



Asthma and influenza vaccination in elderly hospitalized patients: Matched case-control study in Spain

María Morales Suárez-Varela, Agustin Llopis, Estrella Fernandez-Fabrellas, Francisco Sanz, M. Jose Perez-Lozano, Vicente Martin, Jenaro Astray, Jesús Castilla, Mikel Egurrola, Luis Force, Diana Toledo, Àngela Domínguez & Working group of project pi12/02079 'effectiveness of influenza and pneumococcal polysaccharide 23-valent vaccines in people aged 65 years and more'

To cite this article: María Morales Suárez-Varela, Agustin Llopis, Estrella Fernandez-Fabrellas, Francisco Sanz, M. Jose Perez-Lozano, Vicente Martin, Jenaro Astray, Jesús Castilla, Mikel Egurrola, Luis Force, Diana Toledo, Àngela Domínguez & Working group of project pi12/02079 'effectiveness of influenza and pneumococcal polysaccharide 23-valent vaccines in people aged 65 years and more' (2017): Asthma and influenza vaccination in elderly hospitalized patients: Matched case-control study in Spain, Journal of Asthma, DOI: [10.1080/02770903.2017.1332204](https://doi.org/10.1080/02770903.2017.1332204)

To link to this article: <http://dx.doi.org/10.1080/02770903.2017.1332204>



Published online: 21 Jun 2017.



Submit your article to this journal [↗](#)



Article views: 95



View related articles [↗](#)



View Crossmark data [↗](#)



Asthma and influenza vaccination in elderly hospitalized patients: Matched case-control study in Spain

María Morales Suárez-Varela, MD, PhD^{a,b,c}, Agustín Llopis, PhD^{a,b,c}, Estrella Fernández-Fabrellas, MD, PhD^d, Francisco Sanz, MD, PhD^d, M. Jose Perez-Lozano, MD, PhD^e, Vicente Martín, MD, PhD^f, Jenaro Astray, MD, PhD^g, Jesús Castilla, MD, PhD^h, Mikel Egurrola, MD, PhDⁱ, Luis Force, MD, PhD^j, Diana Toledo, MD, PhD^{b,k}, Ángela Domínguez, MD, PhD^{b,k}, and Working group of project pi12/02079 'effectiveness of influenza and pneumococcal polysaccharide 23-valent vaccines in people aged 65 years and more'

^aÁrea de Medicina Preventiva y Salud Pública, Departamento de Medicina Preventiva, Universidad de Valencia, Burjassot, Valencia, Spain; ^bCIBER en Epidemiología y Salud Pública (CIBERESP), Madrid, Spain; ^cCentro Superior de Investigación en Salud Pública (CSISP), Valencia, Spain; ^dHospital General Universitario, Valencia, Spain; ^eServicio de Medicina Preventiva, Hospital Universitario del Valme, Sevilla, Andalucía, Spain; ^fÁrea de Medicina Preventiva y Salud Pública, Departamento de Ciencias Biomédicas, Universidad de León, León, Spain; ^gSubdirección General de Epidemiología de la Comunidad de Madrid, Madrid, Spain; ^hInstituto de Investigación Sanitaria de Navarra (IdiSNA), Recinto de Complejo Hospitalario de Navarra C/Irunlarrea, Pamplona, Navarra, Spain; ⁱServicio de Inmunología, Hospital de Galdakao-Usansolo, Usansolo, Vizcaya, Spain; ^jHospital de Mataró, Mataró, Barcelona, Spain; ^kDepartamento de Salud Pública, Universidad de Barcelona, Barcelona, Spain

ABSTRACT

Objectives: Influenza infection is an exacerbating factor for asthma, and its prevention is critical in managing asthmatic patients. We investigated the effect of influenza vaccination on asthmatic and non-asthmatic patients hospitalized with laboratory-confirmed influenza in Spain. **Methods:** We made a matched case-control study to assess the frequency of hospitalization for influenza in people aged ≥ 65 years. Hospitalized patients with unplanned hospital admissions were recruited from 20 hospitals representing seven Spanish regions. Cases were defined as those hospitalized due to a laboratory-confirmed influenza infection and controls were matched by age, sex, and hospital. Data were obtained from clinical records, and patients stratified by clinical asthma history. Vaccination status and asthma due to influenza infection were analyzed according to sociodemographic variables and medical risk conditions. Multivariable analysis was made using conditional logistic regression models. **Results:** 582 hospitalized patients with influenza (15.8% asthmatic) and 1,570 hospitalized patients without influenza (7.9% asthmatic) were included. In the multivariable conditional logistic regression using unvaccinated and non-asthmatic patients as the reference group, vaccination significantly prevented influenza in non-asthmatic patients (aOR = 0.63; 95% CI: 0.45, 0.88) and also showed a trend for a possibly protective effect in asthmatic patients (aOR = 0.79; 95% CI: 0.34, 1.81). **Conclusion:** Our results suggest that influenza vaccination could be a protective factor for asthmatic patients, although the results are inconclusive and further research is required. Practically, given the better clinical evolution of vaccinated asthma cases, and the lack of better evidence, the emphasis on vaccination of this group should continue.

ARTICLE HISTORY

Received 3 February 2017
Revised 9 May 2017
Accepted 14 May 2017

KEYWORDS

Asthma; asthma management; elderly; influenza; influenza-related hospitalization; laboratory-confirmed influenza; multivariable conditional logistic regression; prevention; protective factor; vaccination

Introduction

One exacerbating factor for asthma is respiratory viral infection, such as those caused by seasonal influenza viruses. Influenza is a serious illness and during epidemics large numbers of infections occur throughout all age groups [1, 2]. Globally, seasonal epidemics are thought to be responsible for around 3–5 million cases of severe illness and anywhere from 250,000 to 500,000 deaths [3]. Of these deaths, 89% occur in patients aged ≥ 65 years [4]. Of the number of deaths among the elderly during influenza season, 11% can be directly labeled as influenza-related [5].

Influenza infection is a major cause of emergency room visits and hospital admissions in asthmatic patients [6, 7]. Although asthmatics are not more likely to suffer influenza infections, they may present with more severe symptoms, even in patients with mild asthma or symptoms well controlled by medication. Influenza infection in the lungs may trigger asthma attacks and worsen asthma symptoms and other acute respiratory diseases. Adults and elderly asthmatics are more likely to develop pneumonia after having influenza [8]. Asthma is the most common medical condition in adults hospitalized with influenza and one of the most frequent medical

CONTACT María Morales Suárez-Varela ✉ maria.m.morales@uv.es Unit of Public Health and Environmental Care, Department of Preventive Medicine, University of Valencia, Avda. Vicente Andrés Estellés s/n, 46100 Burjassot, Valencia, Spain.

conditions in the hospitalized elderly [6]. Therefore, prevention of seasonal influenza virus infection is one of the most important strategies in the management of asthmatic patients [9, 10]. While Spain is an area with low-to-medium asthma prevalence in adults (1.50–5.53%) [11], a European cross-sectional multicenter study in adults [12] observed a generational increase in asthma incidence in most countries, irrespective of asthma prevalence. Given this, it is important to establish clear guidelines to protect this growing vulnerable population.

