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MAJOR ARTICLE

Influenza Vaccination Modifies Disease Severity Among Community-dwelling Adults Hospitalized With Influenza

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Background. We investigated the effect of influenza vaccination on disease severity in adults hospitalized with laboratory-confirmed influenza during 2013–14, a season in which vaccine viruses were antigenically similar to those circulating.

Methods. We analyzed data from the 2013–14 influenza season and used propensity score matching to account for the probability of vaccination within age strata (18–49, 50–64, and ≥65 years). Death, intensive care unit (ICU) admission, and hospital and ICU lengths of stay (LOS) were outcome measures for severity. Multivariable logistic regression and competing risk models were used to compare disease severity between vaccinated and unvaccinated patients, adjusting for timing of antiviral treatment and time from illness onset to hospitalization.

Results. Influenza vaccination was associated with a reduction in the odds of in-hospital death among patients aged 18–49 years (adjusted odds ratios [aOR] = 0.21; 95% confidence interval [CI], 0.05 to 0.97), 50–64 years (aOR = 0.48; 95% CI, 0.24 to 0.97), and ≥65 years (aOR = 0.39; 95% CI, 0.17 to 0.66). Vaccination also reduced ICU admission among patients aged 18–49 years (aOR = 0.63; 95% CI, 0.42 to 0.93) and ≥65 years (aOR = 0.63; 95% CI, 0.48 to 0.81), and shortened ICU LOS among those 50–64 years (adjusted relative hazards [aRH] = 1.36; 95% CI, 1.06 to 1.74) and ≥65 years (aRH = 1.34; 95% CI, 1.06 to 1.73), and hospital LOS among 50–64 years (aRH = 1.13; 95% CI, 1.02 to 1.26) and ≥65 years (aRH = 1.24; 95% CI, 1.13 to 1.37).

Conclusions. Influenza vaccination during 2013–14 influenza season attenuated adverse outcome among adults that were hospitalized with laboratory-confirmed influenza.

Keywords. Influenza vaccination; adults; disease severity.

Influenza vaccination is the best strategy for preventing influenza [1]. Nonetheless, influenza vaccination coverage in the United States is suboptimal, especially among adults 18 to 49 years of age, with vaccination levels as low as ~33% [2]. Reasons for low coverage may include underappreciation of disease severity and skepticism among the public about how well the vaccine works [3].

Although prevention of influenza virus infection is the desirable outcome after influenza vaccination, people may still become infected with influenza despite being vaccinated [4]. However, some studies have suggested that influenza vaccination could modify the severity of illness among vaccinated patients who subsequently develop influenza virus infection [5–8]. Evidence for vaccine modification of influenza-associated disease severity could be an important argument toward improving influenza vaccination coverage in various groups of the population.

Influenza vaccine effectiveness (VE) varies from season to season, depending on host characteristics (such as age and presence of comorbidities) and how well circulating influenza viruses match the viruses contained in the vaccine [9–12]. During the 2013–14 influenza season, influenza A(H1N1) pdm09 virus predominated, the first time in the United States since this virus emerged in 2009 [13]. During that season, influenza viruses that circulated were antigenically similar to viruses included in the vaccine, and the influenza VE estimate against medically attended acute respiratory illness for ages ≥6 months was 52% (95% confidence interval [CI] 44, 59) [9, 14], which allowed us to investigate the impact of influenza vaccination on disease severity. Therefore, we analyzed data from adults hospitalized with laboratory-confirmed influenza during the 2013–14 influenza season in the United States, to assess whether influenza vaccination provided protection against

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severe influenza disease among persons who become infected with influenza despite vaccination.

METHODS

Study Population and Design

We analyzed population-based data from the US Influenza Hospitalization Surveillance Network (FluSurv-NET) that includes over 240 reporting hospitals, with a catchment area representing approximately 9% of the US population. Adult (age ≥18 years) residents of the surveillance area were considered cases if they were admitted to one of the participating hospitals from October 1, 2013, through April 30, 2014, and had a laboratory-confirmed diagnosis of influenza no more than 14 days before admission. Influenza testing and the type of influenza testing used (i.e., reverse transcription–polymerase chain reaction, viral culture, fluorescent antibody staining, or rapid antigen test) was determined by the provider. Medical chart review using a standardized form captured information on demographic characteristics and clinical outcomes during hospitalization [15].

Vaccination status was ascertained from medical charts and vaccine registries by contacting the patient's primary care provider or by interviewing the patient or proxies directly. A complete or partial vaccination date had to be provided in order for the patient to be considered vaccinated. If these criteria were not met, at least one vaccination source had to indicate that the patient did not receive seasonal influenza vaccination [on or after July 1, 2013] to be considered unvaccinated for that season; otherwise vaccination status of the patient was considered unknown.

We excluded cases with unknown vaccination status and cases who had fewer than 14 days between vaccination and hospitalization (time required to develop vaccine-induced protection). We also excluded those living in long-term care facilities because of substantial differences in baseline characteristics (e.g., vaccination coverage, frailty, and immunosenescence) as compared to adults living in the community [16]. Over 80% of the captured FluSurv-NET patients received antiviral medication (oseltamivir). We did not have information on why physicians treated some patients and not others; moreover, there were significant differences between patients who received antivirals and patients who did not (data not shown). Therefore, we decided to exclude patients who did not receive antivirals, those with an unclear history of antiviral treatment, and those who started antiviral treatment ≥4 days before hospitalization (because we could not ascertain whether treatment was completed). The group of patients who were not treated with antiviral was small to be analyzed separately. Also, we excluded pregnant women and those without body mass index (BMI) data.

