

# Effectiveness of influenza vaccine in reducing hospital admissions in people with diabetes

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## SUMMARY

The effectiveness of influenza vaccination in reducing hospitalization of people with diabetes for influenza, pneumonia, or diabetic events during influenza epidemics was assessed in a case control study in Leicestershire, England. Cases were 80 patients on the Leicestershire Diabetes Register who were admitted and discharged from hospital with International Classification of Disease codes for pneumonia, bronchitis, influenza, diabetic ketoacidosis, coma and diabetes, without mention of complications, during the influenza epidemics of 1989–90 and 1993. One hundred and sixty-controls, who were not admitted to hospital during this period, were randomly selected from the Register. Immunization against influenza was assessed in 37 cases and 77 controls for whom consent was obtained to access their clinical notes and for whom notes were available. Significant association was detected between reduction in hospitalization and influenza vaccination during the period immediately preceding an epidemic. Multiple logistic regression analysis estimated that influenza vaccination reduced hospital admissions by 79% (95% CI 19–95%) during the two epidemics, after adjustment for potential confounders.

## INTRODUCTION

Influenza is regularly associated with considerable morbidity and excess winter mortality [1, 2]. Risk factors for influenza complications and death include residential care and a spectrum of medical conditions which are especially prevalent among the elderly [3–9]. Accordingly in the UK annual influenza vaccination is strongly recommended for adults and children with pulmonary disease including asthma, heart disease, renal failure, diabetes mellitus and other endocrine disorders, immunosuppression caused by disease or treatment, and for people who live in residential care and other long-stay facilities where rapid spread may follow the introduction of infection [10]. Despite the recommendations less than half of high-risk patients in the UK are immunized each year [11–15]. Ac-

ording to patients the main reasons for not being vaccinated are ignorance about risk status and inadequate advice from doctors [14, 15], but among doctors concern about vaccine effectiveness and adverse effects are voiced most frequently [13, 16].

To date no studies have considered the effectiveness of influenza vaccine in people with diabetes. The only studies of influenza vaccination in people with diabetes concern immunological responses to the vaccine [17–19]. These show that influenza vaccine elicits comparable antibody responses in people with diabetes and controls. The unpredictability of influenza epidemics and ethical considerations preclude placebo-controlled studies of influenza vaccine efficacy in high-risk subjects. Case-control studies provide an alternative method of assessing vaccine effectiveness. The epidemics of A/England/308/89 (H3N2) and A/Beijing/32/92 (H3N2), which occurred during the

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winters of 1989–90 and 1993–4 respectively provided the opportunity for us to study vaccine effectiveness in reducing hospital admissions during periods when vaccine and wild strains were close antigenically.

## METHODS

### Influenza epidemics

The period from week 1, 1989 to week 40, 1994 was scanned for influenza epidemics, defined as periods when the number of reports of influenza A and B, including virus isolates, microscopic findings, fourfold antibody rises, or single high titres, to the Public Health Laboratory Service (PHLS) Communicable Diseases Surveillance Centre (CDSC) was  $\geq 10$  per week and the Royal College of General Practitioners (RCGP) reports for consultation rates for combined 'epidemic influenza' and 'influenza-like illness' exceeded 150/100 000 population/week. Using these criteria epidemics were identified between 5 Dec 1989 and 2 Jan 1990, when the RCGP consultation rate ultimately exceeded 500/100 000 (a 'major' epidemic), and between 7 Nov 1993 and 5 Dec, when the RCGP consultation rate ultimately exceeded 200/100 000 (a 'moderate' epidemic). Inspection of the epidemic curves for both laboratory reports and consultation rates revealed more prolonged periods of influenza activity in England and Wales during the winters of 1989–90 and 1993–4 than those defined above; accordingly both epidemic periods were extended by a week either side for the purpose of the study.

### Cases and controls

Cases were Leicestershire residents on the Leicestershire Diabetes Register who were admitted from 28 Nov 1989 to 9 Jan 1990, or 31 Oct to 12 Dec 1993, to a hospital within the Trent Regional Health Authority with primary/principal *International Classification of Diseases 9th Revision (ICD-9)* discharge codes which should identify, with a high level of sensitivity but a lower level of specificity, hospitalizations for influenza and its complications in people with diabetes. These discharge codes were: 466, 480·8–483, 484·8–487, 490 and 491, to identify primary viral and bacterial pneumonia, and acute and chronic bronchitis, as used in other studies of non-diabetic people [20, 21]; and 250–250·2, 250·7, 250·9, to identify diabetes without mention of complications, keto-acidosis, or diabetic coma, specifically added by us.

