

Influenza in the United Kingdom 1982–85

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(Received 20 March 1986; accepted 17 April 1986)

SUMMARY

Influenza surveillance in the UK between the years 1982 and 1985 has demonstrated the regular winter appearance of influenza A virus of both H1N1 and H3N2 subtypes and influenza B.

Their antigenic diversity is described and correlated with the national statistics for morbidity and mortality for influenza.

One unexpected finding has been that despite the wide circulation of influenza viruses there has been a continuation of winters without significant increases in influenza deaths or morbidity. A previous report of influenza surveillance (Pereira & Chakraverty, 1982) noted an already unusual series of three consecutive winters with this pattern. This report records a further 4 years bringing a total of seven successive winters without evidence of epidemics of severe disease associated with influenza viruses, as indicated by the national UK statistics.

INTRODUCTION

The worldwide monitoring of influenza has continued under the auspices of the World Health Organization since 1947. The need for this detailed surveillance on an international scale stems from the frequent episodes of the disease throughout the world and their association with antigenic variability in the viruses responsible. Influenza virus is antigenically unstable and continuing small changes in the base sequences of the nucleic acid produce significant changes in the antigenic structure which allow the free spread of such altered viruses in populations thus made newly susceptible.

The study of influenza viruses isolated in the northern and southern hemispheres in their respective winter seasons means that any alterations can be detected and related to epidemics and outbreaks that have occurred already and that might be predicted to occur elsewhere subsequently. Given sufficient time such new antigenic variants could be introduced into vaccines to prevent infection in those most at risk of serious illness.

The aims of influenza surveillance are to isolate viruses from clinical cases, to estimate the morbidity and mortality associated with them and to establish the

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prevalence of relevant antibody. The details of such surveillance vary from country to country depending on the social structure and organization of health services.

In the UK influenza surveillance has been particularly well developed through the existence of a network of virus laboratories and dependable sources of epidemiological information (Public Health Laboratory Service, 1975). Together these have produced a clear and comprehensive picture of the impact of influenza since the appearance of the Asian influenza (H2N2) in 1957.

During the 11 years of circulation of this H2N2 influenza subtype several severe epidemics occurred and these were associated with considerable mortality. During that period there were, however, three winters (1959–60, 1963–4 and 1966–7) when influenza activity was at a low level and no increases in deaths attributed to it were notified.

With the appearance of the Hong Kong (H3N2) sub-type in 1968 an almost identical pattern of epidemic winters followed with, during the next 11 years, several severe epidemics. Nevertheless in the three winters 1970–1, 1973–4 and 1976–7 there was a negligible increase in deaths attributed to influenza.

These patterns of influenza have already been described in detail (Pereira, 1980). So similar were these two 11-year periods with these two different subtypes that there was some expectation that a new subtype might appear in 1979 and start the same process again. However this has not happened and the present paper describes the pattern observed since the last report on influenza surveillance which covered the years 1977–81 (Pereira & Chakraverty, 1982).

MATERIALS AND METHODS

Viruses, ferret antisera and monoclonal antibody preparations

The source and the tests used for the identification of influenza viruses were as described previously (Pereira & Chakraverty, 1982). Briefly, 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. All suspected influenza viruses are sent to the Virus Reference Laboratory where tests are carried out to determine the type, subtype and antigenic reactivity within subtypes. This is done by haemagglutination inhibition tests (HI) against a battery of convalescent ferret antisera and with selected monoclonal antibody preparations. Monoclonal antibodies to the haemagglutinin were selected from those prepared against the A/USSR/90/77 (H1N1) and A/Bangkok/1/79 (H3N2) viruses and were kindly supplied by Dr R. G. Webster, St Jude's Hospital, Memphis, Tennessee, USA. Similar monoclonal antibodies to A/England/333/80 (H1N1) and A/Philippines/2/82 (H3N2) were prepared in our laboratory as described by Pereira *et al.* (1985). Both ferret antisera and monoclonal antibody preparations were treated with receptor-destroyer enzyme (RDE) to remove non-specific inhibitors before they were used in haemagglutination-inhibition tests.

