Reduction in hospital admissions for pneumonia in non-institutionalised elderly people as a result of influenza vaccination: a case-control study in Spain

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Abstract

Objective—To estimate the effectiveness of influenza vaccine in preventing hospital admission for pneumonia in non-institutionalised elderly people.
Design—This was a case-control study.
Setting—All three public hospitals in the Castellón area of Spain.
Participants—Cases were people aged 65 or more not living in an institution who were admitted to hospital for pneumonia between November 15, 1994 and March 31, 1995. Each case was matched with two sex matched control subjects aged 65 years or older admitted to hospital in the same week for acute abdominal surgical conditions or trauma. The sampling of incident cases was consecutive. Eighty three cases and 166 controls were identified and included in the study.
Measurements—Trained interviewers completed a questionnaire for each subject on the vaccination status, smoking habits, previous diseases, health care use, social contacts, family background, the vaccination status of the family carer, home characteristics, and socioeconomic status.
Results—The adjusted odds ratio of the influenza vaccination preventing admission to hospital for pneumonia was 0.21 (95% confidence interval 0.09, 0.55). The variables which best explained the risk of being a case were age, intensity of social contacts, health care use, previous diseases, and the existence of a vaccinated family carer.
Conclusions—Influenza vaccination reduced significantly hospital admissions for pneumonia in non-institutionalised elderly people.

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Influenza is a considerable public health problem. Coexistent with periods of influenza virus circulation there have been reports of significant increases in hospitalisation rates, adjusted by gender and age, for pneumonia, influenza, acute bronchitis, chronic respiratory diseases, and congestive heart diseases.[1][2] Influenza virus circulation is accompanied by an excess mortality, 80% of which occurs in those aged 65 years or older.[3][4] For these reasons yearly influenza immunisation has been recommended in predetermined high risk groups.[5]

Although influenza vaccine has been available for more than five decades, its acceptance in Spain has been slow,[6] as well as in other countries. There are several reasons for this:
• The need for seasonal vaccination,
• Concern about side effects,
• Conflicting evidence of the vaccine's effectiveness in the elderly because there had been no clinical trials in this age group until recently, and most observational studies have shown contradictory findings and weaknesses.[7–9]

Two recent meta-analyses[10][11] on vaccine efficacy in preventing hospital admission for pneumonia in the elderly showed that some of the observational studies performed between 1980 and 1994 had been conducted in populations with low vaccination rates, showed difficulties in defining precisely an adequate study base, or did not include enough subjects with the consequence that they lacked statistical power to reach useful conclusions. These factors may have hampered their ability to show conclusive results and have contributed to the uncertainty about the benefits of influenza vaccination. The reported estimates of vaccine efficacy for preventing hospital admission for pneumonia were similar in both meta-analyses, ranging from 32% to 45%.

The scientific evidence for the effectiveness of interventions is increasing through the accumulation of consistent results in different geographical areas and populations.[12] We have aimed to make a contribution by exploring the impact of vaccination in preventing admission to hospital for pneumonia in people aged 65 years and over living outside institutions.

Methods

The study was conducted in the three public hospitals in the Castellón area of Spain. This area has a reference population of 349 318 inhabitants, of whom 52 015 were 65 years old or older.

IDENTIFICATION OF CASES
Consecutive sampling of incident cases was performed.[13] All those people aged 65 years or older who were admitted to the three hospitals via the emergency services between November 15, 1994 and March 31, 1995; who had been

living for at least six months in any of the municipalities of the Castellón area; and who had a clinical diagnosis of pneumonia supported by radiological images of lung condensation were identified through a systematic daily search of the emergency logs and records of the three hospitals. Later, in order to confirm that the clinical plus radiological diagnoses corresponded to pneumonia, the clinical records were screened for verification by one of the researchers. Criteria for verification were the radiologist's report (not available in the emergency service) and the clinical evolution of the disease. In case of doubt, the attending physicians were contacted and they decided upon the diagnosis. Only after this whole process had been completed was a patient included as a case subject.

