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A Five-Year Study of Influenza in Families

Joint Public Health Laboratory Service/Royal College of General Practitioners Working Group

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SUMMARY

A five year collaborative study of influenza in volunteer families from 1973–78 covered a period in which there were outbreaks every year but no major epidemics of influenza. Volunteers over the age of 15 years were bled before and after each of the five winters, and virus isolation was attempted from as many as possible when they reported episodes of illness. Children under 15 in the volunteer families were also swabbed when they were ill. Although most families experienced one or more attacks by influenza viruses, there was little transmission within families.

INTRODUCTION

The epidemiology of influenza in families has been studied in a number of communities. In the Cleveland study (Jordan, Badger & Dingle, 1958) about 60 families, all with young children, were observed for some years over the latter part of the reign of H_1N_1 influenza A viruses and the antigenic shift to H_2N_2 (Jordan *et al.* 1958). They demonstrated significant increases in titre to both A and B viruses in individuals who were not ill, and at times when the viruses were not being isolated. Philip *et al.* (1961), in a 5 year study, isolated influenza virus A during epidemic periods from a few individuals who were not ill, but all their isolations of influenza virus B were from people with acute febrile or respiratory illnesses. In the Seattle virus watch, Hall, Cooney & Fox (1973) postulated that pre-school children were the spreaders and introducers of influenza viruses to families. They reported serological evidence of infections by both influenza viruses A and B between April and November when there was no other evidence of virus activity.

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Table 1. *Influenza haemagglutination inhibition tests and study population*

Year of test	Antigens used	No. of volunteers	No. of families
1974	A/Hong Kong/68, A/Eng/42/72 A/Port Chalmers/1/73; B/Hong Kong/5/72, B/Eng/21/68, B/Eng/847/73	325	123
1975	A/Port Chalmers/1/73, A/Scotland/840/74; B/Hong Kong/5/72	379	149
1976	A/Port Chalmers/1/73, A/Scotland/840/74, A/Victoria/3/75, A/England/864/75; B/Hong Kong/5/72	391	156
1977	A/Victoria/3/75; B/Hong Kong/5/72	394	164
1978	A/Victoria/3/75, A/Texas/1/77, A/USSR/90/77; B/Hong Kong/5/72	350	150

Table 2. *Number of children under* 15 *years in study families*

	Number of families with the stated number of children						Total
Year	None	1	2	3	4	5	families
1973–4	38	26	40	12	4	3	123
1974–5	46	30	49	18	2	4	149
1975–6	59	30	43	18	4	2	156
1976–7	64	32	42	20	3	3	164
1977–8	75	23	35	14	2	1	150

Stuart-Harris & Schild (1976) found household influenza difficult to explain on the basis of an introduced infection followed by secondary spread. They considered that the part played by subclinical infections should be investigated by serological studies in addition to virus isolation. Our five year study was set up in 1973, following a pilot trial, with the aim of investigating the role of the family in influenza. Serology was based on the regular collection of sera in spring and autumn, and virus isolation was attempted in episodes of illness. A preliminary report, which described the organization of the study and the first winter's work, was published in 1977 (Royal College of General Practitioners and the Public Health Laboratory Service). A separate report of the clinical aspects of the study is being prepared (Royal College of General Practitioners and the Public Health Laboratory Service, 1981).

METHODS

The study ran from the autumn of 1973 to the spring of 1978, covering five winters.

The study population were members of families recruited by general practitioners widely scattered through England and Wales who offered to participate in the study. Each doctor recruited between two and five families who agreed to report their illnesses to him and to allow him to collect specimens for virus isolation when they were ill. All family members aged 15 years and over agreed to be bled in the

autumn (usually October) and spring (April or May) of each year. General practitioners took nose and throat swabs for virus isolation from them when they had acute respiratory or febrile illnesses; they were encouraged to take swabs also from younger children suffering similar illnesses.

