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The laboratory surveillance of influenza epidemics in the United Kingdom 1968–1976

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SUMMARY

The extensive laboratory investigations of respiratory disease in the U.K. over many years have demonstrated the frequency with which influenza viruses, both A and B, are found each winter. Only rarely are none isolated.

These findings correlate well with other indicators of influenza such as increases in sickness benefit claims and in deaths attributed to influenza and pneumonia.

However, outside these demonstrable peaks of incidence influenza viruses have been found to circulate over considerably longer periods often first appearing as early as November and continuing through to April or even May. But there has been no regular or predictable pattern determined.

The period of 1968–76 has seen a series of differently developing influenza winter epidemics caused by a series of the H3N2 virus. The contributions of virus isolation and serology to influenza surveillance is discussed.

INTRODUCTION

The monitoring of influenza in the United Kingdom over many years has demonstrated the regularity with which outbreaks occur almost every winter, such that evidence of the circulation of influenza viruses has been found in all but two of the past 18 years (Pereira, 1976).

However, the extent and severity of outbreaks is variable and unpredictable as is the occasional winter when there is no outbreak at all.

The factors which have been found to be important in making some forecast for each coming winter are the knowledge of which viruses have circulated in previous years, which have been found in the immediately preceding months in the southern hemisphere and what proportion of the population has already been infected with such strains and is immune to further attack.

The surveillance of influenza in the United Kingdom has intensified in recent years so that the impact of the disease is regularly measured in several ways; by the increase in the number of sickness benefit claims by the working population, by the rise in the general practitioner consultation rates for acute respiratory illness and by the notification of deaths attributed to influenza.

These combined indices offer evidence for the occurrence of the disease and

Table 1. *Influenza viruses isolated in the U.K.* 1968–1976

	Influenza A		Influenza B	
	Number	Variant	Number	Variant
1968–69	881	A/Hong Kong/68 (H3N2)	5	B/England/68
1969–70	809	A/Hong Kong/68 (H3N2)	95	B/England/68
1970–71	51	A/Hong Kong/68 (H3N2)	96	B/England/68
1971–72	751	A/Hong Kong/68 (H3N2)	2	B/England/68
1972–73	1290	A/England/42/72 (H3N2)	90	B/England/68 B/Hong Kong/72 B/Intermediate
1973–74	575	A/Port Chalmers/73 (H3N2)	601	B/Intermediate B/Hong Kong/72
1974–75	941	A/Port Chalmers/73 (H3N2) A/Scotland/74 (H3N2) A/Intermediate (H3N2)	5	B/Hong Kong/72
1975–76	2027	A/Victoria/75 (H3N2) A/England/864/75 (H3N2)	582	B/Hong Kong/72

almost invariably this is supported by the isolation of influenza viruses, and by the demonstration of the acquisition of specific antibodies in serum surveys in the general population.

The laboratory investigation of acute respiratory disease continuously throughout each year has allowed the presence of influenza virus to be precisely established and the development, peak and decline of epidemics has now been followed for several years. Not only has this clarified the picture in regard to influenza A but has provided information about the circulation of influenza B virus which tends not to be reflected by the other indices for influenza prevalence since the age groups affected are predominantly below working age and rarely ill enough to be admitted to hospital or die.

The winters of 1968–76 have been particularly interesting because of the remarkable frequency of antigenic changes which have occurred in the influenza viruses during this period. These are indicated in Table 1.

The new subtype A/Hong Kong/68 (H3N2) circulated unchanged for four successive winters causing epidemics each year except the third and was accompanied in the second and third winters by influenza B. In the following four winters the A/Hong Kong/68 virus underwent rapid antigenic drift with the appearance first of the variant A/England/42/72 which circulated in the winter of 1972–3, accompanied by influenza B, and then of the variant A/Port Chalmers/73 in the winter of 1973–4 again accompanied by influenza B virus, some of a new variety typified by B/Hong Kong/72 virus.

