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The return of the historic influenza A H1N1 virus and its impact on the population of the United Kingdom

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SUMMARY

The epidemiology in the United Kingdom of the influenza A H1N1 subtype which returned in 1977 after an absence of 20 years is described for the four winter seasons from 1977/8 to 1980/1. The age distribution of virus isolates and the evidence for antigenic variation is presented. The impact in the susceptible age groups year by year is shown by the change in the population with specific antibody. There was the expected increase of antibody in those under the age of 21 but also evidence for a significant amount of infection or re-infection in the older adult population.

INTRODUCTION

The H1N1 influenza A virus was first detected in 1946 in Australia and in the following year epidemics occurred in military camps in the United States of America. Attention was focussed on this virus as vaccines containing the older influenza viruses had clearly not given protection (Francis, Salk & Quilligan, 1947). The H1N1 virus was reported in many countries of the world during the following 10 years causing widespread epidemics of usually mild disease associated with low mortality rates. The moderate activity of the H1N1 virus may have been due to a continued antigenic drift of the older H0N1 sub-type rather than a full antigenic shift (WHO Memorandum, 1979) and it is possible that in 1947, when the H1N1 strain became epidemic, there was already a substantial proportion of the population with some immunity. In the winter of 1948/9, the H1N1 virus spread widely in western Europe and the strains of viruses isolated that year formed a homogenous group differing slightly from the 1947 FMI strain (Chu, Andrewes & Gledhill, 1950). In the winter of 1949/50 practically no influenza occurred in Europe except in Sweden and Norway where there were small outbreaks in May and June 1950. However, in the winter of 1950/1 epidemics reached major proportions all over Europe. It was suggested (Isaacs, Gledhill & Andrewes, 1952) that there were two prevalent variants of H1N1 virus, one originating in Scandinavia causing high morbidity and low mortality and one which originated in the southern hemisphere and spread to southern Europe and to Liverpool. The strain of H1N1 virus prevalent in Liverpool, in contrast to the general experience with H1N1, caused a much more severe form of influenza with a high death rate

(Isaacs & Andrewes, 1951). In February and March of 1956, a further serologically distinct variant of the H1N1 virus was isolated in Holland, the A/Netherlands/56 strain. This strain also appeared in India, Canada, Tanganyika and Germany. Of 101 virus strains isolated in England and Wales in 1955/6, only two were like the A/Netherlands/56 type (Hatch, 1957). However, in the following winter of 1956/7, all H1N1 viruses isolated in the United Kingdom were like A/Netherlands/56; then in mid-1957 the H2N2 subtype appeared and the H1N1 virus was no longer isolated.

The H2N2 sub-type circulated in the world for the 11 years between 1957 and 1968, when it was replaced by the H3N2 subtype which arose in the Far East in mid-1968 and has circulated in the world up to the present time. On this evidence it was thought that current sub-types always disappeared with the emergence of a new sub-type.

It was therefore a considerable surprise when the influenza A H1N1 virus re-appeared. It was first detected, in May 1977, in the north of China and spread slowly southward during the following months. By November it had crossed the borders northwards to the U.S.S.R. and southward to Hong Kong. From these areas there was rapid spread during the next few months throughout Europe, America and all over South-East Asia, and by April cases had been reported as far as Australia and South America. The epidemics which occurred were largely among older children and young adults. Meanwhile the H3N2 sub-type continued to circulate in the same populations even, on occasion, in the same outbreak.

In this paper we describe the epidemiological behaviour of the H1N1 virus in the United Kingdom for the four winters between 1977/8 and 1980/1.

MATERIALS AND METHODS

Virus Isolations

In the United Kingdom, there are nearly 50 laboratories in the Public Health Laboratory Service (PHLS), universities and some hospitals, all equipped to isolate influenza viruses from specimens sent in from patients with respiratory illnesses.

Influenza virus isolations are now usually made in baboon kidney tissue cultures, but occasionally also in fertile hens' eggs. Early passage materials are sent to the Virus Reference Laboratory where they are examined to determine the antigenic composition of the virus. The test used for the haemagglutinin is the haemagglutination-inhibition (HI) test using a battery of ferret convalescent antisera to the prototype and variant viruses and selected monoclonal antibody preparations (Pereira & Chakraverty, 1982) and for the neuraminidase, the neuraminidase inhibition (NI) test by the method of Aymard-Henry *et al.* (1973).

