PAPERS AND ORIGINALS

Epidemiology of the Hong Kong/68 Variant of Influenza A2 in Britain

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Summary

Two influenza epidemics in Britain in 1968-9 and 1969-70, were due to the Hong Kong/68 variant of influenza A2 virus. The first epidemic was prolonged with low morbidity and mortality rates; the second was sharp with high rates. The difference between total morbidity and mortality in the two epidemics, however, was less than it appeared to be—the estimated excess morbidity and mortality due to all causes in 1969-70 was only about 50% greater than in 1968-9.

Antibody studies showed that about one-quarter of two groups of adults investigated were infected in the first epidemic and about one-third in the second. After the two epidemics about one-third still had no antibody to the A2/Hong Kong/68 virus.

Introduction

Epidemics due to influenza virus A have occurred in Britain every year since the A2 subtype appeared in 1957, except in 1959-60, 1961-2 (when influenza B was prevalent), and 1966-7. In the early part of this period epidemics assumed major proportions, but from 1963 onwards they appeared to decrease in size. This trend was interrupted by a moderately large outbreak in 1965-6 and an even larger one in 1967-8 (Miller and Lee, 1969), when two variants of the original A2 virus were circulating together (Pereira *et al.*, 1969a).

The impact of this major epidemic had hardly faded when news came of another variant of the A2 virus, detected in an explosive outbreak in Hong Kong in July 1968 (Cockburn *et*

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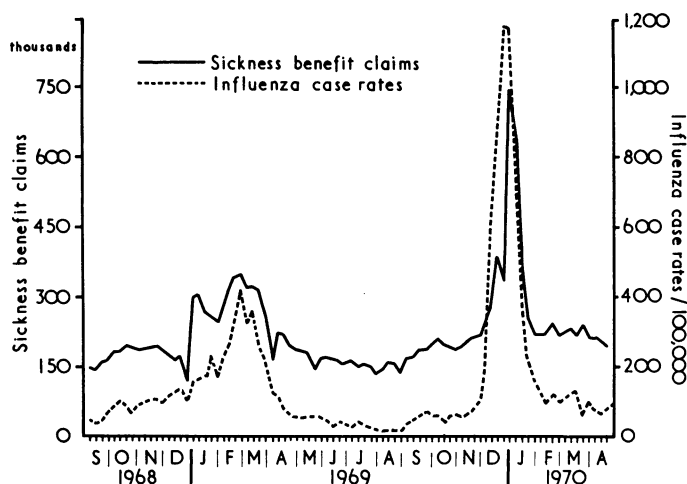
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al., 1969). This variant showed the biggest antigenic change since 1957, but it was still not completely distinct from the original A2 virus, and some cross-neutralization with earlier A2 variants was demonstrable. Nevertheless, the change was sufficiently sharp that population immunity resulting from exposure to previous A2 variants seemed unlikely to prevent widespread epidemics which, predictably, followed at once in South-East Asia, Australia, India, and Iran and shortly after in many other parts of the world.

Hong Kong Influenza in Britain 1968-70

MORBIDITY AND MORTALITY RATES

The A2/Hong Kong/68 virus was first isolated in Britain in August 1968 from a child resident in London who had no known contact with anyone recently arrived from the Far East where the epidemic was then active. Throughout the succeeding autumn months increasing numbers of strains of the virus were isolated, almost all from persons who had recently arrived from areas where epidemics were in progress, or their immediate contacts. A few localized outbreaks in schools and institutions were reported but there was no evidence of extensive spread in the general population.

Towards the end of December 1968 the first community outbreaks were reported and the subsequent course of events can be seen in Fig. 1. This shows changes in two indices which reflect influenza prevalence: firstly, weekly numbers of new claims for sickness insurance benefit submitted to the Department of Health and Social Security, which are supported by medical certificates of incapacity for work for all causes; and, secondly, weekly consultation rates for illnesses diagnosed clinically as influenza or influenza-like, calculated from returns to the General Practice Research Unit of the Royal College of General Practitioners from about 40 general practices in various parts of Britain serving a population of about 150,000 persons. In the first week of January 1969 the number of new claims for sickness benefit increased sharply, an event which usually indicates the start of an influenza epidemic. But the number reached only just over 300,000 in one week, compared with a peak of 485,000 in the

FIG. 1—Sickness benefit claims and influenza case rates. England, Wales, and Scotland 1968-70.

