Influenza Vaccine Effectiveness in Preventing Outpatient, Inpatient, and Severe Cases of Laboratory-Confirmed Influenza

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Background. In most seasons, the influenza vaccine is effective in preventing influenza, but it is not clear whether it is equally effective in preventing mild and severe cases. We designed a case-control study to compare the effectiveness of the influenza vaccine in preventing outpatient, inpatient, and severe or fatal cases of laboratory-confirmed influenza.

Methods. Hospitalized patients (n = 691) with laboratory-confirmed influenza in the 2010–2011 season recruited in 29 Spanish hospitals were individually matched by age, admission/visit date, and province with an outpatient with laboratory-confirmed influenza and an outpatient control. Severe cases were considered those patients admitted to intensive care units or who died in the hospital (n = 177). We compared the influenza vaccine status of controls and outpatient cases, inpatient cases, and severe cases using conditional logistic regression adjusted for potential confounding factors. Severe and nonsevere inpatient influenza cases were compared using unconditional logistic regression. Vaccine effectiveness was (1 – odds ratio) × 100.

Results. Vaccine effectiveness was 75% (adjusted odds ratio [AOR], 0.25; 95% confidence interval [CI], .16–.39) in preventing influenza outpatient cases, 60% (AOR, 0.40; 95% CI, .25–.63) in preventing influenza-associated hospitalizations, and 89% (AOR, 0.11; 95% CI, .04–.37) in preventing severe cases. In inpatients, influenza vaccination was associated with a lower risk of severe influenza (AOR, 0.42; 95% CI, .22–.80).

Conclusions. Influenza vaccination prevented influenza cases and hospitalizations and was associated with a better prognosis in inpatients with influenza. The combined effect of these 2 mechanisms would explain the high effectiveness of the vaccine in preventing severe cases due to influenza.

Keywords. influenza virus; influenza vaccine; vaccine effectiveness; severe influenza.

Influenza affects a significant percentage of the population annually and is associated with excess hospitalizations and mortality [1, 2]. In some people, influenza evolves to serious forms or worsens preexisting chronic conditions and requires hospitalization [3].

Vaccination is the main influenza prevention strategy. In most seasons, influenza vaccination is effective in preventing outpatient cases of laboratory-confirmed influenza [4–11], influenza-associated hospitalizations [12–18], and medically attended influenza in general [19–23]. However, there is little information on the differences in vaccine effectiveness between mild and severe cases.

Studies of influenza vaccine effectiveness in preventing all-cause deaths have generally obtained higher estimates

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than expected given the observed effectiveness against confirmed influenza cases [24]. For this reason, and also due to possible biases, these findings have raised some suspicion [25, 26], which makes new studies evaluating the effect of influenza vaccination in preventing serious cases and deaths due to laboratory-confirmed influenza necessary. Severe cases and deaths may be avoided by preventing influenza or by the contribution of vaccination in reducing complications or the worsening of the illness in people with influenza. However, it is not clear whether people in whom vaccination fails to prevent influenza have a different prognosis than nonvaccinated people with influenza.

The aim of this study was to assess and compare the effect of influenza vaccination in preventing outpatient visits, hospitalizations, and severe or fatal cases of laboratory-confirmed influenza. We also analyzed whether vaccination affects the severity of influenza cases.

METHODS

Study Population and Design

We carried out a matched case-control study with density sampling in 29 hospitals and their respective primary healthcare centers from 7 Spanish regions (Andalusia, the Basque Country, Castile and Leon, Catalonia, Madrid, Navarre, and Valencia Community) in the 2010–2011 season.

In Spain, the trivalent inactivated influenza vaccine was recommended and offered free of charge to people aged ≥65 years (≥60 in some regions) and to those with major chronic conditions. Other people can also be vaccinated if they pay for the vaccine. In all participant hospitals, patients admitted with influenza-like illness or acute respiratory disease were routinely swabbed for diagnosis. In the province where these hospitals are located, sentinel primary healthcare general practitioners take swabs from a systematically selected sample of outpatients with influenza-like illness according to the European case definition [27]. Swabbing criteria do not take into account the severity of patients or the vaccination status.

