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Influenza Vaccine Effectiveness Against Hospitalization in the United States, 2019–2020

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Background. Influenza causes significant morbidity and mortality and stresses hospital resources during periods of increased circulation. We evaluated the effectiveness of the 2019–2020 influenza vaccine against influenza-associated hospitalization in the United States.

Methods. We included adults hospitalized with acute respiratory illness at 14 hospitals and tested for influenza viruses by reserve-transcription polymerase chain reaction. Vaccine effectiveness (VE) was estimated by comparing the odds of current-season influenza vaccination in test-positive influenza cases vs test-negative controls, adjusting for confounders. VE was stratified by age and major circulating influenza types along with A(H1N1)pdm09 genetic subgroups.

Results. A total of 3116 participants were included, including 18% (n = 553) influenza-positive cases. Median age was 63 years. Sixty-seven percent (n = 2079) received vaccination. Overall adjusted VE against influenza viruses was 41% (95% confidence interval [CI], 27%–52%). VE against A(H1N1)pdm09 viruses was 40% (95% CI, 24%–53%) and 33% against B viruses (95% CI, 0–56%). Of the 2 major A(H1N1)pdm09 subgroups (representing 90% of sequenced H1N1 viruses), VE against one group (5A + 187A,189E) was 59% (95% CI, 34%–75%) whereas no VE was observed against the other group (5A + 156K) (–1% [95% CI, –61% to 37%]).

Conclusions. In a primarily older population, influenza vaccination was associated with a 41% reduction in risk of hospitalized influenza illness.

Keywords. influenza; vaccine effectiveness; hospitalization; elderly; immunocompromised.

An estimated 410 000–740 000 influenza hospitalizations and 24 000–62 000 influenza-related deaths occurred in the United States (US) during the 2019–2020 influenza season [1]. Adults hospitalized with influenza are generally older and most have chronic medical conditions that put them at increased risk for complications [2, 3], such as respiratory failure, sepsis, and ischemic coronary events [4–7]. During peak activity, influenza strains healthcare resources including hospital beds and ventilators [8, 9], particularly when influenza A(H3N2) viruses predominate as they disproportionately affect older adults [10–12]. Annual vaccination is recommended in the US starting at 6 months of age as the best means of preventing influenza illness [13]. Despite influenza vaccination offering imperfect protection, in recent US seasons it was estimated that vaccination reduced the risk of influenza-related hospitalization by up to about half in adults but with variability across seasons [2].

The 2019–2020 influenza season was a severe season in the US, despite minimal A(H3N2) activity [1]. Recently emerged influenza B viruses in the Victoria lineage that were rarely observed in previous seasons predominated early in the 2019–2020 season, with children most heavily affected [14, 15]. From February 2020 onward, influenza A(H1N1)pdm09 viruses predominated, with most activity occurring in adults [16]. These circulating viruses were genetically and antigenically (based on ferret antisera testing) drifted from the 6B.1A vaccine components of the 2019–2020 Northern Hemisphere influenza vaccines, and genetic diversification of A(H1N1)pdm09 viruses was observed [17]. Two major A(H1N1)pdm09 6B.1A viruses circulated in the US during the season in the 183-5A subclade but with additional acquired amino acid substitutions in hemagglutinin (HA) antigenic sites ("5A + 187A,189E" and "5A + 156K" viruses). Compared to ambulatory settings, data are more limited on the public health impact of drifted influenza viruses on vaccine effectiveness (VE) against severe disease requiring hospitalization [18]. The association between vaccination and influenza hospitalization in adults was

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therefore evaluated during this unusual 2019–2020 season with multiple drifted viruses.

METHODS

The Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN) investigators enrolled adults (≥18 years of age) with an acute respiratory illness including new or worsening cough and/or change in sputum production with onset ≤10 days at 14 tertiary and community hospitals in 4 states (Michigan, Pennsylvania, Tennessee, and Texas), as previously described [19]. Prior to or at enrollment, upper respiratory tract swabs were collected with research testing performed using a Centers for Disease Control and Prevention (CDC)–developed reverse-transcription polymerase chain reaction assay or a clinically ordered respiratory virus panel molecular assay to determine case status, with additional determination of influenza subtype/lineage [20]. At Michigan hospitals, influenza status was determined by research testing alone. Available influenza-positive samples with a cycle threshold value ≤30 underwent whole-genome sequencing and phylogenetic analysis at CDC [21]. Enrollment began at sites when local surveillance showed sustained influenza activity and stopped when local severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) activity began to increase in mid-March 2020.

