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Effect of vaccination, comorbidities and age on mortality and severe disease associated with influenza during the season 2016–2017 in a Spanish tertiary hospital

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ABSTRACT

Background: Identifying risk factors for complications or death associated with influenza remains crucial to target preventive interventions. Scores like the Charlson comorbidity index (CCI) may be of help. The aims of this study were to assess the effect of vaccination and comorbidities on severe influenza disease and influenza-related death among hospitalized patients during the season 2016/17; and to evaluate the validity of the CCI to predict death among these patients.

Methods: Data from adult patients (≥18 years old) with influenza infection admitted to La Paz University Hospital (LPUH) were recorded during the 2016/17 epidemic. The effect of influenza vaccine to prevent severe influenza or death was evaluated using multivariate logistic regression models. The area under the curve of the CCI and the age-adjusted CCI were compared to assess the predictive effect on mortality.

Results: A total of 342 adult patients with influenza infection were admitted, of which 83 developed severe influenza and 25 died during hospitalization. There were no differences between patients who survived and those who died concerning the CCI, but the age-adjusted CCI was higher in fatal cases (p-value = 0.005). Influenza vaccine had no statistically significant effect on the risk of mortality (p-value = 0.162) while age (OR: 1.12, p-value < 0.001) and dementia (OR: 3.05, p-value = 0.016) proved to be independent predictors for mortality. The seasonal vaccine was found to be protective for severe infection (OR: 0.54, p-value = 0.019). The age-adjusted CCI was a better predictor of mortality than the crude CCI.

Conclusions: Age and dementia are significant independent risk factors for mortality associated with influenza among hospitalized patients. The age-adjusted CCI seems to be a better predictor of mortality than the crude CCI. Influenza vaccine has shown to be effective in preventing severe influenza in the season 2016/17 among hospitalized patients and should be promoted in population at risk.

Introduction

Influenza epidemics are responsible for a great population-burden of morbidity and mortality annually. It is a frequent cause of hospital admissions during the epidemic months and a considerable source of expense. Although most infected people experience an uncomplicated illness, there is a subgroup of patients in which, due to age and/or comorbidities, influenza infection may require hospital admission and even cause death [1].

According to the Spanish National Centre of Epidemiology, during the season 2016–2017 99% of virus samples analysed were influenza A, from which 99% were A(H3N2) [2], agreeing with data reported by the European Centre for Disease Prevention and Control (ECDC) [3].

The influenza vaccine is designed every year based on the subtypes of viruses predominating in the previous season. The World Health Organization recommended for the season

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2016–2017 in the northern hemisphere the trivalent vaccine containing A/California/7/2009 (H1N1) pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus and B/Brisbane/60/2008-like virus [4]. In Spain, the trivalent influenza vaccine is offered at no cost to people older than 65 years or with high-risk comorbidities.

During the influenza season 2016–2017, EuroMOMO reported in its weekly European mortality bulletin an excess all-causes mortality (affecting mostly the group aged 65 years and above), similar to the one observed during the season 2014–2015, also characterized by the dominance of A(H3N2) [5], with an estimated number of 217,000 excess deaths [6]. Some countries also experienced extremely cold weather in the beginning of the year 2017, which could also contribute to the excess mortality [7]. In accordance with this information, the ECDC reported that confirmed cases of influenza A infection notified by hospitals were mainly in adults aged 65 years or older. Besides, the risk of severe infection for influenza A(H3N2) is higher than for A(H1N1) strain as also is the risk of excess of mortality [8].

Risk factors for severe disease have been previously reported [9], but there are fewer studies using a weighted comorbidity index to assess the risk of influenza associated complications or death. Despite the Charlson comorbidity index (CCI) was initially developed to measure the perioperative mortality risk not associated with surgery [10], its use has been extended in medical research as a method to quantify the burden of disease. The CCI is a weighted score of 17 comorbidities based on the 1-year mortality risk of each condition.

The objectives of our study were to describe the population admitted to La Paz University Hospital (LPUH) with influenza during the season 2016–2017, to study the effect of comorbidities and age on the risk of suffering severe illness and/or death and to evaluate the influence of recommended seasonal vaccine on the risk of developing severe influenza episode and/or death among hospitalized patients.

