Factors associated with poor outcomes among adults hospitalised for influenza in France: A three-year prospective multicenter study

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Abstract

Background. Influenza is an important cause of serious illness and death, particularly in elderly and high-risk groups.

Objectives. Aim of this study was to identify factors associated with poor outcomes among adults hospitalized in France for laboratory-confirmed seasonal influenza.

Study design. Patients hospitalized for influenza were identified in a prospective, multicenter study carried out in French hospitals during three consecutive influenza seasons (2012-2015). Influenza virus infection was confirmed by reverse transcription polymerase chain reaction. Sociodemographic and clinical variables were compared according to the virus type and subtype. Risk factors for complications, intensive care unit (ICU) admission and death were analyzed by backward stepwise logistic regression.

Results. The study population consisted of 566 patients, of whom 56% were older than 65 years and 82% had underlying chronic illnesses. Type A influenza viruses infected 422 patients (75%), including subtype H3N2 in 239 patients (57%). The prior vaccine coverage rate was 38%. Complications occurred in 255 patients (45%), consisting mainly of pneumonia (n=143, 30%) and respiratory failure (n=116, 20%). Eighty-three patients (15%) were admitted to an ICU, and the in-hospital mortality rate was 4% (n=21). Sixty-six patients (12%) received oseltamivir. Age over 65 years was the only identified risk factor for complications. Risk factors for ICU admission were an absence of vaccination, no oseltamivir administration before admission, pre-existing chronic respiratory disease, and current smoking. Age over 65 years and ICU admission were risk factors for death.

Conclusions. Older individuals and patients with underlying conditions are most at risk of influenza complications. Vaccination and early oseltamivir administration, both of which are recommended for these patients, appear to reduce ICU admissions.

Background

Influenza is an important cause of serious illness and death, particularly among adults over 65 years old and patients with chronic underlying conditions [1–4]. Each year, 5%–20% of the world population is infected by influenza viruses, and an estimated annual average of 36 000 deaths and 1 200 000 hospital admissions attributable to influenza virus infection occur in the United States [2,5]. Patients over 65 years of age account for 54–70% of hospital admissions and 71–85% of deaths [6].

Influenza is often under-diagnosed in acute-care hospital settings, owing to variable clinical presentations in adults [7–10], late hospital presentation for evaluation or care [11], and predominance of non-pulmonary diagnosis for admissions that may masked the influenza diagnosis [5]. Vaccination is the cornerstone of influenza prevention. Vaccine efficacy is abut 60% overall [12] but varies with age, underlying diseases/comorbidities, the predominant viral strain, and the considered outcome. Vaccination reduces the risk of pneumonia [13], hospitalization and death [14–16]. Early antiviral treatment is also recommended for patients at risk of complications [17–19].

Objectives

The aim of this study was to identify factors associated with poor outcomes among adult patients hospitalized for influenza in 6 French university hospitals participating in a multicenter, prospective, hospital-based epidemiological study carried out during three consecutive influenza seasons from 2012 to 2015.

Study design

We studied cases of laboratory-confirmed influenza occurring during three successive seasons and identified by the FLUVAC study, a French prospective observational hospital-based study [20]. Briefly, we collected data on non-institutionalized adults (≥18 years) hospitalized for at least 24 hours in one of the six participating hospitals (Cochin Hospital, Paris; Bichat Hospital, Paris; Rennes Hospital; Limoges Hospital; St. Eloi Hospital, Montpellier; Edouard Herriot Hospital, Lyon) for influenza-like-illness (ILI), with symptom onset less than seven days prior to inclusion, through an active surveillance system composed of healthcare professionals trained to follow the FLUVAC study protocol. ILI was defined as a combination of the following three criteria: (i) sudden symptom onset, (ii) at least one of the following symptoms: fever (≥38°C), headache, myalgia or malaise, and (iii) at least one of the following respiratory symptoms: cough, sore throat, or shortness of breath (dyspnea) [21]. The "sudden" nature of symptom onset was a subjective concept left to the patients' appreciation.