Patient Recruitment

Inpatient cases were patients admitted >24 hours to participating hospitals between October 2010 and April 2011 with influenza-like illness or acute respiratory infection, with influenza infection confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal flocked swabs or nasopharyngeal wash collection. We excluded children aged <6 months, patients receiving antiviral treatment prior to hospitalization, and patients who had nosocomial infection, defined as influenza appearing ≥48 hours after admission for another cause.

We selected 4 matched subjects for each inpatient case. Two were outpatients attending primary healthcare centers: 1 who sought consultation for influenza that was confirmed by RT-PCR (outpatient case) and 1 who consulted for any reason other than influenza-like illness or acute respiratory infection (outpatient control). In addition, we selected 2 patients with unplanned hospital admission for reasons other than acute respiratory infection, influenza-like illness, septic shock, or multiple organ failure (inpatient controls). Inpatient controls and outpatient cases and controls were matched with each inpatient case according to age (±3 years in people aged <18 years and ±5 years in people aged ≥18 years), date of hospitalization or visit (±10 days), and the province of residence. Of the potentially eligible persons, we chose those who were closest in terms of the date of hospitalization and consultation. Occasionally, we recruited >1 patient who met the matching criteria for the same inpatient case and these were included in the analyses.

In inpatient cases, severe cases were defined as patients admitted to the intensive care unit (ICU) or who died in the hospital.

The study was approved by the ethics committees of the hospitals involved. Written informed consent was obtained from all patients included in the study.

Data Collection

Specifically trained health professionals used a structured questionnaire to collect information on cases and controls by interview and review of medical records. This information included sociodemographic variables, current smoking, pregnancy, major chronic conditions, unplanned hospitalization in the previous 12 months, bed confinement in the 7 days before hospitalization or medical visit, and other preexisting risk factors for complicated influenza. The following major chronic conditions that are an indication for influenza vaccination were recorded: chronic respiratory disease, asthma, cardiovascular disease, chronic renal disease, diabetes mellitus, immunodeficiency, neurologic disease or disability, neoplasia, chronic liver disease, rheumatologic disease, and body mass index ≥40 kg/m^2. Other factors related to influenza complications were: pneumonia in the previous 2 years and systemic or inhaled corticoids.

Information on vaccination status, including the 2010–2011 seasonal trivalent influenza vaccine, monovalent influenza A (H1N1)pdm09 vaccine, 23-valent polysaccharide pneumococcal vaccine, and any of the pneumococcal conjugate vaccines, was obtained from medical records or vaccination cards. Cases were considered vaccinated if they had received a dose of the vaccine at least 14 days before symptom onset. Controls were considered vaccinated if they had received the dose at least 14 days before symptom onset in the matched case.

Statistical Analysis

We estimated the effectiveness of vaccination in preventing 3 main outcomes in patients with laboratory-confirmed influenza. Outpatient controls were considered the reference group and were compared with (1) outpatient cases, to estimate vaccination

