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Effectiveness of influenza vaccine in reducing hospital admissions during the 1989–90 epidemic

A. H. AHMED,[1] K. G. NICHOLSON,[1]* J. S. NGUYEN-VAN TAM[2] AND J. C. G. PEARSON[2]

[1] *Department of Microbiology and Immunology, School of Medicine, Medical Sciences Building, PO Box 138, University Road, Leicester University, Leicester LE1 9HN, UK*
[2] *Department of Public Health Medicine and Epidemiology, University of Nottingham Medical School, Queen's Medical Centre, Nottingham NG7 2UH, UK*

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SUMMARY

The effectiveness of influenza vaccine in reducing hospital admissions for pneumonia, influenza, bronchitis, or emphysema was assessed by a case-control study of people aged 16 years and older who were admitted to 10 Leicestershire hospitals between 1 December 1989 and 31 January 1990. Hospital and general practitioners' records for 156 admissions (the cases) and 289 controls matched for age and sex were reviewed. Information was collected on demography, the usual place of residence (institutional or non-institutional), the existence of chronic illness, and vaccination during the 5 years before admission. The odds ratio for hospital admission among vaccinees was 0·67 (95% CI 0·39–1·12) giving an estimate of vaccine effectiveness in this setting of 33% (95% CI 0–61). However, multivariate logistic regression, adjusting for the effects of institutional care and chronic illness, revealed that influenza vaccination reduced hospital admissions by 63% (95% CI 17–84%). There was a strong trend towards improved vaccine effectiveness when used in institutional settings. Influenza vaccine is effective in reducing hospital admissions for influenza, pneumonia, bronchitis and emphysema, and effectiveness is comparable to that observed for influenza and pneumonia admissions in North America.

INTRODUCTION

Influenza epidemics of variable extent and severity occur almost every winter. They impose an enormous burden in terms of morbidity, mortality, economic, and social costs, and are regularly associated with an increase in hospital admissions for acute respiratory disease [1–4]. Risk factors for influenza complications and death include residential care and chronic medical conditions that are especially prevalent in the elderly [2, 4, 5]. Accordingly, in Britain annual influenza vaccination is strongly recommended for adults and children with chronic pulmonary disease including asthma, chronic heart disease, chronic renal failure, diabetes mellitus, for conditions involving immunosuppression due to disease or treatment, and also for people who live in residential care and other long stay facilities where rapid spread may follow the introduction of infection [6]. Despite these recommendations, less than half of high-risk patients in Britain are immunized each year [7–12]. Scepticism about vaccine effectiveness is partly responsible for the low immunization rate [7, 9].

Although inactivated vaccine offers 80–90% protection against influenza-like illness in young healthy

* Author for correspondence.

individuals when vaccine and epidemic strains are closely related [13], the protection afforded to the frail elderly is less, about 20% [14]. Of greater importance, however, are reductions in complications as reflected by hospital admissions. A recent meta analysis of 20 cohort studies in the elderly revealed a 56% reduction in respiratory illness, a 53% reduction in pneumonia, and a 50% reduction in hospitalization [15]. The shortcomings of such studies are well recognized: the majority involved residential care with no clear distinction between those with and without chronic diseases.

The unpredictability of influenza epidemics and ethical considerations effectively prevent placebo-controlled studies of licensed vaccines in high-risk subjects. Case-control and cohort studies provide an accepted method of assessing the effectiveness of influenza vaccine [16], and have revealed about 40% effectiveness in North America in reducing hospital admissions for pneumonia and influenza [17–20] and similar effectiveness in reducing pneumonia and influenza mortality and deaths from all causes [17, 19]. Consultation and hospitalization rates for acute respiratory infections may vary from country to country and this may have an important effect on estimates of vaccine effectiveness based on morbidity. In Britain the A/England/308/89 (H3N2) epidemic, which occurred during the winter of 1989/90, provided the opportunity to study vaccine effectiveness in reducing hospital admissions for pneumonia, influenza, emphysema, or bronchitis during a period when vaccine and wild strains were well matched. Our findings are reported here.

METHODS

The study was carried out between November 1993 and November 1995, in Leicestershire Health Authority, UK, with a resident population of 892000 in 1989/90. Ethical approval was obtained from the Leicestershire Committee on the Ethics of Clinical Research Investigation.

