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Influenza in the United Kingdom 1977–1981

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SUMMARY

The laboratory surveillance of influenza in the UK has continued to demonstrate the regularity of influenza outbreaks each winter even in the absence of increase in the other indices which reflect the morbidity and mortality associated with influenza.

The period of five years from 1976 to 1981 has seen the appearance of a second sub-type of influenza A with the return of the historic H1N1 virus; and the continued circulation of H3N2 concurrently with H1N1 virus. Variants of both these influenza A viruses have been demonstrated as well as further changes in the strains of influenza B virus isolated during this time.

INTRODUCTION

Influenza in the United Kingdom is monitored regularly throughout the winter season by the collection of weekly data on deaths, sickness benefit claims, reports from general practitioners and laboratory confirmation of influenza virus infections.

These various indices on the whole have correlated well, and increases usually occur in all of them at approximately the same period in the winter of most years (PHLS 1977).

The information obtained from laboratory surveillance of influenza allows an accurate assessment of the types of influenza viruses which are circulating and of the antigenic changes which have occurred year by year. This together with an evaluation of the population antibody to each virus enables some prediction to be made of the likely impact of future epidemics and forms the basis for the formulation of an influenza vaccine designed to offer protection to those most at risk of serious illness should they be infected.

Since the subtype H3N2 (A/Hong Kong/1/68) appeared in the world in 1968 epidemics of varying size and severity have occurred in the UK, associated for the first four winters with the prototype virus and subsequently by a series of variants. These have been described for the period 1968–1976 (Pereira & Chakraverty, 1977).

This report describes the subsequent five winters from 1977 to 1981, a period during which a second subtype, the H1N1 virus, reappeared after an interval of

20 years and circulated concurrently with the H3N2 virus. On the basis of previous experience of influenza epidemiology it was anticipated that the current H3N2 subtype might give way to the new arrival and disappear altogether. So far this has not occurred, and both subtypes continue to circulate and to undergo antigenic drift independently.

MATERIALS AND METHODS

Viruses

Nearly 50 laboratories in the Public Health Laboratory Service, universities and hospitals in the UK undertake the isolation of influenza viruses from cases of clinical disease. Some of the source materials are derived from local community outbreaks or sporadic cases: some result from planned surveillance.

The isolation of influenza viruses in the UK has for many years been made in cell cultures of rhesus monkey kidneys. A few laboratories also use the amniotic inoculation of fertile hens' eggs for this purpose.

When rhesus monkeys became scarce comparative tests were done with cultures of kidneys from other simian species and since 1978 baboon kidney, which was found to be as sensitive as rhesus for most virus isolations, has been the cell culture of choice.

Baboon kidney cells are trypsinized and distributed weekly by the Centre of Applied Microbiology and Research at Porton. Each laboratory prepares tube cultures as required. When monolayers are confluent the medium is changed for one without serum, and after inoculation with the specimens the tubes are incubated at 33 °C until a cytopathic effect or haemadsorption is detected.

All suspected influenza viruses are sent to the Virus Reference Laboratory where tests are done to determine the type, sub-type and antigenic variant. This is done by haemagglutination-inhibition (HI) using the technique described in the WHO Technical Report Series (1959) except that unit volumes of 0·025 ml are used throughout. Each isolate is tested against a battery of convalescent ferret antisera previously treated with receptor-destroying enzyme. For the H1N1 viruses some monoclonal antibody preparations were included in the test. These were kindly supplied by Dr R. G. Webster, who prepared them by the technique described by Koprowski, Gerhard & Croce (1977).

Two of the antibody preparations made available were selected for routine use as they differentiated between the A/USSR/90/77 virus and the variant A/Brazil/11/78. Whereas in the USA isolates like A/Brazil/78 were frequently detected after 1978, in Europe such variants were exceptional. However, some isolates which were intermediate between A/USSR/90/77 and A/Brazil/11/78 with twofold differences between each were allocated as one or other of these on the basis of their reaction with the two monoclonal antibodies 110/1 and 264/2 as shown in Table 2.

Selected isolates were examined for their neuraminidase antigen by neuraminidase-inhibition test by the method described by Aymard-Henry *et al.* (1973).

