Long-term study of influenza in families

THE ROYAL COLLEGE OF GENERAL PRACTITIONERS AND THE PUBLIC HEALTH LABORATORY SERVICE

SUMMARY. This is an account of a five-year study of influenza in families during an inter-epidemic period. Proven influenza seemed to be a more severe illness than an influenza-like illness. The result of the study suggests that factors other than strain-specific antibodies may be responsible in protecting against influenza during a period of drift.

Introduction

MANY studies have been carried out to investigate individual epidemics of influenza, but few have been undertaken to observe the response of individuals within the family to challenges from different strains of influenza over a period of years. In the United States, Jordan (Jordan *et al.*, 1958) studied the epidemiology of influenza in a group of Cleveland families from 1948 to 1953, and Monto and colleagues (1971; 1975) reported on a long-term study of respiratory illnesses in Tecumseh. More recently, also in the United States, Frank and colleagues (1979) described influenza in families, including the longitudinal study of a group of children from birth. Hope-Simpson (1979) in Cirencester, England, described the study of antigenic variation of influenza in households in his practice from 1968 to 1976.

The present study, which extended from October 1973 to April 1978, followed a successful feasibility study with 120 volunteers over the 1972-73 winter period (Royal College of General Practitioners and the Public Health Laboratory Service, 1977).

Methods

Participants

General practitioners from the Royal College of General Practitioners (see Appendix), together with virologists from their nearest public health or hospital laboratory in England and Wales, were invited to join the study (see figure).

General practitioners and virus laboratories participating in the study.

Study procedure

Each general practitioner was asked to recruit two to five families and the members of these families agreed to stay in the study for five years if possible. A general convenor was appointed to each participating laboratory area, and a convenors' meeting was held annually in London. Regular progress reports were sent to all participating general practitioners and directors of the virus laboratories, as well as a less detailed report to each volunteer.

Volunteers over 15 years of age from the recruited families were asked to provide 10 ml of blood in October and April each year. This was delivered to the nearest participating laboratory where the serum was tested for its content of antibodies against the strains of

the current influenza A and B viruses, using antigens provided by the Standards Laboratory, Central Public Health Laboratories, Colindale, London. An aliquot of each sample of serum collected from the volunteers was sent to the Public Health Laboratory Service (PHLS) Virus Reference Laboratory at Colindale, where it was stored and used to retest doubtful or interesting results obtained by the peripheral laboratories.

The volunteers were asked to tell their doctors if they experienced an acute respiratory illness or a febrile illness, however trivial and at any time of the year, including the summer months. The doctor would record clinical details on a questionnaire form and take nose and throat swabs for virus cultures. Every calendar month, the doctor or one of his staff made enquiries to see if any member of the recruited families had failed to report an illness in the previous month, for example if the patient had been taken ill on holiday. A history of such an illness was recorded on a separate questionnaire and with all the other data was stored on computer at the PHLS Epidemiological Research Laboratory at Colindale. Swabs and details of illness were also taken from children under 15 years old, but venepuncture was generally carried out only in those over that age. However, when a member of the family reached 15 he or she was asked to volunteer. Attempts were made to replace the families who dropped out.

Table 1. Participating volunteers in each year of study according to age group.

	Age groups						
Year	15-24	25-34	35-44	45-54	55-64	65+	Total
1973/4	75	55	88	69	17	21	325
1974/5	86	67	88	84	29	25	379
1975/6	84	61	96	87	33	30	391
1976/7	71	63	105	94	37	24	394
1977/8	56	50	82	96	35	31	350

(143 volunteers remained through the whole study)

Results

Participating volunteers

The number of volunteers over 15 in each age group in each year is given in Table 1.