Influenza virus infection was detected by applying the reverse transcription-polymerase chain reaction (RT-PCR) to nasopharyngeal swabs (bronchoalveolar lavage fluid or tracheal aspirate for ICU patients). The FLUVAC study (clinicaltrials.gov NCT02027233) respected Good Epidemiological and Clinical Practices in clinical research and the Declaration of Helsinki, and was approved by regional ethics committees.

Study population and data collection

We included all laboratory-confirmed (RT-PCR-positive) cases of influenza identified during three consecutive influenza seasons (2012/2013, 2013/2014 and 2014/2015) among the 1452 patients included in the FLUVAC study.

We collected data on demographic characteristics, chronic underlying diseases, hospital admissions in the previous 12 months, smoking status, influenza vaccination in the current season and previous two seasons, the hospitalization ward, and the following characteristics of the current influenza episode: clinical presentation and outcome, including date of onset, hospitalization and treatment; length of hospital stay, treatment, and complications.

Data sources included the hospitals' medical records, interviews with the patients, families and regular physicians; vaccination registries, and laboratory databases. Vaccination status was ascertained during interviews with the patients and their families, and was confirmed from pharmacy records.

Laboratory data

The samples were initially tested in the virology laboratories of the participating hospitals by in-house real-time influenza A & B PCR after manual nucleic acid extraction. Amplification was performed in a ABI 7500 thermocycler. All samples were then sent to the French National Influenza Reference Center (CNR-Lyon) for confirmation by RT-PCR. Samples positive in the reference center were molecularly subtyped for viruses known to be circulating at the time namely type A (subtypes H1N1pdm09 and H3N2) and type B. Molecular subtyping was able to determine the H subtype for influenza A and the lineage for influenza B. Subtyping failed in some

cases because of low viral load and samples were thus classified as “unidentifiable”. In case of a discrepancy with local results, the reference center results were considered final. Only the reference center results were taken into account in the analyses.

Statistical analysis

Results were expressed as means and standard deviation (SD) or medians and interquartile range (IQR) for continuous variables, and N (%) for categorical variables. Age was considered as a binary variable (< and ≥ 65 years, the age at which influenza vaccine is recommended in France).

The Wilcoxon rank sum test or Fisher’s exact test was used, as appropriate, for univariable comparisons. To take into account subgroup comparisons, a p value of 0.025 or less was considered statistically significant. Missing data for each variable were excluded from the denominator.

Factors associated with death, complications and ICU admission were identified in a backward stepwise logistic regression model that included all variables with a p value <0.20 in univariate analysis and was adjusted for potential confounders, including “age”, “sex”, “influenza season”, “time from symptom onset to admission” and “chronic respiratory disease”, as appropriate. Results are expressed as odds ratios (OR) and adjusted odds ratios (aOR) with their 95% confidence intervals (95%CI). In the final model, a p value of 0.05 or less was considered statistically significant.

All analyses were performed using Stata software (V12, © Copyright 1996–2014 StataCorpLPt).

Results

Patient characteristics (Table 1)

A total of 566 cases of laboratory-confirmed influenza were diagnosed during the study period, comprising respectively 162, 112 and 292 cases during the 2012/2013, 2013/2014 and 2014/2015 seasons. Median age was 67 years (IQR, 51-81), 316 patients (56%) were older than 65 years, and 296 patients (52%) were men. Chronic underlying diseases were present in 462 patients (82%), and consisted mainly of chronic respiratory diseases (n= 230, 40% of all patients), chronic heart disease (n=224, 40%) and diabetes (n=140, 25%). Twelve women were pregnant (influenza A/H1N1 in 7 cases, influenza B in 5 cases). Two hundred forty patients (40%) had been hospitalized in the previous year, and the average number of admissions among these 240 patients was 2.2 (SD 2.6). The prior vaccination rate was 38% (215/566). According to French recommendations (www.sante.gouv.fr/calendrier-vaccinal.html), 472 patients (88%) should have been vaccinated, but this was the case of only 197 (42%) of these patients. The vaccination rate was 19% (n=47) among patients under 65 years old and 53% (n=168) among patients aged 65 years or more (p=0.001).