After obtaining consent, trained study staff interviewed patients or proxies about demographic characteristics, presenting symptoms, current season vaccination status, self-rated general health status, hospitalization in the past year, baseline immunocompromising medical conditions in the past year including chemotherapy and/or immunosuppressive drug use or a history of transplantation (solid organ or bone marrow or stem cell), and oxygen use (home nonventilator oxygen use, home ventilator, or noninvasive positive pressure ventilator use). Vaccination status was independently verified through review of medical records, state immunization registries, and records from immunization providers. A participant was considered vaccinated if receipt of a licensed influenza vaccine was documented after 1 July 2019 or based on plausible self-report (in which the participant identified the date and location of vaccination, as previously described [22]), ≥14 days before symptom onset. Six influenza vaccine product types were available in the US during the 2019–2020 season, although the Advisory Committee on Immunization Practices does not provide preferential recommendations for any age-indicated type [13]. Trivalent vaccines, including high-dose and adjuvanted types, contained a B/Colorado/06/2017-like B component (B/Victoria lineage). When available, vaccine type (standard dose, high dose, or adjuvanted) was documented.

Baseline demographic and clinical characteristics were compared between vaccinated and unvaccinated participants as well as influenza-positive cases and influenza-negative control participants using χ^2 or Wilcoxon rank-sum tests. Using the test-negative study design [23], VE was estimated using logistic regression by comparing the odds of current-season vaccination in influenza-positive cases vs influenza-negative controls (VE = 100 × [1 – odds ratio]). Models were adjusted a priori for study site, age, sex, race/ethnicity, interval from symptom onset to testing, and time (categorized by tertile of influenza case onset date as pre-peak, peak, and post-peak) [2]. Individual baseline health indicators (presence of immunocompromising conditions, self-rated general health status, one or more prior hospitalizations in the last year, and home oxygen use) associated with exposure (ie, influenza vaccination status) and outcome (ie, influenza status) were added stepwise and indicators were included in the final VE models if they further modified the odds ratio (OR) by >5% (absolute difference), which was a predetermined threshold. Only prior-year hospitalization was included in final models; addition of other baseline health indicator covariates had little additional effect on the OR. VE was estimated against all influenza viruses overall and within age categories (18–49, 50–64, ≥65 years), and for influenza A(H1N1)pdm09 and B viruses (all Victoria of B viruses among isolates that had lineage information). Those vaccinated 0–13 days prior to illness onset, with unknown vaccination status, who tested negative for influenza outside of the study period, had early, late, or missing specimen collection dates, or illness onset after hospital admission were excluded from the analysis (detailed reasons for exclusion in Supplementary Table 1). As a post hoc analysis, we explored presence of a reported immunosuppressive condition as a potential effect modifier. An interaction term was added between immunosuppressive condition and vaccination status, with a likelihood ratio test $P < .15$ considered significant. We also performed a sensitivity VE analysis excluding participants with self-reported vaccine receipt without documentation.

A formal power analysis was not conducted for this analysis. However, at a significance threshold of .05 in the primary VE analysis and 80% power, with 500 influenza cases and 2500 test-negative control participants and 70% of control participants vaccinated, a minimum overall detectable VE was estimated as 25%. Analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, North Carolina). The study was approved by institutional review boards at the CDC and at all participating sites.

RESULTS

Baseline Patient Characteristics

Of 3795 adults enrolled with acute respiratory illness, 679 met exclusion criteria (Supplementary Table 1), leaving 3116 eligible adults with illness onset dates 28 October 2019–15 March 2020. Enrollment by location ranged from 16% (Tennessee) to 33% (Texas) of included participants, and 59% were admitted to tertiary care centers (Table 1). Eighteen percent

(n = 553) of participants were influenza-positive cases and 82% (n = 2563) influenza-negative controls. The median age overall was 63 years (interquartile range, 53–73 years), 58% (n = 1796) were female, and 66% (n = 2047) were non-Hispanic white and 24% (n = 760) non-Hispanic black. Fifty-nine percent (n = 1844) had been hospitalized at least once in the past year. Thirty-eight percent (n = 1172) of participants reported an immunocompromising condition and 30% (n = 939) reported home oxygen use. Sixty-seven percent (n = 2079) received current-season influenza vaccination (75% with available documentation and 25% based on plausible self-report alone), including 72% of non-Hispanic whites, 57% of non-Hispanic blacks, and 59% of Hispanics. Differences in vaccination status by racial/ethnic group were seen across ages. Older patients, non-Hispanic whites, and patients with immunocompromising conditions, home oxygen use, or hospitalized in the past year were more likely to have received vaccination (all $P < .01$).

