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Influenza vaccination status and outcomes among influenza-associated hospitalizations in Columbus, Ohio (2012–2015)

P. N. ZIVICH[1]*, L. TATHAM[2], K. LUNG[2], J. TIEN[3], C. E. BOLLINGER[4] AND J. K. BOWER[1]

[1] *Division of Epidemiology, The Ohio State University College of Public Health, Columbus, Ohio, USA*
[2] *Bureau of Infectious Diseases, Ohio Department of Health, Columbus, Ohio, USA*
[3] *Department of Mathematics, The Ohio State University, Columbus, Ohio, USA*
[4] *Division of Environmental Health Sciences, The Ohio State University College of Public Health, Columbus, Ohio, USA*

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SUMMARY

Prior studies suggest that the influenza vaccine is protective against some outcomes in hospitalized patients infected with influenza despite vaccination. We utilized surveillance data from Columbus, Ohio to investigate this association over multiple influenza seasons and age groups. Data on laboratory-confirmed influenza-associated hospitalizations were collected as a part of the Influenza Hospitalization Surveillance Project for the 2012–2013, 2013–2014, and 2014–2015 influenza seasons. The association between influenza vaccination status was examined in relation to the outcomes of severe influenza and diagnosis of pneumonia among patients receiving antiviral treatment. Data were analyzed using multivariable logistic regression. We observed no overall association between influenza vaccination status and severe influenza among hospitalized patients. During the 2013–2014 season, those who were vaccinated were 41% less likely to be diagnosed with pneumonia compared with those who were unvaccinated (OR = 0·59 95% CI 0·41–0·86). The influenza vaccine may provide a secondary preventive function against pneumonia among influenza cases requiring hospitalization. However, a protective effect was only observed in 2013–2014, an influenza H1N1 dominant year. Differences in circulating influenza virus strains and vaccine matching to the circulating strains during influenza seasons may impact this association.

Key words: Influenza, influenza vaccine, pneumonia, severe illness.

INTRODUCTION

Influenza is a viral pathogen that is a continuing threat to human health. Each year in the USA, influenza causes more than 220 000 hospitalizations [1] and 3000–49 000 deaths [2]. Influenza vaccination is a key primary preventive strategy and is particularly important for persons at high risk for serious influenza-associated complications [3]. Those at high risk include children younger than 5 years old, adults older than 65 years old, immunosuppressed individuals, and persons with underlying medical conditions, such as chronic lung disease or immunosuppression. In the absence of contraindications, influenza vaccination is recommended universally for persons older than 6 months of age [3].

* Author for correspondence: P. N. Zivich, 135 Dauer Drive 2101 McGavran-Greenberg Hall, CB #7435, Chapel Hill, NC 27599, USA.
(Email: zivich.5@gmail.com)

Despite the efficacy of the vaccine at reducing influenza-associated hospitalizations, a subset of persons who receive the influenza vaccine develop influenza severe enough to require hospitalization. Generally, this is observed in elderly or immune suppressed individuals, and is thought to be due to inadequate immune response to the vaccine [4, 5]. Less is known if the vaccine confers protection or other benefits in this subpopulation of vaccine recipients. There is emerging evidence that the influenza vaccine may prevent serious outcomes in vaccinated hospitalized patients, namely pneumonia, admission to the intensive care unit (ICU), and death [6–9]. This secondary effect of vaccination was not consistently evaluated across prior studies [10, 11]. Furthermore, previous studies are limited by select patient subpopulations [8–10], restriction to a single influenza season [6, 8, 10, 11], or not controlling for the potential impact of antiviral treatment [6–9, 11]. Additionally, none of these studies looked at the influence of time between vaccination and hospitalization on the prevention of serious outcomes. There is evidence that suggests vaccine effectiveness wanes in regards to influenza infection [12–15].

This study examined the impact of vaccination status on outcomes among laboratory-confirmed influenza-associated hospitalizations in the Columbus, Ohio metropolitan statistical area (MSA). Multiple seasons and all age groups eligible for vaccination were included in the analysis. The two primary outcomes of interest were severe influenza (defined as admission to the ICU or death during the hospitalization) and pneumonia. A secondary aim of this study was to assess the role of time between vaccination and hospitalization to determine if waning immunity affected any observed secondary protective effect.