Incidence of influenza

During the five years of study there were no major influenza epidemics. There was a total of 709 recorded illnesses in adult volunteers, of which 34 were proven influenza by virus isolation. In addition there was one volunteer from whom blood was taken during the convalescent period of an illness which showed a four-fold rise in antibodies, although no virus had been isolated. This makes a total of 35 proven cases in adults. In 92 ill volunteers there were seroconversions to influenza A or B in the pre- and post-winter samples without isolation of the organism. The remaining 582

Table 2. Prevalence of symptoms in different categories of illness (adult volunteers).

	Proven influenza			Illness with seroconversion (over the winter period)				Illness without seroconversion (over the winter period)	
	Type A		Type B	Type A		Type B			
	Number of cases	%	Number of cases*	Number of cases	%	Number of cases	%	Number of cases	%
First symptom									
Nasal symptoms	9	*26*	—	29	*43*	10	*42*	372	*64*
Pharyngeal symptoms	17	*50*	—	29	*43*	7	*29*	320	*55*
Cough	15	*44*	—	17	*25*	3	*13*	140	*24*
Retrosternal pain	4	*12*	—	5	*7*	—	—	29	*5*
Pyrexia	11	*32*	—	17	*25*	2	*8*	87	*15*
Vomiting	2	*6*	—	3	*4*	—	—	17	*3*
Headache	15	*44*	—	15	*22*	4	*17*	151	*26*
Muscle pain	15	*44*		11	*16*	1	*4*	93	*16*
General symptoms									
Nasal symptoms	8	*24*	—	18	*27*	5	*21*	175	*30*
Pharyngeal symptoms	8	*24*	—	11	*16*	3	*13*	128	*22*
Cough	9	*26*	—	19	*28*	3	*13*	169	*29*
Retrosternal pain	1	*3*	—	3	*4*	—	—	23	*4*
Pyrexia	7	*21*	—	11	*16*	2	*8*	93	*16*
Vomiting	—	—	—	2	*3*	—	—	6	*1*
Headache	7	*21*	—	16	*24*	4	*17*	134	*23*
Muscle pain	5	*15*	—	14	*21*	3	*13*	93	*16*
Total number of illnesses	34	*100*	1	68	*100*	24	*100*	582	*100*

*The number of proven influenza B was only 1 and therefore there is no analysis in this column.

Table 3. Monthly distribution of proven influenza (all ages).

Year	Jan	Feb	Mar	Apr	May	June-Dec	A	B	Total
1974	3(1)*	1	7	2	—	—	13	1	14
1975	1	6	1	—	—	(1)*	8	1	9
1976	2	10(2)*	4	—	—	—	16	2	18
1977	1	—	4	1	—	1	7	—	7
1978	—	2	—	—	—	—	2	—	2
Total							46	4	50

*Influenza B

(82·0 per cent) illnesses were associated with neither seroconversion nor virus isolation, and were assumed to have non-influenzal causes. In addition to the 127 illnesses accompanied by virological or serological evidence of infection, there were 156 seroconversions without recorded illness (asymptomatic infections).

Fifteen influenza virus isolations were also made from children under the age of 15.

Clinical pattern

There were three categories of diagnosis:

1. Proven influenza.
2. Probable influenza—those who reported one or more illnesses during the winter and had a fourfold or greater increase in antibody titre between the autumn and spring bleeds.
3. Not influenza—no virus isolation and no significant rise in antibody titre.

The difference of proportion test was used to assess the significance of differences between the symptoms present in these three categories of illness. In the general pattern of symptoms, once the illness had become established, there were no significant differences between these categories (Table 2). However, there were some significant differences in the way the illness started.

Nasal symptoms such as a running nose or sneezing were very much less common at the start of proven and probable influenza than in the non-influenza group ($p<0·001$). An onset with muscle pain, a cough or a headache was significantly more common in proven influenza than in the non-influenzal illnesses (muscle pain—$p<0·001$; cough—$p<0·010$; headache—$p<0·025$) (Table 2).