The winter of 1974–5 saw the return of the A/Port Chalmers/73 virus, accompanied by another variant A/Scotland/74, both of which disappeared by the following winter when further variants A/England/864/75 and A/Victoria/3/75 became the predominant viruses, again with influenza B.

The effect of these changes on the epidemiology of influenza in the United Kingdom is here described.

MATERIALS AND METHODS

Virus isolations

There exists in the U.K. a network of nearly 50 laboratories, both in the PHLS and in hospitals, all equipped to isolate influenza viruses from specimens sent in from patients with respiratory illnesses either in the local hospital or living in the surrounding area.

The virus isolations are usually made in monkey kidney cultures, sometimes also in fertile eggs. Once evidence of the presence of influenza virus is obtained by haemadsorption and haemadsorption-inhibition the cultures are sent direct to the Virus Reference Laboratory for further identification. In the Figs. 2–5, the number of viruses recorded each week is based on the date the original throat swab was taken if information on the date of onset was not available.

Serum surveys

Sera for antibody surveys after each winter were obtained from several sources. Samples sent for W. R. tests were passed on to us regularly by Dr C. E. D. Taylor of the Central Middlesex Hospital, London. These were predominantly from ante-natal patients and thus, although comparable year by year, do not cover a full age range. From time to time, for more comprehensive surveys, similar serum samples were collected from different regions of the country.

Sera from people of all age groups have also been collected regularly from samples sent for anti-streptolysin O tests.

Antibody was measured against appropriate antigens either by haemagglutination-inhibition after treatment with RDE or by single radial diffusion (Schild, Henry-Aymard & Pereira, 1972) or by single radial haemolysis (Schild, Pereira & Chakraverty, 1975).

RESULTS

Influenza in the winters of 1968–72

Influenza A

The subtype A/Hong Kong/68 (H3N2) virus which appeared in the middle of 1968 in the Far East circulated unchanged for four successive winters in the United Kingdom causing epidemics or outbreaks of varying size.

The impact of the first 2 years has already been described (Pereira, Miller & Clarke, 1969; Miller, Pereira & Clarke, 1971) and followed, for a new virus in a susceptible population, a somewhat unusual pattern.

The first epidemic of 1968–9 was prolonged with low morbidity and mortality at any given time. However, by the time it was over it was apparent that the virus had spread widely and about a fifth of the population appeared to have been infected.

The second epidemic in 1969–70 was sharp and severe with high morbidity and mortality rates. At the end of this winter nearly half of the population had acquired antibody.