Methods

Setting

In December 2010, following national and European recommendations, a hospital-based influenza sentinel surveillance started in the Autonomous Community of Madrid. LPUH was selected as one of the sentinel sites for the surveillance of severe influenza confirmed cases. [11]. This is a tertiary hospital located in the city of Madrid, with a reference population of more than 500,000 people, serving as a referral hospital for several diseases. It has 1300 beds and approximately 50,000 admissions per year.

Inclusion criteria and microbiological diagnosis

All adult patients (≥18 years) admitted to LPUH with a confirmed microbiological diagnosis of influenza A, B or C virus during the influenza season 2016–2017 were included. The microbiological diagnosis was established by Polymerase Chain Reaction (PCR). This test was performed on patients with influenza-like symptoms and underlying chronic diseases or at high risk of complications by obtaining a nasopharyngeal swab. According to the hospital's protocol, patients with confirmed influenza infection received treatment with oseltamivir.

Data collection

In Spain, the monitoring for the influenza season starts at week 40 and runs until week 20 of the following year. Confirmed influenza cases admitted to the hospital during the season 2016–2017 were prospectively recorded by the Department of Preventive Medicine (infection-control physicians at hospitals), based on clinical records. Information on different variables was also prospectively obtained: sex; age; length of stay attributable to influenza (calculated since the sample collection for influenza laboratory confirmation); type of influenza virus; comorbidities included in the CCI; history of influenza vaccination on current season, according to Spanish Ministry of Health criteria (≥65 years, pregnant women or patients with major chronic conditions) based on the clinical records of primary healthcare information system; criteria of severe influenza, as defined in the guidelines for influenza surveillance in Spain (pneumonia, multiple organ failure, adult respiratory distress syndrome or septic shock) [12]; and whether death from any cause occurred during admission. From these data, we calculated the CCI as well as the age-adjusted CCI (aCCI) by allocating one point to the score for each decade over 40 years.

Statistical analysis

First, the differences between patients admitted with influenza who survived and those who died during admission were assessed, using the Wilcoxon rank-sum test for those continuous variables and the chi-square test or the Fisher's exact test for those categorical. Subsequently, to evaluate the effect of influenza vaccine on the risk of death or severe influenza, a multivariate logistic regression adjusted for sex, age and comorbidity was fitted. The influence of some specific comorbidities on mortality was also explored with a logistic regression, adjusting in this case for sex, age and vaccination status. The significance level was established at $p < 0.05$. To evaluate the accuracy of the CCI in comparison to the aCCI to predict death, ROC curves were performed using a ROC contrast test with the DeLong nonparametric approach [13]. Finally, the proportion of vaccination among those patients who had indication of immunization was calculated.

Analyses were performed using the statistical packages Stata 14, SPSS 23 and SAS 9.3.

Ethics

Data collection and management was performed by the Preventive Medicine Department as part of the mandatory activity during the influenza season. Data were managed anonymously and following the ethical code of the hospital. No informed consent was required.

Results

A total of 342 adults with a confirmed influenza diagnosis were admitted to LPUH during the season 2016–2017. The epidemic curve is represented in Fig. 1. First cases appeared at week 48 2016, and the last one at week 9 2017.

From the total of patients, 98.82% had influenza A, 0.88% influenza B and 0.29% influenza C. Twenty-four point six percent of the patients suffered a severe influenza episode, 2% of the patients admitted required intensive care at some point of the episode and 7.3% died. Only 1.46% of patients were pregnant women. The most frequent cause of severe influenza was pneumonia (83.1%), followed by septic shock (19.3%).

The distribution of demographic variables (age and sex), vaccination, severe influenza, length of stay and the CCI (adjusted for age and crude) in the total population, deceased and alive, is shown in Table 1, as so are p-values from univariate analysis. The mean age of people who died was significantly higher than in those who survived ($p < 0.001$). No differences were found in admitted patients and mortality according to sex ($p = 0.512$). There was no difference either in length of stay or in the percentage of vaccination.