Severity of illness

The duration of the illness in the three categories was similar, but of the patients who went to bed, those who suffered from proven influenza stayed there an average of three days compared with only one day in those with non-influenzal illnesses.

Prevalent strains

A/Port Chalmers was isolated from 13 volunteers during the first four months of 1974 (Table 3). There was also one isolation of B/Hong Kong/5/72 in January of that year. During the first three months of 1975, there were eight isolations of A/Scotland/840/74 but none of A/Port Chalmers. In January, February and March 1976 there were 16 isolations of A/Victoria/3/75 but none of the previous two strains. Two isolations of B/HK/5/72 were made in February of that year and one in December 1975. In 1977 a further five isolations of A/Victoria/3/75 were made in the first four months, and one isolation of the same strain at the end of June, the only summer isolation in the study. In February 1978, A/Texas/1/77 was isolated from one patient and, in the same month, A/USSR/90/77 from a girl aged 20.

Influenza virus like B/HK/5/72 was isolated from a 12-year-old girl in February 1976. Three weeks later she developed a second similar febrile illness but this time a swab yielded influenza virus like A/Victoria/3/75.

No isolations were made of A/Hong Kong/1/68, A/England/42/72 or A/England/864/75 like strains.

Proven influenza

In the five years of study there was a total of 50 proven cases in 35 adults and 15 children from 43 families; 46 were of influenza A and the remaining four were of influenza B.

Households in which there were proven cases of clinical influenza

Out of four proven cases of influenza B, three were in children under the age of 15, while the fourth was in a patient aged 15 (Table 4). Of the 46 proven influenza A infections, 12 were in children under the age of 15, and the rest were in adults over 15. There were 143 adults aged 15 years and over and 56 children under 15 in these households, therefore clinical illness due to influenza infections was proven in 27 per cent of the adults and 24 per cent of the children in the five years of study.

Illness in infected households

Out of 199 persons in the infected households, 73 reported an illness around the time an influenza virus was isolated from one of the family. Fifty of these adults and children were proven cases. Of the remaining 23, eight showed a fourfold or more increase in antibodies over the winter period to the same influenza strain as that isolated from the relevant household; two converted to an unlike strain and the remaining 13 who were ill showed no seroconversion. Nine volunteers in these families showed a significant seroconversion over the winter period without reporting an illness. All but one conversion corresponded to the influenza strain which was known to have infected their own particular household.

The first onset cases in households

There were 43 families exposed to proven infection by an influenza virus (40 to influenza A and three to

influenza B). First onset cases were all those who became ill within 48 hours of the time of onset of the first case in the house. Proven cases occurred as first onset cases in 38 exposures and in nine of these they were shared by two people in one household with proven or probable influenza of the same strain. There were only three instances in which the first onset case showed a seroconversion and no isolation of virus. In the other three instances, the person who had the first date of onset showed neither a positive swab nor a seroconversion to the infecting strain over the winter period. One of them, a child of 14, did not have blood taken for serology.

There were 11 occasions when the first onset case was a child under 15 years of age and from nine of these the virus was isolated. In 24 cases the first onset was in adults and from 18 of these the virus was isolated. In nine family incidents simultaneous first onset cases occurred, twice with parent and child, and seven times with two adults sharing a household.

Secondary onset cases in households

Secondary onset cases were those who started their illness between the third and tenth day after the time of onset of the first case in the house. Any cases occurring after the tenth day were regarded as fresh introductions of infection to the house. There were 13 secondary onset cases, and the virus of the infecting strain of influenza A was isolated from 10 of these; two showed a seroconversion to a similar strain and one had no such seroconversion in spite of a pre-winter antibody titre to the relevant influenza A antigen of less than 1/10.

Secondary attack rate

The overall household secondary attack rate was nine per cent (Table 5), and the rate was the same whether they were adults or children. When the first onset case was an adult, the secondary attack rate among the rest of the adults was again nine per cent, but nil among the children. In households where the first onset was a child, the secondary attack rate among the adults was 11 per cent and 31 per cent among the children.

