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Determinants of Fatal Outcome in Patients Admitted to Intensive Care Units With Influenza, European Union 2009–2017

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Background. Morbidity, severity, and mortality associated with annual influenza epidemics are of public health concern. We analyzed surveillance data on hospitalized laboratory-confirmed influenza cases admitted to intensive care units to identify common determinants for fatal outcome and inform and target public health prevention strategies, including risk communication.

Methods. We performed a descriptive analysis and used Poisson regression models with robust variance to estimate the association of age, sex, virus (sub)type, and underlying medical condition with fatal outcome using European Union data from 2009 to 2017.

Results. Of 13 368 cases included in the basic dataset, 2806 (21%) were fatal. Age ≥40 years and infection with influenza A virus were associated with fatal outcome. Of 5886 cases with known underlying medical conditions and virus A subtype included in a more detailed analysis, 1349 (23%) were fatal. Influenza virus A(H1N1)pdm09 or A(H3N2) infection, age ≥60 years, cancer, human immunodeficiency virus infection and/or other immune deficiency, and heart, kidney, and liver disease were associated with fatal outcome; the risk of death was lower for patients with chronic lung disease and for pregnant women.

Conclusions. This study re-emphasises the importance of preventing influenza in the elderly and tailoring strategies to risk groups with underlying medical conditions.

Keywords: age; EU; influenza virus; intensive care units; underlying medical conditions.

Influenza viruses pose a permanent threat to public health due to seasonal epidemics with surges of associated morbidity and mortality and their pandemic potential [1–5]. Therefore, intense global surveillance is conducted to constantly monitor and assess the epidemiological and virological situation and evaluate prevention and control measures [6–8]. The World Health Organization underlines the need to specifically monitor severe disease and its clinical patterns, causative viral strains, and population groups at risk [9]. The severity and impact of annual influenza epidemics are key indicators for assessing both seasonal and pandemic situations, particularly indicators based on influenza-related hospitalizations and deaths. These data are used to inform stakeholders, prioritize and allocate resources, and target prevention strategies to the most vulnerable. Vaccination programs in particular depend on the identification of specific risk groups [10].

Many studies performed during and after the 2009 influenza pandemic have described risk factors in the context of an influenza pandemic or seasonal epidemics, but they used different study populations and different end points, eg, disease progression, hospitalization, intensive care unit (ICU) admission, or death [11–13]. Previously identified risk factors include increasing age, cardiovascular disease, malignancy, immunosuppression, hypertension, neuromuscular disease, diabetes

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mellitus, chronic lung, liver, or metabolic renal disease [14, 15]. Obesity and pregnancy were associated with increased risk of severe outcomes in some but not all studies [15–18]. According to European data, infection with influenza virus A(H1N1) pdm09, older age, immunosuppression, pregnancy, and lung or heart disease are associated with increased risk of fatal outcome of influenza [11, 16].

The European Centre for Disease Prevention and Control (ECDC) has conducted hospital-based surveillance of severe influenza since the pandemic in 2009 [19]. Aggregate data are published weekly during the influenza season [6], but case-based data have not been systematically analyzed at the European level [20, 21]. Therefore, our aim was to analyze data on laboratory-confirmed influenza cases admitted to ICUs to identify common determinants of fatal outcome that may inform risk communication and help target prevention strategies.

METHODS

Data Source

During each influenza surveillance season, ECDC collects weekly case-based data on hospitalized laboratory-confirmed influenza cases admitted to ICU from a number of European Union (EU)/European Economic Area (EEA) Member States [22, 23]. The data for the seasons 2009–2010 to 2016–2017 (weeks 40–20) were retrieved from the European Surveillance System (TESSy) database. A description of the surveillance systems in the countries reporting data is available at FluNewsEurope webpage [24].

Data Set

Reported information on laboratory-confirmed cases in ICUs included the following: influenza virus type; subtype (A(H1N1) pdm09, A(H3N2)) and lineage (B/Victoria, B/Yamagata); age (year); sex; duration of hospitalization (time between admission to hospital and either discharge or death); complications (acute respiratory distress syndrome [ARDS], bronchitis, encephalitis, myocarditis, pneumonia, sepsis, other); vaccination status (not vaccinated, pandemic, seasonal, or both vaccines); date of vaccination; respiratory support (not required, ventilation or oxygen support); and outcome (deceased or alive). Due to limited data reported on B-lineage, specific analysis in relation to B lineages was not feasible. The following underlying conditions were reported: asthma, cancer, chronic heart, kidney, liver or lung disease, diabetes, human immunodeficiency virus (HIV)/other immune deficiency, neurocognitive and neuromuscular disorders, pregnancy, obesity, and morbid obesity. Countries were also able to report additional other underlying conditions in a free text field, and those covered a mix of various different genetic and acquired conditions as well as infectious diseases such as tuberculosis, hepatitis B or C, etc. Asthma and lung disease were pooled as chronic lung condition. Morbid obesity and obesity were pooled because analyzing them separately did not show any differences. Information about the date of vaccination and vaccine type was very limited. A full overview of reported data by country is available in Supplementary Tables.