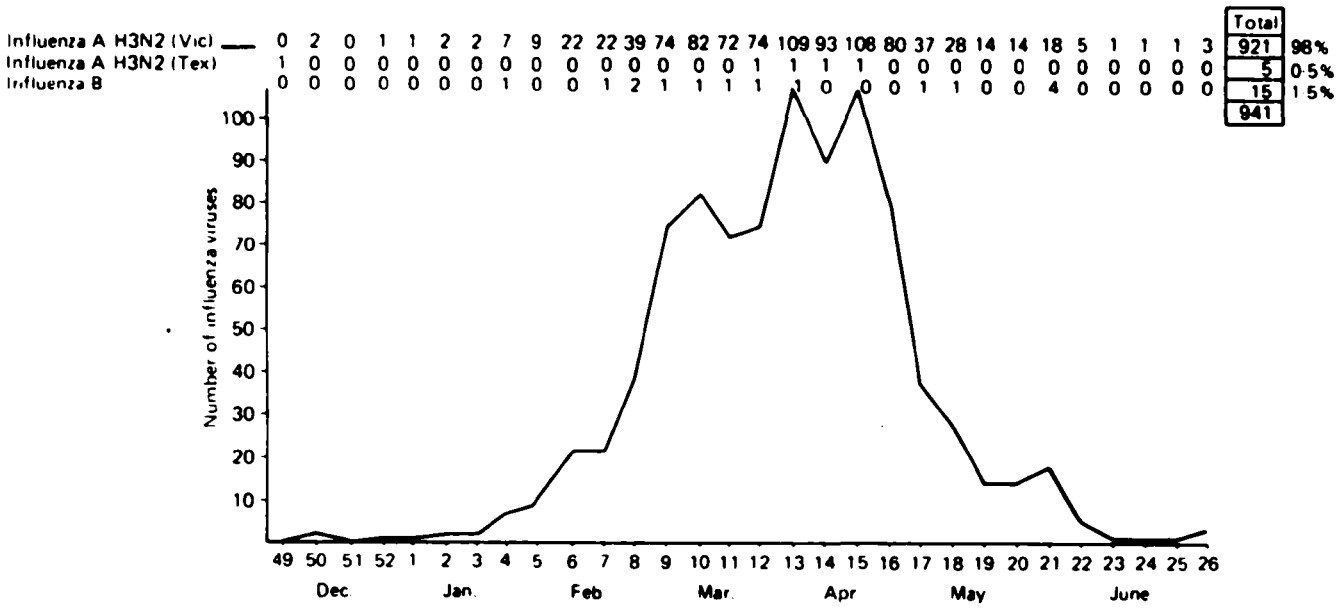

Fig. 1. Influenza viruses: winter 1976–7. Influenza A H3N2 Vic = A/Victoria/3/75, influenza A H3N2 Tex = A/Texas/1/77 and influenza B = B/Hong Kong/8/73.

Serum survey

Serum samples sent to the laboratory for various tests are collected from different regions of the country during each inter-epidemic period of the year. Antibody to the haemagglutinin of appropriate viruses is measured either by HI after treatment with receptor-destroying enzyme or by single radial haemolysis (SRH) following the technique described by Schild, Pereira & Chakraverty (1975). Preliminary tests were necessary with the H1N1 sub-type to select out a suitable pool of complement, as several otherwise satisfactory batches were found to be poorly reactive in SRH.

RESULTS

The viruses associated with epidemics of influenza from 1968 to 1975 have already been described (Pereira & Chakraverty, 1977). Since then, in the subsequent five winters not only further variants of the H3N2 sub-type continued to circulate but the historic H1N1 sub-type reappeared in 1977. During these five winters the number of influenza deaths reached only modest levels in the first two years and in the last three years the numbers did not even reach the mean threshold level of non-epidemic years.

Influenza in the winter of 1976–7

After a very severe influenza epidemic early in 1975 the responsible influenza A variant A/Victoria/3/75 finally disappeared at the end of April 1976.

At the end of December 1976 A/Victoria/3/75 began to be isolated once again (Fig. 1) from sporadic cases of influenza. This low detection rate continued till mid-February when spread began to occur more rapidly, and by mid-April illness was widespread and the deaths among the elderly began to increase. The epidemic subsided slowly and the virus was still encountered up to the end of June 1977.

