Original Article

Effectiveness of influenza vaccination in hospitalized cases in Catalonia during the 2017-2018 season

Lesly Acosta[1], Nuria Soldevila[2,3], Nuria Torner[2], Ana Martínez [4,2], Xavier Ayneto [4], Cristina Rius [2,5], Mireia Jané[2,3,4], Angela Domínguez[2,3] and the PIDIRAC Severe Hospitalized Influenza Surveillance Network of Catalonia Working group

1. Polytechnic University of Catalonia/ BARCELONATECH
2. CIBER Epidemiologia Salud Publica. CIBERESP. PREVICET Program
3. Department of Medicine. University of Barcelona
4. Public Health Agency of Catalonia.
5. Public Health Agency of Barcelona

* Correspondence: nuriatorner@ub.edu; Tel.: +34 93 402 45 66

Abstract: Seasonal flu is a common cause of hospital admission, especially in populations with comorbidities or extreme ages. The objective was to investigate the effectiveness of influenza vaccination in hospitalized laboratory confirmed influenza cases (HLCI). A retrospective case-to-case study of HLCI adults in Catalonia, during the 2017-2018 season was carried out. Differences in means, proportions, factors associated with vaccine effectiveness (VE) and intensive care unit (ICU) were assessed by t-test, Chi-squared test, logistic regression and multivariate logistic regression, accordingly. A total of 1414 HLCI aged 18 years and older were included in the analysis, 465 (33%) vaccinated, (of these 94% were ≥ 60 yrs.), 804 (56.9%) were men, 61% were type B influenza and 15.1% required ICU admission. An age of 60 or older was associated with lower ICU admission (OR 0.44; 95%CI 0.32-0.61; <0.001). Mean length of hospital stay (LOS) and ICU stay (LICS) did not differ significantly between vaccinated and unvaccinated, although ICU admission proportion did (11.2% in vaccinated vs. 17.1% in unvaccinated). A longer hospital stay was observed in those patients being admitted to ICU being 22.4 (SD 20.3) days vs 11.1(SD14.4) days (p<0,001) for those not admitted to ICU. Being vaccinated avoids ICU admission, aOR of 69% (95%CI 0.49-0.99; 0.04). Considering types A and B jointly, VE to avoid ICU admission was 31% (95%CI 1-52). For type B virus only, VE was 25% (95%CI 18-51). Annual influenza vaccination can reduce the need of admission to ICU in cases of laboratory confirmed influenza virus infections. A shorter mean hospital stay was observed in vaccinated cases, but the result is not statistically significant.

Keywords: influenza; Intensive Care Unit; vaccine effectiveness; length of stay

1. Introduction

Seasonal flu is a common cause of hospital admission, especially in populations with comorbidities or extreme ages. Each year, seasonal influenza epidemics cause an estimated 3 to 5 million severe illnesses and 290,000 to 650,000 deaths worldwide [1].Severe outcomes are more frequently observed in the very young and elderly, as well as in pregnant women, immunocompromised individuals, and patients of any age with chronic diseases [2]. Despite the overall moderate protection the vaccine may offer to prevent influenza virus infection, the main preventive measure to spare severity and hospitalization is yearly vaccination to the above-mentioned groups of population at risk. Severity implies not only complications such as pneumonia, severe respiratory distress, multiorgan failure and death but also implies intensive care unit (ICU) admission because of the complications derived from influenza infection. ICU admission has been associated with adverse outcomes and excess costs to the health care system especially with longer hospital stays (LOS) [3].

Since the 2009 AH1N1$_{pdm09}$ influenza pandemic several countries and regions have collected substantial data on severe cases of influenza to be able to assess the severity of influenza epidemics. In the Spanish region of Catalonia, the Public Health Agency's Sub-directorate of Surveillance and Response to Public Heath Emergencies of Catalonia collects data on hospitalizations with severe laboratory-confirmed influenza illness through a network of sentinel third level hospital covering approximately 62% of the population [4]. These data are used in turn for decision making on

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prevention strategies, diagnosis, and treatment. However, data that are more detailed are needed from those hospitalizations due to laboratory confirmed influenza that are not classified upon admission as a severe case. Recognizing this need, the hospital sentinel surveillance network of the PIDIRAC (Daily Information Plan for Acute Respiratory Infections) surveillance system expanded its registry to include all sentinel hospital's emergency room admissions of laboratory confirmed influenza cases[4].
The objective was to describe the behavior of laboratory confirmed influenza hospitalized cases according to seasonal influenza vaccination and whether influenza vaccination prevented ICU admission and how it related to the LOS and length of ICU stay (LICS) according to their vaccination status for the 2017–2018 influenza season in Catalonia.