Antibody surveys

Serum samples for antibody surveys were kindly provided by several laboratories in different parts of the country. The sera were obtained from patients of all ages

bled during the summer months for a variety of routine clinical pathological tests.

Antibody to currently circulating viruses was measured either by HI tests after treatment of sera with RDE or by single radial haemolysis (SRH). Details of the methods used have already been described (Schild, Pereira & Chakraverty, 1975; Pereira & Chakraverty, 1982).

Recent isolates of influenza A virus have been found, not infrequently, to be particularly sensitive to non-specific inhibitors in human sera so that many antibody profiles had to be defined by SRH after several batches of commercial and in-house preparations of RDE failed to remove all inhibitor.

Sources of epidemiological data

These were obtained through the Communicable Disease Surveillance Centre from the Office of Population Censuses and Surveys (OPCS) and the Royal College of General Practitioners (Tillett & Spencer, 1982).

RESULTS

The most striking aspect of the period 1982-5 has been the continued absence of the normal winter increase in influenza deaths which had been such a regular feature from 1957 up to 1978. There have now been seven sequential winters from 1978-9 to 1984-5 without any significant excess of deaths attributed to influenza.

It might be assumed that influenza viruses had not circulated in the population during these years or had ceased to undergo antigenic changes. Details of the considerable number of influenza viruses each winter in the UK have shown that neither explanation is correct. There has been little evidence of major epidemics of disease or the involvement of the whole population but both influenza A subtypes, H3N2 and H1N1, as well as influenza B, have been isolated from patients in outbreaks and sporadic cases of infection each winter.

Antigenic variants were detected every year but none replaced all the others to become predominant and a heterogenous collection of co-circulating strains has become the usual pattern.

Influenza in the winter of 1981-2

During this winter season both influenza A and influenza B circulated and were detected in almost equal numbers. The first virus to be isolated was an influenza B from a sporadic case in October 1981. After a slow start the number of cases began to increase and, as schools re-assembled in January 1982, outbreaks of influenza B began to be reported. These, together with occasional outbreaks in old peoples' homes continued until the middle of March 1982 although individual cases of infection were detected up to June 1982 (Fig. 1).

Fifty-three per cent of the total number of influenza viruses isolated during this winter were influenza B with the majority similar antigenically to B/Singapore/222/79.

Influenza A of the H3N2 subtype was first isolated this season from a sporadic case during December 1981. It became increasingly common during January and was found throughout the next 4 months associated particularly with outbreaks in hospitals and old peoples' homes.

Although a few of the nearly 400 isolates examined were like A/Texas/1/77 or

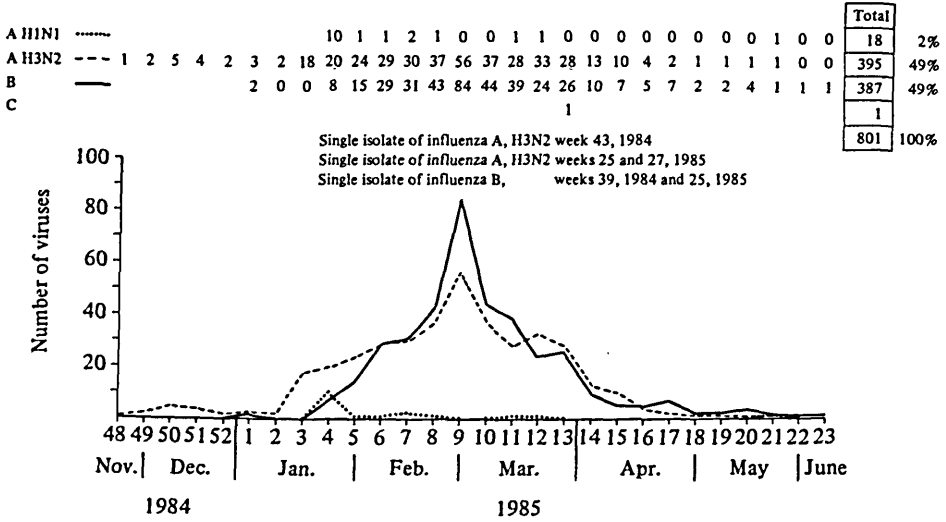


Fig. 4. Influenza viruses, United Kingdom 1984-5.