SELECTION OF CONTROLS

Each case was matched by gender, hospital, and week of admission with two controls. Controls were identified and included in the study following the same procedures described for the cases. It was assumed that the patients admitted as emergencies in the same hospitals in which the cases had been admitted were members of the same study base, and that this fact made them comparable to the cases in their chances of being hospitalised.[14-16] Inclusion criteria for controls were: age 65 years old or older, having the same gender as the case, admission to hospital as close as possible in time to the case,[17] preferably the same day or at least within a seven day interval, and admission for an acute abdominal surgical condition or trauma.

DATA COLLECTION

Trained interviewers completed a structured questionnaire with the assistance of the patient, or the family carer, while the patient was in hospital. A subject was considered vaccinated if they, the family carer, or both, said that a dose of vaccine had been administered, if it had been administered at least 15 days earlier than the patient's admission to hospital and if the patient, the family carer, or both, remembered the month, the place, and the kind of health professional who had administered the influenza vaccine.

Information was collected on previous chronic diseases (cardiopathy, respiratory tract disease, and diabetes), smoking history, vaccination status of the usual family carer, living arrangements, level of home equipment (bathroom, washing machine, telephone, heating, elevator, television, video), level of social interaction (varying from "always at home" to "going out daily and having social relationships"), the number of previous contacts with primary health care services in the past three months, and the number of hospital admissions during the past 12 months.

The protocol was approved by the investigation committees of the participating hospitals.

STATISTICAL ANALYSIS

A descriptive analysis of the distribution of the characteristics between cases and controls was

KEY POINTS
- The risk of being admitted to hospital for pneumonia increased with age between 70 and 79, and with intense social contacts, diabetes, chronic obstructive pulmonary disease, and the existence of a family carer who had been vaccinated.
- Influenza vaccination is effective in preventing the admission to hospital for pneumonia of people aged 65 or more who are not living in an institution.
- In this series, if elderly, unvaccinated people had received the vaccine they would have reduced their risk of being admitted to hospital for pneumonia by 79%.

performed. The differences were evaluated using χ^2 statistics, and crude exposition matched odds ratios were calculated using a bivariate conditional logistic regression. Ninety five per cent confidence intervals were estimated using the standard errors.[18]

A conditional logistic regression model for matched data was used to adjust for confounding factors, effect modification, and interaction terms.[19 20] The criteria[21 22] used in order to build the regression model were that the influenza vaccination status had to be present in any of the possible adjusted models, and those variables whose score test had a p value ≤ 0.25 when systematically and jointly compared with the model that already included previous selected variables, were sequentially introduced in the model one by one.

Influenza vaccination odds ratios, given the sampling method (incident cases), provided an estimation of the relative risk (RR).[23] Population impact was estimated as the preventable fraction of the disease due to vaccination: $(1-RR)*100$.[24]

The absolute reduction in admissions to hospital for pneumonia as a result of influenza vaccination in our study context was estimated through the difference between the cumulative incidence in the exposed (p1) minus the cumulative incidence in the non-exposed (p2).[25] Both parameters were estimated from the cumulative incidence in the general population (p). The percentage of population vaccinated (e) was assumed to be that observed in the controls.[14] Thus $p2=p/(RR*e+(1-e))$ and $p1=RR*p2$.

Results

RESPONSE AND POPULATION CHARACTERISTICS

During the study period 94 emergency hospital admissions for pneumonia were identified. Of these, four were institutionalised elderly people and one was residing outside the study region. Of the 89 remaining cases, 2 (2.25%) declined to participate and in 4 cases (4.49%) it was not possible to identify any control who had been admitted to hospital within seven days of cases. With regard to the 83 remaining cases, 166 matched controls were identified and included (no control refused to participate).

Table 1   Baseline characteristics of study subjects

Characteristic	Controls (n=166) %	Cases (n=83) %	p value
Background:			
Urban	40.4	42.2	
Semiurban	42.2	41.0	
Rural	17.5	16.9	0.963
Age group:			
65–69	18.1	13.3	
70–74	24.7	19.3	
75–79	17.5	34.9	
≥80	39.8	32.5	0.023
Female sex	42.2	42.2	1

$*\chi^2$ with k-1 degrees of freedom.