Serum Surveys

Antibody surveys are carried out after each winter with serum samples obtained from various Public Health Laboratories from different regions of the country. These sera are received originally for various laboratory tests. Antibody is measured against appropriate antigens either by HI tests after treatment with RDE or by single radial haemolysis (SRH) (Schild, Pereira & Chakraverty, 1975).

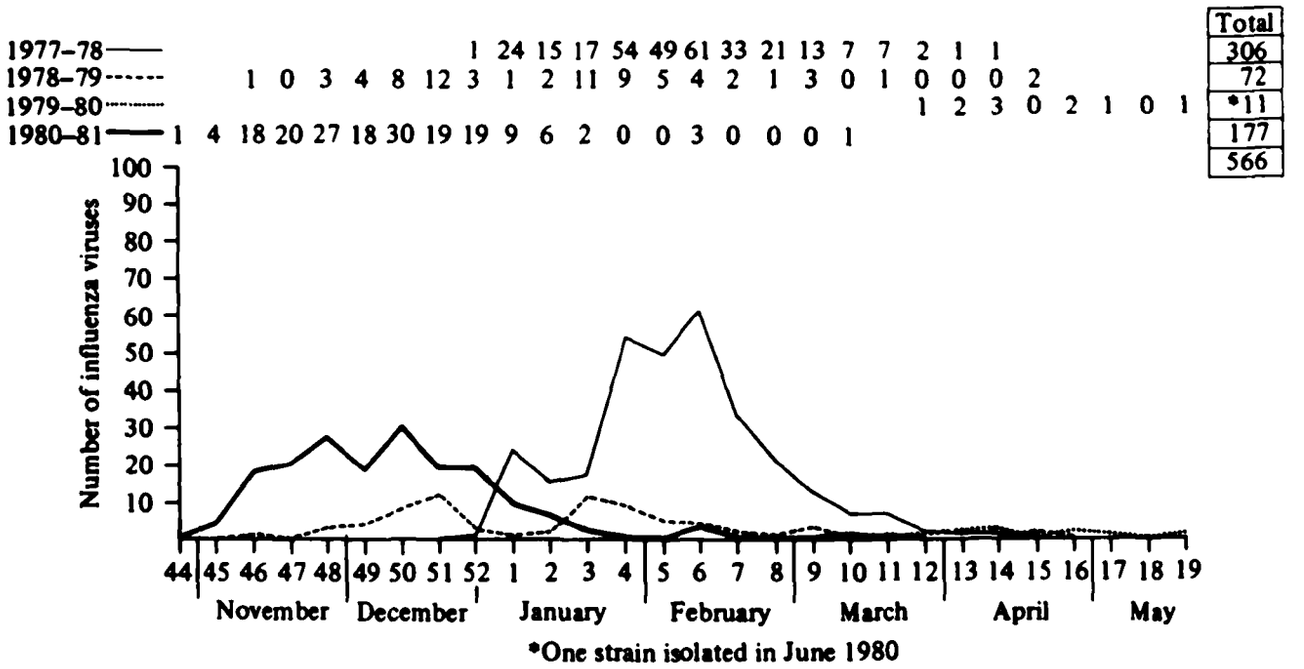

Fig. 1 Influenza A H1N1 Viruses 1977–81 U.K.

RESULTS

The distribution of influenza viruses which were isolated and examined over the four winters from 1977/8 to 1980/1 is as shown in Fig. 1.

Influenza in the winter of 1977/8

In the United Kingdom the first influenza A H1N1 viruses were isolated early in January 1978 from young adults in an Air Force camp, almost certainly introduced by persons returning from a visit to Moscow where outbreaks of influenza were in progress. Shortly after, outbreaks of influenza in boarding schools in different parts of the country began to be reported. The H1N1 virus seemed to spread rapidly in boarding schools and other residential establishments affecting predominantly people under the age of 20 years and with attack rates varying between 20 and 70%. At the same time H3N2 virus was also being detected all over the country but with this virus people of older age groups as well as children were affected. There were six outbreaks in schools where both influenza A/Texas/1/77 (H3N2) and A/USSR/90/77 (H1N1) viruses were found and in one both A/Victoria/3/75 (H3N2) and A/USSR/90/77 (H1N1). Although the epidemics in schools were a striking feature of this first winter season a number of H1N1 viruses were isolated from cases of sporadic illness among children and young adults, and a few persons over the age of 22 years (Table 1). As can be seen in Fig. 1 most of the H1N1 viruses were isolated in January and February 1978 although the virus continued to be detected until the middle of April.