Year	Age in Years					All Ages
	0–4	5–14	15–44	45–64	65 and over	
1968-9	557	285	487	493	148	420
1969-70	944	377	1,323	1,689	1,092	1,260

*From returns to the Royal College of General Practitioners' General Practice Research Unit.

highest rate was in adults aged 45-64, but the group showing the greatest proportional increase in rate was those over 64. The rate in children aged 5-14 was low in both years. These figures, however, have been calculated only for the peak week of each epidemic, and different age groups may be affected at different times during an epidemic (Miller and Lee, 1969). Final interpretation of these figures must, therefore, await full analysis.

1967-8 epidemic, before declining. There was a further increase during an extended period from early February to the middle of April, but the maximum number of claims in one week never exceeded 350,000. Consultation rates for influenza and influenza-like illnesses followed a similar pattern. The rate reached a peak of 420 per 100,000 at the end of February 1969, but this was well below the rate of 514 per 100,000 in one week recorded at the height of the previous year's epidemic. The number of deaths attributed to influenza, pneumonia, and bronchitis also remained comparatively low throughout this winter; the highest number in one week was 2,550 compared with over 5,300 in the peak week of the previous winter.

This pattern of rather desultory spread with low morbidity and mortality rates was quite unlike that expected after the introduction of a new influenza virus variant into a susceptible population. Moreover, it stood in strong contrast to the pattern in the United States, where the Hong Kong variant caused a sharp epidemic during the early winter with large numbers of deaths (Sharrar, 1969).

In the winter 1969-70, however, the pattern was quite different, as shown in Fig. 1. Sickness benefit claims began to increase steeply in early December, and, except for a brief interruption at the time of the Christmas holiday, climbed dramatically to a peak of nearly 750,000 in the week ending 6 January 1970, exceeding the peak reached during the 1957 Asian influenza epidemic, one of the highest previously recorded weekly numbers. Consultation rates for influenza and influenza-like illnesses followed a similar pattern, reaching a peak of 1,260 per 100,000 in the last week of December and the first week of January. Also in contrast to the previous winter, deaths attributed to influenza, bronchitis, and pneumonia rose steeply to a peak of over 10,500 in the week ending 2 January 1970 compared with 2,550 in the peak week of the previous winter. The outbreak ended as abruptly as it had begun, and by the end of January morbidity and mortality rates were about average for the time of year.

AGE DISTRIBUTION

Provisional analysis of age-specific consultation rates for cases of influenza and influenza-like illness during the peak weeks of the two epidemics (personal communication from the Royal College of General Practitioners) showed higher rates in all age groups in the second epidemic than in the first (Table I). The group with the highest age-specific consultation rate in 1968-9 was children aged under 5 years; the lowest rate was in adults aged 65 and over. In 1969-70 the

LABORATORY RESULTS

Influenza virus isolations and cases with serological evidence of recent influenza infection (fourfold or greater rise in antibody titre) are reported each week by public health and hospital virus diagnostic laboratories in Britain to the Public Health Laboratory Service. The weekly numbers of reports according to the date on which the specimen was received in the laboratory during each of the last two winters are shown in Fig. 2. The number of reports in 1968-9 (nearly 2,000) was higher than in any previous winter, partly no doubt because of the widespread interest in looking for the A2/Hong Kong/68 virus. The general pattern of the epidemic shown by these reports was similar to that shown by the morbidity figures given above; cases were being reported in large numbers from late December continuously until exceptionally late in the spring, with a few cases still arising in May. In 1969-70 the number of reports was even greater (nearly 2,300). They showed the same sharp increase as morbidity and mortality rates during December and reached a peak at about the same time before declining rapidly during January. All strains of influenza virus A isolated during the 1968-9 epidemic were shown to be antigenically similar to the A2/Hong Kong/68 strain. In the epidemic of 1969-70 a small proportion (4%) showed a slight but significant antigenic shift (Pereira and Schild, 1971).

