these curves two quite separate aspects need to be noted. First, the degree of concurrence during the first six 7-day intervals; and second, the position of the curve for the observed cases after the sixth interval in relation to the two baseline figures 0.275 and 0.14 that were discussed in the earlier section of this report.

To the first point, the observed curves for all three cohorts follow the lognormal curve almost identically. There is a slight tendency for the curves of the observed cases to be higher than the lognormal curve but this is to be anticipated because the lognormal curve was derived after subtracting the weekly baseline figure of 0.14 per million person-weeks. During the fourth 7-day interval the observed rate of the *late* cohort was low (0.25) but this deficit is fully compensated by the distinctly higher rates in the fifth and sixth 7-day interval and, therefore, may be disre-

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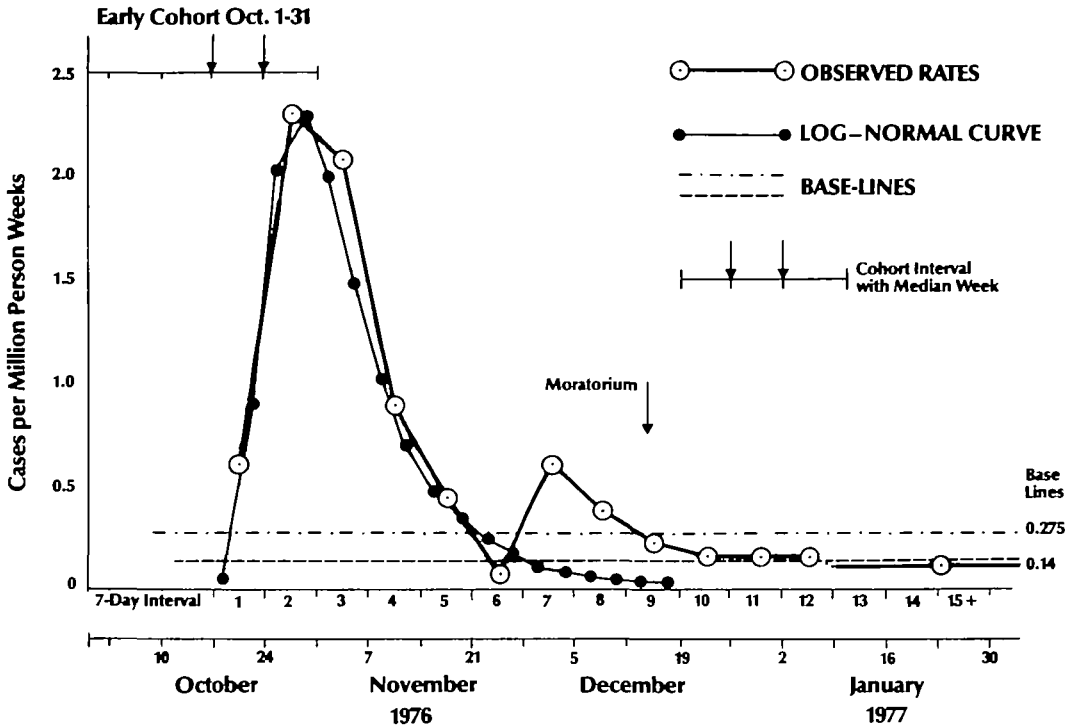


FIGURE 4. Guillain-Barré syndrome in the United States: incidence rates (person-weeks × $10^6$) among cases with "extensive" motor involvement by 7-day intervals following vaccination. *Early* cohort with vaccinations from October 1 to 31, 1976, with onsets from October 2, 1976 to January 31, 1977 compared with lognormal distribution for the total experience.

garded as a chance variation due to small numbers.

From the consistency of these findings, the panel concludes that the adequacy of case ascertainment for "extensive" vaccinated cases did not vary significantly during the 11-week program from October 1 to December 16 and considering the moderately high rates in the fifth and sixth weeks of the *late* cohort, case ascertainment appears to have continued at the same level into late December and early January. As a consequence, although the panel concluded from its study of unvaccinated cases (tables 8 and 9, and figure 2) that reporting declined rather abruptly after December 19, it does not find evidence of a similar decline in reporting of the "extensive" vaccinated cases.

Turning to the period from the seventh to eighteenth 7-day interval, only the *early* cohort was completely followed for as long as seven additional weeks. During the seventh and eighth week, the observed incidence rates rose above the baseline rates to 0.59 and 0.37, respectively. These rates were based on eight and five cases, respectively, and therefore are subject to considerable random variation. Adding the figures for the sixth, seventh, and eighth intervals together gives a total of 14 cases and an average weekly rate of 0.34 with a 95 per cent confidence limit of $\pm 0.18$, which is significantly different from the baseline of 0.14 but not the baseline of 0.275. Thus it is probable that the observed rates during the seventh and eighth 7-day interval are significantly elevated but the observation is a borderline one.

From the ninth 7-day interval onward,

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the observed incidence rates fall below the higher baseline figure of 0.275 and rapidly approximate the lower baseline of 0.14. During the tail of the curve after the twelfth 7-day interval, the rate is 0.11, slightly lower than the baseline of 0.14 but again this difference is not statistically significant.

The observed rates for the *middle* cohort fall below the baseline of 0.275 during the seventh 7-day interval and in no subsequent period do the rates exceed that baseline. After the eighth 7-day interval, the tail end of the curve levels off at 0.09.

The *late* cohort was observed for such a short time after the sixth 7-day interval that it contributed little additional information. The average rate for the short "tail" was again 0.09, based on only three cases.

The cohort study applied to the "limited" cases is shown in table 11 and figure 7. No pattern is discernible. The numbers for each 7-day interval are small and highly variable. No deviation appears in a consistent fashion. The *early* cohort fluctuates without apparent trend for the first nine 7-day intervals; the *middle* cohort does likewise for six intervals with only a single slight peak in the third week, and the *late* cohort shows a high incidence in the first interval with an irregular decline for the next five. The tails of each of the cohorts during the month of January decline to levels falling between the two baseline figures of 0.13 and 0.07.