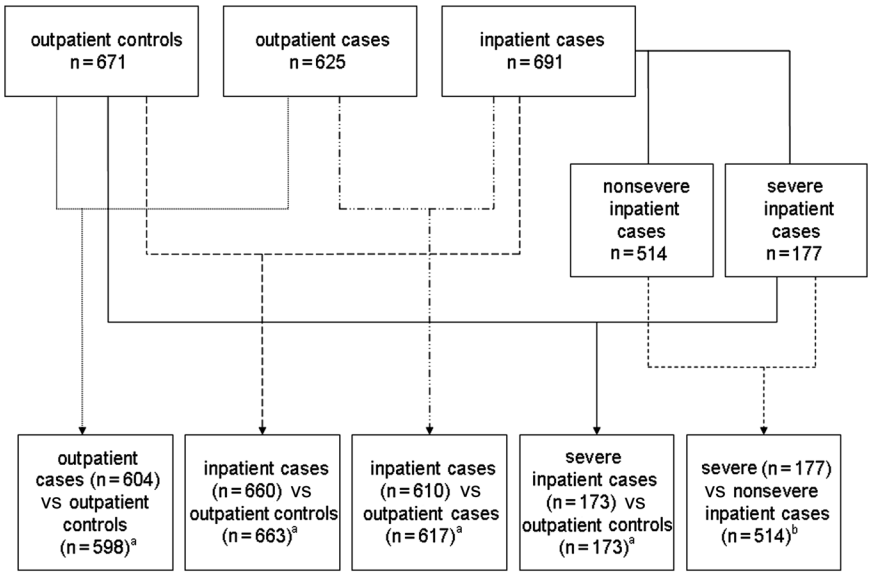

Figure 1. Scheme of the main study groups and the comparisons made. [a]Matched comparison. [b]Unmatched comparison.

effectiveness in preventing medically attended influenza; (2) inpatient cases, to estimate effectiveness against influenza-related hospitalizations; and (3) severe inpatient cases, to estimate vaccine effectiveness in preventing influenza-related admissions to ICUs and deaths. In the sensitivity analysis, objectives 2 and 3 were also evaluated by comparison with inpatient controls. Additionally, inpatient cases were compared with outpatient cases, and severe inpatient cases were compared with nonsevere inpatient cases to assess vaccine effectiveness in preventing complications and disease progression in patients with influenza (Figure 1).

Matched odds ratios (ORs) for vaccination, with their 95% confidence intervals (CIs), were calculated using conditional logistic regression models adjusted for potential confounding. Analyses including inpatient cases were also adjusted for pneumococcal vaccination. Matched groups lacking the outpatient case or control were excluded from the corresponding analyses.

Severe inpatient cases and nonsevere inpatient cases with confirmed influenza, which were not matched groups in the study design, were compared using unconditional logistic regression adjusted for the covariates mentioned, by age group (<5, 5–14, 15–44, 45–64, and ≥65 years) and by hospital (Figure 1).

To rule out possible confounding due to the type of influenza virus, the analyses were repeated for patients with influenza A (H1N1)pdm09 and their respective controls. We also performed separate analyses in people aged ≥65 years versus the remaining patients.

Bivariate comparisons were made using the χ^2 test or Student *t* test. Vaccine effectiveness was calculated as (1 − OR) × 100.

RESULTS

A total of 857 inpatients with confirmed influenza were considered for the study. Seventeen patients were excluded because influenza was acquired after hospital admission, 148 because they did not give consent to participate, and 1 because he or she had received antiviral treatment before admission. Therefore, 691 inpatients with confirmed influenza ("inpatient cases") were finally matched with 625 outpatients ("outpatient cases") with confirmed influenza, 671 outpatient controls, and 1326 inpatient controls. Of inpatient cases, 93% (n = 646) were due to influenza A(H1N1) pdm09 and the remainder to influenza B (n = 45), whereas all outpatient cases were caused by influenza A(H1N1)pdm09.

Despite matching, outpatient cases were slightly younger than outpatient controls and inpatient cases. Pregnancy, pneumonia in the previous 2 years, and lack of influenza vaccination were more frequent among inpatient and outpatient cases. Current smoking was more frequent among inpatients cases and controls. Bed confinement 7 days before admission or medical visit, corticoid treatment, unplanned hospitalization in the previous 12 months, major chronic conditions, and pandemic influenza vaccination in the 2009–2010 season were more frequent in inpatient cases (Table 1 and Supplementary Table 1).