Cases did not differ from controls in respect of urban area of residence. Differences were observed in the age distribution (table 1)—cases being more numerous in the 75 to 79 years age group (p=0.023).

Fewer cases (3.5%) than controls (12.7%) had central heating in their houses (table 2). A larger percentage of cases (53%) were current smokers or past smokers than controls (44.6%), with a matched odds ratio (OR) of 3 ;95% CI 1.0, 7.4. Cases mentioned more frequently than controls the presence of previous cardiac diseases (matched OR 2.2; 95% CI 1.2, 4.0), chronic obstructive pulmonary disease (matched OR 5.8; 95% CI 3.1, 11.1), and diabetes (matched OR 3.5; 95% CI 1.6, 7.5) (table 2).

There were no significant differences in the number of times previously cases and controls had used of primary care health services or in

Table 2   Distribution of risk and protection factors between cases and controls. Crude matched odds ratios (95% confidence intervals) of being a case

Risk/protection factors	Controls (n=166) (%)	Cases (n=83) (%)	Odds ratio (95% CI)
Socioeconomic factors:			
House equipment (high v low)	27.7	25.3	0.9(0.5, 1.6)
House has central heating	12.7	3.6	0.3(0.1, 0.9)
Lived in its own home (v otherwise)	27.1	22.9	0.8(0.4, 1.5)
Lived alone	9.0	10.8	1.3(0.5, 3.4)
Family carer has received this season influenza vaccine	45.2	51.8	1.3(0.8, 2.2)
Gets outdoors everyday an shares activities with pairs	50.0	51.8	1.1(0.6, 1.8)
Smoking history:			
Smoker or ex-smoker	44.6	53.0	3.0(1.0, 7.4)
Comorbidity:			
Cardiopathy	27.1	42.2	2.2(1.2, 4.0)
Chronic obstructive pulmonary disease	23.5	63.9	5.8(3.1, 11.1)
Diabetes	8.4	24.1	3.5(1.6, 7.5)
Previous use of health care services:			
Two or more contacts with primary health care services (v one or none)	79.5	88.0	1.8(0.9, 3.9)
Hospitalised in last 12 months	25.3	32.5	1.5(0.8, 2.6)
Has received this season's influenza vaccine?			
Yes	61.4	56.6	0.8(0.5, 1.4)

Table 3   Estimated effect of influenza vaccination* and of the rest of risk factors in cases compared with matched controls

Risk factor	Odds ratio†	(95% CI)
Influenza vaccination	0.21	(0.08, 0.55)
Age 70–74	2.11	(0.62, 7.21)
Age 75–79	5.57	(1.65, 18.83)
Age ≥80	1.72	(0.54, 5.47)
Family carer has received influenza vaccine	2.71	(1.16, 6.33)
Goes outdoors and socialises	2.58	(1.18, 5.66)
Cardiopathy	2.08	(0.86, 5.05)
Chronic obstructive pulmonary disease	10.82	(4.50, 26.04)
Diabetes	6.32	(2.22, 18.03)
Two or more contacts with primary health care services	2.85	(0.99, 8.20)

*Through a conditional logistic regression model.
†Adjusted odds ratios.

the number of hospital admissions in the past 12 months (table 2).

Vaccination levels were not statistically different between cases (56.6%) and controls (61.4%), with a matched OR of 0.8; 95% CI 0.5, 1.4.

INFLUENZA VACCINE EFFECTIVENESS

A regression model was -built to adjust for the effect of those confounding factors that were influencing the probability of being vaccinated and of suffering an emergency hospital admission for pneumonia, or which acted as effect modifiers (table 3). Age, chronic obstructive pulmonary disease, diabetes, vaccination status of the family carer, and the level of social contacts were significantly associated with the risk of an emergency admission, and either confounded or acted as effect modifiers of the estimated influenza vaccination main effect; whereas use of health care services showed a marginally non-significant confounding effect.