### *Relative risks and attributable incidence*

In both the Schonberger et al. (9) and Langmuir (10) papers, relative risks were calculated using baseline estimates for reference denominators that were

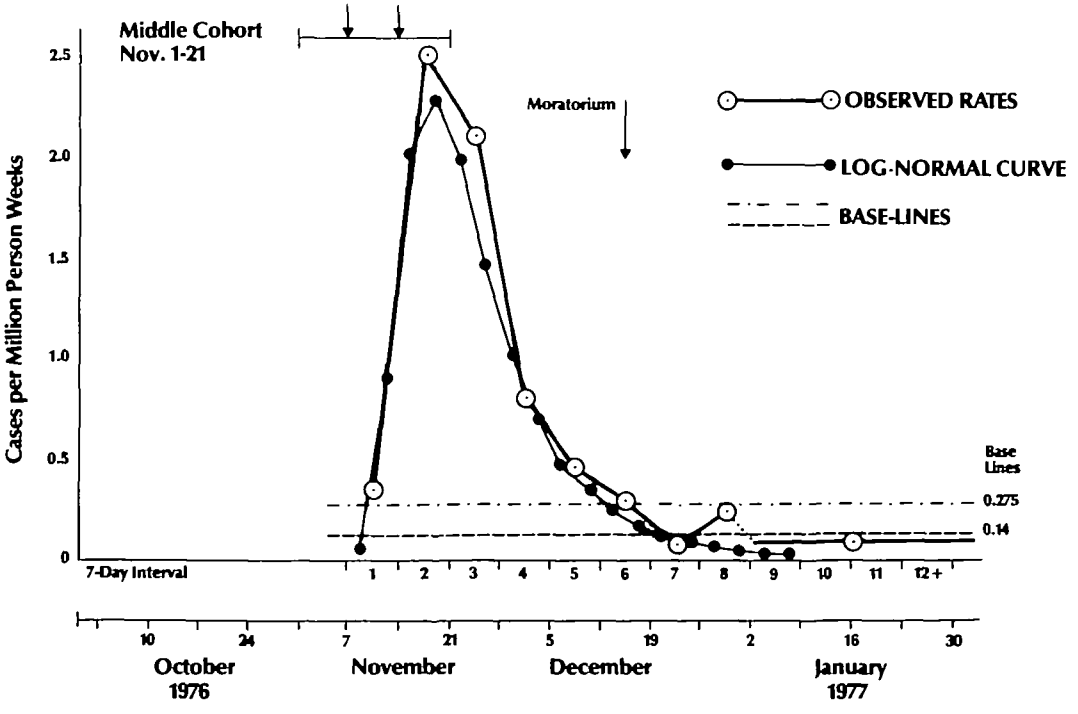


FIGURE 5. Guillain-Barré syndrome in the United States: incidence rates (person-weeks × $10^6$) among cases with "extensive" motor involvement by 7-day intervals following vaccination. *Middle* cohort with vaccinations from November 1 to 21, 1976, with onsets from November 2, 1976 to January 31, 1977 compared with lognormal distribution for the total experience.

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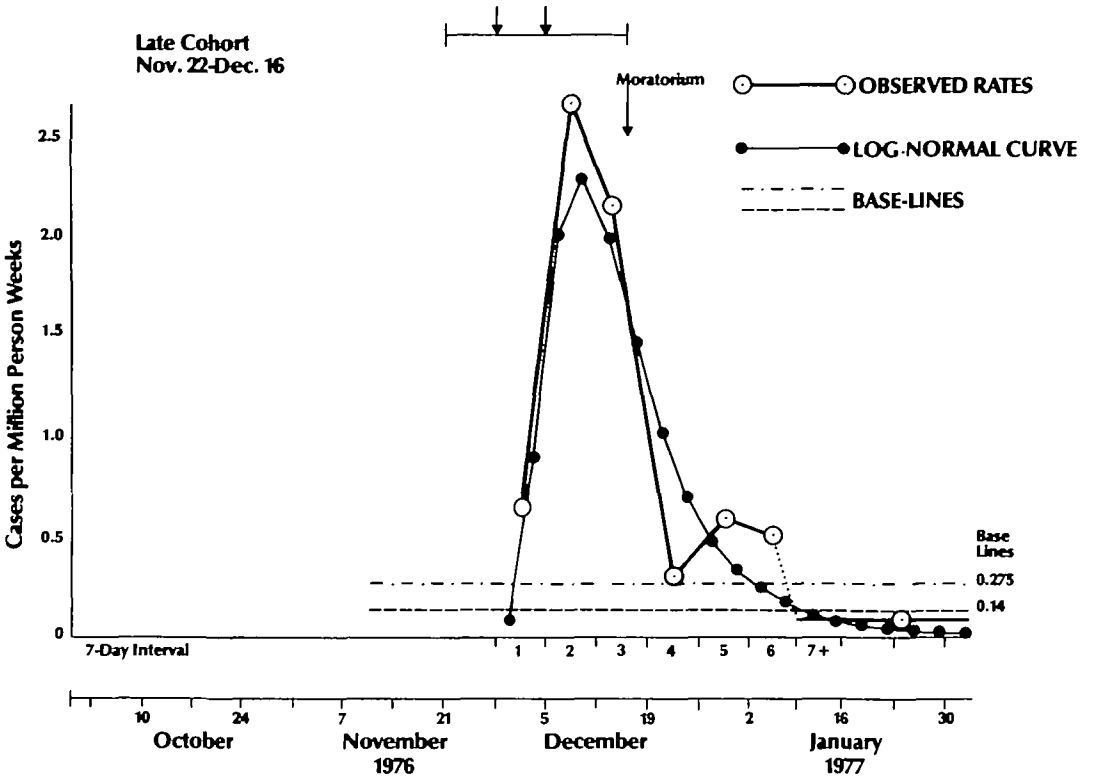


FIGURE 6. Guillain-Barré syndrome in the United States: incidence rates (person-weeks × $10^6$) among cases with "extensive" motor involvement by 7-day intervals following vaccination. *Late* cohort with vaccinations from November 22 to December 16, 1976, with onsets from November 23, 1976 to January 31, 1977 compared with lognormal distribution for the total experience.

thought, at the time, to be the best available. Recalculation of these ratios are now indicated taking into account the new findings: 1) the epidemiologically distinct pattern of the "extensive" cases; 2) the availability of two separate estimates of baselines specific for the extent of motor involvement; and 3) the radical change in incidence rates after the sixth 7-day interval resulting from the use of the weekly estimates of vaccinees based on the National Health Survey data.

Being unable to decide on a single set of baseline rates, the panel has chosen to present two sets of computations for the "extensive" cases based on the higher rate of 0.275 derived from the Olmsted County (19–21) and Michigan (23) studies combined, and the lower estimate of 0.14 taken directly from the mean rate for unvaccinated cases from October 1 to December 19, 1976.

These relative risks are presented in table 12. Using the higher baseline estimate of 0.275, the relative risk starts at 1.9, peaks at 9.0 at the second 7-day interval and drops rapidly to 1.0 at the sixth 7-day interval. Evidence of an association with the date of vaccination terminates in the fifth 7-day interval since the risk in the sixth interval is 1.0 and less than 1.0 for the later intervals.