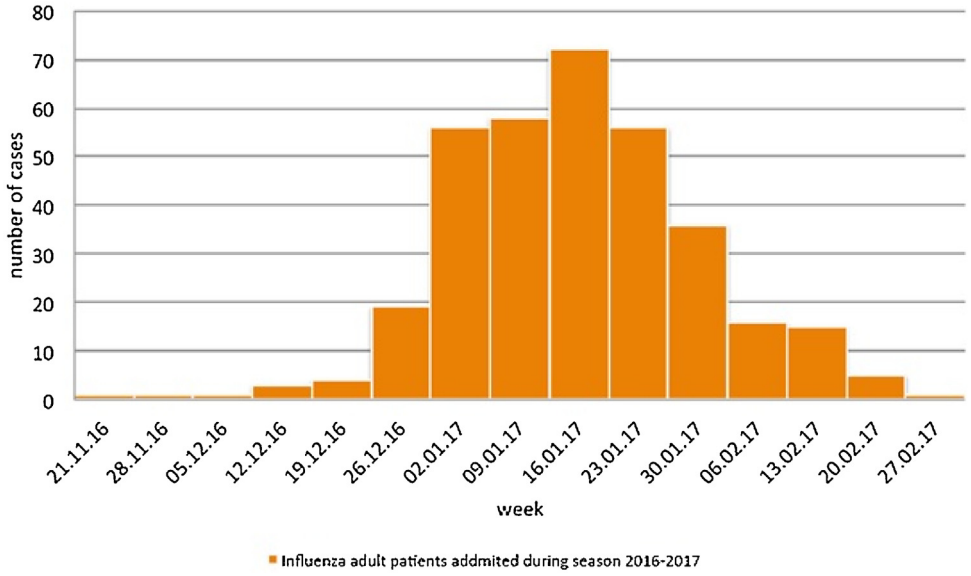

Fig. 1. Weekly influenza adults admitted in LPUH during the season 2016–2017.

Table 1
Characterization of total, deceased, and alive patients hospitalized with flu infection.

Variables	Total (n = 342)	Deceased (n = 25)	Alive (n = 317)	p
Age-yr. mean ± sd	78.04 ± 14.54	88.22 ± 8.93	77.18 ± 14.65	**<0.001**
Sex no. (%)				0.512
Women	182 (53.2%)	15 (60%)	167 (52.7%)	
Men	160 (46.8%)	10 (40%)	150 (47.3%)	
Length of stay- days median (IQR)	7 (5–10)	7 (3–13)	7 (3–13.5)	0.830
Vaccinated no. (%)	175 (51.6%)	11 (44.0%)	164 (52.2%)	0.436
Severe influenza no. (%)	84 (24.6%)	21 (84.0%)	63 (19.9%)	**<0.001**
Charlson comorbidity Index median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.482
CCI adjusted for age median (IQR)	5 (4–7)	6 (6–7)	5 (4–6)	**0.005**

Bold values highlight statistically significant differences (<0.05).

Table 2
Logistic regression models for mortality and severe influenza.

Variables	OR	Confidence interval		p-Value
		Lower	Upper	
Mortality				
Vaccinated	0.54	0.23	1.28	0.162
Age	1.12	1.06	1.19	**<0.001**
Sex (female)	0.88	0.36	2.17	0.788
Charlson index	1.06	0.85	1.33	0.584
Severe influenza				
Vaccinated	0.54	0.32	0.90	**0.019**
Age	1.01	0.99	1.02	0.520
Sex (female)	0.63	0.38	1.06	0.082
Charlson index	1.04	0.92	1.18	0.552

Bold values highlight statistically significant differences (<0.05).

However, there were statistically significant differences in the presence of severe influenza episode among deceased (84%) and alive (19.9%) patients (p < 0.001). Lastly, no differences in the CCI were found between both groups (p = 0.482), but the age-adjusted CCI was significantly higher in fatal cases (p = 0.005).

Only 52.2% of the patients admitted with influenza had been vaccinated against influenza in the current season, although 98.5% of them met the criteria for receiving vaccination.

Table 2 presents the results from multivariate logistic regressions to assess the effect of vaccination on the risk of mortality and severe influenza episode adjusted for sex, age and comorbidities (CCI). In the regression model for mortality, the seasonal vaccine did not have a significant effect (OR: 0.54, p-value = 0.162). We did not find differences either according to sex or the CCI, but age proved to be an important risk factor for mortality (OR: 1.12, p-value < 0.001).

However, in logistic regression model for severe influenza episode, the vaccine showed a statistically significant protective effect (OR: 0.54, p-value = 0.019) and in this case, neither sex, age nor the CCI seem to have any effect (Table 2).