In the comparison of outpatient cases and outpatient controls using conditional logistic regression adjusted for the covariates mentioned, estimated vaccine effectiveness was 75% (adjusted OR [AOR], 0.25; 95% CI, .16–.39) in preventing outpatient cases with confirmed influenza. Comparison of inpatient cases with outpatient controls showed a vaccine effectiveness of 60% (AOR, 0.40; 95% CI, .25–.63) in preventing

Table 1. Characteristics of Cases and Controls

Characteristic	Outpatient Controls (n = 671)	Outpatient Cases (n = 625)	*P* Value[a]	Inpatient Cases (n = 691)	*P* Value[b]
Age group			<.001		.602
0–17 y	111 (16.5)	157 (25.1)		125 (18.1)	
18–64 y	431 (64.2)	430 (68.8)		426 (61.6)	
≥65 y	129 (19.2)	38 (6.1)		140 (20.3)	
Female	368 (54.8)	311 (49.8)	.076	291 (42.1)	<.001
Pregnant women	12 (1.8)	28 (4.5)	.005	36 (5.2)	.001
Current smoker	126 (18.8)	119 (19.0)	.904	171 (24.7)	.008
Hospitalization in previous 12 mo	58 (8.6)	46 (7.4)	.395	205 (29.7)	<.001
Confined to bed	1 (0.1)	5 (0.8)	.085	42 (6.1)	<.001
Major chronic conditions					
Chronic respiratory disease	17 (2.5)	14 (2.2)	.730	94 (13.6)	<.001
Asthma	42 (6.3)	39 (6.2)	.989	61 (8.8)	.073
Cardiovascular disease	45 (6.7)	27 (4.3)	.061	107 (15.5)	<.001
Chronic renal disease	14 (2.1)	20 (3.2)	.210	63 (9.1)	<.001
Diabetes mellitus	58 (8.6)	20 (3.2)	<.001	105 (15.2)	<.001
Immunodeficiency	8 (1.2)	31 (5.0)	<.001	93 (13.5)	<.001
Neurologic disease	13 (1.9)	12 (1.9)	.982	45 (6.5)	<.001
Neoplasia	32 (4.8)	28 (4.5)	.805	95 (13.7)	<.001
Chronic liver disease	8 (1.2)	9 (1.4)	.695	42 (6.1)	<.001
Rheumatologic disease	20 (3.0)	10 (1.6)	.099	30 (4.3)	.182
Body mass index ≥40 kg/m^2	2 (0.3)	0 (0.0)	.172	15 (2.2)	.002
No. of major chronic conditions			.034		<.001
0	488 (72.7)	489 (78.2)		267 (38.6)	
1	129 (19.2)	87 (13.9)		215 (31.1)	
> 1	54 (8.0)	49 (7.8)		209 (30.2)	
Other risk factors for complications					
Pneumonia in previous 2 y	23 (3.4)	38 (6.1)	.024	78 (11.3)	<.001
Corticoid treatment	50 (7.5)	39 (6.2)	.389	196 (28.4)	<.001
Pandemic influenza vaccine 2009–2010	36 (5.4)	25 (4.0)	.246	73 (10.6)	<.001
Seasonal influenza vaccine 2010–2011	139 (20.7)	46 (7.4)	<.001	105 (15.2)	.008
Pneumococcal vaccination	118 (17.6)	94 (15.0)	.216	109 (15.8)	.370

Data are presented as No. (%) unless otherwise specified.

[a] Comparison of outpatient cases and outpatient controls.

[b] Comparison of inpatient cases and outpatient controls.

influenza-associated hospitalizations (Figure 2). However, vaccination had no appreciable effectiveness in preventing hospital admission of influenza cases when inpatient cases were compared with outpatient cases (AOR, 1.53, 95% CI, .86–2.72). The adjusted comparison between severe inpatient cases and outpatient controls showed that vaccination effectiveness increased to 89% (AOR, 0.11; 95% CI, .04–.37; Table 2).

In the sensitivity analysis using inpatient controls as the comparison group, the estimated vaccine effectiveness was 57% (AOR, 0.43; 95% CI, .29–.62) in preventing influenza-associated hospitalizations and 72% (AOR, 0.28; 95% CI, .12–.62) in preventing severe inpatient cases of influenza (Supplementary Table 2).