A number of volunteers withdrew from the study for various reasons. Some members of families left, for example to go to university, some died and some entire families withdrew, usually because they moved. In a few instances a general practitioner left his practice and his successor was unable to continue the study. One hundred and forty three of the original 325 volunteers remained throughout the study. Before each winter, general practitioners were encouraged to recruit new families, and the number of volunteers participating in each winter is shown in Table 1. Children of volunteers were encouraged to join the study when they reached the age of 15. There was an average of 1·4 children per family in the first two winters of the study, but this figure fell in subsequent winters to 1 in 1977–78. Details are given in Table 2.

Laboratory Investigations

Sera and throat swabs were examined in laboratories of the PHLS and in other virus laboratories accessible to the participating general practitioners. The sera were stored at −20 °C and tested for complement fixing and haemagglutination-inhibiting (HI) antibodies in the summer of each year. The antigens used in the HI test are listed in Table 1. They were prepared by the PHLS Standards Laboratory, Colindale, and were issued with titrated control positive sera. Study sera were treated with *V. cholerae* receptor-destroying enzyme of known potency before HI tests were carried out. In the summer of 1974, sera collected in autumn 1973 and spring 1974 were examined. In 1975, spring and autumn 1974 sera and spring 1975 sera were tested together. Parallel testing of spring–autumn–spring serial sera was continued in each subsequent year. Laboratories sent aliquots of all sera to the Virus Reference Laboratory, where a proportion, including those from which unexpected results were obtained, were retested. If there was disagreement the results from the Virus Reference Laboratory were accepted.

The nose and throat swabs in transport medium were sent to local laboratories where they were inoculated into monkey kidney cells for influenza virus isolation.

Recording of information

Details of illnesses reported, viruses isolated and serological findings were collated centrally, and an interim report was issued to participating laboratories, general practitioners and volunteer families after each winter. The information collected enabled the following groups from among the volunteers to be identified:

Proven influenza. Those from whom virus was isolated at the time of illness or whose antibody titres to the relevant virus showed a fourfold or greater rise during convalescence. Only a few convalescent sera were sent to laboratories.

Probable influenza. Those who reported one or more illnesses during the winter and developed a fourfold or greater rise in antibody titre between the autumn and spring specimens.

Asymptomatic influenza. Those who did not report an illness during the winter, but developed a fourfold or greater rise in antibody titre between autumn and

spring sera. There were also a few volunteers who developed rising titres during the summer, but most of them could be accounted for because the spring specimen of serum was collected before the end of the influenza outbreak.

Non-influenzal illness. Those who reported illnesses but whose sera showed no significant rises in antibody titre.

The clinical details of the illnesses were recorded and form part of a separate report.

RESULTS

Proven influenza

The number of cases in each winter is recorded in Table 3.

Table 3. *Cases of proven influenza*

	Influenza A			Influenza B	
Year	Adults	Children	Strain type	Adults	Children
1973–4	9	4	A/Port Chalmers	0	1
1974–5	5	3	A/Scotland/840/74	0	0
1975–6	12	4	A/Victoria/3/75	1	2
1976–7	5	1	A/Victoria/3/75	0	0
1977–8	3*	0	A/Texas/1/77, A/USSR/90/77	0	0
Total	34	12		1	3

* Includes one isolation of an A/Victoria/3/75-like strain in June 1977.

Probable influenza and asymptomatic influenza

The number of seroconversions (excluding those in patients reported in table 3) is shown in Table 4.

Table 4. *Probable influenza infections*

	Influenza A		Influenza B	
Year	With illness	Asymptomatic	With illness	Asymptomatic
1973–4	13	12	16	15
1974–5	13	23	2	2
1975–6	26	39	4	13
1976–7	10	21	1	4
1977–8	6	26	1	2
Total	68	120	24	36

Non-influenzal illnesses

Numbers of cases of reported illness without seroconversion during each winter are recorded in Table 5.