In the following winter although there was no measurable outbreak, A/Hong

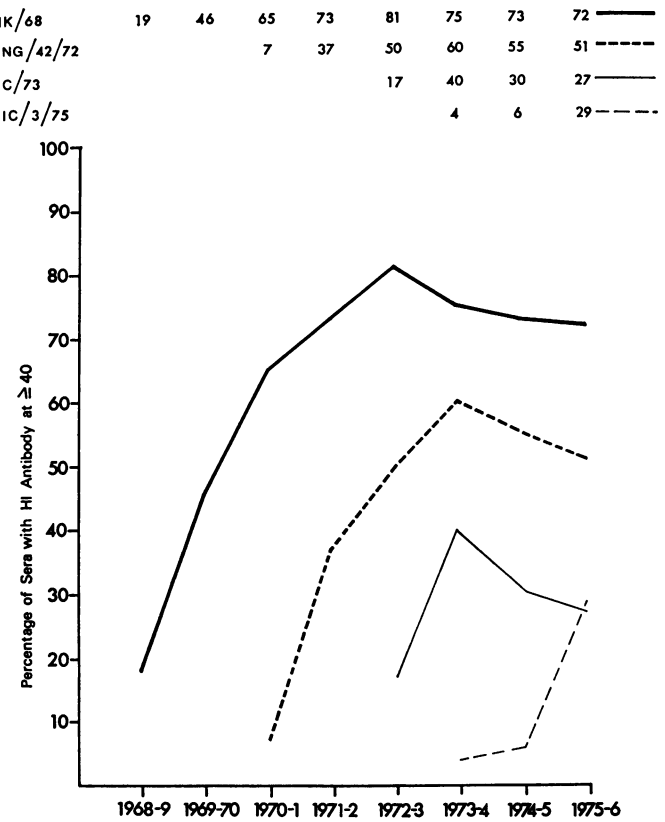

Fig. 1. Acquisition of antibody to successive variants of A/Hong Kong/68 (H3N2) virus – post-winter levels.

Kong/68 viruses were isolated in small numbers from sporadic cases of influenza from March to May.

The virus reappeared at the end of November of the same year, spread rapidly throughout the country causing widespread illness during the next months and finally disappeared at the end of February 1972. This was the last time the A/Hong Kong/68 virus was encountered.

At the end of this fourth winter antibody to A/Hong Kong/68 was found in approximately 70 % of sera examined (Fig. 1).

During this winter of 1971–2, however, one isolation among the 751 viruses examined showed a considerable antigenic difference from the otherwise homogeneous collection in A/Hong Kong/68 viruses. This strain numbered A/England/42/72 was sufficiently drifted that a survey for antibody showed that only about a third of the sera examined had titres of antibody likely to be protective should this virus reappear (Pereira *et al.* 1972).

Influenza B

During this 4-year period 1968–72, influenza B virus played a significant part in causing respiratory disease in two of the winters.

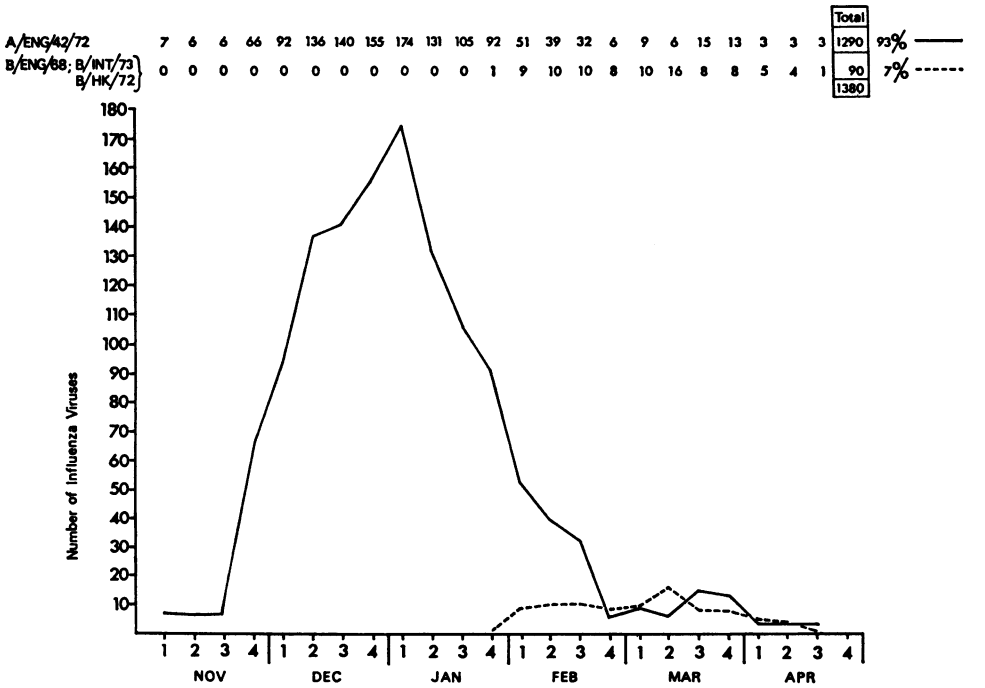

Fig. 2. Influenza viruses, winter 1972–3.