Repetition of the analyses including only cases of influenza A(H1N1)pdm09 showed similar results. The inclusion of the monovalent vaccination against influenza A(H1N1)pdm09 in the 2009–2010 season showed no effectiveness in preventing outpatient cases of influenza A(H1N1)pdm09 (AOR, 1.49; 95% CI, .76–2.92) and hardly modified the estimates of seasonal influenza vaccination effectiveness (Supplementary Table 3). Compared with subjects aged <65, those aged ≥65 had lower point estimates of influenza vaccine effectiveness in preventing inpatient cases and higher estimates in preventing severe cases, although none of these differences were statistically significant (Table 2, Figure 2, Supplementary Table 4).

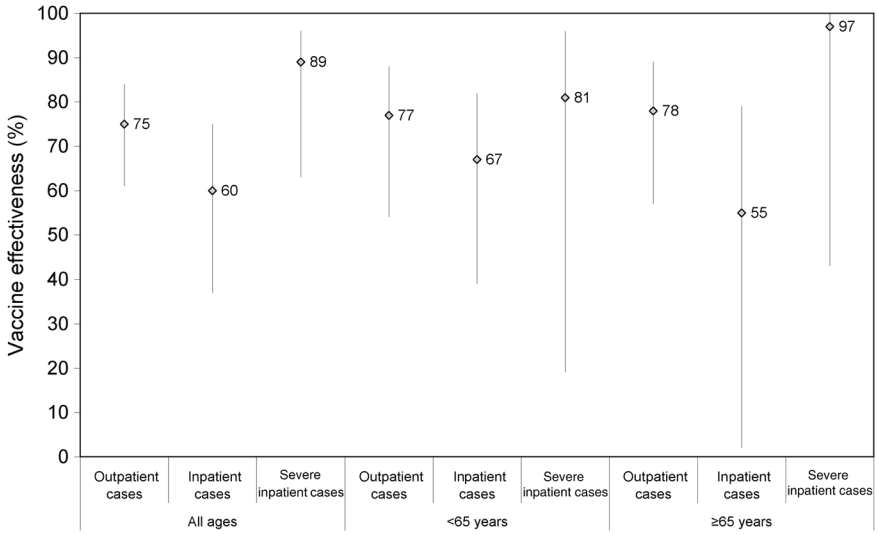

Figure 2. Influenza vaccine effectiveness in preventing outpatient visits, hospitalizations, and severe inpatient cases due to laboratory-confirmed influenza in the 2010–2011 season by age group.

Of inpatient cases, 25.6% (177/691) were admitted to the ICU or died. Compared to nonsevere inpatient cases, severe inpatient cases were more often male, aged 45–64 years, and smokers; had a previous diagnosis of cardiovascular disease or diabetes mellitus; and less frequently had a diagnosis of pneumonia in the 2 previous years. There were no statistically significant differences in other characteristics (Table 3). In inpatient cases, those vaccinated against influenza were less likely to be severe cases (AOR, 0.42; 95% CI, .22–.80), and this protective effect was even more pronounced in inpatient cases aged ≥65 years (AOR, 0.15; 95% CI, .03–.71), although the interaction between vaccine status and age group (<65 and ≥65 years) was not statistically significant ($P = .513$). After excluding patients who died from the analysis, there continued to be a lower, although nonsignificant, probability of vaccinated inpatient cases being severe cases (AOR, 0.51; 95% CI, .26–1.02). Repetition of the analysis including only cases of influenza A(H1N1)pdm09 showed similar results (Table 4 and Supplementary Table 5).

The mean time between the onset of influenza symptoms and the primary healthcare visit did not differ between vaccinated (2.5 ± 2.6 days) and unvaccinated (2.2 ± 2.0 days, $P = .563$) patients. In inpatient cases, there was no difference in the time between the onset of symptoms and hospital admission in vaccinated (5.1 ± 4.5 days) and unvaccinated (5.0 ± 4.2 days, $P = .889$) patients.

DISCUSSION

The results of this study show that the 2010–2011 influenza vaccine had a moderate to high effect in preventing outpatient cases and hospitalizations due to laboratory-confirmed influenza in Spain, and a high preventive effect against severe cases. Influenza vaccination was not associated with differences in the probability of hospitalization in influenza cases, but was associated with lesser severity in inpatients, especially in older patients.