METHODS

Data collection

Data from three influenza seasons (2012–2013/2013–2014/2014–2015) were collected through the Influenza-Associated Hospitalization Surveillance Project (FluSurv-NET) for the Columbus, Ohio MSA (Fig. 1). FluSurv-NET is funded by Centers for Disease Control and Prevention (CDC) and began in Ohio in 2009; data collection methods have been previously described [16]. Each influenza season begins on the 1 October and ends on the 30 April of the subsequent year. FluSurv-NET collects demographic information, risk factors, medical history, vaccination status, and outcomes on all laboratory-confirmed influenza-associated hospitalization cases in the catchment area. While FluSurv-NET collects data from around the USA, this study focused on data obtained from the Columbus, Ohio MSA. Influenza-associated hospitalizations are a mandatory reportable condition in Ohio, so cases were identified from the Ohio Disease Reporting System, Ohio's surveillance system for reportable infectious diseases. Approximately 16·5% of Ohio's population resides in this catchment area [17].

FluSurv-NET surveillance definitions

An influenza-associated hospitalization was defined as a person who lived within the catchment area who experienced a hospitalization with laboratory-confirmed influenza. Testing methods were chosen by the attending physician and therefore varied; testing was performed by viral culture (0·9%), rapid antigen testing (34·8%), or real-time reverse transcriptase-polymerase chain reaction (64·2%). Vaccination status and dates were obtained from the medical record. If vaccination status was missing, FluSurv-NET staff retrieved this information from the vaccination registry, by contacting primary care providers, or by direct interview of patients.

Inclusions and exclusions

Children younger than 6 months were excluded from analysis since vaccination is not recommended for this age group [3]. Pregnant women were excluded since pregnancy is associated with distinct complications due to influenza and because of the small number of hospitalized pregnant women ($n = 87$). Individuals who were prescribed antivirals >4 days before they were hospitalized were excluded from analysis since it could not be determined whether they completed their antiviral regimen. Those who did not receive antiviral treatment were excluded ($n = 234$).

To ensure that a patient's hospitalization was directly associated with influenza, the individual must have had an influenza diagnostic test no more than 14 days before the admission date. To decrease the likelihood of including nosocomial influenza patients, individuals with a positive test >3 days after hospitalization were excluded, as were individuals with a

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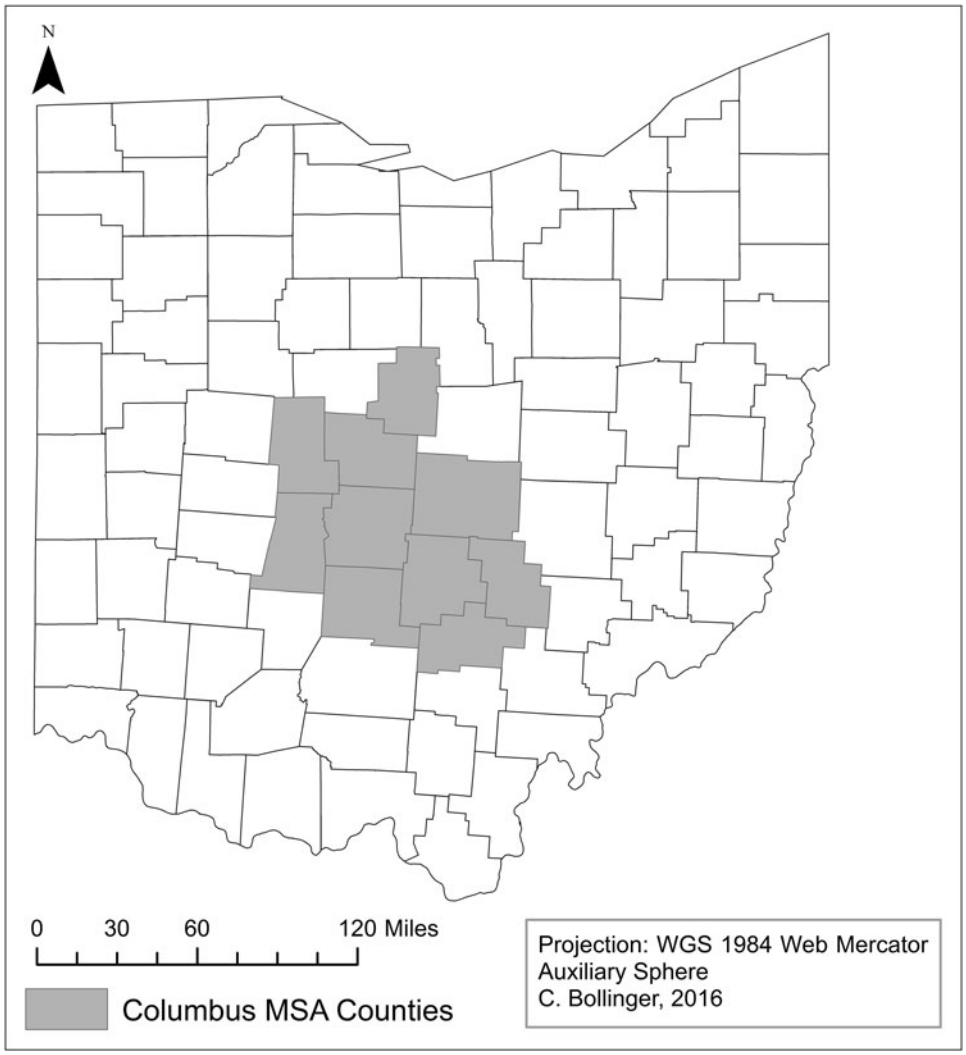