2. Materials and Methods

A retrospective cohort study of confirmed influenza cases admitted to hospital facilities belonging to the 14 third level hospitals that are part of the Influenza Acute Respiratory Disease Surveillance Network in Catalonia (PIDIRAC) during the influenza season 2017-2018 was carried out. Study sample was made up of laboratory confirmed influenza cases aged 18 and older, admitted to sentinel network hospitals for more than 24 hours from October 1, 2017 to May 22, 2018.
For the study, two subsets of samples were studied:
Subset 1 was made up of severe hospitalized laboratory confirmed influenza cases (SHLCI), defined as a case of laboratory confirmed influenza virus infection that required hospitalization due to pneumonia, acute respiratory distress syndrome, septic shock, multiorgan failure, or any other severe condition, ICU admission or who developed these criteria during hospitalization for any other reason.
Subset 2 was made up of laboratory confirmed influenza cases recorded by the minimum hospital discharge data from emergency room (ER) (CMBDH-ER) discharge register according to the International Classification of Diseases (ICD-10) codes. Influenza cases being classified in the following categories: J09 Influenza due to certain identified influenza viruses – this includes the following types: AH1N1$_{pdm09}$ and influenza of animal origin; J10 Influenza due to other identified influenza viruses – this includes any specified type not of animal origin and not listed as one of the types under the novel influenza A virus category and J11 Influenza due to unidentified influenza viruses – not documented as a specific type. Only cases that were admitted to hospital ward in the same facility were included [5].
In order to assess coincident cases, both database files were merged using the patient's unique personal identifier as the merger. From the non-coincident cases with ER discharge recovered after merging, a random sample selection with stratification by hospital facility was performed to obtain a representative sample for each facility and then followed by the anonymization of data. The following clusters were predetermined: age, gender and flu week in which it was registered in order to preserve representability of the population attended in each facility. Figure 1.
Laboratory confirmation was carried out by Polymerase Chain reaction (PCR) and/or culture techniques on nasal aspirate or nasopharyngeal swab sampling described in previous publications [4,6,7].
All hospitalized cases were followed up until discharge to determine the disease progression and outcome. The variables studied were collected from each reported case using a structured questionnaire for the SHLCI cases [4]; for those cases derived from ER discharge with no available questionnaire, the information was completed by consultation of medical records. The variables studied were: gender, age, pre-existing chronic disease (chronic obstructive respiratory disease [COPD], obesity, diabetes, chronic kidney, cardiovascular and liver disease, immunodeficiency and other comorbidities which include hemoglobinopathies, severe neuromuscular diseases, impaired cognitive dysfunction), date of symptom onset and date of hospital and intensive care unit admission and discharge, antiviral treatment received and whether timing of treatment is < 48h or > 48h. of symptom onset, seasonal influenza vaccination status and influenza viral type and subtype when available.

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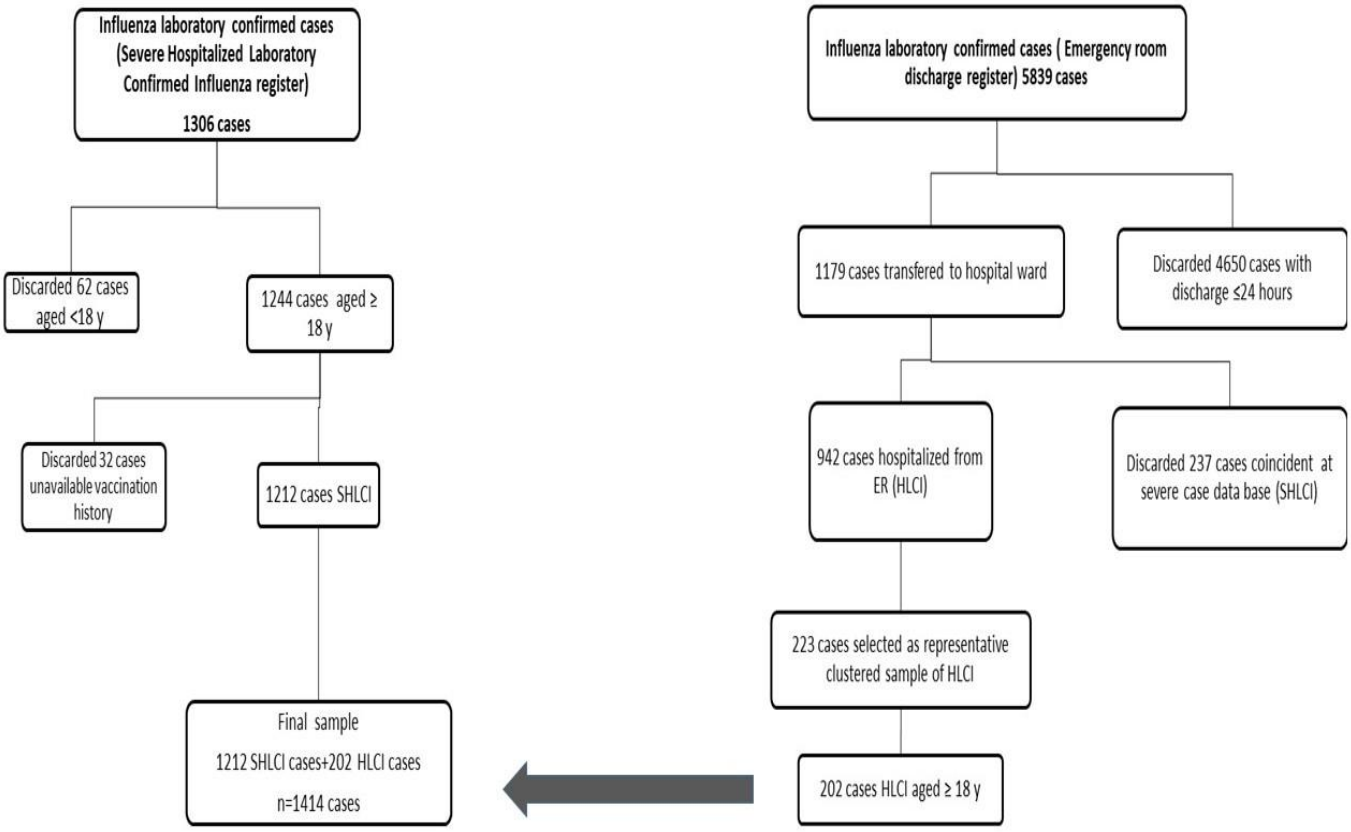