Admissions with ICD codes identifying renal, ophthalmic, neurologic and vascular complications with diabetes and pneumonia caused by adenovirus, respiratory syncytial virus, parainfluenza virus, measles, cytomegalovirus, or chlamydia, and patients with whooping cough, aspergillosis or systemic mycoses were excluded.

The source of controls was the Leicestershire Diabetes Register which contained 4045 subjects during the first epidemic and 7487 subjects during the second. Two controls per case were selected at random from the register (using a random number generator) and were unmatched other than being diabetic during the epidemic for which they were matched. Until 1991 only individuals taking insulin were registered, and after that all diabetic individuals. By ensuring that cases and controls had to be registered at the time of the relevant epidemic comparability was maximized. For analysis, insulin-dependence was defined as 'diagnosis before age 30 and insulin treatment started within 12 months of diagnosis'.

### Consent

Ethical approval was obtained from the Leicestershire Committee on the Ethics of Clinical Research Investigation. Written consent to review the General Practice notes of cases and controls was sought first from general practitioners (GPs) and, on obtaining GP consent, from the subjects. Non-respondents were sent reminder letters 3 weeks later. GPs who did not respond to either letter were contacted by telephone 2 weeks later.

### Data collection

The GP notes of cases and controls were reviewed for information on age and sex; date of diagnosis of diabetes; presence of other chronic medical disorders at the beginning of the epidemic; number of consultations with general practitioners during the 12 months before the epidemic; and influenza vaccination during the 3 years before the epidemic. A person was considered to be appropriately immunized if they had received vaccine during the vaccination season immediately preceding the epidemic period. Previous vaccinees were vaccinated during either of the 2 years prior to the epidemic, but not during the vaccination season immediately prior to the epidemic. Non-vaccinees did not receive influenza vaccine during any of the 3 years prior to the epidemic. The WHO

recommendations for vaccines were A/Shanghai/11/87 (H3N2) in 1989 and A/Beijing/32/92 (H3N2) in 1993, which were similar to the influenza viruses isolated during the epidemics.

### Statistical analysis

Descriptive analyses were performed to compare the distribution of variables by case or control status. Variables with frequency distributions that were significantly different ( $P < 0.05$ ) between cases and controls were identified by Chi-square analysis and relative risks were estimated by crude odds ratios. Further analyses used multiple logistic regression. The purpose of the analysis was to estimate the relative risk of hospitalization for individuals vaccinated compared with individuals not vaccinated by calculating an adjusted odds ratio, adjusted to assess the effect of vaccination independent of confounding and modifying variables. The modelling strategy used was initially to fit a model including all variables of interest, i.e. the exposure of interest (current vaccination status), potential confounders (age, sex, epidemic year, type and duration of diabetes, comorbidity, number of GP consultations in the previous 12 months and number of admissions to hospital in the same period) and interactions of these variables (potential effect modifiers). The effects of interactions were assessed together, by removing all variable combinations reflecting interactions together and performing a likelihood ratio test. Effects of confounders were assessed individually, with reference to changes observed in the odds ratio for vaccination status when variables reflecting confounders were individually removed from the model. After checking regression diagnostics, the final model was considered to fit the data adequately and to be biologically plausible. Vaccine effectiveness was calculated as a percentage using the formula:  $100(1 - \text{odds ratio})$  [22]. Bivariate analyses were performed using SPSS/PC and multivariate analysis was performed using SAS.

### RESULTS

Eighty patients admitted under appropriate ICD-9 criteria were identified but GP notes were available for only 37. Diabetes in one hospitalized patient was first diagnosed after the epidemic and he was excluded from further analysis. Of 166 controls, general practitioner notes were available for only 77. Retrieval

Table 1. Characteristics of study subjects

Characteristic	Number (percentage)	
	Cases ( <i>n</i> = 37)	Controls ( <i>n</i> = 77)
Age		
≤ 19	6 (16)	9 (12)
20–44	8 (21)	17 (22)
45–64	17 (46)	28 (36)
65–74	4 (11)	17 (22)
75–85	2 (5)	6 (8)
Sex		
Male	22 (59)	42 (55)
Female	15 (41)	35 (45)
Duration of diabetes (years)		
≤ 9	17 (50)	38 (53)
10–19	11 (32)	21 (29)
≥ 20	6 (18)	13 (18)
Insulin dependence		
Yes	18 (49)	21 (27)
No	19 (51)	56 (73)
Chronic diseases		
None	6 (16)	12 (16)
Cardiovascular disease	16 (43)	37 (48)
Pulmonary disease	5 (14)	8 (10)
Renal disease	0	1 (1)
Endocrine disorders	1 (3)	2 (3)
Immunosuppression	0	0
Malignant disease	2 (5)	4 (5)
CNS disease	5 (14)	4 (5)
Peripheral nerve disorders	9 (24)	7 (9)
Musculoskeletal	11 (30)	28 (36)
Influenza vaccine received		
1989 or 1993	3 (8)	24 (31)
During preceding two seasons	3 (8)	7 (9)
Neither	31 (84)	46 (60)
	Median (range)	
GP consultations, previous 12 months	8 (0 to 46)	9 (0 to 26)
Hospital admissions, previous 12 months	0 (0 to 8)	0 (0 to 3)