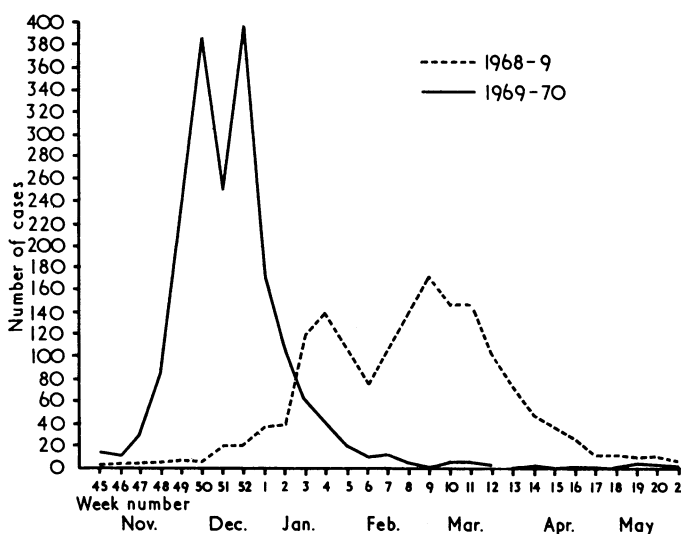The extent of infection with the Hong Kong variant during

FIG. 2—Influenza virus A isolations and serology 1968-9 and 1969-70 (by week specimen received).

TABLE II—*Haemagglutination-inhibiting Antibody to Influenza A2/Hong Kong/68 Virus in Various Population Groups*

Source of Sera		Autumn 1968				Summer 1969				Summer 1970			
		Titre			Total	Titre			Total	Titre			Total
		<10	10–40	≥80		<10	10–40	≥80		<10	10–40	≥80	
Mixed children	No.	76	66	15	157	—	—	—	—	12	51	58	121
	%	48	42	10	100	—	—	—	—	10	42	48	100
Mixed adults	No.	213	150	3	366	473	346	285	1,104	637	636	866	2,139
	%	58	41	1	100	43	31	26	100	30	30	40	100
R.A.F.	No.	268	121	8	397	214	110	73	397	105	95	197	397
	%	68	30	2	100	54	28	18	100	26	24	50	100
Lambeth	No.	244	55	3	302	156	83	63	302	119	55	128	302
	%	81	18	1	100	52	27	21	100	40	18	42	100
Both	No.	512	176	11	699	370	193	136	699	224	150	325	699
	%	73	25	2	100	53	28	19	100	32	22	46	100

the last two years has been assessed by the examination of sera from several different sources for haemagglutination inhibiting antibody to this virus by previously described methods (Pereira et al., 1964). The groups labelled "mixed children" and "mixed adults" in Table II refer to patients from whom serum samples were sent to Public Health Laboratories in many parts of England for a variety of tests such as antistreptolysin O estimations and Wassermann reactions. The results of tests on large numbers of such sera, taken just before the Hong Kong variant was introduced to Britain and after the two epidemics which followed, are shown in the top half of Table II. The proportion of children (0-15 years) without antibody in the autumn of 1968 was slightly lower than that of adults (over 15 years), but after the second epidemic the proportion of children without antibody had fallen more than in adults, suggesting a higher incidence of infection in children. Unfortunately no specimens from children were tested between the two epidemics and it is uncertain whether children were infected more often in the first epidemic or the second. The fall in the proportion of adults without antibody was similar in each of the two epidemics.