Fig. 1. Columbus, Ohio Metropolitan Statistical Area (MSA) Counties in gray are part of the Columbus, OH MSA. The counties included in the MSA, in alphabetical order, are Delaware, Fairfield, Franklin, Hocking, Licking, Madison, Morrow, Perry, Pickaway, and Union. Approximately 16·5% of Ohio's population lives in this area.

hospitalization within 1 week prior to the influenza-associated hospitalization.

Definitions

A patient was considered vaccinated if they received the influenza vaccine for the respective influenza season and if vaccination occurred at least 14 days before the date of hospitalization. If the vaccination date was unavailable ($n = 261$), patients were categorized as vaccinated but not considered in vaccine timing analyses. Patients younger than 9 years old needed to receive two doses that season or one dose in the previous season and one in the current season to be considered vaccinated [3]. Two clinical outcomes were evaluated: severe influenza and diagnosis of pneumonia. Severe influenza was defined as admission to the ICU or death during the influenza-associated hospitalization. Pneumonia was defined as a chest X-ray indicating pneumonia and either diagnosis of pneumonia at discharge or ICD-9 discharge code for pneumonia (480–487·0). Patients were categorized into four age groups: young children (6 months–<5 years), school-age persons (5–24 years), adults (25–64 years), and elderly adults (65+ years old) for consistency with empirical data on contact rates between age groups and risk of influenza hospitalization [18].

Confounders identified *a priori* were sex (male/female), race (White/other), age, presence of underlying medical conditions (asthma/chronic lung

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disease/cardiovascular disease/chronic metabolic disease/neurologic disease/immunosuppression/hematologic disorder/renal disease/liver disease), alcohol abuse (current/former/never), tobacco use (current/former/never), and influenza virus type (influenza A/influenza B/influenza A & B). Since all patients in the analysis received antivirals, designations were made regarding whether the antiviral medication was administered prompt or late. There is evidence that hospitalized individuals who are given antivirals promptly have better outcomes than hospitalized individuals who receive them late [19, 20]. Prompt antiviral administration was defined as having antivirals administered within 2 days of admission [19]. Late antiviral administration was defined as having antiviral medication administered 3 or more days after admission.

Multivariable logistic regression

Multivariable logistic regression was utilized to evaluate the association between influenza vaccination, and (1) severe influenza and (2) diagnosis of pneumonia. We refer to the model that included all designated confounders (season, age, sex, race, all underlying medical conditions, alcohol use, tobacco use, influenza type, antiviral administration time) as the fully-adjusted model.

We formally assessed the interaction of vaccination status with age group and season; where appropriate, results were stratified by age and season. Collinearity was assessed by observing Pearson's correlation coefficient for all variable combinations; all correlations were <0·4. All analyses were conducted in SAS version 9·3 (Cary, NC).

