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Acute upper respiratory tract viral illness and influenza immunization in homes for the elderly

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SUMMARY

Occupants of 482 long-stay and 33 short-stay beds in 11 Leicester City Council homes for the elderly were studied during a 30-week period from September 1988 to March 1989 to determine the incidence, aetiology, morbidity, and mortality of acute upper respiratory tract viral infections and the use of influenza vaccine.

Influenza immunization rates by home ranged from 15·4 to 90% (mean 45%). There were no differences in the distribution of medical conditions by home. The highest immunization rates were seen in people with chest disease (77%), heart disease (60%), diabetes (56%), and those with three medical conditions (75%). There was an average of 0·7 upper respiratory episodes per bed per annum with a mortality of 3·4% (6/179). Half of all episodes were seen by a general medical practitioner and 81 of 90 (90%) referrals were prescribed antibiotics costing approximately £7.50 per patient. Lower respiratory tract complications developed during 45 (25%) of 179 episodes including 3 of 12 coronavirus infections, 3 of 9 respiratory syncytial virus infections, 2 of 4 adenovirus infections, 1 of 11 rhinovirus infections, but none of 5 influenza infections. Respiratory infections were caused mostly by pathogens other than influenza virus during the influenza period documented nationally. This highlights the role of coronaviruses, respiratory syncytial virus, and unidentified agents in the elderly, and questions the assumptions made in American estimates on the impact of influenza and the value of influenza vaccines.

INTRODUCTION

Excesses of serious morbidity and death have consistently been demonstrated in elderly patients with certain chronic medical conditions during outbreaks of influenza [1–4]. On the basis of these observations, the Department of Health, the Welsh Office, and the Scottish Home and Health Department suggest that annual influenza immunization be considered for elderly persons living in residential homes and long-stay hospitals, and for patients, especially the elderly, suffering with chronic pulmonary disease, chronic heart disease, chronic renal disease, diabetes and other less common endocrine disorders, and conditions involving immunosuppressive therapy [5]. Only 10–20% of elderly and high-risk patients are, however, immunized each year [6, 7]. Concern over vaccine safety and

scepticism about vaccine efficacy are the most common reasons for poor vaccine distribution in both the United Kingdom and United States [6, 8].

Having no pathognomonic features, influenza is one of many respiratory infections that circulates during the autumn, winter and spring months, causing illness ranging from a mild asymptomatic infection to life-threatening influenza virus pneumonia and secondary staphylococcal pneumonia. Accordingly estimates of the socio-economic impact of influenza and the benefits of vaccination during interpandemic years may be grossly inaccurate without laboratory confirmation of the diagnosis. We therefore examined the use of influenza vaccine in 11 residential homes for the elderly in Leicester during the 1988/9 influenza season and studied the incidence, aetiology, morbidity and mortality of acute upper respiratory tract viral infections in ambulatory patients.

SUBJECTS AND METHODS

Subjects

The study was conducted in Leicester, a city with a population of 280000 in the English Midlands that is predominantly involved in the hosiery trade. Subjects enrolled in the study were residents of 11 Leicester City Council homes for the elderly who had symptoms of upper respiratory tract viral infection during the 30-week period including the week ending 2 September 1988 (week 35) and the week ending 24 March 1989 (week 12) inclusive. The homes had 482 'long-stay' beds, with an occupancy of approximately 95% by patients who may expect to remain there for the rest of their lives, and 33 'short-stay' beds occupied by temporary residents.

Criteria for inclusion were symptoms lasting for at least 2 days and including two or more of nasal and throat symptoms, cough, lacrimation, or systemic features. Patients with increasing dyspnoea, wheeze, severe cough, or productive cough for at least 2 days were deemed to have lower respiratory tract involvement. Details of the patients' medical, drug, and immunization histories for 1985–8 were obtained from the medical practitioners and home wardens. Symptoms of acute respiratory infection were recorded according to the date of onset, duration, severity, use of medical services, antibiotic usage, and hospitalization for any reason. Risk factors other than residence in a nursing home for the elderly were categorized as follows: chronic heart disease, notably coronary and valvular heart disease and congestive heart failure requiring medication; chronic lung disease, including asthma and chronic restrictive and obstructive lung disease; renal failure, diabetes mellitus; other endocrine disorders requiring medication; malignancy involving the viscera; and Parkinson's and other chronic neurological disease.