Subjects

Admissions meeting the case-definition were identified using Leicestershire Health Authority's Patient Administration System. All patients aged 16 years or over who were admitted to Leicestershire hospitals between 1 December 1989 and 31 January 1990 inclusive, and whose primary discharge diagnosis or cause of death was either pneumonia, influenza, emphysema, or bronchitis (*ICD-9-CM* codes 466, 480.9 through 482.9, and 485 through 492.8) were identified. Two controls matched for age (same year of birth) and sex but from a different general practice were identified for each case. For cases who died during the admission or up to 9 calendar months after discharge, two controls who survived the 1989/90 epidemic but died more than 6 and less than 12 months after the index case were identified; these were the first and second records matching the index case for age and sex in the general practitioner records of deceased individuals retained by Leicestershire Family Health Services Authority. In order to avoid over-matching caused by practice-wide policies for influenza vaccine, controls for survivors were selected from neighbouring general practices in Leicestershire using the same method.

Information was collected from the hospital and general practitioner records of cases and general practitioner records of controls on basic demography; the subjects' usual place of residence classified into institutional (nursing and residential care homes, 'part III' accommodation, and long stay hospital beds), and non-institutional (all other residences including warden assisted complexes); the presence of chronic medical conditions until the beginning of the epidemic; medications prescribed; length of hospital stay; and influenza vaccination history during the 5 years before admission in 1989/90. Chronic medical conditions were identified from specific entries in hospital and general practitioner records, and grouped as chronic pulmonary disease including asthma; heart disease (including angina, arrhythmia, myocardial infarction, heart failure, hypertension, valvular heart disease, and cardiomyopathy); diabetes mellitus and other endocrine disease; renal disease; malignancy; neurological disease (including dementia, Parkinson's disease, and cerebrovascular disease); musculoskeletal and connective tissue disease; immunosuppression including haemopoietic malignancy and those taking steroids and immunosuppressive medications; other conditions.

Cases who received the 1989/90 vaccine before 15 December 1989 and whose admissions were not less than 2 weeks after vaccination were considered as *current* vaccinees. Controls who received the 1989/90 vaccine up to 15 December were also considered vaccinees for 1989. Cases and controls who received vaccine during one or more seasons between 1985 and

1988 were considered as *previous* vaccinees. These categories were not mutually exclusive.

Statistical analysis

Based on 156 cases, the study had a power in excess of 80% to detect an odds ratio of 0·4 (60% vaccine effectiveness) at 95% significance level. Descriptive analyses were performed to describe the distribution of each variable (including current and previous vaccination) by case or control status. Subsequently conditional logistic regression methods for matched case control studies were employed. A model was constructed containing firstly those variables with frequency distributions which differed significantly ($P < 0{\cdot}05$) between cases and controls (chronic pulmonary disease, musculoskeletal/connective tissue disease, and institutional living); variables representing the remaining high-risk medical categories specified by the DoH [6] were also included as were neurological disease, malignancy and previous influenza vaccination because previous work has shown these to be determinants of death from influenza [20]. Current influenza vaccination was then added to the model, and percent vaccine effectiveness was calculated as 1 minus the odds ratio in vaccinated subjects $\times 100$.

In extensions to the basic model, product terms were added to explore the possibility that vaccine effectiveness was different among patients living in institutions compared to those in the community, and between patients with high-risk medical conditions [6] and those without. The aim was to demonstrate any trends towards differential vaccine effectiveness between subgroups. However, it was acknowledged that the study had not been designed to test such hypotheses and would probably lack statistical power to demonstrate significant differences between subgroups.

RESULTS

Three hundred and three admissions meeting the case-definition were identified. In-patient records were successfully retrieved for 264 admissions (87·1%). Figure 1 shows the temporal relation between the 264 admissions and consultation rates for epidemic influenza and influenza-like illness as reported by the Royal College of General Practitioners' sentinel practices. For 156 of these admissions (the cases) (59·1% of the 264 and 51·5% of the 303 admissions), we were able to access the primary care records and matched 289 controls.