Timing of vaccination

To assess the impact of time between vaccination and hospitalization on pneumonia for those with recorded vaccination times, logistic regression was utilized. Due to the small sample size, only the impact of time between vaccination and hospitalization on pneumonia was examined. Time was expressed in time in weeks (continuous) and as an indicator variable (>100 days *vs.* ⩽100 days).

Sensitivity analysis

Two sensitivity analyses were performed. The first sensitivity analysis was to check that the assumption that those missing recorded vaccination times were vaccinated at least 14 days before hospitalization was not introducing bias. Those without recorded vaccination times were excluded and the analysis was repeated. Secondly, those who did not receive antivirals were analyzed to see if differences were observed in this group.

Ethics

The Ohio Department of Health Institutional Review Board (IRB) determined FluSurv-NET to be public health practice and exempt. The analytic protocol was reviewed and approved by The Ohio State University IRB.

RESULTS

Patient characteristics

After exclusions, 2071 patients out of 2818 were included in the analytic sample (Supplementary Fig. S1). A total of 474 individuals were hospitalized in 2012–2013, 524 in 2013–2014, and 1073 in 2014–2015. Over all three seasons, 1086 individuals were vaccinated (52·4%). The prevalence of vaccination was 41·9% for 2012–2013, 44·7% for 2013–2014, and 61·0% for 2014–2015.

The distributions of age and race differed between vaccinated and unvaccinated patients (Table 1) and by season (Supplementary Table S1). Overall, individuals 25–64-year-old patients and 65 years and older patients made up the majority of hospitalizations (40·1%, 47·1%, respectively). For all three seasons, individuals 25–64-year-old patients represented the majority of the unvaccinated population (51·8%), while those 65 years and older made up most of the vaccinated population (60·4%).

Most of the population had at least one underlying medical condition (94·5%). Patients generally received antivirals within 2 days of admission (95·8%), and there was no independent association of antiviral treatment with vaccination status. The median length of hospitalization stay was 3 days (IQR: 2–6 days). There were 718 diagnoses of pneumonia (34·7%) and 260 cases of severe influenza (21·6%), including 58 deaths (2·8%).

Vaccination and severe influenza

There was no significant association between vaccination and severe influenza in unadjusted (OR = 0·89;

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Table 1. *Characteristics of influenza-associated hospitalized patients who received antivirals by vaccination status (Ohio, 2012–2015)*