Data Analysis

A basic dataset was compiled to analyze the relationship between age, sex, virus type, and fatal outcome. Inclusion criteria were as follows: laboratory-confirmed influenza cases admitted to ICU, influenza virus type A or B confirmation, known age, sex, and outcome (Basic dataset) (Figure 1).

Underlying medical conditions and A virus subtypes were only available for a subset of cases within the basic dataset but were considered important factors for analysis. Therefore, we created a subset of the basic dataset that included cases with known influenza A virus subtype (or B type) and underlying condition(s) (Specific dataset) (Figure 1).

Additional variables analyzed independently were duration of hospitalization, complications, vaccination status, and respiratory support. Because these additional variables were only incompletely reported, they were not included in any multivariable analysis because they would have substantially reduced the number of eligible cases. For the analysis of pregnancy, the analysis was restricted to women 17–50 years of age adjusting for the reporting country.

We performed a descriptive analysis of the pooled data across seasons and reporting countries. Descriptive statistics included absolute and relative frequencies of each study variable. Continuous variables were compared by using Wilcoxon rank-sum test, Mann-Whitney test, and Student's *t* test. We applied different statistical models according to Barros et al [25] as a sensitivity analysis to identify the best possible method. Poisson regression models with robust variance were applied to identify statistically significant determinants of fatal outcome. The use of robust variance intended to improve the variance estimation to adjust for dispersion of the data by reducing the effect of outliers. Crude and adjusted risk ratios (incidence rate ratio [IRR]) and 95% confidence intervals (CIs) were determined. The reporting country was included in the final model to adjust for country effects. A second model was developed based on the subset of the basic dataset that included cases with known underlying conditions and influenza A virus subtype (A(H3N2) or A(H1N1)pdm09) or B type. The significance level was set at 0.05. Stata 14 (StataCorp) was used for the statistical analysis.

RESULTS

Descriptive Analysis

The inclusion criteria for the basic dataset were met by 13 368 cases reported from 12 countries during the study period 2009–2010 to 2016–2017 (Figure 1). The number of reporting countries varied each season with France and Spain reporting the

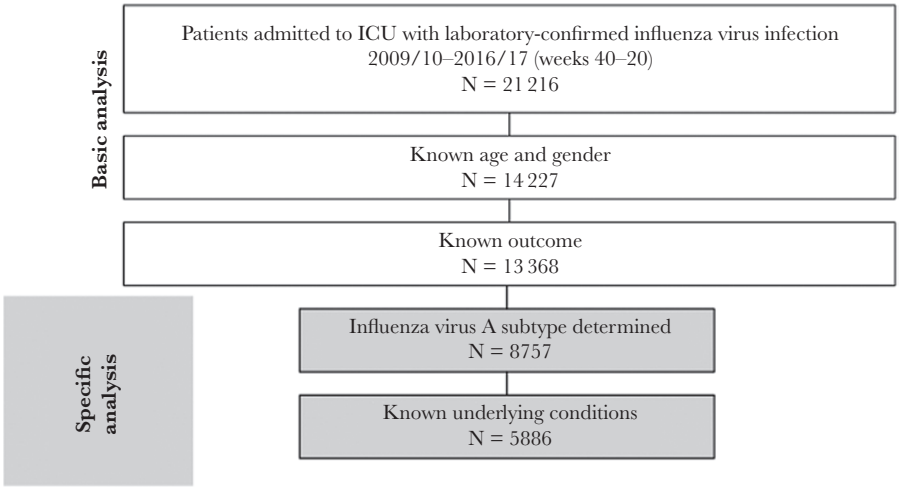

Figure 1. Flow chart of cases included in the analysis. ICU, intensive care unit.

majority of cases (57% and 26%, respectively). Of the 13 368 patients in ICU with laboratory-confirmed influenza virus infection, 2806 (21%) died (Table 1). The majority of cases were male (7604; 57%). The median age was 59 years (interquartile range, ±14 years; range, 0–104 years). Most of the cases (7566; 57%) were between 50 and 79 years of age, and 10% of the cases were 18 years old or younger.

