Guillain–Barré syndrome: the swine influenza virus vaccine incident in the United States of America, 1976–77: preliminary communication[1]

Professor Alexander D Langmuir MD MPH[2]
Harvard University, Cambridge, Massachusetts and
Center for Disease Control, Atlanta, Georgia

Introduction

The four months from October 1976 to January 1977 were in two respects unique in the annals of epidemiology in the United States of America. First, more than 40 million adult citizens were vaccinated with swine influenza virus vaccine, a remarkable response to a nationally sponsored programme based on the prediction of the probability of an impending epidemic (Schonberger *et al.* 1979). Second, during the same period more than 500 cases of Guillain–Barré syndrome (Landry 1859, Guillain *et al.* 1916) occurred among the vaccinated persons, with 25 deaths.

Previous attempts had been made to forestall the spread of a new pandemic strain of influenza virus by preparing sufficient quantities of specific influenza virus vaccine. In 1957, during the pandemic associated with the Asian strain, antigenically H2 N2, the United States embarked on a national programme along these lines. Maximum production of monovalent (H2 N2) vaccine was achieved as the pandemic was reaching its peak, only a few weeks too late for the vaccine to be used effectively. In 1968, when the Hong Kong (H3 N2) strain appeared, the United States again tried to achieve mass control with vaccine and again nearly succeeded.

In February 1976, with the occurrence at Fort Dix, New Jersey, of human infections with a swine influenza strain (Hswl N1), the likelihood that a mass vaccination programme would succeed seemed greater than ever before. The antigenic composition of the virus was interpreted as a major shift to antigens that had been prevalent in the past and the presumed association of this or some closely related strain to the influenza pandemic of 1918 added excitement and fear (Langmuir & Schoenbaum 1977). The expected pandemic might not begin until the fall of 1976, allowing six to eight months for the preparation of enough vaccine to vaccinate the entire population of the United States. The one flaw in this analysis, which slowly became evident as plans for the campaign progressed, was that the new strain showed no capability of epidemic spread. The winter of 1976–77 turned out to be one of the most salubrious for more than a decade.

From the standpoint of epidemiological surveillance, the country had never been so thoroughly organized for the investigation and reporting of vaccine reactions as it was at the beginning of October 1976, when the programme of vaccination was initiated. This organization was put to effective use when vaccine-associated cases of Guillain–Barré syndrome were recognized to be occurring with more than expected frequency. A moratorium on further use of the vaccine was declared on 16 December 1976.

This paper is a preliminary report on the incident. Detailed studies have been in progress since December 1976 and the results will be published in due course (Schonberger *et al.* 1979).

Methods

Because of the existence in the United States of the Freedom of Information Act, familiarly known as the 'Sunshine Law', detailed reports of the nationally collected surveillance data

[1] Based on paper read to Section of Pathology, 11 April 1978. Accepted 17 May 1979
[2] Visiting Professor sponsored by the Royal Society of Medicine Foundation, Inc. Mailing address: RFD Abel's Hill, Chilmark, Massachusetts 02535, USA

0141–0768/79/090660–10/$01.00/0

have been publicly released. Such full disclosure of technical data with a minimum of interpretative discussion is in the great tradition of William Farr in England a century ago, at the General Register Office. The data presented in this preliminary report have been taken from the public release of revised and corrected data in August 1977, with some of my own statistical analyses and epidemiological interpretations. Concurrently with the vaccine-associated cases of Guillain–Barré syndrome other cases, more than 500, among unvaccinated persons in the population were collected through a network of collaborating neurologists and practising physicians, organized on an emergency basis throughout all 50 states of the United States. This large body of data forms the substance of this report.

Results

Figure 1A shows the numbers of swine influenza virus vaccinations by week of vaccination. The programme began on 1 October 1976 when sufficient vaccine was to hand and production was proceeding apace. The numbers of doses given each week increased rapidly from less than one million in early October to more than four million in the later weeks of the month, and reached a peak of more than six million doses a week in the middle of November. With the recognition of vaccine-associated cases of Guillain–Barré syndrome a moratorium was declared on 16 December and no more vaccine was administered.