The effectiveness in preventing outpatient cases was slightly higher than that reported by other authors in Europe and the United States in the same season using the test-negative case-control design [5, 6, 23]. Likewise, the effectiveness in preventing hospitalization found is in the range reported in other studies conducted in Spain using different designs [16, 17]. Both effects were consistent with the virus-vaccine match in this season in Spain [27].

Vaccination was substantially effective in preventing severe cases: this was evident in comparisons with outpatient controls, inpatient controls, and nonsevere inpatient cases. This suggests that influenza vaccination was a factor for a good prognosis, reducing the incidence of complications and progression to more severe clinical forms in people in whom it did not prevent influenza infection. Vaccination generates an immune response and the production of antibodies but does not always prevent infection, but even in these cases it can reduce the viremia and the length of the illness, resulting in a better prognosis.

These findings could have alternative explanations. Vaccinated persons may attend hospital earlier, anticipating complications and avoiding evolution to severe forms: however, the time between the onset of symptoms and hospitalization was similar in vaccinated and unvaccinated patients. Likewise, we cannot totally discount the "healthy vaccinee effect" whereby frail

Table 2. Analysis of the Effectiveness of the Influenza Vaccine in Preventing Hospitalizations or Outpatient Visits due to Laboratory-Confirmed Influenza in the 2010–2011 Season

Group of Patients and Comparison	Patients in the Group Evaluated, No.(% Vaccinated)	Patients in the Reference Group, No.(% Vaccinated)	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)[a]	*P* Value
All subjects						
Outpatient cases vs outpatient controls	604 (7)	598 (21)	.25 (.16–.39)	<.001	.25 (.16–.39)	<.001
Inpatient cases vs outpatient controls	660 (16)	663 (21)	.64 (.46–.88)	.006	.40 (.25–.63)	<.001
Severe inpatient cases vs outpatient controls	173 (10)	173 (23)	.32 (.16–.64)	.001	.11 (.04–.37)	<.001
Inpatient cases vs outpatient cases	610 (17)	617 (7)	2.50 (1.66–3.77)	<.001	1.53 (.86–2.72)	.153
Influenza A(H1N1)pdm09						
Outpatient cases vs outpatient controls	604 (7)	598 (20)	.25 (.16–.39)	<.001	.25 (.16–.39)	<.001
Inpatient cases vs outpatient controls	617 (16)	620 (21)	.63 (.45–.87)	.006	.40 (.25–.63)	<.001
Severe inpatient cases vs outpatient controls	172 (10)	172 (23)	.32 (.16–.64)	.001	.12 (.04–.39)	<.001
Inpatient cases vs outpatient cases	568 (16)	575 (7)	2.53 (1.66–3.87)	<.001	1.67 (.92–3.05)	.094
Cases <65 y						
Outpatient cases vs outpatient controls	477 (3)	471 (11)	.24 (.13–.45)	<.001	.23 (.12–.46)	<.001
Inpatient cases vs outpatient controls	521 (10)	524 (12)	.85 (.57–1.26)	.414	.33 (.18–.61)	<.001
Severe inpatient cases vs outpatient controls	144 (8)	144 (15)	.47 (.21–1.05)	.065	.19 (.04–.81)	.025
Inpatient cases vs outpatient cases	484 (14)	491 (3)	3.39 (1.82–6.28)	<.001	1.25 (.53–2.95)	.607
Cases ≥65 y						
Outpatient cases vs outpatient controls	127 (23)	127 (54)	.25 (.13–.45)	<.001	.22 (.11–.43)	<.001
Inpatient cases vs outpatient controls	139 (36)	139 (55)	.39 (.22–.68)	.001	.45 (.21–.98)	.044
Severe inpatient cases vs outpatient controls	29 (21)	29 (66)	.13 (.03–.58)	.007	.03 (.001–.57)	.020
Inpatient cases vs outpatient cases	126 (46)	126 (24)	1.90 (1.09–3.30)	.024	1.40 (.62–3.19)	.419