Virus isolation

The 11 homes were telephoned twice-weekly to establish the presence of upper respiratory tract infections. Nasal swabs were placed high in the anterior nares of symptomatic residents and throat swabs were passed firmly over the pharynx and tonsils. Nasal and throat swabs from each patient were placed together in 2·5 ml of virus transport medium containing nutrient broth, 10% fetal calf serum,

penicillin, streptomycin and amphotericin B. Occasional specimens were stored at −70 °C but most were inoculated in volumes of 0·3 ml onto monolayers of Ohio HeLa cells, MRC-5 human lung fibroblasts, Madin–Darby canine kidney (MDCK) cells, and C16 cells. Those inoculated onto Ohio HeLa cells were routinely passaged once and those producing equivocal results were passaged up to three times. Rhinovirus infection was diagnosed after observation of characteristic cytopathic effect and confirmed by acid stability tests on the virus isolates. Influenza and parainfluenza viruses were identified by haemadsorbtion-inhibition on MDCK cells.

Serological studies

A 10 ml blood sample was collected during the respiratory episode and again 3–4 weeks later. Acute and convalescent paired sera were tested for complement fixing antibodies to adenovirus, influenza A and B, respiratory syncytial virus (RSV), and *Mycoplasma pneumoniae*. A non-commercially available enzyme-linked immunosorbent assay was used to detect a rise in antibody titre to coronavirus 229E and OC43 [9].

RESULTS

Demography and influenza immunization

The age, sex, frequency of specific risk factors, number of risk factors per subject, and distribution of subjects by home for vaccinees and non-vaccinees is shown in Table 1. There were 3·6 time as many women as men and there were no sex or age differences between vaccinees and non-vaccinated residents. There was a significant difference between the immunization rates by home ($\chi^2 = 34{\cdot}6$, $P < 0{\cdot}001$), ranging from 8·3 to 90% (mean 45%), but there were no significant differences in the distribution of medical conditions by home ($\chi^2 = 14{\cdot}3$, 10 D.F.). Immunization rates were significantly influenced by the number ($\chi^2 = 11{\cdot}7$, $P < 0{\cdot}02$) and type ($\chi^2 = 19{\cdot}9$, $P < 0{\cdot}01$) of risk factors – thus the highest rates were seen in people with chest disease (77%), heart disease (60%) and diabetes (56%), and the likelihood of immunization increased with an increase in number of medical conditions to a maximum of 75% for three. Few residents refused the offer of influenza vaccine and the different immunization rates in the homes reflected the policies of individual medical practitioners.

Symptomatic respiratory viral infections

A total of 170 residents developed 179 symptomatic upper respiratory tract infections during 33506 patient-days of observation; the homes reported 28 additional events that did not satisfy the inclusion criteria. Overall there were 1·88 acute upper respiratory tract episodes per 1000 bed-days (range 0·4–3·45, S.D. 1·08), equivalent to 0·7 episodes per bed per annum.

Nasopharyngeal swabs and acute and convalescent sera were obtained for 119 episodes, and swabs, but no sera, were available for 60. The mean interval between onset of symptoms and collection of acute-phase specimens was 3 days (range 0–15) and 87·5% of samples were collected within 5 days. A viral pathogen was established for 29% of cases providing swabs and serology (34 of 119) and for 13% (8 of 60) of those providing swabs only. An additional 22 pairs of acute and

Table 1. *Characteristics of the study population*

	Number (and %) of the study population			
	Total study population	Influenza vaccinees	Non-vaccinees	Significance
Age				
Mean	85·3	84·7	85·8	n.s.
Range	67–97	70–96	67–97	—
Sex				
Female	133*	55*	72*	n.s.
Male	37*	18*	18*	
Medical conditions†				
None	—	21 (31.8)	45	
Chronic heart	—	27 (60)	18	
Chronic lung	—	17 (77)	5	
Diabetes	—	10 (56)	8	$P < 0·01$
Endocrine	—	3 (33)	6	
Malignancy	—	3 (30)	7	
Other (mostly Parkinsons)	—	14 (42)	19	
Number of medical conditions per person				
0	66	21 (32)	45	
1	63	31 (49)	32	
2	27	17 (63)	10	$P < 0·02$
3	4	3 (75)	1	
4	2	0	2	
By home				
1		2 (29)	5	
2		2 (15)	11	
3		7 (33)	14	
4		3 (25)	9	
5		9 (56)	7	
6		6 (40)	9	
7		1 (8)	11	$P < 0·001$
8		2 (67)	1	
9		18 (56)	14	
10		5 (42)	7	
11		18 (90)	2	

* Vaccination status of 4 female and 1 male patient is unknown; 2 patients died during the immunization season; and the medical records of 1 patient were unavailable.

