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Study of the effectiveness of influenza vaccination in the elderly in the epidemic of 1989–90 using a general practice database

D. M. FLEMING[1], J. M. WATSON[2]*, S. NICHOLAS[2], G. E. SMITH[2] AND A. V. SWAN[2]

[1] *Birmingham Research Unit of the Royal College of General Practitioners, 54 Lordswood Road, Harborne, Birmingham B17 9DB.*

[2] *PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ*

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SUMMARY

The effectiveness of influenza vaccination in preventing serious illness and death was determined in an elderly population during the influenza epidemic of 1989–90. A retrospective cohort study was carried out using computerized general practitioner records on nearly 10000 patients aged 55 years and over. After adjustment for potential confounding factors, recent immunization was found to have a protective effect of 75% (95% confidence intervals: 21–92%) against death. Protection did not appear to vary with either age or the presence of underlying chronic disease. As the complications of influenza are most common in those with underlying chronic disease, the study findings are consistent with the recommended policy for the use of influenza vaccine in the UK. Further work is necessary to determine the cost-effectiveness of extending immunization to other groups.

INTRODUCTION

The unpredictable nature of influenza has made it extremely difficult to mount prospective studies to determine the efficacy of influenza vaccines in the elderly. However, the influenza epidemic in Britain during the winter of 1989–90 provided an opportunity to assess vaccine efficacy retrospectively. The Royal College of General Practitioners (RCGP) Research Unit in Birmingham, as part of a programme of continuous morbidity recording, holds comprehensive morbidity and prescribing data from five general practices covering approximately 50000 individuals collected over a period of 3 years [1].

The aim of the study was to assess the efficacy of prior influenza vaccination in preventing serious illness and death in elderly people during the influenza epidemic of 1989–90. The intention was to do this by extracting information on vaccination status and major outcomes, such as death and respiratory illness, from patients registered in the practices who were at risk during the epidemic

* Author for correspondence and reprint requests.

period. Demographic and clinical data were also required so that the effects of possible confounding factors could be taken into account and the possibility of efficacy varying among different risk groups investigated.

METHODS

Data

From the computerized database, all persons aged 55 years or over on 1 November 1989 were selected. Those individuals for whom no consultations had occurred between 1 June 1988 and 31 March 1990 were then removed from the set to reduce the chance of including patients who had in fact left the practice, i.e. 'ghost patients'. From each patient record, demographic details including date of birth and sex were extracted. In addition, the number of consultations in total, and classified as consultations for respiratory illness or for underlying chronic diseases during the period 1 June 1988 to 31 October 1989, were noted. Those patients who died or suffered from a *severe* or *non-severe respiratory illness* during the epidemic period were identified and the information used to obtain the primary outcome measure, i.e. *death* and the subsidiary outcome measures involving non-fatal respiratory disease; *death or severe respiratory illness* or *death or any respiratory illness*.

The analysis was aimed at estimating the effects of vaccination on these outcomes, allowing for the effects of the potentially confounding variables *age*, *sex* and *number of previous consultations* in the 17 months preceding the start of the epidemic. In addition patients were classified according to their status with respect to the two 'risk' factors.

(*a*) The presence or not of *major chronic disease*, i.e. with one or more consultations for the conditions associated with increased risk of the complications of influenza as listed in the letter from the Chief Medical Officer to all doctors in the UK in 1989: (i) chronic pulmonary disease; (ii) chronic heart disease; (iii) chronic renal disease; (iv) diabetes mellitus and other endocrine disorders associated with adrenal suppression; and (v) other conditions which may themselves or as a result of treatment give rise to immunosuppression.

(*b*) The presence or not of *minor chronic disease*, i.e. with one or more consultations during the specified time period for conditions such as hypertension, depression, osteoarthritis and rheumatoid arthritis.

Finally it was possible that respiratory illness, prior to the epidemic period (i.e. between June 1988 and October 1989), may have conferred protection against illness in subsequent years (by acquired immunity) or, alternatively, have been indicative of a higher risk of subsequent respiratory illness. For this reason those who had experienced respiratory illness were specifically identified in the analyses with a risk variable defined by: The occurrence or not of *previous respiratory illness*, i.e. with one or more consultations for acute bronchitis, 'epidemic influenza', 'influenza-like illness', pneumonia or lower respiratory tract infection in the 17 months prior to the epidemic period.