Compared to influenza-negative controls, influenza-positive cases were slightly younger (median age, 60 vs 63 years, $P < .01$) and had lower prevalence of baseline indicators of poor health status, including poor-to-fair self-rated general health status, home oxygen use, previous hospitalization in the past year, and immunosuppressive condition (all $P < .05$) (Table 2). Influenza-positive cases were less likely to report receiving influenza vaccination most years or every year (63% vs 73%, $P < .01$).

Table 1. Characteristics of Adults Enrolled by Vaccination Status, Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN), 2019–2020

Characteristic	Overall	Vaccinated[a,b]	Unvaccinated	*P* Value[c]
No. (%)	3116 (100)	2079 (67)	1037 (33)	
Site				
Central Texas	1042 (33)	678 (33)	364 (35)	<.01
Southeast Michigan	754 (24)	468 (23)	286 (28)	
Western Pennsylvania	824 (26)	583 (28)	241 (23)	
Central Tennessee	496 (16)	350 (17)	146 (14)	
Baseline characteristics				
Demographics and behavioral risk factors				
Age, y, median (IQR)	63 (53–73)	65 (56–76)	57 (43–66)	<.01
Age group				
18–49 y	665 (21)	319 (15)	346 (33)	<.01
50–64 y	1053 (34)	664 (32)	389 (38)	
≥65 y	1398 (45)	1096 (53)	302 (29)	
Female sex	1796 (58)	1221 (59)	575 (55)	.08
Race/ethnicity				
White, non-Hispanic	2047 (66)	1474 (71)	573 (55)	<.01
Black, non-Hispanic	760 (24)	431 (21)	329 (32)	
Other race, non-Hispanic	146 (5)	78 (4)	68 (7)	
Hispanic, any race	163 (5)	96 (5)	67 (6)	
Insured	2913 (93)	2016 (97)	897 (87)	<.01
Current tobacco smoking	804 (26)	421 (20)	383 (37)	<.01
Health status indicators[d]				
General health status fair/poor (88 missing)	1492 (49)	1020 (51)	472 (47)	.03
Home oxygen use (30 missing)	939 (30)	726 (35)	213 (21)	<.01
≥1 hospitalization in prior year	1844 (59)	1300 (63)	544 (52)	<.01
Transplantation, chemotherapy/radiation, immunosuppressive medications	1172 (38)	859 (41)	313 (30)	<.01
Influenza vaccination habit[d]				
Never/rarely	678 (22)	72 (3)	606 (58)	<.01
Some years	211 (7)	85 (4)	126 (12)	
Most years/every year	2227 (71)	1922 (92)	305 (29)	
Admission characteristics				
Days from illness onset to specimen collection, median (IQR)	3 (1–6)	3 (1–6)	3 (2–6)	.36
Admitted to tertiary care hospital	1846 (59)	1199 (58)	647 (62)	.01

Data are presented as No. (%) unless otherwise indicated.

Abbreviation: IQR, interquartile range.

[a]Vaccination defined as documented and/or plausible self-report.

[b]Among vaccinated patients in whom information was available (n = 1095), 63% (n = 686) received standard-dose vaccines, 35% (n = 382) high-dose vaccines, and 2% (n = 27) adjuvanted products.

[c]*P* value for test of difference across case and control groups based on χ^2 statistic for categorical variables and Wilcoxon rank-sum test for continuous variables.

[d]Defined by patient self-report during enrollment interview.