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	49	50	51	52	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Total	
Influenza A H1N1	0	0	0	1	24	15	17	54	49	61	33	21	13	7	7	2	1	1	0	0	0	0	0	306	30%
Influenza A H3N2 (Tex)	0	0	0	0	9	7	26	78	71	100	98	63	67	59	36	19	2	2	7	0	1	1	0	646	64%
Influenza A H3N2 (Vic)	0	1	0	1	0	0	10	3	5	7	3	0	3	1	1	1	0	0	0	0	0	0	0	37	4%
Influenza B	1	0	0	0	0	0	0	0	1	1	6	0	1	3	1	1	0	0	1	0	0	2	0	19	2%
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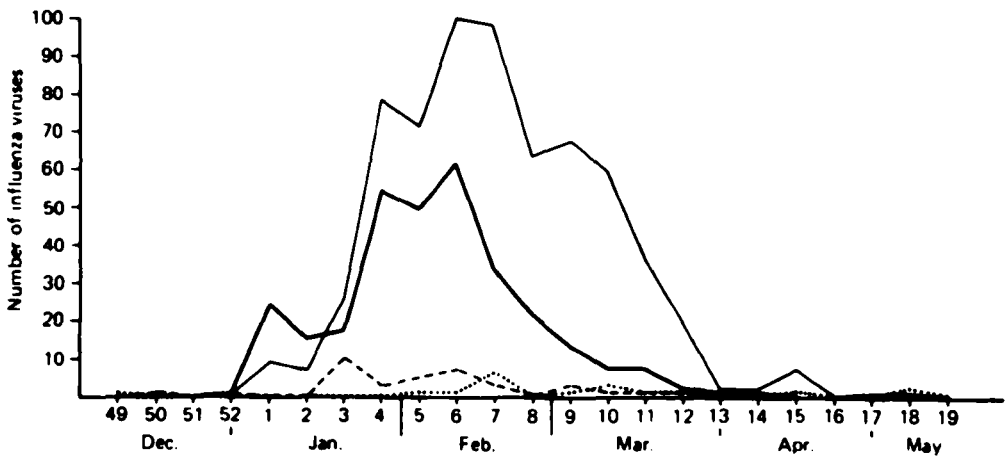

Fig. 2. Influenza viruses: winter 1977–8. Influenza A H1N1 = A/USSR/90/77, influenza A H3N2 (Tex) = A/Texas/1/77, influenza A H3N2 (Vic) = A/Victoria/3/75 and influenza B = B/Hong Kong/8/73.

In contrast to the previous winter A/Victoria/3/75 circulated almost alone with only a few strains of A/England/864/75 (later known as A/Texas/1/77) and influenza B being isolated.

Influenza in the winter of 1977–8

Late in 1977 news came of the reappearance of the influenza A H1N1 sub-type, a virus which had circulated in the world for 10 years between 1947 and 1957. It was first detected causing outbreaks in the north of China earlier that year and had been moving slowly southward during the following months. In November 1977 outbreaks began to occur in adjacent countries, to the north in the USSR and to the south in Hong Kong. This was followed by spread all over Europe from the USSR and all over South-East Asia from Hong Kong and in a matter of months the H1N1 virus was widespread in the world. In the UK the first H1N1 viruses were isolated early in January 1978, almost certainly introduced by people returning from a visit to Moscow where outbreaks of influenza were in progress.

For the next three months viruses were isolated (Fig. 2) all over the UK, particularly from outbreaks in schools and institutions for young people. The H1N1 virus was the main cause of these outbreaks although several variants of sub-type H3N2 were also encountered. On a few occasions the H3N2 variant was A/Victoria/3/75, but more often the virus isolated was found to be antigenically close to the A/England/864/75 which had appeared two years previously. It was now re-named A/Texas/1/77. This became the predominant virus of the winter, not only associated with outbreaks in schools as already mentioned but also causing infections among the adult population, including outbreaks in geriatric units with the usual accompanying increased mortality. This winter saw the last