Most influenza viruses (11 809; 88%) were type A: 5223 (44%) were subtyped as A(H1N1)pdm09, 1975 (17%) were subtyped as A(H3N2), and 4611 (39%) were reported without subtype. In all seasons, there were more influenza A viruses (>60% of viruses) compared with B viruses among ICU cases. In seasons with higher proportions of A(H3N2) detections, the proportion of unsubtyped A viruses was also higher than in seasons with A(H1N1)pdm09 dominance. The proportion of influenza B virus cases was greater than 20% in both the 2012/2013 and 2015/2016 season. The highest proportion of B viruses (20%) was observed in those aged less than 20 years.

Duration of Hospitalization

The duration of hospitalization was available for 952 cases (7%) whose median stay was 10 days (range, 0–198 days) and did not significantly differ between influenza virus types (P = .1). However, the median stay of cases who recovered was significantly longer than in fatal cases (13 vs 10 days; P = .003).

Underlying Conditions and Virus Type/Subtype

Among 5886 cases with known influenza virus type and A subtype (A(H1N1)pdm09 and A(H3N2)) and underlying conditions (Specific dataset) (Figure 1), 23% percent (1349) died (Table 1). More cases were male (3205; 54%) than female. A total of 2552 cases (43%) were reported to have no underlying condition. One condition was reported for 2498 (42%) cases, 2 conditions were reported for 569 cases (10%), 3 conditions were reported for 198 cases (3%), and 4 to 6 conditions were reported for less than 2% of the patients. The most commonly reported underlying conditions were chronic lung disease (18%) and obesity (15%). Influenza virus A(H1N1)pdm09 was detected in the majority (3512; 60%) of the patients, followed by A(H3N2) (1286; 22%) and type B (1088; 18%).

Respiratory Support

Data about respiratory support were available for 8667 (65%) of the 13 368 patients. Support was not required for 1005 (12%) patients, oxygen was given to 506 (6%) patients, and 7156 (83%) patients were ventilated. Of 579 patients reported to have pneumonia, 430 (74%) were ventilated, 118 (20%) received oxygen, and 31 (5%) received no respiratory support. Of 3085 patients with ARDS, 2843 (92%) were ventilated, 134 (4%) were reported to be given oxygen, and 108 (3.5%) received no respiratory support. The risk of death increased more than 4-fold when ventilation had to be commenced (IRR, 3.98; 95% CI, 3.03–5.23), but not for patients only given oxygen support (IRR, 1.02; 95% CI, 0.68–1.52) compared with patients without any respiratory support, adjusting for reporting country, age, and sex.

Complications

Data about complications during the course of disease were available for 7592 (57%) cases. The most commonly reported complications were ARDS (51%) and pneumonia (41%). Acute respiratory distress syndrome (IRR, 1.02; 95% CI, 0.92–1.13), encephalitis (IRR, 1.16; 95% CI, 0.78–1.70), and pneumonia (IRR, 0.91; 95% CI, 0.82–1.02) were not associated with an increased risk of death adjusting for reporting country, age, and sex. Although sepsis and myocarditis were reported only for 6% and less than 2% of the 7592 cases, respectively, both were associated with increased risk of death (sepsis: IRR, 2.65; 95% CI, 2.41–2.90; myocarditis: IRR, 1.30; 95% CI, 1.00–1.67).

Vaccination

Vaccination status was known for 9215 (69%) of the 13 368 cases, with 2162 (23%) reported as having been vaccinated with either seasonal (2011 cases), pandemic (42), or both vaccines (109). The median duration of hospitalization did not differ between vaccinated and nonvaccinated patients (10.5 vs 10 days). Vaccination was preventive for fatal outcome (IRR, 0.86; 95% CI, 0.78–0.95) adjusting for reporting country, virus type, age, and sex.

Information on vaccination and underlying conditions were only provided for a limited number of cases (6052). In addition, information on date of vaccination was only available for 40 of all cases, and for 28 of them the date of onset of disease was provided in addition with a range of 0–185 days between vaccination and disease onset. Therefore, reporting on vaccination was considered biased and not included in the overall multivariable analysis.