When we use the lower baseline estimate of 0.14, the relative risk starts at

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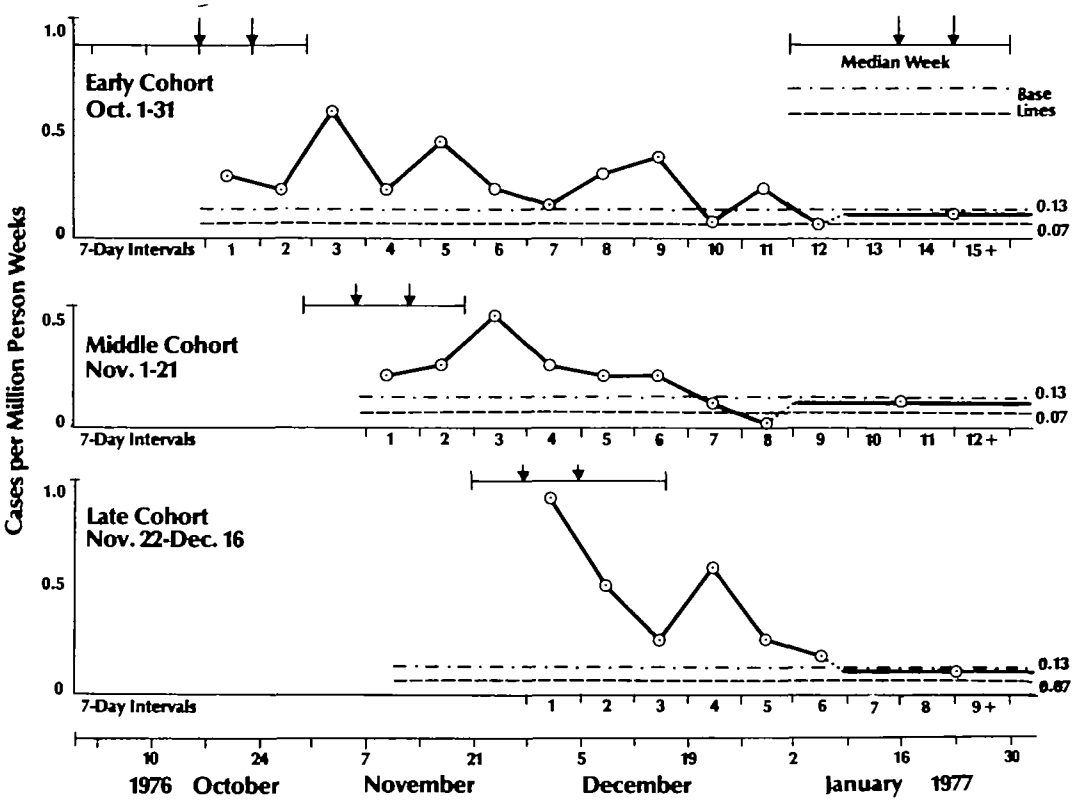


FIGURE 7. Guillain-Barré syndrome in the United States: incidence rates (person-weeks × $10^6$) among cases with "limited" motor involvement by 7-day intervals following vaccination. *Early, middle* and *late* cohorts.

3.6 during the first 7-day interval, rises to a peak of 17.6 during the second interval and then falls to 2.0 by the sixth interval and to 1.7 by the eighth. From the ninth 7-day interval onward, the relative risk is based on very small numbers and averages 0.7, not significantly different from 1.0. This calculation supports the earlier conclusion that an association with the date of vaccination persisted for at least six intervals and may have continued at a low level of increased risk as long as eight intervals, but not longer.

Interpretation of these two series of risk estimates depends wholly on an evaluation of the validity of the two alternate baselines. The combined Olmsted County-Michigan baseline is almost certainly too high, simply because it is not reasonable to expect that the surveillance and case ascertainment throughout the country was conducted with similar thoroughness and consistency. On the other hand, there is reason to believe that the 0.14 baseline drawn from the unvaccinated cases that occurred from October 1 to December 19, 1976 was at least somewhat too low. As revealed in table 4, both vaccinated and unvaccinated cases seemed to have been investigated with equal care once they came to recognition. However, it is only reasonable to believe that the history of a swine influenza vaccination in the individual patient may well have influenced his physician to

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TABLE 12

*Guillain-Barré syndrome in the United States: computation of relative risks and attributable incidence for "extensive" cases associated with swine influenza vaccine using higher and lower baseline estimates (onsets from October 2, 1976 through January 31, 1977)*

| 7-day interval | Vaccinated rate | Relative risk* by baseline estimate | | Attributable rate† by baseline estimate | |
|---|---|---|---|---|---|
| | | 0.14 | 0.275 | 0.14 | 0.275 |
| 1 | 0.51 | 3.6 | 1.9 | 0.37 | 0.24 |
| 2 | 2.47 | 17.6 | 9.0 | 2.33 | 2.20 |
| 3 | 2.10 | 15.0 | 7.6 | 1.96 | 1.83 |
| 4 | 0.67 | 4.8 | 2.4 | 0.53 | 0.40 |
| 5 | 0.48 | 3.4 | 1.7 | 0.34 | 0.21 |
| 6 | 0.28 | 2.0 | 1.0 | 0.14 | 0.00 |
| 7 | 0.26 | 1.9 | 0.9 | 0.12 | (0.02) |
| 8 | 0.24 | 1.7 | 0.9 | 0.10 | (0.04) |
| 9–18 | 0.10 | 0.7 | 0.4 | (0.04) | (0.18) |
| Total | | | | | |
| Intervals 1–6 | 6.51 | 7.75 | 3.96 | 5.67 | 4.88 |
| Intervals 1–8 | 7.01 | | | 5.89 | 4.88 |
| No. of attributable cases | | | | | |
| Intervals 1–6 | | | | 246 | 211 |
| Intervals 1–8 | | | | 255 | 211 |

* Relative risk = vaccinated rate/baseline rate.

† Attributable rate = vaccinated rate − baseline rate.

more seriously consider both the diagnosis of Guillain-Barré syndrome and the reporting of the case if so diagnosed. In addition, patients who had received swine influenza vaccine may well have sought medical care more promptly.

The panel has been unable to find objective measures to confirm this reasoning or to estimate its quantitative effect, but it believes that the most valid baseline for comparative purposes lies somewhere between the two sets of estimates shown. Because of our inability to be more precise, confidence limits have not been calculated. It is felt that their presentation might lead some readers to infer a greater degree of accuracy than the intrinsic limitations of the data permit. Furthermore, the detailed data are presented so that more elaborate statistical computations can be performed at will.

Relative risks for the "limited" cases have not been calculated for the simple reason that the panel does not find an epidemiologic basis for concluding that these cases have occurred in a causal relationship to swine influenza vaccination.

From the same data, it is possible to compute two estimates of the attributable risks, and total numbers and attack rates that can be associated with the vaccine status. These are also shown in table 12. Considering the first six weeks (7-day intervals) following vaccination, the total attributable attack rate for "extensive" cases based on the higher baseline of 0.275 becomes 4.88 and the number of attributable cases becomes 211. This number does not increase with adding further experience because the observed incidence rate from the sixth interval onward is equal to or less than the baseline. The use of the lower, 0.14, baseline leads to an estimate of an attributable attack rate of 5.67 and a total of 246 attributable cases. If the longer period of eight weeks is chosen the total attributable rate be-

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comes 5.89 and the total number of cases slightly higher, 255.

The attributable risk per cent (25) over the first six 7-day intervals using the higher baseline becomes 74.8 (211/282) and using the lower baseline becomes 87.2 (246/282).

