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Influenza and its relationship to circulatory disorders

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SUMMARY

Three sources of data (general practice episode data from the Weekly Returns Service of the Royal College of General Practitioners, national hospital admission data for England and national mortality data by date of death) were examined separately in each winter (1994/1995 to 1999/2000) to investigate the impact of influenza on circulatory disease. Weekly data on incidence (clinical new episodes) hospital emergency admissions and deaths certified to circulatory disorders and to respiratory diseases (chapters VII and VIII of ICD9) during influenza epidemic periods (defined from combined clinical/virological surveillance) were examined in age groups 45–64, 65–74 and $\geqslant$75 years. Data collected in the four winters in which there were substantial influenza A epidemics were consolidated for the period 6 weeks before to 6 weeks after each peak of the epidemic, and associations between the variables at different time lags examined by calculating cross-correlation coefficients. We also examined deaths due to ischaemic heart disease (IHD) as a proportion of all circulatory deaths and deaths due to influenza/pneumonia as a proportion of all respiratory deaths. There were no increases of GP episodes nor of emergency admissions for circulatory disorders in any of the three age groups during epidemic periods. Increased circulatory deaths occurred in all age groups and particularly in the oldest group. The large cross-correlation coefficients of deaths (circulatory and respiratory) with GP respiratory episodes at weekly lags of 0, -1 and 1 were evidence that the deaths and episode distributions were contemporaneous. The ratios of excess circulatory deaths relative to excess respiratory deaths during epidemic periods were 0·74 (age 45–64), 0·72 (65–74) and 0·57 ($\geqslant$75 years). Increased circulatory deaths contemporary with new incident cases of respiratory episodes but with no concomitant increase in admissions suggests rapid death during the acute phase of illness. Influenza contingency planning needs to take account of these deaths in determining policy for prophylaxis and in providing facilities for cardio-respiratory resuscitation.

INTRODUCTION

Cardiovascular complications of influenza were widely reported during the early part of the twentieth century. Nicholson [1] reviewed the evidence and amassed 12 references between 1891 and 1927. Electrocardiographic (ECG) abnormalities in patients hospitalized with influenza have been well documented [2–4]. Verel et al. described ECG abnormalities in 43% of cases in the community and pointed out that most of them had no cardiac symptoms [5]. Myocarditis and pericarditis have been described as complications of influenza confirmed by seroconversion. In an examination of excess mortality attributable to influenza in England and Wales between

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winters 1968/1969, and 1977/1980, 67% of 120000 excess deaths were attributed to respiratory causes and 31% to circulatory causes [6]. It is widely recognized that excess mortality during influenza epidemics is seen in many diagnoses and hence all cause mortality data are generally used to measure the impact of influenza.

In 1986, Barker analysed American national hospital discharge data to calculate excess rates of hospital admission attributable to influenza [7]. He concluded that excess cardiac admissions were much less than those for respiratory disorders and mainly observed in the elderly. Nichol et al. examined the effects of influenza vaccination on hospitalization for cardiac disease in persons $\geqslant 65$ years during the 1998/1999 and 1999/2000 influenza seasons [8]. They concluded the vaccination reduced the likelihood of admission for cardiac disease by 19% compared to 30% for pneumonia and influenza. Analysis of respiratory admissions during influenza epidemics in England between 1989 and 2000 highlighted the importance of increasing age [9]. Thompson and colleagues studied excess mortality in the United States between 1976/1977 and 1998/1999 attributable to influenza and respiratory syncytial virus (RSV) infection concluding that influenza was responsible for three times as many deaths as RSV [10]. In their analysis they distinguished between deaths attributable to underlying pneumonia and influenza (average for influenza-related deaths 8097), to total cardio-respiratory disease (36155) and to all causes (51203). The difference between deaths due to pneumonia and influenza and total cardio-respiratory deaths is particularly notable. Neuzil and colleagues reported an excess of influenza-related cardio-respiratory admissions and deaths in women <65 years old and drew attention to the increased risk for persons with comorbidity [11].

The impact of influenza on circulatory disorders is here examined in general practice (GP) morbidity episodes, hospital admissions and deaths referable to circulatory and respiratory disease both during influenza active and non-active periods. We were particularly interested to know if there was any substantial element of excess morbidity attributable to influenza which was not recognized as respiratory disease and which may influence policy on vaccination and treatment.