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Conditional logistic regression adjusted for sex, pregnancy, smoking, hospitalization in previous 12 months, bed confinement, major chronic conditions (0, 1, >1), pneumonia in the previous 2 years, and corticoid treatment. Pneumococcal vaccination was included in the analysis of inpatient cases.

patients may be less likely to be vaccinated and more likely to evolve to greater severity or death [26]; however, severe and nonsevere inpatient cases were similar in many characteristics and the analyses were adjusted for factors related to frailty, such as pneumonia in the previous 2 years, bed confinement, and previous hospitalization. This effect remained in the analysis stratified by age, and was even more pronounced in older adults. The effect found was of sufficient magnitude that the possibility of it being due to factors unrecognized in the design and analysis is low. Vaccine effectiveness was assessed in severe cases of influenza confirmed by RT-PCR, in contrast to other studies that evaluated less specific outcomes [25, 28].

These findings suggest that influenza vaccination may have additional benefits not detected by most studies evaluating vaccine effectiveness in confirmed cases. The prevention of severe cases of influenza, even though the numbers are lower, may have greater benefits in terms of health and health costs than the prevention of outpatient cases and nonsevere inpatient cases. It may also explain, at least partly, the substantial effectiveness of the vaccine in preventing deaths [25]. These findings reinforce the recommendation of annual influenza vaccination in people with risk factors and seniors.

Some studies have suggested that the pandemic influenza vaccine administered in the 2009–2010 season could have a residual protective effect in the 2010–2011 season [6, 10], but we found no evidence for this, similar to other studies [11, 18]. *Streptococcus pneumoniae* can cause added complications in inpatient cases of influenza [29, 30] and pneumococcal vaccination could prevent hospitalizations regardless of influenza vaccination: for this reason, all analyses of inpatient cases were adjusted for a history of pneumococcal vaccination.

Most recent studies of influenza vaccine effectiveness compare laboratory-confirmed cases with negative controls [4–11], but the comparison between estimates against different outcomes cannot be usually made using this design. Using a conventional matched case-control design and analyzing subjects with comparable characteristics due to the matching used and adjustment for potential confounders, we studied the effect of influenza vaccination on 3 types of outcomes representing different levels of influenza severity.

Table 3. Comparison of Characteristics of Severe Inpatient Cases (Intensive Care Unit Admission and Hospital Deaths) and Nonsevere Inpatient Cases With Confirmed Influenza

Characteristics	Severe Inpatient Cases (n = 177)	Nonsevere Inpatient Cases (n = 514)	*P* Value
Age group			.001
<5 y	12 (6.8)	71 (13.8)	
5–14 y	4 (2.3)	32 (6.2)	
15–44 y	53 (29.9)	149 (29.0)	
45–64 y	78 (44.1)	152 (29.6)	
≥65 y	30 (16.9)	110 (21.4)	
Female	59 (33.3)	232 (45.1)	.006
Pregnant women	5 (2.8)	31 (6.0)	.098
Current smoker	60 (33.9)	111 (21.6)	.001
Major chronic conditions with indication for vaccination			
Chronic respiratory disease	31 (17.5)	63 (12.3)	.078
Asthma	11 (6.2)	50 (9.7)	.155
Cardiovascular disease	40 (22.6)	67 (13.0)	.002
Chronic renal disease	14 (7.9)	49 (9.5)	.518
Diabetes mellitus	41 (23.2)	64 (12.5)	.001
Immunodeficiency	20 (11.3)	73 (14.2)	.329
Neurologic disease	12 (6.8)	33 (6.4)	.867
Neoplasia	27 (15.3)	69 (13.2)	.500
Chronic liver disease	13 (7.3)	29 (5.6)	.414
Rheumatologic disease	11 (6.2)	19 (3.7)	.156
Body mass index ≥40 kg/m^2	5 (2.8)	10 (1.9)	.489
No. of major chronic conditions			.224
0	59 (33.3)	208 (40.5)	
1	58 (32.8)	157 (30.5)	
> 1	60 (33.9)	149 (29.0)	
Hospitalization in previous 12 mo	51 (28.8)	154 (30.0)	.773
Confined to bed	16 (9.0)	26 (5.1)	.056
Other risk factors for complications			
Pneumonia in the previous 2 y	11 (6.2)	67 (13.0)	.013
Corticoid treatment	47 (26.6)	149 (29.0)	.535
Seasonal influenza vaccine 2010–2011	18 (10.2)	87 (16.9)	.031
Pneumococcal vaccine	20 (11.3)	89 (17.3)	.058