Severity Outcomes

We evaluated intensive care unit (ICU) admission, in-hospital death (including hospice transfer), diagnosis of pneumonia, and ICU and hospital length of stay (LOS) as measures of disease severity (study outcomes). Pneumonia was defined by presence of bronchopneumonia/pneumonia, air space density/opacity, pleural effusion/empyema, consolidation and/or lobar (not interstitial) infiltrate on chest radiography within the first 3 days of hospital admission, and a discharge diagnosis of pneumonia. For the analysis of the impact of influenza vaccination on pneumonia, our denominator included only those who had chest radiography taken within the first 3 days of hospital admission. All analyses were performed by age stratum (18–49, 50–64, and ≥65 years) because vaccine response and coverage varies by age [4, 17–19].

Statistical Analysis

We described epidemiologic and clinical characteristics of patient-population by vaccination status, using Pearson X^2 test, Fisher exact test, or Wilcoxon-Mann-Whitney test.

For each age group mentioned above, we performed propensity score matching (PSM) to balance the differences between vaccinated and unvaccinated groups based on their probability of being vaccinated [20], given differences in demographic characteristics (sex, age, and race/ethnicity, and state of residence), BMI, chronic underlying conditions (asthma, chronic lung disease, cardiovascular disease, chronic metabolic disease, neurologic disease, immunosuppression, blood disorder, renal disease, and liver disease), and lifestyle risk factors (alcohol abuse and smoking). For PSM, we used the nearest neighbor matching approach, which requires a 1:2 vaccinated-to-unvaccinated ratio for best model fit [21, 22]. For adults ≥65 years, because we had a similar number of vaccinated and unvaccinated patients, we randomly sampled approximately 1/2 of vaccinated patients to meet the 1:2 matching requirement. We repeated the random sample selection a thousand times to obtain an averaged point estimate for each outcome and lower and upper 95% CI [23]. After PSM, no significant differences remained for each of these variables by vaccination status.

Finally, for each age group, we evaluated the association of influenza vaccination with ICU admission, death, and pneumonia using multivariable logistic regression (MLR) models, adjusting odds ratios (aOR) for timing of antiviral treatment (calculated from day of symptom onset and categorized as ≤2 days, 3–5 days, and >5 days), and day to hospital admission (calculated from symptom onset and categorized as ≤2 days and >2 days). Similarly, we used competing risk (CR) models to evaluate the association of influenza vaccination and ICU and hospital LOS (in days), adjusting relative hazards (aRH) for timing of antiviral treatment and time to hospital admission, and accounted for in-hospital death as a CR. All analyses were performed using R software (version 3.2.2).

Ethics

FluSurv-NET was considered nonresearch for public health purposes by the institutional review board (IRB) at the Centers for Disease Control and Prevention (CDC). Participating sites

submitted the FluSurv-NET protocol to its state and local IRBs for review, if required.

RESULTS

Baseline Characteristics (Before Propensity Score Matching)

Of the 8354 hospitalized adult cases that were identified in the 2013–14 season, 3444 (41%) were excluded, leaving 4910 cases for analysis (Figure 1). There were 1551 cases aged 18–49 years (31.6%), 1771 were 50–64 years (36.1%), and 1588 were ≥65 years (32.3%); age group-specific influenza vaccination coverage was 19%, 33%, and 54%, respectively. Vaccinated cases were more likely to have chronic medical conditions than unvaccinated cases, except among those aged ≥65 years, in whom fewer differences in the prevalence of medical conditions were observed. Influenza vaccination was inversely associated