† Patients with 2 or more medical conditions are considered more than once.

convalescent sera had high levels of antibody against coronavirus OC43, suggesting recent infection.

The weekly distribution of acute respiratory illness with virological evidence of infection is shown in Figure 1. Peak activity occurred during weeks 39 and 48 and 49 of 1988. The first corresponded with the peak activity of rhinovirus infection and with sporadic infections with adenovirus and coronavirus OC43. The second coincided with peak activities of RSV and coronavirus OC43, but infections with rhinovirus, adenovirus, influenza type A, and coronavirus 229E also occurred. Five influenza type A infections occurred during week 50 (1988) to week 2 (1989) which corresponded with the peak influenza activity nationally (week 50 to week 9) when most isolates were A/Taiwan/1/86 (H1N1). The homes experienced a

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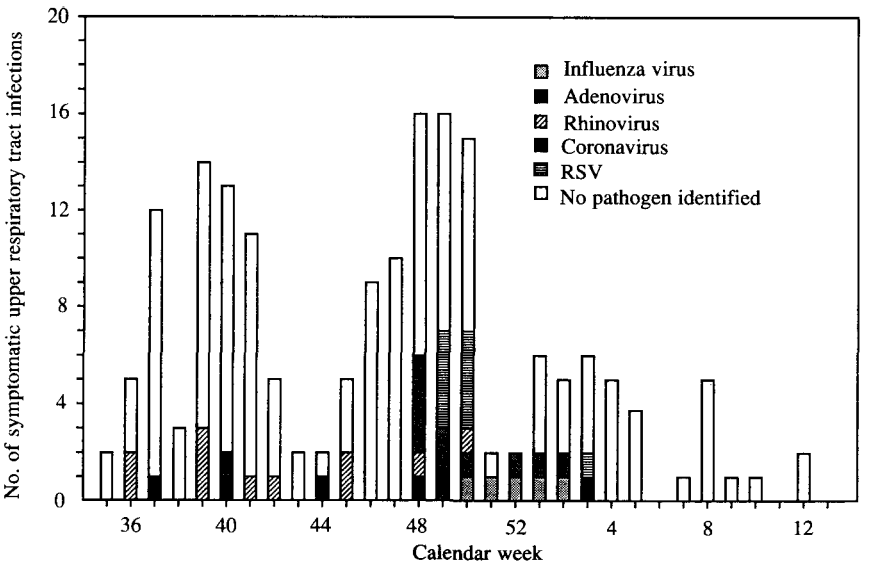

Fig. 1. Symptomatic upper respiratory tract illness by calender week, 1988–9.

small third peak of symptomatic illness in January 1989 which corresponded with infections with influenza type A, coronavirus OC43, adenovirus, RSV and unidentified pathogens.

Outcome

Most episodes (128/179; 72%) resolved within 1 week, 27 (15%) resolved within 14 days, 6 (3%) within 3 weeks, 3% within 4 weeks, and 0·6% after 4 weeks. 50·2% of all episodes resulted in at least one visit by the patients' general practitioners and there was an average of 0·64 consultations per episode. Eighty-one (90%) of the 90 episodes referred to a general practitioner resulted in the prescription of antibiotics and other drugs costing approximately £7.50 per treatment, equivalent to £3.50 per episode.

Lower respiratory tract complications developed during 45 of the 179 episodes (25%) including 3 of the 12 coronavirus infections, 3 of 9 RSV infections, 2 of 4 adenovirus infections, 1 of 11 rhinovirus infections, but none of 5 influenza infections. Comparison of the different virus infections revealed no differences between the duration of symptoms, lower respiratory complications, general practitioner visits, prescription of antibiotics, or hospitalization. Presence of chronic heart and/or lung disease was not significantly associated with lower respiratory complications, and none of the respiratory episodes resulted in hospital admission, including those who died.

Six deaths occurred within 4 weeks of onset of upper respiratory illness. One non-immunized patient died 2 weeks after the appearance of symptoms which occurred during an outbreak of coronavirus OC43 in the home and influenza in the community. The second patient had a rhinovirus infection prior to the influenza vaccination programme and progressively deteriorated and died after 4 weeks from pneumonia. The third (non-immunized), and fourth (immunized), patients died on days 5 and 8 of illness which coincided with RSV in the home and influenza in the community. A fifth patient was immunized and died on day 13 during infections with adenovirus, coronavirus OC43, and influenza in the home. The

sixth patient, who had been immunized, died on day 5 of illness when there were a number of viruses including influenza in the community.