Meanwhile the A/Texas/1/77 (H3N2) virus circulated widely in people of all ages. Besides this variant a few isolates were identified as A/Victoria/3/75 (H3N2). Of the total influenza viruses isolated that year 30% were influenza A H1N1; 64%

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were influenza A/Texas/1/77 (H3N2) and 4% were influenza A/Victoria/3/75 (H3N2). Besides these there were 19 influenza B viruses isolated (Pereira & Chakraverty, 1982).

An increase in the number of deaths attributed to influenza rose above the epidemic threshold at the peak incidence of the H3N2 virus infections. The morbidity indices for social benefit claims and general practitioners consultation rates remained below the epidemic threshold levels (Tillett & Spencer, 1982).

Influenza in the winter of 1978/79

Influenza B was the predominant influenza virus throughout this winter. Influenza A showed little activity but all the isolates (16% of the total) belonged to the H1N1 subtype. This virus appeared in the beginning of November 1978 and was isolated in small numbers until April 1979, with a few isolates showing minor antigenic drift towards a variant A/Brazil/11/78. The national statistics of social benefit claims and influenza related mortality remained below the epidemic threshold (Tillett & Spencer, 1982).

Influenza in the winter of 1979/80

The H3N2 virus re-appeared in November 1979 and became the predominant influenza virus (76%) of this winter season. Only 12 H1N1 viruses were isolated. The first was from a patient, ill at the beginning of April 1980, and the rest from sporadic cases up to June 1980. Of these 12 strains of H1N1, eight showed a further minor antigenic drift typified by the variant A/England/333/80. Twenty-one per cent of the strains isolated this winter were influenza B.

The national statistics of social benefit claims and influenza related mortality remained below the epidemic threshold (Tillett & Spencer, 1982).

Influenza in the winter of 1980/81

Influenza began with school outbreaks reported during November and December 1980. These were nearly all caused by H1N1 virus. By the end of December these outbreaks ended and thereafter only occasional H1N1 viruses were isolated, the last one identified was at the beginning of March 1981. The H3N2 virus appeared later in the season and formed the majority of isolates in early 1981, and over the winter the two sub-types were indentified in almost equal numbers. All the H1N1 viruses were found to be similar to A/England/333/80 variant.

In one of the boarding schools which experienced an H1N1 epidemic with this variant, blood samples were available from the youngest pupils who had entered the school 2 months previously. In these samples we found low levels of antibody to A/USSR/90/77 that were clearly detectable by SRH suggesting that these children had already had an infection with this virus. However several of these pupils were re-infected in this outbreak producing high levels of antibody to the H1N1 virus.

The national statistics of social benefit claims and influenza related mortality remained below the epidemic threshold (Tillett & Spencer, 1982).

Table 1. *Isolation of influenza* A *H1N1 virus in various age-groups in the* U.K. 1977/81

Age groups in years	1977/8 total (%)	1978/9 total (%)	1979/80 total	1980/1 total (%)
	First time exposed to H1N1 virus			
0–5	22(7)	18(22·5)	5	47(27)
6–10	30(9·5)	12(15)	0	37(21)
11–15	103(33)	9(11)	4	31(18)
16–21	143(45)			
16–22		19(24)		
16–23			2	
16–24				34 + 1*(20)
	Second time exposed to H1N1 virus			
22–50	11(3)			
23–50		13(16)		
24–50			1	
25–50				15 + 3*(10)
51 +	1(0·3)	2(2·5)	0	2(1)
Age not known	6(2)	7(9)	0	5(3)
All ages	316(100)	80(100)	12	175(100)

* Fatal cases.

Isolation of H1N1 viruses in various age groups 1977/81

The age distribution of the patients from whom influenza A H1N1 viruses were isolated in the United Kingdom in the winters of 1977/81, is shown in Table 1. H1N1 virus appeared to spread particularly among children and young adults under the age of 21 years although a few strains were isolated each winter except 1979/80 from persons who were born in or before 1957. In the first winter of prevalence 1977/8, 45% of the 315 H1N1 viruses, were isolated from the 16–21 year age group, 33% from 11–15 year olds and only 16% were isolated from children under the age of 10 years. Twelve strains were isolated from persons over the age of 22 years, the majority of whom were aged between 22–50 years. One was from a person aged 64 years. In the second winter (1978/9) H1N1 virus spread more uniformly in all age groups under the age of 22, and this time 23% of the strains were isolated from children under the age of 5. Thirteen strains were isolated from persons aged between 23 and 50 years (16% of the total isolates) and two from persons over the age of 51.