Table 2. Characteristics of Influenza-Positive Cases and Influenza-Negative Controls, Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN), 2019–2020

Characteristic	Overall	Influenza-Positive Cases	Influenza-Negative Controls	*P* Value[a]
No. (%)	3116 (100)	553 (18)	2563 (82)	
Site				
Central Texas	1042 (33)	115 (21)	927 (36)	<.01
Southeast Michigan	754 (24)	175 (32)	579 (23)	
Western Pennsylvania	824 (26)	151 (27)	673 (26)	
Central Tennessee	496 (16)	112 (20)	384 (15)	
Baseline characteristics				
Demographics and behavioral risk factors				
Age, y, median (IQR)	63 (53–73)	60 (49–70)	63 (53–74)	<.01
Age group				
18–49 y	665 (21)	141 (26)	524 (20)	<.01
50–64 y	1053 (34)	200 (36)	853 (33)	
≥65 y	1398 (45)	212 (38)	1186 (46)	
Female	1796 (58)	325 (59)	1471 (57)	.55
Race/ethnicity				
White, non-Hispanic	2047 (66)	341 (62)	1706 (67)	.07
Black, non-Hispanic	760 (24)	147 (27)	613 (24)	
Other race, non-Hispanic	146 (5)	35 (6)	111 (4)	
Hispanic, any race	163 (5)	30 (5)	133 (5)	
Insured	2913 (93)	511 (92)	2402 (94)	.26
Current tobacco smoking	804 (26)	154 (28)	650 (25)	.23
Health status indicators[b]				
General health status fair/poor (88 missing)	1492 (49)	238 (44)	1254 (50)	.01
Home oxygen use (30 missing)	939 (30)	128 (23)	811 (32)	<.01
≥1 hospitalization in prior year	1844 (59)	244 (44)	1600 (62)	<.01
Transplantation, chemotherapy/radiation, immunosuppressive medications	1172 (38)	165 (30)	1007 (39)	<.01
Influenza vaccination habit[b]				
Never/rarely	678 (22)	163 (29)	515 (20)	<.01
Some years	211 (7)	40 (7)	171 (7)	
Most years/every year	2227 (71)	350 (63)	1877 (73)	
Admission characteristics				
Days from illness onset to specimen collection, median (IQR)	3 (1–6)	3 (2–5)	3 (1–6)	.12
Admitted to tertiary care hospital	1846 (59)	289 (52)	1557 (61)	<.01

Data are presented as No. (%) unless otherwise indicated.

Abbreviation: IQR, interquartile range.

[a] *P* value for test of difference across case and control groups based on χ^2 statistic for categorical variables and nonparametric Wilcoxon rank-sum test for continuous variables.

[b] Defined by patient self-report during enrollment interview.

Influenza Virus Characterization

Of 553 influenza cases included in the analysis, 72% (n = 400) were positive for A(H1N1)pdm09, 21% (n = 117) for B viruses (93/93 were Victoria lineage among those with lineage determination), 4% (n = 22) for unsubtyped influenza A, 3% (n = 15) for influenza H3N2, and one mixed A(H1N1)pdm09 and B infection (Supplementary Table 2). Most sequenced A(H1N1)pdm09 viruses belonged within the 6B.1A 183P-5A subclade (90% [183/203]; Supplementary Table 2). There were 2 major viruses circulating within this 183-5A subclade that had additional amino acid substitutions in the HA protein. These included viruses with additional amino acid substitutions D187A and Q189E (5A + 187A,189E viruses; n = 80) and K130N, N156K, L161I, V250A, and E506D (5A + 156K viruses; n = 102). Among sequenced B viruses (n = 53), all were viruses within the Victoria lineage. Most (52/53) belonged to the V1A.3 subclade, which contains 3 amino acid deletions in the HA protein (162–164). One belonged to the V1A.1 subclade found in the 2019–2020 Northern Hemisphere Victoria lineage vaccine component with a 2-amino-acid deletion in the HA protein (162–163).

Estimated Influenza Vaccine Effectiveness

Unadjusted overall VE against influenza during the 2019–2020 season was estimated at 42% (95% confidence interval [CI], 30%–52%) (Supplementary Table 3). Adjusting for potential confounders, overall VE against influenza was similar at 41% (95% CI, 27%–52%) (Figure 1 and Supplementary Table 3). Adjusted VE was highest among adults ≥65 years of age (54% [95% CI, 35%–67%]) whereas VE was not statistically