	Overall $n = 2071$ (%)	Vaccinated $n = 1086$ (%)	Unvaccinated $n = 985$ (%)	P*
2012–2013	474 (22·9)	199 (18·3)	275 (27·9)	<0·0001
2013–2014	524 (25·3)	232 (21·4)	292 (55·7)	
2014–2015	1073 (51·8)	418 (39·0)	655 (60·3)	
Female	1092 (52·7)	555 (51·1)	537 (54·5)	0·12
Age group				
0·5–4 years	121 (5·8)	31 (2·8)	90 (9·1)	<0·0001
5–24 years	144 (6·9)	79 (7·3)	65 (6·6)	
25–64 years	830 (40·1)	320 (29·5)	510 (51·8)	
65+ years	976 (47·1)	656 (60·4)	320 (32·5)	
Race				
White	1432 (70·4)	829 (77·6)	603 (62·5)	<0·0001
Other	601 (29·6)	239 (22·4)	362 (37·5)	
Missing	38			
BMI†				
Not obese (<18·5–29·9 kg/m^2)	1319 (64·1)	709 (65·8)	610 (62·2)	0·0268
Obese (30·0–39·9 kg/m^2)	533 (25·9)	278 (25·8)	255 (26·0)	
Morbidly obese (>40 kg/m^2)	206 (10·0)	90 (8·4)	116 (11·8)	
Missing	13			
Medical condition				
Asthma	506 (24·4)	260 (23·9)	246 (25·0)	0·58
Cardiovascular disease	1229 (59·3)	734 (67·6)	495 (50·2)	<0·0001
Chronic lung disease	861 (41·6)	498 (45·9)	363 (36·8)	<0·0001
Chronic metabolic disease	916 (44·2)	560 (51·6)	356 (36·1)	<0·0001
Neurologic disease	870 (42·0)	519 (47·8)	351 (35·6)	<0·0001
Immunosuppression	417 (20·1)	245 (22·6)	172 (17·5)	0·0039
Blood disorder	463 (22·4)	286 (26·3)	177 (18·0)	<0·0001
Renal disease	485 (23·4)	298 (27·4)	187 (19·0)	<0·0001
Liver disease	86 (4·1)	45 (4·1)	41 (4·2)	0·98
$\geqslant$1 condition	1958 (94·5)	1057 (97·3)	901 (91·5)	<0·0001
Alcohol abuse				
Current	72 (3·5)	24 (2·2)	48 (4·9)	0·0006
Former	56 (2·7)	37 (3·4)	19 (1·9)	
Never	1943 (93·8)	1025 (94·4)	918 (93·2)	
Smoking status				
Current	544 (26·3)	214 (19·7)	330 (33·5)	<0·0001
Former	579 (28·0)	373 (34·3)	206 (20·9)	
Never	948 (45·8)	499 (45·9)	449 (45·6)	
Influenza virus type				
Influenza A	1495 (72·2)	786 (72·4)	709 (72·0)	0·62
Influenza B	542 (26·2)	285 (26·2)	257 (26·1)	
Influenza A&B	34 (1·6)	15 (1·4)	19 (1·9)	
Severe influenza‡	448 (21·6)	225 (20·7)	223 (22·6)	0·29
Admission to the ICU	437 (21·1)	215 (19·8)	222 (22·5)	0·18
Death	58 (2·8)	36 (3·3)	22 (2·2)	0·14
Diagnosis of pneumonia†	718 (34·7)	384 (35·4)	334 (33·9)	0·49
Antiviral treatment				
Prompt ($\leqslant$2 days)	1984 (95·8)	1044 (96·1)	940 (95·4)	0·43
Late (>2 days)	87 (4·2)	42 (3·9)	45 (4·6)	

* χ^2 test.

† Diagnosis of pneumonia is defined as a chest X-ray indicating pneumonia and either diagnosis of pneumonia at discharge or ICD-9 discharge code for pneumonia (480–487·0).

‡ Severe influenza is defined as either admission to the intensive care unit or death.

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95% CI 0·72–1·10) or fully adjusted models (OR = 0·87; 95% CI 0·69–1·10). Null odds ratios were consistent for season (*P*-for-interaction = 0·52) and age-group (*P*-for-interaction = 0·72) stratified models (Supplementary Table S2).

Vaccination and pneumonia

For pooled seasons, there was no association between vaccination status and pneumonia (Fig. 2). However, the association of vaccination status with pneumonia differed between seasons (*P*-for-interaction = 0·017). A protective effect of vaccination against odds of pneumonia was seen in the 2013–2014 fully adjusted model (OR = 0·59; 95% CI 0·40–0·85). No effect was seen in either the 2012–2013 or 2014–2015 seasons (Fig. 2). In an analysis stratified by season and age group, the protective effect was seen only in 25–64-year-old patients in the 2013–2014 season (Fig. 3). Conversely, being vaccinated was a significant risk factor for pneumonia among 25–64-year-old patients in 2014–2015 in the fully adjusted model. Results were null for other age groups by season.

Timing

There were 825 patients with recorded vaccination times. The median time between vaccination and hospitalization was 97 days (range: 14–262 days). There was no association between time between vaccination and hospitalization and likelihood of pneumonia for categorical or continuous time models (Supplementary Table S3).

Sensitivity analysis

Similar overall results were obtained for both severe influenza and diagnosis of pneumonia when the 261 patients without recorded vaccination times were excluded from the analysis (Supplementary Table S4). The association remained significant for diagnosis of pneumonia and vaccination for 2013–2014. The only difference was that the associations for 25–64-year-old patients in both 2013–2014 and 2014–2015 were no longer significant, likely due to the reduced sample size.

For those who did not receive antivirals, no impact of vaccination was observed in the unadjusted or fully adjusted models for either outcome (Supplementary Table S5 and S6).