Figure 1. Patient selection flowchart from severe hospitalized laboratory confirmed (SHLCI) and laboratory confirmed influenza cases from minimum hospital discharge data set from emergency room that remained hospitalized (HLCI). Catalonia, 2017-2018.

Statistical analysis

Associations between seasonal vaccination and outcome variables (intensive care unit [ICU] admission and length of stay) and the independent variables (variables sociodemographic, virological and clinical characteristics) were assessed by a t- Student test or a Chi-squared test, accordingly. To quantify the association between the outcome variable ICU admission and each of the independent variables, crude odds ratios (OR) were obtained via univariate logistic regression models.

A multivariate logistic regression model for ICU admission, adjusted by age, gender, having at least one comorbidity, and timing of neuraminidase inhibitor treatment (NI), was employed to estimate the adjusted OR (aOR) associated with seasonal vaccination. In addition, a logistic regression model adjusted by a propensity score taking vaccination status as the outcome and based on the same adjustment covariates was explored. Vaccine effectiveness was calculated as (1-aOR) ·100%. To assess robustness of vaccine effectiveness estimates subgroups according to age, gender, influenza virus type, antiviral treatment and source of cases were calculated. The analysis was performed using the SPSS v.25 statistical package and the R v3.6.2 statistical software (http://cran.r-project.org).

Ethical aspects: The information used in the study is part of routine monitoring in the surveillance of influenza as a public health activity and does not require informed consent. Final database was anonymized at all times to preserve confidentiality of cases.

3. Results

A total of 1529 (1306 SHLCI and 223 HLCI from ER discharge selection) cases were initially recorded, 115 cases were discarded because of age or lack of vaccination status information, thus 1414 cases were included in the analysis; 465 (33%) were vaccinated cases (of these 94% were ≥ 60 y.), 804 (56.9%) were men, 859 (61%) belonged to influenza type B. Influenza A subtype was available for 160 cases (26.2%), 90 (56.3%) were $AH1N1_{pdm09}$ and 70 (43.7%) AH3N2. At least one underlying comorbidity was present in 1127 (79.7%) cases admitted to hospital, of these 406 (36%) were

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vaccinated vs 721 (64%) unvaccinated cases (OR 2.17; 1.60-2.99; p<0.001). Cardiovascular disease was the most frequent comorbidity (614 cases, 43.4%) with vaccine coverage of 38.6%. The comorbidity associated with a higher vaccine coverage was COPD (41.2%). Among 63 women of childbearing age (18 to 49 y.) included in the study, there were 8 pregnancies (12.3%) of which 2 (25%) had received influenza seasonal vaccine vs 7.3% vaccine coverage in non- pregnant women (OR 4.36 (0.64-28.32; p=0.110). At discharge, the overall difference in average length of hospital stay (LOS) with respect to vaccination status was not relevant, being 12.1 days (SD 14.1) in vaccinated patient's vs 13.1days (SD 16.8) in the unvaccinated (p=0.228). Length of ICU stay (LICS) average values were: 9.5 days (SD 9.3) in vaccinated patients vs. 9.3 days (SD 10.8) in unvaccinated patients (p=0.917) (Table 1).

Mean age of cases was 71.5y (SD 15.2), there was significant difference between SHLCI and HLCI cases (71.1y [15.3] vs 68.5y [16]; p=0.008) respectively. There was higher percentage of presence of at least one comorbidity (77.9% vs 91.4%; p<0.001) and in number of cases belonging to >60 y age group (78.2% vs 85%; p=0.040) in the HLCI cases, while seasonal vaccination coverage (35.9% vs 13.4%;<0.001) and receiving NI treatment (93.4% vs 82.3%; <0.001) was higher for SHLCI with respect to HLCI. (Table 2)

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Table 1. Distribution of influenza hospitalized cases according to influenza vaccination status. Catalonia, 2017-2018