Seroconversion without illness

Although 71 of the adult volunteers in these households reported no illness, eight showed a seroconversion to the same strain of influenza A as that which had infected their own family. Of the remaining 63 who had each been in contact with a proven case, none showed evidence of infection by seroconversion. Fifty-two (82·5 per cent) of them had a pre-winter antibody titre of 1/10 or less to the relevant infecting strain, six (9·5 per cent) had titres of 1/20, three (4·8 per cent) of 1/80, and one each of 1/320 and 1/640.

Discussion

It was very difficult to distinguish clinically between influenza and other non-influenzal illnesses once the disease had become established. The statistical difference of proportion test showed no significant difference in the clinical pattern at this stage. However, there were differences in the way the illness started in the two groups. Proven influenza more often started with general symptoms, like aching muscles or a headache; naso-pharyngeal symptoms came later. On the other hand, naso-pharyngeal symptoms more often heralded the non-influenzal group. These differences were also proved significant by the tests described earlier in this paper. In a previous study of influenza, Williams (1971) found that the feeling of being abnormally cold was the commonest first symptom and that respiratory symptoms followed later. In this study, influenza itself seemed to be a more severe illness than that seen in the other group; patients who had taken to their bed stayed there an average of three days compared with one day in the non-influenzal group. However, not all influenzal infections produced an illness.

In 156 adult volunteers there was a fourfold increase in antibody titre to influenza between the pre- and post-winter periods without a reported illness, compared with 127 cases who were ill and showed sero-

Table 4. Proven influenza infections according to age groups.

Influenza type	Age groups 0-4	5-14	15-24	25-34	35-46	47-54	55-64	65+	Total
A	2	10	14	1	10	6	3	—	46
B	—	3	1	—	—	—	—	—	4
Total	2	13	15	1	10	6	3	—	50

Table 5. Secondary attack rate in households with proven cases.

	Number of first onset cases	Number of persons in households of first onset cases		Number of secondary cases		Percentage secondary attack rate	
		Adults	Children	Adults	Children	Adults	Children
First onset in adults only	38	70	29	6	—	9	—
First onset in children only	11	28	13	3	4	*11*	*31*
Simultaneous in a child and an adult	4	2	4	—	—	—	—

Table 6. Individuals with two or more seroconversions to influenza A.

Survey number	Year	Antigen	Year	Antigen	Year	Antigen	Age in 1977/8
01-111	1976/7	A5	1977/8	A8			46
01-123	75/6	A3/5/6	77/8	A8			18
03-324	73/4	A2	76/7	CFT A			24
04-241	74/5	A3/4	76/7	A5			62
05-121	73/4	A1	76/7	A5			61
05-134	73/4	A1/2/3*	77/8	A5			19
09-312	73/4	A1/3*	75/6	A5			30
13-332	74/5	A4	77/8	A8			34
15-213	73/4	A1/2/3	77/8	A5/7			20
16-121	73/4	A1/2/3	75/6	A5			56
16-124	73/4	A1/2/3	77/8	A5/7			16
16-134	74/5	A3	75/6	A3			43
17-141	74/5	A3	75/6	A3/4/5/6	76/7	A5	50
20-126	74/5	A3/4	75/6	A3/4/5/6	77/8	A8	18
21-111	73/4	A1/2/3	75/6	A3			42
22-155	76/7	A5	77/8	A8			19
25-211	73/4	A2	75/6	CFT A			45

*Isolation of virus.
Key: A1 = A/HK/1/68, A2 = A/Eng/42/72, A3 = A/Port Chalmers/73, A4 = A/Scot/840/74, A5 = A/Vic/3/75, A6 = A/Eng/864/75, A7 = A/Tex/1/77, A8 = A/USSR/90/77.

logical or virological conformation. Volunteers were under surveillance in order to make sure, as far as possible, that no illness was missed. Nevertheless, there was a fall in reported illnesses in the last year of the study. This was due to either lack of reporting or to less illness. The PHLS surveillance study had shown a steady fall in consultations for respiratory illness over the same period of the study. Even if there was some lack of reporting in the last year of the present study, the weight of evidence is sufficient to show that well over half of the serologically proven cases were asymptomatic. This supports the findings of Miller and colleagues (1973) in their study of influenza among airforce personnel.