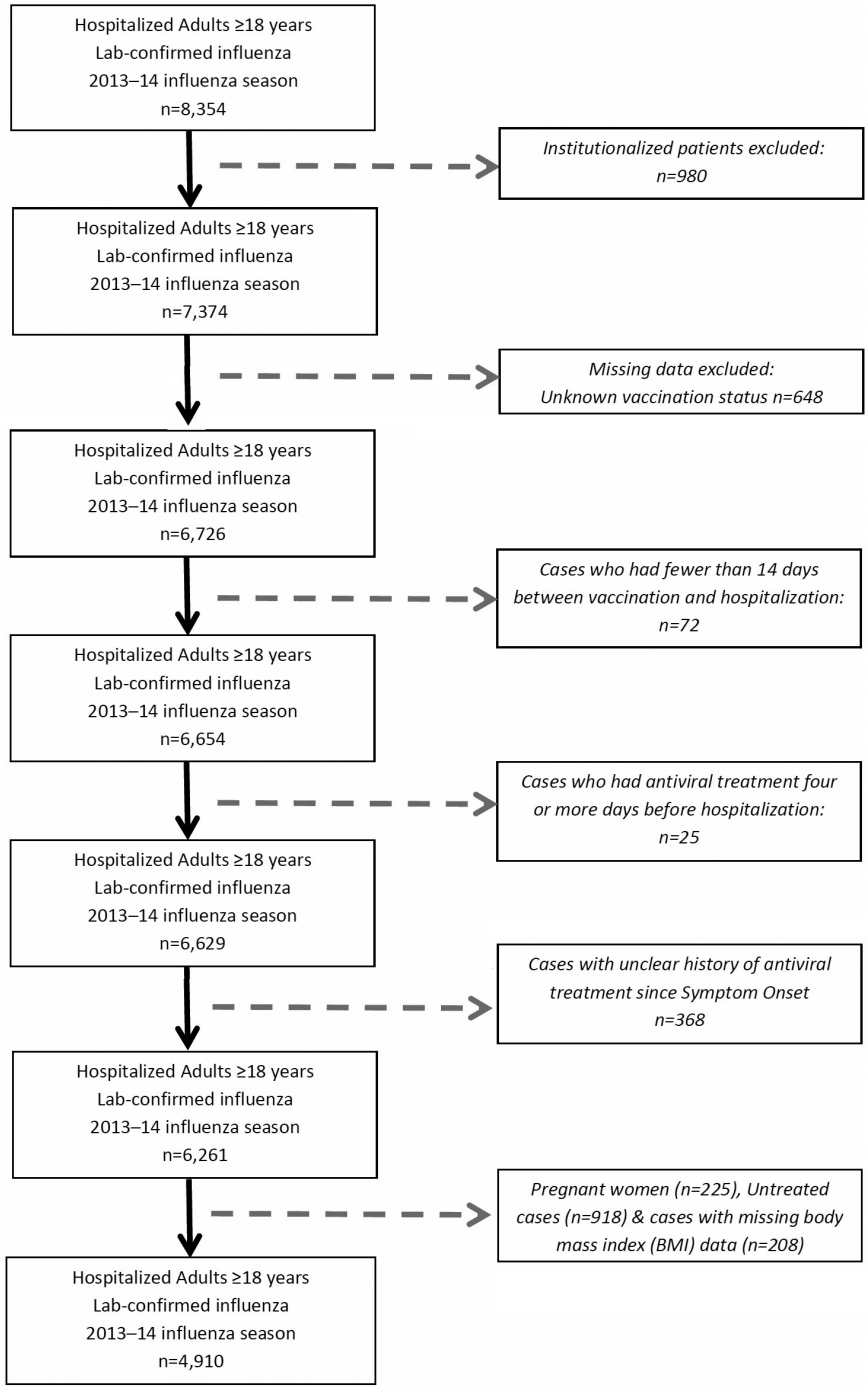

Figure 1. Exclusion criteria and data cleaning algorithm.

with smoking among adults ≥50 and with alcohol abuse in those 50–64 years of age. In addition, among adults aged 18–64 years, influenza vaccination was associated with earlier antiviral treatment and with receiving hospital care within 2 days of symptom onset ($P < .02$; Table 1).

Within each age group, the proportion of in-hospital deaths among the unvaccinated was higher than among the vaccinated ($P < .04$). Among those aged 18–49 and ≥65 years, a higher proportion of unvaccinated cases were admitted to the ICU as compared to the vaccinated group ($P \leq .01$). For those aged 18–49 years, diagnosis of pneumonia was more likely among the unvaccinated ($P = .01$). For those 50–64 years, the median of ICU LOS was higher among the unvaccinated as compared to the vaccinated ($P = .03$).

Propensity Score Matching and Evaluation of Influenza Vaccination and Severe Disease Outcomes

After performing PSM on the probability of being vaccinated, we obtained matched samples of 600, 1186, and 732 cases among 18–49, 50–64, and ≥65 year age groups, respectively. We found no differences in proportions for any of the variables used for PSM by vaccination status (data not shown). For those aged 18–49 years, we found a protective effect of influenza vaccine against ICU admission (aOR = 0.63; 95% CI, 0.42 to 0.93) and in-hospital death (aOR = 0.21; 95% CI, 0.05 to 0.97). For those aged 50–64 years, we found a protective effect of the vaccine against in-hospital death (aOR = 0.48; 95% CI, 0.24 to 0.97), shorter ICU LOS (aHR for ICU discharge = 1.36; 95% CI, 1.06 to 1.74), and shorter hospital LOS (aHR for discharge = 1.13; 95% CI, 1.02 to 1.26). For those aged ≥65 years, we found a protective effect of the vaccine against ICU admission (aOR = 0.63; 95% CI, 0.48 to 0.81), in-hospital death (aOR = 0.39; 95% CI, 0.17 to 0.66), shorter ICU LOS (aRH = 1.34; 95% CI, 1.06 to 1.73), and shorter hospital LOS (aRH = 1.24; 95% CI, 1.13 to 1.37). We did not observe statistical differences for the association between influenza vaccination and pneumonia (Table 2). Figure 2 shows 95% CIs for the risk parameters evaluating the effect of influenza vaccination on influenza disease severity by 1000 random sample simulations for age group ≥65, after PSM and after adjusting for timing of antiviral treatment and time to hospital admission, and accounting for death in the survival models. In the graphs, the red lines represent 95% CI with a statistically significant value; the black lines represent 95% CI that did not achieve statistical significance. The 4 graphs show a trend of 95% CI toward rejecting the null hypothesis, which is consistent with results in Table 2. Figure 3 shows the cumulative incidence function for time to ICU discharge and hospital discharge for the 3 age groups, respectively. Overall, the probability of earlier discharge from the ICU or hospital, after accounting for in-hospital death, was higher for those vaccinated versus those unvaccinated at different points in time; this is also consistent with results in Table 2.

DISCUSSION

We showed a significant protective effect of 2013–14 seasonal influenza vaccination against disease severity outcomes among hospitalized adults with laboratory-confirmed influenza. Overall, vaccinated adults had a 52–79% reduction in in-hospital death and a 37% reduction in ICU admission (among those aged 18–49 and ≥65 years) compared to those unvaccinated. In addition, the probability of being discharged earlier from the ICU and from the hospital was 34–36% and 13–24% higher among vaccinated cases aged ≥50 years compared to unvaccinated cases. Our data suggest that although influenza vaccination may have failed to prevent influenza virus infection among some of those vaccinated for the 2013–14 season, it may have still protected those same people against more severe influenza-associated outcomes. Our findings underscore the importance of annual influenza vaccination for adults, particularly among those aged 18–49 years (historically the group with the lowest influenza vaccination coverage in the US) [2], and among those ≥65 years (accounting for 71–85% of estimated annual influenza-associated deaths in the US) [24].

We had previously assessed the effect of influenza vaccination on disease severity among adults aged 50 years and older during the 2012–13 season using a similar analytical approach [5]. In that study, we did not find a substantial effect of vaccination on clinical outcomes (we only found a modest effect of vaccination on ICU LOS in the 50–64 year olds). Influenza season 2012–13 was primarily an H3N2 season with nonsignificant VE reported for older age groups [10, 25]. Influenza VE against medically attended cases due to influenza A in outpatients ≥65 years was 11% [95% CI −41 to 43] for the 2012–13 season, whereas the VE for the same age group during 2013–14 season was 51% (95% CI 12, 73) [10, 14]. Thus, the benefit of influenza vaccination on attenuating influenza-associated disease severity may be influenced by robustness of VE, especially among older adults.

