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The Effects of Shifts and Drifts on the Epidemiology of Influenza in Man

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The effects of shifts and drifts on the epidemiology of influenza in man

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Accurate information on the epidemiology of influenza over the World is difficult to obtain as it is dependent on both national statistics of morbidity and mortality and on adequate virological confirmation of suspected cases. Only a few countries have the facilities for these and in much of the World it is difficult to establish exactly the impact of influenza. For this reason, our knowledge on the natural history of the disease and the virus causing it is restricted to what happens in a few areas of the World where the necessary information is obtainable.

In one of these areas, the U.K., it has been possible to follow the appearance of influenza in successive years throughout the 11 years of prevalence of the H2N2 virus and throughout the 10 years of prevalence of the H3N2 virus. What are still unknown are the factors that determine this pattern. Various hypotheses have been proposed to explain the epidemiology of influenza.

The world has known about influenza for centuries, for what can have been nothing else is clearly described in the accounts that survive. One can read of widespread illness in Queen Mary's Court in the sixteenth century, the falling ill of thousands in certain towns in the seventeenth century and the well documented epidemic of 1732 which was recorded in Paris in February, in Naples in March, spreading all over Europe and to America, beginning in New England and spreading southwards to Barbados, Jamaica, Mexico and Peru. Eleven years later, in 1743, another epidemic became rife over Europe when the disease acquired the name it has now.

In the intervals between these major epidemics, little was recorded and the natural history and epidemiology remained obscure until the discovery of the aetiological agent.

Since then the amount of information that has been accumulated about the virus is considerable but the actual epidemiology of the disease is still only poorly understood in most of the world and what is known has been derived from detailed surveillance in the few countries that have the necessary organization to establish the extent of morbidity and mortality and to link them with this one infection, which is clinically often indistinguishable from others caused by many different infectious agents. What we know of influenza epidemiology is therefore largely restricted to the developed areas of the world and whether the pattern is the same everywhere is by no means certain.

Since the discovery of the virus in the 1930s it became possible to relate the epidemics as they occurred to a particular antigenic strain. That major changes occurred was soon recognized and as time went on the antigenic lability of the virus producing minor changes became apparent. But in the early years, although viruses could be isolated and identified, procedures were cumbersome and sampling was on a restricted scale often confined to localized outbreaks, particularly in military establishments, which poorly reflect the situation in the general population.

In the last 20 years, virological surveillance of influenza in the U.K. has been extensively developed, and now some 60 laboratories attempt to isolate influenza virus from clinical specimens. Many of these laboratories maintain the search for viruses throughout the whole year. Their results have demonstrated what has happened to the viruses. Serological surveys done between epidemics have also been used to measure the proportion of the population acquiring antibody year by year.

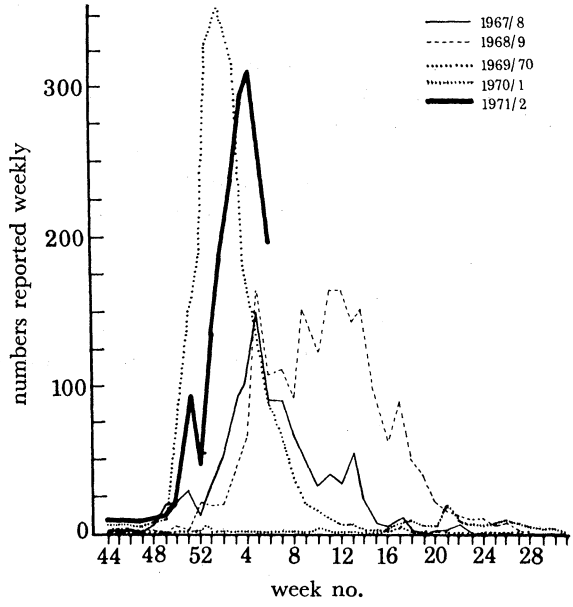

FIGURE 1. The number of influenza A virus infections reported weekly through the winter seasons from 1967/8 to 1971/2.