METHODS

The study is based on a comparison of weekly data on clinical incidence of new episodes of illness presenting to general practitioners in the Weekly Returns Service (WRS) of the Royal College of General Practitioners [12], national hospital admissions and deaths, attributed to circulatory or respiratory disease during successive winters 1994/1995 to 1999/2000. It is focused particularly on the impact of influenza and the presentation is confined to a consideration of the relationship in the age groups 45–64, 65–74 and $\geqslant 75$ years. Hospital admissions and deaths from respiratory and circulatory disease are comparatively infrequent in younger persons.

Clinical incidence

Weekly data on new episodes of illness (episode data) aggregated at chapter level have been available in the WRS since the service became fully automated. We examined data for diseases of the circulatory system (chapter VII, ICD9; chapter G, ICD10) and diseases of the respiratory system (chapter VIII, ICD9; chapter J, ICD10). The recording protocol distinguishes new episodes of illness from ongoing or follow-up consultations.

Hospital admissions

Weekly data on emergency admissions (England) for circulatory and respiratory disorders were made available to us by the West Midlands Safe Haven.

Deaths

Mortality data based on the date of death, provided by the Office for National Statistics (ONS), were aggregated by week coterminous with the episode and the hospital admission data using the underlying cause of death as determined by the national certification protocol [13]. For some purposes, we examined deaths attributed to IHD (ICD 410–414) as the underlying cause separately from other circulatory deaths (ICD 390–409, 415–459) and deaths from influenza and pneumonia (ICD 480–487) separately from other respiratory causes (ICD 460–479, 488–519).

Influenza active periods (epidemics) were identified from information on clinical illness reported in the WRS complemented by virological information as has been described previously [14]. Weekly data on GP episodes, hospital admissions and certified deaths were examined separately in each winter (1994/1995 to 1999/2000). Average rates per 100000 were

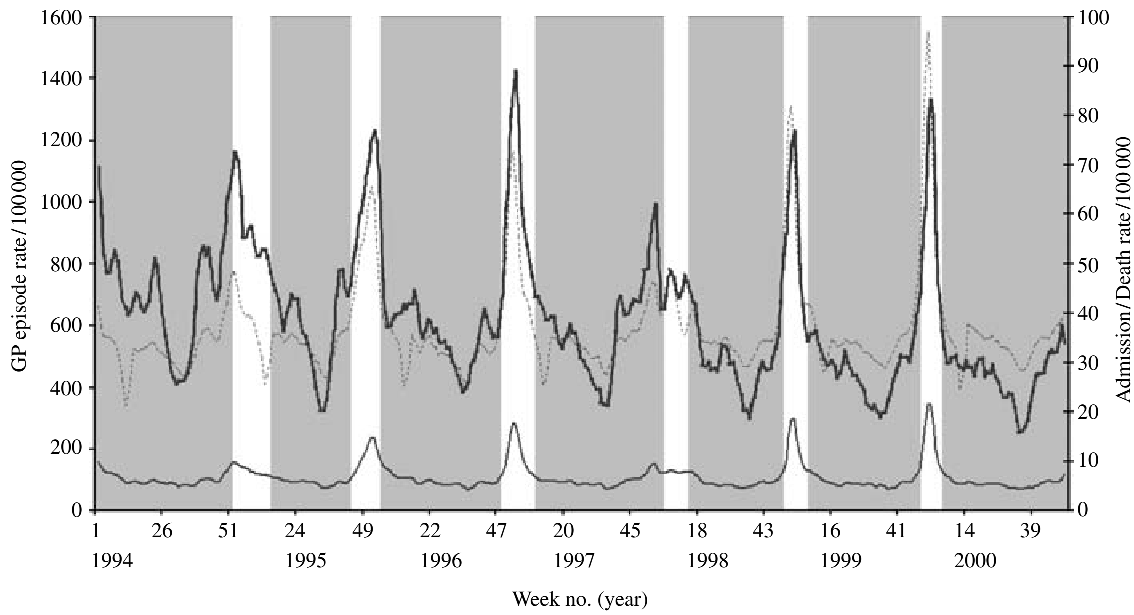

Fig. 1. General practice (GP) episodes, admissions, deaths for respiratory diseases (65–74 years). □, Flu epidemic; ▬, respiratory GP; ········, respiratory admissions; ——, respiratory deaths.