As previously explained in the discussion of relative risks, the panel could find no justifiable basis for attempting to calculate meaningful attributable rates for the "limited" cases.

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## APPENDIX A

*Characterization of data available*

The data available to the panel consisted of approximately 1,300 single sheet computer print-outs released as a result of the "Gesell order." These sheets comprised a codification of the data that had been collected and recorded on the standard case investigation form distributed by the Centers for Disease Control to the state epidemiologists in early January 1977.

The data utilized in the present study included:

1) State of residence (for Michigan only).
2) Age in years.
3) Diagnosis by neurologist, yes, no, or unknown.
4) Onset of neurologic symptoms, month, day, year.
5) Clinical characterization:
   a) progressive motor weakness — yes, no, or unknown
   b) bilateral signs of paresis or paralysis — yes, no, or unknown
   c) lower motor neuron signs — yes, no, or unknown
6) Extent of motor involvement:
   a) 1 or 2 extremities — yes, no, or unknown
   b) 3 or 4 extremities — yes, no, or unknown
   c) trunk — yes, no, or unknown
   d) cranial nerves — yes, no, or unknown
   e) respiratory impairment — yes, no, or unknown
   f) in respirator — yes, no, or unknown
7) Swine influenza vaccine:
   a) received — yes, no, or unknown
   b) date of vaccination — month, day, year
8) Other influenza vaccine by type
   a) received — yes, no, or unknown
   b) date of vaccination — month, day, year
9) Cerebrospinal fluid protein
   a) positive $\geq$50 mg/100 ml, negative $\leq$49 mg/100 ml, or unknown

Other data that might be utilized in subsequent studies included state and country of residence, sex, race, manufacturer and lot number of swine influenza vaccine administered, and the occurrence and date of onset of "other acute illness".

Information regarding dates of admission to and discharge from hospital, and outcome, recovered or died, were too inconsistently recorded to permit effective analysis.

It soon became apparent from a study of the records that each represented a cross-sectional study made at some unspecified time during the course of the patient's illness. Follow-up of the patient to recovery or death was not a requirement of the surveillance system. Therefore, case-fatality rates are not a part of this study.

The source of the recorded information, whether obtained from the neurologic consultant, the private physician, or the hospital record is not stated. Presumably, multiple sources were invoked from time to time on many patients. The panel senses that when sufficient data had been collected to warrant a diagnosis of Guillain-Barré syndrome little further effort to collect more data was made in a consistent fashion. At least it was not reported to the Centers for Disease Control.

For these reasons, the panel screened the recorded data for evidence to support the

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diagnosis of Guillain-Barré syndrome and developed the classification of cases by "extent of motor involvement." It felt this term was more descriptive of the situation than "severity" would have been.

Although the standard form asked for such information as clinical findings at the "height of the current neurologic illness" and cerebrospinal fluid findings "with highest protein," the recorded data were not deemed to be sufficiently consistent or complete to warrant more sophisticated clinical evaluations at the present time. Several potentially important studies can be visualized, however, and the data are in the public record and available to interested investigators.

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APPENDIX TABLE B

*Weekly reports of the numbers of vaccinations performed each week: 1) as reported by the Centers for Disease Control (CDC) in response to the "Gesell order," and, 2) by the National Health Survey, conducted by the National Center for Health Statistics (NCHS) with 3) the adjusted estimate calculated by the panel*

| Week ("mid-period")* | 1 CDC data—adjusted weekly vaccinations (in thousands) | 2 NCHS data—weekly estimates swine flu shots (in thousands) | | 3 Panel adjustment† (in thousands) |
|---|---|---|---|---|
| October 3 | 624 | Oct. 1–10 | 1,668 | 1,781 |
| 10 | 1,924 | 11–17 | 2,378 | 2,539 |
| 17 | 2,820 | 18–24 | 4,014 | 4,286 |
| 24 | 4,032 | 25–31 | 4,634 | 4,948 |
| 31 | 4,503 | Nov. 1– 7 | 5,019 | 5,359 |
| November 7 | 4,930 | 8–14 | 6,391 | 6,824 |
| 14 | 6,311 | 15–21 | 5,154 | 5,504 |
| 21 | 4,893 | 22–28 | 3,921 | 4,187 |
| 28 | 5,170 | Nov. 29–Dec. 5 | 3,972 | 4,241 |
| December 5 | 4,821 | Dec. 6–12 | 2,361 | 2,521 |
| 12 | 3,299 | 13–19 | 1,063 | 1,135 |
| | 43,327 | | 40,575 | 43,325 |

* The exact interval covered by the term "mid-period" is not clear in the data released by the "Gesell order." The data in Appendix table F-3 strongly suggest that "mid-period" probably reflects week beginning.

† Adjustment consists of multiplying each weekly NCHS estimate by the factor 1.068 = 43,327/40,575.

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APPENDIX TABLE C-1

*Guillain-Barré syndrome in the United States: numbers of vaccinated cases according to muscle areas affected and clinical characteristics, by extent of motor involvement (onsets from October 2, 1976 through January 31, 1977)*

| Motor involvement group* | Total no. of vaccinated cases | No. of vaccinated cases | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Muscle areas affected | | | | | Clinical characteristics | | | | | |
| | | 1–2 extremities | 3–4 extremities | Trunk | Cranial | Respiratory | Progressive motor weakness | Bilateral involvement | Lower motor neuron signs | Seen by neurologist | Lumbar puncture | |
| | | | | | | | | | | | Done | Positive† |
| | | | | | | *Positive findings* | | | | | | |
| A | 158 | 116 | 151 | 132 | 119 | 158 | 154 | 155 | 147 | 115 | 144 | 129 |
| B | 162 | 114 | 138 | 98 | 111 | | 158 | 148 | 131 | 113 | 143 | 123 |
| C | 89 | 51 | 89 | | | | 84 | 87 | 78 | 59 | 67 | 50 |
| D | 32 | 32 | | | | | 31 | 32 | 29 | 20 | 23 | 21 |
| E | 63 | 12 | 10 | 4 | 9 | 3 | 21 | 14 | 8 | 17 | 28 | 14 |
| | | | | | | *Negative findings* | | | | | | |
| A | 158 | 5 | 4 | 13 | 28 | | 3 | 1 | 3 | 10 | | |
| B | 162 | 5 | 16 | 46 | 46 | 152 | 2 | 6 | 19 | 20 | | |
| C | 89 | 3 | | 71 | 74 | 83 | 3 | 1 | 6 | 15 | ‡ | |
| D | 32 | | 27 | 27 | 28 | 31 | | | 3 | 6 | | |
| E | 63 | 13 | 17 | 19 | 12 | 31 | 8 | 7 | 13 | 10 | | |
| | | | | | | *Findings unknown* | | | | | | |
| A | 158 | 37 | 3 | 13 | 11 | | 1 | 2 | 8 | 33 | | |
| B | 162 | 43 | 8 | 18 | 5 | 10 | 2 | 8 | 12 | 29 | | |
| C | 89 | 35 | | 18 | 15 | 6 | 2 | 1 | 5 | 15 | ‡ | |
| D | 32 | | 5 | 5 | 4 | 1 | 1 | | | 6 | | |
| E | 63 | 38 | 36 | 40 | 42 | 29 | 34 | 42 | 42 | 36 | | |

* See table 2 for criteria defining Groups A–E.