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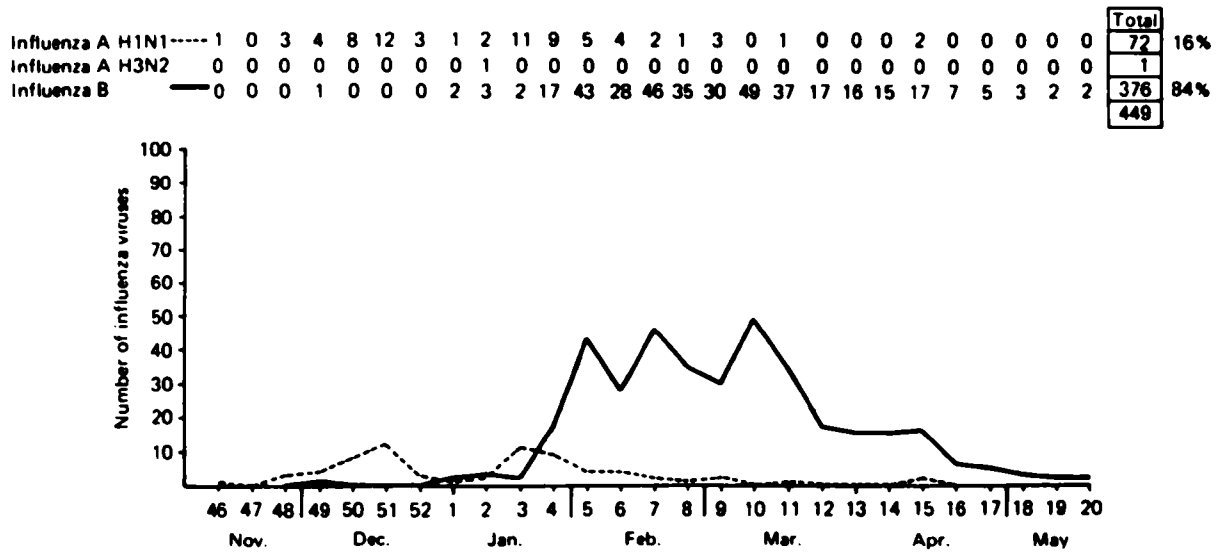

Fig. 3. Influenza viruses: winter 1978–9. Influenza A H1N1 = A/USSR/90/77, influenza A H3N2 = A/Texas/1/77 and influenza B = B/Hong Kong/8/73.

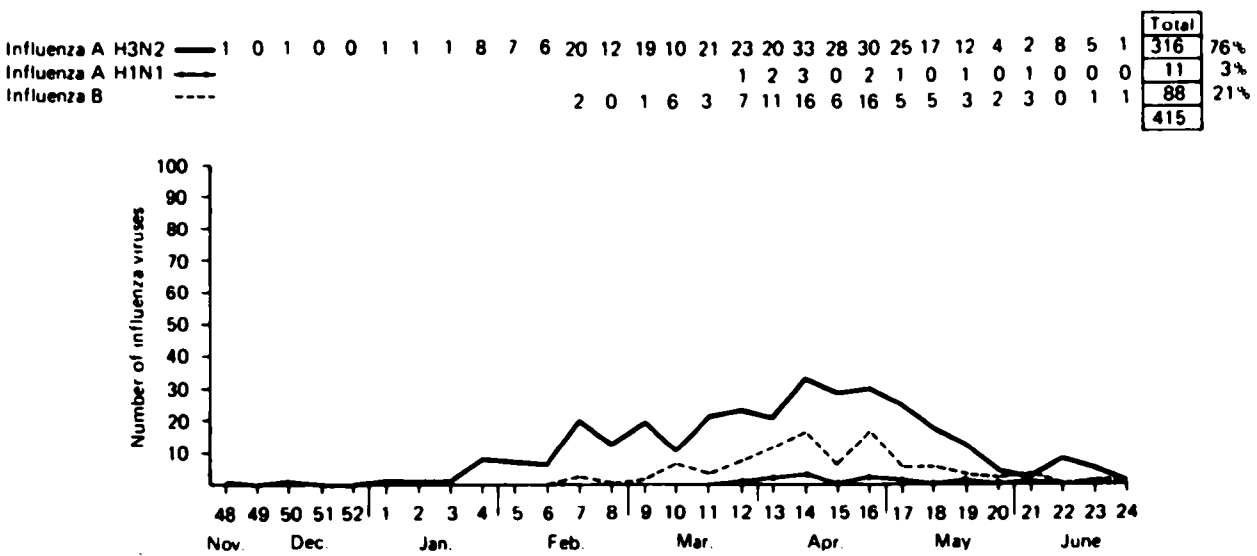

Fig. 4. Influenza viruses: winter 1979–80. Influenza A H3N2 = Intermediate A/England/496/80 (78%), A/Texas/1/77 (19%) and A/Bangkok/79 (3%), influenza A H1N1 = A/England/333/80 and influenza B = B/Singapore/222/79.

appearance of A/Victoria/3/75, which has not been encountered since. Only a few strains of influenza B were detected.