DISCUSSION

Our analysis demonstrated reduced odds of diagnosis of pneumonia among vaccinated individuals with laboratory-confirmed influenza-associated hospitalizations during the 2013–2014 season but not for either of the other seasons studied. Additionally, the protective effect was only observed in 25–64-year-old patients. Further, we observed no difference in this effect by time between vaccination and hospitalization.

There were known differences among the three influenza seasons included in these analyses. The 2012–2013 influenza season was moderately severe with higher rates of hospitalization and death compared with previous years (2010–2012) with H3N2 as the dominant virus [21]. The 2013–2014 influenza season had lower levels of mortality but higher incidence of hospitalization among adults (18–64 years old) compared with the previous four seasons, and 2009 pH1H1 was the dominant strain [22]. The 2014–2015 season was dominated by H3N2 and had the highest hospitalization rate for laboratory-confirmed influenza since FluSurv-NET began in 2005 [23]. Vaccine effectiveness against outpatient influenza illness also varied by season: 49% (43–55%) for 2012–2013 [24], 62% (53–69%) for 2013–2014 [25], and 19% (10–27%) for 2014–2015 [26].

The difference in 2012–2013 may be due to heterogeneity of virus subtype in patients or age of hospitalized patients. Virus subtype seems to be related to disease severity in hospitalized patients [19]. Limited information on influenza subtype was recorded so this could not be assessed on the individual level. The age composition of our study's patients also differed significantly between years. The 2012–2013 season included more patients who were 65 years and older, while 2013–2014 had more patients aged 25–64 years. The vaccine may also be effective in those younger than 25 but the number of patients in those age groups may have been too small to detect a difference.

The vaccine used for the 2014–2015 seasons may have lacked a protective effect due to virus subtype, age of infected individuals, or vaccine effectiveness/vaccine matching to the circulating strain. Vaccine matching likely plays an important role, as vaccination was associated with elevated pneumonia odds for 25–64-year-old patients during 2014–2015. A possible explanation for this observation is the presence of residual confounding by severity within comorbid

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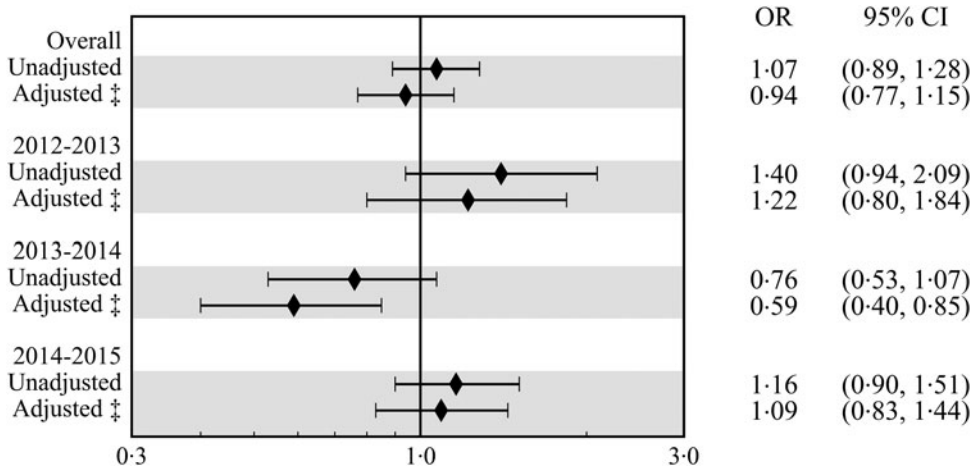

Fig. 2. Odds of pneumonia diagnosis with respect to vaccination status by influenza season, Odds ratio compares odds of pneumonia in vaccinated patients relative to unvaccinated patients among influenza-associated hospitalized patients treated with antivirals. Odds ratios and corresponding confidence intervals are plotted on the logarithmic scale. OR: odds ratio, 95% CI, 95% confidence interval. Pneumonia is defined as a chest X-ray indicating pneumonia and either diagnosis of pneumonia at discharge or ICD-9 discharge code for pneumonia (480–487·0). Age is modeled as a continuous variable. ‡Adjusted by all factors (season-vaccine interaction term, prompt treatment with antivirals, age, race, sex, obesity, asthma, CVD, CLD, CMD, neurological disease, blood disorders, renal disease, liver disease, immunosuppression, alcohol abuse, smoking status, and virus type).