† Positive = cerebrospinal fluid protein ≥50 mg/100 ml. In five cases, cerebrospinal fluid protein was merely recorded as "elevated."

‡ Negative and unknown coding were merged and could not be separated out.

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APPENDIX TABLE C-2

*Guillain-Barré syndrome in the United States: numbers of unvaccinated cases according to muscle areas affected and clinical characteristics, by extent of motor involvement (onsets from October 1, 1976 through January 31, 1977)*

| Motor involvement group* | Total no. of unvaccinated cases | No. of unvaccinated cases | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Muscle areas affected | | | | | Clinical characteristics | | | | | |
| | | 1–2 extremities | 3–4 extremities | Trunk | Cranial | Respiratory | Progressive motor weakness | Bilateral involvement | Lower motor neuron signs | Seen by neurologist | Lumbar puncture | |
| | | | | | | | | | | | Done | Positive† |
| | | | | | | *Positive findings* | | | | | | |
| A | 145 | 86 | 137 | 116 | 91 | 145 | 144 | 140 | 130 | 120 | 128 | 94 |
| B | 115 | 77 | 99 | 79 | 64 | | 111 | 113 | 103 | 92 | 105 | 82 |
| C | 84 | 52 | 84 | | | | 84 | 77 | 73 | 64 | 73 | 56 |
| D | 37 | 37 | | | | | 37 | 37 | 31 | 25 | 31 | 23 |
| E | 59 | 14 | 5 | 2 | 12 | 4 | 20 | 19 | 13 | 20 | 30 | 19 |
| | | | | | | *Negative findings* | | | | | | |
| A | 145 | 6 | 6 | 19 | 41 | | | | 8 | 12 | | |
| B | 115 | 6 | 8 | 30 | 47 | 110 | 2 | 1 | 5 | 9 | | |
| C | 84 | 7 | | 66 | 74 | 78 | | 3 | 4 | 8 | ‡ | |
| D | 37 | | 27 | 33 | 33 | 35 | | | 3 | 4 | | |
| E | 59 | 8 | 18 | 21 | 12 | 32 | 9 | 7 | 12 | 8 | | |
| | | | | | | *Findings unknown* | | | | | | |
| A | 145 | 53 | 2 | 10 | 13 | | 1 | 5 | 7 | 13 | | |
| B | 115 | 32 | 8 | 6 | 4 | 5 | 2 | 1 | 7 | 14 | | |
| C | 84 | 25 | | 18 | 10 | 6 | | 4 | 7 | 12 | ‡ | |
| D | 37 | | 10 | 4 | 4 | 2 | | | 3 | 8 | | |
| E | 59 | 37 | 36 | 36 | 35 | 23 | 30 | 33 | 34 | 31 | | |

* See table 2 for criteria defining Groups A–E.

† Positive = cerebrospinal fluid protein ≥50 mg/100 ml. In five cases, cerebrospinal fluid protein was merely recorded as "elevated."

‡ Negative and unknown coding were merged and could not be separated out.

APPENDIX TABLE D

*Computations of populations at risk for Guillain-Barré syndrome by person-weeks × $10^6$ for vaccinated and unvaccinated persons, October 1, 1976 through January 31, 1977*

| Calendar dates | Vaccinated during interval: Revised NCHS estimate* (1)† | Vaccinated during interval: Person-weeks × $10^6$ (2) (1) × 0.5‡ | Previously vaccinated (3) cumulated (1) | Person-weeks × $10^6$: Vaccinated (4) (2) + (3) | Person-weeks × $10^6$: Unvaccinated (5)§ 151.2 − (4) |
|---|---|---|---|---|---|
| Oct. 1–10‖ | 1.781 | 1.272‖ | 0.000 | 1.3 | 214.7‖ |
| 11–17 | 2.539 | 1.270 | 1.781 | 3.1 | 148.1 |
| 18–24 | 4.286 | 2.143 | 4.320 | 6.5 | 144.7 |
| 25–31 | 4.948 | 2.474 | 8.606 | 11.1 | 140.1 |
| Nov. 1– 7 | 5.359 | 2.680 | 13.554 | 16.2 | 135.0 |
| 8–14 | 6.824 | 3.412 | 18.913 | 22.3 | 128.9 |
| 15–21 | 5.504 | 2.752 | 25.737 | 28.5 | 122.7 |
| 22–28 | 4.187 | 2.094 | 31.241 | 33.3 | 117.9 |
| 29–Dec. 5 | 4.241 | 2.121 | 35.428 | 37.5 | 113.7 |
| Dec. 6–12 | 2.521 | 1.261 | 39.669 | 40.9 | 110.3 |
| 13–19 | 1.135 | 0.811 | 42.190 | 43.0¶ | 108.2¶ |
| 20–26 | 0 | 0 | 43.325 | 43.3 | 107.9 |
| 27–Jan. 2 | 0 | 0 | 43.325 | 43.3 | 107.9 |
| Jan. 3– 9 | 0 | 0 | 43.325 | 43.3 | 107.9 |
| 10–16 | 0 | 0 | 43.325 | 43.3 | 107.9 |
| 17–23 | 0 | 0 | 43.325 | 43.3 | 107.9 |
| 24–31†† | 0 | 0 | 43.325 | 49.5†† | 123.3†† |
| | 43.325 | | | | |

* From Appendix B. NCHS, National Center for Health Statistics.
† Column no.
‡ Computation.
§ Column (5) 151.2 × $10^6$ estimated civilian population aged 18 years and over, January 1, 1977.
‖ Adjusted for 10-day period.
¶ Adjusted for moratorium December 16.
†† Adjusted for 8-day period.

APPENDIX TABLE E

*Computation of populations of vaccinees at risk of acquiring Guillain-Barré syndrome by 7-day intervals from vaccination, for total group and early, middle and late cohorts (see table 11 and appendix D)**

| 7-day intervals after vaccination | Total group | Person-weeks observed × $10^6$ by cohort† | | |
|---|---|---|---|---|
| | | Early | Middle | Late |
| 1 | 43.3 | 13.6 | 17.7 | 12.1 |
| 2 | 43.3 | 13.6 | 17.7 | 12.1 |
| 3 | 43.3 | 13.6 | 17.7 | 12.1 |
| 4 | 43.3 | 13.6 | 17.7 | 12.1 |
| 5 | 43.3 | 13.6 | 17.7 | 12.1 |
| 6 | 43.3 | 13.6 | 17.7 | 12.1 |
| 7 | 43.1 | 13.6 | 17.7 | 11.9 |
| 8 | 41.3 | 13.6 | 17.7 | 10.0 |
| 9 | 38.1 | 13.6 | 17.7 | 6.9 |
| 10 | 33.9 | 13.6 | 17.7 | 2.7 |
| 11 | 29.3 | 13.6 | 15.7 | 0.1 |
| 12 | 23.3 | 13.6 | 9.7 | |
| 13 | 17.0 | 13.6 | 3.5 | |
| 14 | 11.8 | 11.7 | 0.1 | |
| 15 | 7.1 | 7.1 | | |
| 16 | 3.4 | 3.4 | | |
| 17 | 1.3 | 1.3 | | |
| 18 | 0.2 | 0.2 | | |

* *Early*, October 1–31; *Middle*, November 1–21; and *Late*, November 22–December 16.
† The size of each cohort is computed as the total number of persons receiving vaccine within the respective dates (see Appendix table D).