calculated separately for epidemic weeks, and for the remaining winter weeks. Winter was defined as from week 40 in one year to week 10 in the next. The analysis ended at week 10 because of the unreliability of hospital admission data in the study years over weeks 11–13 at the end of the financial year [15]. In 1998/1999 by convention there was a week 53: for simplicity of analysis and presentation this was classified as week 1, 1999 and weeks 1–9, 1999 were classified as weeks 2–10: data for weeks 25/26, 1999 were averaged.

The difference between the respective rates in each epidemic and non-epidemic winter period weighted by the number of epidemic flu weeks; and finally this product was applied to the population of England 2000 to estimate the number of persons in each age group (45–64, 65–74 and ⩾75 years) presenting to general practice (GP), admitted to hospital or dying.

Data for the winters 1995/1996, 1996/1997, 1998/1999 and 1999/2000, years in which influenza A viruses predominated, were consolidated to study possible lags between the episode, admission and death data. Three of these epidemics peaked around Christmas/New Year when (particularly for the episode data but also to a lesser extent for admissions), patterns of health-care utilization are seriously disrupted by holiday working arrangements. Accordingly episode and admission data (but not deaths) for weeks 51, 52 and 1 were examined as the 3-week averages centred on these respective weeks. For each winter, each week was denoted as -6 to $+6$ with zero as the week of peak GP episode incidence. Summing the data over the four winters in which influenza A predominated, cross-correlation coefficients between respiratory episodes and the remaining variables were calculated by age group.

To assist interpretation of the data we made use of virus isolate reports made available to us by the Health Protection Agency (formerly PHLS) and of an analysis of death certification for the year 2001 provided by the ONS (C. Griffith, personal communication).

RESULTS

In Figure 1, graphical data are presented describing GP morbidity episodes, hospital admissions and deaths allocated to respiratory disease in the age group 65–74 years over the entire period from January 1994 to December 2000. Influenza epidemic periods are indicated by a white panel on the graph for each winter. The presentation is made as 3-week moving averages in order to smooth random variation and the disruption associated with health-care services over the Christmas and New Year period. Figure 1 shows surges of respiratory episodes, admissions and deaths around the influenza active periods. Troughs in admission data evident over

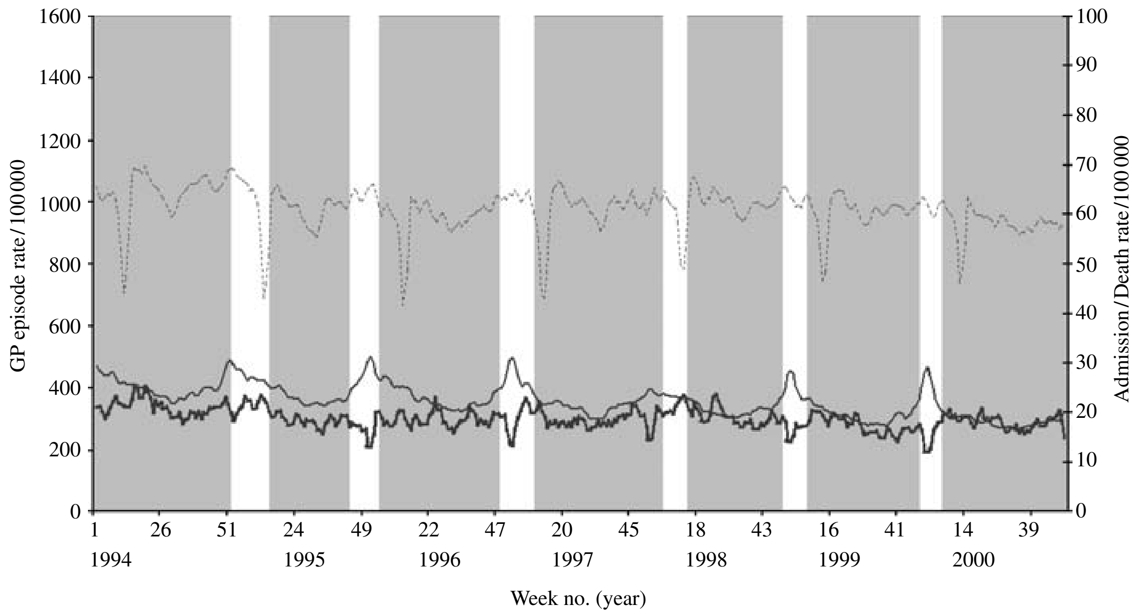

Fig. 2. General practice (GP) episodes, admissions, deaths for circulatory diseases (65–74 years). □, Flu epidemic; ——, circulatory GP; ········, circulatory admissions; ——, circulatory deaths.