Table 1. Characteristics, clinical presentation and outcomes of the 566 influenza patients diagnosed between 2012 and 2015 in six French University hospitals

	n	%
Baseline characteristics		
Men	296	52%
Median age, years (IQR)	67 (51-81)	-
Age ≥65 years	316	56%
Median BMI, kg/m^2 (IQR)	25 (22-28)	-
BMI ≥ 40	15	3%
Chronic diseases (indicating Influenza vaccination)	462	82%
Chronic respiratory disease	230	40%
Chronic heart disease	224	40%
Diabetes	140	25%
Chronic renal failure	66	12%
Immunosuppression	56	8%
Others	237	42%

Pregnancy	12	2%*
Current smokers	266	48%
Indication for vaccination	472	88%
Vaccination in current season	215	38%
ICU admission	83	15%
Hospitalization in the previous 12 months	240	42%
Mean number of hospitalizations in the previous 12 months (SD) among patients hospitalized at least once	2.2 (2.6)	-
Clinical presentation		
Median time from symptom onset to hospitalization, days (IQR)	2 (1-3)	
Fever (≥38°C)	504	89%
Cough	487	86%
Dyspnea	387	69%
Sudden symptom onset	289	51%
Weakness/malaise	164	29%
Headache	154	28%
Myalgia	128	23%
Outcome and treatment		
At least one complication during the hospital stay	255	45%
Pneumonia	143/473	30%
Respiratory failure	116/473	20%
Acute heart failure	67/473	12%
Acute respiratory distress syndrome (ARDS)	58/473	10%
Antiviral use	66	12%
Median length of stay, days (IQR)	6 (3-10)	-
Death	21	4%

IQR: interquartile range

* Pregnant women represented 2% of all patients and 4% of the 270 women.

Clinical presentation (Table 1)

Median time from symptom onset to hospitalization was 2 days (IQR, 1-3). The most frequent symptoms were fever and cough, present in respectively 504 (89%) and 487 (86%) cases. Dyspnea was reported by 387 patients (69%). Other symptoms were each present in 20% to 30% of patients. Sudden symptom onset was reported by 289 patients (51%). After adjustment for the influenza season and vaccination status, older age was associated with less intense symptoms. In particular, fever, headache and myalgia were less common in patients over 65 (OR 0.53; 95%CI 0.29-0.96,

p=0.036; OR 0.40; 95%CI 0.26-0.61, p=0.001; and OR 0.39; 95%CI 0.25-0.62,p=0.001, respectively). ICU admission was necessary in 83 cases (15%).

***Outcome and treatment (*Table 1)**

A total of 473 medical complications related to influenza occurred among 255 patients (45%) during their hospital stay. Pneumonia (143 episodes, 30% of complications), respiratory failure (116, 20%), heart failure (67, 12%) and ARDS (58, 10%) were the most frequent.

Oseltamivir was prescribed to 66 patients (12%), 75% of whom had a chronic underlying condition. Oseltamivir therapy was initiated less than 48 h after symptom onset in 88% of cases.

The median length of hospital stay was 6 days (IQR 3-10).

Twenty-one patients (4%) died during the hospital stay. All of them had at least one chronic underlying disease and 19 (90%) were over 65 years old. The median time from admission to death was 12 days (IQR 7–20).

Virologic data (Table 2)

Influenza virus type A was detected in 422 patients (75%); it was subtype H1N1 in 163 cases (39%), H3N2 in 239 cases (57%), and “unidentifiable” in 20 cases (4%). Type B was detected in 144 patients (25%), and was subtype Yamagata, Victoria and “unidentifiable” in respectively 115 (80%), 9 (6%) and 20 (14%) cases.

Table 2. Virologic data for 566 cases of influenza diagnosed between 2012 and 2015 in 6 French University hospitals

	2012/2013	2013/2014	2014/2015	Total
Influenza cases	***162***	***112***	***292***	***566***
Type A	80 (49%)	109 (97%)	233 (80%)	422 (75%)
H1N1	30	59	74	163
H3N2	50	44	145	239
Unidentifiable	0	6	14	20
Type B	82 (51%)	3 (3%)	59 (20%)	144 (25%)
Victoria	7	0	2	9
Yamagata	64	3	48	115
Unidentifiable	11	0	9	20
Considered viral circulation [(1)]	A(H1N1)pdm09 + B (Yamagata)	A(H1N1)pdm09 + A(H3N2)	A(H3N2)**	-