Previous cardiopathy showed a tendency to be a risk factor, with a statistical significance of p=0.106 and an adjusted OR of 2.08 (95% CI 0.86, 5.05).

Age behaved in a non-linear fashion, showing an inverted "U" shaped effect (table 4), essentially due to those over 79 years of age who had similar levels of risk of being a case (adjusted OR 1.72; 95% CI 0.54, 5.47) as those aged 65 to 69 (reference level, OR equal to 1).

The possible interaction terms examined did not contribute to a better explanation of the influenza vaccination effect, with the exception of the interaction term between having diabetes and the vaccination status of the family carer. However, this interaction was not included in the results because it made the final model less parsimonious and numerically stable.

Influenza vaccination protected significantly those vaccinated, with an adjusted OR estimate for influenza vaccination of 0.21 and a 95% CI of 0.08, 0.55.

PREVENTED FRACTION

If the unvaccinated elderly had received the vaccine, they would have seen their risk of admission to hospital with pneumonia reduced by 79% (95% CI 45, 92) (table 5). During the study period the cumulative incidence of pneumonia emergency hospitalisations was 1.7 admissions for 1000 individuals 65 years old or older, being the cumulative incidence of 0.7 admissions for 1000 in those vaccinated and of 3.3 admissions for 1000 in those not vaccinated. The number of pneumonia emergency admissions prevented by the vaccine, given the level of vaccination in our study context, were 2.6 per 1000 people aged ≥ 65 years.

Discussion

Our results are consistent with other recently published studies,[26][27] and support the evidence for the effectiveness of vaccination in preventing influenza and its ability to reduce considerably the number of hospital admissions among the non-institutionalised elderly. The present

Table 4 Age performance in the adjusted model*

Age interval	65-69	70-74	75-79	≥80
Mean	67.1	71.5	76.9	85.0
No of subjects	41	57	58	93
Percentage of cases	26.8	28.1	50.0	29.0
Odds ratio†	1	2.11	5.57	1.72
(95% CI)	—	(0.62, 7.21)	(1.65, 18.83)	(0.54, 5.47)

*Age behaviour was significantly non-linear. When age was introduced in the model following Box-Tidwell transformation[22] (age in years*ln(age in years)), the estimated coefficient for age resulted in a significant Wald's test (p=0.03). For this reason age was included in the model as a categorical variable.
†As they are estimated in the final model (table 3).

Table 5 Percentage of admissions to hospital for pneumonia prevented by influenza vaccination. Number of pneumonia hospitalisation prevented given the vaccination rates observed in the study per 1000 subjects aged 65 years or older vaccinated

	Estimated value (%)	(95% CI)
Prevented admissions to hospital	79.0	(45.0, 92.0)
Emergency hospital admissions for pneumonia prevented per 1000 aged ≥65y vaccinated*	2.6	(1.1, 3.6)

*Identified cases, 89; elderly population (≤65 and older), 52015; estimated elderly vaccinated (e) 61.4%. Cumulative incidence of emergency hospitalisation for pneumonia in non-vaccinated elderly (p2), 3.32 per 1000. Cumalitive incidence in those vaccinated (p1), 0.69 per 1000. See methods for calculations.

Table 6 Interaction effect* between the presence of an influenza-vaccinated family carer and having diabetes on the risk of admission to hospital for pneumonia in the study subjects

	Influenza-vaccinated family carer Adjusted odds ratio (95% CI)	
Diabetes	No	Yes
No	1	4.3 (1.6, 12)
Yes	29.4 (4, 218)	0.12 (0.01, 1.1)

*Odds ratio of being a case for a diabetic with a vaccinated family carer v being diabetic and a nonvaccinated family carer: (4.3*0.12*29.4/29.4)=0.52. When this interaction term was introduced in the final model (table 3) the likelihood ratio statistic with 1 degree of freedom was 3.76; p=0.05.

study has some advantages over other previous case control studies.[28-34]

In the first place, our study has been conducted in a context in which the vaccination levels were high (greater than 60%) and the population size was considerable. Secondly, we examined the effect of some factors which have not been evaluated in previous studies and which showed a strong confounding effect. These were the level of social interactions and of other variables that probably behaved as surrogates of a severe degree of comorbidity - primary health care services and family carer vaccination status. In addition, our controls were not elective admissions. This aspect improved their comparability to the cases in respect of their experience of access to health care, preventing a potential bias produced by a different hospitalisation probability between cases and controls.