Influenza in the winter of 1978–9

This winter was one where influenza B virus was predominant with only one H3N2 virus isolated, imported from abroad, and only small numbers of the H1N1 virus encountered (Fig. 3). There was no increase in the number of deaths attributed to influenza.

Influenza in the winter of 1979–80

In November 1979 the first isolation of the season was a strain of A/Texas/1/77 (H3N2). After a slow start the number of sporadic cases began to increase and small

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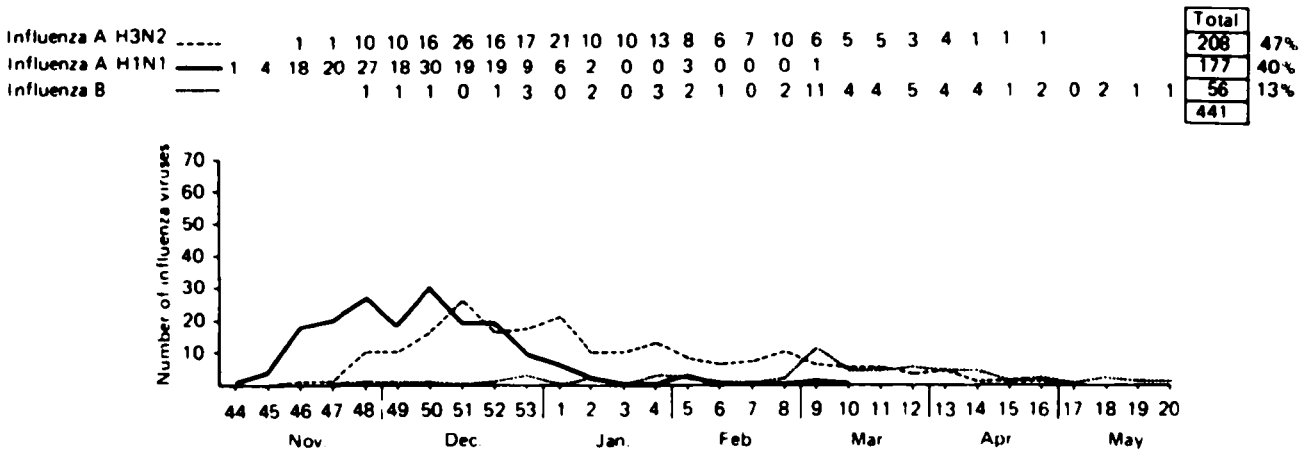

Fig. 5. Influenza viruses: winter 1980–1. Influenza A H3N2 = Intermediate: A/England/496/80, influenza A H1N1 = A/England/333/80 and influenza B = B/Singapore/222/79.

outbreaks occurred (Fig. 4). These were predominantly caused by viruses antigenically intermediate between the A/Texas/1/77 virus and another variant which had been detected in Thailand, A/Bangkok/1/79. A few H1N1 viruses were isolated, some also showing some modest antigenic drift and closer to but not identical with a variant, A/Brazil/11/78. The strain A/England/333/80 typifies these (Table 2). Later in the winter influenza B viruses were encountered in moderate numbers and continued to circulate until late June. The influenza mortality figures for the second year remained low.

Influenza in the winter of 1980–1

Influenza began early in the season with school outbreaks reported throughout November and December 1980. These were nearly all caused by the H1N1 virus. By the end of December these outbreaks were over and thereafter only scanty H1N1 viruses were encountered. The H3N2 sub-type began to circulate in December 1980, continued at a modest level for the next two months and finally ceased to be detected in May 1981 (Fig. 5). Influenza B viruses were found in small numbers over a period of six months.

The H3N2 viruses this season were antigenically similar to those which had circulated the previous winter, most of them intermediate between A/Texas/1/77 and A/Bangkok/1/79. The H1N1 viruses mostly showed a modest drift away from A/Brazil/11/78 and were nearer A/England/333/80. The influenza B viruses were antigenically close to B/Singapore/222/79.

The presence of these two influenza A viruses and influenza B viruses for the third winter once again caused no significant increase in the morbidity or mortality statistics.