(1) From the Flunet database (http://www.who.int/influenza/gisrs_laboratory/flunet/); Indicate the viral dominant type or subtype;
** circulating strains differed from vaccine strains

Compared to patients with type B influenza, patients with type A influenza were more likely to have a chronic respiratory disease (44% vs 31%, p=0.01), dyspnea (72% vs 59%, p=0.007) and sudden symptom onset (56% vs 41%, p=0.003). (**Table 3**)

Compared to patients with H1N1 influenza, patients with H3N2 influenza were significantly older (73 years, IQR 58-83 vs 60 years, IQR 47-74; p=0.001), more likely to have an underlying chronic respiratory disease (45% vs 34%, p=0.02) or diabetes (30% vs 18%, p=0.01), and more likely to have dyspnea (78% vs 67%, p=0.02) and ARDS (15% vs 8%, p=0.02). (**Table 3**)

The vaccine coverage rate was higher among patients with H3N2 influenza (45%) than among those with H1N1 influenza (30%, p=0.003), in each of the three seasons (**Table 3**).

Table 3. Characteristics, clinical presentation and outcomes according to virologic data in 566 patients diagnosed with influenza between 2012 and 2015 in 6 French University hospitals

	A n (%)	B n (%)	p-value	H1N1 n (%)	H3N2 n (%)	p-value
Total	422 (75%)	144 (25%)	-	163 (41%)*	239 (59%)*	-
Baseline characteristics						
Men	222 (53%)	74 (51%)	0.85	88 (54%)	127 (53%)	0.91
Median age, years (IQR)	68 (52-80)	66 (48-88)	0.31	60 (47-74)	73 (58-83)	0.001
Median BMI, kg/m^2 (IQR)	25 (22-28)	24 (21-28)	0.12	26 (22-29)	25 (22-28)	0.86
Chronic diseases (indicating influenza vaccination)	350 (83%)	112 (78%)	0.17	132 (81%)	202 (85%)	0.42
Chronic respiratory disease	185 (44%)	45 (31%)	0.01	55 (34%)	108 (45%)	0.02
Chronic heart disease	173 (41%)	51 (35%)	0.28	67 (41%)	112 (47%)	0.26
Diabetes	107 (25%)	33 (23%)	0.58	30 (18%)	71 (30%)	0.01
Chronic renal failure	47 (11%)	19 (13%)	0.55	13 (8%)	34 (14%)	0.05
Immunosuppression	31 (7%)	15 (10%)	0.29	12 (7%)	19 (8%)	0.98
Pregnancy	7 (2%)	5 (3%)	0.18	7 (4%)	0 (0%)	0.002
Current smoker	209 (50%)	57 (41%)	0.1	91 (56%)	106 (45%)	0.03
Indication for vaccination	356 (91%)	116 (92%)	0.85	138 (92%)	202 (91%)	0.71
Vaccination in current season	161 (39%)	54 (38%)	0.92	49 (30%)	106 (45%)	0.003
ICU admission	66 (16%)	16 (11%)	0.22	29 (18%)	33 (14%)	0.33
Hospitalization in the previous 12 months	238 (56%)	88 (61%)	0.33	97 (60%)	128 (54%)	0.33
Mean number of hospitalizations in the previous 12 months (SD) among patients hospitalized at least once	0.9 (1.6)	1.1 (3.0)	0.19	1 (0.03)	1 (0.02)	0.89
Clinical presentation						
Median time from symptom onset to hospitalization, days (IQR)	2 (1-3)	2 (1-4)	0.12	2 (1-3)	2 (1-3)	0.30
Fever (≥38°C)	378 (90%)	126 (88%)	0.54	151 (92%)	207 (87%)	0.08
Cough	365 (87%)	122 (85%)	0.58	143 (88%)	205 (86%)	0.66
Dyspnea	302 (72%)	85 (59%)	0.001	127 (78%)	161 (67%)	0.02