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## APPENDIX F

### *Michigan baseline data*

The approximately 1,300 single sheet computer print-outs of cases of Guillain-Barré syndrome reported by state health departments to the Centers for Disease Control as part of the national surveillance program were sorted by individual states. An examination of the reports from Michigan revealed 133 cases. Interestingly, these cases had onsets of neurologic symptoms ranging from July 1976 to June 1977. It became apparent that Michigan had routinely reported to the Centers for Disease Control the data on the cases detected in their intensive surveillance program (22). These had been released as a result of the "Gesell order" (12).

The records in most instances were quite complete. Eight cases were under 18 years of age, seven cases had onsets during May and June 1977, and in one case the vaccination date was unknown. These 16 cases have been excluded, leaving 117 with onsets during the 10-month period July 1, 1976–April 30, 1977 in which vaccine status was clearly recorded. It was possible for us to classify all of the cases according to the extent of motor paralysis by the same criteria specified in table 2. In Appendix table F-1, the findings are given by vaccination status and in three time intervals: before, during, and after the swine influenza vaccine program and the ensuing national surveillance.

Two sources of data on vaccinations performed were available: one was the news release dated January 6, 1977 giving numbers of vaccinations reported to the Centers for Disease Control by states and weeks, the other was the data released as a result of the "Gesell order." The two sets of data are compared in Appendix table F-2. Although the exact dates are not clearly specified in the reports, presumably the 1977 data are based on weeks ending on the specified dates. The 1981 tabulation lists dates as "mid-period" without further elaboration. In spite of this confusion, the close concordance between the two tabulations is striking except for the last week when a 28.6 per cent increase in the numbers of vaccinations is reported in 1981 compared to 1977. Presumably, this increase reflects late reports forwarded by the state to the Centers for Disease Control. The 1981 data have been used in calculating populations at risk since they have been considered to be the best available. No effort has been made to adjust for the obvious delayed reporting of vaccinations. The effect on the results would be trivial. As shown in Appendix table F-3, the rate for unvaccinated extensive cases was 0.27 and that for limited cases 0.10 without evidence of a seasonal variation.

An interesting point, not germane to calculating baseline data, deserves a brief note. A total of 17 vaccinated cases with "extensive" motor involvement were discovered in Michigan during the first six post-vaccination weeks. These give a rate of 7.6 per million vaccinees, only slightly higher than the total rate of 6.51 observed for the entire United States (table 12). In view of the intensity of the case ascertainment program in Michigan, it would be most appropriate to deduct the observed unvaccinated rate of 0.27 to calculate the attributable rate for the six-week period. This becomes $(7.6 - 6 \times 0.27) = 6.0$, very close to the national rate of 5.67. This small single observation supports the hypothesis that the reporting of "extensive" vaccinated cases was remarkably good on a nationwide basis.

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APPENDIX TABLE F-1

*Cases of Guillain-Barré syndrome reported from Michigan by vaccine status and extent of motor involvement*, July 1, 1976–April 30, 1977*

| Onset during time interval | Vaccine status | | | | | |
|---|---|---|---|---|---|---|
| | Unvaccinated cases by extent of motor involvement | | | Vaccinated† cases by extent of motor involvement | | |
| | "Extensive" A + B | "Limited" C + D | "Insufficient" E | "Extensive" A + B | "Limited" C + D | "Insufficient" E |
| July 1–September 30, 1976 | 22 | 6 | | | | |
| October 1, 1976–January 31, 1977 | 21 | 9 | 1 | 17 | 11 | 3 |
| February 1–April 30, 1977 | 15 | 6 | 1 | 5 | | |
| | 58 | 21 | 2 | 22 | 11 | 3 |

* See table 2 for criteria defining Groups A + B, C + D, and E.
† Six cases vaccinated after onset, all with onsets July–September, 1976, were classified in the unvaccinated cases.

APPENDIX TABLE F-2

*Reported weekly swine influenza vaccinations in Michigan from two sources, October 1–December 16, 1976*

| Week | | CDC news release, January 6, 1977 (1) | "Mid-period" | | "Gesell Order," 1981 (2) | Ratio (2)/(1) |
|---|---|---|---|---|---|---|
| October | 1 | 0 | | | 0 | |
| | 9 | "No report" | October | 3 | – | |
| | 16 | 18,108 | | 10 | 18,043 | 0.9964 |
| | 23 | 91,256 | | 17 | 90,927 | 0.9964 |
| | 30 | 227,349 | | 24 | 226,528 | 0.9964 |
| November | 6 | 205,186 | October | 31 | 204,445 | 0.9964 |
| | 13 | 336,725 | November | 7 | 335,509 | 0.9964 |
| | 20 | 395,891 | | 14 | 394,461 | 0.9964 |
| | 27 | 349,159 | | 21 | 347,898 | 0.9964 |
| December | 4 | 136,018 | November | 28 | 135,527 | 0.9964 |
| | 11 | 205,347 | December | 5 | 204,605 | 0.9964 |
| | 18 | 216,293 | | 12 | 278,051 | 1.2855 |
| Totals | | 2,181,332 | | | 2,235,994 | 1.0251 |

Note: The population, 18 years of age and older in Michigan was 6.145 million according to Bureau of Census estimates for July 1, 1975. The unvaccinated population at risk July 1 to September 30, 1976 was calculated ($6.145 \times 13.14$ weeks = 80.8 person-weeks $\times 10^6$). From October 1, 1976 to January 31, 1977, the estimated population at risk, 83.2, was computed by simple subtraction of the weekly vaccinees from the starting total of 6.145. From February 1 to April 30, 1977, the calculation was $3.909 \times 12.7$ weeks = 49.7 person-weeks $\times 10^6$.