Pregnancy

Pregnancy was reported for 244 women between 17 and 59 years of age. Twenty-four (10%) of the pregnant women died. Of the 153 pregnant women with known vaccination status, 3 were vaccinated and 150 were unvaccinated. The risk of death was lower for pregnant women when restricting the analysis to the age group 17–50 years old compared with nonpregnant women of the same age group (IRR, 0.57; 95% CI, 0.38–0.85) and adjusting for reporting country within the basic dataset. No difference was seen between France reporting the majority of cases and other countries as well as between pandemic and nonpandemic seasons (Supplementary Data).

Within the specific dataset when restricting the analysis to women 17–50 years old and adjusting for reporting country, pregnant women were less likely to die (IRR, 0.63; 95% CI, 0.41–0.96). Underlying conditions such as HIV/immunosuppression (IRR, 2.11; 95% CI, 1.48–3.03) or heart disease (IRR, 1.81; 95% CI, 1.12–2.91) increased the risk to die.

Univariable and Multivariable Analysis

In the basic model including cases with known gender, age, and influenza virus type, the determinants associated with fatal outcome in the univariable analysis were male sex, age of 40 years and older, and infection with influenza A virus (Table 1). The risk for fatal outcome increased by 1.5% with each year of age (IRR, 1.02; 95% CI, 1.01–1.02), using age as continuous variable. In the multivariable model, influenza A virus infection and older age (≥40 years) were significantly associated with mortality. The highest risk ratio was identified in people of 80 years of age and older.

The univariable analysis of cases with detailed information about influenza A virus subtype and underlying conditions again identified being male and 40 years or older as determinants of fatal outcome (Table 2). Cancer, heart, liver, and kidney disease, HIV infection/other immune deficiencies as well as other underlying conditions were identified as risk factors for fatal outcome, whereas patients of younger age and with chronic lung disease were less likely to die. In the multivariable model, age 60 years and older, cancer, chronic heart, kidney, and liver disease, as well as HIV infection/other immune deficiency and other underlying conditions were confirmed as determinants of fatal outcome. In addition, infection either with A(H1N1) pdm09 or A(H3N2) virus was retained.

DISCUSSION

This is the first published analysis of confirmed influenza ICU cases reported from 12 EU countries over 8 consecutive seasons. Confining the analysis to ICU cases was intended to improve data comparability across countries, although criteria for ICU admission might not have been uniform across countries and hospitals. We confirmed several known determinants contributing to a greater risk of fatal outcome. In addition, the association between sepsis as a clinical complication and an increased risk of death underlines the clinical impact of early treatment and care in these severely ill patients. No information was available on why some patients admitted to ICU did not receive respiratory support, ie, the information was missing or not reported: either such patients had been transferred to ICU for precautionary reasons, there was missing case information, or data were not reported. In addition, no information on timing of complications in relation to ICU admission was available within this dataset as well as on other complications such as secondary bacterial infections or related treatment.

The present study is limited by the small number of EU countries reporting. Cases were reported from only 12 of the 31 EU/EEA Member States, and so their cases might not be representative of all severe cases across the EU/EEA. A further limitation of this study is the differences in ICU reporting systems between Member States and the pooling of such case-based data across countries that have different underlying healthcare systems and surveillance [26]. The imbalance between the contributions of the various countries over time might also limit the comparability of the data. Nevertheless, we assessed the variation by applying different statistical methods and identified a reasonable test to compensate for the reporting country effect according to Barros et al [25]; however, different underlying data collection cannot be solved by pure statistics. We believe that this study, even with its limitations, provides valuable information on several determinants relevant for increased risk of fatal outcome due to influenza in Europe. The identified limitations of reporting and pooling of such case-based clinical data across countries will need to be addressed to develop more robust variables and apply clinical severity scores. This process needs to create data independent from the respective underlying surveillance system to be useful to identify determinants for severe disease and fatal outcome.

Table 1. Risk Factors for Fatal Outcome in Laboratory-Confirmed Influenza Cases in ICU, 12 EU/EEA Countries, 2009/10–2016/17, Basic Dataset