Data are presented as No. (%) unless otherwise specified.

This study had some possible limitations. The interviewers knew whether interviewees were cases or controls, and this could have influenced information gathering. However, the same protocol was followed in cases and controls, almost all of the data evaluated in this study were obtained by review of medical records, and information on the vaccination history was collected from medical records, vaccination cards, or registers; therefore, there is unlikely to be any relevant information bias. Despite the matching, selection bias due to the recruitment criteria for each group cannot be totally excluded; however, the consistent results of sensitivity analyses in a different control group (inpatient controls) suggest that this possible bias does not affect the main conclusions. If, during a comparison, a case had no matched control, it was excluded. This might have caused some differences in the characteristics of the population included in the different analyses. However, the number of incomplete matching groups was very small, and therefore it is unlikely this factor affected the results. The repetition of the analysis including only fully matched groups showed similar results to the main analysis. The study was conducted in a season in which the predominant influenza virus circulating was A(H1N1)pdm09, whose pattern of involvement might differ somewhat from other influenza viruses, and it would be interesting to compare our finding with those from other seasons. Finally, cases and controls were included in the study when they sought medical treatment, and this would

Table 4. Effect of the 2010–2011 Seasonal Influenza Vaccine in Avoiding Severe Inpatient Cases of Influenza According to Patient Characteristics

Inpatient Cases of Influenza Included in the Analysis	Severe Cases, No. (% Vaccinated)	Nonsevere Cases, No. (% Vaccinated)	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)[a]	*P* Value
All	177 (11)	514 (17)	.56 (.32–.95)	.033	.42 (.22–.80)	.009
Excluding deaths	155 (10)	514 (17)	.57 (.32–.99)	.048	.51 (.26–1.02)	.058
Influenza A(H1N1)pdm09	176 (10)	470 (17)	.54 (.31–.93)	.026	.40 (.20–.77)	.006
Aged <65 y	147 (7)	404 (11)	.68 (.34–1.36)	.272	.55 (.24–1.25)	.156
Aged ≥65 y	30 (23)	110 (40)	.46 (.18–1.16)	.098	.15 (.03–.71)	.017

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Unconditional logistic regression adjusted for sex, age (<5, 5–14, 15–44, 45–64, and ≥65 years), pregnancy, smoking, hospitalization in previous 12 months, major chronic conditions (0, 1, >1), bed confinement, pneumonia in the previous 2 years, corticoid treatment, pneumococcal vaccination, and recruitment hospital.

have helped to make them more alike in the use of health services; however, the care-seeking patterns may have had some influence in the comparisons between inpatient and outpatient cases. The similarity between the estimates obtained in our study and in studies using other designs in the same season [5, 6, 16, 17, 23] would rule out the existence of important unmeasured confounders affecting the results.

In conclusion, this multicenter study, carried out in Spain in the 2010–2011 season, found that the influenza vaccine was moderately to highly effective in preventing outpatient and inpatient cases of laboratory-confirmed influenza. Moreover, in influenza patients, vaccination seems to improve the prognosis, avoiding evolution to greater severity. The combined effect of these 2 mechanisms was to prevent serious cases and deaths from influenza. This suggests that vaccination effectiveness may be greater in preventing severe cases than in preventing mild cases, and that the benefits of vaccination may be greater than suggested by most studies of effectiveness against confirmed cases. Our results reinforce the recommendation of annual influenza vaccination in high-risk populations.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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