APPENDIX TABLE F-3

*Attack rates (person-weeks $\times 10^6$) for unvaccinated cases of Guillain-Barré syndrome reported from Michigan according to extent of motor paralysis and time period of onset, July 1, 1976 through April 30, 1977*

| Onset during time interval | Population at risk† (person-weeks $\times 10^6$) | Motor involvement* (person-weeks $\times 10^6$) | |
|---|---|---|---|
| | | "Extensive" | "Limited" |
| July 1 to September 30, 1976 | 80.8 | 0.27 | 0.07 |
| October 1, 1976 to January 31, 1977 | 83.2 | 0.25 | 0.11 |
| February 1 to April 30, 1977 | 49.7 | 0.30 | 0.12 |
| | 213.7 | 0.27 | 0.10 |

* See table 2 for criteria defining "extensive" and "limited" groups.
† See Appendix table F-2.

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## APPENDIX G

### *The fitting of the lognormal curve to the distribution of "extensive" vaccinated cases of Guillain-Barré syndrome*

Dennis J. Bregman

The panel concluded that the length of incubation periods are governed by a biologically random process. In developing this conclusion, it was helpful to bear in mind three considerations: 1) The extensive group includes two kinds of vaccinated cases. One kind of case is presumably triggered by the vaccine, the other is not. These are called the attributable and background cases, respectively. 2) It was necessary to measure the influence of biologic randomness and chance on the observed incubation periods of the attributable cases. 3) It was desirable that the choice of statistical principles and methods be guided by relevance and simplicity. These considerations and the communication from Dr. Sartwell in May 1977 (1) led the panel to the lognormal model.

The lognormal model was first scientifically described in a pair of communications published by the Royal Society in 1879. Galton (2) wrote about the need to consider a law of nature whose measurements should be expressed in units of relative excess and deficiency of some value of central tendency. Until that time, scientific research had used absolute differences in excess or deficiency. McCalister (3) followed Galton with a presentation of the lognormal probability model which described the statistical formulations of such a law. This probability model is expressed as:

$$f_x(x_j) = \frac{1}{\sqrt{2\pi}\,\sigma x_j}\exp\left(\frac{-(\log x_j - \mu)^2}{2\sigma^2}\right), \quad x > 0$$

The following algebraic presentation, used to derive the lognormal (4), captures a deterministic perspective of the process

$$X_{j+1} = X_j + E_j(X_j)$$

One interpretation of the expression follows

- $j$ is an instant of time;
- $X_{j+1}$ is some measurement at instant $j + 1$ such as the extent of biological damage. Presumably, when the measurement exceeds some threshold the incubation period ends and the incubation time is known. We used the interval to reflect the time at which the measurement exceeds the threshold.
- $X_j$ is some measurement comparable to $X_{j+1}$ taken at an instant $j$ just prior to the stimulus.
- $E_j$ is the independent random stimulus at instant $j$ which increases the amount of biological damage from $X_j$ to $X_{j+1}$.

The extent of biologic damage at any instant $j + 1$ is equal to the cumulative damage of previous stimuli, then some additional fraction of that and random variation. Or, the effect of a stimulus upon a body is proportional to the stimulus itself and the area available for the stimulus to act upon (5).

The lognormal distribution has been used to describe the variability observed in experiments on toxicity (6), incubation periods of infectious diseases (7, 8), polio (9), and chronic diseases (10). The panel used this distribution to describe the observed

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incubation periods of the attributable cases, as shown in Appendix table G-1 and figure G-1.

The weekly incidence rate of the "extensive" group was divided into attributable and background components by subtracting a constant background rate of 0.14 (Appendix table G-1, column 3). There was no attributable rate beyond eight weeks. Thus, the total attributable rate of 5.89 (sum of weeks 1–8) was used to calculate the percentiles of the weekly rate. These percentiles are shown in column 4 and displayed as the circled line in Appendix figure G-1. In this figure, the horizontal axis is a log scale and the vertical axis is the normal probability scale. It is well known that data which follow a straight line in this display characterize the lognormal distribution.

The black thread method of fitting the straight line in these data yielded a reasonable result but is not as reproducible (10). Instead, a fitted distribution curve was computed by regressing the lognormal deviates (column 5) (12) upon the corresponding natural log of the week number (column 1). This yielded the equation shown at the bottom of Appendix table G-1. From this, the fitted deviates (column 6) were computed and rates for each half-week interval (column 7) could be directly derived. The rates are expressed as cases per million person-weeks for graphic purposes (figures 3–6).

The lognormal distribution explains over 99 per cent of the observed variability in the incubation periods of the attributable cases. This degree of regularity is statistically persuasive evidence of an orderly disease mechanism underlying the incubation periods in a portion of the "extensive" cases. The attributable rate passes below the background rate at seven weeks. At this point, "extensive" cases are more likely to be associated with background rather than vaccine attributable causes. By the eighth week, over 99 per cent of the attributable cases will have finished their incubation period.

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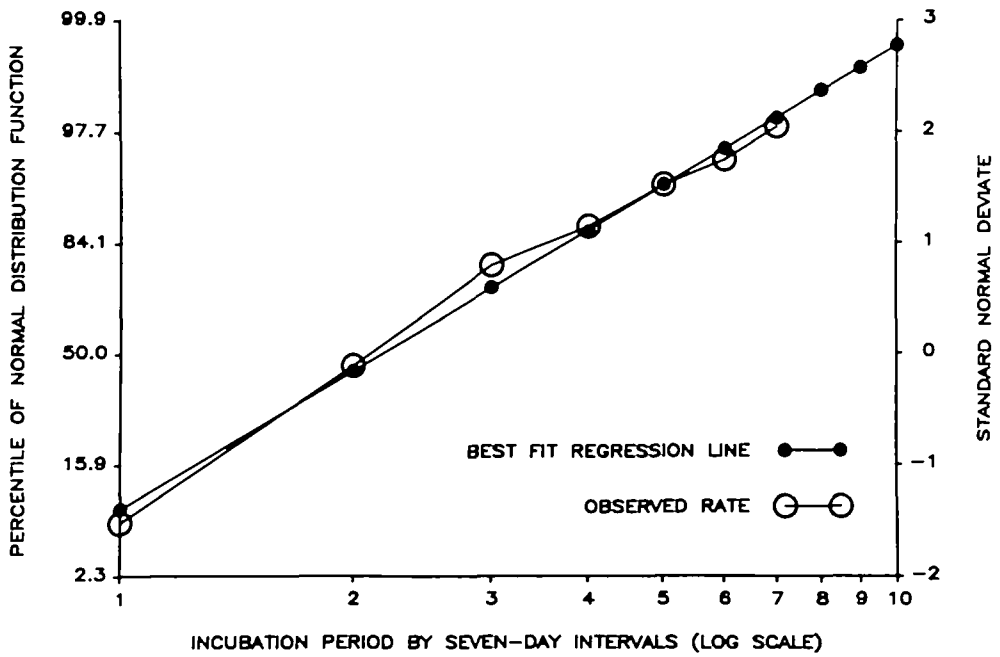
APPENDIX TABLE G-1