Figure 1B shows the numbers of cases of Guillain–Barré syndrome among the vaccinated persons by week of onset. These cases are referred to subsequently as 'vaccinated cases'. A

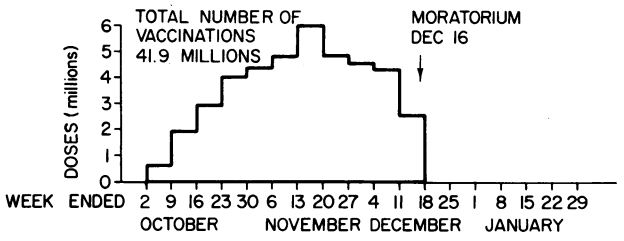

Figure 1A. Swine influenza virus vaccinations by week of vaccination

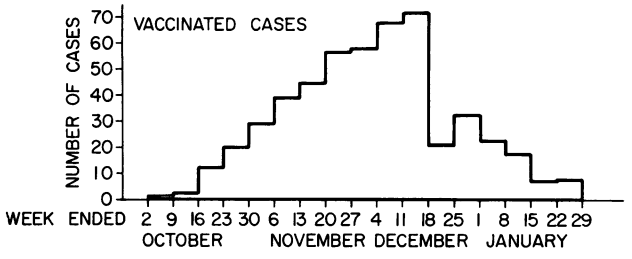

Figure 1B. Cases of Guillain–Barré syndrome in vaccinated persons by week of onset

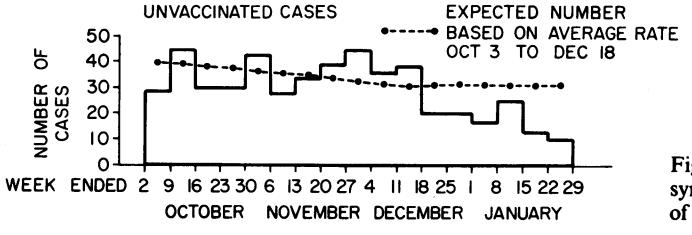

Figure 1C. Cases of Guillain–Barré syndrome in unvaccinated persons by week of onset

small number appeared early in October. The incidence rose rapidly through late October and November to reach a peak in the week ended 18 December. There was a sudden drop from more than 70 cases to 22 in the subsequent week, a moderate rise in the last week of December, and then a progressive fall to a low level by the end of January 1977.

Figure 1c shows the numbers of cases of Guillain–Barré syndrome among unvaccinated persons during the same period. These cases are referred to subsequently as 'unvaccinated cases'. The incidence was relatively constant, ranging from 28 to 45 cases each week from early October to the middle of December, after which it suddenly declined to about half its previous level.

Incidence rate among unvaccinated persons

Table 1 presents a statistical analysis of the weekly incidence of unvaccinated cases from 3 October (i.e. the beginning of the week ended 9 October) to 18 December. The average rate for this eleven-week period, 0.185 per million person-weeks, was used to calculate the expected weekly numbers (E). These differed from the observed numbers (O) only within the limits of chance variation ($P=0.05$–0.10). The unvaccinated population progressively declined as the vaccinated population increased, with a corresponding decrease in the expected weekly numbers (E) of unvaccinated cases. The relative constancy of the weekly incidence rate throughout the eleven-week period conforms with the general impression of most neurologists and epidemiologists that Guillain–Barré syndrome is an endemic disease with little seasonal fluctuation.

The decline in incidence of unvaccinated cases after 18 December could be interpreted as a seasonal variation but it seems more likely that it was due to a decline in the reporting of cases. This could be expected to have affected the number of unvaccinated cases to a greater degree than that of vaccinated cases.

Clinical features

Table 2 summarizes the clinical features of the vaccinated and unvaccinated cases in terms of the percentage of cases, in each of the two groups, in which these features were observed. In

Table 1. Guillain–Barré syndrome: test of constancy of incidence rate among unvaccinated persons