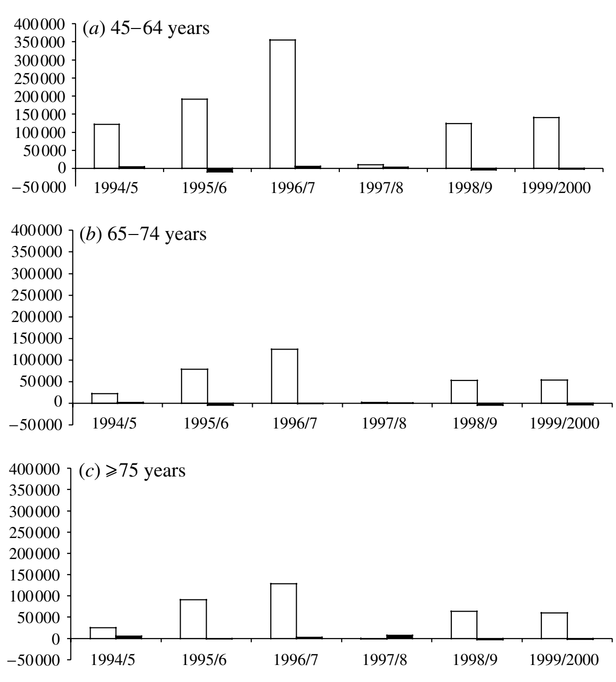

Fig. 3. Estimates of excess respiratory and circulatory disease episodes during influenza epidemic periods. (*a*) 45–64 years; (*b*) 65–74 years; (*c*) ⩾75 years. □, Respiratory general practice; ■, circulatory general practice.

weeks 11–13 should be disregarded (see Methods section above).

Similar data are provided for circulatory disorders in Figure 2, which shows no recognizable surge in episodes or admissions but a modest surge in deaths. The magnitude of the respective surges varied: in 1994/1995 and in 1997/1998 the surges were evident before influenza was well established in the community. Graphical examination of the data for the age groups 45-64 years and ⩾75 years disclosed similar patterns, although the magnitudes of the surges, especially those relating to admissions and deaths, were weaker in the younger and stronger in the older of the age groups.

The impact of influenza as seen in primary care is shown in the estimates of excess persons in epidemic periods over those in non-epidemic weeks for episodes of respiratory and of circulatory disorders in the three age groups (Fig. 3*a*, 45–64 years; Fig. 3*b*, 65–74 years; Fig. 3*c*, ⩾75 years). Similar presentations are made for admissions (Fig. 4*a–c*) and deaths (Fig. 5*a–c*). Each graph should be studied separately because of the differing scales on the *y*-axes and the differing widths of the age bands. Nevertheless some common features are noteworthy. The relativity of the excesses over the six winters in respiratory disorders was broadly consistent in each data series (three age groups, three parameters). For circulatory disorders there was no impact on GP episodes and minimal and inconsistent impact on admissions. There were wide variations between winters; 1996/1997 was the winter of maximum impact, 1997/1998 was the winter of least impact and a low impact was evident for the winter of 1994/1995.