Table 1. Cross reactivity of influenza A H3N2 viruses (haemagglutination inhibition)

Viruses	Ferret antisera							
	A/BK/1/79	A/Bel/1/81	A/Ph/2/82	A/Caen/1/84	A/HK/1/84	A/HK/3/84	A/CT/2/85	A/ChCh/4/85
A/Bangkok/1/79	1280	640	320	80	640	320	640	640
A/Belgium/1/81	640	1280	160	80	640	640	1280	640
A/Philippines/2/82	80	640	640	160	160	320	640	1280
A/Caen/1/84	320	320	160	1280	320	1280	640	1280
A/Hong Kong/1/84	640	160	160	160	1280	640	640	640
A/Hong Kong/3/84	40	20	80	80	80	640	320	640
A/Cape Town/2/85	160	80	160	160	1280	640	320	320
A/Christchurch/4/85	80	80	80	320	320	640	1280	2560

a new group was identified whose members reacted with only 2 of the 4 monoclonal antibodies to A/Philippines/2/82.

In this group could also be placed viruses which circulated widely in the southern hemisphere in the later months of 1985 causing outbreaks of influenza in New Zealand, Malaysia, South Africa and South America.

Of the influenza B viruses which were isolated with about the same frequency as influenza A H3N2, 70% were found to be like B/USSR/100/83; 20% were like the variant B/Norway/1/84 while the remainder were heterogeneous but most showed a decreasing reactivity with the ferret antisera in current use.

The few influenza A H1N1 isolates showed modest changes, with most of them antigenically closest to the variant A/Chile/1/83 and a few like A/Switzerland/79/85 (Table 3).

Once again over this winter season the morbidity and mortality statistics remained at low levels.

Table 2. *Antigenic groupings of H3N2 influenza viruses with monoclonal antibodies*

Viruses	M/C to A/BK/1/79*				M/C to A/Ph/2/82				UK				
	Group	4/1	85/1	67/1	31/5	Group	10	19	22	2	1982-3	1983-4	1984-
A/Philippines/2/82	1	++	++	-	-	1	++	++	++	++	13	11	48
A/Hong Kong/1/84		++	++	-	-		++	++	++	++			
A/Cape Town/2/85	2	++	++	-	-	2	++	++	-	-	2	1	5
A/Kuala Lumpur/44/85		++	++	-	-		++	++	-	-			
A/Wellington/4/85		++	++	-	-		++	++	-	-			
A/Christchurch/4/85	2	-	-	-	-	3	++	++	-	-	1	3	4
A/Caen/1/84		-	-	-	-		-	-	-	-			
A/Hong Kong/3/84		-	-	-	-		-	-	-	-			
Number of isolates examined											24	20	87

* Received from Dr Webster.

+ = > 3200 Haemagglutination inhibition titres.

- = < 200 Haemagglutination inhibition titres.

Table 3. *Cross reactivity of influenza A H1N1 viruses (haemagglutination inhibition)*

Influenza A H1N1 Viruses	Ferret antisera					A/Switzerland/79/85
	A/Brazil/11/78	A/England/333/80	A/Chile/1/83	A/Dunedin/27/83	A/Victoria/7/83	
A/Brazil/11/78	160	80	40	<40	40	160
A/England/333/80	160	640	160	<40	160	640
A/Chile/1/83	<40	80	160	<40	40	320
A/Dunedin/27/83	<40	<40	<40	1280	40	320
A/Victoria/7/83	160	640	640	320	5120	640
A/Switzerland/79/85	80	320	1280	40	80	1280

Antibody surveys

Each summer, when influenza viruses ceased to be detected, sera taken from people of all age groups were examined for antibody to the viruses which had been circulating in the previous winter months.