In two other studies sequential sera were collected from the same persons before and after the first epidemic and again after the second: one group comprised volunteers in Royal Air Force stations in different parts of the country and the other was a group of men living in the London Borough of Lambeth (Pereira et al., 1969b). The results in these groups, which are also shown in Table II, were essentially similar to those in the mixed group of adults. All groups show the same step-wise decrease in the proportion of people without detectable antibody to the Hong Kong virus and a corresponding increase in those with high titres after each epidemic. The combined results of the R.A.F. and Lambeth sera are shown Table II.

The proportions of persons in the R.A.F. and Lambeth groups who showed serological evidence of infection (fourfold or greater rise in antibody titre) in each of the two winters is shown in Table III. In spite of the relatively mild impact of the first epidemic on morbidity and mortality in Britain, these studies showed that about a quarter of those examined had evidence of having been infected with the new strain; in the second winter, when the impact of the epidemic was generally greater, about one-third were infected.

Comparison of the Two Epidemics

The impact of an influenza epidemic can be measured either by the clinical attack rate or by the fatality rate. Unfortunately neither rate is easily determined owing to the imprecision of a clinical diagnosis unsupported by laboratory evidence. Some illnesses and deaths attributed to influenza are often due to other causes and some that are diagnosed as acute bronchitis or pneumonia, and probably certain other diagnoses such as heart failure, may in fact be the result of influenza virus infection. One way of meeting these difficulties is to estimate excess morbidity and mortality during an epidemic by comparison with corresponding periods in a year or years when there was no evidence of widespread influenza. Estimates of this type, using two different indices, have been made for both the Hong Kong influenza epidemics: (1) excess numbers of sickness insurance benefit claims, and (2) excess numbers of deaths from all causes and of those ascribed to influenza, bronchitis, and pneumonia have been calculated by comparison with figures for the winter of 1966-7, when there was almost no clinical or laboratory evidence of influenza recorded in Britain.

In 1968-9 there was an excess of just over 1 million new sickness benefit claims in the five months, December to April, during which influenza was prevalent (Table IV). In 1969-70 the excess was just over 1½ million, only about 50% greater than in the previous winter. However, whereas in the first

TABLE IV—*Excess Sickness Insurance Benefit Claims*

Year	Total Claims (million)	Excess Claims compared with 1966-7 (million)
1966–7*	3.93	—
1968–9*	4·97	1·04
1969–70*	5·47	1·54

*December (weeks 49–52 or 50–53) and January–April (weeks 1–17).

winter the excess was spread over several months (Fig. 1), in the second winter most of the excess was crowded into about six weeks from mid-December to the end of January, resulting in a much more dramatic impact.

The numbers of deaths attributed to influenza, bronchitis, and pneumonia, and the numbers of deaths from all causes during each winter are shown in Table V. In 1968-9 there were about 1,000 excess deaths attributed to influenza, whereas in 1969-70 there were 10,000. However, the excess number of deaths, including those from bronchitis and pneumonia as well as from influenza, was over 12,000 in 1968-9 and over 32,000 in 1969-70, and excess deaths from all causes in 1968-9 numbered 31,000 and in 1969-70 nearly 47,000.

These figures suggest, firstly, that the true mortality due to influenza was much greater than appeared from the number of deaths certified as due to this cause in both winters, particularly the first; and, secondly, that the difference between mortality in the first winter and that in the second was less

TABLE III—*Proportion of Persons with Serological Evidence of Infection*

	1968-9			1969-70		
	R.A.F.	Lambeth	Total	R.A.F.	Lambeth	Total
Total persons not vaccinated during survey	805	367	1,172	397	302	699
Persons with fourfold or greater rise in antibody titre	175 (22)	112 (31)	287 (24)	160 (40)	85 (28)	245 (35)

Percentages are given in parentheses.