of medical data for 42 cases and 89 controls was precluded by; non-registration with a general practitioner (2 cases and 6 controls), destruction of the records of deceased patients (6 cases), failure to obtain consent from the general practitioner (13 cases and 31 controls), failure to obtain patient consent (17 cases and 49 controls), and inability to retrieve case-notes and relevant information (4 cases and 3 controls). Of 37 cases, 32 (86%) were admitted for reasons of diabetic control, and only 5 had primary diagnostic codes for respiratory conditions.

Table 2. Evaluation of factors potentially influencing admissions for influenza-related illness in people with diabetes

Factor	Hospital admission	
	Adjusted odds ratio	95% confidence interval
Influenza vaccination in 1989 or 1993	0.21	(0.05–0.81)
Sex (F:M)	0.72	(0.31–1.67)
Age	1.01	(0.98–1.05)
Type of diabetes (IDDM:NIDDM)	2.98	(0.75–11.86)
Year of epidemic (1993:1989)	0.98	(0.41–2.36)
No. of GP consultations in previous 12 months	1.03	(0.97–1.09)

Table 1 shows the characteristics of study subjects. Cases and controls were comparable with respect to age, sex, duration of diabetes, co-morbidity, and the number of GP consultations during the previous 12 months, and the number of hospital admissions during the previous 12 months. Significantly more cases than controls had suffered from insulin-dependent diabetes mellitus than controls  $\chi^2$  (1 D.F. = 5.074),  $P = 0.024$ . Significantly fewer cases had been vaccinated than controls  $\chi^2$  (1 D.F. = 6.590),  $P = 0.01$ ; the crude odds ratio for hospital admission comparing those people with diabetes vaccinated during the immunization season immediately preceding the two epidemics with the rest, was 0.19 (95% CI 0.05–0.70), which gives an estimated vaccine effectiveness of 81% (95% CI 30–95%). The crude odds ratio for hospital admission comparing those people with diabetes vaccinated during either of the 2 years prior to the epidemic, but not during the vaccination season immediately prior to the epidemic with those who had not been vaccinated, was 0.64 (59% CI 0.15 to 2.65), i.e. there was no evidence of protection from previous vaccination.

Removal during multiple logistic regression modelling of all variable combinations reflecting interactions revealed no significant effect and all interaction terms were thereafter omitted from the model. In addition, duration of diabetes, co-morbidity and hospital admissions in previous 12 months were also removed from the model to yield the simplest model of good fit and biological plausibility (Table 2). The adjusted odds ratio for hospital admission

comparing patients vaccinated during the immunization season immediately preceding the epidemic compared with the rest was 0.21 (95% CI 0.05–0.81), which gives an estimated vaccine effectiveness of 79% (95% CI 19–95%). This is an estimate of the effect of vaccination, allowing for differences between cases and controls with respect to the other confounding variables in the analysis. In this model, vaccine effectiveness appears to be independent of sex, age, type of diabetes, year of epidemic, or number of GP consultations in the previous 12 months. For example, if IDDM individuals were three times more likely to be admitted than non-IDDM individuals, vaccine effectiveness would be the same for both groups in that the same proportion (e.g. 79%) in each group would be prevented. However, the number of IDDM admissions prevented would, in this case, be three times the number of NIDDM admissions prevented.

## DISCUSSION

The humoral immune response to influenza vaccination in people with diabetes does not differ from that observed in normal subjects [17–19], suggesting that influenza vaccine may be beneficial in this high risk group. Our study demonstrated significant vaccine effectiveness among people with diabetes during periods of peak virus circulation and peak consultations for ‘epidemic influenza’ and ‘influenza-like illness’. There have been no other protection studies of influenza vaccination in people with diabetes, but the estimated 79% reduction (95% CI 19% to 95%) in hospitalization for pneumonia, bronchitis, influenza, diabetes without mention of complications, diabetic coma, and ketoacidosis is in accord with North American case-controlled and cohort studies in the elderly [20, 21, 23–25]. These have shown that influenza vaccine reduces hospitalization for pneumonia and influenza by up to 80% (mean c. 40%), when vaccine and wild strains are antigenically similar. Moreover our estimate (79% CI 19–95%) of the effectiveness of influenza vaccine in reducing hospitalization in people with diabetes is compatible with the estimated protection rate of 41% in a case-control study of influenza vaccine in reducing mortality in England during the 1989–90 epidemic [26].