conditions. Those with a more severe condition are more likely to access healthcare resources and subsequently receive the influenza vaccine. Severe comorbid conditions are also associated with more severe influenza-associated disease. Since the vaccine offered little-to-no protection from influenza infection in the 2014–2015 seasons, these two associations may have led to the association between vaccination receipt and elevated risk of pneumonia. The fully adjusted model does not account for differences in severity within each condition. An alternative explanation is that those individuals with more severe conditions are more likely to receive the pneumococcal vaccine (PCV). By not adjusting for PCV, residual confounding due to this may bias the estimates. The presence of residual confounding in 2014–2015 implies there likely is residual confounding in the 2012–2013 and 2013–2014 estimates as well. Since the 2014–2015 estimate is biased up and away from the null, it might be possible that the true protective effect in 2013–2014 is even stronger than the reported association.

Overall, antiviral use in this population (90%) was similar to overall reported antiviral use (83–89%) in all FluSurv-NET surveillance sites during the same influenza seasons [27]. High antiviral use among hospitalized patients aligns with CDC guidelines [28]. No impact of vaccination against pneumonia was seen in the patients who did not receive antivirals, but this may be a result of a small sample size. Additionally, we were unable to see an influence of time between vaccine receipt and hospitalization date.

This study expands previous work by including multiple influenza seasons, all age groups eligible for influenza vaccination, and stratification by antiviral use. To our knowledge, this is the first study to examine time between vaccination and hospitalization on severe outcomes to assess for evidence of waning of this secondary protective effect.

There are several limitations that should be noted. First, perhaps due to the small sample size in the two younger age categories, we did not detect a significant association in these subgroups. Next, we did not have data on, and hence were unable to adjust for, receipt of PCV; previous research suggests simultaneous PCV administration with influenza vaccination can reduce mortality in elderly adults [29]. Inability to adjust for PCV likely impacted the results since the PCV coverage for individuals $\geqslant 65$ was estimated to be at 61·3% for 2014 [30]. PCV may also have impacted the data in adults (18–64) since coverage was estimated to be 20·3% for high-risk adult populations, who are more likely to experience an influenza-associated hospitalization. Third, type of influenza vaccine received was not available and thus we were unable to compare vaccine types, which may have impacted immunity as previously