Antigenic variants

H3N2 sub-type. Antigenic drift in the H3N2 sub-type since 1968 has produced several variants, some of which have had a considerable epidemic impact. The

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Table 1. *Antigenic drift of influenza A H3N2 viruses between 1968 and 1981*

Antigen	HI titres with post-infection ferret antisera								
	A/HK/ 1/68	A/E/ 42/72	A/PC/ 1/73	A/Scot/ 840/74	A/E/ 459/75	A/Vic/ 3/75	A/Tex/ 1/77	A/BK/ 1/79	A/E/ 496/80
A/Hong Kong/1/68 (H3N2)	*5120*	1280	160	80	80	<	<	<	<
A/England/42/72 (H3N2)	160	*2560*	320	160	320	80	40	<	<
A/Port Chalmers/1/73 (H3N2)	*<	160	*640*	160	320	80	<	<	<
A/Scotland/840/74 (H3N2)	<	80	160	*640*	640	80	<	<	<
A/England/459/75 (H3N2)	<	160	160	1280	*640*	80	<	<	<
A/Victoria/3/75 (H3N2)	<	80	160	<	40	*2560*	320	80	160
A/Texas/1/77 (H3N2)	<	40	40	<	40	320	*2560*	640	2560
A/Bangkok/1/79 (H3N2)	<	<	<	<	<	80	320	*1280*	1280
A/England/496/80 (H3N2)	<	<	<	<	<	80	640	320	*1280*

* = < 40.

Table 2. *Antigenic drift of influenza A H1N1 viruses between 1977 and 1981*

	HI titre with				
	Post-infection ferret sera			Monoclonal antibody*	
Antigen	A/USSR/ 90/77	A/Brazil/ 11/78	A/England/ 333/80	110/1	264/2
A/USSR/90/77	*1280*	160	320	3200	1600
A/Brazil/11/78	320	*640*	320	1600	< 200
A/England/333/80	320	160	*1280*	< 200	< 200

* Received from Dr R. G. Webster.

relationships between all these variants as demonstrated by haemagglutination inhibition are shown in Table 1.

The first variant to spread widely and replace completely the original A/Hong Kong/1/68 virus was known as A/England/42/72. This in turn was replaced by A/Port Chalmers/73/, A/Scotland/74 and strains intermediate between the two. The variant A/Victoria/3/75 – antigenically considerably different from the A/Hong Kong/1/68 virus – spread widely in 1975–6 causing the worst epidemics since 1969–70 with a heavy mortality. This virus circulated for three consecutive winters but in the third of these it formed a mere 4 % of the H3N2 viruses identified. The majority of viruses isolated were like A/Texas/1/77, a variant which had appeared two years previously without causing major epidemics. This variant predominated for the winters 1977–8 and 1979–80 when it was joined by a new variant A/Bangkok/1/79. In the winter of 1980–1 the majority of H3N2 viruses isolated were intermediate between A/Texas/1/77 and A/Bangkok/79, typified by A/England/496/80 (Table 1).

The opportunity arose to examine some of the viruses isolated in the school outbreaks which occurred in the winter of 1977–8 where H3N2 and H1N1 viruses circulated concurrently. As recombination between influenza viruses occurs with ease, it was interesting to see if this would happen in a natural outbreak.

In all the viruses identified by their haemagglutinin the expected neuraminidase antigen was found. There was no evidence of recombination, at least between the surface antigens.

H1N1 sub-type. Antigenically the H1N1 virus which reappeared in the world in 1977 was closest to the H1N1 virus which circulated in 1950–1 (Kendal *et al.* 1978). It was designated A/USSR/90/77. In the UK this virus spread widely among young people under the age of 20, particularly in the older children and young adults rather than in pre-school or primary school children. It formed about one-third of the total influenza A viruses identified during the first winter of 1977–8 and was the only influenza A virus isolated in the following winter 1978–9. In the UK there was little evidence of antigenic drift during these two winter seasons although in the Americas a variant known as A/Brazil/11/78 appeared in significant numbers.

In the winter of 1979 only a dozen H1N1 viruses were isolated but of these the

Table 3. *Antigenic drift of influenza B virus between 1973 and 1981*

	Post-infection ferret antisera			
Antigen	B/HK/ 8/73	B/J'burg/ 9/75	B/Hann/ 13/78	B/Sing/ 222/79
B/Hong Kong/8/73	*640*	160	80	1280
B/Johannesburg/9/75	20	*320*	80	1280
B/Hannover/13/78	20	160	*320*	640
B/Singapore/222/79	80	160	320	*1280*

majority, of which A/England/333/80 is representative, showed a degree of drift. They could be differentiated from both A/USSR/90/77 and from A/Brazil/11/78 by the use of two monoclonal antibody preparations. In the next winter, 1980–1, almost all the H1N1 viruses isolated in the UK showed this same modest antigenic difference and viruses similar to A/England/333/80 were detected in many parts of the world. The cross-reactivity of these variants is shown in Table 2.