A complete list of the conditions constituting *severe respiratory illness*, *any respiratory illness* and *minor chronic disease* is available from the authors on request.

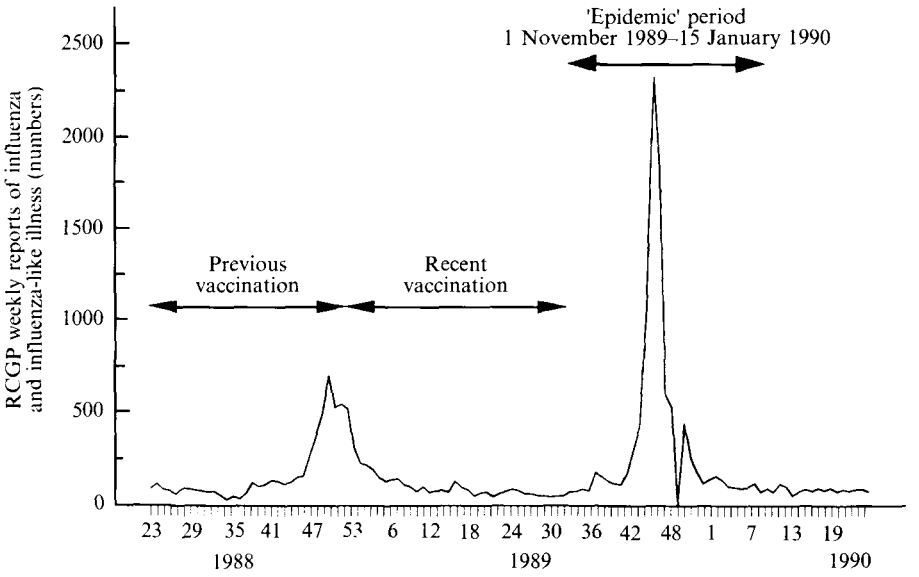

Fig. 1. Details of vaccination status and epidemic period.

The 'epidemic' period was defined as 1 November 1989 to 15 January 1990 (Fig. 1). based on the weekly incidence data of influenza and influenza-like illness reported in the Weekly Returns Service of the RCGP [2].

The influenza vaccines in use in the UK were trivalent containing influenza A H_3N_2. H_1N_1 and influenza B components. In 1988 the H_3N_2 component was an A/Sechuan/2/87-like strain and in 1989 an A/Shanghai/11/87-like strain. These two strains are antigenically closely related but distinguishable. Influenza immunization is recommended on an annual basis: protection is generally believed to last for about 1 year and antigenic drift of the circulating influenza virus strains means that the composition of the vaccine is reviewed, and usually changed, each year. Patients who had received influenza vaccine between 1 January 1989 and 31 October 1989 were classified as *recently vaccinated*, and those between 1 June 1988 and 31 December 1988 (but not subsequently) as *previously vaccinated* (Fig. 1).

Analysis

Data manipulation and descriptive analysis were performed in SPSS [3]. Individual observations were then aggregated into grouped data according to a multi-way classification by the variables of interest. Regression analyses were performed using a variant of logistic regression assuming a binomial response with a log link for the outcomes using GLIM [4]. This means that the fitted coefficients are logarithms of the relative risks and that the relative risks needed for estimating vaccine efficacy (= 1 − relative risk) and appropriate confidence intervals can be obtained directly.

Single variable analyses were performed comparing the vaccination groups to obtain unadjusted relative risks and 95% confidence intervals to give a preliminary indication of the effect of vaccination on the above outcome measures. Multivariable analyses were then performed to determine the effect of vaccine status on the outcomes whilst controlling for the potentially confounding

Table 1. *Study population by vaccination status (percentage of totals in each age group given in brackets)*