Current practical guidelines recommend influenza vaccination for patients with diseases that may be exacerbated by influenza infection in order to reduce potential complications [12–14]. In Spain, influenza vaccination is included in the National Health System Primary Care catalog of health benefits [15], and is recommended for people at increased risk of complications from influenza, including all adults aged ≥ 65 years and chronic patients. However, although studies of the effectiveness of influenza vaccination in the elderly found that vaccination is associated with lower hospitalization and death rates [16–18], a systematic review concluded that there still remains much uncertainty for the asthmatic population [19]. Given the nature of asthma as well as the debatable effectiveness of the vaccination in itself, health professionals are wary of recommending vaccination to asthmatics [20]. The possible adverse effects of the vaccine on patients with altered immune systems such as asthmatics and the perceived ineffectiveness of the vaccine due to the possible differences between the dominant circulating strains and the vaccines strains are all factors alleged for not recommending vaccination to elderly asthmatics [20]. The aim of this study was to examine the effect of influenza vaccination on elderly asthmatic patients in Spain.

Methods

Study design

A matched case-control study in 20 hospitals from the main cities of seven Spanish regions (Andalusia, Basque Country, Catalonia, Castile and Leon, Madrid, Navarra and the Valencian Community) was conducted. Patients with unplanned hospital admission with and without influenza (cases and controls, respectively) were recruited between November 2013 and May 2015.

Setting and participants

Patients were included as cases in the study if they met the following criteria: age ≥ 65 years; arrived at the emergency department with influenza-like symptoms. The

clinical suspicion of influenza infection must have been laboratory confirmed and patients with concomitant influenza were not included. Once influenza infection was confirmed, cases were hospitalized in the internal medicine service. The inclusion criteria for controls were patients ≥ 65 years admitted to general surgery, otorhinolaryngology, ophthalmology, dermatology or traumatology services via the emergency department due to a non-respiratory pathology. These departments were chosen because they presented the highest volume of patients in the hospitals involved in the study. Controls were selected at a ratio of 3:1 by matching according to sex, age, hospital facility, and date of admission. Patients who presented other lung diseases and cases with unmatched controls were excluded. Both cases (with influenza) and controls (without influenza) were stratified by the presence or absence of a previous clinical diagnosis of asthma, resulting in four different groups of patients:

- Cases (with influenza) with asthma
- Cases (with influenza) without asthma
- Controls (without influenza) with asthma
- Controls (without influenza) without asthma

Outcome of interest and assessment of exposure

Specifically-trained health professionals used a structured questionnaire to collect information through both personal interviews and by review of medical records. Both methods of data collection were used for all the patients included. Demographic information (date of birth, sex, marital status, educational level, occupation, living situation, Barthel Index, tobacco and alcohol consumption and number of previous medical visits in the last year) was obtained during the personal interview. The interviews were carried out in person in the patients' hospital room during their hospital stay. All participants in this study completed the personal interview. Information on influenza infection and its type (influenza A: H1, H3, non-subtyped; influenza B; influenza C) was obtained from hospital medical records: all diagnoses were laboratory-confirmed. Also obtained from hospital medical records was the information on other pulmonary diseases, comorbidities, treatment and evolution during hospital stay. Information on asthma and vaccination status was obtained from primary health care records, hospital medical records, vaccination registers or vaccination cards (patients were considered vaccinated if they had received a dose of the influenza vaccination at least 14 days before symptom onset).

During the 2013–2014 influenza season, the trivalent inactivated vaccine administered in the northern hemisphere and therefore in Spain contained an A/California/7/2009(H1N1)pdm-09-like

virus, an A(H3N2) virus antigenically similar to the cell-propagated prototype virus A/Victoria/361/2011, and a B/Massachusetts/2/2011-like virus. During the 2014–2015 season, the A/Victoria/361/2011 component was changed to A/Texas/50/2012. During the first season studied, there was no mismatch for the influenza A components; however, during the second season there was some mismatch for A(H3N2) [21, 22]. No high-dose influenza vaccines were used in either season.

Information was also collected on potential confounders in the interaction between asthma and the vaccination status on influenza infection. This included: age, sex, civil status, level of education, smoking status, alcohol consumption, body mass index (BMI) and Barthel's index. In addition, information on various pathologies (chronic obstructive pulmonary disease, diabetes, renal failure, nephritic syndrome, heart failure, autoimmune diseases) was obtained.

Specific information on cases, including: the reason for admission, specific influenza symptoms, duration of symptoms prior to hospitalization, characteristics of hospitalization and treatments was collected.

Statistical analysis

Quantitative variables were expressed as means and standard deviations (SD) or as medians and interquartile range (IQR), while qualitative variables were expressed as frequencies and proportions. The characteristics of cases and controls with and without asthma and of patients with influenza were compared according to the vaccination status and asthma diagnosis using the chi-square test for categorical variables (using 1000 Monte Carlo simulations) and Analysis of Variance (ANOVA) or the Kruskal–Wallis test for quantitative variables.

A univariate conditional logistic model was used to estimate the crude odds ratios (ORs) for influenza infection in the four groups created by combining the asthma diagnosis and vaccination status (unvaccinated, non-asthmatic; vaccinated, non-asthmatic; unvaccinated, asthmatic; vaccinated, asthmatic), using unvaccinated non-asthmatic patients as the reference. To adjust for potential confounders, a multivariable conditional logistic model was built. Candidate variables to be included in the multivariable model were selected according to the potential biasing paths detected. To correct for overfitting, model performance was assessed using the area under the curve, the Brier score and slope and intercept calibration factors, with 1000 bootstrap samples [23].

Considering the plausibility of a biological interaction between asthma and influenza vaccination, using the adjusted conditional logistic model the interaction

contrast ratio (ICR) on the additive scale [24] and its confidence intervals (CIs) [25]: ICR = 0 means no interaction (exactly additivity), ICR > 0 means positive interaction (superadditivity), and ICR < 0 means negative interaction (subadditivity) were calculated.

Finally, symptoms at presentation in patients hospitalized with asthma and influenza according to vaccination status were compared by means of the chi-square test for categorical variables (using 1000 Monte Carlo simulations) and the Mann–Whitney *U* test for quantitative variables.

The level of statistical significance was set at $\alpha = 0.05$. All analyses were made using IBM SPSS.

Data confidentiality and ethical issues

The study was approved by the Ethics Committees of all participating hospitals and the data inspectorates of the participating regions. All patients provided signed informed consent.

Results

Characteristics of the study participants

In total, 2,554 patients were eligible, of whom 402 were excluded. Therefore, 2,152 patients (582 influenza cases and 1,570 controls) were included (Figure 1).