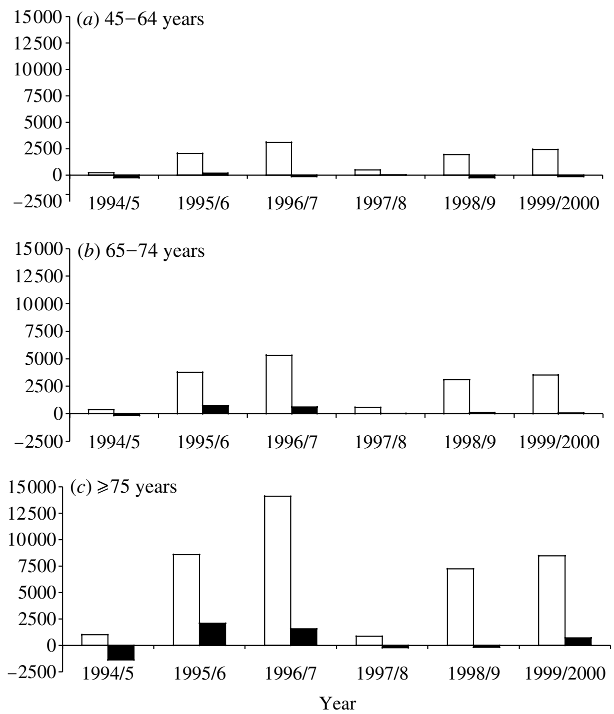

Fig. 4. Estimates of excess hospital admissions during influenza epidemic periods. (*a*) 45–64 years; (*b*) 65–74 years; (*c*) ⩾75 years. □, Respiratory admissions; ■, circulatory admissions.

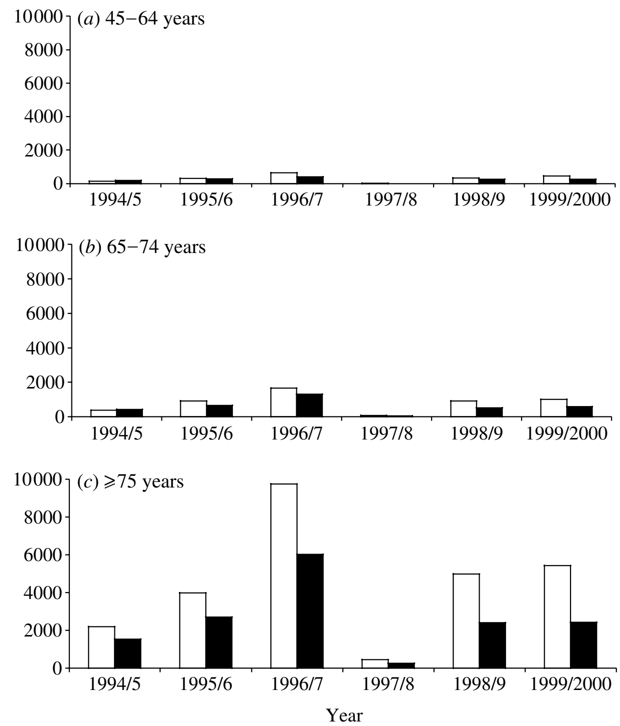

Fig. 5. Estimates of excess deaths during influenza epidemic periods. (*a*) 45–64 years; (*b*) 65–74 years; (*c*) ⩾75 years. □, Respiratory deaths; ■, circulatory deaths.

The winter average estimates of excess episodes, admissions and deaths attributable to influenza for both respiratory and circulatory diseases, and the census 2000 population to which they relate are summarized in Table 1. The overall impact on hospital admissions and deaths was greatest in persons over 75 years. In this age group, the estimated number of respiratory admissions exceeded deaths by only 50%, excess circulatory admissions were less than 20% of excess deaths. The average annual excess respiratory and circulatory mortality in the six winters examined totalled 8982 deaths, 5600 (62%) of which were respiratory deaths. Using the same method of investigation, we estimated there were a further 1456 deaths attributable to causes certified to other chapters of the ICD (data not presented) totalling 10438. The ratios of excess circulatory relative to excess respiratory deaths during epidemic periods were 0·74 (age 45–64 years), 0·72 (65–74 years), 0·57 (⩾75 years) and in total over all age groups 0·60.

Deaths certified due to IHD accounted for 54% of all circulatory deaths between January 1994 and December 2000; deaths certified due to influenza and pneumonia accounted for 61% of all respiratory deaths. The proportion of excess deaths attributable to IHD during influenza active periods was 53% of all circulatory deaths and, excess deaths due to influenza and pneumonia was 65% of all respiratory deaths.

The cross-correlation coefficients in the three age groups between (*a*) weekly circulatory deaths and (*b*) weekly respiratory deaths, with respiratory episodes are given in Table 2 for weekly lags of −2 to +2. This range includes all relevant values, although it is inappropriate to test the coefficients for statistical significance because each series contains a degree of autocorrelation.