Week ended		No. of vaccinated persons (1000s)	Unvaccinated persons			χ^2 computation			
			Population (1000s)	Cases	Rate●	E ■	O–E	$\frac{(O-E)^2}{E}$	
October	2	13	215 000						
	9	657	214 330	29	0.135	39.7	−10.7	2.9	
	16	1943	212 387	45	0.212	39.3	+5.7	0.8	
	23	2968	209 419	30	0.143	38.8	−8.8	2.0	
	30	4100	205 319	30	0.146	38.0	−8.0	1.7	
November	6	4424	200 895	43	0.214	37.2	+5.8	0.9	$\sum \frac{(O-E)^2}{E} = 16.3$
	13	4866	196 029	28	0.143	36.3	−8.3	1.9	
	20	6132	189 897	34	0.179	35.2	−1.2	0.1	10 d.f.
	27	4835	185 062	39	0.211	34.3	+4.7	0.6	$P = 0.05$–0.10
December	4	4611	180 448	45	0.249	33.4	+11.6	4.0	
	11	4391	176 057	36	0.205	32.6	+3.4	0.3	
	18	2545	173 512	38	0.219	32.1	+5.9	1.1	
	25	—	173 512	21	0.121	32.1	−11.1		
January	1	—	173 512	21	0.121	32.1	−11.1		
	8	—	173 512	17	0.098	32.1	−15.1		
	15	—	173 512	25	0.144	32.1	−7.1		
	22	—	173 512	13	0.075	32.1	−19.1		
	29	—	173 512	10	0.058	32.1	−22.1		

● Per million per week

■ Calculated from average rate 3 October to 18 December = 0.185 per million per week

Table 2. Clinical features of vaccinated and unvaccinated cases (percentages)

	Vaccinated	Unvaccinated
Seen by neurologist	83.4	89.2
Clinical features:		
Bilateral paresis	96.2	97.3
Lower motor neuron signs	89.1	91.8
3 or 4 extremities involved	85.6	84.7
Cranial nerves involved	54.6	44.1
Respiratory impairment	35.7	39.1
Acute illness in past 4 weeks	30.2	59.3●
Case fatality rate	5.2	4.7

●$P<0.001$

both groups more than 80% of the cases were seen by a neurologist. Most of the cases had bilateral paresis. About 90% showed signs of lower motor neuron disease and almost as high a proportion, about 85%, had involvement of three or four extremities. About half had involvement of the cranial nerves and slightly more than one-third had respiratory impairment. The one statistically significant difference between the vaccinated and the unvaccinated cases was the higher proportion in the latter group who had experienced an acute illness, of a nonspecific character, during the four weeks preceding the onset of Guillain–Barré syndrome.

The case fatality rate in the two groups was essentially the same. This and the correspondence of the clinical features make it seem likely that the completeness of reporting and the quality of the clinical information were for the most part similar.

Age distribution

Figure 2 shows the distribution of the vaccinated and the unvaccinated cases in 5-year age groups. The vaccine was not generally recommended for persons under the age of 18 years and there were virtually no vaccinated cases under the age of 15. From 15 years onwards there was a progressive increase until the age range of 35–50 years, with a fall within the range of 50–60 years and a moderate rise from 60 to 75 years, after which the number of vaccinated cases fell abruptly. The data cannot be related to the number of vaccinations performed, since these were not systematically recorded by 5-year age groups. The relatively large number of cases in the age range 35–50 years may have reflected the success of mass vaccination programmes in

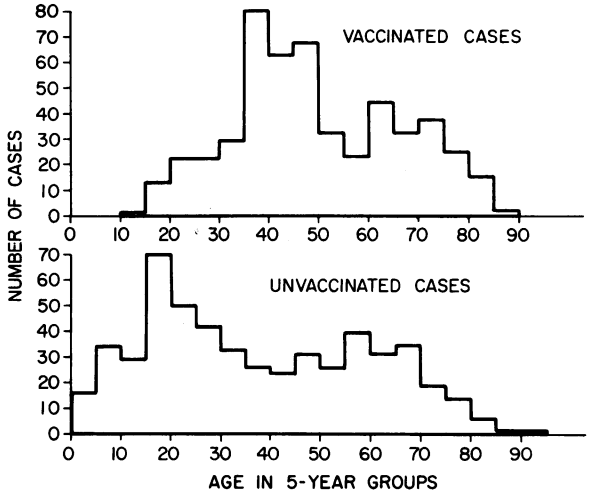

Figure 2. Guillain–Barré syndrome: distribution of cases by age

offices, industrial establishments and shopping centres, but the smaller number in the age range 50–60 years is not readily explicable.

The unvaccinated cases were most numerous within the age range of 15–30 years, a distribution influenced undoubtedly by the large number of persons at these ages, which resulted from the increased birth rate that began in 1947 and continued for at least 15 years. The smaller number of unvaccinated cases within the age range of 35–50 years reflects a previously lower birth rate and the possibility of a greater response to the vaccination programme, as suggested by the age distribution of the vaccinated cases.