There were only 12 strains isolated in the winter of 1979/80, all of which were isolated from children and young adults. In 1980/1 H1N1 viruses were isolated in modest numbers. Although there was spread in all the younger age groups, the highest number was found in children under the age of 5 (27%) followed by 6–10 year olds (21%). Four strains were isolated from persons of over the age of 30 (31, 40, 53 and 55 years). One young person aged 16 years and three older persons died

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Table 2. *Cross HI tests with* 1977/8 *influenza* A *H1N1 variants*

	Post-infection ferret sera					Monoclonal antibody preparations	
Antigens	A/USSR/ 90/77	A/Lack/ 3/78	A/Braz/ 11/78	A/Cal/ 45/78	A/Fuku/ 103/78	110/1	264/2
A/USSR/90/77	2560	80	320	320	<*	6400	3200
A/Lackland/3/78	160	640	160	320	<	800	<**
A/Brazil/11/78	320	40	640	320	<	3200	<
A/California/45/78	80	80	160	320	<	3200	<
A/Fukushima/103/78	160	<	320	80	2560	1600	<

*, < 40; **, < 100.

Table 3. *Cross HI tests with influenza A H1N1 variants* 1977/80

	Post-infection ferret sera					Monoclonal antibody preparations		
	USSR/77	Brazil/78	E/333/80	Ind/6263/80	Ost/12/80	110/1	264/2	18/1
A/USSR/90/77	1280	160	320	40	< 40	3200	1600	12800
A/Brazil/11/78	320	640	320	40	< 40	1600	< 200	6400
A/England/333/80	320	160	1280	320	80	< 200	< 200	3200
A/India/6263/80	40	80	640	640	80	< 200	< 200	800
A/Ostrava/12/80	< 40	< 40	80	160	80	< 200	< 200	< 200

Table 4. *NI tests with influenza A H1N1 viruses with hyperimmune rabbit antiserum to A/Equi/Prague/56(H) – A/USSR/90/77 (N)*

Viruses	NI titre of rabbit antiserum
A/USSR/90/77	640
A/Brazil/11/78	640
A/Lackland/3/78	320
A/California/45/78	640
A/Fukushima/103/78	240
A/England/333/80	160

this winter due to influenza A H1N1 virus infection (27 years, 30 years and one adult age not known). This was the first year since the re-appearance of the H1N1 virus that fatal cases were confirmed in the U.K.

Antigenic Variants

In the first year (1977/8) of the H1N1 virus, four variants of the prototype A/USSR/90/77 were detected. Only one of them, A/Brazil/11/78, spread widely in the world, while the others were found only sporadically. A/Fukushima/103/78 a variant which was isolated only in Japan appeared to be close to an earlier variant A/FLW/1/52. Table 2 shows the cross reactivity of these variants.

The antigenic drift which has occurred among the H1N1 influenza A virus from 1977 to 1980 as demonstrated by cross HI tests with ferret antisera and monoclonal antibody preparations (kindly supplied by Dr R. G. Webster) is shown in Table 3. In the winter of 1979/80 the majority of the influenza A H1N1 isolates showed a degree of drift to A/England/333/80. They could be differentiated clearly from A/USSR/90/77 and from A/Brazil/11/78 by the use of two monoclonal antibody preparations. In the next winter almost all the H1N1 viruses isolated in the United Kingdom were similar to A/England/333/80 variant and similar viruses were detected in many parts of the world. Two other variants, A/India/6263/80 and A/Ostrava/12/80 were found sporadically in some parts of the world.

A neuraminidase inhibition tests with some influenza AH1N1 viruses with hyperimmune rabbit antiserum to A/Equi/Prague/56 – A/USSR/90/77 (H7N1) recombinant virus is shown in Table 4. Some drift has occurred among the neuraminidase antigens of H1N1 viruses, although, by the methods used, this is less than in the haemagglutinin antigens.

Search for natural recombinants in H3N2/H1N1 outbreaks

From the six school outbreaks where both H3N2 and H1N1 viruses were circulating concurrently a total of 23 isolates were available. These were tested by H1 and N1 to see if the haemagglutinin and neuraminidase antigens of the two serotypes had re-assorted. No evidence for this was found and in all cases the haemagglutinin was associated with the expected neuraminidase. Tests were not performed other than for the surface antigens.