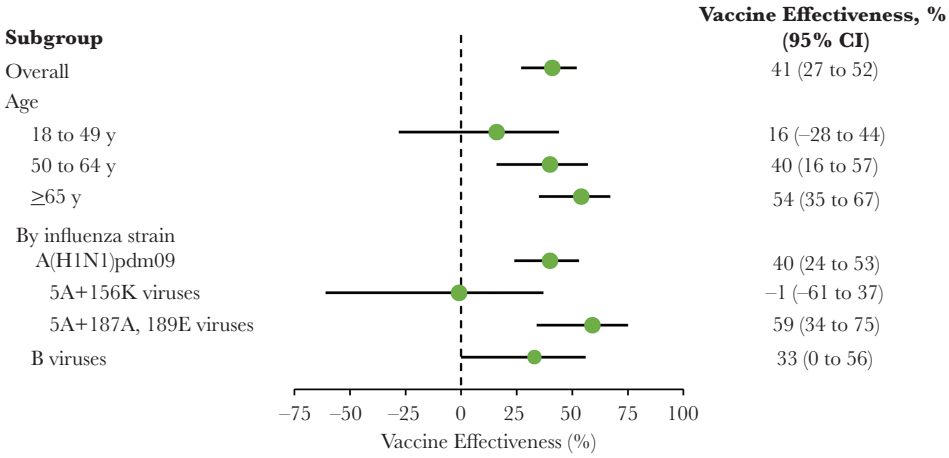

Figure 1. Adjusted vaccine effectiveness against influenza, Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN), 2019–2020. Models adjusted for age, sex, site, race/ethnicity, days from illness onset to specimen collection, timing of illness onset, and ≥1 vs 0 self-reported prior hospitalizations in the preceding year. Abbreviation: CI, confidence interval.

significant among younger adults aged 18–49 years (16% [95% CI, –28% to 44%]). Adjusted VE was estimated at 40% (95% CI, 24%–53%) against influenza A(H1N1)pdm09 viruses. Of sequenced A(H1N1)pdm09 viruses, adjusted VE against 187A,189E viruses was 59% (95% CI, 34%–75%) whereas no significant VE was observed for 156K viruses (–1% [95% CI, –61% to 37%]). Unadjusted VE against influenza B viruses was estimated at 56% (95% CI, 36%–70%), but with an adjusted VE of 33% (95% CI, 0–56%; $P = .05$).

Given large differences in unadjusted and adjusted B virus estimates as well as differences in VE observed across age groups, potentially contributing factors were explored. No significant interaction was observed between presence of an immunocompromising condition and vaccination status, overall or by subgroup (all $P > .15$). Notably, a larger proportion of young adults (18–49 years of age) with influenza had received solid organ or bone marrow or stem cell transplantation (13% [18/141] of case patients vs 6% [33/524] of influenza-negative controls), even though the overall prevalence of any immunocompromising condition (transplantation, chemotherapy, and/or use of immunosuppressive drugs) was similar (35%–37%) in both groups. In a sensitivity analysis excluding participants with self-reported vaccination without documentation, VE findings were similar (overall adjusted VE, 40% [95% CI, 26%–52%]).

DISCUSSION

Preventing influenza illness can significantly reduce morbidity and mortality and health resource utilization. Hospitalized adults enrolled in HAIVEN during the 2019–2020 season were primarily older (median age, 63 years) and a large proportion were chronically ill, with almost 60% reporting ≥1 hospitalization in the previous year, almost one-third reporting home oxygen use, and almost 40% reporting immunocompromising conditions. Because these populations have historically had decreased immune responses and vaccination has been less effective [24], an approximate 40% reduction in risk of influenza hospitalizations in association with vaccination is encouraging, especially during a season with 2 drifted viruses circulating. Based on evidence of cost-effectiveness of influenza and other adult vaccines [25, 26], this decrease in hospitalization likely led to commensurate reductions in economic burden and resource utilization because of the high burden of complicated influenza-related hospitalizations in these complex patient groups.