Although it was absent throughout both the first and second epidemics of A/Hong Kong/68, hardly had the effects of the second severe epidemic subsided when influenza B began to circulate causing outbreaks in schools and sporadic cases of influenza all over the country through March, April and May 1970. In January 1971 it reappeared and was isolated in many parts of the country over a period of 4 months together with, from March 1971 onwards, A/Hong Kong/68 virus as already described. In the last year of the A/Hong Kong/68 (1971–2) influenza B virus was not encountered.

These strains of influenza B virus were all broadly similar to each other and to strains which had been found in previous years, typified by B/England/21/68 virus.

Influenza in the winter of 1972–3

Influenza A

The detection during the winter of 1971–2 of a single strain (A/England/42/72) showing a significant difference from the predominant A/Hong Kong/68 virus raised the possibility that it might become a predominant virus. In fact, in the summer months of 1972 similar viruses were isolated in many parts of the southern hemisphere from outbreaks of influenza and by the end of November 1972 viruses identical with A/England/42/72 began to be isolated in the United Kingdom.

A sharp epidemic followed, reaching a peak early in January 1973 and declining so that by the middle of February the epidemic was virtually over (Fig. 2). Throughout this epidemic all the influenza A viruses isolated were identical with

Table 2. *Cross haemagglutination-inhibition test with three variants of Influenza B*

	B/E/1/71	B/E/847/73	B/HK/5/72
B/E/1/71	**320**	20	20
B/E/847/73 'intermediate'	80	**160**	160
B/HK/5/72	< 20	20	**160**

A/England/42/72. At the end of this period the proportion of sera with antibody had increased from 37% to 50%.

Influenza B

Influenza B viruses began to appear in the population at the tail end of the influenza A epidemic. Some of these were easily recognizable as like the familiar B strains of previous years. However, some showed a considerable degree of antigenic drift and were found to be identical with influenza B viruses which had been detected in Hong Kong in 1972. Some strains were intermediate in reactivity between the two sorts. Table 2 shows the antigenic diversity of these three strains as demonstrated by haemagglutination-inhibition tests with specific ferret antisera.

Antiserum to the old influenza B strains as typified by B/England/1/71 did not inhibit the B/Hong Kong/72 virus although a slight cross reactivity was found with the antiserum to B/Hong Kong/72. These two strains could be readily distinguished from each other.

The so-called 'intermediate' strains could be identified since they were inhibited by antisera to both the old and the new influenza B viruses.

These three variants were isolated in small numbers over a period of about 10 weeks.

Influenza in the winter of 1973–4

Influenza A

Later in 1973 in October, influenza A viruses began to circulate once again. The A/England/42/72 was now replaced entirely by another variant, A/Port Chalmers/73 which had been causing outbreaks in the southern hemisphere immediately before. The A/England/42/72 virus did not appear again although half the population was still without antibody.

The A/Port Chalmers/73 virus was isolated in small numbers in many parts of the United Kingdom from October 1973 onwards. However, it was only in the middle of March 1974 that it began to make its presence felt and a sharp increase in deaths attributed to influenza coincided with a sharp increase in the number of viruses being isolated. This peak at the end of March then declined slowly and the last strains were detected as late as the beginning of June (Fig. 3). During this period 11 strains of the 575 examined showed some antigenic difference; the first of these viruses was called A/England/635/74.

The proportion of sera with antibody to A/Port Chalmers/73 increased during this period of high influenza activity from 17% to 40%.