Respiratory deaths were strongly associated with respiratory episodes at week 0 in all age groups, and to a somewhat lesser degree for weekly lags of ±1. The picture disclosed for circulatory deaths in the age group ⩾75 years, where most deaths occur showed these two distributions were also contemporaneous; for the other age groups the coefficients at weeks 0 and +1 were relatively large and similar. Table 2 indicates that all the noteworthy coefficients were encompassed within the range of weekly lags −1 to +1. There was no association between respiratory episodes and circulatory episodes; nor between respiratory episodes and circulatory admissions (data not presented).

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Table 1. *Estimated average excess respiratory and circulatory disease episodes, admissions and deaths associated with influenza epidemic periods between 1994 and 2000*

Age group (years)	Reference population (1000)	Episodes		Admissions		Deaths	
		Respiratory	Circulatory	Respiratory	Circulatory	Respiratory	Circulatory
45–64	11 679	157 130	(−489)	1702	(−109)	312	232
65–74	4088	55 585	(−1681)	2771	222	825	591
⩾75	3712	61 091	1476	6696	418	4463	2559
45+	19 479	273 806	(−694)	11 169	531	5600	3382

Table 2. *Cross-correlation coefficients at weekly lags of −2 to +2 for circulatory deaths and respiratory deaths with GP respiratory episodes, by age group*

Wk no.	Circulatory deaths			Respiratory deaths		
	45–64	65–74	⩾75 yr	45–64	65–74	⩾75 yr
−2	−0·22	0·10	0·34	0·15	0·33	0·54
−1	0·41	0·53	0·75	0·61	0·71	0·86
0	0·77	0·87	0·98	0·95	0·95	0·93
+1	0·82	0·86	0·77	0·79	0·75	0·59
+2	0·52	0·56	0·34	0·34	0·30	0·07

DISCUSSION

The main findings of this paper can be summarized in two statements. Influenza is associated with increased mortality from circulatory disease (~60% of respiratory mortality) but is not associated with an increase in new episodes of circulatory disease presenting to general practitioners nor with any consistent increase in hospital admissions attributable to circulatory disease as the primary cause. Deaths from both respiratory and circulatory disease occurred at a similar time to episodes of respiratory disease presenting to general practitioners.

We examined each dataset (episodes, admissions and deaths) separately in each winter. The estimates of excess deaths were slightly higher than those previously made using similar data but deriving the expected from a baseline applicable to the winters 1987/1988 to 1996/1997 combined [16], because in this analysis we did not take into account the excess winter mortality commonly seen around the new year period whether or not influenza is active. Our primary purpose was to investigate the relative importance of circulatory disease rather than estimate the excess directly attributable to influenza. The midwinter causes of increased mortality include RSV infection which was consistently highest in December in every year of this study as judged by virus isolate data notified to the HPA [17], although it must be recognized that more than 90% of these are reported in children <2 years of age. It is worth noting that the 'misfit' between respiratory episodes, admissions and deaths and the influenza active periods reported in the winters of 1994/95 and 1997/98 fitted well with the circulation of RSV demonstrating that it causes increased mortality as well as morbidity as has been reported previously [10, 18, 19]. Furthermore, in some winters (1995/1996 particularly and to a lesser extent in 1999/2000) influenza and RSV were circulating over the same period with little overlap. There is some evidence associating mortality (especially cardiac) with low temperature [20, 21]. Mortality generally peaks around the New Year, although this is not usually the coldest part of the winter. There is no consistent relationship between influenza and ambient temperature, nor between acute respiratory illness and temperature [22]. A recent publication from the United States suggests that 'the cause of the winter increase in US mortality is singular and probably influenza' and that 'weather and other factors may determine the timing and modulate the magnitude of the winter-season increase in mortality' [23].