TABLE V—*Excess Deaths due to Influenza, Bronchitis, Pneumonia, and All Causes*

Year					No. of Deaths (thousands)†				All Causes	Excess Deaths (thousands)	All Causes
					Influenza	Bronchitis	Pneumonia	Total		Influenza, Bronchitis, and Pneumonia	
1966-7*	..	..	..		0·2	12·5	17·5	30·2	233·7	—	—
1968-9*	..	..	..		1·2	17·3	24·0	42·5	264·8	12·3	31·1
1969-70*	..	..	..		10·2	20·8	31·8	62·8	280·6	32·6	46·9

*December (weeks 49–52 or 50–53) and January–April (weeks 1–17).
†From provisional figures recorded in the Registrar General's Weekly Returns for England and Wales.

than appeared from a comparison of the number of influenza deaths alone. The number of excess deaths attributed to influenza was 10 times as great in 1969-70 as in 1968-9, whereas the excess from influenza, bronchitis, and pneumonia combined was only two and a half times as great, and the excess from all causes was, like the excess in sickness benefit claims, only about 50% greater. Two factors, however, may affect these calculations. Mortality rates in 1966-7 may have been exceptionally low for reasons other than the absence of influenza, and those in the winters 1968-9 and 1969-70 may have been exceptionally high owing to causes other than the presence of influenza. Either of these circumstances would have the effect of exaggerating the apparent excess mortality in the two winters studied, and of diminishing the difference between them. But it seems unlikely that either condition was operating to a sufficient degree to significantly modify the general conclusions for two reasons: (1) that mortality in 1966-7 was not a great deal less than in other recent winters, when there was little or no influenza, and (2) that most of the excess mortality from both respiratory and other causes in 1968-9 and 1969-70 occurred during the epidemic periods and followed a similar pattern to the other indices of influenza prevalence (Figs. 1 and 3), suggesting that the two were directly related, though the possibility remains that another factor causing increased mortality was operating simultaneously with influenza.

Discussion

The behaviour of the Hong Kong/68 variant of the A2 influenza virus was quite different from that expected of a new antigenic variant. During the first winter after its introduction

FIG. 3—Excess mortality in winters of 1968-9 and 1969-70 compared with winter of 1966-7.

to Britain, in 1968-9, the virus failed to spread as rapidly as expected, and illness and mortality rates remained comparatively low. The epidemic was exceptionally prolonged, however, and the antibody studies reported here show that about one-quarter of two groups of adults investigated were infected during the winter and that by the summer of 1969 about one-half of them had detectable antibody. In contrast, during the second winter, in 1969-70, there was an explosive epidemic of a kind expected the first year, with exceptionally high morbidity and mortality rates during a six-week period in December and January. Antibody studies in the summer of 1970 showed that about one-third of the same groups of persons as were studied before had been infected in the second epidemic and that now about two-thirds of them had antibody.

A comparison of morbidity and mortality in the two epidemics with that in the winter 1966-7, when there was no clinical or laboratory evidence of influenza, brought out two points. Firstly, the number of deaths ascribed to influenza in both winters was much less than the estimated excess number of deaths due to influenza, bronchitis, and pneumonia combined, which, in turn, was less than the excess due to all causes. Much of the excess was, presumably, due to the influenza epidemics and, if so, the number of deaths ascribed to influenza greatly underestimated mortality from this cause, particularly in the first winter. Secondly, while the differences between the two epidemics were dramatic and real, the contrast between them in their total effect was probably less than had been supposed. Excess morbidity, shown by the excess numbers of sickness insurance benefit claims compared with 1966-7, and excess mortality due to all causes, were only about 50% greater in 1969-70 than in 1968-9. Reasons have been given for regarding these estimates of excess morbidity and mortality as wholly attributable to influenza with caution, but the general conclusions are probably still valid.

The factors responsible for the differences between the epidemics are not apparent. The virus in both years was the same. Vaccination was probably used on too modest a scale to have modified either epidemic to any important extent. The proportion of the population which had antibody was much greater after the first year's outbreak than it had been before, which might have been expected to reduce the likelihood of a second epidemic or to modify its intensity. Other environmental features that may account for the difference, such as weather, air pollution, population movement, and extra crowding for seasonal reasons, have not been evaluated. It may be that a combination of circumstances was responsible. It is clear that firm predictions of epidemics cannot be made without further study of the interaction between the many variables that determine their occurrence.