The most frequent comorbidities from those included in the CCI in patients admitted with influenza were chronic pulmonary disease (38.9%), diabetes mellitus (25.7%) and congestive heart failure (22.2%) (Table 3). Dementia and congestive heart failure were significantly associated with fatal cases (p < 0.001 and p = 0.026 respectively). Another regression model for mortality was performed including these comorbidities, adjusting for the same variables (age, sex and vaccination status) (Table 4). Congestive heart failure lost statistical significance (OR: 1.46, p = 0.417) while dementia remained as an independent risk factor for mortality in these patients (OR 3.05, CI 95% 1.23–7.57, p = 0.016).

In order to compare the effectiveness of the CCI (adjusted for age and crude) for the prediction of influenza mortality, the area under the curve (AUC) was performed for both indexes (Fig. 2), proving a significant prediction in case of the CCI adjusted for age (C-statistic 0.66) but not significant for the crude CCI (C-statistic 0.543), being ROC Contrast Test p-value < 0.001.

Discussion

This study provides a complete characterization of patients admitted with influenza infection during the season 2016–2017

Table 3
Comorbidities by total, deceased and alive patients hospitalized with influenza infection.

Disease	Total (n = 342)	Deceased (n = 25)	Alive (n = 317)	p
Myocardial infarction n. (%)	35 (10.2%)	2 (8.0%)	33 (10.4%)	0.702
Congestive heart failure n. (%)	76 (22.2%)	10 (40.0%)	66 (20.8%)	**0.026**
Peripheral vascular disease n. (%)	7 (2.0%)	0 (0.0%)	7 (2.2%)	0.453
Cerebrovascular disease n. (%)	44 (12.9%)	2 (8.0%)	42 (13.2%)	0.450
Hemiplegia or paraplegia n. (%)	11 (3.2%)	0 (0.0%)	11 (3.5%)	0.343
Dementia n. (%)	59 (17.3%)	11 (44.0%)	48 (15.1%)	**<0.001**
Chronic pulmonary disease n. (%)	133 (38.9%)	9 (36.0%)	124 (39.1%)	0.758
Rheumatologic disease n. (%)	17 (5.0%)	3 (12.0%)	14 (4.4%)	0.093
Peptic ulcer disease n. (%)	14 (4.1%)	1 (4.0%)	13 (4.1%)	0.980
Diabetes without chronic complications n. (%)	78 (22.8%)	6 (24.0%)	72 (22.7%)	0.883
Diabetes with chronic complications n. (%)	10 (2.9%)	1 (4.0%)	9 (2.8%)	0.740
Renal disease n. (%)	6 (1.8%)	0 (0.0%)	6 (1.9%)	0.488
Malignant neoplasm n. (%)	31 (9.1%)	1 (4.0%)	30 (9.5%)	0.360
Leukemia n. (%)	7 (2.0%)	0 (0.0%)	7 (2.2%)	0.453
Lymphoma n. (%)	6 (1.8%)	0 (0.0%)	6 (1.9%)	0.488
Metastatic solid tumor n. (%)	16 (4.7%)	1 (4.0%)	15 (4.7%)	0.868
Mild liver disease n. (%)	17 (5.0%)	2 (8.0%)	15 (4.7%)	0.469
Moderate or severe liver disease n. (%)	5 (1.5%)	0 (0.0%)	5 (1.6%)	0.527
AIDS n. (%)	3 (0.9%)	0 (0.0%)	3 (0.9%)	0.625

Bold values highlight statistically significant differences (<0.05).

Table 4
Logistic regression model for mortality by comorbidities.

Variables	OR	Confidence interval		p-Value
		Lower	Upper	
Congestive heart failure	1.46	0.58	3.67	0.417
Dementia	3.05	1.23	7.57	**0.016**
Sex (female)	0.74	0.30	1.86	0.524
Age	1.10	1.04	1.17	**0.002**
Vaccine	0.53	0.22	1.26	0.149

Bold values highlight statistically significant differences (<0.05).

in a tertiary hospital in Spain. It also allows assessing the effect of comorbidities, sex and age as well as the recommended vaccine on the risk of suffering severe illness and/or death. Characterizing patients with severe or fatal influenza enables us to target vaccination and improvements in clinical management strategies towards high-risk groups.

As we have described, most of our cases were people with underlying risk conditions, chronic lung disease presenting as the most common comorbidity.