Age group (years)	Recently vaccinated		Previously vaccinated		No vaccination		Totals	
	Males	Females	Males	Females	Males	Females	Males	Females
55–64	64	74	82	99	1432	1696	1578	1869
	(4·1)	(4·0)	(5·2)	(5·3)	(90·8)	(90·7)	(100)	(100)
65–74	105	158	150	201	1078	1567	1333	1926
	(7·9)	(8·2)	(11·3)	(10·4)	(80·9)	(81·4)	(100)	(100)
75–84	63	104	121	151	571	1141	755	1396
	(8·3)	(7·5)	(16·0)	(10·8)	(75·6)	(81·7)	(100)	(100)
85+	9	22	19	37	129	318	157	377
	(5·7)	(5·8)	(12·1)	(9·8)	(82·2)	(84·4)	(100)	(100)
Total	241	358	372	488	3210	4722	3823	5568
	(6·3)	(6·4)	(9·7)	(8·8)	(84·0)	(84·8)	—	—

variables of *age*, *sex*, *underlying chronic diseases*, *previous respiratory illness* and *number of previous consultations*.

RESULTS

Descriptive analysis

There were 9878 records on patients aged 55 years and over on 1 November 1989. A total of 487 patients were excluded from the analysis, because they had not consulted between 1 June 1988 and 31 March 1990 ($n = 317$), or were known to have left the practice before March 1990 ($n = 168$), or because their sex was not known ($n = 2$). Thus the total number of patients available for analysis was 9391.

The distribution of the study population by age group, sex and vaccination status is given in Table 1. There was little difference in the proportions of males and females *recently vaccinated*, the proportions being 6·3% for men and 6·4% for women. The proportion who were *recently vaccinated* increased with age in both males and females up to the age group 65–74 years, but fell in the 85+ year group to a level half-way between the 55–64 and 65–74 years age groups.

Table 2 shows details of the vaccination status by *previous respiratory illness* and chronic disease status. It can be seen that the proportion *recently vaccinated* was substantially higher in those with a chronic disease; 10·8% compared with 3·3% in those without *previous respiratory illness*, and 12·5% compared with 4·5% in those with such an illness. This difference and the difference in vaccination rates between those with and without *previous respiratory illness* were both highly significant ($P < 0·001$). If those individuals with *major chronic disease*, both with and without *previous respiratory illness*, are combined, there are a total of 2344 people in the analysis in groups recommended by the Chief Medical Officer for immunization, of whom, 265 (11·4%) were *recently vaccinated*, and a further 381 (16·3%) *previously vaccinated*.

Table 3 shows the death rates by underlying disease and vaccination status. There was no obvious pattern indicating consistent differences in risk or vaccine efficacy, but the groups were not necessarily comparable with respect to age and

Table 2. *Study population by risk group status (percentage of totals in each risk group given in brackets)*

	Vaccination status			
	No vaccination	Previously vaccinated	Recently vaccinated	Total
No previous respiratory illness				
No chronic disease	3775 (92·2)	184 (4·5)	137 (3·3)	4096
Minor chronic disease	1738 (84·7)	182 (8·9)	128 (6·3)	2048
Major chronic disease	1279 (75·4)	233 (13·7)	184 (10·8)	1696
Previous respiratory illness				
No chronic disease	508 (84·8)	64 (10·7)	27 (4·5)	599
Minor chronic disease	213 (70·1)	49 (16·1)	42 (13·8)	304
Major chronic disease	419 (64·7)	148 (22·8)	81 (12·5)	648
Total	7932 (84·5)	860 (9·2)	599 (6·4)	9391
Number of previous consultations				
1–10	5810 (91·3)	338 (5·3)	214 (3·4)	6362
11–20	1581 (75·4)	306 (14·6)	209 (10·0)	2096
> 20	541 (58·0)	216 (23·2)	176 (18·9)	933
Total	7932	860	599	9391

Table 3. *Percentage death rates and numbers at risk by risk factors and vaccination status*

	Vaccination status							
	No vaccination		Previously vaccinated		Recently vaccinated		All	
	%	*n*	%	*n*	%	*n*	%	*n*
No previous respiratory illness								
No chronic disease	0·53	3775	0·54	184	0·73	137	0·54	4096
Minor chronic disease	0·40	1738	0·55	182	0·00	128	0·39	2048
Major chronic disease	3·13	1279	3·00	233	0·00	184	2·77	1696
Previous respiratory illness								
No chronic disease	1·38	508	0·00	64	3·70	27	1·33	599
Minor chronic disease	0·47	213	0·00	49	0·00	42	0·33	304
Major chronic disease	2·15	419	3·38	148	1·20	81	2·32	648

other potential risk factors. The confounding effects of these when estimating variables was allowed for efficacy in the logistic regression analysis.