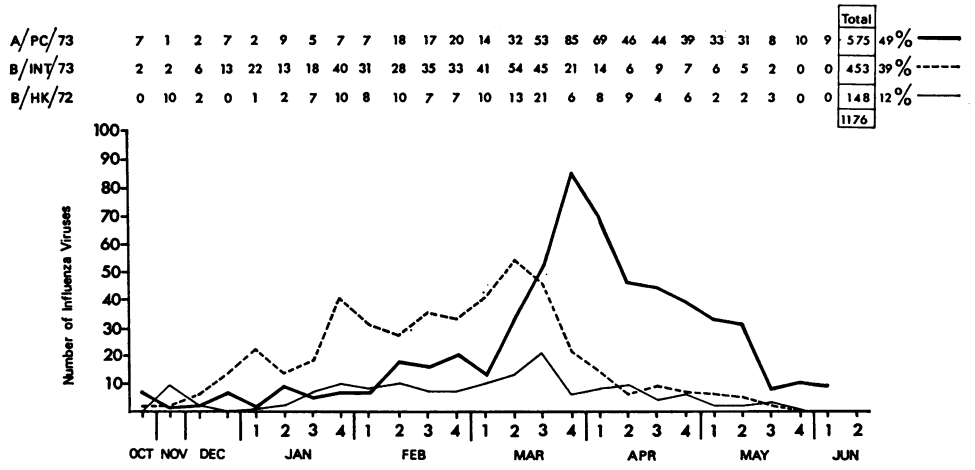

Fig. 3. Influenza viruses, winter 1973–4.

Influenza B

Influenza B viruses had begun to circulate at about the same time as the new A/Port Chalmers/73 variant, and in October 1973 both B/Hong Kong/72 and Intermediate strains were isolated. The old B/England/68 viruses were no longer detected.

These newer influenza B viruses spread widely causing many outbreaks in schools all over the country.

The incidence began to decline as the numbers of A/Port Chalmers/73 virus began to increase, but influenza B viruses were still being isolated in small numbers up to the middle of May 1974.

Influenza in the winter of 1974–5

Influenza A

Again as in the previous winters, influenza viruses began to be isolated early in the winter with the first cases detected at the end of November (Fig. 4).

However, this winter the A/Port Chalmers/73 virus was not replaced but was accompanied by two other easily distinguishable variants, A/Scotland/74 which was identical with the A/England/635/74 strain isolated the previous winter and strains intermediate between it and the A/Port Chalmers/73. Table 3 shows the antigenic drift which has occurred among the H3N2 influenza viruses as demonstrated by cross HI tests with ferret antisera.

The successive variants have been clearly identified one from the other with a progressive loss of reactivity with antisera in the earlier strains. It has been found essential to include such antisera when identifying new viruses as, whereas the differences between consecutive drifted variants may be small, the general pattern can indicate a significant move away from the parent strain.

The A/Scotland/840/74 variant for example was no longer inhibited by antisera to A/Hong Kong/68 virus and was only poorly inhibited by antisera to the 1972 and 1973 variants. The so-called 'intermediate' viruses although also poorly