Our analysis was limited to patients hospitalized with laboratory-confirmed influenza and those treated with antivirals; we do not know if our findings could be generalizable to non-hospitalized populations or whether the effects we found could be even more robust in a population without access to antiviral treatment. Evidence to support the benefit of antiviral treatment in reducing influenza disease severity suggests that best results are seen if treatment initiated early (first 4 days after illness onset) [26–28] for which we account in our adjustment analysis. One of the explanations for not seeing a significant association between influenza vaccination and shorter ICU and hospital LOS among those aged 18–49 years may be the small sample size. Despite representing about one third of hospitalizations during the 2013–14 season, a smaller percentage of cases within this age group were vaccinated. Interestingly, in this age group, we observed that influenza vaccination was associated with a lower prevalence of pneumonia compared to the

Table 1. Demographic and Clinical Characteristics, Lifestyle Risk Factors, and Clinical Course of Hospitalization of Cases Who Received Antivirals by Age Group and Vaccination Status, FluSurv-NET, 2013–14 Influenza Season

	Age group 18 to 49 (n = 1551) Vaccination Status 2013–14			Age group 50 to 64 (n = 1771) Vaccination Status 2013–14			Age group 65+ (n = 1588) Vaccination status 2013–14		
Characteristics	Vaccinated n = 300 (19) n (%)	Unvaccinated n = 1251 (81) n (%)	*X*2 test *P*-value	Vaccinated n = 593 (33) n (%)	Unvaccinated n = 1178 (67) n (%)	*X*2 test *P*-value	Vaccinated n = 856 (54) n (%)	Unvaccinated n = 732 (46) n (%)	*X*2 test *P*-value
Female sex	168 (56)	635 (51)	.12	346 (58)	611 (52)	.01	454 (53)	419 (57)	.10
Race									
Non-Hispanic white	162 (55)	582 (47)	.18	368 (62)	689 (58)	.57	613 (72)	445 (61)	<.001
Non-Hispanic black	76 (25)	343 (27)		124 (21)	284 (24)		97 (11)	140 (19)	
Hispanic	34 (11)	170 (14)		50 (8)	95 (8)		64 (7)	64 (9)	
Other	10 (3)	61 (5)		20 (3)	42 (4)		45 (5)	41 (6)	
Unknown	18 (6)	95 (8)		31 (5)	68 (6)		37 (4)	42 (6)	
Weight status based on BMI									
Underweight	13 (4)	40 (3)	.31	24 (4)	37 (3)	.55	34 (4)	33 (5)	.87
Normal	75 (25)	257 (21)		132 (22)	245 (21)		239 (28)	206 (28)	
Overweight	70 (23)	292 (23)		159 (27)	300 (25)		248 (29)	199 (27)	
Obese	88 (29)	397 (32)		191 (32)	398 (34)		270 (32)	231 (32)	
Morbid obese	54 (18)	265 (21)		87 (15)	198 (17)		65 (8)	63 (9)	
Chronic conditions									
Asthma	113 (38)	386 (31)	.03	172 (29)	253 (21)	<.001	143 (17)	123 (17)	1.00
Chronic lung disease	61 (20)	121 (10)	<.001	260 (44)	416 (35)	<.001	390 (46)	274 (37)	.001
Cardiovascular disease	59 (20)	165 (13)	.005	243 (41)	378 (32)	<.001	528 (62)	400 (55)	.005
Chronic metabolic disease	103 (34)	275 (22)	<.001	256 (43)	417 (35)	.002	433 (51)	348 (48)	.25
Neurologic disease	68 (23)	152 (12)	<.001	103 (17)	162 (14)	.06	172 (20)	152 (21)	.76
Immunosuppression	98 (33)	176 (14)	<.001	197 (33)	204 (17)	<.001	198 (23)	107 (15)	<.001
Blood disorder	26 (9)	61 (5)	.02	41 (7)	74 (6)	.68	68 (8)	39 (5)	.05
Renal disease	44 (15)	76 (6)	<.001	112 (19)	135 (11)	<.001	225 (26)	156 (21)	.02
Liver disease	10 (3)	30 (2)	.47	52 (9)	78 (7)	.12	30 (4)	14 (2)	.08
≥1 chronic condition	275 (92)	844 (67)	<.001	557 (94)	967 (82)	<.001	800 (93)	663 (91)	.04
Alcohol abuse									
Current	10 (3)	68 (5)	.29	26 (4)	111 (9)	<.001	26 (3)	16 (2)	.53
Former	10 (3)	34 (3)		30 (5)	64 (5)		25 (3)	24 (3)	
Never	280 (93)	1149 (92)		537 (91)	1003 (85)		805 (94)	692 (95)	
Smoking									
Current	110 (37)	498 (40)	.50	231 (39)	533 (45)	.004	127 (15)	163 (22)	<.001
Former	33 (11)	117 (9)		154 (26)	231 (20)		367 (43)	233 (32)	
Never	157 (52)	636 (51)		208 (35)	414 (35)		362 (42)	336 (46)	
Time of antiviral treatment from symptom onset									
≤2 days	124 (41)	453 (36)	.02	235 (40)	418 (35)	.01	305 (36)	287 (39)	.31
3–5 days	128 (43)	507 (41)		232 (39)	432 (37)		345 (40)	273 (37)	
>5 days	48 (16)	291 (23)		126 (21)	328 (28)		206 (24)	172 (23)	
Delay in seeking care (>2 d)	134 (45)	661 (53)	.01	291 (49)	652 (55)	.01	446 (52)	365 (50)	.40
Admitted in ICU	56 (19)	324 (26)	.01	141 (24)	317 (27)	.17	140 (16)	169 (23)	<.001
Deceased	2 (1)	37 (3)	.04	12 (2)	50 (4)	.02	18 (2)	32 (4)	.01
Diagnosis of pneumonia[a]	60 (21)	367 (31)	.001	130 (22)	304 (27)	.06	212 (26)	169 (24)	.43
Length of ICU stay, days (median, IQR)	4 (2–9)	5 (3–15)	.10[b]	4 (2–8)	5 (3–12)	.03[b]	4 (2–7)	4 (2–8)	.29[b]
Length of hospital stay, days (median, IQR)	4 (3–6)	4 (3–7)	.51[b]	4 (3–7)	5 (3–8)	.09[b]	5 (3–7)	5 (3–8)	.007[b]

Percentages reflect numbers that had information available. Percentages may not sum to 100% due to rounding.