Regression analysis

The main analysis was performed using *death* as the outcome allowing for the effects of age, sex and the other factors. Mortality was significantly higher in those with *major chronic disease*, but was not associated with *previous respiratory illness* and was actually lower in those with non-relevant chronic diseases (i.e. *minor chronic disease*) when compared with those with neither *major* nor *minor chronic disease*. There was a highly significant upward trend in mortality with age. Females had a significantly lower mortality. Mortality was positively associated with the *number of previous consultations*. In the model allowing for these effects there was clear evidence that vaccination was associated with lower mortality ($P \sim 0{\cdot}012$).

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Table 4 *ıck rates, relative risks (unadjusted and adjusted) and estimated efficacies (and 95% confidence i* *'als [CI])*

Outcome meas	Vaccine status	Attack rates	(%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	*P*-value	Ef (9:	I)
Death	Not vaccinated	84/7932	(1·06)	1·00	1·00			
All patients	Previously vaccinated	14/860	(1·63)	1·54 (0·88, 2·69)	0·77 (0·44, 1·37)		2:	·37·0, 56·1)
	Recently vaccinated	3/599	(0·50)	0·47 (0·15, 1·48)	0·25 (0·08, 0·79)	0·012	7·	·2, 91·9)
Those with	Not vaccinated	49/1698	(2·89)	1·00	1·00			
major chro	Previously vaccinated	12/381	(3·15)	1·09 (0·59, 2·03)	0·84 (0·45, 1·57)		1(	·57·1, 55·4)
disease	Recently vaccinated	1/265	(0·38)	0·13 (0·02, 0·92)	0·10 (0·01, 0·66)	0·022	9(	·4, 98·5)
Death or sever	Not vaccinated	102/7932	(1·29)	1·00	1·00			
respiratory ill	Previously vaccinated	18/860	(2·09)	1·63 (0·99, 2·66)	0·84 (0·51, 1·39)		1:	·39·3, 49·3)
	Recently vaccinated	10/599	(1·67)	1·30 (0·69, 2·45)	0·70 (0·37, 1·36)	0·48	2:	·36·0, 63·4)
Death or any	No vaccine	1174/7932	(14·8)	1·00	1·00			
respiratory ill	Previously vaccinated	218/860	(25·3)	1·71 (1·51, 1·94)	1·04 (0·92, 1·18)		—·	·17·5, 7·6)
	Recently vaccinated	144/599	(24·0)	1·62 (1·40, 1·89)	1·03 (0·89, 1·19)	0·77	—:	·18·8, 10·6)

Table 4 shows the effect of vaccination on mortality rates, severe respiratory illness or non-severe respiratory illness before and after adjustment, using the regression models, for *age*, *sex*, *underlying respiratory illness* and *number of previous consultations*.

With death alone as the outcome variable, vaccination was significantly associated with a reduction of risk ($P \sim 0{\cdot}012$) particularly for those who were fully vaccinated. The estimated vaccine efficacy in those previously vaccinated was 22% (95% confidence intervals: −37 to 56%) and in those recently vaccinated it was 75% (95% confidence intervals: 21 to 92%).

Using *death or severe respiratory disease* as the adverse outcome appears to reduce the estimated effects of vaccination, and hence the estimated efficacies to the extent that they are no longer statistically significant. Using *death or any respiratory disease* obscures the effects entirely (Table 4).

If the analysis, using *death* as the outcome, is restricted to those with *major chronic disease* the vaccine effect is still clear and significant although the benefits of *previous vaccination* appear slightly less, with an efficacy of 16% (95% confidence intervals: −57 to 55%) and of *recent vaccination* slightly more, with an efficacy of 90% (95% confidence intervals: 34 to 99%). However these estimates are less reliable as the effects of age, sex and other factors, used in calculating the estimates, are based on less data.