Age-specific incidence rates

Age-specific incidence rates, in broader age groupings, were obtained from selected States, comprising more than half the entire country. Table 3 compares the rates, per million person-months, for vaccinated cases, of onset within 6 weeks of vaccination, with rates for unvaccinated cases. Over all age groups the rate for vaccinated cases was 7.3 and for unvaccinated cases 0.77, a ratio or relative risk of 9.5 to 1.

Table 3. Age-specific incidence rates among vaccinated and unvaccinated populations in selected States

Age group (years)	Vaccinated cases		Unvaccinated cases		Relative risk
	No.●	Rate■	No.	Rate■	
0–17	1	—	88	0.47	—
18–24	23	3.3	60	0.89	3.7
25–44	151	9.3	95	0.73	12.7
45–64	118	7.4	103	1.05	7.1
65+	74	7.2	62	1.27	5.6
Total	367	7.3	409	0.77	9.5

● Within 6 weeks of vaccination
■ Per million person-months

Among the vaccinated cases, the small number in the age group 18–24 years gave a relatively low incidence rate of 3.3, but in older age groups the rates were higher and showed little variation. Among the unvaccinated cases the rate was lowest in the age group 0–17 years and rose moderately and irregularly in older age groups. The rates suggest uniformity, rather than diversity, in the age-specific incidence of the unvaccinated cases.

Interval from vaccination to onset

Figure 3 shows the distribution of the intervals, in weeks, from vaccination to the onset of Guillain–Barré syndrome. A substantial number (44) of the vaccinated cases began within one week. A sharp rise, to 123, occurred in the second week, progressing to a peak of 144 in the third week, followed by a rapid decline.

Table 4 shows the incidence rates of vaccinated cases for each week from the time of vaccination and the risks relative to the average rate of unvaccinated cases (0.185 per million person-weeks). The relative risk was greatest in the second and third weeks and some increased risk remained discernible up to the tenth week.

Analysis of numbers of vaccinated cases

Using the incidence rates shown in Table 4 and the numbers of persons known to have been vaccinated in each calendar week, it is possible to calculate the weekly numbers of vaccinated

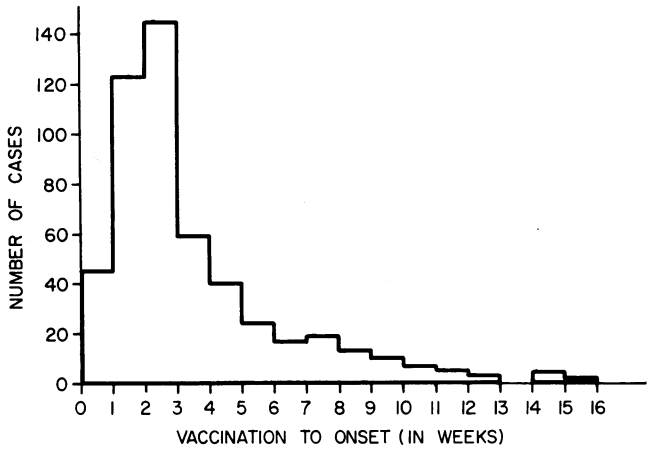

Figure 3. Distribution of the intervals from vaccination to onset of Guillain–Barré syndrome

Table 4. Guillain–Barré syndrome: incidence rates by weeks from vaccination

Weeks from vaccination	Cases	Rate●	Relative risk■	Weeks from vaccination	Cases	Rate●	Relative risk■
1	44	1.06	5.7	9	14	0.34	1.8
2	123	2.96	16.0	10	11	0.27	1.6
3	144	3.74	20.2	11	7	0.17	0.9
4	59	1.42	7.7	12	6	0.14	0.8
5	40	0.96	5.2	13	3	0.07	0.4
6	24	0.58	3.1	14	—	—	—
7	18	0.43	2.3	15	4	0.10	0.5
8	19	0.46	2.5	16	1	0.02	0.1

● Per million person-weeks
■ Assumed constant rate for unvaccinated cases 3 October–18 December = 0.185 per million person-weeks

cases that could be expected to have occurred. Table 5 shows the method of calculation, which resembles a cohort analysis. It has been assumed that the relative risks by week from the time of vaccination applied similarly to each weekly cohort of vaccinated persons, that the data on week of vaccination were accurately recorded and that the reporting of cases by date of onset was consistent.