The personal and clinical profile characteristics of the study participants are summarized in Table 1. Cases and controls are shown divided according to asthma diagnosis. There are significant differences among the groups for the following variables: vaccination status, sex, smoking status, BMI, respiratory insufficiency, COPD, congestive cardiomyopathy, comorbidities, corticosteroid treatment, and average hospital stay. When asthmatic cases and controls are compared to non-asthmatic cases and controls, it can be observed that the cases presented with a higher vaccination coverage. Asthmatics were more likely to be female and less likely to smoke. The asthmatic group had higher BMIs. In relation to other pathologies, asthmatics presented more events of respiratory insufficiency and of chronic obstructive pulmonary disease, the latter was especially noticeable within the patients with influenza. Asthmatics also had fewer cases of congestive cardiomyopathy and other comorbidities. A higher proportion of asthmatics received treatment with corticosteroids, especially in patients with influenza. The average hospital stay was similar for asthmatic and non-asthmatic cases as well as for asthmatic and non-asthmatic controls. However, the difference was noticeable between cases and controls. With respect to the vaccination status, 50.0% of asthmatic cases had received the seasonal influenza vaccination,

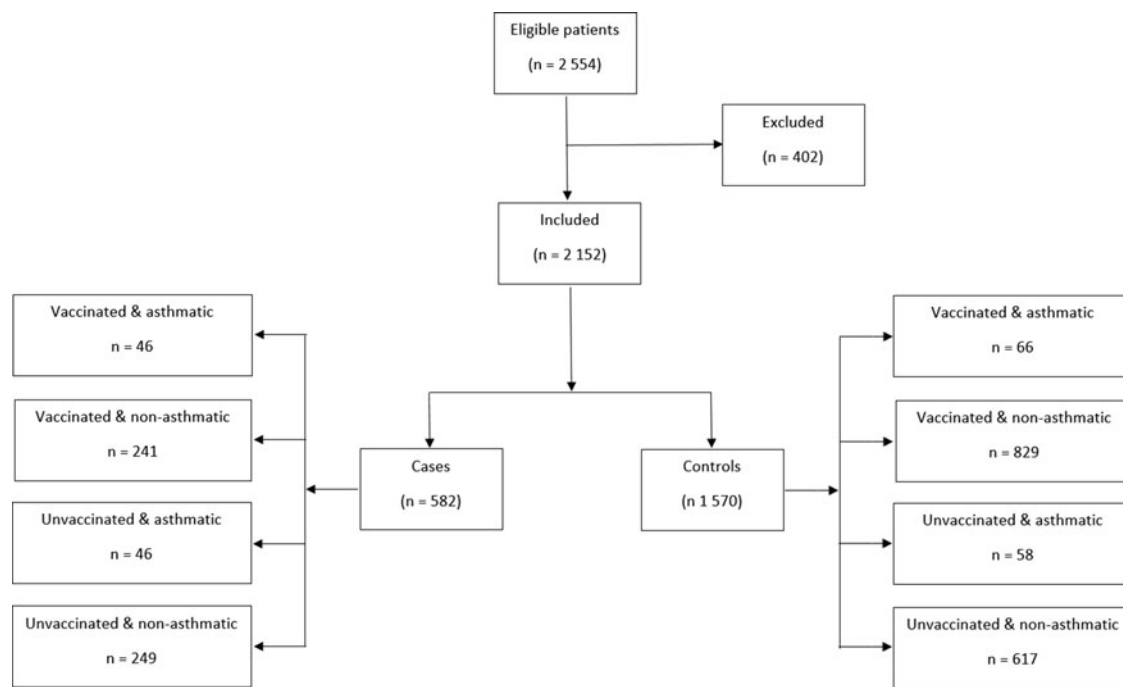


Figure 1. Patient flow diagram.

versus 49.2% of non-asthmatic cases, 53.2% of asthmatic controls, and 42.7% of non-asthmatic controls.

Table 2 shows the characteristics of cases according to the vaccination status and asthma diagnosis. Compared with unvaccinated and asthmatic patients, vaccinated asthmatic patients had a higher proportion of males and smokers, less cases of renal failure, less comorbidities, had received corticosteroids more frequently and had shorter hospital stays.

Main results

Univariate conditional logistic regression (conditioned by sex, age, hospital facility and date of admission) showed a significant protective effect for the vaccinated and non-asthmatic group (OR = 0.73; 95% CI: 0.59, 0.91). On the other hand, a significant risk of influenza infection appeared for both unvaccinated asthmatic (OR = 2.06; 95% CI: 1.30, 3.25) and vaccinated asthmatic patients (OR = 2.02; 95% CI: 1.28, 3.18) (Table 3).

The multivariable conditional logistic regression model was adjusted for smoking status, pneumonia, corticosteroid treatment, Barthel index, educational level, comorbidities, and obesity. The adjusted results are shown in Table 3: vaccination significantly prevented influenza in the non-asthmatic group (aOR = 0.63; 95% CI: 0.45, 0.88) and, although there appears to be a trend toward a possibly protective effect for the asthmatic group, the result was not significant (aOR = 0.79; 95% CI: 0.34, 1.81) and no definitive conclusions may be extracted.

Table 4 compares vaccinated and unvaccinated hospitalized asthmatic patients with influenza (cases). The only significant differences relating to patient treatment were found between the proportion of patients that required corticosteroid treatment (higher proportion in vaccinated patients) and invasive and non-invasive and mechanical ventilation (lower proportion in vaccinated patients). While the difference was non-significant, unvaccinated patients were more likely to be admitted to the intensive care unit (15.2% versus 2.2% for vaccinated patients). No deaths occurred during hospitalization or the first 30 days after discharge in vaccinated patients while 4.3% of unvaccinated patients died in hospital and 6.5% died during the first 30 days after discharge.

Discussion

Main findings

A matched case-control study was used to examine the effect of influenza vaccination in patients with an asthma diagnosis aged ≥ 65 years hospitalized due to influenza infection. Although vaccination showed a strong, significant protective effect in non-asthmatic patients, in asthmatic patients the protective effect was not significant. The literature seems to be sparse (we found no article regarding people aged ≥ 65 years), however, a 2013 systematic review reported similar results for adults aged ≤ 64 years, i.e., influenza vaccination has an uncertain effect on asthmatic patients [19].

Table 1. Characteristics of patients with and without influenza, stratified by asthma diagnosis.