Abbreviations: BMI, body mass index; ICU, intensive care unit; IQR, interquartile range.

[a]Among those who had a chest x-ray taken *within 3 days* of admission (n = 1481, 1720, and 1546, respectively).

[b]Wilcoxon-Mann-Whitney test was used to calculated *P*-values.

Table 2. Influenza Vaccination and Severity of Influenza Disease Analysis for the 2013–14 Season by Age Category, After Propensity Score Matching[a] and Adjusted for Timing of Antiviral Treatment and Time Seeking Hospital Care[b]

	Influenza Vaccine 2013–14 Season					
	18–49 years (n = 600)		50–64 years (n = 1186)		65+ years (n = 732) ×1000sim	
Clinical Outcomes	Point Estimate	(95% CI)	Point Estimate	(95% CI)	Point Estimate[c]	(95% CI)[c]
Admitted to ICU (OR)	0.63	(0.42; 0.93)	1.05	(0.80; 1.37)	0.63	(0.48; 0.81)
Deceased (OR)	0.21	(0.05; 0.97)	0.48	(0.24; 0.97)	0.39	(0.17; 0.66)
Pneumonia[d]	0.77	(0.52; 1.15)	1.10	(0.83, 1.46)	1.02	(0.81, 1.27)
Shorter ICU length of stay (RH)[e]	1.40	(0.97; 2.02)	1.36	(1.06; 1.74)	1.34	(1.06; 1.73)
Shorter hospital length of stay (RH)[e]	1.11	(0.95; 1.29)	1.13	(1.02; 1.26)	1.24	(1.13; 1.37)

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio; RH, relative hazard.

[a]Matched by age (subcategorized in age groups 18 to 29, 30 to 39 and 40 to 49, and 65 to 74 and 75+ for age categories 18–49 and 65+ years, respectively), sex, race, state, weight status based on Body Mass Index (BMI), chronic underlying conditions (asthma, chronic lung disease, cardiovascular disease, chronic metabolic disease, neurologic disease, immunosuppression, blood disorder, renal disease, liver disease, and having at least one of these conditions), and alcohol abuse and smoking.

[b]Timing for antiviral treatment was calculated from symptom onset and categorized as ≤2 days, 3–5 days, and >5 days or no treatment; time seeking hospital care (≤2 vs >2 days).

[c]Based on 1000 simulations; point estimate and lower and upper confidence interval represent 50th, 2.5th and 97.5th percentiles of point estimates (n = 1000), respectively.

[d]Pneumonia analysis was performed among those who had chest x-rays within 3 days of admission.

[e]RH represents ICU or hospital discharge accounting for death.

unvaccinated group, which has been described elsewhere [29, 30]. However, when adjusted for all other characteristics, this association was no longer significant. Sample size could again explain that as the number of patients to assess pneumonia as an outcome was reduced to those with chest x-rays done within the first 3 days of admission.