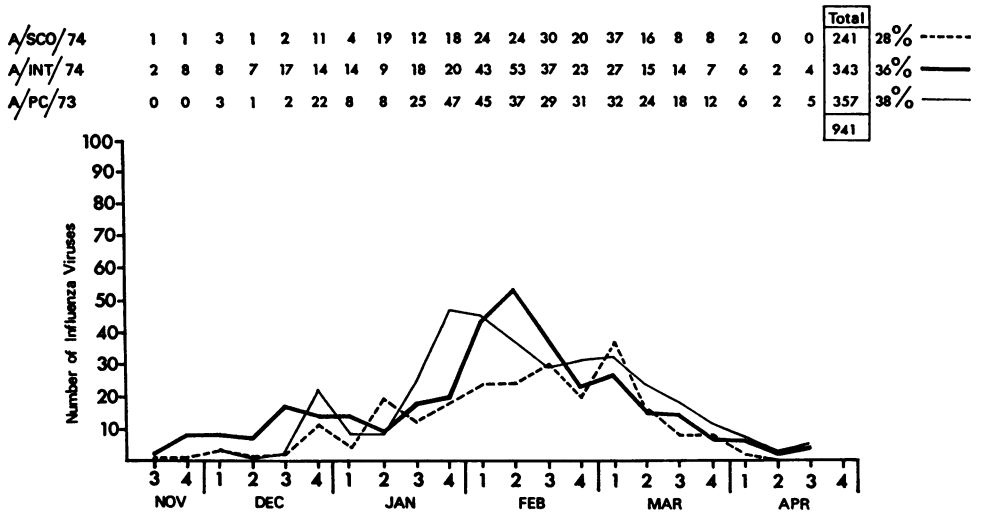

Fig. 4 Influenza viruses, winter 1974–5.

inhibited by the earlier sera, were clearly still close to the A/Port Chalmers/73 virus.

These three variants circulated concurrently from December 1974 to March 1975 in approximately equal numbers without any one of them becoming predominant. At the end of this winter the antibody pattern was barely altered.

Influenza B

No influenza B viruses were isolated through this winter.

Influenza in the winter of 1975–6

Influenza A

During the summer of 1975 reports came of outbreaks of influenza in the southern hemisphere associated with a further variant of the A/Hong Kong/68 virus called A/Victoria/3/75. This virus showed considerable drift from A/Port Chalmers/73 virus and serum surveys indicated that only a small proportion had antibody titres likely to be protective should this new variant come to the United Kingdom.

In the event influenza A viruses did appear as early as November 1975 but were found to be not like A/Victoria/75 but drifted in another direction. This variant called A/England/864/75 was isolated in small numbers until the middle of March 1976. However, the A/Victoria/75 was finally found on the last day of December 1975 and immediately spread throughout the country causing widespread illness and outbreaks accompanied by a heavy mortality rate, reaching a peak in the middle of February 1976 and declining slowly to end in the last week of April (Fig. 5).

The proportion of sera with antibody to A/Victoria/75 virus increased during this period of prevalence from 7% to about 30%.

Table 3. *Antigenic drift of influenza A viruses between* 1968 *and* 1975

(Haemagglutination-inhibition tests with post-infection ferret sera.)

	Serum							
8AD Antigen	F 155 A/HK/1/68	F 175 A/E/42/72	F 184 A/PC/1/73	F 177 A/E/459/74	F 174 A/Scot/840/74	F 183 A/Vic/3/75	F 188 A/E/864/75	F 189 A/Tokyo/1/75
A/HK/1/68	**2560**	2560	320	80	80	20	20	< 20
A/E/42/72	40	**1280**	320	320	160	40	40	< 20
A/PC/1/73	20	640	**640**	320	160	40	40	< 20
A/E/459/74	< 20	80	160	**640**	1280	40	20	< 20
'Intermediate' A/Scot/840/74	< 20	40	40	640	**640**	< 20	< 20	< 20
A/Vic/3/75	< 20	20	< 20	40	20	**1280**	160	80
A/E/864/75	< 20	40	80	40	20	320	**5120**	< 20
A/Tokyo/1/75	< 20	< 20	< 20	< 20	< 20	320	40	**1280**