	Patients without influenza (controls)		Patients with influenza (cases)		p-value ^a
	(n = 1570)		(n = 582)		
	Without asthma (n = 1446; 92.1%)	With asthma (n = 124; 7.9%)	Without asthma (n = 490; 84.2%)	With asthma (n = 92; 15.8%)	
Vaccination status, n (%)					
Unvaccinated	617 (42.7)	58 (46.8)	249 (50.8)	46 (50.0)	0.014
Vaccinated	829 (42.7)	66 (53.2)	241 (49.2)	46 (50.0)	
Age (years), mean (SD)	78.1 (7.1)	78.8(7.6)	78.1 (7.6)	78.3 (7.2)	0.759
Sex, n (%)					
Male	753 (52.1)	42 (33.9)	260 (53.1)	26 (28.3)	0.001
Female	693 (47.9)	82 (66.1)	230 (46.9)	66 (71.7)	
Civil status, n (%)					
Married	807 (55.8)	62(50.0)	279 (56.9)	61 (66.3)	0.161
Single	114 (7.9)	9 (7.3)	28 (5.7)	3 (3.3)	
Widow/er	491 (34.0)	49 (39.5)	163 (33.3)	28 (30.4)	
Separated	30 (2.1)	4 (3.2)	19 (3.9)	0	
Missing data	4 (0.3)	0	1 (0.2)	0	
Educational level, n (%)					
Incomplete primary studies	630 (43.6)	53 (42.7)	195 (39.8)	38(41.3)	0.328
Primary studies	360 (24.9)	31 (25)	137 (28.0)	34 (37.0)	
Secondary studies	290 (20.1)	25 (20.2)	95 (19.4)	12 (13.0)	
Higher education	166 (11.5)	15 (12.1)	63 (12.9)	8 (8.7)	
Smoking status, n (%)					
Non-smoker	858 (59.3)	885 (71.0)	262 (53.5)	65 (70.7)	0.008
Former smoker	489 (33.8)	32(25.8)	188 (38.4)	25 (27.2)	
Current smoker	99 (6.8)	4 (3.2)	40 (8.2)	2 (2.2)	
Alcohol consumption, n (%)					
Never or occasionally	1219 (84.3)	112 (90.3)	411 (83.9)	83 (90.2)	0.121
Regularly	227 (15.7)	12 (9.7)	79 (16.1)	9 (9.8)	
BMI, mean (SD)	26.9 (5.4)	27.6 (4.8)	27.4 (5.5)	28.8 (5.5)	0.019
Barthel index, mean (SD)	81.7 (27.1)	83.4 (25.3)	82.8 (27.1)	85.3 (25.6)	0.518
Respiratory insufficiency, n (%)					
No	1342 (92.8)	111 (89.5)	430 (87.8)	84 (91.3)	0.012
Yes	104 (7.2)	13 (10.5)	60 (12.2)	8 (8.7)	
COPD, n (%)					
No	1301 (90.0)	115 (92.7)	371 (75.7)	80 (87.0)	0.001
Yes	145 (10.0)	9 (7.3)	119 (24.3)	12 (13.0)	
Diabetes, n (%)					
No	965 (66.7)	92 (74.2)	342 (69.8)	65 (70.7)	0.231
Yes	481 (33.3)	32 (25.8)	148 (30.2)	27 (29.3)	
Renal failure, n (%)					
No	1173 (81.1)	98 (79.0)	390 (79.6)	75 (81.5)	0.855
Yes	273 (18.9)	26 (21.0)	100 (20.4)	17 (18.5)	
Nephritic syndrome, n (%)					
No	1435 (99.2)	123 (99.2)	486 (99.2)	90 (97.8)	0.581
Yes	11 (0.8)	1 (0.8)	4 (0.8)	2 (2.2)	
Congestive cardiomyopathy, n (%)					
No	929 (64.2)	91 (73.4)	333 (68.0)	71 (77.2)	0.009
Yes	517 (35.8)	33 (26.6)	157 (32.0)	21 (22.8)	
Autoimmune diseases, n (%)					
No	1378 (95.3)	118 (95.2)	460 (93.9)	89 (96.7)	0.533
Yes	68 (4.7)	6 (4.8)	30 (6.1)	3 (3.3)	
Comorbidities ^b , n (%)					
No	505 (34.9)	57 (46.0)	144 (29.4)	44 (47.8)	0.001
Yes	941 (65.1)	67 (54.0)	346 (70.6)	48 (52.2)	
Immunotherapy, n (%)					
No	1392 (96.3)	119 (96.0)	463 (94.5)	91 (98.9)	0.167
Yes	54 (3.7)	5 (4.0)	27 (5.5)	1 (1.1)	
Corticosteroid treatment, n (%)					
No	1418 (98.1)	120 (96.8)	274 (55.9)	28 (30.4)	0.001
Yes	28 (1.9)	4 (3.2)	216 (44.1)	64 (69.6)	
Hospital stay (days), median (IQR)	13.1 (11.3)	13.6 (11.8)	11.1 (11.4)	10.0 (10.4)	0.001

Notes. BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SD, standard deviation.

^aBased on 1000 Monte Carlo simulations of the chi-square test for qualitative variables, or ANOVA for quantitative variables.

^bWe considered that the patients had comorbidities if they had more than one of the following diseases: diabetes, renal failure, nephritic syndrome, autoimmune disease, congestive cardiomyopathy, chronic obstructive pulmonary disease.

Table 2. Characteristics of vaccinated and unvaccinated patients with influenza, stratified by asthma diagnosis.