Evidence of transmission of influenza within households

One or more members of each of 40 families had proven influenza A. In 12 families there was evidence that another member had influenza at about the same

Table 5. *Non-influenzal illnesses*

Year	No. of illnesses without seroconversion		Volunteers in study	Illness rate (%)
1973–4	113		325	35
1974–5	125		379	33
1975–6	136		391	35
1976–7	121		394	31
1977–8	087		350	25
Total illnesses	582	Volunteer/ years	1839	32

Table. 6. *Transmission of influenza within families*

	Cases of proven influenza		Number of families (Number of members)		Number of families with: Other proven or probable cases of influenza	Asympto-matic influenza	No evidence of other influenzal infection
Year	Adults	Children					
1973–4 'flu A	9	4	10	(38)	4	1	5
'flu B	0	1	1	(5)	0	0	1
1974–5 'flu A	5	3	7	(31)	1	1	5
'flu B	0	0	—	—	—	—	—
1975–6 'flu A	12	4	15	(73)	4	2	9
'flu B	1	2	3	(15)	0	0	3
1976–7 'flu A	5	1	5	(22)	3	0	2
'flu B	0	0	—		—	—	—
1977–8 'flu A	3	0	3	(15)	0	0	3
'flu B	0	0	—		—	—	—
Total 'flu A	34	12	40	(179)	12	4	24
'flu B	1	3	4	(20)	0	0	4

1 family was affected by both influenza A and B in 1975/6.

time and serological evidence of asymptomatic infection was found in one or more members of four other families. Details are given in Table 6. Figure 1 shows the percentage of cases occurring on each day of household outbreaks. Seven cases of 'probable influenza' occurring beyond the ninth day of the outbreak were excluded (Jordan *et al.* 1958). It is noteworthy that of the family contacts that showed no evidence of seroconversion, 61 had antibody titres of 10 or less to the relevant antigen, in seven the titre was 20 and in five there was a titre of 40 to the relevant antigen or one closely related to it. The antibody status of seven adult members of the families was unknown.

There were four isolations of influenza B, three from children and one from a 15 year old. There was no evidence of transmission of this virus in the families, and only 2 of the adult family contacts had antibody titres of 40 or more.

In one family a child had influenza B followed three weeks later by influenza A.

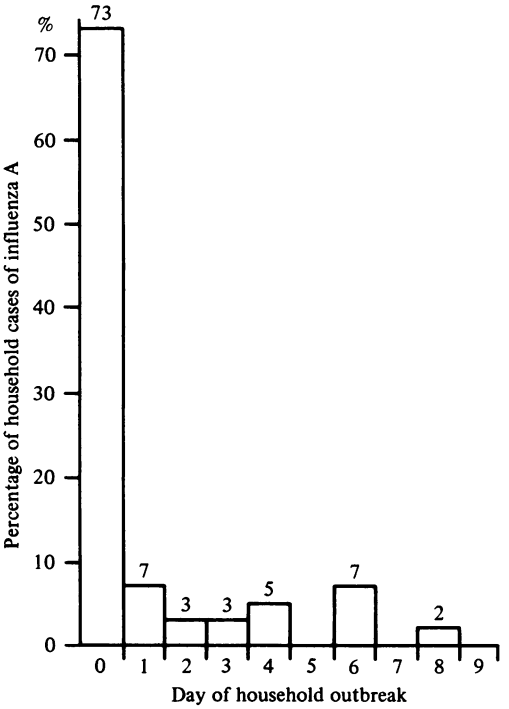

Fig. 1. Percentage of cases occurring on each day of household outbreaks.

Families without evidence of infection

Twenty seven families, with 56 adult volunteers, spending at least three years in the study, showed no serological evidence of infection.

Uninfected individuals from families that had influenza

Influenza A. Ninety-two individuals from 62 families comprising 216 volunteers in which there was evidence of influenza A failed to produce rising antibody titres. They were exposed to 23 proven infections and 68 probable or asymptomatic infections. The highest HI titre to any influenza A antigen at entry to the study was $\geqslant 40$ in 42, 20 in 16 and 10 or less in 34.