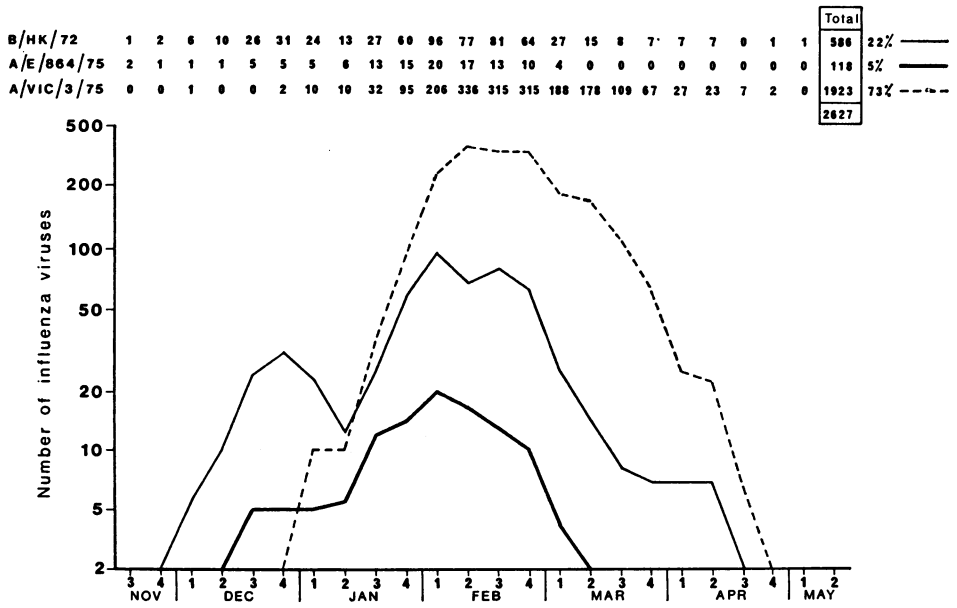

Fig. 5. Influenza viruses, winter 1975–6.

Influenza B

Influenza B viruses began to be isolated at the end of November 1975, again associated with numerous outbreaks in schools. This winter most strains were like the B/Hong Kong/72 virus. However, some strains were poorly inhibited by antisera to B/Hong Kong/72 and appeared to be antigenically different.

DISCUSSION

The continuous laboratory monitoring of influenza in the community forms an important part of the surveillance programme as outlined in a report of a working group of the Public Health Laboratory Service (PHLS, 1977). In this programme the effect of influenza in the United Kingdom is recorded from the collection of various statistics: the number of deaths from all causes, the number of new claimants for sickness benefit and the consultation rates for acute respiratory disease recorded by over 60 general practitioners throughout the country.

On the whole, these statistics correlate well with each other and are providing a useful picture of the disease pattern year by year.

However, the information obtained by laboratory investigations covers several other aspects of influenza epidemiology. The search for influenza viruses throughout the year has demonstrated clearly the extent and duration of their circulation. The dates of onset of the first and last cases from which virus was isolated can be accurately noted and it has become clear that there is no regular or predictable pattern. Viruses may begin to circulate in November and continue up to May. Influenza B sometimes appears first, sometimes influenza A. Sometimes they succeed each other, sometimes circulate together.

Once the viruses cease to be isolated in any winter they do not reappear until the next winter season except in an occasional outbreak of influenza in boarding schools in September when the source of infection is usually felt to have been a child returning from summer holidays in the southern hemisphere where influenza may have been epidemic at that time.

During the prevalence of the H3N2 viruses, antigenic variation has been frequent and the end of a winter season has seen on three occasions the disappearance of the prevalent virus and the complete replacement in the following winter by the succeeding variant.

An unexpected finding from the examination of the large numbers of viruses isolated in the United Kingdom has been that on occasion two or even three antigenic variants have circulated concurrently.

This frequent antigenic change has ensured an abundant supply of susceptibles for the virus to attack but the serological evidence has not indicated a need for such frequent drift as a single winter by no means exhausts the numbers of people open to infection.

Virological studies also show that even in a winter when influenza is apparently making no impact on the community from the evidence of national statistics, the viruses may none-the-less be found in abundance. This is particularly the case with influenza B where the age groups affected, being mostly young, are not likely to induce significant changes in the national statistics of either morbidity or mortality.

A case can be made for broadening the epidemiological surveillance to cover school children. At present the absence rates from schools are hard to discover except at the local level. When co-operation with school teachers has been obtained, often by the personal approach of an interested virologist, the results have frequently been rewarding, and have revealed what antibody studies have demonstrated; that children are an early target for influenza viruses, even though their clinical response is, on the whole, less severe than in older age groups.

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