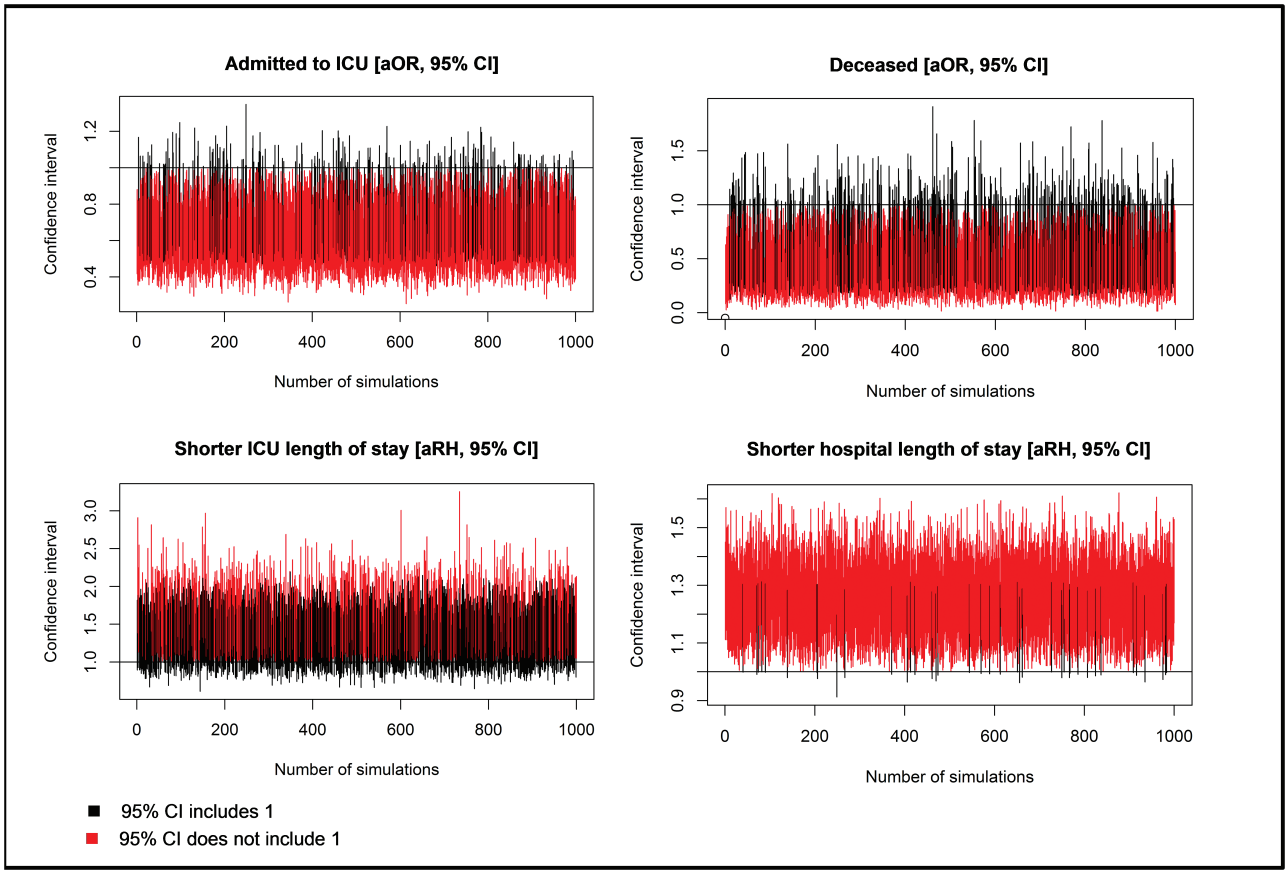

Figure 2. Confidence intervals [95% CI] of severe disease outcomes obtained by random sample simulations (N = 1000) for age group 65 years and older. Relative Hazard (RH) represents ICU or hospital discharge accounting for death; For age group 65+ years: aOR for ICU admission = 0.63 (95% CI: 0.48, 0.81), aOR for death = 0.39 (95% CI: 0.17, 0.66), aRH for ICU Discharge = 1.34 (95% CI: 1.06, 1.73), aRH for Hospital Discharge = 1.24 (95% CI: 1.13, 1.37). Abbreviations: aOR, adjusted odds ratio; aRH, adjusted relative hazard; CI, confidence interval; ICU, intensive care unit.

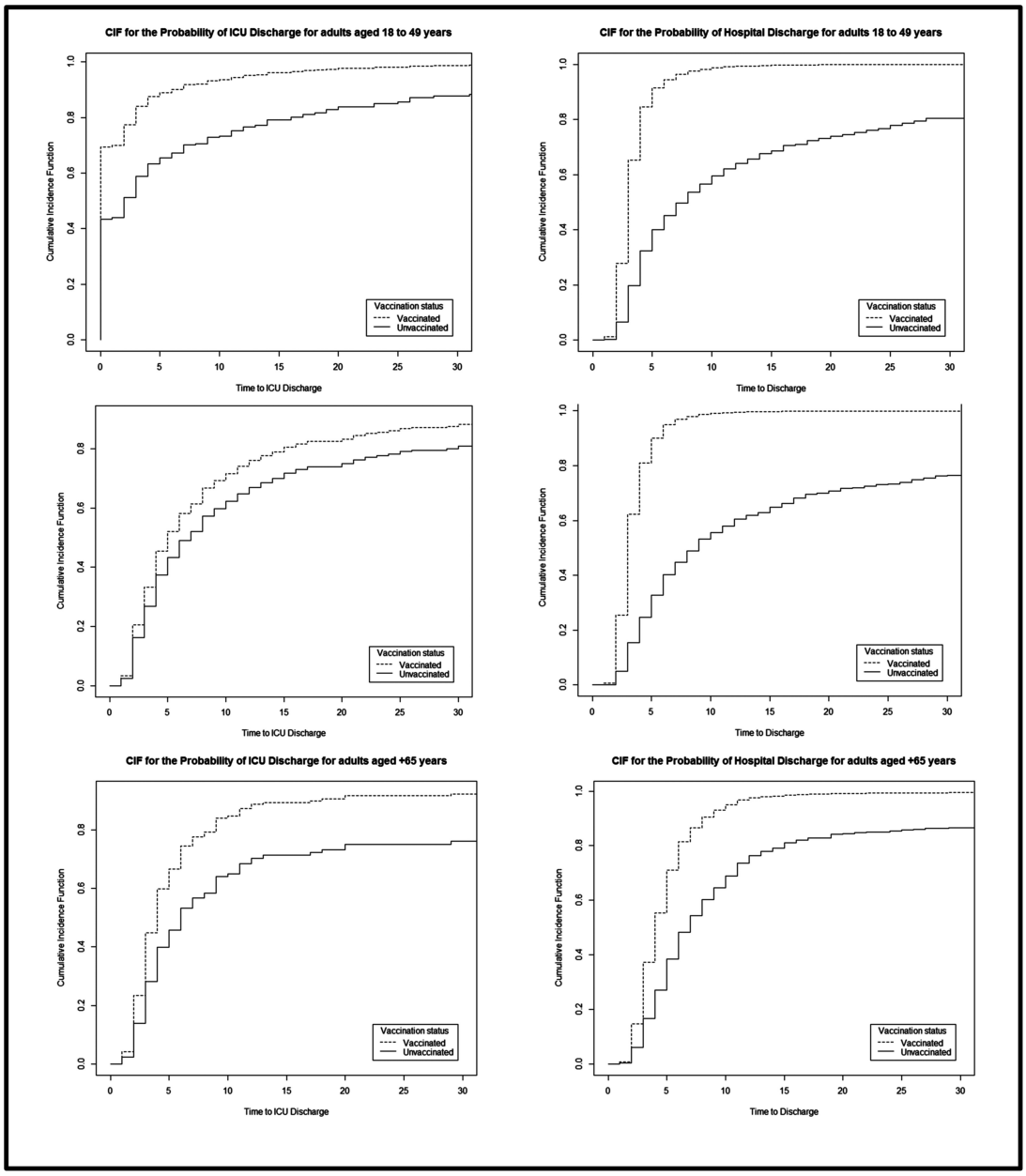

Figure 3. Cumulative incidence function for shorter ICU length of stay and length of hospital stay for age groups 18 to 49 years, 50 to 64 years, and 65 years and older by vaccination status accounting for death as a competing risk.