Antibody surveys after the winter of 1981-2 (Fig. 5) showed the proportion of these sera with antibody to A/England/333/80 (H1N1), A/England/496/80 (H3N2) (the variant antigenically like A/Belgium/1/81 which was accepted as the prototype) and B/Singapore/222/79. Antibody to all three strains was present in half to three quarters of all age groups except for the youngest and oldest.

Similar patterns were obtained in 1983 with the same viruses as antigens but

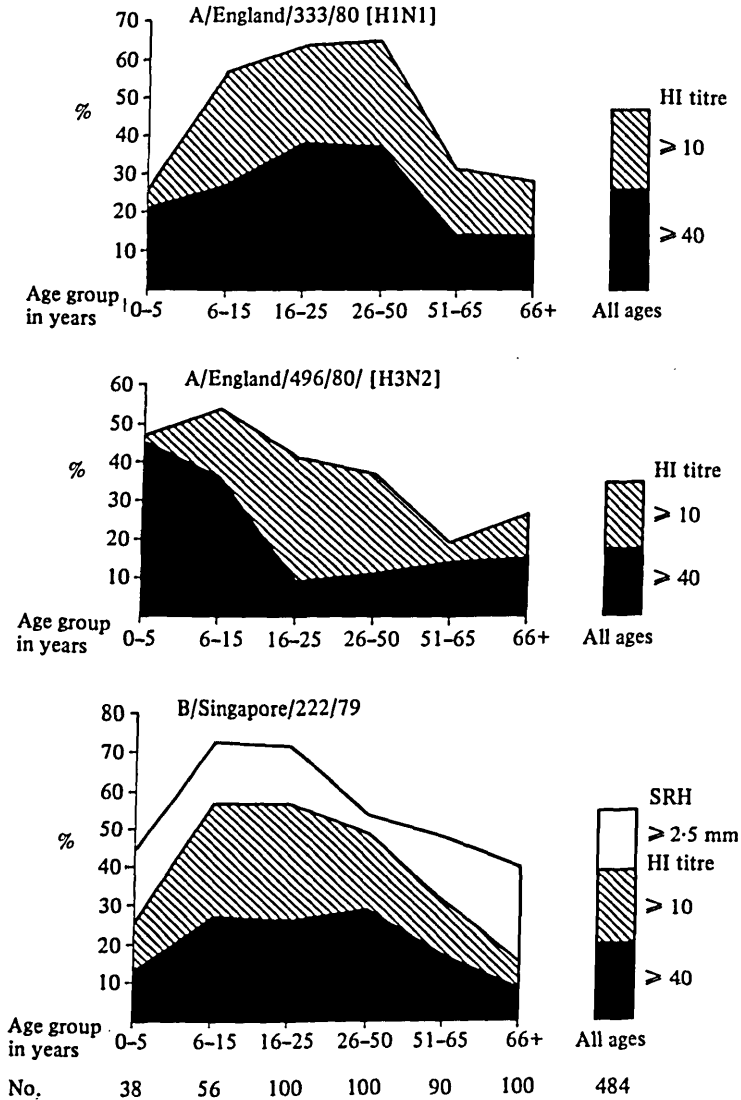


Fig. 5. Age distribution of antibody to influenza viruses (sera collected June 1982). (Haemagglutination-inhibition and single radial haemolysis).

tests with A/Philippines/2/82 (H3N2) showed a lower proportion of sera with antibody against this variant and this virus was later included in the influenza vaccines used in the following year in the hope of preventing its spread in a population with poor immunity to it. In fact H3N2 viruses were uncommon in the following winter (1983-4) and the predominant viruses were H1N1 strains and influenza B. Sera taken in the summer of 1984 consequently showed little change in the pattern of antibodies compared to the previous year.