	Unvaccinated patients with influenza (Cases)		Vaccinated patients with influenza (Cases)		p-value ^a
	(n = 295)		(n = 287)		
	Without asthma (n = 249; 84.4%)	With asthma (n = 46; 15.6%)	Without asthma (n = 241; 84.0%)	With asthma (n = 46; 16.0%)	
Age (years), mean (SD)	77.2 (7.4)	78.3 (7.0)	79.2 (7.6)	78.3 (7.5)	0.030
Sex, n (%)					
Male	125 (50.2)	12 (26.1)	135 (56.0)	14 (30.4)	0.001
Female	124 (49.8)	34 (73.9)	106 (44.0)	32 (69.6)	
Civil status, n (%)					
Married	130 (52.2)	28 (60.9)	149 (61.8)	33 (71.7)	0.289
Single	18 (7.2)	1 (2.2)	10 (4.1)	2 (4.3)	
Widow/er	90 (36.1)	17 (37.0)	73 (30.3)	11 (23.9)	
Separated	10 (4.0)	0 (0.0)	9 (3.7)	0 (0.0)	
Missing data	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	
Educational level, n (%)					
Incomplete primary studies	94 (37.8)	22 (47.8)	101 (41.9)	16 (34.8)	0.465
Primary studies	75 (30.1)	15 (32.6)	62 (25.7)	19 (41.3)	
Secondary studies	46 (18.5)	6 (13.0)	49 (20.3)	6 (13.0)	
Higher education	34 (13.7)	3 (6.5)	29 (12.0)	5 (10.9)	
Smoking status, n (%)					
Non-smoker	137 (55.0)	32 (69.6)	123 (51.9)	33 (71.7)	0.009
Ex-smoker	86 (34.5)	14 (30.4)	102 (42.3)	11 (23.9)	
Current smoker	26 (10.4)	0 (0.0)	14 (5.8)	2 (4.3)	
Alcohol consumption, n (%)					
Never or occasionally	202 (81.1)	42 (91.3)	209 (86.7)	41 (89.1)	0.148
Regularly	47 (18.9)	4 (8.7)	32 (13.3)	5 (10.9)	
BMI, mean (SD)	27.6 (5.2)	28.5 (5.5)	27.3 (5.8)	28.9 (5.5)	0.309
Barthel index, median (IQR)	98.0 (75.0, 100.0)	95.0 (71.2, 100.0)	99.0 (78.0, 100.0)	100.0 (91.8, 100.0)	0.331
Respiratory insufficiency, n (%)					
No	220 (88.4)	40 (87.0)	210 (87.1)	44 (95.7)	0.408
Yes	29 (11.6)	6 (13.0)	31 (12.9)	2 (4.3)	
COPD, n (%)					
No	193 (77.5)	39 (84.8)	178 (73.9)	41 (89.1)	0.089
Yes	56 (22.5)	7 (15.2)	63 (26.1)	5 (10.9)	
Diabetes, n (%)					
No	175 (70.3)	29 (63.0)	167 (69.3)	36 (78.3)	0.487
Yes	74 (29.7)	17 (37.0)	74 (30.7)	10 (21.7)	
Renal failure, n (%)					
No	211 (84.7)	34 (73.9)	179 (74.3)	41 (89.1)	0.009
Yes	38 (15.3)	12 (26.1)	62 (25.7)	5 (10.9)	
Nephritic syndrome, n (%)					
No	247 (99.2)	44 (95.7)	239 (99.2)	46 (100.0)	0.174
Yes	2 (0.8)	2 (4.3)	2 (0.8)	0 (0.0)	
Congestive cardiomyopathy, n (%)					
No	166 (66.7)	32 (69.6)	167 (69.3)	39 (84.8)	0.118
Yes	83 (33.3)	14 (30.4)	74 (30.7)	7 (15.2)	
Autoimmune diseases, n (%)					
No	231 (92.8)	45 (97.8)	229 (95.0)	44 (95.7)	0.503
Yes	18 (7.2)	1 (2.2)	12 (5.0)	2 (4.3)	
Comorbidities ^b , n (%)					
No	86 (34.5)	17 (37.0)	58 (24.1)	27 (58.7)	0.001
Yes	163 (65.5)	29 (63.0)	183 (75.9)	19 (41.3)	
Immunotherapy, n (%)					
No	238 (95.6)	46 (97.8)	225 (93.4)	46 (100.0)	0.187
Yes	11 (4.4)	1 (2.2)	16 (6.6)	0 (0.0)	
Corticosteroid treatment, n (%)					
No	153 (61.4)	20 (43.5)	121 (50.2)	8 (17.4)	0.001
Yes	96 (38.6)	26 (56.5)	120 (49.8)	38 (82.6)	
Hospital stay (days), median (IQR)	8.0 (5.0, 13.0)	8.0 (5.2, 13.0)	8.0 (5.0, 14.0)	5.0 (4.0, 8.8)	0.027

BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SD, standard deviation.

^aBased on 1000 Monte Carlo simulations of the chi-square test for qualitative variables, or ANOVA for quantitative variables (except for Barthel index and hospital stay, where the Kruskal–Wallis test was used).

^bWe considered that the patients had comorbidities if they had more than one of the following diseases: diabetes, renal failure, nephritic syndrome, autoimmune disease, congestive cardiomyopathy, chronic obstructive pulmonary disease.

Table 3. Crude and adjusted ORs on influenza infection according to vaccination status and patients' asthma (analysis conditioned to sex, age, hospital facility, and date of admission).

	Non-asthmatics			Asthmatics			ORa (95%CI) ^a for asthmatics within strata of vaccination
	N cases/controls ^a	ORc (95%CI)	ORa (95%CI) ^b	N cases/controls ^a	ORc (95%CI)	ORa (95%CI) ^b	
Unvaccinated	249/617	1 (Reference)		46/58	2.06 (1.30, 3.25)	1.08 (0.51, 2.28)	1.08 (0.41, 2.87)
Vaccinated	241/829	0.73 (0.59, 0.91)	0.63 (0.45, 0.88)	46/66	2.02 (1.28, 3.18)	0.79 (0.34, 1.81)	1.32 (0.39, 4.54)

CI, confidence interval; ORc, crude odds ratio; ORa, adjusted odds ratio.

^aCases are defined as patients with influenza and controls as patients without influenza.

^bAdjusted for smoking status, pneumonia, cortisone intake, Barthel's Index, educational level, comorbidities, and obesity. We considered that the patients had comorbidities if he/she had more than one of the following diseases: diabetes, renal failure, nephritic syndrome, autoimmune disease, congestive cardiomyopathy, chronic obstructive pulmonary disease.

In general, the sociodemographic characteristics of asthmatic patients with and without influenza were similar. Cases had a lower vaccination rate and prevalence of comorbidities than controls. However, although there is no conclusive evidence about the protective effect of

vaccination, vaccinated cases with asthma had fewer symptoms and better outcomes than non-vaccinated cases with asthma, e.g. no death occurred during hospitalization or during the first 30 days after discharge in vaccinated cases with asthma. There are reasons to

Table 4. Symptoms at presentation in asthmatic and influenza hospitalized patients according to vaccination status.

	Asthmatic patients with influenza (n = 89)		p-value ^a
	Unvaccinated (n = 46; 50.0%)	Vaccinated (n = 46; 50.0%)	
Age (years), median (IQR)	79.0 [74.0, 82.0]	79.0 [73.2, 84.0]	0.851
Sex (male), n (%)	12 (26.1)	14 (30.4)	0.816
Cough (yes), n (%)	35 (76.1)	42 (91.3)	0.095
Headache (yes), n (%)	11 (23.9)	13 (28.3)	0.926
Fever (yes), n (%)	33 (71.7)	29 (63.0)	0.379
Fever (°C), median (IQR)	38.0 [38.0, 39.0]	38.0 [38.0, 39.0]	0.872
Rhinorrhea (yes), n (%)	7 (15.2)	7 (15.2)	1
Odynophagia (yes), n (%)	9 (19.6)	10 (21.7)	1
Myalgia (yes), n (%)	16 (34.8)	14 (30.4)	0.729
Arthralgia (yes), n (%)	9 (19.6)	11 (23.9)	0.846
Respiratory distress (%)	39 (84.8)	39 (84.8)	1
General discomfort (yes), n (%)	31 (67.4)	30 (65.2)	0.823
Diarrhea (%)	6 (13.0)	5 (10.9)	0.750
Symptom's duration previous to admission (days), median (IQR)	3.0 [2.0, 6.0]	4.0 [3.0, 7.0]	0.074
Reason for admission, n (%)			
Severe alteration of general condition	4 (8.7)	6 (13.0)	—
Decompensated pneumonia	31 (67.4)	34 (73.9)	
Decompensation of existing disease	4 (8.7)	4 (8.7)	
Multiple organ failure	0 (0.0)	1 (2.2)	
Other	7 (15.2)	1 (2.2)	
Type of influenza, n (%)			
Influenza A (H1)	17 (37.0)	18 (39.1)	—
Influenza A (H3)	14 (30.4)	14 (30.4)	
Influenza A without subtyping	13 (28.3)	14 (30.4)	
Influenza B	1 (2.2)	0 (0.0)	
Antiviral therapy (yes), n (%)	41 (89.1)	42 (91.3)	1
Antibiotics (yes), n (%)	33 (71.7)	39 (82.6)	0.107
Systemic corticosteroids (yes), n (%)	26 (56.5)	38 (82.6)	0.006
Antipyretics/anti-inflammatory treat (yes), n (%)	34 (73.9)	33 (71.7)	0.298
Stay in ICU (yes), n (%)	7 (15.2)	1 (2.2)	0.065
Days in ICU, median (IQR)	3.0 [2.0, 4.8]	13.0 [13.0, 13.0]	0.299
Mechanical ventilation (yes), n (%)	13 (28.3)	2 (4.3)	0.004
Invasive mechanical ventilation (yes), n (%)	4 (8.7)	1 (2.2)	0.007
Noninvasive mechanical ventilation (yes), n (%)	10 (21.7)	2 (4.3)	0.011
Days invasive mechanical ventilation, median (IQR)	8.0 [4.0, 15.5]	4.0 [4.0, 4.0]	0.48
Hospital discharge destination, n (%)			
Home	41 (89.1)	42 (91.3)	—
Another hospital center	0 (0.0)	2 (4.3)	
Health center	3 (6.5)	2 (4.3)	
Death	2 (4.3)	0 (0.0)	
Mortality 30 days after admission (yes), n (%)	3 (6.5)	0 (0.0)	0.220