Patient parameters	Total number of hospitalized influenza cases n=1414	Vaccinated cases n=465 (32.9%)	Unvaccinated cases n=949 (67.1%)	OR[a] (95%CI)	p value
Age mean (SD) [b]	71.5 (15.2)	77.6 (11.3)	68.5 (16.0)	1.05 (1.04;1.06)	<0.001
Age group					
>=60y	1118 (79.1%)	437 (39.1%)	681 (60.9%)	6.11 (4.13;9.37)	0.000
18-59y	296 (20.9%)	28 (9.46%)	268 (90.5%)	Ref	
Gender					
Male	804 (56.9%)	269 (33.5%)	535 (66.5%)	1.06 (0.85;1.33)	0.600
Female	610 (43.1%)	196 (32.1%)	414 (67.9%)	Ref	
Comorbidities (at least one)					
Yes	1127 (79.7%)	406 (36.0%)	721 (64.0%)	2.17 (1.60;2.99)	<0.001
No	287 (20.3%)	59 (20.6%)	228 (79.4%)	Ref	
COPD [c]					
Yes	461 (32.6%)	190 (41.2%)	271 (58.8%)	1.73 (1.37;2.18)	<0.001
No	953 (67.4%)	275 (28.9%)	678 (71.1%)	Ref	
Obesity (BM I >40) [d]					
Yes	111 (7.85%)	37 (33.3%)	74 (66.7%)	1.02 (0.67;1.54)	0.909
No	1303 (92.1%)	428 (32.8%)	875 (67.2%)	Ref	
Diabetes					
Yes	385 (27.2%)	141 (36.6%)	244 (63.4%)	1.26 (0.98;1.61)	0.069
No	1029 (72.8%)	324 (31.5%)	705 (68.5%)	Ref	
Chronic renal disease					
Yes	275 (19.4%)	106 (38.5%)	169 (61.5%)	1.36 (1.04;1.79)	0.028
No	1139 (80.6%)	359 (31.5%)	780 (68.5%)	Ref	
Immunodeficiency					
Yes	230 (16.3%)	68 (29.6%)	162 (70.4%)	0.83 (0.61;1.13)	0.242
No	1184 (83.7%)	397 (33.5%)	787 (66.5%)	Ref	
Cardiovascular disease					
Yes	614 (43.4%)	237 (38.6%)	377 (61.4%)	1.58 (1.26;1.97)	<0.001
No	800 (56.6%)	228 (28.5%)	572 (71.5%)	Ref	
Chronic liver disease					
Yes	88 (6.22%)	28 (31.8%)	60 (68.2%)	0.95 (0.59;1.50)	0.836
No	1326 (93.8%)	437 (33.0%)	889 (67.0%)	Ref	
Other comorbidities [e]					
Yes	165 (11.7%)	66 (40.0%)	99 (60.0%)	1.42 (1.01;1.98)	0.041
No	1249 (88.3%)	399 (31.9%)	850 (68.1%)	Ref	
Pregnancy [f]					
Yes	8 (12.3%)	2 (25.0%)	6 (75.0%)	4.36 (0.64; 28.32)	0.110

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No	55 (87.7%)	4 (7.3%)	51 (92.7%)	Ref	
NI [g] treatment					
Yes	1299 (91.9%)	437 (33.6%)	862 (66.4%)	1.55 (1.01;2.45)	0.045
NI [g] treatment (timing)					
<=48h from onset of symptoms)	511 (36.9%)	169 (33.1%)	342 (66.9%)	1.51 (0.96;2.44)	0.075
>48h from onset of symptoms)	759 (54.8%)	257 (33.9%)	502 (66.1%)	1.57 (1.01;2.50)	0.046
No	114 (8.07%)	28 (24.6%)	86 (75.4%)	Ref	
Type of influenza virus					
B	859 (60.9%)	295 (34.3%)	564 (65.7%)	1.17 (0.93;1.48)	0.174
A	551 (39.1%)	170 (30.9%)	381 (69.1%)	Ref	
Outcome variables [ł]:					
ICU admission					
Yes	214 (15.1%)	52 (24.3%)	162 (75.7%)		0.005
No	1200 (84.9%)	413 (34.4%)	787 (65.6%)		
LOS [h]					
Mean days (SD)	12.8 (15.9)	12.1 (14.1)	13.1 (16.8)		0.228
LICS [i]					
Mean days (SD)	9.35 (10.4)	9.49 (9.30)	9.31 (10.8)		0.917

[a] OR: Crude odds ratio; [b] SD: Standard deviation; [c] COPD: Chronic obstructive pulmonary disease; [d] BMI: Body mass index; [e] Other comorbidities include: Hemoglobinopathies and cognitive impairment ; [f] Only women of childbearing age (from 18-49y); [g] NI: Neuraminidase inhibitor; [h] LOS: Length of hospital stay ; [i] LICS: Length of ICU stay; ł t-student or Chi_squared used for outcome variables

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Table 2 Distribution of main characteristics of influenza hospitalized cases by source: Severe hospitalized laboratory confirmed influenza (SHLCI) and Hospitalized laboratory confirmed influenza from emergency room discharge data (HLCI). Catalonia, 2017-2018

Patient parameters	Total hospitalized laboratory confirmed influenza cases n=1414	SHLCI[a] n=1227	HLCI[b] n=187	p value
Age mean (SD) [c]	71.5 (15.2)	71.1 (15.3)	68.5 (16.0)	0.008*
Age group				
>=60y	1118 (79.1%)	959 (78.2%)	159 (85.0%)	0.040
18-59y	296 (20.9%)	268 (21.8%)	28 (15.0%)	
Gender				
Male	804 (56.9%)	709 (57.8%)	95 (50.8%)	0.086
Female	610 (43.1%)	518 (42.2%)	92 (49.2%)	
Comorbidities (at least one)				
Yes	1127 (79.7%)	956 (77.9%)	171 (91.4%)	<0.001
No	287 (20.3%)	271 (22.1%)	16 (8.56%)	
Influenza vaccination				
Yes	465 (32.9%)	440 (35.9%)	25 (13.4%)	<0.001
No	949 (67.1%)	787 (64.1%)	162 (86.6%)	
NI [d] treatment				
Yes	1299 (91.9%)	1146 (93.4%)	153 (82.3%)	<0.001
NI [d] treatment (timing)				
<=48h from onset of symptoms)	511 (36.9%)	452 (37.7%)	59 (31.7%)	<0.001
>48h from onset of symptoms)	759 (54.8%)	665 (55.5%)	94 (50.5%)	
No	114 (8.07%)	81 (6.60%)	33 (17.7%)	