Only a small number of cases were confirmed by virus isolation. It could be argued that the technique of collecting and the attempt at isolation were below standard, but a possible explanation is that the study had been carried out during a period of drift when the isolation of the virus may not be as successful as during an epidemic, especially that caused by a major antigenic change (a period of shift). During a period of drift the virus may be disappearing quickly from the nasopharyngeal cavity by adopting a form not identifiable by swabbing and possibly not by electron microscopy. This could be the latent stage suggested by Hope-Simpson (1979) and Stuart-Harris (1965). This may also explain the difficulty of isolating the virus during the summer months; there was one isolation in June in this study. Another reason for the difficulty in isolation may be cross-reacting antibodies which are common to viruses within the H_3N_2 subtype. These factors during a drift may exert an inhibiting influence on the replication of the virus. This would result in fewer virus particles being produced, making isolation more difficult and the person less infectious.

In this period of drift the secondary attack rate in the infected households was lower than usually seen in a period of shift, in spite of the virus being isolated from at least one member of the house, confirming Hope-Simpson's (1979) observations in his long-term studies of influenza in his practice. Insofar as our present data are concerned, in the 43 infected households children seemed to infect children more often than they infected adults and vice versa. The number, however, is very small, and there is a need to replicate the exercise with the same or larger numbers to see if the situation is repeated. One simple explanation would be that persons of similar age groups are more in contact with each other than with other groups. It is surprising that the secondary attack rate was nil among the children when the first onset case was an adult. Although the volunteers in the study were over 15 years of age, families were asked to report illnesses in their children under 15, but blood samples were not taken as a routine. Reporting of illnesses in children in the study as a whole may possibly not have been as consistent as in the adult volunteers, but in households where the virus had been isolated there was a stimulus for the parent to report illnesses in their children. The doctor, also, in such cases would be more likely to investigate and report accurately. It is interesting that 52 adult volunteers in these households reported no illness and had no serological evidence of recent influenzal infection, in spite of having a pre-winter antibody level to the relevant infecting strain of 1/10 or less. If a haemagglutination inhibiting titre of 1/40 is regarded as the level of protection, then a great number of these volunteers were unprotected and susceptible to infection by the strain of virus present in the house at the time. It is reasonable, therefore, to suspect that some factors other than strain specific antibodies may be playing a part in their

protection as, for example, a cell mediated immunity, a non-specific antiviral agent such as interferon or a cross-immunity from previous strain specific antibodies. In fact, not enough is yet known about the relevance of previous influenza infection to subsequent susceptability. The present study provides some information of this kind, but the numbers are too small for firm conclusions to be drawn (Table 6).

Laver and colleagues (1974) and Schild and colleagues (1977) describe cross-reactive antibodies as well as strain specific antibodies for various strains of the H_3N_2 subtype. "Pre-existing antibody or antigenic memory of the strain specific determinant of an earlier strain actively blocks the immunological expression of the strain specific determinant of a later strain although the mechanism of the block is not known" (Schild *et al.*, 1977). The population immunity to the preceding strains in the same subtype may, therefore, be sufficient to reduce the effects of challenges from each new strain. This was also observed by Gill and Murphy (1977) in their study of volunteers in general practice in Epping, New South Wales, Australia. They also found that patients with a previous history of laboratory proven infections by one of the earlier strains of the Hong Kong subtype had an illness not as severe as those with no previous history.

Appendix

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