ICU, intensive care unit; IQR, interquartile range.

^aBased on 1000 Monte Carlo simulations of the chi-square test for qualitative variables, or Mann-Whitney U test for quantitative variables.

consider the biological plausibility of a protective effect of influenza vaccination on asthmatic patients, and to therefore recommend routine influenza vaccination for asthmatic patients or to include them in practice guidelines [12, 14]. However, due to its safety [26], vaccination should be offered on an individual basis. Given our results, some of these individual factors that would push for vaccination in asthmatic patients include being older than 65, female, smoking, high BMI, and previous respiratory comorbidities such as COPD.

The use of health care resources by elderly patients with asthma and influenza is an important issue during hospitalization and after discharge. The lower mortality rate shown in this study would suggest that a treatment protocol which places emphasis on the more frequent and detailed management of the evolution of the asthmatic elderly during seasonal influenza periods may be key to developing more effective interventions. New strategies aimed at efficient care of elderly patients with asthma and influenza should be developed because funding for health care resources for the elderly is becoming increasingly scarce.

The results, which showed that only around 50% of asthmatics are vaccinated, indicated that there is room for improvement in administering influenza vaccinations in asthmatic patients, and an opportunity for targeted interventions such as establishing asthmatics as a priority group within the vaccination campaign or once they present influenza-like symptoms, prioritizing their treatment, given that the elderly are at increased risk for serious complications due to influenza [17].

Some factors may account for the vaccination rates. Vaccination coverage in hospitalized asthmatic patients with influenza was 50.0%, similar to that of non-asthmatic patients (49.2%), but lower than that of hospitalized asthmatic patients without influenza (53.2%). In Spain, 56.2% of people aged ≥ 65 years received influenza vaccination in the 2014–2015 season, with some variations between regions [27]. This was similar to the reported 58% in the USA [28]. Influenza vaccination coverage ranged from 26 to 49% in Italy [29] and 44 to 59% in the United Kingdom [30], and the global coverage was estimated at 57% in 2009 in France [31]. Therefore, the level of vaccination in the elderly in Spain is similar to that of other countries. However, influenza vaccination in Spain is still sub-optimal and awareness among the elderly is low [32]. Spanish studies have shown that a very small percentage of elderly people have a proactive attitude toward influenza vaccination [33]. These results stress the need for continued surveillance of vaccination coverage in elderly asthmatic people, in order to direct attention to under-vaccinated populations who may be disproportionately affected by vaccine-preventable diseases.

Some asthmatic patients were not vaccinated against influenza, possibly because they or their physicians did not consider it necessary, but the results of this study suggest a benefit of vaccination in asthmatic patients. In addition, influenza vaccination is indicated in Spain for people aged ≥ 65 years. The results suggest that physicians should emphasize influenza vaccination for asthmatics during vaccination campaigns. Suitable asthma control could provide protection against influenza hospitalization in these patients.

Vaccinated, asthmatic patients diagnosed with influenza at admission, were characterized by: cough, longer duration of symptoms before hospitalization (which were probably milder), lower requirement for mechanical ventilation (less requirement of and fewer days on invasive mechanical ventilation), and no mortality during hospital stays or in the 30 days after discharge. All this indicates milder clinical symptoms and a better evolution in these patients.

Strengths and limitations

This study utilized a single protocol in 20 different public hospitals within the Spanish universal health care system in which there is no selection bias and therefore the included patients accurately reflect the Spanish population. The main strength of this study is that the clinical characteristics and vaccination status were obtained from written documents (hospital medical records, vaccination cards or primary health care registers), avoiding memory bias. Another strength is that only patients with unplanned hospital admission were included (patients included for a variety of reasons and who tended to better represent the general population). Furthermore, every case was matched with at least two controls according to age, sex, hospital facility, and date of admission. The use of such similar and carefully chosen matched-controls greatly improves the internal validity of our study.

This study has several limitations. First, hospitalized patients whose reason for admission was a respiratory disease (such as pneumonia or influenza-like illnesses) were excluded, and patients hospitalized due to these diseases had probably received influenza vaccination less frequently than the overall elderly population. Although this might have led to some selection bias, their exclusion does not affect the potential associations studied, improving the comparison between groups.

Another potential issue is the antigenic match between vaccination and the circulating influenza virus during a season. This problem was initially tackled by studying two seasons, matching every case with a control from the same season. Once the seasons had past, it was seen that as

we have previously stated, vaccine and circulating viruses' strains were well matched in the studied seasons [21, 22].

Regarding their variable structure, there is a major problem in defining asthma, asthma type, and asthma intensity. It is not easy to distinguish between influenza symptoms and asthma exacerbations, and medication for influenza infection can exacerbate asthma. Bacterial infection following influenza infection may be mistaken for asthma. Measuring the incidence of a chronic intermittent disease like asthma is difficult, partly because of its complex intermittent natural history [34, 35]. The wide CIs of the ORs of influenza infection in vaccinated asthmatic patients could be due to the very nature of asthma and its heterogeneity in type and severity.

Since no significant association between vaccinated and asthmatic patients on influenza infection was detected, the simplest explanation is that this study may have a lack of power. The sample size of the study is consistent with the level of prevalence of asthma in Spain, which is considered low to medium, [11] and therefore an accurate and valid representation of the target population of this study. Nevertheless, the reasonable sample size should have allowed for the detection of a medium effect size, and the fact that no such effect was detected may indicate that, if it exists, it is probably not very large.

The heterogeneity of the patient group in itself is a limitation for this study. Factors such as cognitive status, frailty, level of disability, other comorbidities and even age, that may have mediated in the association have not been considered in this study. Finally, it must be mentioned that in this study, the severity of asthma was not assessed and this may have as well influenced the association between asthma and influenza. This could lead to a certain type of residual confounding bias that, unfortunately, is very difficult to deal with.