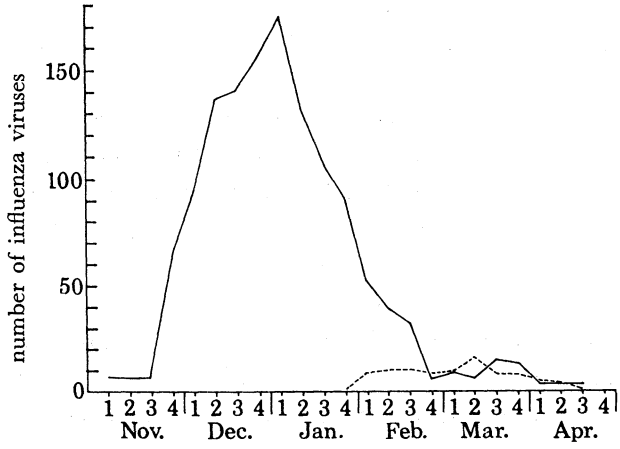

FIGURE 2. The number of influenza viruses isolated in the winter of 1972/3. Total number of viruses, 1380; A/Eng/42/72 (1290 viruses (93%)); - - -, B/Eng/68, B/Int/73, B/HK/72 (90 viruses (7%)).

Figures 1–8 show the number of influenza A and B viruses isolated from clinical specimens each week during the winters of 1967/8 to 1977/8. They show when viruses first appear each season and when they disappear, and demonstrate the succession of epidemics due to different variants. During this period, several other variants were identified in the U.K. and in other parts of the world but they did not spread widely or cause any significant impact.

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Figure 1 compares the number of viruses isolated and cases of serologically confirmed influenza during the winter of 1967/8, the last winter of H2N2 virus prevalence and the first 4 years of H3N2 virus prevalence. In the winter of 1967/8 the final variant of A/Singapore/1/57 (H2N2) called A/England/68/68 circulated together with another variant, A/Tokyo/1/67; between them they caused a severe epidemic which ended in April 1968. The appearance later that year of the new A/Hong/Kong/68 (H3N2) virus heralded a long smouldering epidemic which only ended in May 1969. The virus disappeared until December 1969 when it suddenly returned to cause an explosive epidemic which lasted about 8 weeks and then disappeared again. In the following winter only a few influenza A viruses were detected despite active search but in December 1971 the same virus returned to cause a last sharp epidemic before its final disappearance in March 1972.

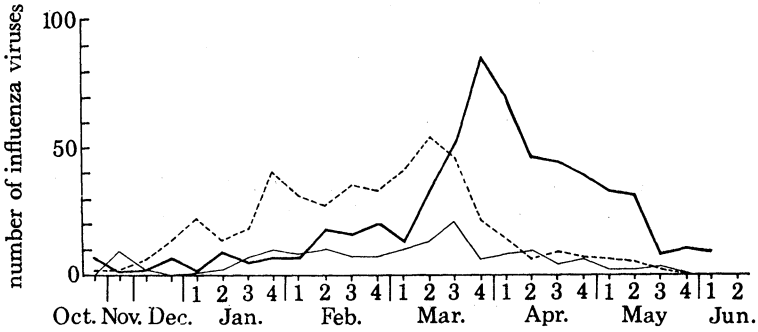

FIGURE 3. The number of influenza viruses isolated in the winter of 1973/4. Total number of viruses, 1176; ——, A/PC/73 (575 viruses (49%)); - - -, B/Int/73 (453 viruses (39%)); ——, B/HK/72 (148 viruses (12%)).

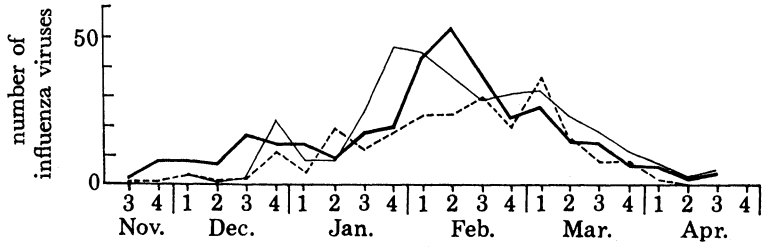

FIGURE 4. The number of influenza viruses isolated in the winter of 1974/5. Total number of viruses, 941; - - -, A/Scot/74 (241 viruses (28%)); ——, A/Int/74 (343 viruses (36%)); ——, A/PC/73 (357 viruses (38%)).

During the second epidemic in the winter of 1969/70, of the 809 isolates of A/Hong Kong/68 viruses, 35 showed a significant antigenic difference and similar strains were detected in Scotland, France, Portugal and New Zealand (Pereira & Schild 1971). However, such strains were never subsequently encountered anywhere in the world.