Table 6 shows the completed analysis, which compares the weekly numbers of vaccinated cases observed with numbers expected from the calculation and with the estimated numbers of coincidental cases, the latter being derived by applying the average incidence rate of unvaccinated cases to the cumulative totals of vaccinated persons. Figure 4 shows the same analysis in the form of a graph.

The general correspondence of the observed and expected numbers of vaccinated cases justifies the assumptions underlying the analysis. The excess of observed cases in early December, with a compensating drop after the middle of the month, has the appearance of a statistical artefact. It was during December that awareness of a possible association of Guillain–Barré syndrome with swine influenza virus vaccine led to urgent nationwide surveillance and reporting, and it would seem reasonable to expect prompter diagnosis than during the period before the association was suspected. The concurrence of observed and expected cases in later weeks, through January 1977, suggests no under-reporting of vaccinated cases, even though reporting of unvaccinated cases may by then have declined.

Table 5. Guillain–Barré syndrome – vaccinated cases: calculation of 'expected' numbers

Week Ended		No. of vaccinated persons (1000s)	Week from vaccination	Rate by week from vaccination●	Expected cases for week ended: October 9	16	23	30	November 6	13	20	→
October	2	13										
	9	657	1	1.1	0.7	1.9	2.3	0.9	0.6	0.4	0.3	This
	16	1 943	2	3.0		2.1	5.7	6.7	2.8	1.9	1.1	calculation
	23	2 968	3	3.5			3.1	8.8	10.3	4.2	2.9	continues for
	30	4 100	4	1.4				4.4	12.1	14.2	5.8	16 weeks
November	6	4 424	5	1.0					4.7	13.1	15.3	from the
	13	4 866	6	0.6						5.2	14.4	December 16
	20	6 132	7	0.4							6.5	moratorium
	27	4 835	8	0.5								
December	4	4 614	9	0.3								
	11	4 391	10	0.3								
	18	2 546	11	0.2								
	25	—	12	0.1								
January	1	—	13	0.1								
	8	—	14	—								
	15	—	15	0.1								
	22	—	16	0.02								
Total		41 490		12.5	0.7	4.0	11.2	20.8	30.5	39.0	46.3	→

● From Table 4

Note: (1) Numbers on each horizontal line represent the epidemic in each week's cohort of vaccinated persons
(2) Sum of vertical columns represents expected number of cases to be observed each calendar week

Table 6. Guillain–Barré syndrome: vaccinated cases, observed and expected, with estimated coincidental cases

Week ended		Observed	Expected●	Estimated■	Week ended		Observed	Expected●	Estimated■
October	9	1	0.7	0.1	January	8	23	19.5	7.7
	16	2	4.0	0.5		15	18	14.2	7.7
	23	12	11.2	1.0		22	7	10.7	7.7
	30	20	20.8	1.8		29	8	8.4	7.7
November	6	29	30.5	2.6	February	5	—	6.4	7.7
	13	39	39.0	3.5		12	—	4.5	7.7
	20	45	46.3	4.7		19	—	3.0	7.7
	27	57	53.3	5.5		26	—	2.1	7.7
December	4	58	56.4	6.4	March	5	—	1.3	7.7
	11	68	55.3	7.2		12	—	0.7	7.7
	18	72	53.2	7.7		19	—	0.5	7.7
	25	21	44.3	7.7		26	—	0.3	7.7
January	1	33	30.6	7.7	April	2	—	0.1	7.7
					Total		513	517	

● From Table 5
■ Estimated coincidental cases calculated by applying average weekly rate of unvaccinated cases to the increasing cumulative totals of vaccinated persons

Discussion

Guillain–Barré syndrome is a well recognized form of polyradiculoneuropathy. Originally described by Landry (1859), it was differentiated from poliomyelitis and other neuroparalytic diseases by Guillain, Barré & Strohl (1916). During the past thirty years, studies (Asbury *et al.* 1969, Arnason 1975) in experimental pathology and immunology have resulted in a clear definition of its pathogenesis, which can now be ascribed almost certainly to a genetically influenced autoimmune delayed hypersensitivity.