Conclusion

This study provides evidence that asthma is an important risk factor for influenza in hospitalized elderly people. The results show a trend in which vaccinated asthmatics present a better evolution of the infection and therefore vaccination might have a possibly protective effect, although the results are inconclusive. With these results, given the vulnerability of this population and the lack of other protective factors currently available, the promotion of vaccination within the asthmatic community seems to be justified. However, further research, such as that being carried out by the Seasonal Influenza Vaccine Effectiveness II group is required to explore this interaction.

Acknowledgements

The other members of the Working Group for Project FIS PI12/02079 'Effectiveness of influenza and pneumococcal polysaccharide 23-valent vaccines in elderly people' are: J.M. Mayoral (Servicio de Vigilancia de Andalucía), J. Díaz-Borrego (Servicio Andaluz de Salud), A. Morillo (Hospital Universitario Virgen del Rocío), J. Gutiérrez (Hospital Universitario Puerta del Mar), M. Pérez-Ruiz, M.A. Fernández-Sierra (Hospital Universitario San Cecilio y Virgen de las Nieves), S. Tamames (Dir. General de Salud Pública, Investigación, Desarrollo e Innovación, Junta de Castilla y León), S. Rojo-Rello (Hospital Clínico Universitario de Valladolid), R. Ortiz de Lejarazu (Universidad de Valladolid), M.I. Fernández-Natal (Complejo Asistencial Universitario de León), T. Fernández-Villa (GIIGAS-Grupo de Investigación en Interacción Gen-Ambiente y Salud, Universidad de León), A. Pueyo (Hospital Universitario de Burgos), A. Vilella (Hospital Clínic), A. Antón (Hospital Universitari Vall d'Hebron; Universitat Autònoma de Barcelona), G. Navarro (Corporació Sanitària i Universitària ParcTaulí), M. Riera (Hospital Universitari Mútua Terrassa), E. Espejo (Hospital de Terrassa), M.D. Mas, R. Pérez (ALTHAIA, Xarxa Hospitalaria de Manresa), J.A. Cayla, C. Rius (Agència de Salut Pública de Barcelona; CIBERESP), P. Godoy (Agència de Salut Pública de Catalunya; Institut de Recerca Biomèdica de Lleida, Universitat de Lleida; CIBERESP), N. Torner (Agència de Salut Pública de Catalunya; Universitat de Barcelona; CIBERESP), C. Izquierdo, R. Torra (Agència de Salut Pública de Catalunya), N. Soldevila, I. Crespo (Universitat de Barcelona; CIBERESP), M.F. Domínguez-Berjon, M.A. Gutiérrez, S. Jiménez, E. Gil, F. Martín, R. Génova-Maleras (Consejería de Sanidad), M.C. Prados, F. Enzine de Blas (Hospital Universitario la Paz), J.C. Galán, E. Navas, L. Rodríguez (Hospital Ramón y Cajal), C.J. Álvarez, E. Banderas (Hospital Universitario 12 de Octubre), J. Chamorro (Complejo Hospitalario de Navarra), I. Casado, J. Díaz (Instituto de Salud Pública de Navarra), M.J. López de Goicoechea (Hospital de Galdakao).

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding source

This study was funded by the National Plan of I + D + I 2008–2011 and ISCIII-Subdirección General de Evaluación y Fomento de la Investigación (Project PI12/02079), and was cofounded by Fondo Europeo de Desarrollo Regional (FEDER, Unión Europea. Una manera de hacer Europa), and the Catalan Agency for the Management of Grants for University Research (AGAUR Grant number 2014/SGR 1403). Funders played no role in the study design, data collection and analysis, the decision to publish, and manuscript preparation.