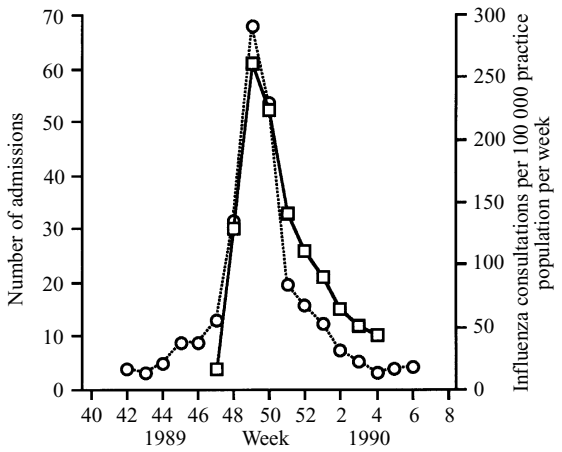

Fig. 1. Temporal relationship between admissions for pneumonia, influenza, emphysema or bronchitis in Leicestershire and rate of consultations for 'epidemic influenza' and 'influenza-like illness' in sentinel practices in England and Wales. □, Number of admissions; ○, RCGP influenza consultations/100000.

Table 1 shows the characteristics of cases and controls; 78 of 156 cases (50·0%) died during their stay in hospital and a further 32 (20·5%) during the following 9 months. The median length of inpatient care was 7 days (range 1–54). Twenty-three (14·7%) cases and 48 (16·6%) controls had received both current and previous vaccine, and 120 (76·9%) cases and 212 (73·4%) controls had received no vaccine at all. Twenty-seven of 156 cases (17·3%) received influenza vaccine in 1989 compared to 69 to 289 controls (23·9%), $\chi^2 = 1{\cdot}58$, $P = 0{\cdot}11$; this gave an odds ratio of hospital admission among vaccinees of 0·67 (95% CI 0·39–1·12), and vaccine effectiveness could be estimated at 33% (95% CI 0–61%).

Based on the final conditional logistic regression model, Table 2 shows the risk of hospital admission for influenza, pneumonia, emphysema, or bronchitis associated with various chronic conditions. Each risk is adjusted for all of the other variables in Table 2 and including current and previous vaccination. The risk of hospital admission was significantly increased among individuals with chronic pulmonary disease and those living in residential care. However, patients with musculoskeletal or connective tissue disorders were less likely to be admitted. Overall the risk of admission for patients in the high-risk groups specified by the DoH [6] was more than doubled.

The risks associated with the two types of vaccination status are also shown in Table 2, each being

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Table 1. *Demographic characteristics, chronic diseases and residential status of cases and controls*

Characteristic	Number (percentage)	
	Cases $n = 156$	Controls $n = 289$
Age in years		
16–44	13 (8·3)	26 (9·0)
45–64	13 (8·3)	22 (7·6)
65–74	30 (19·2)	53 (18·3)
75–84	56 (35·9)	105 (36·3)
85–94	38 (24·4)	73 (25·3)
⩾ 95	6 (3·8)	10 (3·5)
Sex		
Male	72 (46·2)	132 (45·7)
Female	84 (53·8)	157 (54·3)
Residential status		
Institution*	24 (15·3)	25 (8·7)
Community	132 (84·6)	264 (91·3)
Chronic diseases		
Heart disease*	70 (44·9)	125 (43·3)
Chronic pulmonary disease*	47 (30·1)	43 (14·9)
Renal disease*	2 (1·3)	10 (3·5)
Diabetes*	17 (10·9)	20 (6·9)
Other endocrine disease*	6 (3·8)	9 (3·1)
Immunosuppression*	1 (0·6)	5 (1·7)
Malignancy	14 (9·0)	37 (12·8)
Neurological disease	23 (14·7)	46 (15·9)
Musculoskeletal and connective tissue disease	13 (8·3)	49 (17·0)
Other chronic illness	35 (22·4)	66 (22·8)
Influenza vaccine recommended by DoH		
Yes	113 (72·4)	171 (59·2)
No	43 (27·6)	118 (40·8)
Influenza vaccine received		
Current (1989)	27 (17·3)	69 (23·9)
Previous (1985–8)	32 (20·5)	56 (19·4)

* DoH designated high-risk group.