During the third epidemic in the winter of 1971/2 a single isolate of a new variant, A/England/42/72, was found among about 900 isolates of A/Hong Kong/68 virus. At the same time another variant, A/Hong Kong/5/72, was detected in Hong Kong. This was responsible for small outbreaks and limited spread whereas A/England/42/72 replaced completely the A/Hong Kong/68 virus and became the dominant strain throughout the world in the following winter of 1972/3 (figure 2).

This virus in turn disappeared to be replaced by a further variant, A/Port Chalmers/73, during the winter of 1973/4 (figure 3) when several other variants were detected in various parts

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of the world: A/Hannover/73, A/Puerto Rico/74 and A/Scotland/74. These variants all had limited spread, and in the U.K. the A/Scotland/74 and A/Port Chalmers/73 circulated together during the following winters of 1974/5, neither becoming dominant. Strains intermediate between them were clearly distinguishable during this period (figure 4).

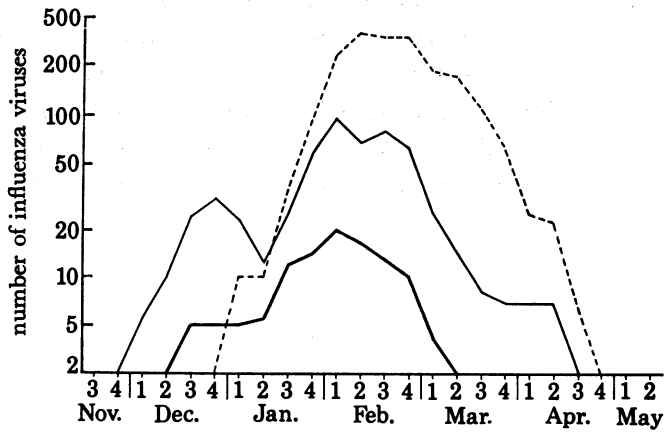

FIGURE 5. The number of influenza viruses isolated in the winter of 1975/6. Total number of viruses, 2627; ——, B/HK/72 (586 viruses (22%)); ——, A/E/864/75 (118 viruses (5%)); - - -, A/Vic/3/75 (1923 viruses (73%)).

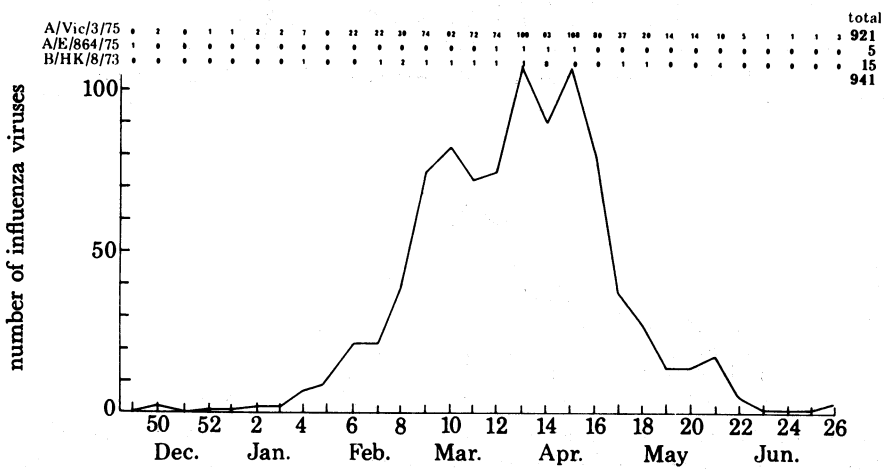

FIGURE 6. The number of influenza viruses isolated in the winter of 1976/7.

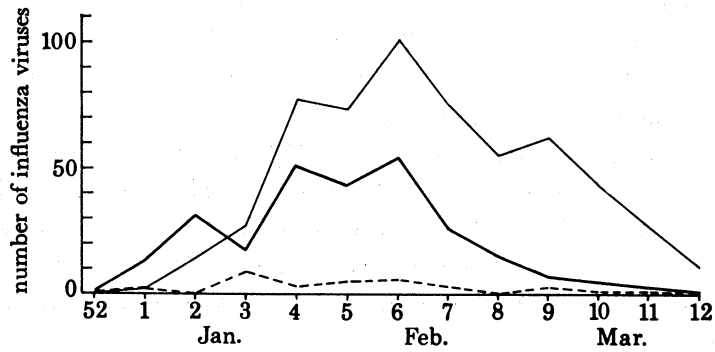

FIGURE 7. The number of influenza viruses isolated in the winter of 1977/8. Total number of viruses, 880; ——, A/USSR/90/77 (267 viruses (30%)); ——, A/Texas/1/77 (567 viruses (64%)); – – –, A/Vic/3/75 (33 viruses (4%)); not plotted, B (13 viruses (1%)).