[a] SHLCI: Severe hospitalized laboratory confirmed influenza; [b] HLCI: Hospitalized laboratory confirmed influenza from emergency room discharge data ; [c] SD: Standard deviation; [d] NI: Neuraminidase inhibitor; * t-Student

Two hundred and fourteen cases (15.1%) were admitted to ICU, with an average age of 64y (SD 13.6) vs 72.8y (DS 15.1) for those not admitted at ICU (p <0.001). Having an underlying chronic liver disease was associated with a higher ICU admission (OR 2.25; 95%CI 1.35-3.64; p = 0.002). Being older than 60y was associated with a lower ICU admission (OR 0.44, 0.32-0.61, <0.001) while being male was associated with a higher ICU admission (OR 1.36, 95% CI 1.01-1.84, p = 0.046). The proportion of ICU admissions was lower in the vaccinated than in the unvaccinated, with 52 (11.2%) in the vaccinated vs. 162 (17.1%) in the unvaccinated (OR 0.61; 0.40-0.85; =0.003). Being pregnant is associated, but not statistically significant, with a higher ICU admission; OR of 1.19 (95%CI 0.21-6.69), p=0.83). A longer hospital stay was observed in those patients being admitted to ICU being 22.4 (SD 20.3) days vs 11.1(SD14.4) days (p<0,001) for those not admitted to ICU. (Table 3).

Main results for vaccine effectiveness obtained via multivariate logistic regression adjusting by variables age, gender, presence of comorbidities and timing of NI treatment are shown on table 4. A model using a propensity score was also fitted with very similar results attained and thus not shown herein. Vaccination prevented admission to ICU with an adjusted odds ratio aOR of 0.69 (95%CI 0.48-0.99; p = 0.04); this holds regardless of the viral type. The corresponding adjusted vaccine effectiveness (aVE) to prevent admission to ICU was 31% (CI 95% 1-52). If stratification made by viral type, the aVE estimates to prevent admission to ICU, were 40% for type A (aOR 0.6; 95%CI 0.32-1.11; p = 0.09) and 25% for type B (aOR 0.75; 95%CI 0.48-1.18 p = 0.21). The proportion of males ≥ 60y admitted to ICU is lower in vaccinated (31; 12.2%) than in unvaccinated (60; 15.9%) with aOR of 0.68 (95%CI 0.42-1.10, p=0.12) and aVE of 32% (95%CI -10-58). Other adjusted VE according to specific age and gender groups are shown in Table 4.

As occurred globally, will all 1414 data together, differences in the effect of seasonal influenza vaccination in SHLCI and HLCI cases was also observed; the crude ORs were 0.53 (95%CI 0.38-0.75) for SHLCI and 0.69 (95%CI 0.005-6.78) for HLCI. When sample size allowed, adjusted ORs and aVE were calculated. For SHLCI cases the aVE was 40% (95%CI 13-58; p=0.007) and with the whole data set it was 31% (95%CI 1-52; 0.04). All results suggest that vaccination reduces ICU admission. Differences in the effect of seasonal influenza vaccination in SHLCI and HLCI cases was observed: VE 47% (95%CI 25-62) for SHLCI and 31% (95%CI -578-99.5) for HLCI. The aVE calculated for SHLCI cases was 40% (95%CI 13-58, p=0.007); aVE was not calculable for HLCI cases due to small sample subset (Table 5).

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Table 3. Distribution of influenza hospitalized cases according to intensive care unit admission. Catalonia, 2017-2018