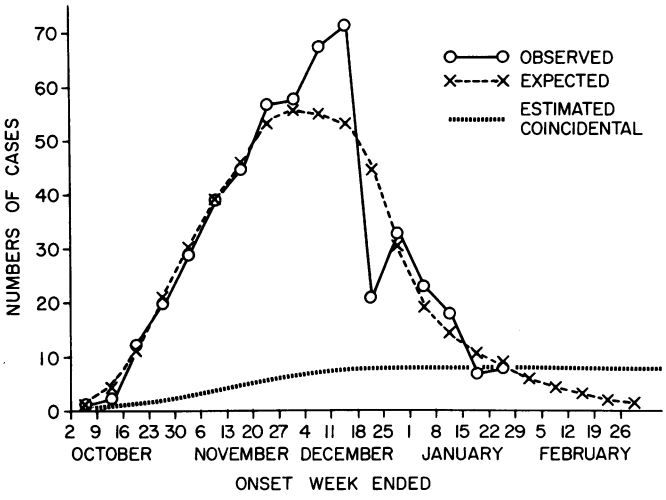

Figure 4. Guillain–Barré syndrome: vaccinated cases, observed and expected, with estimated coincidental cases

Much of the available epidemiological information about Guillain–Barré syndrome is based on data from hospital records and is difficult to interpret because of lack of accurate estimates of the populations from which the cases were drawn. The general impression is that the syndrome is widely distributed, affecting people of all races and of both sexes at all ages and at all seasons. The few studies that have been based on defined populations have shown the incidence rate to be low, about one case per 100 000 population per year. Kurland and colleagues (1973) summarized five such studies from different countries and estimated the annual incidence to have varied from 0.6 to 1.8 per 100 000. From 3 October to 18 December 1976, the incidence rate of unvaccinated cases of Guillain–Barré syndrome in the United States was 0.185 per million person-weeks (0.96 per 100 000 population per year). The correspondence of this rate with previous estimates is impressive.

In the numerous reports that have been made on single cases, or small groups of cases, evidence for specific aetiological factors is scanty and conflicting. Many such reports focus on some event that occurred during the month preceding the onset of the syndrome and was presumed to have acted as an inciting cause, but the variety of the presumed causes suggests that most of them were temporal coincidences without aetiological significance. More than 50% of cases of Guillain–Barré syndrome are preceded by a vague illness, usually febrile. This is almost certainly not viral influenza, since the symptoms are variable and the illness is generally mild and occurs at all seasons, independent of known influenza epidemics.

A few localized outbreaks of Guillain–Barré syndrome have been reported in recent years. At Itagui, a city of 95 000 inhabitants in the State of Antioquia, Colombia, 17 cases occurred in six weeks, from late March to early May 1968, mostly among persons less than 25 years of age (Lopez *et al.* 1973). The source of this outbreak was obscure. Upper respiratory infections had been common during the preceding month. No exposure to toxic substances was uncovered and no general programme of immunization had been in progress.

In January 1976, an outbreak of 16 cases was reported from El Sult, a town of 30 000 inhabitants about 30km west of Amman, Jordan (Sliman 1978). The cases followed, by 8–24 days, a waterborne outbreak of acute diarrhoea (5000 cases), typhoid fever (74 cases) and hepatitis (30 cases). People of both sexes and of all ages were involved.

The swine influenza virus vaccine incident of 1976–77 was the first outbreak of Guillain–Barré syndrome to have been associated with a general programme of immunization and formed one of the most dramatic and scientifically important events in the long history of vaccine disasters. Although different in its nature, the seriousness of the incident may be compared with that of the Lübeck disaster of 1930 (Wilson 1967), the yellow fever vaccine

incident in the Armed Forces of the United States in 1942 (J Fox, personal communication), and the Cutter poliovirus vaccine incident in 1955 (Nathanson & Langmuir 1963). The investigation of such incidents in the past has led to improved methods for the production and safety testing of vaccines and the recognition of diseases, such as hepatitis B, whose importance had not previously been sufficiently appreciated. It is to be hoped that a full analysis of the data collected during the swine influenza virus vaccine incident (Schonberger *et al.* 1979) will similarly lead to a better understanding of the pathogenesis of Guillain–Barré syndrome. A full resolution and elimination of this hazard will be necessary to restore public and professional confidence in influenza vaccination as a public health measure.