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In the middle months of 1975 a new variant, A/Victoria/1/75, appeared in Australia and spread rapidly in the Southern Hemisphere. Before it was detected in the U.K. on the last day of 1975, another variant called A/England/864/75 had already been isolated in small numbers in the U.K. (figure 5).

Both of these variants were found during the winter of 1975/6 but the A/Victoria/1/75 spread rapidly and widely and was responsible for a major epidemic which caused a large number of deaths. In the winter of 1976/7, the A/Victoria/75 virus returned once more; only a handful of viruses like A/England/864/75 were isolated (figure 6). In the following winter, however, viruses almost identical with A/England/864/75 began to be isolated in the U.S.A. and, as A/Texas/75, were encountered worldwide as the predominant influenza A variant. In the U.K. they were found throughout the winter of 1977/8 together with the A/USSR/90/77 (figure 7) H1N1 virus which had reappeared first in China and then in the U.S.S.R. and Southeast Asia and continued its spread worldwide. During this time small numbers of A/Victoria/75 virus were still found but the main impact was from A/Texas/77 in all age groups and A/USSR/90/77 in those under the age of 25 years. That winter saw the co-circulation of two different subtypes with two different variants of one of these subtypes.

The H2N2 period seems to have been less marked with variants. This may be a true reflexion of a more stable subtype or may reflect the lower level of virological surveillance during this period. Whatever the case, the two periods show a not dissimilar pattern in the frequency and extent of epidemics.

Table 1 shows the deaths from influenza and pneumonia during the 11 years from 1957 to 1968. The number of deaths may be used as a measure of the severity of an epidemic. The U.K. figures are drawn from the weekly reports from the Office of Population Censuses and Surveys (O.P.C.S.). The figures for the U.S.A. are drawn from the National Center of Health Statistics, Vital Statistics of the United States. These cover each calendar year whereas those of the U.K. are related to the winter months. The severity of each epidemic has been assigned a number of pluses depending on the number of deaths attributed to influenza and pneumonia. Table 2 gives the comparable data during the 10 years from 1968 to 1978. Table 3 gives the accumulated deaths from influenza and pneumonia in the U.K. divided into those that occurred during the three epidemics each of the pandemic strains A/Singapore/1/57 and A/Hong Kong/1/68 and those that occurred in the subsequent epidemics associated with variants of these strains. The totals demonstrate the significant mortality resulting from influenza and suggest that the H3N2 subtype was more severe in its impact than the H2N2 subtype. The importance of epidemics due to variants as compared with the pandemic strains cannot be overestimated. Table 4 compares the pattern of epidemics due to pandemic strains, variants and influenza B. The two periods of H2N2 and H3N2 prevalence show a remarkable similarity in the number of epidemics that occurred. Even influenza B may be equally matched when the final figures for the winter of 1978/9 are available, as outbreaks in February 1979 have become frequent and increasing.

These tables illustrate some of the things that one can learn from epidemiological and virological surveillance. They demonstrate the varying severity of influenza epidemics; the shifts and drifts in antigenic composition offer an explanation for the continuing problem. Laboratory experiments have shown how antigenic shift and drift could be produced but there is still much that remains entirely unknown and many unanswered questions.