Patient parameters	Total number of hospitalized laboratory confirmed influenza cases n=1414	ICU[a] admission n=214	No ICU admission n=1200	OR[b] (95%CI[c])	p value
Influenza vaccination					
Yes	465 (32.9%)	52 (11.2%)	413 (88.8%)	0.61 (0.4;0.85)	0.003
No	949 (67.1%)	162 (17.1%)	787 (82.9%)	Ref	
Age					
Mean years (SD)[d]	71.5 (15.2)	64.0 (13.6)	72.8 (15.1)	0.96 (0.96;0.97)	<0.001*
Age group					
>=60y	1118 (79.1%)	141 (12.6%)	977 (87.4%)	0.44(0.32;0.61)	<0.001
18-59y	296 (20.9%)	73 (24.7%)	223 (75.3%)	Ref	
Gender					
Male	804 (56.9%)	135 (16.8%)	669 (83.2%)	1.36(1.01;1.84)	0.046
Female	610 (43.1%)	79 (13.0%)	531 (87.0%)	Ref	
Comorbidities					
Yes	1127 (79.7%)	164 (14.6%)	963 (85.4%)	0.81(0.57;1.15)	0.230
No	287 (20.3%)	50 (17.4%)	237 (82.6%)	Ref	
COPD[e]					
Yes	461 (32.6%)	74 (16.1%)	387 (83.9%)	1.11(0.8;1.51)	0.502
No	953 (67.4%)	140 (14.7%)	813 (85.3%)	Ref	
Obesity (BMI>30)[f]					
Yes	111 (7.85%)	23 (20.7%)	88 (79.3%)	1.53(0.92;2.44)	0.098
No	1303 (92.1%)	191 (14.7%)	1112 (85.3%)	Ref	
Diabetes					
Yes	385 (27.2%)	60 (15.6%)	325 (84.4%)	1.05(0.75;1.45)	0.767
No	1029 (72.8%)	154 (15.0%)	875 (85.0%)	Ref	
Chronic renal disease					
Yes	275 (19.4%)	31 (11.3%)	244 (88.7%)	0.67 (0.44;0.99)	0.043
No	1139 (80.6%)	183 (16.1%)	956 (83.9%)	Ref	
Immunodeficiency					
Yes	230 (16.3%)	33 (14.3%)	197 (85.7%)	0.93(0.61;1.30)	0.728
No	1184 (83.7%)	181 (15.3%)	1003 (84.7%)	Ref	
Cardiovascular disease					
Yes	614 (43.4%)	79 (12.9%)	535 (87.1%)	0.73(0.54;0.98)	0.037
No	800 (56.6%)	135 (16.9%)	665 (83.1%)	Ref	
Chronic liver disease					
Yes	88 (6.22%)	24 (27.3%)	64 (72.7%)	2.25(1.35;3.64)	0.002
No	1326 (93.8%)	190 (14.3%)	1136 (85.7%)	Ref.	
Other comorbidities [g]					

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Yes	*165 (11.7%)*	*27 (16.4%)*	*138 (83.6%)*	*1.12(0.70;1.71)*	*0.630*
No	*1249 (88.3%)*	*187 (15.0%)*	*1062 (85.0%)*	*Ref.*	
Pregnancy [h]					
Yes	*8 (12.3%)*	*2 (25.0%)*	*6 (75.0%)*	*1.19(0.21;6.69)*	*0.839*
No	*55 (87.7%)*	*12 (21.8%)*	*43 (78.2%)*	*Ref*	
NI [i] ***treatment***					
Yes	*1299 (91.9%)*	*199 (15.3%)*	*1100 (84.7%)*	*1.18(0.69; 2.17)*	*0.552*
No	*114 (8.07%)*	*15 (13.2%)*	*99 (86.8%)*	*Ref.*	
NI treatment (timing)					
<=48h from onset of symptoms	*511 (36.9%)*	*62 (12.1%)*	*449 (87.9%)*	*0.91(0.51;1.72)*	*0.750*
>48h from onset of symptoms	*759 (54.8%)*	*128 (16.9%)*	*631 (83.1%)*	*1.33(0.77;2.45)*	*0.323*
No	*114 (8.24%)*	*15 (13.2%)*	*99 (86.8%)*	*Ref*	
Influenza virus type					
A	*551 (39.1%)*	*92 (16.7%)*	*459 (83.3%)*		
B	*859 (60.9%)*	*122 (14.2%)*	*737 (85.8%)*	*0.83 (0.62;1.11)*	*0.205*
LOS[i]					
Mean days (SD)[d]	*12.8 (15.9)*	*22.4 (20.3)*	*11.1 (14.4)*		*<0.001**

[a] ICU: Intensive Care Unit; [b] OR: crude Odds ratio ;[c] CI: Confidence Interval; [d] SD: Standard Deviation; [e] COPD= Chronic obstructive pulmonary disease ;[f] BMI : Body mass index; [g] Other comorbidities: include hemoglobinopathy, severe neurological disorder and cognitive impairment ; [h] Only women of childbearing age (from 18-49y)= 63 cases ; 14 admitted to ICU and 49 not required ICU admission. [i] NI: Neuraminidase inhibitor ; [j] LOS: Length hospital stay; * t Student

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Table 4: Vaccine effectiveness in preventing intensive care unit admission of hospitalized cases of laboratory confirmed influenza according to virus type and age and gender group. Catalonia, 2017-2018

All patients n=1414	*ICU admission n=214 (15.1%)*	*No ICU admission n=1200 (84.9%)*	*aOR[a] (95%CI) [b]*	*p value*	*Adjusted VE 95%CI*
Influenza vaccination					
Vaccinated (465; 32.9%)	*52 (11.2%)*	*413 (88.8%)*	*0.69 (0.48;0.99)*	*0.04*	*31% (1;52)*
Unvaccinated (949;67.1%)	*162 (17.1%)*	*787 (82.9%)*	*Ref.*		
Influenza B					
n = 859 (60.7%)					
Vaccinated (295; 34.3%)	*33 (11.2%)*	*262 (88.8%)*	*0.75 (0.48;1.18)*	*0.21*	*25% (18;52)*
Unvaccinated (564; 65.7%)	*89 (15.8%)*	*475 (84.2%)*	*Ref.*		
Influenza A					
n = 551 (38.9%)					
Vaccinated (170; 30.9%)	*19 (11.2%)*	*151 (88.8%)*	*0.60 (0.32;1.11)*	*0.09*	*40% (-11; 68)*
Unvaccinated (381; 69.1%)	*73 (19.2%)*	*308 (80.8%)*	*Ref.*		
Female < 60 y					
n = 125 (8.8%)					
Vaccinated (14; 11.2%)	*1 (7.1%)*	*13 (92.9%)*	*0.28 (0.03;2.35)*	*0.24*	*72% (-135;97)*
Unvaccinated (111; 88.8%)	*28 (25.2%)*	*83 (74.8%)*	*Ref.*		
Female >= 60 y					
n = 485 (34.3%)					
Vaccinated (182; 37.5%)	*17 (9.3%)*	*165 (90.7%)*	*0.77 (0.4;1.48)*	*0.43*	*23% (-48;60)*
Unvaccinated (303; 62.5%)	*33 (10.9%)*	*270 (89.1%)*	*Ref.*		
Male < 60 y					
n = 171 (24.2%)					
Vaccinated (14; 8.2%)	*3 (21.4%)*	*11 (78.6%)*	*0.71 (0.18;2.74)*	*0.62*	*29% (-74;82)*