Influenza B. Thirty-six individuals from, 28 families comprising 97 volunteers in which there was evidence of infection by influenza virus B did not produce rising antibody titres to the virus. They were exposed to two proven infections, and 30 of their family contacts developed rising antibody titres to influenza B. The highest titre on entry to the study was $\geqslant 40$ in 8, 20 in 6 and < 10 in 25.

Families participating for five years

Seventy families remained in the study throughout the period. Of the 216 members of these families who volunteered, 143 participated for five years. Influenza virus A infections were detected in 57 families, influenza B in 3 and in 10 there was no serological evidence of infection.

Table 7. *Volunteers in study for 5 years with more than one seroconversion*

Strains	No. of volunteers	Ages at entry to study
Influenza A H_3N_2 & H_1N_1	2	16, 42
Influenza A H_3N_2 & H_3N_2	7	15, 16, 26, 39*, 40, 52, 58
Influenza A H_3N_2 & Influenza B	4	21, 39*, 42, 49
Influenza A H_1N_1 & Influenza B	1	33

* Same patient.

Of the 143 volunteers, there was evidence of infection by influenza virus A in 67, 15 had seroconversions to influenza virus B only and no evidence of infection was detected in 61. Thirteen had seroconversions in more than one winter; details are given in Table 7. Fourfold or greater rising titres to influenza A viruses of H_3N_2 serotype were observed twice in 7 volunteers, in one of whom rises to A/Port Chalmers were observed in both 1974–75 and 1975–76. Seroconversions to H_3N_2 viruses were followed by evidence of H_1N_1 infections in only two volunteers, but a boy from one of these families who joined the trial at the age of fifteen and stayed the remaining four years was infected successively by two H_3N_2 strains as well as one of influenza virus B. One patient showed two seroconversions to H_3N_2 strains as well as one to influenza virus B.

DISCUSSION

The period of the study was one of antigenic drift of influenza virus A in which the H_3N_2 viruses had become established. In 1973–74 the A/Port Chalmers sero-type predominated, and although it remained the most frequently isolated strain in the United Kingdom in 1974–75, the predominant strain from volunteers was like A/Scotland/840/74. In 1975–76 and 1976–77, A/Victoria/3/75-like strains were the only ones found in the study. In 1977–78 there was one isolation each of an A/Texas-like strain and an A/Victoria-like strain in June 1977. In none of the winters was influenza severe.

Seventy of the original 123 families that joined the study continued throughout it. Of the 325 volunteers at the outset of the study, 143 remained in it for the full 5 years. Ten (14%) of the families and 61 (19%) of the volunteers showed no serological evidence of infection, but thirteen volunteers experienced more than one infection in the five year study period. This is comparable with the 6% of reinfections in adults reported by Frank *et al.* (1979) in their study of 2–3 years. The reinfection rates in children reported by these authors and by Hall, Cooney & Fox (1973) was much higher.

The spread of influenza through families was very limited, as in the Cleveland study (Jordan *et al.* 1958). There was evidence of transmission in only 12 of the 40 families in which there were cases of proven influenza infection. Buchan (1972), describing the impact of influenza A on the island of Lewis in 1969–70, observed that the presence of school children in a household almost doubled the chance of infection in that household, but Hall, Cooney & Fox (1973) considered that they were not as important as pre-school children. Both these studies included the period immediately following the introduction of the H_3N_2 (Hong Kong/68) virus and

are therefore probably not comparable with this study which was conducted during a period of virus 'drift' rather than 'shift'. As Table 2 shows, the families in this study contained sufficient children to enable their importance as introducers of virus to be observed.