The cause of the seasonal appearance of influenza has not been explored nor why each epidemic stops even when susceptible hosts remain in abundance. It has not been determined

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Table 1. H2N2 influenza epidemics 1957–68, U.K. and U.S.A.

winter ...	1957/8	1958/9	1959/60	1960/1	1961/2	1962/3	1963/4	1964/5	1965/6	1966/7	1967/8
virus H2N2	A/Sing/1/57	A/Sing/1/57	0	A/Sing/1/57	0	A/E/63	0	A/E/64	A/E/64	0	A/E/68, A/Tok/67
U.K. influenza/ pneumonia deaths (thousands)	19	23	0	21	21	25	0	4	19	0	23
U.K. epidemics	+ +	+ + +	0	+ +	+ +	+ + +	0	+	+ +	0	+ + +
U.S.A. influenza/ pneumonia deaths (thousands)	61	57	55	67	55	66	71	60	62	64	57
U.S.A. epidemics	+ +	+	0	+ + +	0	+ + +	+ + +	+ +	+ +	+ +	+

Table 2. H3N2 influenza epidemics 1968–78, U.K. and U.S.A.

winter ...	1968/9	1969/70	1970/1	1971/2	1972/3	1973/4	1974/5	1975/6	1976/7	1977/8	1978/9
virus H3N2	A/HK/68	A/HK/68	0	A/HK/68	A/E/42/72	A/PC/73	A/PC/73, A/Scot/74	A/Vic/75, A/E/864/75	0	A/Tex/77, A/USSR/90/77 (H1N1)	
U.K. influenza/ pneumonia deaths (thousands)	22	31	0	18	24	12	17	27	13	15	0
U.K. epidemics	+ +	+ + +	0	+ +	+ + +	0	+ +	+ + +	0	+	
U.S.A. influenza/ pneumonia deaths (thousands)	74	68	63	57	63	63	55	56			
U.S.A. epidemics	+ + +	+ + +	+ +	+	+ +	+ +	0	0			

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TABLE 3. U.K. INFLUENZA PNEUMONIA DEATHS (THOUSANDS) (O.P.C.S.)

1957–68	H2N2	epidemics: A/Sing/57	epidemics: variants	total
		63.4	90.2	153.6
1968–78	H3N2	epidemics: A/Hong Kong/68	epidemics: variants	
		70.8	109.1	179.9

TABLE 4. COMPARISON OF H2N2 AND H3N2 PERIODS, U.K.

winter ...	1957/8	1958/9	1959/60	1960/1	1961/2	1962/3	1963/4	1964/5	1965/6	1966/7	1967/8	total
H2N2												
original pandemic strain	+	+	0	+	0							3
variants						+	0	+	+	0	+	4
influenza B	0	+	0	0	+	0	0	+	+	0	+	5
winter ...	1968/9	1969/70	1970/1	1971/2	1972/3	1973/4	1974/5	1975/6	1976/7	1977/8	1978/9	
H3N2												
original pandemic strain	+	+	0	+								3
variants					+	0	+	+	0	+		4
influenza B	0	+	+	0	0	+	0	+	0	0		4

whether virus continues to spread between epidemics at a subclinical level nor whether the same antigenic change occurs spontaneously in different areas of the world or whether a single mutant arises somewhere and all spread derives from a single focus.

The mechanisms producing antigenic shift and drift that have most experimental support are genetic recombination between animal and human viruses to create new subtypes and immunological pressure against a parent virus allowing the survival of a mutant drifted virus.

However, in the absence of proof that these mechanisms have actually operated, speculation continues about the origin of the virus causing pandemic and epidemic influenza.

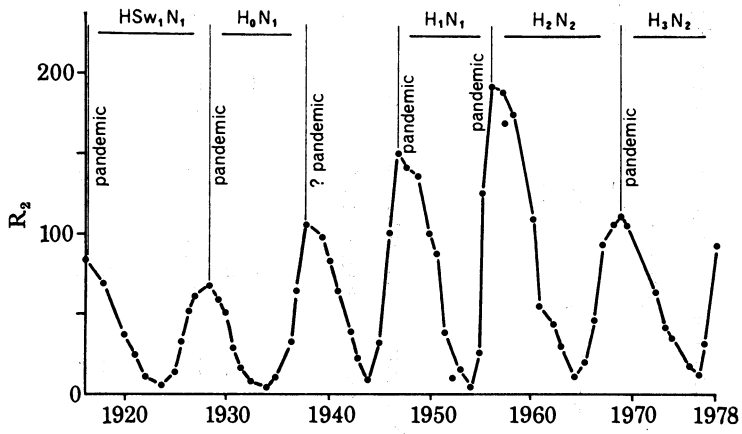

FIGURE 8. Sunspot cycles and major variants of influenza A. R_2 Zurich yearly means of daily relative sunspot numbers. Updated from Hope-Simpson (1978).