Relative Hazard (RH) represents ICU or hospital discharge accounting for death; For age group 18 to 49 years: RH for ICU Discharge = 1.40 (95% CI: 0.97, 2.02), RH for hospital discharge = 1.11 (95% CI: 0.95, 1.29). For age group 50 to 64 years: RH for ICU discharge = 1.36 (95% CI: 1.06, 1.74), RH for hospital discharge = 1.13 (95% CI: 1.02, 1.26). For age group 65+ years: RH for ICU discharge = 1.34 (95% CI: 1.06, 1.73), RH for hospital discharge = 1.24 (95% CI: 1.13, 1.37). Abbreviations: CI, confidence interval; CIF, cumulative incidence function; ICU, intensive care unit; RH, relative hazard.

Similar to our findings, one large multicenter case-control study in Spain [6] found a reduction of over 50% in the risk of severe influenza-related outcomes among those ≥65 years old who were vaccinated against influenza. In addition, 2 smaller studies assessed 2013–14 influenza vaccination in adults and its effects on disease severity. One of them [31] reported no effect of influenza vaccination on in-hospital mortality or respiratory failure among older adults hospitalized with influenza. In contrast, the other study reported lower influenza vaccination rates among those who presented with more severe respiratory illness, including need for ICU admission and positive pressure ventilation [32]. These studies, unlike ours, were neither powered to control for confounders nor assessed the propensity for vaccination in their study population. Our findings suggest that, in addition to a VE against medically attended laboratory-confirmed influenza of about 50% in season 2013–14, influenza vaccination seemed to attenuate influenza-associated severe outcomes, including reduction in ICU admission and death.

Additional findings that support the benefit of influenza vaccination in attenuating influenza disease severity come from VE studies. Deiss et al [33], based on symptoms at disease presentation, described a milder disease among vaccinated individuals infected with H3N2 viruses compared to unvaccinated individuals during the 2009–2014 seasons. Others have estimated VE for mild and severe cases separately, finding higher protection against severe cases that would suggest that influenza vaccine could attenuate illness [34, 35]. This implies that our study outcomes may not represent the full spectrum of the effect of influenza vaccination on disease attenuation. Therefore, studies assessing the benefit of annual influenza vaccination in terms of cases, hospitalizations, and/or deaths averted without including the potential for disease severity modification may be underestimating the total benefits of influenza vaccination [1, 12].

Observational studies of this kind demand robust methods to ensure that biases in the data are limited (e.g., vaccine is more commonly administered to patients with comorbidities and older adults). To minimize the impact of confounding by indication and healthy vaccinee bias, we used PSM to balance the comparison groups accounting for the probability of vaccination and used CR models to account for death during hospitalization that could affect our ability to assess LOS as a reliable measure of severity [36–38]. Nonetheless, our study has limitations. There might be unmeasured or incompletely measured confounders that we could not account for in PSM. We were reassured by the fact that we were able to include an extensive list of variables reported to be associated with vaccination in our PSM, achieving well-balanced comparison groups [26], and adjusting for other variables associated with the outcomes of interest in the final models. Nonetheless, the benefit of vaccination may have been underestimated because we only included in-hospital deaths. Future studies could evaluate the impact of influenza vaccination accounting for deaths occurring after hospital discharge [37]. We excluded 8% of participants due to unknown vaccination status that could inadvertently introduce bias; however, the number was not large, and when we compared the excluded group's characteristics related to vaccination, severity, and time from disease onset to hospitalization, we did not find any substantial differences (Supplementary Table A1). We performed our analyses among hospitalized patients treated with antivirals, excluding untreated patients (less than 20% of FluSurv-NET patients) [16], and this could also have underestimated the effect of vaccination on influenza-associated severe outcomes as antiviral treatment can attenuate disease severity [39].

In conclusion, our study demonstrated that despite vaccinated individuals became infected with influenza viruses, vaccination can reduce disease severity. Our study focused on adults hospitalized with laboratory-confirmed influenza in 2013–14, a year in which the vaccine virus components matched the circulating viruses. This additional benefit of influenza vaccination on disease severity may be observed in future seasons when vaccine is shown to provide significant protection, especially among people aged ≥65 years.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

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References

1. Kostova D, Reed C, Finelli L, et al. Influenza illness and hospitalizations averted by influenza vaccination in the United States, 2005–2011. PLoS One **2013**; 8:e66312.
2. Centers for Disease Control and Prevention. FluVaxView. **2016** Available at: http://www.cdc.gov/flu/fluvaxview/. Accessed 26 May 2016.
3. Health, R. Seasonal Flu Vaccination: Why Don't More Americans Get It? Research Highlights, Rand Health, **2011**.
4. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis **2012**; 12:36–44.
5. Arriola CS, Anderson EJ, Baumbach J, et al. Does influenza vaccination modify influenza severity? Data on older adults hospitalized with influenza during the 2012–2013 season in the United States. J Infect Dis **2015**; 212:1200–8.
6. Casado I, Domínguez A, Toledo D, et al.; Project Pi12/2079 Working Group. Effect of influenza vaccination on the prognosis of hospitalized influenza patients. Expert Rev Vaccines **2016**; 15:425–32.
7. Patriarca PA, Weber JA, Parker RA, et al. Efficacy of influenza vaccine in nursing homes. Reduction in illness and complications during an influenza A (H3N2) epidemic. JAMA **1985**; 253:1136–9.
8. Ruben FL, Johnston F, Streiff EJ. Influenza in a partially immunized aged population. Effectiveness of killed Hong Kong vaccine against infection with the England strain. JAMA **1974**; 230:863–6.
9. Centers for Disease Control and Prevention. Seasonal influenza Vaccine Effectiveness, 2005–2015. **2015** Available at: http://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm. Accessed 17 November 2015.
10. McLean HQ, Thompson MG, Sundaram ME, et al. Influenza vaccine effectiveness in the United States during 2012–2013: variable protection by age and virus type. J Infect Dis **2015**; 211:1529–40.
11. Fry AM, Kim IK, Reed C, et al. Modeling the effect of different vaccine effectiveness estimates on the number of vaccine-prevented influenza-associated hospitalizations in older adults. Clin Infect Dis **2014**; 59:406–9.