Table 5. *Demonstration by SRH of the acquisition of antibody to A/USSR/90/77 (H1N1) in two age groups from* 1977 to 1981

	Age group (years)			
	11–15		31–50	
	Number tested	(% positive)*	Number tested	(% positive)*
1977	99	(2)	88	(45)
1978	98	(23)	100	(54)
1979	98	(60)	100	(75)
1980	73	(63)	83	(78)
1981	78	(67)	102	(79)

* SRH zone diameter ⩾ 2·5 mm.

Table 6. *Age distribution of influenza virus HI antibodies to* H1N1 *variants in* U.K. *in* 1981

		Percentage with stated HI titre to								
		A/USSR/90/77			A/England/333/80			A/Ostrava/12/80		
Age in years	Number sera tested	< 10	10–20	⩾ 40	< 10	10–20	⩾ 40	< 10	10–20	⩾ 40
0–5	94	68	16	16	64	22	14	68	22	10
6–15	173	32	34	34	27	28	45	35	45	20
16–25	130	32	27	41	41	31	28	36	50	14
26–50	145	28	33	39	34	28	38	35	39	26
51–65	72	46	37	17	33	53	14	28	40	32
66+	98	50	40	10	50	31	19	39	41	20
Total	712	40	31	29	39	31	30	39	41	20

Antibody to influenza A H1N1 viruses in the United Kingdom

The changes found over the period 1977–81 in the proportion of people with antibody to A/USSR/90/77 (H1N1) is shown in Table 5. Of the sera collected before the H1N1 virus re-appeared in 1977 nearly half of those obtained from persons over the age of 30 had antibody to H1N1 virus, presumably acquired during the previous decade of prevalence 1947–57. Of the sera from people under 20, antibody was detected in only 2% of the samples tested. After the first year of prevalence of the H1N1 virus, the proportion of this age group found to have antibody rose to 23% and from 45% to 54% among older persons. By the end of the winter of 1978/9 a considerable proportion of the population in the United Kingdom had antibody to H1N1 virus (60% among 11–15 years and 75% among 30–50 age group). In the following two winters 1979/80 and 1980/1 despite the evidence of the circulation of the virus there was only a small increase in those with antibody. By the end of 1980/1, 67% of the 11–15 year olds, and 79% of the 30–50 year-olds had antibody to this virus.

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Table 6 shows the age distribution of influenza A H1N1 virus antibodies to three variants in 1981.

Although the three H1N1 viruses used in this study vary considerably in their haemagglutinin surface antigens, the antibody demonstrated in the human sera to these viruses appears to be widely cross-reactive and the proportion of samples without detectable antibody is the same with all three variants.

DISCUSSION

The H1N1 viruses which were associated with outbreaks and epidemics of influenza in 1977 were found to be similar to viruses that had circulated around 1950 (Kendal *et al.* 1978; Nakajima, Deselberger & Palese, 1978; Scholtissek, Von Honingen & Rott, 1978). During this first year of recirculation of H1N1 virus several strains already showed minor antigenic drift away from the prototype virus A/USSR/90/77. Only one of these drifted strains A/Brazil/11/78 spread widely. Of the various drifted strains, none were close to variants which had appeared during the period of 1946–57 except A/Fukushima/103/78 which caused a localized outbreak in Japan and was found to be close to A/FLW/1/52 virus.

The reappearance of the H1N1 virus raises some interesting questions not only as to its origin but also as to its future role in the epidemiology of influenza. In the past the emergence of a new influenza sub-type has led to the disappearance of the previous sub-type. In the 1977/8 winter the prevailing H3N2 sub-type did not disappear but circulated together with the H1N1 viruses. Dual infection with both sub-types in individuals have been reported from Japan (Yamane *et al.* 1978) and U.S.A. (Kendal *et al.* 1979; Young & Palese, 1979), and there has been great interest in the possible occurrence of natural recombinants. Bean, Cox & Kendal (1980) described some strains with H1N1 surface antigens which could be shown to contain genes from an H3N2 parent by RNA-RNA hybridization and by competitive RNA-RNA re-association techniques. Nakajima Cox & Kendal (1981) reported a strain A/California/10/78 which when analysed by RNA-RNA hybridization, oligonucleotide mapping and monoclonal antibody tests, was found to be a recombinant virus possessing A/Brazil/11/78-like surface antigens, haemagglutinin and neuraminidase but polymerase and nucleoprotein genes originating from H3N2 strains. In the U.K. in the winter of 1977/8 both H3N2 and H1N1 sub-types circulated concurrently and caused extensive outbreaks in at least six boarding schools (Pereira & Chakraverty, 1982). Of the strains available from these outbreaks no evidence was obtained that the surface antigens of the H1N1 and H3N2 viruses had recombined. Tests for possible recombination of the non-surface antigen genes have not so far been done.