DISCUSSION

In the United States an estimated 47·7 million illnesses are associated with influenza virus infection annually, giving an attack rate of up to 37·5 episodes per 100 person years and costing around $4·6 billion [10]. These estimates were calculated by the Committee on Issues and Priorities for New Vaccine Development which applied incidence rates derived from the Houston Family Study to US population figures. The Committee's estimates depend on various assumptions including that all consultations for acute respiratory disease during the peak influenza season are due to influenza virus and that deaths from acute respiratory disease (pneumonia and influenza) during the influenza virus activity period are due overwhelmingly to influenza. Calculating the cost of influenza and the cost–benefit of influenza vaccine is hampered by a dearth of data on the prevalence and impact of influenza in the general population and high-risk groups. Difficulties in developing accurate information arise from a variety of sources – many episodes of influenza may not come to medical attention, a specific diagnosis of influenza may not be made, the disease is not notifiable, outbreaks or epidemics may occur only in certain regions, and many of the hospitalizations and deaths due to influenza may be attributed to other causes, and vice versa. There have been no comparable estimates of the effect of influenza in the UK and this study is the first to address prospectively the prevalence and impact of respiratory viral infections in a large, elderly, ambulatory population during an interpandemic year.

During the first 6 weeks of the study, when sporadic influenza A, parainfluenza virus, RSV and rhinovirus isolates were reported from various Public Health Laboratory Service (PHLS) and hospital laboratories in England, Wales and Ireland to the Central Laboratory at Colindale, the nursing homes in Leicester witnessed the first peak of upper respiratory symptoms which was associated mostly with rhinoviruses. Subsequently the country experienced substantial outbreaks of RSV and influenza type A infections, the former peaking during week 50 of 1988 and the latter during week 1 of 1989. In Leicester the second peak occurred during weeks 48 and 49 which was mostly associated with RSV and coronavirus OC 43; influenza virus activity was detected during weeks 50 of 1988 to week 2 of 1989; and a smaller third period of respiratory viral activity, which occurred in January 1989, was associated with infections due to influenza type A, coronavirus, adenovirus and RSV. Thus although the local experience generally reflected the national experience respiratory symptoms in the study population evidently were caused mostly by pathogens other than influenza virus during the influenza period documented nationally. Such data question the validity of assumptions used by the US Committee on Issues and Priorities for New Vaccine Development in its assessment of the impact of influenza and value of vaccines against the disease [10]. Overall we identified only five cases of influenza and these occurred in homes with low immunization rates of 15, 33 and 42%. Here the attack rates in vaccinated and non-vaccinated groups were not significantly

different, but the number were too small to make any meaningful assessment of vaccine efficacy. Only one patient in a home which experienced influenza died during the outbreak. The home also had adenovirus and coronavirus infections at the same time, so the role of influenza in the patient's death is unclear.

Although the disease burden of RSV infection is concentrated in infants and young children, several severe outbreaks have recently occurred in elderly patients in hospitals and nursing homes. This suggests that RSV may be a more frequent cause of respiratory illness and pneumonia among the elderly in institutions than has been recognized previously. One outbreak in a psychogeriatric hostel in the West Midlands affected 17 of 40 (42.5%) residents, of whom one gradually deteriorated and died 1 month later [11]. Two of 24 patients in a psychogeriatric unit died during one outbreak reported to the PHLS, Communicable Diseases Surveillance Centre and in a geriatric hospital 15 patients were affected, 8 (53%) of whom died [12]. In a fourth outbreak in Devon at least 20 of 50 (40%) residents of an old people's home were affected and 4 patients died within a week of onset of illness [13]. In Missouri, USA, an outbreak in a nursing home affected 15 of 77 (19%) residents, 7 of whom (47%) developed pneumonia [14]. In Rochester, New York, Mathur and colleagues [15] investigated 71 cases of upper respiratory illness in the institutionalized elderly during a community outbreak of RSV and influenza A/Texas/77 infections; of 32 patients with an aetiologic diagnosis, 7 had RSV, 24 had influenza, and 1 had both. A comparison of the clinical features revealed no significant differences in respiratory or constitutional symptoms or signs, except coryza which was commoner in the RSV group. None of the patients died, but 2 of those infected with RSV developed pneumonia. Morales and co-workers [16] reported 12 RSV infections with 2 deaths among 159 respiratory episodes during a 6-month study of respiratory infections in geriatric wards in Edinburgh, and Sorvillo and colleagues [17] describe an outbreak in a Los Angeles County nursing home in which 40 out of 101 (40%) residents were affected, 22 (55%) of whom had pneumonia and 8 (20%) died. In the current study RSV infections were proven in 9 residents in 3 homes. All 9 survived, but one-third developed lower respiratory complications and 2 other residents in the homes died during the outbreak on days 5 and 8 of their illness and may have been infected with RSV.