Data from all three sources (GP morbidity episodes, hospital admissions and death certificates) are all subject to misclassification of diagnosis. Only a minority of deaths (33% of circulatory and 17% of respiratory – ONS, personal communication) are based on autopsy reports and even these have limitations. Based on classification by underlying cause, 22% of deaths attributable to circulatory disease reported an additional respiratory cause and 26% of those attributed to respiratory disease reported an additional circulatory cause (ONS data, personal communication). There is considerable overlap between these groups of conditions in mortality data, yet in the respiratory episode and hospital admission data, excess morbidity during influenza active periods is almost completely confined to respiratory disease. This either implies a failure to recognize the associated circulatory disorders or a failure to record them. We favour the former of these explanations for three reasons. The analysis undertaken was of the excess in one period compared with another and it is very unlikely that diagnostic misclassification is more or less likely to have occurred during influenza periods than the rest of the winter. During influenza epidemic periods there were similar relative increases in deaths from IHD as from other circulatory disorders and in deaths from influenza and pneumonia as from other respiratory causes. There were no delays greater than 1 week, between peak levels of GP episodes and both respiratory and circulatory deaths.

The importance of timing is critical to the interpretation of this material. Perrotta and colleagues [24] studied the relationship between hospitalization of acute respiratory disease and hospital admission in children (0–14 years) and in adults (⩾15 years). They concluded that the peak of adult respiratory disease hospitalization followed the peak of influenza virus isolations by 1 week. Glezen et al. observed that the peak of influenza virus activity coincided with the peak of consultations for acute respiratory illness and the peak number of deaths certified due to pneumonia and influenza followed 2 weeks later, although this analysis was based on a consideration of data for all ages combined [25]. In this report we have compared the timing of events in each of the three age groups separately and we find no lag between the peak incidence of respiratory illness episodes in the community (which is also the peak of influenza-like illness) and the peak of respiratory or circulatory deaths. Indeed, the respiratory admission peak sometimes preceded the episode peak. It is particularly relevant to note that three of the four influenza A epidemics occurred around Christmas/New Year when access to primary care is restricted and patients commonly defer consultation. Admissions for circulatory disease were not associated with episodes of respiratory illness.

We conclude from this analysis that influenza does not cause increased episodes of circulatory disorder reported to general practitioners or increased admissions but it does cause increased mortality approximately equivalent to 60% of respiratory excess mortality. The coincident timing suggests that death is occurring in the acute phase of the illness and is not due to a process of increasing complications such as congestive cardiac failure or secondary bacterial pneumonia. Nicholson noted that among patients admitted to hospital in Leicester with influenza during the 1989/1990 epidemic, one third died within 2 days of admission [1]. Barker & Mullooly examined hospital admissions data and noted increases for pneumonia and influenza during influenza epidemics but no increased admissions for circulatory disease [26]. Our conclusions are further supported by the relative numbers of excess admissions and excess deaths. In the oldest age group (⩾75 years) where deaths are maximal, the estimate of excess admissions exceeded deaths by only 50%. Many of the deaths must, therefore, be occurring in the community suggesting rapid progress of the illness or sudden death. This would be consistent with the many reports of ECG abnormalities associated with influenza. Sudden death from dysrhythmia is rarely diagnosed and is not evident on autopsy findings.

We have previously reported on excess GP respiratory episodes [9] and hospital admissions [16] attributable to influenza but have not hitherto considered those attributable to circulatory disease. From a management perspective, our results suggest that ECG investigation should be used more frequently especially in older people where there is increased likelihood of cardiac impairment. The potential of therapeutic intervention to suppress dysrhythmic tendencies might be considered as an appropriate subject for a clinical trial. More importantly, the findings emphasize the importance of primary preventive measures. Older people do not contact the doctor early in the illness [27] when they are most vulnerable. The immune response to vaccination deteriorates with advancing age and, thus, these findings also support the use of prophylaxis in the highest risk groups when influenza is known to be circulating. In the 45–64 years age group, currently not included in the target group for routine influenza vaccination if healthy, excess mortality attributable to circulatory disease was scarcely recognizable, and there were no increases in GP episodes or hospital admissions for circulatory disease during epidemic periods.

The findings are particularly significant in the context of pandemic planning, which, as in 1918, may have maximum impact on age groups other than the elderly. In the event of a pandemic, sudden deaths from circulatory disease are likely to occur. Though we cannot speculate on the extent to which these can be minimized, facilities for cardiac resuscitation will be needed as much as intensive-care facilities for severe respiratory problems. Logistically, access to such facilities will present difficulty but to be forewarned is to be forearmed.

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