ORCID

Àngela Domínguez  <http://orcid.org/0000-0003-0219-1907>

References

- Koyanagi K, Koya T, Sasagawa M, Hasegawa T, Suzuki E, Arakawa M, et al. An analysis of factors that exacerbate asthma, based on a Japanese questionnaire. *Allergol Int* 2009;58(4):519–527. Epub 2009/08/25. doi: [10.2332/allergolint.09-OA-0095](https://doi.org/10.2332/allergolint.09-OA-0095). PubMed PMID: 19700931
- Treanor J. Influenza (including avian influenza and swine influenza). In: Bennet JD, Dolin R, Blaser MJ, editors. *Principles and practice of infectious diseases*, 8th ed. Philadelphia, PA: Elsevier; 2015:2000–2029.
- World Health Organization. Influenza (seasonal). Fact sheet 211: World Health Organization 2016 [December 16 2016]. Available from: <http://www.who.int/mediacentre/factsheets/fs211/en/>
- Foppa IM, Cheng PY, Reynolds SB, Shay DK, Carias C, Bresee JS, et al. Deaths averted by influenza vaccination in the U.S. during the seasons 2005/06 through 2013/14. *Vaccine* 2015;33(26):3003–3009. Epub 2015/03/23. doi: [10.1016/j.vaccine.2015.02.042](https://doi.org/10.1016/j.vaccine.2015.02.042). PubMed PMID: 25812842; PubMed Central PMCID: PMCPCMC4834450.
- Bonmarin I, Belchior E, Lévy-Bruhl D. Impact of influenza vaccination on mortality in the French elderly population during the 2000–2009 period. *Vaccine* 2015;33(9):1099–1101. Epub 2015/01/17. doi: [10.1016/j.vaccine.2015.01.023](https://doi.org/10.1016/j.vaccine.2015.01.023). PubMed PMID: 25604800
- Fiore AE, Shay DK, Broder K, Iskander JK, Uyeki TM, Mootrey G, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Mortal Wkly Rep* 2008;57 SRC – GoogleScholar:1–60.
- Heymann PW, Platts-Mills TA, Johnston SL. Role of viral infections, atopy and antiviral immunity in the etiology of wheezing exacerbations among children and young adults. *Pediatr Infect Dis J* 2005;24(11 Suppl):S217–S222, discussion S20–S21. Epub 2005/12/27. PubMed PMID: 16378049
- Koshio N, Hasegawa T, Suzuki K, Tanabe Y, Koya T, Sakagami T, et al. Analysis of the influenza A (H1N1) 2009 pandemic infection in Japanese asthmatic patients: using a questionnaire-based survey. *Allergol Int* 2014;63(1):67–74. Epub 2014/01/25. doi: [10.2332/allergolint.13-OA-0609](https://doi.org/10.2332/allergolint.13-OA-0609). PubMed PMID: 24457814
- Nicholson KG, Nguyen-Van-Tam JS, Ahmed AH, Wiselka MJ, Leese J, Ayres J, et al. Randomised placebo-controlled crossover trial on effect of inactivated influenza vaccine on pulmonary function in asthma. *Lancet (Lond Engl)* 1998;351(9099):326–331. Epub 1998/07/04. doi: [10.1016/S0140-6736\(97\)07468-0](https://doi.org/10.1016/S0140-6736(97)07468-0). PubMed PMID: 9652613
- Watanabe S, Hoshiyama Y, Matsukura S, Kokubu F, Kurokawa M, Kuga H, et al. Prevention of asthma exacerbation with vaccination against influenza in winter season. *Allergol Int* doi102332allergolint54305. 2005;54 SRC – GoogleScholar:305–309. doi: [10.2332/allergolint.54.305](https://doi.org/10.2332/allergolint.54.305)
- Basagana X, Sunyer J, Zock JP, Kogevinas M, Urrutia I, Maldonado JA, et al. Incidence of asthma and its determinants among adults in Spain. *Am J Respir Crit Care Med* 2001;164(7):1133–1137. Epub 2001/10/24. doi: [10.1164/ajrccm.164.7.2012143](https://doi.org/10.1164/ajrccm.164.7.2012143). PubMed PMID: 11673198
- European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996;9(4):687–695. Epub 1996/04/01. PubMed PMID: 8726932
- Centers for Disease Control and Prevention. Use of influenza A (H1N1) monovalent vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2009;58(10):1–7.
- Nordin J, Anderson R, Garvis M, Kephart K, Myers C, Ottis B, et al. Institute for Clinical Systems Improvement (ICSI). Bloomington (MN): Immunizations. Institute for Clinical Systems Improvement (ICSI) 2012.
- Guarga A, Gil M, Pasarin M, Manzanera R, Armengol R, Sintés J. Comparison of primary care teams in Barcelona according to management formulas. *Atencion Primaria* 2000;26(9):600–606. Epub 2001/02/24. PubMed PMID: 11198338
- Dominguez A, Castilla J, Godoy P, Delgado-Rodriguez M, Martin V, Saez M, et al. Effectiveness of pandemic and seasonal influenza vaccines in preventing pandemic influenza-associated hospitalization. *Vaccine* 2012;30(38):5644–5650. Epub 2012/07/17. doi: [10.1016/j.vaccine.2012.06.090](https://doi.org/10.1016/j.vaccine.2012.06.090). PubMed PMID: 22796136
- Nordin J, Mullooly J, Poblete S, Strikas R, Petrucci R, Wei F, et al. Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: data from 3 health plans. *J Infect Dis* 2001;184(6):665–670. Epub 2001/08/23. doi: [10.1086/323085](https://doi.org/10.1086/323085). PubMed PMID: 11517426
- Lang PO, Mendes A, Socquet J, Assir N, Govind S, Aspinall R. Effectiveness of influenza vaccine in aging and older adults: comprehensive analysis of the evidence. *Clin Interv Aging* 2012;7:55–64. Epub 2012/02/24. doi: [10.2147/CIA.S25215](https://doi.org/10.2147/CIA.S25215). PubMed PMID: 22393283; PubMed Central PMCID: PMCPCMC3292388.
- Cates CJ, Rowe BH. Vaccines for preventing influenza in people with asthma. *Cochr Datab Syst Rev* 2013;(2):CD000364. Epub 2013/03/02. doi: [10.1002/14651858.CD000364.pub4](https://doi.org/10.1002/14651858.CD000364.pub4). PubMed PMID: 23450529
- Kaya A, Altinel N, Karakaya G, Çetinkaya F. Knowledge and attitudes among patients with asthma and parents and physicians towards influenza vaccination. *Allergol Immunopathol (Madr)* 2016. Epub 2016/10/24. doi: [10.1016/j.aller.2016.08.003](https://doi.org/10.1016/j.aller.2016.08.003). PubMed PMID: 27789065
- Sistema de Vigilancia de la Gripe en España. Informe de Vigilancia de la Gripe en España. Temporada 2013–2014. Semana 40/2013–20/2014 2014.
- Sistema de Vigilancia de la Gripe en España. Informe de Vigilancia de la Gripe en España. Temporada 2014–2015. Semana 40/2014–20/2015 2015.
- Harrell FEJ, York NY. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. 2015:978–971.
- Modern epidemiology. Rothman KJ, Greenland S, Lash TL, editors. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
- Zou GY. On the estimation of additive interaction by use of the four-by-two table and beyond. *Am J Epidemiol* 2008;168(2):212–224. Epub 2008/05/31. doi: [10.1093/aje/kwn104](https://doi.org/10.1093/aje/kwn104). PubMed PMID: 18511428

26. American Lung Association Asthma Clinical Research Centers. The safety of inactivated influenza vaccine in adults and children with asthma. *N Engl J Med* 2001;2001(345):1529–1536.
27. Spanish Ministry of Health Social Services and Equality. Vaccines-Vaccination coverage 2016.
28. Singleton JA, Greby SM, Wooten KG, Walker FJ, Strikas R. Influenza, pneumococcal, and tetanus toxoid vaccination of adults—United States, 1993–1997. *MMWR CDC surveillance summaries: Morbidity and mortality weekly report CDC surveillance summaries*. 2000;49(9):39–62. Epub 2000/10/04. PubMed PMID: 11016877
29. Pregliasco F, Sodano L, Mensi C, Selvaggi MT, Adamo B, Argenio P, et al. Influenza vaccination among the elderly in Italy. *Bull World Health Organ* 1999;77:127–131.
30. Joseph C, Goddard N. Influenza vaccine uptake in the elderly: results from a rapid assessment of the effectiveness of new government policy in England for the winters 2000/2001 and 2001/2002. *Vaccine* 2003;21(11–12):1137–1148. Epub 2003/02/01. PubMed PMID: 12559791
31. Privilegio L, Falchi A, Grisoni ML, Souty C, Turbelin C, Fonteneau L, et al. Rates of immunization against pandemic and seasonal influenza in persons at high risk of severe influenza illness: a cross-sectional study among patients of the French Sentinelles general practitioners. *BMC Publ Health* 2013;13:246. Epub 2013/03/22. doi: [10.1186/1471-2458-13-246](https://doi.org/10.1186/1471-2458-13-246). PubMed PMID: 23514534; PubMed Central PMCID: PMC3621692.
32. Krieger JW, Castorina JS, Walls ML, Weaver MR, Ciske S. Increasing influenza and pneumococcal immunization rates: a randomized controlled study of a senior center-based intervention. *Am J Prev Med* 2000;18(2):123–131. Epub 2000/03/04. PubMed PMID: 10698242
33. Sarria A, Timoner J. Determination of influenza vaccination in persons 65 sources of age and older. *Rev Espanola Salud Publ* 2002;76(1):17–26. Epub 2002/03/22. PubMed PMID: 11905396
34. Carreiro-Martins P, Gomes-Belo J, Papoila AL, Caires I, Palmeiro T, Gaspar-Marques J, et al. Chronic respiratory diseases and quality of life in elderly nursing home residents. *Chronic Respir Dis* 2016;13(3):211–219. Epub 2016/03/12. doi: [10.1177/1479972316636990](https://doi.org/10.1177/1479972316636990). PubMed PMID: 26965222
35. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ (Clinical research ed)*. 1996;312(7040):1195–1199. Epub 1996/05/11. PubMed PMID: 8634562; PubMed Central PMCID: PMC3621692.