Coronavirus serology is not routinely available in PHLS and hospital laboratories and so the impact of OC43 and 229E strains in elderly residential patients is unknown. We identified one 229E and 13 OC43 infections in 5 homes, the peak activity coinciding with the peak RSV activity and the first influenza infection locally. Reinfection with the same or related strains of coronavirus is common [18] and oubtreaks typically occur during the winter and early spring when influenza is generally prevalent. Human coronavirus infections are noted for their pronounced coryza, but in the study population the illness was clinically indistinguishable from RSV and influenza, and lower respiratory complications occurred in a quarter. Rhinoviruses and adenoviruses caused sporadic infections with only 1 of 11 rhinovirus infections having lower respiratory tract complications.

An often cited reason for failing to give or receive influenza vaccine is scepticism concerning its efficacy [6]. Protection rates have ranged from 0% to almost 90%

depending upon the method of assessment, the interval between vaccination and the outbreak, the age of the study population, the degree of antigenic difference between vaccine and field strains, and whether assessed by a challenge study or during a natural outbreak. The present study highlights the problems of diagnosing influenza clinically and even during well-defined outbreaks the clinical diagnostic rate for influenza by medical practitioners when later assessed by serology can be less than 30% [19, 20]. Our study shows that there is considerable potential for influenza to be over-diagnosed and accordingly the efficacy of the vaccine could be underestimated.

The present study again highlights the generally poor immunization status of elderly residents in nursing homes in the UK. All the patients, by virtue of being in a home, are at increased risk from influenza and should be considered for immunization [5]. We identified the presence of chronic medical conditions, i.e. additional risk factors, in almost 70% of residents, yet the overall immunization rate was only 45% – well below the 80% target suggested by the U.S. Public Health Service [21]. Although we failed to demonstrate a protective effect of influenza vaccine or a reduction in complications associated with influenza, several vaccine trials in the elderly have shown such benefits. In a 3-year study in Glamorgan, South Wales, Howells and colleagues [22] noted a reduction of over 80% in the incidence of bronchopneumonia and mortality in immunized patients. Serie and co-workers [23] in France similarly found that complications and mortality were reduced by 90–95%, and Gross and co-workers [24] noted a reduction in mortality of almost 60%. Patriarca and colleagues [25] showed that vaccination of nursing homes residents in Michigan reduced hospitalization by half, bronchopneumonia by 58%, and mortality by 76%. Thus if we assess protective efficacy in elderly residential populations in terms of complications rather than protection against 'flu-like' illness, it is evident that influenza vaccines can indeed be effective.

The economic impact of respiratory infections in the elderly are not inconsiderable. Overall there were 1·88 respiratory episodes per 1000 bed-days, equivalent to 0·7 episodes per bed per annum. Half of all episodes resulted in at least one domiciliary consultation and there was an average of 0·64 consultations per episode. Ninety per cent of episodes referred to a general practitioner resulted in the prescription of antibiotics and other drugs costing approximately £7.50 per treatment, equivalent to £3.50 per episode. None of the local residential patients were admitted to hospital and it is uncertain as to how representative this is of the national picture. For the winter 1988–9, when there was little influenza activity in the homes, the medical and drug costs for acute upper respiratory infections is estimated at almost £14 per bed per annum, equivalent to approximately £4 million for all elderly people living in communal establishments in Great Britain. Influenza vaccine, even if it were completely protective, would have reduced the treatment costs only marginally in the Leicester homes during 1988–9, and a national programme of vaccination for all communal residents would have cost approximately £3 million. Extrapolating from local data suggests that such a programme would not have been cost-effective in 1988–9 and there would need to be a considerable increase in influenzal activity on a regular basis for it to be economically worthwhile.

Amantadine and the structurally-related compound rimantadine are effective prophylactic agents against influenza type A and could have been prescribed in view of the local increase in respiratory complaints during a period of influenza type A infections nationally [26]. The national cost of a 4-week course for communal elderly patients would have been approximately £3 million and, extrapolating from local experience, it would have been of little clinical benefit. Indeed more people would have suffered from the adverse effects of the drug than would have been protected against influenza. Ribavirin, a broad spectrum antiviral agent, is an effective therapeutic agent in the treatment of influenza types A and B and also respiratory syncytial virus when given as an aerosol [26]. The possibility of using oral ribavirin prophylactically deserves study.

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