An international study performed in northern hemisphere countries during the 2013–2014 season, where subtype A(H3N2) was also the dominant virus, proved that hospitalization risk was also higher in cardiovascular disease, asthma, immunosuppression, renal disease, liver disease, autoimmune disease and pregnancy

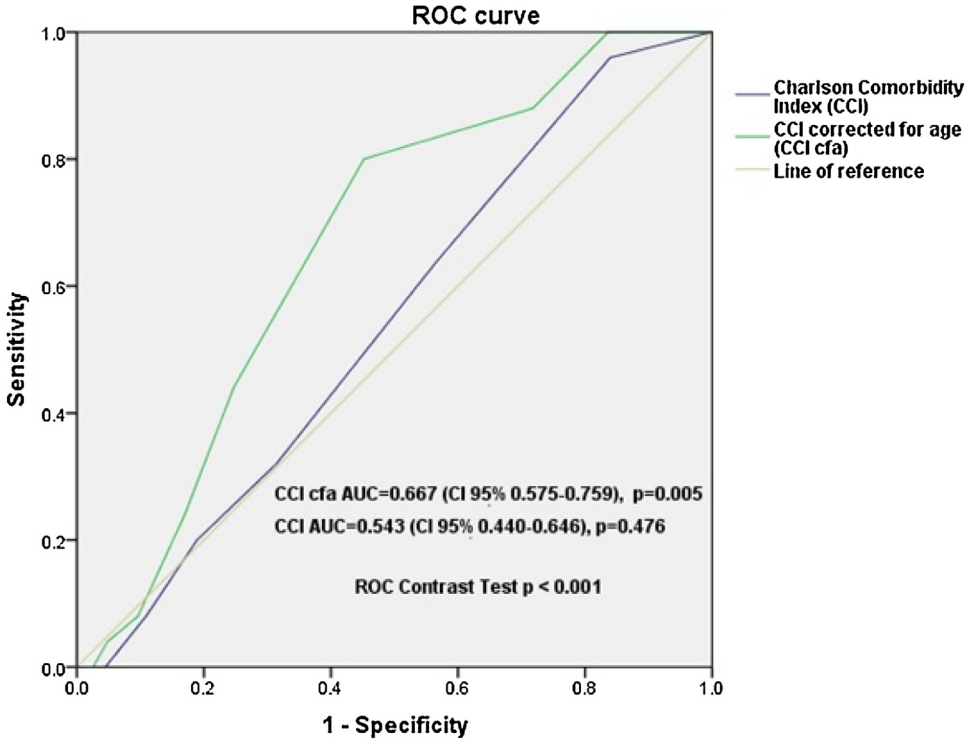

Fig. 2. CCI and aCCI ROC curves for mortality.

[14]. However, it must be considered that subtype A(H1N1)pdm09 was also present in that season, consequently data are not entirely comparable.

Regarding the association of specific comorbidities with the risk of developing severe influenza infection, some studies have reported, during the 2009 A(H1N1) pandemic, a direct relationship between some conditions (chronic respiratory, renal, hepatic and cardiac disease, advanced age, obesity and pregnancy), very similar to those increasing the risk for seasonal influenza [15]. In our study, mortality was significantly associated with dementia, which has been reported as an independent risk factor for death in patients with influenza only in a few studies, increasing by 50% the risk of death from influenza in demented patients [16]. A direct relationship between influenza-related death and low scores in cognitive tests in patients with dementia has also been reported [17]. Although a relation between pneumonia and dementia has been described before, in our study we did not find it, agreeing with other studies in which an independent association between dementia and non-pneumonia-related death has been described [18,19]. This increased risk seems to be related to a more insidious clinical presentation and delayed diagnosis/under-diagnosis of influenza in these patients [16], in addition to suboptimal care in acute hospitalization and a greater number of adverse effects [20].

Regardless of the fact that the CCI has been used to predict severe or fatal influenza in other studies [21], to the best of our knowledge the age-adjusted CCI has been scarcely used to predict short-term death risk associated with influenza infection. The age-adjusted CCI seems to predict mortality associated with influenza infection better than the crude index, although the area under the curve has a modest value and a C- statistic of 0.66 proves a not very good prediction of this index for influenza-related mortality. We suggest incorporating the age-adjusted CCI as a predictor of influenza associated mortality and highlight the importance of taking into account age as a "comorbidity" frequently forgotten.

The vaccine against A(H3N2) is known to have a low effectiveness in preventing influenza infection due to antigenic changes during the vaccine production process and season circulation [22]. It has been recently described that this could be explained by an antigenic change of HA (haemagglutinin) which hinders the ability of influenza vaccine to induce an antibody response that effectively protects against circulating seasonal A(H3N2) viruses [23]. Also, an age-related decline of cellular immune response to influenza A(H3N2) has been described in subjects of 60 years and older [24].