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All patients n=1414	***ICU admission n=214 (15.1%)***	***No ICU admission n=1200 (84.9%)***	***aOR[a] (95%CI) [b]***	***p value***	***Adjusted VE*** *95%CI*
Unvaccinated (157; 91.8%)	*41(26.1%)*	*116 (73.9%)*	*Ref.*		
Male >= 60 y					
n = 633 (44.7%)					
Vaccinated (255; 40.3%)	*31 (12.2%)*	*224 (87.8%)*	*0.68 (0.42;1.10)*	*0.12*	*32% (-10;58)*
Unvaccinated (378; 59.7%)	*60(15.9%)*	*318 (84.1%)*	*Ref.*		

[a] aOR: Odds ratio adjusted by age, sex, at least one comorbidity and NI treatment (if yes, administered < or >48h after symptom onset) [b] CI: Confidence Interval

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Table 5: Vaccine effectiveness in preventing intensive care unit admission in severe hospitalized laboratory confirmed influenza cases and in hospitalized laboratory confirmed influenza cases. Catalonia, 2017-2018

All patients n=1414	*ICU admission n=214 (15.1%)*	*No ICU admission n=1200 (84.9%)*	*OR (95%CI)*	*aOR* (95%CI)*	*p value*	*Adjusted VE 95%CI*
Influenza Vaccination						
Vaccinated (465; 32.9%)	*52 (24.3%)*	*413 (34.4%)*	*0.61 (0.44;0.85)*	*0.69 (0.48;0.99)*	*0.040*	*31% (1;52)*
Unvaccinated (949;67.1%)	*162 (75.7%)*	*787 (65.6%)*		*Ref.*		
SHLCI[a] n=1227	***210 (17.1%)***	***1017 (82.9%)***				
Vaccinated (440: 35.9%)	*52 (24.8%)*	*388 (38.2%)*	*0.53 (0.38;0.75)*	*0.60 (0.42;0.87)*	*0.007*	*40% (13;58)*
Unvaccinated (787; 64.1%)	*158 (75.2%)*	*629 (61.8%)*		*Ref.*		
HLCI[b] n=187	***4 (2.1%)***	***183 (97.9%)***				
Vaccinated (25;13.3%)	*0 (0.0%)*	*25 (13.7%)*	*0.69 (0.005;6.78)*	*Not computable*	*----*	*----*
Unvaccinated (162; 86.7%)	*4 (100%)*	*158 (86.3%)*				

*Odds ratio adjusted by age, sex, at least one comorbidity and NI treatment NI: Neuraminidase Inhibitor [a]SHLCI:Severe hospitalized laboratory confirmed influenza; [b]HLCI: Hospitalized laboratory confirmed influenza (due to separation, penalized Firth's logistic regression used)

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4. Discussion

In general, flu is a self-limiting disease and recovery occurs in about two weeks without medical care or antiviral drugs [1,2]. Yet some subsets of population are at higher risk for more severe disease which may require hospitalization and/or intensive care unit admission due to complications such as pneumonia or acute respiratory distress. It is well known that the elderly (≥65 years of age) have the highest risk of increased morbidity including respiratory failure, and mortality; It is estimated that over 60% of all seasonal-influenza-related hospitalizations and 90% of seasonal-influenza-related deaths each year occur in the elderly [2, 3-7]. Influenza vaccination can reduce influenza illnesses, and in turn reduce work load at primary health care facilities, work and school absenteeism due to flu as well as prevent flu-related hospitalizations and deaths, especially in the elderly and those with underlying medical conditions [4]. The recommendations at national level for annual flu vaccination differs depending on the country, for all individuals ≥ 6 months of age in the US [4], for example, and recommended to individuals belonging to risk groups in other countries, such as Spain.

Our study found that vaccinated patients had a lower ICU admission rate than those unvaccinated although level was not significant, similar to results obtained by Joshi et al. during the 2013-2014 season in the US where there was no evident protection infered by the vaccine as to hospitalization, ICU admission nor mechanical ventilation [8.] The 2017-2018 influenza season was a B lineage-mismatched season, with predominant influenza B/Yamagata viruses circulating and a B/Victoria lineage virus included in the trivalent vaccine. Our data, as observed in other countries in Europe [9], suggest that vaccination offered only slight protection for severe outcome due to this fact and because there was a high proportion of elderly hospitalizations (79.1%) and that older age is associated with a lower ICU admission [10].Data on the inverse relation between age and ICU admission has also been pointed out by other authors who found higher rate of ICU admission among SHCIC at 15-64 y [11–14].