We did not examine vaccine effectiveness during a non-epidemic control period; however, we did evaluate protection from vaccination given during either of the 2 years before the epidemics, and found no

evidence of protection during the epidemics in 1989–90 and 1993. Conceivably the comparatively small study groups resulted in a Type II error, but the absence of a protective effect from vaccination given during the 2 years prior to the epidemics was anticipated since antigenic drift, requiring revision of the H3N2 components of vaccine in 1989 and 1993, occurred during both periods. The observed lack of effect of previous vaccination is in agreement with the findings of a case-control study of influenza vaccine in the elderly in England during the 1989–90 epidemic [26].

The outcome used in this study was hospitalization for pneumonia, bronchitis, influenza, diabetes without mention of complications, diabetic coma, and ketoacidosis. Of 37 cases 32 (86%) were admitted for reasons of diabetic control, and only 5 had primary diagnostic codes for respiratory conditions. It was not possible to establish whether any of these diabetes related admissions were actually the result of influenza. The study periods coincided with peak influenza activity, but it is probable that the criteria used for influenza-related admissions must have included cases that were not actually caused by influenza. The effect of this misclassification bias would be to diminish the estimate of vaccine effectiveness, so the estimate of its effectiveness in reducing hospital admissions is probably conservative.

The low response rates of 46.8% among cases and 48.1% among controls was primarily a consequence of requiring two levels of consent, and the individuals responding may not be representative of all diabetic individuals. However, it is unlikely that cases and controls differed systematically because of poor response because the response rates of GPs enabling us to contact their patients were good and virtually identical for both cases and controls (78.6 vs. 79.6%), and the response rates of cases and controls were also similar (64.6 vs. 59.5%). We therefore believe that the higher immunization rate in controls is genuine, and does not reflect a more enthusiastic response by those GPs or patients with the higher immunization rates. In the UK influenza vaccine is almost wholly provided by patients' general practitioners and is available only by prescription. Under-reporting of administration of vaccine has potential medico-legal implications, and we believe that this is no more likely to occur in cases than in controls.

Similar problems of multi-level consent have occurred in other general practice based studies in our Department (personal communications) and have

been reported from elsewhere [27]. Strictly speaking, there may have been no need to contact patients in this study if guidelines issued by the Department of Health [28] had been operative at the time in that they recommend that patient consent is not needed for notes-based research. In addition the new draft by the Council of the European Union of its European Directive on 'protection of individuals with regard to the processing of personal data and on the free movement of data' also states that written consent is not always required when accessing data if, for example, the data are to be used for Public Health reasons [29]. Implementation of such recommendations would facilitate the undertaking of a larger study of vaccine effectiveness which would yield a more precise estimate of effectiveness.

Although our study focused on epidemics during 1989–90 and 1993, virological surveillance reveals annual influenza outbreaks which make substantial contributions to increases in respiratory morbidity and mortality each winter [30]. The importance of influenza in patients with diabetes has been highlighted by several recent studies on deaths and hospitalization, indicating that even during the era of improved diabetic control, acute respiratory infections can be life-threatening. Endocrine deaths (mostly diabetic) increased by about 1350 (i.e. by 30%) in England, Wales and Scotland during the 1989–90 epidemic, as compared with 1985–6 [31]. Older onset diabetics are 1.7 times more likely to die from pneumonia and influenza as compared with the general population, and 1 in 33 die from these conditions overall [32]. During epidemics in 1976 and 1978, national hospital admissions in Holland for influenza were six times more common among diabetics than controls with duodenal ulcer, and admissions for ketoacidosis increased by 50% in 1978, as compared with years with low influenza activity. During the 1978 epidemic, one out of every 1300 patients with diabetes mellitus was hospitalized because of pneumonia. The Dutch investigators estimated that one of every 260 patients with insulin dependence was hospitalized for diabetic acidosis during the epidemic and they concluded that patients with diabetes have a very high influenza-associated morbidity.

Because diabetes is common, especially among the elderly, a 19–95% reduction in hospital admissions and related costs of medical consultations, drugs, transportation and sickness benefit could lead to a substantial reduction in health costs, and benefit

patients. Our results support the current UK guidelines for annual vaccination of patients at high risk of influenza complications including people with diabetes.

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