	Recovered Cases N = 10 562		Fatal Cases N = 2 806		Univariable Analysis			Multivariable Analysis		
Determinants	n	%	n	%	Risk Ratio	(95% CI)	*P* Value	Adjusted[a] Risk Ratio (95% CI)		*P* Value
Gender										
Female	4603	44	1161	41	Ref.			Ref.		
Male	5959	56	1645	59	**1.08**	**(1.01–1.15)**	.030	1.05	(0.98–1.12)	.143
Age in Years										
0–19	1191	11	123	4.4	**0.59**	**(0.48–0.72)**	<.001	**0.60**	**(0.49–0.74)**	<.001
20–39	1274	12	233	8.3	Ref.			Ref.		
40–59	3278	31	787	28.1	**1.27**	**(1.12–1.45)**	<.001	**1.26**	**(1.10–1.44)**	.001
60–79	3777	36	1289	45.9	**1.70**	**(1.50–1.93)**	<.001	**1.70**	**(1.50–1.93)**	<.001
80+	1042	10	374	13.3	**1.87**	**(1.61–2.16)**	<.001	**1.87**	**(1.61–2.16)**	<.001
Virus Type										
A	9249	88	2560	91	**1.37**	**(1.21–1.54)**	<.001	**1.31**	**(1.16–1.47)**	<.001
B	1313	12	246	9	Ref.					

Significant findings ($p < 0.05$) in bold.

Abbreviations: CI, confidence interval; EEA, European Economic Area; EU, European Union; ICU, intensive care unit; Ref., Reference.

[a]Adjusted for reporting country.

Table 2. Risk Factors for Fatal Outcome in Laboratory-Confirmed Influenza Cases in ICU, 12 EU/EEA Countries, 2009/10–2016/17, Specific Dataset

	Recovered Cases N = 4 537		Fatal Cases N = 1 349		Univariable Analysis			Multivariable Analysis		
Determinants	n	%	n	%	Risk Ratio	(95% CI)	*P* Value	Adjusted[a] Risk Ratio (95% CI)		*P* Value
Gender										
Female	2113	47	586	42	Ref.			Ref.		
Male	2424	53	781	58	**1.15**	**(1.05–1.26)**	.003	**1.12**	**(1.02–1.23)**	.019
Age in Years										
0–19	504	11	60	5	**0.59**	**(0.44–0.78)**	<.001	**0.66**	**(0.50–0.87)**	.003
20–39	645	14	137	10	Ref.				Ref.	
40–59	1439	32	421	31	**1.29**	**(1.09–1.53)**	.003	**1.23**	**(1.04–1.46)**	**.013**
60–79	1547	34	581	43	**1.62**	**(1.37–1.90)**	<.001	**1.71**	**(1.45–2.02)**	<.001
80+	402	9	150	11	**1.68**	**(1.37–2.05)**	<.001	**2.00**	**(1.61–2.47)**	<.001
Underlying Conditions										
Cancer	92	2	74	6	**2.22**	**(1.83–2.70)**	<.001	**1.84**	**(1.51–2.23)**	<.001
Diabetes	371	8	154	11	1.08	(0.94–1.26)	.284	[b]		
Heart disease	418	9	230	17	**1.32**	**(1.16–1.51)**	<.001	**1.19**	**(1.04–1.37)**	.012
HIV/Immune deficiency	169	4	146	11	**1.80**	**(1.58–2.07)**	<.001	**1.67**	**(1.45–1.91)**	<.001
Kidney disease	106	2	86	6	**1.71**	**(1.45–2.02)**	<.001	**1.38**	**(1.16–1.64)**	<.001
Liver disease	114	3	67	5	**1.42**	**(1.17–1.73)**	<.001	**1.29**	**(1.06–1.57)**	.013
Chronic lung infection	651	14	222	17	**0.86**	**(0.76–0.97)**	.016	**0.82**	**(0.73–0.93)**	.002
Neurocognitive	45	1	14	1	1.05	(0.67–1.65)	.819	[b]		
Neuromuscular disorders	88	2	29	2	0.97	(0.71–1.33)	.872	[b]		
Obesity	673	15	211	16	1.05	(0.92–1.19)	.690	1.05	(0.92–1.20)	.486
Other	110	2	49	4	**1.32**	**(1.03–1.69)**	.031	**1.32**	**(1.02–1.71)**	.037
Virus Subtype										
B	912	20	176	13	Ref.			Ref.		
A(H1N1)pdm09	2632	58	880	65	**1.52**	**(1.31–1.76)**	<.001	**1.56**	**(1.35–1.82)**	<.001
A(H3N2)	993	22	293	22	**1.31**	**(1.10–1.55)**	.002	**1.19**	**(1.00–1.41)**	.047

Significant findings ($p < 0.05$) in bold.

Abbreviations: CI, confidence interval; EEA, European Economic Area; EU, European Union; HIV, human immunodeficiency virus; ICU, intensive care unit; Ref., Reference.

[a]Adjusted for reporting country and pregnancy.

[b]Not included in the final mode.