12. Valenciano M, Ciancio B, Moren A; Influenza Vaccine Effectiveness Working Group. First steps in the design of a system to monitor vaccine effectiveness during seasonal and pandemic influenza in EU/EEA Member States. Euro Surveill **2008**; 13.
13. Arriola CS, Brammer L, Epperson S, et al.; Centers for Disease Control and Prevention (CDC). Update: influenza activity - United States, September 29, 2013–February 8, 2014. MMWR Morb Mortal Wkly Rep **2014**; 63:148–54.
14. Gaglani M, Pruszynski J, Murthy K, et al. Influenza vaccine effectiveness against 2009 pandemic influenza A(H1N1) virus differed by vaccine type during 2013–2014 in the United States. J Infect Dis **2016**; 213:1546–56.
15. Chaves SS, Lynfield R, Lindegren ML, Bresee J, Finelli L. The US Influenza Hospitalization Surveillance Network. Emerg Infect Dis **2015**; 21:1543–50.
16. Arriola CS, Chaves SS. Reply to Chughtai *et al*. J Infect Dis **2015**; 212:1684–5.
17. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine **2006**; 24:1159–69.
18. Herrera GA, Iwane MK, Cortese M, et al. Influenza vaccine effectiveness among 50–64-year-old persons during a season of poor antigenic match between vaccine and circulating influenza virus strains: Colorado, United States, 2003–2004. Vaccine **2007**; 25:154–60.
19. Reber AJ, Chirkova T, Kim JH, et al. Immunosenescence and challenges of vaccination against influenza in the aging population. Aging Dis **2012**; 3:68–90.
20. Williamson EJ, Forbes A, Introduction to propensity scores. Respirology **2014**; 19:625–35.
21. Rosenbaum PR, Rubin DB. The bias due to incomplete matching. Biometrics **1985**; 41:103–16.
22. Rubin DB, Thomas N. Matching using estimated propensity scores: relating theory to practice. Biometrics **1996**; 52:249–64.
23. Davison AC, Hinkley DV, eds. Bootstrap Methods and Their Application. New York: Cambridge University Press, **1997**.
24. Reed C, Chaves SS, Daily Kirley P, et al. Estimating influenza disease burden from population-based surveillance data in the United States. PLoS One **2015**; 10:e0118369.
25. Flannery B, Zimmerman RK, Gubareva LV, et al. Enhanced genetic characterization of influenza A(H3N2) viruses and vaccine effectiveness by genetic group, 2014-2015. J Infect Dis **2016**; 214:1010–9.
26. Chaves SS, Pérez A, Miller L, et al. Impact of prompt influenza antiviral treatment on extended care needs after influenza hospitalization among community-dwelling older adults. Clin Infect Dis **2015**; 61:1807–14.
27. Fry AM, Goswami D, Nahar K, et al. Efficacy of oseltamivir treatment started within 5 days of symptom onset to reduce influenza illness duration and virus shedding in an urban setting in Bangladesh: a randomised placebo-controlled trial. Lancet Infect Dis **2014**; 14:109–18.
28. Lee N, Chan PK, Hui DS, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. J Infect Dis **2009**; 200:492–500.
29. Jhung MA, Swerdlow D, Olsen SJ, et al. Epidemiology of 2009 pandemic influenza A (H1N1) in the United States. Clin Infect Dis **2011**; 52 Suppl 1:S13–26.
30. Grijalva CG, Zhu Y, Williams DJ, et al. Association between hospitalization with community-acquired laboratory-confirmed influenza pneumonia and prior receipt of influenza vaccination. JAMA **2015**; 314:1488–97.
31. Joshi M, Chandra D, Mittadodla P, Bartter T. The impact of vaccination on influenza-related respiratory failure and mortality in hospitalized elderly patients over the 2013–2014 season. Open Respir Med J **2015**; 9:9–14.
32. Catania J, Que LG, Govert JA, Hollingsworth JW, Wolfe CR. High intensive care unit admission rate for 2013–2014 influenza is associated with a low rate of vaccination. Am J Respir Crit Care Med **2014**; 189:485–7.
33. Deiss RG, Arnold JC, Chen WJ, et al. Vaccine-associated reduction in symptom severity among patients with influenza A/H3N2 disease. Vaccine **2015**; 33:7160–7.
34. Castilla J, Godoy P, Domínguez A, et al.; CIBERESP Cases and Controls in Influenza Working Group Spain. Influenza vaccine effectiveness in preventing outpatient, inpatient, and severe cases of laboratory-confirmed influenza. Clin Infect Dis **2013**; 57:167–75.
35. Jain VK, Rivera L, Zaman K, et al. Vaccine for prevention of mild and moderate-to-severe influenza in children. N Engl J Med **2013**; 369:2481–91.
36. Remschmidt C, Wichmann O, Harder T. Frequency and impact of confounding by indication and healthy vaccinee bias in observational studies assessing influenza vaccine effectiveness: a systematic review. BMC Infect Dis **2015**; 15:429.
37. Hak E, Hoes AW, Nordin J, Nichol KL. Benefits of influenza vaccine in US elderly–appreciating issues of confounding bias and precision. Int J Epidemiol **2006**; 35:800–2; author reply 799–800.
38. Wong K, Campitelli MA, Stukel TA, Kwong JC. Estimating influenza vaccine effectiveness in community-dwelling elderly patients using the instrumental variable analysis method. Arch Intern Med **2012**; 172:484–91.
39. O'Hagan JJ, Wong KK, Campbell AP, et al. Estimating the United States demand for influenza antivirals and the effect on severe influenza disease during a potential pandemic. Clin Infect Dis **2015**; 60 Suppl 1:S30–41.