The exhaustive incidence density sampling used in our study accounted for the representativeness of the identified cases from our actual population of potential cases, and the OR was a good estimator of the risk ratio.[23]

It is not possible in our study to reject the existence of a non-differential classification bias due to the low specificity of the pneumonia diagnosis in respect of its influenza infection origin. Yet this bias would undervalue the estimated protector effect of influenza vaccination, because some non-cases would have been classified as cases. This situation strengthens the results obtained in this study.

With regard to the selection of cases and controls, they were chosen before any knowledge of their vaccination status had been obtained, and because of this selection bias by exposure was avoided. Vaccination status was ascertained after inclusion in the study by four highly structured items in the questionnaire. There is evidence that the level of recollection of influenza vaccination is high.[35] In our study, 100% of those who said that they had received the influenza vaccine could recall the month, the place, and the kind of health professional who had administered it. This lessens the possible information bias as far as the exposure to the vaccine is concerned. Moreover, our response rate in comparison with other recently published studies was high.[33 34] In addition, we were able to distinguish between vaccination and the effect (emergency pneumonia hospitalisation), as a latency period of 15 days from the time of vaccination to hospitalisation was established before an individual could be regarded as vaccinated.

In the final logistic model the factors that met the specified inclusion criteria were: influenza vaccination, previous chronic diseases, age (in five year intervals), vaccination status of the family carer, level of previous contacts with primary health care services, and the level of social interactions.

Chronic obstructive pulmonary disease and diabetes were the two risk factors that made a major contribution to the probability of being a case in our study, independently of the rest of the measured variables.

The "U" shaped age behaviour could be attributed to a selection of healthier subjects with less comorbidity who therefore reached older ages or to the fact that those elderly who were healthier had, in our study base, more chance of being admitted to hospital. In fact, the existence of previous comorbidity was significantly higher (p=0.026) in subjects aged 75 to 79 years age (70.7%) than in those 80 years old or older (54.8%).

The vaccination status of the family carer was a strong and significant confounder of the estimated effect of influenza vaccination. The vaccination status of the family carer seemed to be acting as an indicator of the severity of any underlying previous diseases in the study subjects. It added information about this circumstance, which was not measured as we categorised comorbidity as a dichotomous variable (present or not). Vaccination of the family carer could happen more frequently in those individuals for whom the perception of risk was high. Thus, the vaccination of the family carer was more usual in the family carers of diabetics (64.7%) than in those without this condition (55.3%), and in the family carers of those with cardiopathy (51.3%) than in those without this disorder (45.6%). All these facts reinforce our assumption that this factor behaved as a surrogate of the gravity level of the underlying disorder.

In addition, if we forced the model introducing the interaction term between being diabetic

and the vaccination status of the family carer, the risk of being admitted to hospital for pneumonia was substantially reduced. The adjusted OR of the protection conferred to a diabetic subject by a vaccinated family carer versus an unvaccinated family carer was 0.52 (table 6). However, when the interaction term was introduced into the model it became numerically unstable. As our goal was to estimate the main effect of influenza vaccination and not to predict the risk of being a case, we opted for its exclusion from the final model.

The level of social interaction behaved, as was expected, as a risk factor as it increased the probability of contagion. Influenza activity was documented in Spain from October 1994 until March 1995. Influenza A(H3N2) virus was reported as the predominant cause of influenza and the match between the vaccine composition and the circulating influenza virus strains was reported as similar.[36]

It can be concluded that influenza vaccination is an effective public health strategy as it significantly reduces the number of pneumonia hospitalisations in the non-institutionalised elderly. Future efforts should be directed towards the continuous monitoring of vaccine effectiveness[37] and assuring elderly access to influenza vaccination.[38-41]

Conflicts of interest: none.

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