*Computations for fitting lognormal distribution to observed attributable rates for "extensive" cases by 3.5-day intervals following vaccination*

| 7-day interval (1) | Observed incidence rate (2) | Observed attributable rate | | | Fitted distribution* | |
|---|---|---|---|---|---|---|
| | | Rate (3) | Percentile (4) | Lognormal deviate (5) | Lognormal deviate (6) | Rate per million person-weeks (7) |
| 0.5 | | | | | −2.70 | 0.04 |
| 1.0 | 0.51 | 0.37 | 6.28 | −1.531680 | −1.14 | 0.88 |
| 1.5 | | | | | −0.67 | 2.04 |
| 2.0 | 2.47 | 2.33 | 45.84 | −0.104465 | −0.14 | 2.28 |
| 2.5 | | | | | 0.27 | 1.92 |
| 3.0 | 2.10 | 1.96 | 79.12 | 0.810592 | 0.61 | 1.43 |
| 3.5 | | | | | 0.89 | 1.01 |
| 4.0 | 0.67 | 0.53 | 88.12 | 1.181007 | 1.14 | 0.69 |
| 4.5 | | | | | 1.36 | 0.47 |
| 5.0 | 0.48 | 0.34 | 93.89 | 1.545605 | 1.55 | 0.32 |
| 5.5 | | | | | 1.73 | 0.22 |
| 6.0 | 0.28 | 0.14 | 96.26 | 1.781688 | 1.89 | 0.15 |
| 6.5 | | | | | 2.04 | 0.10 |
| 7.0 | 0.26 | 0.12 | 98.30 | 2.120069 | 2.17 | 0.07 |
| 7.5 | | | | | 2.30 | 0.05 |
| 8.0 | 0.24 | 0.10 | 100.00 | | 2.42 | 0.03 |
| | | 5.89 | | | | |
| 9+ | 0.10 | — | | | | |

* $Z = -1.418899 + 1.845725 \ln(\text{interval})$; ($r = 0.996$, df = 5); mean = 2.16 weeks, dispersion factor = 1.23 weeks.




APPENDIX FIGURE G-1. Guillain-Barré syndrome in the United States: observed and expected cumulative attack rates in 7-day intervals using lognormal probability scales for "extensive" vaccinated cases, October 2, 1976–January 31, 1977. See table 2 for criterion defining "extensive."

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APPENDIX TABLE H-1

*Guillain-Barré syndrome in the United States: incidence of cases with "extensive" motor involvement by 7-day intervals from vaccination to onset of neurologic symptoms according to weekly cohorts of vaccinees, October 2–December 19, 1976*

| Group | "Extensive" cases (Groups A + B)* | | | Interval vaccination to onset in 7-day periods | | | | | | | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cohort | Dates vaccinated | No. vaccinated × $10^6$ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | |
| *Early* | 1 | Oct. 2–10 | 1.78 | 1 | | 5 | 2 | | | 1 | 1 | 1 | | | | | | | | 11 |
| | 2 | 11–17 | 2.54 | 2 | 8 | 7 | 2 | | | 3 | 2 | | | 1 | | | | 1 | 1 | 27 |
| | 3 | 18–24 | 4.29 | 2 | 7 | 3 | 2 | 2 | | 2 | | 1 | | | 1 | | | 1 | | 21 |
| | 4 | 25–31 | 4.95 | 3 | 16 | 13 | 6 | 4 | 1 | 2 | 2 | 1 | 2 | 1 | 1 | 1 | | | | 53 |
| *Middle* | 5 | Nov. 1– 7 | 5.36 | | 15 | 9 | 5 | 1 | | 1 | | 1 | 1 | 1 | | | | | | 34 |
| | 6 | 8–14 | 6.82 | 3 | 11 | 18 | 5 | 6 | 4 | | 3 | | | | | | | | | 50 |
| | 7 | 15–21 | 5.50 | 3 | 18 | 10 | 4 | 1 | 1 | | 1 | | 1 | | | | | | | 39 |
| *Late* | 8 | Nov. 22–28 | 4.19 | 2 | 7 | 11 | | 3 | 4 | 2 | 1 | | | | | | | | | 30 |
| | 9 | 29– 5 | 4.24 | 3 | 17 | 6 | 2 | 2 | | | | | | | | | | | | 30 |
| | 10 | Dec. 6–12 | 2.52 | 3 | 7 | 8 | 1 | 2 | 2 | | | | | | | | | | | 23 |
| | 11 | 13–16† | 1.14 | | 1 | 1 | | | | | | | | | | | | | | 2 |
| Total | | | 43.33 | 22 | 107 | 91 | 29 | 21 | 12 | 11 | 10 | 4 | 4 | 3 | 2 | 1 | | 2 | 1 | 320 |

* See table 2 for criteria defining Groups A + B.

† 4-day period when vaccinations performed.

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APPENDIX TABLE H-2

*Guillain-Barré syndrome in the United States: incidence of cases with "limited" motor involvement by 7-day intervals from vaccination to onset of neurologic symptoms according to weekly cohorts of vaccinees, October 2–December 19, 1976*

| Group | "Limited" cases (Groups C + D)* | | | Interval vaccination to onset in 7-day periods | | | | | | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cohort | Dates vaccinated | No. vaccinated × $10^6$ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | |
| *Early* | 1 | Oct. 2–10 | 1.78 | | | | 1 | | 1 | 1 | | 1 | | | | | | | | 4 |
| | 2 | 11–17 | 2.54 | | | 1 | | | | | 1 | 2 | | 1 | | 1 | | 2 | | 8 |
| | 3 | 18–24 | 4.29 | 1 | 2 | 4 | 1 | 1 | 1 | | 1 | 1 | 1 | 2 | | 1 | | | | 16 |
| | 4 | 25–31 | 4.95 | 3 | 1 | 3 | 1 | 5 | 1 | 1 | 2 | 1 | | | 1 | | | | | 19 |
| *Middle* | 5 | Nov. 1– 7 | 5.36 | 1 | 2 | 1 | 3 | 1 | 1 | | | 1 | | | 1 | | | | | 11 |
| | 6 | 8–14 | 6.82 | 2 | 2 | 2 | | 2 | 2 | 1 | | 1 | 1 | | | | | | | 13 |
| | 7 | 15–21 | 5.50 | 1 | 1 | 6 | 2 | 1 | 1 | 1 | | | 1 | | | | | | | 14 |
| *Late* | 8 | Nov. 22–28 | 4.19 | 2 | 1 | 1 | 1 | | 1 | | 1 | | | | | | | | | 7 |
| | 9 | 29– 5 | 4.24 | 3 | 4 | | 4 | 1 | | 1 | 1 | | | | | | | | | 14 |
| | 10 | Dec. 6–12 | 2.52 | 3 | 1 | 2 | 2 | 2 | 1 | 1 | | | | | | | | | | 12 |
| | 11 | 13–16† | 1.14 | 3 | | | | | | | | | | | | | | | | 3 |
| Total | | | 43.33 | 19 | 14 | 20 | 15 | 13 | 9 | 6 | 6 | 7 | 3 | 3 | 2 | 2 | | 2 | | 121 |

* See table 2 for criteria defining Groups C + D.

† 4-day period when vaccinations performed.