Hoyle & Wickramasinghe (1977) cast doubt on suggestions that major pandemics start with random mutation or genetic recombination and have put forward suggestions based on the evidence that amino acids, nitrogen-bearing heterocyclic compounds and polysaccharides are formed in space. They believe that virus formed in the galaxy from such constituents could be carried in meteoritic dust as the Earth crosses the debris of a new long-period comet. If the virus were dispersed in a new diffuse cloud of small particles the incidence could be global, or smaller aggregates falling over a limited area could provide a geographically more localized invasion, infecting either man directly or through an intermediate animal host. These authors have produced evidence in school outbreaks to support their ideas that person-to-person transmission is not significant in the development of outbreaks of influenza.

Hope-Simpson (1979), on the basis of careful studies in patients in general practice, is also not convinced that direct transmission can explain epidemic influenza and has put forward alternative proposals. These include the concept of an unknown seasonal factor and, while accepting that recombination between animal and human strains will produce antigenic shift, he does not believe that fortuitous hybridization is necessarily the only mechanism. He has linked (Hope-Simpson 1975) the appearance of new subtypes with peaks in sunspot activity and figure 8 reproduces his figure brought up to date to confirm the approaching peak of activity predicted. If this association is verified, a further explanation is required on how this could be brought about. Sunspots have no effect on weather nor apparently on the amount of energy sent out. However, at peak times solar flares occur; these send out magnetized particles which,

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for example, upset wireless reception on Earth and there are striking effects on animal behaviour at peak or low incidence sunspot periods. It is probable that such effects could produce a change in bird migration patterns. This could lead to a situation that allows an interchange of viruses between wild and domestic birds, initiating recombinants which, in areas where man lives in close communion with his domestic animals, could lead to the appearance of strains with a predeliction for the human host.

Another hypothesis put forward by Hope-Simpson involves latency. He proposes that after primary infection, the influenza patient does not immediately infect his non-immune companion because the virus rapidly becomes latent in his tissues. During the inter-epidemic periods the virus is inactive and inaccessible to present methods of detection. When the next unidentified seasonal influence operates, the latent virus is activated and the patient becomes highly infectious to his non-immune contacts while he himself suffers no illness. The reassembled progeny of the parent virus consist of parent-like particles and mutant particles of varied composition and abundance. Parent-like particles cannot escape, because of specific immunity, and the mutant virus goes on to spread in the contacts who in turn become carriers whose virus will be reactivated in the next influenza season. It is easy to find facts that will not fit this picture: the most difficult is the multiplicity of mutant viruses that would emerge unless one postulates single line pathways for mutants.

The concept of latency has also been proposed by Laver & Webster (1979) to explain, among other things, the reappearance of the H1N1 virus in China and the apparent frequency with which new subtypes arise in that part of the world. They suggest that virus could remain latent in man or in a parasite of man.

Some of the available evidence would fit certain parts of each of these proposals, but as virological surveillance becomes more comprehensive and detailed the more difficult it becomes to accept them to explain influenza epidemiology.

Summary and conclusions

Virological surveillance in the U.K. has demonstrated that influenza A or B, or sometimes both, have been found every winter without exception in the past 22 years. The number of isolates has varied from only six in a 'non-influenza winter' (1959/60) to 2027 in 1975/6, and on the whole the other morbidity and mortality statistics relating to influenza epidemics have been proportional to these figures. However, there have been winters when these national statistics have not indicated the presence of influenza in the community and this has been particularly so in some years of minor antigenic drift when influenza B outbreaks predominantly affect children; in the last two winters of H1N1 epidemics, these have predominantly affected the young where influenza does not usually result in time off work, admission to hospital, or death.

The regular surveillance of respiratory illness has shown that influenza viruses may circulate for long periods in the year, often appearing in November and continuing up to May or even June the following year. Very occasionally an influenza virus is isolated from a sporadic case during the summer months but this is exceptional and a possible explanation is infection by a visitor from the Southern Hemisphere where influenza epidemics could be in progress. Spread from such contact cases appear to be very rare. Influenza B may appear before influenza A or take over when an A epidemic is over. In some winters the two viruses circulate together.

More than one influenza A variant has also been found in several winters but the expected

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predominance of one over the other has not always occurred. Besides this the co-circulation of two different subtypes of influenza A in 1978/9 continues the erosion of once firmly held beliefs about influenza epidemiology.

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