In the winter of 1977/8, in the U.K. all the viruses of H1N1 subtype were found to be similar to the prototype virus A/USSR/90/77. In the following winter, by HI tests using specific ferret antisera, most of the strains were found to be close to the original A/USSR/90/77 but when examined with monoclonal antibody preparations in HI tests some showed drift towards A/Brazil/11/78. In the 1979/80 winter only 12 strains of influenza A H1N1 virus were isolated and of these

four were similar to A/Brazil/11/78 and eight showed further drift to a variant, A/England/333/80. These minor variants could be easily identified by the addition of two monoclonal antibody preparations to the range of ferret antisera employed in HI tests. In the next winter of 1980/1 all H1N1 viruses isolated were similar to A/England/333/80.

As happened in other countries, when the H1N1 virus first reappeared in the U.K. it spread almost entirely in children and young adults under the age of 21 and less than 4 % of the isolates were from older people. This virus seemed to need a close population for spread and a striking feature of the first winter was the number of outbreaks in boarding schools and institutions for young people. The attack rate in these communities varied between 21 and 67 %. Evidence for spread in day schools or in the general population was more difficult to obtain although moderate numbers of H1N1 viruses were isolated from sporadic cases. An interesting feature of this first winter was the sparing of younger children. Only 7 % of isolates were from children under 5 and only three strains came from children under 1 year of age. Serological evidence obtained by Pyhala, Aho & Visakorpi (1979) and Haaheim (1980) suggests that a similar pattern of infection also existed in Finland and Norway.

During the second year of circulation of the H1N1 virus this sparing effect in the very young was no longer observed and there was also clearly some spread in the adult population. Although there was evidence by both virus isolation and serology that older people were infected, no outbreaks were reported in the U.K. nor was there an increase in reported influenza deaths.

In New York however, an outbreak did occur in an institute for old people (Mathur *et al.* 1981) and demonstrated that the H1N1 virus could cause serious illness in elderly institutionalised patients even though in this outbreak there were no deaths.

The severity of the illness associated with H1N1 virus was on the whole mild to moderate although Hoskins (1979) reported that in an explosive outbreak, which occurred in 1977/8 in a boarding school in England where 411 boys were affected out of a total of 821 at risk, 29 boys had severe illnesses with prolonged fever and productive cough and 7 boys had X-ray evidence of lung consolidation. Infection was confirmed in only a few infants during the first winter but their illnesses were no less severe than is usual in this age group. In the subsequent winters, when the H1N1 virus more generally distributed in the population, this characteristic picture of febrile illnesses with croup or convulsions or other serious clinical conditions which bring children to hospital was found in the usual high proportion associated with influenza due to the H3N2 virus.

It was not anticipated that the H1N1 virus infections would be accompanied by an increase in deaths because of the age distribution of cases and the evidence that influenza deaths are predominantly among older people. In the first three winters of H1N1 circulation there were no confirmed deaths from this virus infection. However in the fourth winter 1980/1 there were five deaths where infection was confirmed by virus isolation. The ages of the fatal cases were 8, 16, 27 and 30 years, and one adult, age unknown. In three of these cases a staphylococcal pneumonia was also implicated in the death.

Staphylococci were also found associated with H1N1 virus in two fatal cases of bronchotracheitis and bronchiolitis in young people in the Netherlands in the winter of 1978/9 (Schaap *et al.* 1979).

As the adult working population has been, on the whole, little affected by the H1N1 virus, the level of sickness benefit claims remained unchanged during the 4 years of prevalence although in the Shetland Islands a sharp increase in claims coincided with an outbreak of H1N1 influenza in 1980/1. This increase was found to be almost entirely due to sickness absences in young adults who had been exposed to this virus for the first time in their lives (Dr G. D. McGregor personal communication). Of the other epidemic indices for influenza there was no increase indicating the presence of influenza in the community except during the winter of 1977/8 when the deaths attributed to influenza rose above the threshold level coinciding with the peak of incidence of H3N2 virus infections.

A series of three successive winters without increases in influenza-related statistics is exceptional and in the past 25 years there has never been more than a single winter without such evidence.

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