adjusted for the other, and all of the chronic conditions shown in the table. Current influenza vaccination made a significant contribution to the model after adjustment for the effects of the other variables ($P = 0{\cdot}011$). The use of influenza vaccine in the 'current' season reduced the likelihood of hospital admission by 63% (95% CI 17–84) whereas 'previous' vaccination offered no protection when adjusted for current vaccination and the other factors. The interaction between current and previous vaccination status was examined but not found to be significant ($P = 0{\cdot}82$). Furthermore, no significant interaction was found between the effect of vaccine in subjects with high-risk conditions and those without ($P = 0{\cdot}23$). Despite a marked trend towards enhanced vaccine effectiveness among subjects living in residential care (V_E 70%; 95% CI 32–87) compared to the open community (V_E 19%; 95% CI 0–82) after adjusting for the variables in Table 2, the interaction term failed to show a significant effect ($P = 0{\cdot}88$) when added to the model.

DISCUSSION

This analysis demonstrated significant vaccine effectiveness in reducing hospital admissions for influenza, pneumonia, bronchitis and emphysema during the 1989/90 influenza epidemic in Leicestershire, UK. Although generalizability is limited by the case definitions we employed, our finding corroborates the results of early observational studies [14, 15] as well as four recent North American cohort and case-control studies [17–20]. We did not examine vaccine effectiveness during a non-epidemic control period, but we did examine effectiveness of vaccine administered during 1985–8, and found no protection. Conceivably the small number of vaccinees during 1985–8 provided insufficient power to detect small degrees of protection, but the lack of vaccine effectiveness from vaccine given during the years prior to the 1989/90 epidemic was expected since antigenic drift requiring revision of the H3N2 vaccine component occurred in 1989. Moreover the observed lack of effect of prior vaccination during 1989/90 is in agreement with observations from two recent British mortality studies [21, 22].

In our mortality study we demonstrated that influenza vaccine provided a significantly higher level of protection against death among individuals who were repeat (as opposed to the first time) vaccinees [21]. In the present study we failed to show the same difference. Cases were selected on the basis of hospital admission which partly depends on general practitioner behaviour; the decision to admit to hospital depends on many factors including a belief that hospital treatment would be worthwhile and that the same care could not be provided in the patient's own home. It is therefore possible that well-organized practices with established programmes for repeat annual immunization may also have operated different thresholds for triggering hospital admission than less well-organized practices.

Reported levels of vaccine effectiveness differ markedly between young and elderly adults [13, 14]. However, relatively few studies have considered how the effectiveness of vaccine varies among the elderly.

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Table 2. *Risk factors for admission with pneumonia, influenza, emphysema or bronchitis during the 1989/90 influenza A epidemic in Leicestershire, UK*

Factor	Odds ratio for hospital admission	95% confidence interval	% V_E (95% CI)
Risk factors			
Institutional care*	2·96	1·35–6·53	
Chronic pulmonary disease*	2·63	1·59–4·35	
DoH high-risk groups combined*	2·04	1·29–3·25	
Diabetes mellitus*	1·48	0·66–3·34	
Cardiac disease*	1·20	0·74–1·94	
Other endocrine disorders*	0·98	0·27–3·58	
Neurological disease	0·94	0·52–1·70	
Immunocompromised*	0·73	0·08–6·91	
Malignancy	0·63	0·29–1·36	
Musculoskeletal/connective tissue disease	0·42	0·21–0·85	
Renal disease*	0·52	0·11–2·51	
Vaccination status			
Previous vaccination (1985–8)	2·25	1·0–5·09	0
Current vaccination (1989)	0·37	0·16–0·83	63 (17–84)

* DoH designated high-risk groups.
Odds ratios for hospital admission adjusted for all other variables in table, and for current and previous influenza vaccination.

Although failing to reach statistical significance, our study shows a strong trend towards enhanced vaccine effectiveness among the elderly in residential care compared to those living in the open community. This finding is in agreement with a review of 16 studies of influenza vaccine in preventing morbidity in the elderly, which also demonstrated a non-significant trend [23].