Figure 6 shows the antibody profiles by age after the winter of 1984-5 and includes those to the variants of the H3N2 viruses which had been detected in the UK and subsequently in the southern hemisphere, A/ChristChurch/4/85 and A/Cape Town/2/85. The antibody profiles to all the variants were broadly similar

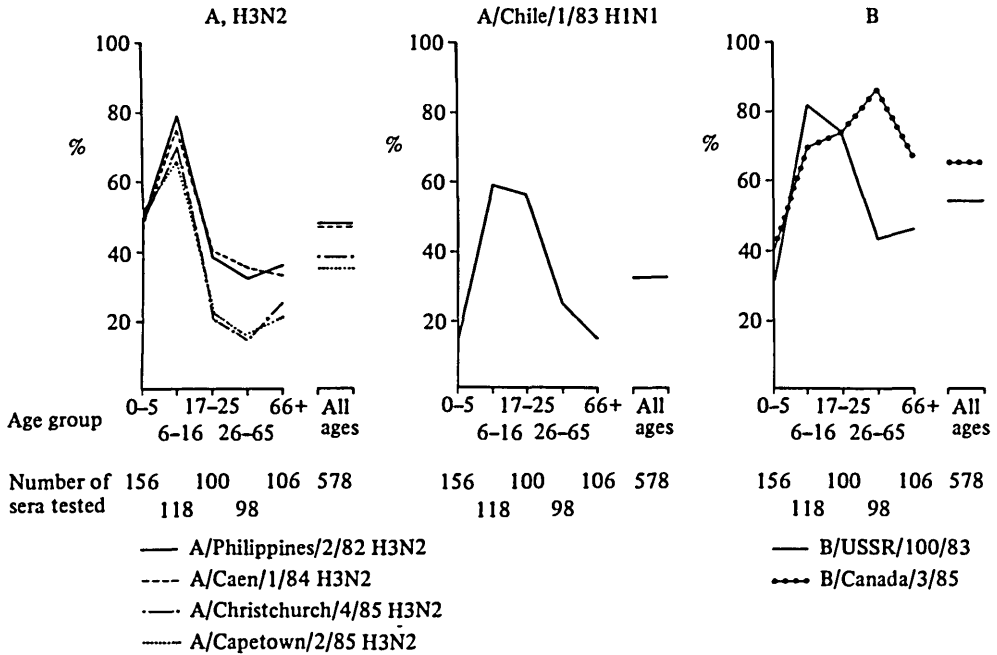


Fig. 6. Age distribution of antibody to influenza viruses (sera collected June–July 1985). (Single radial haemolysis.) SRH zone diameter ≥ 3.00 mm.

Table 4. Cross reactivity of influenza B viruses (haemagglutination inhibition)

Viruses	Ferret antisera										
	1	2	3	4	5	6	7	8	9	10	11
1 B/Hong Kong/8/73	640	640	20	160	640	10	160	—	80	1280	80
2 B/Singapore/222/79	40	160	10	160	160	20	80	—	40	320	160
3 B/Hong Kong/1/83	—	40	80	20	80	20	80	40	40	160	320
4 B/USRR/100/83	—	40	—	80	320	—	20	—	10	40	40
5 B/Norway/1/84	—	80	—	160	2560	20	40	—	40	80	80
6 B/Texas/1/84	—	40	10	40	320	320	20	—	10	20	160
7 B/England/177/85	—	20	—	20	80	—	160	20	20	80	20
8 B/England/244/85	—	—	—	—	40	—	10	160	—	—	20
9 B/Minnesota/1/85	—	20	—	10	40	—	80	20	80	40	80
10 B/Canada/3/85	10	80	10	40	80	—	160	20	80	320	160
11 B/Victoria/3/85	—	40	10	10	80	—	80	20	20	80	320

— = <10.

with antibody considerably more common in children and young adults. Antibody to the H1N1 subtype variant which had been only infrequently isolated was again more common in young adults.