Swabbing of children below the age of 15 when they were ill produced useful additional evidence of influenza in families, but it was of limited value because antibody studies were not in general possible since the children were not bled for reasons of protocol. Our Figure 1, like the figure produced by Hope-Simpson (1979) shows a low rate of secondary cases within families and indicates that in households with more than one infection, most cases became ill on the same day. This suggests a common source of infection or possibly the reactivation of virus previously latent in a member of the household as Hope-Simpson (1979) postulated. He suggested that latency followed by reactivation might be responsible for infection in household contacts in the following year. Hall, Cooney & Fox (1973) observed that influenza viruses A and B were being transmitted at a low level in Seattle 'off season' and considered that this was a more likely explanation for the persistence of the viruses in the community. Our study showed little evidence of influenza virus activity out of season, but, unlike the studies in Seattle and in Tecumseh (Monto & Keoumehr, 1975) we did not collect sera from children under 15, in whom they found the highest incidence of seroconversions to influenza viruses. Latency might be expected to show itself by the observation that one member of a family was infected in one influenza outbreak, with evidence of influenza in other members of the family some months later, probably in the following winter. However, among the 70 families that participated throughout the study, there were ten instances in which two or more members were infected in consecutive years by H_3N_2 strains of influenza virus A, 12 families with more than one member infected in the same winter and nine in which two or more years elapsed between infections in different individuals. If failure to stimulate an antibody response is to be regarded as evidence of virus latency, this might account for the two isolations in 1977–78 which were not followed by rising titres of antibody, but it must be emphasized that these were the only such instances we recorded, and both volunteers were ill. It has long been known that virus isolation from cases of influenza is not inevitably followed by a serological response (Stuart-Harris, 1953). Although this study produced little evidence of influenza virus activity at times when influenza was not seen in the community (one influenza virus A isolate and five summer seroconversions) the findings do nothing to advance the theory of virus latency.

One hundred and two volunteers developed proven or probable influenza A (Tables 3, 4) and 120 had evidence of asymptomatic infection. The possession of antibody at what are usually regarded as protective levels (an HI titre of 40 (Pereira *et al.* 1972; Miller *et al.* 1973)) does not appear to have been important in preventing the spread of influenza virus to other members of the families of cases of proven or probable influenza. There was no evidence that asymptomatic influenza was associated with the spread of virus in families. The high proportion of infections by influenza virus A that do not cause symptoms have been observed by others (Hope-Simpson, 1970; Miller *et al.* 1973). We have confirmed this finding over a period of five years of antigenic 'drift' but it would be useful to mount a study of this kind when there is a major antigenic change in the virus circulating in the community being studied.

Table 8. *Consultation rates for acute respiratory illnesses from PHLS influenza surveillance study*

	Ages			
	15–24	24–44	45–64	'64+
1973/4	16·2%	12·6	11·1	11·1
1974/5	14·5	11·2	9·1	8·0
1975/6	13·4	10·5	8·1	6·9
1976/7	12·8	9·3	7·5	5·7
1977/8	12·0	8·2	6·9	5·5

The large number of non-influenzal illnesses recorded in the study (Table 5) may be compared with the reports of first consultations for acute respiratory illnesses by general practitioners participating in the PHLS collaborative influenza surveillance programme (PHLS 1977) for the period of our study in Table 8. Since our volunteers were required to notify illness for which they did not consult their general practitioners, it is not surprising that our rates were higher. We recorded illness rates of 33% or more in the first three winters of our study, followed by a fall in 1976–77 and 1977–78. The acute respiratory consultation rates reported by general practitioners in the influenza surveillance programme for age groups similar to those in the family study (Table 8) fell throughout the period. The incidence of influenza A in 1973–74 was less than half that of 1974–75 (PHLS 1977) so it does not seem that influenza had a marked effect on either the number of recorded incidents of illness in this study or the number of consultations with general practitioners for acute respiratory illnesses.

This study has yielded further information on the occurrence of influenza in families and demonstrated that there is surprisingly little virus transmission within them. Families do not seem to be important in the dissemination of influenza viruses, at least in times of antigenic 'drift'.

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