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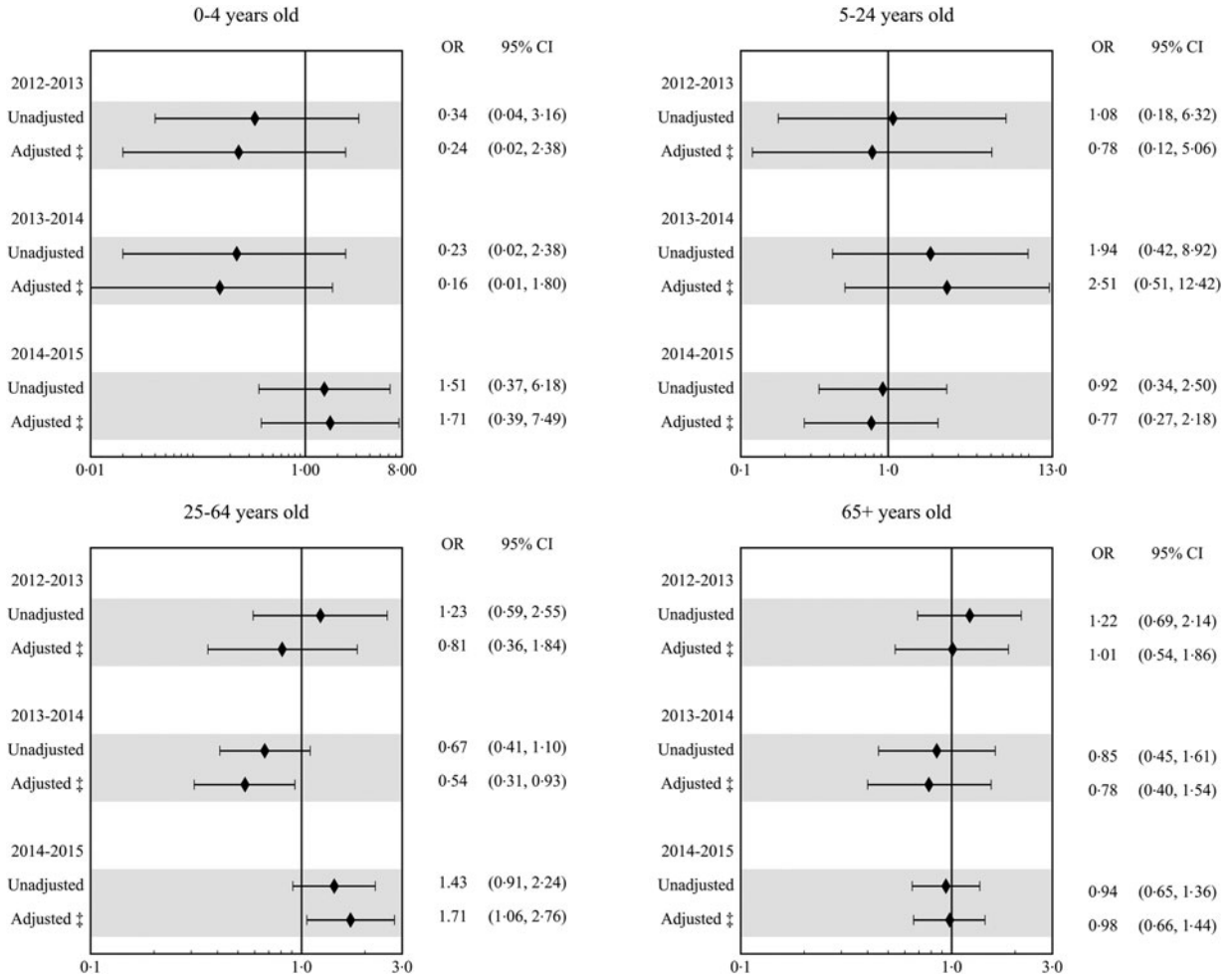

Fig. 3. Odds of pneumonia diagnosis with respect to vaccination status by influenza season stratified by age group, Odds ratio compares odds of pneumonia in vaccinated patients relative to unvaccinated patients among influenza-associated hospitalized patients treated with antivirals. Odds ratios and corresponding confidence intervals are plotted on the logarithmic scale. OR, odds ratio; 95% CI, 95% confidence interval. Pneumonia is defined as a chest X-ray indicating pneumonia and either diagnosis of pneumonia at discharge or ICD-9 discharge code for pneumonia (480–487·0). Age is modeled as a categorical variable. Each season is modeled separately. ‡Adjusted by all factors (age category-vaccine interaction term, prompt treatment with antivirals, age, race, sex, obesity, asthma, CVD, CLD, CMD, neurological disease, blood disorders, renal disease, liver disease, immunosuppression, alcohol abuse, smoking status, and virus type).

seen [31, 32]. Fourth, hospitalization date was used instead of symptom onset date to determine the time between vaccination and illness. This is likely an overestimate of the actual time between vaccination and illness. Hospitalization date was chosen because it was less subject to recall bias. Fifth, physicians may be less likely to test for influenza with less severe presentations, underestimating the secondary protective effect of vaccination. Finally, since we were not able to control for influenza A subtypes, we could not determine the role influenza subtype may have played.

CONCLUSION

This study found that influenza vaccination might provide mild protection against pneumonia for individuals who, despite receiving the influenza vaccine, experienced an influenza-associated hospitalization and were treated with antivirals. This effect was only observed in an influenza H1N1 dominant year and was potentially driven by 25–64-year-old patients. The differences in seasons may be related to vaccine matching to the predominant circulating strain, age group affected, or virus subtype. Further information

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from other participating FluSurv-NET sites should be analyzed to elucidate the true impact of influenza vaccination on reduction of influenza-related outcomes by influenza vaccination status.

SUPPLEMENTARY MATERIAL

The supplementary material for this article can be found at https://doi.org/10.1017/S0950268817002163.

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DECLARATION OF INTEREST

None.

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