The proportion of fatal cases among patients in ICU was higher in this study (21%) than in previous analyses (mean 16%) [11, 27], which might be due to the inclusion criteria we used: known virus type, age, gender, and outcome. The results showed an increasing risk of death associated with influenza A and increasing age over 40 years, which partly confirms the findings of other studies that indicate mortality during A(H3N2) seasons mostly affects people 65 years of age and older and middle-aged during A(H1N1) pdm09-dominated seasons [28, 29]. However, fatality in ICU represents only a small fraction of the mortality toll of influenza, particularly in the elderly, which are less likely to be admitted to ICU and have also been shown to be less likely tested for influenza virus infection in the hospital setting [30].

The data reported to TESSy were not complete regarding influenza virus A subtype and B lineage as well as underlying conditions. A considerable number of cases (4611; 34%) from the basic dataset had to be dropped from the specific subset analysis due to missing virus subtype information. The high proportion of unsubtyped influenza A viruses, ranging from 0.1% during the pandemic season 2009/2010 to 60% in 2016/2017, limited determination of the dominant virus subtype for most of the seasons in the analysis. We also observed that the proportion of unsubtyped influenza A viruses was higher in A(H3N2)-predominant seasons than in A(H1N1) pdm09 seasons. This might be explained by the fact that detection systems specifically developed for A(H1N1)pdm09 during the 2009 pandemic continue to be used in diagnostics, so if influenza A viruses test negative in the specific A(H1N1)pdm09 test, they are reported as "influenza A unsubtyped", which creates a bias towards more A(H1N1)pdm09 cases in the subtype-specific analyses. Another reason could be an increased testing for influenza A and B in acute hospital settings using point-of-care tests without further subtyping. Better virological data would be desirable for a better assessment of the clinical impact of the virus subtype but also regarding vaccine effectiveness. In a French study, female sex and influenza vaccination were described as protective factors with regard to ARDS in severely ill patients [16]. In our study, vaccination showed some protection; however, the data on vaccination status had several limitations in the available information on vaccination date, vaccine type, and onset of disease. The small number of cases with information on underlying conditions and vaccination status did not allow for a more in-depth analysis.

Our analysis supports previous findings that HIV infection/other immune deficiency, cancer, heart, kidney, and liver disease increase the likelihood of fatal outcomes as do increasing age over 40 years and influenza A infection [14, 15, 31]. All EU/EEA Member States recommend annual influenza vaccination for persons 65 years of age and older. Recommendations for persons with the following chronic medical conditions vary across countries: respiratory (pulmonary), cardiovascular, chronic neurological, hepatic and renal disease, immunosuppression, metabolic disorders, HIV/acquired immune deficiency syndrome, and morbid obesity [32, 33]. Our analysis showed that HIV infection/other immunosuppressive disorders are associated with an increased risk of death; however, no specific information on "other immune deficiencies" was provided. People with HIV infection are known to be at greater risk of dying from influenza and its complications due to their susceptibility to infection, and they are specifically targeted by Member State vaccination programs [10, 34–36]. With the constant number of approximately 30 000 newly diagnosed HIV infections each year and over 500 000 estimated people with HIV in EU/EEA countries, influenza vaccines as well as early antiviral treatment should be offered to them as a priority group [37–39].

Others identified an association between pre-existing lung, neuromuscular or neurocognitive disease, or obesity and fatal outcome in hospitalized patients; however, this was not seen among ICU patients in this analysis [14, 15]. In our study, chronic lung condition including asthma was not associated with an increased risk of death in line with a recent meta-analysis [31]. A previous study described an association of earlier hospital admission and less severe outcomes in asthmatics compared with nonasthmatics [40]. Pregnancy is considered a risk factor for severe influenza [11], and a large majority of EU/EEA Member States recommended influenza vaccination for pregnant women [32, 33]. Although approximately 3% of all our cases were pregnant women, our findings did not show any increased risk for fatal outcome when admitted to ICU and confirm findings of others [15, 31]. Pregnancy, chronic lung disease, and obesity may increase the risk for hospitalization and ICU admission, rather than fatal outcome. It can be speculated that early hospitalization, early onset of treatment, and transfer to ICU as a precaution in these patients' populations may prevent severe disease progression. The earlier identification of these conditions as risk factors might have contributed to increased awareness and better clinical care preventing fatal outcomes.

CONCLUSIONS

This study highlights the importance of preventing influenza virus infection, particularly in the elderly, but also in tailoring strategies to protect risk groups with underlying conditions, which includes the use of antiviral treatment and vaccination [41].

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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