Sudden symptom onset	236 (56%)	59 (41%)	0.03	85 (53%)	143 (61%)	0.3
Weakness/malaise	118 (28%)	46 (32%)	0.39	44 (27%)	70 (29%)	0.65
Headache	109 (26%)	45 (31%)	0.23	51 (31%)	46 (19%)	0.07
Myalgia	94 (22%)	34 (24%)	0.71	43 (27%)	46 (19%)	0.09
Outcome and treatment						
At least one complication during the hospital stay	198 (47%)	48 (39%)	0.09	76 (47%)	113 (47%)	0.92
Pneumonia	100 (24%)	43 (30%)	0.15	38 (23%)	55 (23%)	1.0
Respiratory failure	91 (22%)	25 (17%)	0.34	35 (21%)	51 (21%)	1.0
Acute heart failure	54 (13%)	13 (9%)	0.30	21 (13%)	30 (12%)	0.96
ARDS	46 (11%)	12 (8%)	0.43	25 (15%)	19 (8%)	0.02
Antiviral use	51 (12%)	15 (11%)	0.73	24 (15%)	26 (11%)	0.28
Median length of stay, days (IQR)	6 (3-10)	5 (2-9)	0.025	7 (3-10)	6 (3-10)	0.59
Death	15 (3%)	6 (4%)	0.79	4 (2%)	10 (4%)	0.42

IQR: interquartile range; SD: standard deviation

* Twenty patients with an “unidentifiable” subtype of type A influenza were excluded from the comparison

Factors influencing outcome

The median hospital stay was longer among patients with influenza A than those with influenza B (5 days, IQR 2-9 vs 6 days, IQR 3-10; p=0.02) but was similar across A subtypes (**Table 3**). Vaccination status did not influence the length of stay. The patients who died had type A/H3N2 (n=10), A/H1N1 (n=4), A/unidentifiable (n=1), or B (n=6) influenza. The mortality rate did not differ according to the virus type or subtype, vaccination status, or the influenza season. The virus types and subtypes did not influence these outcomes, and neither did the time from symptom onset to hospitalization.

Multivariate analysis

After adjustment for age, sex, the influenza season and time from symptom onset to admission, the risk of ICU admission was increased by the absence of antiviral therapy, no prior influenza vaccination, current smoking, and chronic respiratory disease (all p<0.05) (**Table 4**).

Table 4. Risk factors for ICU admission among 566 patients hospitalized for influenza from 2012 to 2015, as identified in the final logistic regression model

	aOR (95%CI)	p value
Age ≥65 years	0.77 (0.45-1.30)	*0.33*
Female gender	0.79 (0.47-1.32)	*0.36*
Influenza season		
2012/2013	1 (Ref.)	-
2013/2014	1.12 (0.50-2.48)	*0.78*
2014/2015	1.73 (0.92-3.24)	*0.09*
Time between symptom onset and admission*	1.1 (0.89-1.15)	*0.88*
Vaccination in current season	0.50 (0.28-0.90)	*0.02*
Oseltamivir use	0.35 (0.19-0.66)	*0.01*
Current smoking	1.82 (1.06-3.12)	*0.04*
Chronic respiratory disease	1.66 (1.01-2.77)	*0.05*

The outcome analyzed was ICU admission during the initial hospital stay.
The model was adjusted for "sex", "age", "influenza season" and "time from symptom onset to admission".
**Continuous variable*
aOR: adjusted odds ratio; 95%CI: 95% confidence interval; Ref.: Reference

After adjustment for sex, the influenza season, time from symptom onset to admission, and chronic respiratory disease, the only risk factor for clinical complications was age over 65 years (OR 1.72; 95%CI 1.22-2.44,p=0.002). After the same adjustment, age over 65 years (OR 10.31; 95%CI 2.31-45.90, p=0.002) and ICU admission (OR 5.37; 95%CI 2.0-14.56, p=0.001) were both associated with the risk of death.

Discussion

This prospective multicenter study involved 566 patients with laboratory-confirmed influenza admitted to 6 hospitals during three winter seasons, from 2012 to 2015. Most of the patients were over 65 years old and had at least one underlying disease. Nearly half the patients developed influenza complications during their hospital stay. Antiviral therapy and vaccination had a preventive effect on ICU admission.