A comparison of the prevalence of antibodies to the various influenza B strains showed that they were more common to B/Canada/3/85, which had only rarely been isolated, than to the older variant B/USRR/100/83.

DISCUSSION

Systematic virological surveillance of influenza in the UK over the past 30 years has shown that influenza A or B viruses, and often both, circulate every winter without exception. Their presence has usually been associated with changes in some of the routine weekly statistical indices which give a measure of the morbidity and mortality associated with influenza. Examples of such data are hospital admissions, general practice consultation rates for acute respiratory illness, industrial sickness absence, new claims for sickness benefit, school sickness absence and, for mortality, deaths attributed to influenza, death due to influenza, bronchitis and pneumonia, and deaths from all causes.

In recent years the most reliable statistics have been general practitioner consultation rates and influenza deaths (Tillett & Spencer, 1982) and these two have been found to reflect quickly and accurately the presence and size of an influenza epidemic. However, despite the evidence that influenza viruses were present in the community, these statistics have not provided figures to support any suggestion that the viruses were responsible for a significant increase in morbidity or mortality over a period, now, of 7 years.

The reasons for this apparent change in the epidemic behaviour of influenza are not clear but there are various possibilities. The first must be the virus itself. The regular impact of influenza epidemics has been thought to be a reflection of the antigenic variation which occurs continuously if unpredictably with both influenza A and B but particularly with influenza A virus. Changes in the antigenic structure of the virus produce variants which are able to outflank the immunological barrier induced by previous infections with earlier influenza viruses.

Such changes, however, are still observed and, over the 7 years when influenza has not caused epidemics of severe disease, new variants of the H3N2 sub-type have appeared, predominated and disappeared to be replaced by others exactly as during the previous 20 years. As shown in Table 1, the A/Bangkok/1/79 variant which followed on A/Texas/1/77, itself responsible for several epidemics with considerable morbidity and mortality, was followed in turn by the closely related A/Belgium/1/81 then by A/Philippines/2/82 and A/Caen/1/84 variants from Hong Kong and, more recently during the middle of 1985, by several variants from the southern hemisphere such as A/Cape Town/2/85 and A/Christchurch/4/85.

Table 1 shows the small differences between these successive variants as demonstrated in HI tests with ferret antisera, and it has been difficult to distinguish these viruses by this means. The resort to monoclonal antibody preparations has made it simpler to allocate viruses into groups and the progression of the prevalent strains, from fully reactive, through partially reactive to non-reactive in tests with these reagents is consistent with continued antigenic drift. This was demonstrated in the previously reported study (Pereira *et al.* 1985) and can also be seen in Table 2.

It could be that this minor degree of change year by year has allowed sufficient immunity to be maintained in the population so that influenza has not been able to spread with enough vigour to cause the customary increases in morbidity and mortality. However, this may not be the decisive factor because the results of the

antibody surveys show that the proportion of people in various age groups with antibody to the recent and current variants is not particularly high except in the case of school age children.

It has always been difficult to predict the behaviour of influenza but the very moderate impact, and absence of the usual mortality, reported both in the UK and most of Europe and in Australia (Gill & Murphy, 1985) during the past 7 years have been unexpected. Curiously, this has not been the case in the USA and mortality due to influenza seems to have reached and passed the threshold indicating epidemic spread in three seasons – in 1980/1 (with influenza A H3N2 Bangkok/1/79 virus), to a lesser extent in 1982/3 (with the same variant) and in 1984/5 (with A/Philippines/2/82). The variants in circulation were apparently the same as those identified in other countries but for unknown reasons their impact seems to have been more severe in the USA than elsewhere in the world. It is impossible to tell how long this period without a new variant capable of causing a major impact, including significant mortality, will last, and it is as important as ever to maintain constant surveillance.

We should like to thank all those who sent us their isolates of influenza viruses and serum samples for antibody surveys.

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