In Catalonia influenza vaccine recommendations include population 60 years and older, and for risk groups at any age with comorbidities such as COPD, cardiovascular diseases, diabetes, immunodeficiency, obesity and other chronic conditions as well as pregnant women and health care personnel [15]. Despite these guidelines, vaccine coverage among risk groups is below recommended levels set by the Venice Network of the European Center for Disease Control (ECDC) that targets for a 75% coverage [16]. The reported vaccine coverage for this particular season in Catalonia was of 55.7% in the ≥60 y age group which was similar to coverage reported in the United States for the same season (59.6%) [17] . As to population with chronic diseases and <60 y. , the coverage in Catalonia was estimated to be 20% in contrasts with several European countries where the coverage for this risk group had a median coverage of 44.9% [15,18]. All of them values to be improved in order to achieve a better protection and decrease hospitalization rates. In our study, a high percentage (79.7%) of adults hospitalized with confirmed influenza presented at least one comorbidity and only 36% were vaccinated against influenza. A similar coverage was found for patients with comorbidities ranging from 29.6% (immunocompromised patients) to 41.2% (COPD patients) both far from 75% target recommended.

In the sample studied, 15.1% of cases required ICU admission, which is in agreement with other countries such as Ireland with a 16% ICU admission rate and a 15 % reported by Lina et al. in a global study of the 2017-2018 season with 14 participating countries [19,20]. The most common

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underlying medical condition in this study cohort of hospitalized influenza cases related to ICU admission was chronic liver disease, while in other studies COPD has been described as one of the major comorbidities in hospitalized influenza patients requiring ICU admission [21]. Furthermore, influenza can cause severe illness and ICU admission even in individuals without known comorbidities as observed in our study (17.4%) and in the 15.3% observed in the study by Lina et al. [20].

Vaccination reduced ICU admission for all ages by 31%, similar to values found by Arriola et al. during the 2013-2014 influenza season (37%). No difference was observed as to reducing LOS and LICS in contrast to the findings by Arriola et al. in two different seasons where vaccination shortened both hospital and ICU lengths of stay, yet the shorter LOS in patients not admitted to ICU exhibits an indirect benefit from vaccine preventing ICU admission [22,23]. In influenza hospitalizations during pregnancy, although the small size of the sample did not confer statistical significance in the present study, some protection from vaccination to avoid ICU admission was observed, and in accordance with Mazagatos et al., results support that pregnant women could benefit from seasonal influenza following recommendations [24]. This fact highlights the need for large studies taking into account several seasons and countries in the line of the PREVENT protocol described by Naleway et al. to assess inactivated influenza VE in preventing severe influenza disease during pregnancy [25].

There are several limitations to this study that derive from the lack of equivalent questionnaire registered in the surveillance system for hospitalized cases that are not classified as severe cases according to the Influenza Surveillance guidelines. This fact made it difficult to retrospectively obtain risk factors, influenza vaccination status and length of ICU for all those laboratories confirmed influenza cases hospitalized in the sentinel network facilities that had not been registered as severe cases. Yet the main outcome, influenza vaccine effectiveness to prevent ICU admission did not differ significantly between the subgroup of SHLCI cases from those recruited from the Emergency Room discharge data of HLCI cases (VE 47% vs VE 31%, respectively). Table 5 shows robustness results of vaccination effectiveness estimates regardless of data sources (SHLCI and HLCI) and supports the validity of results of merged data.

A possible explanation is that those cases admitted from the emergency room to the hospital ward had resembling traits to those hospitalized as severe cases according to case definition. In fact, 4 cases included in the HLCI subgroup were admitted to ICU and, therefore, should have been classified as SHLCI cases. However, this limitation does not invalid our results because the direction of the effect is the same for both subgroups.

Another issue is the decision making as to whether a patient is to be admitted to ICU or not, as well as when to discharge which may vary according to each hospitals ICU admission inclusion criteria. Inclusion criteria include requirements for respiratory support or vasopressor and shock, yet exclusion criteria are not that concise except for devastating brain injury or metastatic cancer with poor prognosis [26,27]. Older age has been postulated as an exclusion criteria when ICU capacities are overwhelmed, especially at times of seasonal epidemic peak activity or the recently experience of COVID-19 pandemic. Length of stay at ICU is also an uncertain variable subject to individual hospital policies. A study carried out by Garland and Connors observed that there is an optimal timing for patients to leave the ICU, with an increasing risk of subsequent death if patients leave the ICU either too early or too late.[28] Clinical judgment may not be reliable for determining the optimal time window

and intensivists have subjective clinical judgment to guide them in determining when patients should be admitted and discharged from the ICU [27].The finding of this study represent a single season and, therefore, they should be taken with caution when generalizing its results.

In conclusion, this study shows that vaccination reduced the need of admission to ICU and longer hospitalization in cases of laboratory confirmed influenza virus infections detected during the 2017–2018 influenza season. Vaccination uptake in elderly patients, pregnant women and those with at least one comorbidity hospitalized with laboratory confirmed influenza was below recommended value. Further efforts are needed to increase vaccination coverage in groups at risk of hospitalization and subsequent ICU admission at any age.

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