DISCUSSION

The epidemic of influenza A of the H_3N_2 subtype [5] in the UK in the winter of 1989–90 was the largest epidemic since 1975–6 and was associated with a substantial excess mortality [6]. Most of this excess of deaths was observed in the elderly age group. The epidemic was associated with the influenza A virus, of the H_3N_2 subtype, which was closely related to the H_3N_2 component contained both the 1988 and 1989 recommended influenza vaccines. Thus, in ideal circumstances, immunization would be expected to provide some protection against influenza infection in the 1989–90 epidemic. Doubts have been expressed about the protection offered by influenza vaccination in the elderly, particularly in those with conditions that put them at high risk of the complications of influenza [7, 8]. This study supports the suggestion from earlier studies conducted in nursing homes [9], and more recent studies on the elderly in the community [10–14], that influenza immunization provides a valuable degree of protection against the severe complications of influenza.

The RCGP database provides a convenient resource from which the vaccination history, mortality and morbidity for a large sample of individuals from a defined demographic population can be obtained. Studies using similar methodology have recently been reported from North America [13–15]. Validation of data items, including vaccination history, on patients included in this study was not carried out. However, validation of the computerization of data recorded in the medical notes disclosed a transcription error rate of less than 5% [1]. The study demonstrates the value of comprehensive data collection in primary care of morbidity, prescribing and other health related events.

The proportion vaccinated did not differ between the sexes, but generally increased with age, the presence of underlying chronic disease and number of consultations with the GP in the year preceding the epidemic year. After adjustment for the effects of age, sex, underlying illness and number of consultations with the GP, the analysis showed that vaccination was significantly associated with a reduction in mortality.

The best estimate of protection against *death* of influenza vaccination is thus 75% (95% confidence intervals: 21 to 92%) for vaccination in the epidemic year and 22% (95% confidence intervals: −37 to 56%) for vaccination in the previous year. Protection was also suggested when the definition of the outcome of interest was expanded to include *respiratory illness in the epidemic period*, but this was not statistically significant.

Some of the deaths occurring in both the vaccinated and unvaccinated groups were likely to be due to causes unrelated to influenza and such mis-classification will bias estimates of efficacy against influenza related deaths. However this bias would tend to produce an under-estimate of protection and, despite this, the results suggest an overall protective effect of influenza vaccination, in those over 55 years of age in this population, against death. It is not possible to determine the precise causes of death in the patients involved in this study as this information was not included on the database. Conversely it seems that including respiratory disease in the adverse outcome category increases the level of mis-classification to such an extent that the benefits of vaccination are more or less entirely obscured. The high background levels of acute respiratory infection due to microorganisms other than influenza viruses, such as respiratory syncytial virus, must be recognized [16].

A possible alternative explanation for the apparent protection against death in those who are vaccinated, is that this group is more effective in other ways at preserving their health and life. Adjustment was made in this analysis for the number of consultations that patients had with their general practitioner in the period prior to the epidemic, and propensity to visit a doctor may provide an indication of an individual's concern to preserve their health. However, this sort of bias cannot be discounted, particularly as the uptake of vaccination was relatively low. Although the results of this study are consistent with a protective efficacy as low as 21%, the true efficacy against death from influenza, or precipitated by influenza, may be substantially higher. More precise estimates would require virological confirmation of diagnosis of influenza and accurate information on causes of death as well as a larger study population.

There is no evidence that efficacy changes with age, but since deaths are more frequent in the older age groups the results suggest that more deaths can be prevented, for a given amount of vaccine, if it is given to individuals in those groups. Similarly there was no evidence that protection was significantly affected by the risk category status of the patients, although those with *major chronic disease* are at higher risk of the complications of influenza. Thus a given amount of influenza vaccine would be likely to prevent more deaths in this group. Consequently, although this study revealed no evidence that protection changed with age or risk status, the current policy for the use of influenza vaccine in the UK, which recommends immunization of 'those who are at increased risk of

complications should they develop influenza' [17], may be the most cost effective policy. Further research needs to be carried out to determine the appropriateness of extending immunizations to the elderly without high risk conditions. More accurate identification of death and illness caused by influenza virus infection would be needed if more precise estimates of the protective efficacy of the vaccine are to be determined in any given year.

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