Highest VE was observed in the elderly (age ≥65 years) with a lower and nonsignificant VE in young adults (18–49 years of age), which was similar across vaccine strains. This finding was unexpected and may have several explanations. First, most elderly patients (≥65 years of age) with influenza were infected with A(H1N1)pdm09 viruses (79% [167/212], with 5 additional nonsubtyped A viruses). Birth cohort effects from initial exposure to A(H1N1) viruses and immunologic imprinting may have contributed to higher VE observed among elderly patients in this study, as described previously [27]. Second, because most of these hospitalized patients had complex underlying conditions, unmeasured confounding or selection bias may also have differentially affected VE estimates by age. Specifically, young adults diagnosed with influenza may have differed in important ways from those who tested negative. For example, a high proportion of young case patients reported highly immunocompromising conditions including solid organ, bone marrow, or stem cell transplant, and this may have contributed to the reduced VE observed within this age group. Third, vaccine product types differed between elderly and younger adults. Among vaccinated adults ≥65 years of age, 65% (375/575) received high-dose vaccines vs 1% (7/520) of those <65 years of age with information on vaccine type.

As previously reported [17], increasing diversification of influenza A(H1N1)pdm09 viruses has been observed with circulation of multiple viruses during the 2019–2020 season drifted from the vaccine. Among the 2 major circulating A(H1N1)pdm09 strains (5A + 156K and 5A + 187A,189E), VE varied considerably although with a net moderate overall VE. This finding highlights that VE can be observed even in the setting of differences between vaccine components and circulating viruses. The 156K viruses that were associated with a lack of VE predominated in the US toward the end of the influenza season after Northern Hemisphere influenza vaccine strain selection (ie, they were not included in the 2020–2021 Northern Hemisphere vaccine component) [17], and ongoing surveillance including genetic sequencing data is needed to monitor circulating strains in the US during the 2020–2021 season. As previously observed, hospitalized illness with B viruses was relatively uncommon in adult populations during the 2019–2020 influenza season despite having a large impact in pediatric populations [14, 15]. For adults, despite vaccine mismatch associated with emergence of B/Victoria viruses within the V1A.3 subclade distinct from the V1A.1 vaccine component, some VE was observed.

Severe influenza seasons have typically been associated with major circulation of influenza A(H3N2) viruses, which cause high rates of hospitalization and mortality in older adults [10] and are generally associated with lower influenza VE compared to influenza A(H1N1)pdm09 and B viruses [28]. Despite minimal circulation of A(H3N2) viruses in the US, a high burden of influenza cases was observed in the US during the 2019–2020 season, with the second highest estimated number of cases over the previous decade [1]. With the possibility of co-circulation of SARS-CoV-2 and influenza viruses, increased influenza vaccination may be important for reducing hospital resource utilization. Notably, SARS-CoV-2 infections in the US have heavily impacted groups including non-Hispanic black populations also found to have lower influenza vaccine uptake compared to non-Hispanic whites in this study [29, 30], a difference that persisted accounting for age. More effective public health strategies are needed to increase influenza vaccine uptake and reduce racial disparities.

This study provides evidence on the effectiveness of influenza vaccination in preventing influenza-associated hospitalizations, drawing from a large sample within 4 geographically dispersed states including a combination of tertiary centers and community hospitals. However, the study was subject to certain limitations. Vaccine receipt was determined by plausible self-report in a subset of cases and vaccination status may have been misclassified. However, we performed a sensitivity analysis excluding participants with plausible self-report alone, and results were similar. VE was not measured by type of vaccine, for example, standard-dose inactivated vs high-dose or adjuvanted products (often used in elderly populations), which may influence immunogenicity and VE [31, 32]. Although VE models adjusted for important potential confounders, there may have been some degree of unmeasured confounding. In VE models, measures of baseline health status were collected based on self-report, which may have potentially resulted in some misclassification. As cases of influenza B generally had a young age distribution [15], few influenza B cases were included in this analysis of mostly older adults. Thus, B virus VE estimates had wide CIs and may have been more prone to residual or unmeasured confounding. Enrollment ended in March due to increasing SARS-CoV-2 circulation, although influenza cases were already declining in part due to nonpharmacologic interventions and this is unlikely to have significantly impacted influenza VE results [33]. Finally, as observed before [19], some groups (particularly Hispanic/Latino populations) may have been underrepresented compared to the general US population.

In conclusion, even with a high proportion of elderly or otherwise high-risk populations, vaccination was associated with a 41% reduction in risk of hospitalized influenza illness. With a potential for co-circulation of SARS-CoV-2 and potential strain on hospital resources, prevention of influenza-associated hospitalizations through increased vaccine uptake, along with other preventive measures, pharmacologic and nonpharmacologic, will be important in future influenza seasons.

Supplementary Data

Supplementary materials are available at *The Journal of 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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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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