Influenza B. The appearance of the variant B/Hong Kong/73 led to the eventual disappearance of the earlier influenza B virus typified by B/England/1/68 with bridging by so-called 'intermediate' strains. Several variants have appeared during the period of prevalence of B/Hong Kong/73 but since 1979 a new variant B/Singapore/222/79 has displaced B/Hong Kong/73 in the UK and in many parts of the world. The cross-reactivity of these influenza B viruses is shown in Table 3.

Antibody to influenza viruses in the UK

The pattern of antibody in different age groups in the summer of 1980 after the above-described winters of influenza prevalence is shown in Fig. 6. The proportion of the population with antibody to the currently circulating influenza viruses is considerable in all age groups.

With the H1N1 viruses the lack of evidence of infection of the adult population during the recent winters can be explained by the large numbers with antibody presumably acquired in the previous decade of prevalence, 1947–57. And whereas in 1977 persons under 20 had no detectable antibody, by 1980 this picture has markedly altered.

All age groups have been affected by influenza during the H3N2 epidemics in the past winters and the antibody which has been acquired is clearly demonstrated.

Antibody to influenza B, particularly by single radial haemolysis, can be shown to be present in a high proportion of all age groups except in children under five.

DISCUSSION

The intensive virological surveillance of influenza in the UK continues to yield a large harvest of influenza viruses available for antigenic analysis. By this means not only does the number of viruses detected give some reflexion of the wide spread of the disease in the community but also, in periods of prevalence of viruses such as the sub-type H1N1 which attacks the young age groups, the isolation of virus