Older age and chronic underlying conditions are known risk factors for severe influenza. In a Spanish multicenter study comparing influenza inpatients and outpatients in 2010/2011, Castilla et *al.* found that hospitalized patients were older and had more chronic diseases [22].

We found that patients over 65 years old tended to have atypical symptoms, confirming previous reports [23]. Babcock et *al.* and Walsh et *al.*, studying respectively 207 and 56 elderly patients hospitalized with influenza, found that cough and fever were the most common symptoms, while fever was absent in around 30% of cases [10,24]. We found a high rate of complications, ICU admission and death, confirming the severity of influenza in older patients with underlying conditions [11,25].

Vaccination rates varied according to the influenza virus type and subtype, underlining differences in vaccine efficacy between these groups, owing mainly to differences in age and underlying conditions. In particular, the vaccination rate was higher among patients with H3N2 infection, suggesting that vaccination was less effective in this subgroup. This may be due partly to immune senescence, as these patients were significantly older than patients with H1N1 infection, and partly to vaccine mismatch in the northern hemisphere during the 2014-2015 season, due to A/H3N2 antigenic drift from the vaccine virus, while subtype A/H3N2 accounted for more than 70% of all subtyped influenza A viruses [26].

Vaccination of elderly persons prevents only 30-40% of influenza cases, and its impact on the severity of influenza is controversial [27,28]. However, many studies have shown a beneficial impact of vaccination on hospitalization, complications and death [22,29–34]. More recently, Grijalva *et al.* reported that vaccination reduced hospitalizations for influenza-associated pneumonia by 56% in a large US case-control study [13].

We found no impact of vaccination on mortality, whereas ICU admission was less frequent among vaccinees, underlining the importance of vaccination for at-risk patients.

In a recent study of 5614 patients hospitalized for laboratory-confirmed influenza, selected from a US population-based influenza-related hospitalization surveillance system during the 2012/2013 season, Arriola et *al.* found that 71% of patients were over 65 years old, 91% had medical conditions, 14% were admitted to an ICU, and 2% died. Fifty-five percent of the patients had been vaccinated. No association was found between vaccination status and ICU admission, death, pneumonia, or the length of hospital or ICU stay. However, after restricting the analysis to patients treated with

antiviral drugs and matching them for a vaccination propensity score, they found that the length of ICU stay was reduced by a factor of 0.6 (95%CI 0.4-0.8) among vaccinated 50- to 64-year-olds compared to their unvaccinated counterparts. A similar but non significant trend was found among patients aged from 65 to 74 [25]. Castilla et *al*. found that vaccination protected against severe influenza, defined as ICU admission or in-hospital death, and suggested that vaccination might be more effective in preventing severe than mild illness [22]. By comparison with the latter study, antiviral use in our patients was very low, probably owing to a lack of diagnostic confirmation during the recommended period of antiviral introduction (<48h after symptom onset). We found that antiviral use was associated with a lower risk of ICU admission among patients with underlying respiratory diseases, but not with lower mortality. These results are in agreement with several studies showing a reduction in mortality and complications among patients with severe influenza who received antivirals [19,35–38].

The strengths of this study include the large number of patients hospitalized for influenza, the multicenter, prospective design, uniform patient screening in the different centers, diagnostic confirmation in an influenza reference center, the lengthy study period spanning three consecutive influenza seasons, and precise documentation of influenza virus types and subtypes. Several limitations must also be acknowledged. First, as all the participating centers were teaching hospitals, the proportion of patients with underlying diseases may have been higher than in the general population, owing to a referral bias. Second, although the sample was large, the study was probably underpowered to identify a moderate impact of antivirals and vaccination on mortality. Finally, a small number of samples were misclassified by on-site tests, 9 false positives and 25 false negatives being identified by centralized

testing in the reference center. This should be taken into account when considering the way patients were treated.

In conclusion, most patients hospitalized for severe influenza in France are elderly individuals with underlying conditions, leading to a high risk of complications and ICU admission. It is noteworthy that almost all the patients in this study qualified for influenza vaccination according to national guidelines. As recommended, antiviral treatment should be used in the first 48h after 'flu-like symptom onset in order to reduce the duration of required medical care.

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