To interpret our results we must consider these facts joined to immunosenescence, since one of the main reasons for influenza vaccination according to the Spanish Ministry of Health recommendations is being 65 or more years old. It is widely known that an advanced age produces changes in the immune system, resulting in an impaired response to infectious agents and vaccination [25]. As population ageing is increasing and severe and fatal influenza episodes affect mostly older people, some authors have suggested that a booster vaccine or a more antigenic vaccine development might be contemplated [26].

In our study, we have assessed the effect of vaccination on the risk of severe disease and mortality, finding a protective effect just for severe episodes but not for death, which might be partially explained by a small sample size. We should also highlight that, despite the fact that only hospitalized patients constituted our study population, we found a protective effect of vaccine for severe episodes, which could be amplified when extrapolating these results to the total population. For this reason, the protection for fatal episodes might be underestimated too.

Other studies carried out in Spain found a protective effect of vaccination on severe cases, but in seasons when subtype A(H1N1)pdm09 was dominant and criteria for severe influenza were different, therefore our study adds more evidence to this matter [27]. No protective effect of vaccination on mortality was also described during the season 2012–2013, when A(H3N2) was dominant in the northern hemisphere too, which agrees with our results [28]. Regarding pneumonia, our results are also consistent with previous studies [29], suggesting that influenza vaccination can reduce the incidence of pneumonia in patients with influenza.

Even though we have not found a significant vaccination effect on mortality, it played an important role in the reduction of severity of influenza episode. A severe episode in patients who need hospital admission means a reduction in quality of life because of a destabilization of chronic diseases, and a higher risk of nosocomial infections like pneumonia, which is a very frequent complication of influenza infection. Although vaccination does not always prevent infection, it has been proved to reduce viremia and length of illness [27]. Therefore, severe influenza results in an increase of direct costs and resources employed, which sometimes causes hospitals overcrowding during the influenza season. This kind of studies are very useful for health planners and clinicians to anticipate future needs.

Another aspect to highlight is the main role of infection prevention and control units on active influenza hospital-based surveillance by following-up epidemics, notifying and controlling all influenza admitted cases as indicated in standard operating procedures previously established, being one of the main strengths of our study. The fact that it was conducted in a tertiary hospital, including all confirmed cases of influenza that were hospitalized (low classification bias) was another relevant point of our study. Clinical data and vaccination history were obtained through the review of medical records and registers which implies a lower risk of information bias than self-referred data. Using the age-adjusted CCI to predict risk of severe influenza and mortality, including in this evaluation comorbidities that do not mean *per se* an indication for vaccination like dementia or liver disease was also a strength.

However, our study had also some limitations: clinical details or comorbidities may have not been well registered in the clinical records. Our sample was limited to only one centre (LPUH), including exclusively hospitalized patients, which determines the sample size and affects the power of study. Although the CCI is a good scale to evaluate the risk of death attributable to comorbidities, it does not include other clinical features like organ transplants, obesity or tobacco consumption, which can certainly affect the outcome, especially pneumonia, and therefore severe influenza.

Conclusions

The age adjusted CCI is a better predictor of influenza-related mortality than the crude CCI among hospitalized patients. Advanced age is a high-risk factor for influenza-related death and should be considered as a criterion for hospital admission independently of comorbidities. Patients suffering from cognitive impairment/dementia and influenza infection are also under a higher risk of mortality. The recommended vaccine for the season 2016–2017 has shown a protective effect in hospitalized patients for developing severe disease. There is still a great proportion of patients who would benefit from influenza vaccination that are not being vaccinated. Consequently, strategies to immunize patients at high risk of severe disease or mortality should be emphasized.

Contributions

Enrique Gutiérrez-González, José Miguel Cantero-Escribano and Lidia Redondo-Bravo equally contributed to the design of the study, acquisition of data, analysis, interpretation of results and drafting of the article.

Isabel San Juan-Sanz, Ana Robustillo-Rodela and Emilio Cendejas-Bueno contributed to the design of the study, acquisition of data and revised the article critically.

The Influenza working group contributed to the design of the study and revised the article critically.

All authors have approved the final version of this article.

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Competing interests

None declared.

Ethical approval

Not required.

Appendix A.

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