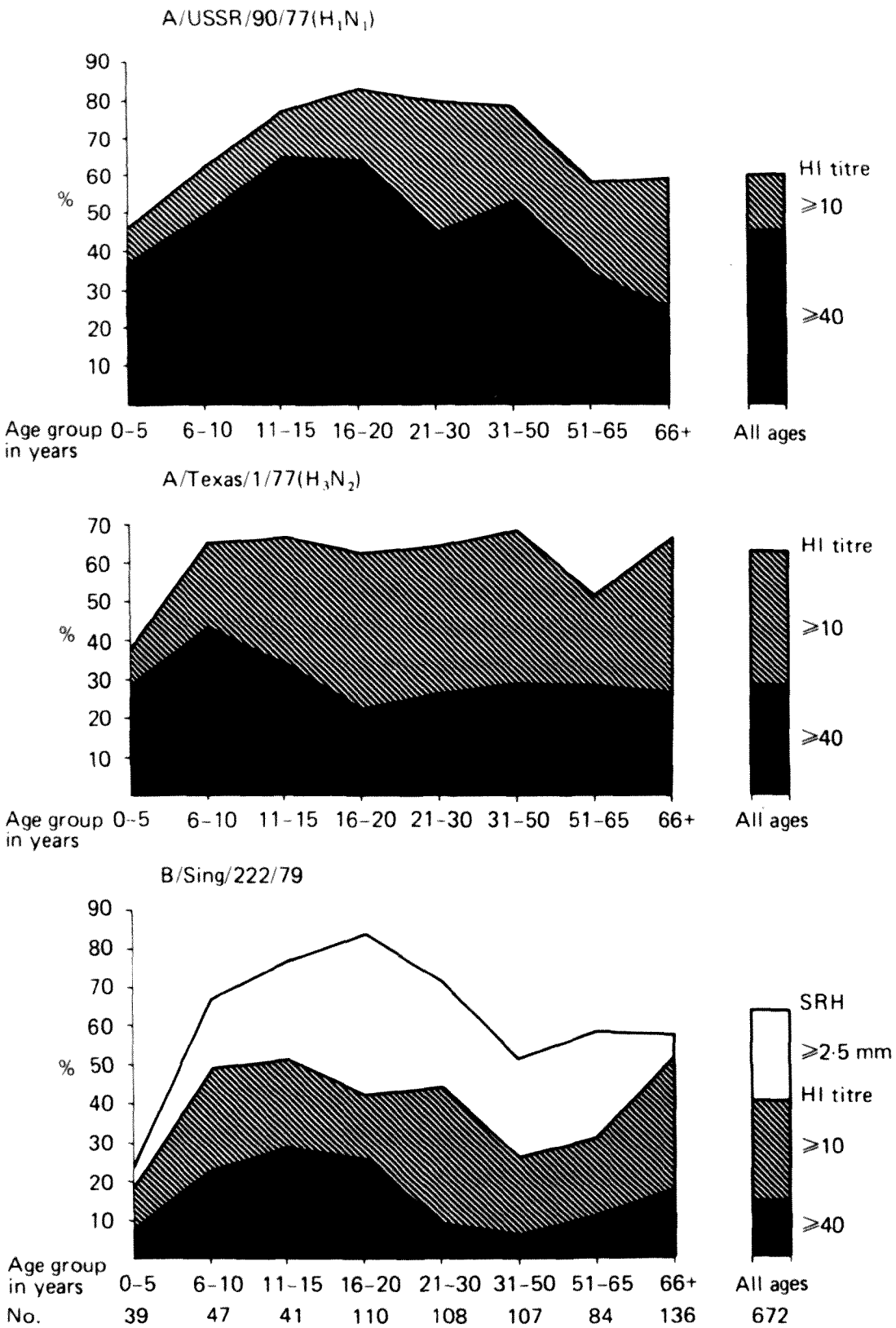

Fig. 6. Percentage of individuals with HI and SRH antibody to influenza viruses; sera collected June 1980.

becomes almost the only way to determine the presence of influenza, as the normal indices for surveillance do not operate.

Thus surveillance of influenza during the years 1976–81 has underlined two things: one is the importance of virus isolation in defining the viruses which are circulating; the other is the inadequacy of the indices previously used for measuring

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morbidity since the appearance of the H1N1 sub-type. As the adult population is largely immune to this virus it has spread principally among the young. This has meant that information on illness is not revealed by increases in the sickness benefit claims, as those at risk being mostly under 20 comprise only a small proportion of the employed population. The monitoring of increases in influenza deaths has similarly revealed little change as the young have not, in recent decades at least, died as a consequence of influenza.

It is recognized that the number of deaths attributed to influenza is an inaccurate measure of the true impact of influenza, and total respiratory or total excess deaths are a better reflexion of the consequences of influenza.

However, during the period of prevalence of the H3N2 virus the severity of epidemics has correlated reasonably well with this one national statistic, and during these last three winters as well as a lack of significant numbers of deaths attributed to influenza there was a lack of all increases in the other statistics which are used for monitoring influenza.

Information on the impact of the H1N1 viruses has been gleaned mostly from the investigation of outbreaks in boarding schools and institutions when the attack rate has been high enough to call for investigation. Whether the H1N1 virus spread outside such semi-closed communities could not be ascertained, and only the change in the proportion of young people who were found, at the end of each epidemic winter, to have specific antibody allowed some estimation to be made of the extent of circulation of this sub-type.

As a consequence of this weakness in surveillance, efforts have been made to monitor regularly acute respiratory illness in schools. This has proved relatively simple in boarding schools where children are under observation by the same medical or nursing staff and weekly reports are now available from the Medical Officers of Schools Association. In day schools where children are attended by their own doctor at home information is not readily obtainable. In all events the boarding school data are proving a rewarding addition to surveillance. Besides this the collection of regular information from doctors all over the country does provide through the Royal College of General Practitioners a measure of the number of patients attending surgery with acute respiratory illness, and although increases are not necessarily due to influenza the information gives the alert that this may herald the start of an epidemic.

The antigenic changes among the influenza viruses during this last five year period have been of a minor nature. In the H3N2 subtype the variant A/Bangkok/1/79 showed a degree of drift which could well have led to it replacing the previous variant A/Texas/1/77 throughout the world. In fact the two have circulated often concurrently and the most frequent virus encountered has been antigenically intermediate between the two. The H1N1 subtype has shown some degree of antigenic instability and the minor drift shown by A/England/333/80 has been found in nearly all the more recent H1N1 isolates.

Influenza B similarly has shown a steady drift away from the B/Hong Kong/73 virus and the more recent B/Singapore/79 virus seems now to be replacing it consistently. Antibody to all these currently circulating influenza viruses is fairly

widely found in all age groups in the UK and widespread epidemics do not seem likely unless further changes in the virus take place.

We should like to thank all those who sent us their isolates of influenza viruses and serum samples for antibody surveys, and Mr P. Cunningham and Mrs K. Kakad for their technical assistance.

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