The preliminary analysis of the data presented in this communication establishes that the swine influenza virus vaccine preparations distributed in the United States during the fall of 1976 contained an inciting factor or 'trigger element' that resulted in the development of clinically recognized Guillain–Barré syndrome in one in 100 000 recipients of the vaccine. The relative risk of acquiring the disease during the six weeks after vaccination was about 10 times the endemic expectation. No marked differences were observed in age incidence, geographical distribution, manufacturer or type of vaccine, whether whole or split virus, or method of administration, whether by needle or jet gun.

The crucial question is what specific component of the vaccine contained the 'trigger element'. If one can accept the close analogy between experimental allergic neuritis and Guillain–Barré syndrome, for which the evidence is persuasive (Arnason *et al.* 1968), and the even closer analogy between experimental allergic neuritis and experimental allergic encephalomyelitis, then one could postulate that the 'trigger element' might be a specific protein or polypeptide sequence related to the basic protein of peripheral nerve myelin. Eylar and colleagues have synthesized a specific nonapeptide fragment of basic myelin protein which incites experimental allergic encephalomyelitis (Eylar *et al.* 1970). Polyneuritis, as well as allergic encephalomyelitis, is known to occur after the use, at one time common, of Semple-type rabies vaccine, which is prepared in tissues of the nervous system.

The postulated 'trigger element' could have been a component of the strain (Fort Dix) of swine influenza virus used in 1976 for making the vaccine. It could also have been present in the total mix that is common to all influenza virus vaccines, but not previously recognized because earlier vaccine surveillance systems were less sensitive and alert. Perhaps the simplest hypothesis is that residual myelin protein of chick embryo origin was retained in the vaccine through all its stages of manufacture, zonal centrifugation and other forms of purification. This hypothesis is widely accepted in the United States at the present time.

I favour the view that the 'trigger element' was an intrinsic part of the Fort Dix strain and was not present, at least not in similar concentration, in previous large batches of commercially prepared influenza virus vaccine. My reasons are based on confidence in the surveillance system originally established in the United States in the summer of 1957, when the Asian pandemic threatened. With this system an incidence of 1 per 100 000 of a syndrome as distinctive as Guillian–Barré syndrome should have been detected. Moreover, a seasonal variation in the incidence rate should have been induced by large-scale use of the vaccine and retrospective studies of Guillain-Barré syndrome should have revealed the association. But this has not previously been reported (Lenneman 1966).

Acknowledgment: I am particularly grateful to Dr Lawrence R Schonberger and Mr Dennis Bregman for their full cooperation in making the surveillance data available to me.

References

Arnason B G W (1975) In: Peripheral Neuropathy, vol 2. Ed. P J Dyck *et al.* Saunders, Philadelphia; pp 1110–1148, 233

Arnason B G W, Asbury A K, Astrom K E & Adams R D (1968) *Transactions of the American Neurological Association* **93**, 133–136

Asbury A K, Arnason B G W & Adams R D (1969) *Medicine (Baltimore)* **48**, 173–215

Eylar E H, Carram J, Jackson J J, Westall F C & Robinson A B (1970) *Science* **168**, 1220

Guillain G, Barré J A & Strohl A (1916) *Bulletin de la Société Médicale des Hôpitaux de Paris* **40**, 1462–1470
Kurland L T, Kurtze J F & Goldberg I D (1973) Epidemiology of Neurologic and Sense Organ Disorders. Harvard University Press; pp 221–223
Landry O (1859) *Gazette Hebdomadaire Médicale de Paris* **6**, 472–474, 486–488
Langmuir A D & Schoenbaum S C (1977) *Hospital Practice*, October; pp 7–14
Lenneman F (1966) *Archives of Internal Medicine* **118**, 139–144
Lopez F, Lopez J H, Holguin J & Flewett T H (1973) *American Journal of Epidemiology* **98**, 226–230
Nathanson H & Langmuir A D (1963) *American Journal of Hygiene* **78**, 16–81
Schonberger L B, Bregman D M, Sullivan-Bolyai J Z, Keenlyside R A, Ziegler G W, Retailliau H F, Eddins D L & Bryan J A (1979) The Guillain–Barré Syndrome following vaccination in the national influenza program in the United States, 1976–77 (in press)
Sliman N A (1978) *British Medical Journal* i, 751–752
Wilson G S (1967) The Hazards of Immunization. Athlone Press, London.