Although the outcome used in this study was hospitalization for pneumonia, influenza, bronchitis or emphysema, it was not possible to establish whether any of these admissions were actually the result of influenza. However, the study period coincided with peak clinical activity, and hospital admissions in Leicestershire closely mirrored Royal College of General Practitioners consultation rates in sentinel practices (Fig. 1). Despite a strong association between acute respiratory disease hospitalization and virus isolation during major epidemics, as in 1989/90, it is still probable that cases were included which were not actually caused by influenza. The effect of this misclassification bias would be to underestimate vaccine effectiveness, so the estimate in the present study is probably conservative.

The major source of bias in our study stems from the non-availability of primary care records in almost 50% of the cases we originally identified, although hospital records were available for almost 90%. It may be the case that general practitioners who did not operate an active policy of influenza immunization in 1989 were less likely to give their permission for us to access the notes of patients who were admitted. Thus the level of vaccine uptake measured among cases may, if anything, have been spuriously high resulting in an underestimation of vaccine effectiveness.

Another possible limitation of the study is its reliance on the documentation of vaccination status. Virtually all influenza vaccine is prescribed and administered by patients' general practitioners in the UK, and its administration has potential medico-legal implications. Under-recording of vaccination is thus likely to have been infrequent and no more likely to have occurred among cases than controls, therefore having no appreciable effect on estimates of vaccine effectiveness. The vaccine uptake of 23·9% among controls in the present study is similar to the uptake described in other studies in England that took place around 1989/90 involving reviews of medical records or self-reporting [7–12, 21]. Moreover the immunization rate of 17·3% among cases in this study is very close to the rate (18·1%) found in 36 district health authorities in England during 1989/90 among 315

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fatalities with influenza as the certified cause of death [21].

Mortality statistics indicate that influenza epidemics can hasten the deaths of many people whose underlying illness would be fatal in the ensuring months [24, 25]. Accordingly we chose controls who died shortly after the epidemic for cases who died in hospital or shortly after discharge. Although overall 32·6% (86/264) of cases died during admission, the mortality rate among the cases we studied (50·2% during hospitalization and an additional 20·5% during the 9 months thereafter) was very high, suggesting that we focused on a debilitated population and introduced an element of potential bias. Notwithstanding, the validity of the study design is supported by our identification of institutional care and chronic pulmonary disease as independent risk factors for hospitalization. As in our mortality study [21] we did not confirm the recognized risk factors chronic heart disease, diabetes mellitus, and renal disease individually, possibly because they were important factors contributing to the deaths of controls, or because of the small numbers studied. Nevertheless, we did find that the risk of admission among groups for whom the DoH strongly recommends vaccination [6] was significantly increased. The identical observation was found previously with respect to deaths [21].

Besides comorbidity, previous pneumococcal vaccination might have modified an individual's risk from influenza complications. Virtually no pneumococcal vaccine was distributed among high-risk subjects in the UK during the study period and preceding 5 years [21], so it is very unlikely that pneumococcal vaccination had any effect on the risk of hospitalization among those studied.

In Britain very little information is available concerning the health costs incurred during influenza epidemics. During the study in Leicestershire the number of admissions for acute respiratory illness with *ICD-9-CM* codes 466, 480.9 through 482.9, and 485 through 492.8 increased by 42% in comparison with the mean number of admissions during the corresponding periods in 1987/8 ($n = 172$), 1988.9 ($n = 261$), and 1990/1 ($n = 205$) when influenza activity was less. The median duration of stay for cases was 7 days. During the influenza season a 63% (95% CI 17–84) reduction in admissions for acute respiratory illness with concomitant reductions in drug costs could represent a considerable reduction in health costs and reduce the pressure on acute medical admissions. Overall 72·4% of the admissions had 'high-risk' conditions for which influenza vaccine is recommended by the DoH. Thus application of the current UK recommendations might have prevented about 45% of all admissions that occurred, and a similar proportion of deaths.

Considered together, this study, the recent case-control study on the effectiveness of influenza vaccine in reducing mortality in the UK [21] and similar studies in North America [17–20] provide a solid basis for concluding that despite different health care systems, influenza vaccine has substantial effectiveness in preventing deaths and respiratory complications from influenza. Our results support the current UK guidelines for annual vaccination and the continuing effort to increase vaccine coverage in at-risk groups.

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