The results of antibody studies given here show that even after two epidemics about one-third of adults may be without antibody and susceptible to infection. Whether this proportion is high enough to allow epidemic spread, given other suitable circumstances, is not known.

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Analgesic Nephropathy: Clinical Syndrome and Prognosis

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Summary

Over a five-year period 86 patients presented to a renal unit with a history of prolonged analgesic abuse and no other obvious cause of renal damage. Anaemia and peptic ulceration were common, and neurological states suggestive of chronic analgesic intoxication occurred in 22 patients. Thirty-two patients died during follow-up, but the prognosis was much better in patients who ceased abuse of compound analgesics, and improvement could occur even in advanced renal failure. While 84 patients had taken mixtures containing both aspirin and phenacetin, papillary necrosis was also found in two patients who had abused only aspirin, and when phenacetin was withdrawn from several leading compound analgesics, renal function continued to deteriorate in patients ingesting those preparations.

Introduction

Though the association between analgesic abuse and renal impairment has often been recorded (Spuhler and Zollinger, 1953; Nordenfelt and Ringertz, 1961; Rapoport *et al.*, 1962; Harvald, 1963; Dawborn *et al.*, 1966; Prescott, 1966; Gault *et al.*, 1968; McMillan *et al.*, 1968; Fellner and Tuttle, 1969), there have been few reports on the long-term prognosis of such patients. The present report concerns our clinical experience of the syndrome and the outcome of prolonged follow-up.

Patients and Methods

The study included all patients presenting to a renal unit in the period 1965–9 with a history of ingestion of more than 1 kg of phenacetin or aspirin and no other obvious cause of renal damage. Estimation was made of the patients' blood urea and electrolytes, creatinine clearance, urine cell and bacterial counts, plus full haematological examination and intravenous pyelography. Where indicated, isotope renogram, barium meal, and electroencephalography were performed.

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All patients were initially acquainted with the dangers of continued analgesic abuse and advised either to abstain from analgesics completely or to substitute small doses of paracetamol for their previous analgesic. Thereafter they were repeatedly questioned regarding their analgesic habits at regular outpatient appointments, and all those still attending were admitted to the unit early in 1970 for reassessment.

Findings

Clinical Features.—A total of 86 patients were seen over the period of the study. Their ages ranged from 27 to 72, with a mean of 53 years. Females predominated over males in the ratio 5·1:1. The analgesics implicated are shown in Table I. In only two cases did the analgesic not contain both phenacetin and aspirin. The daily intake varied from 2 to

TABLE I—*Analgesics Taken by Patients*

Analgesic	No. of Patients	Content of Analgesic (mg)		
		Aspirin	Phenacetin	Codeine
Askit Powders*.. ..	59	550	400	—
Tab. codeine co. ..	12	250	250	8
Beecham's powders* ..	6	300	210	—
Aspirin	2	300	—	—
Others	7	+	+	—

*Phenacetin has been withdrawn from these preparations.

more than 15 preparations daily and the duration of abuse from 3 to 45 years (average of five daily for 16 years). The approximate total dose ingested ranged from 2 kg of phenacetin plus 2 kg of aspirin to 51 kg of phenacetin plus 69 kg of aspirin (average 13 kg of phenacetin plus 17 kg of aspirin). Only six patients took analgesics for pain of an obviously organic nature. Fifty-six took analgesics for headache of a psychogenic type, four for other psychogenic pain, and 20 for what they believed were their psychopharmacological effects.

Gastrointestinal Features.—Dyspeptic symptoms were very common; alimentary bleeding had occurred in 16 patients, radiological evidence of peptic ulceration was obtained in 24, and 14 had undergone gastric surgery.

Haematological Features.—Seventy-four patients had haemoglobin levels of less than 80% (11·8 g/100 ml). In 40 this appeared to be due to diminished renal function, while frank haemolysis was found in 14 patients with seven having sulphaemoglobinaemia or methaemoglobinaemia. Iron deficiency and gastrointestinal bleeding accounted for anaemia in a further 16 patients, while one had a sideroblastic anaemia and three a macrocytic blood picture.