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Vaccine Effectiveness Against Influenza A(H3N2)–Associated Hospitalized Illness: United States, 2022

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Background. The COVID-19 pandemic was associated with historically low influenza circulation during the 2020–2021 season, followed by an increase in influenza circulation during the 2021–2022 US season. The 2a.2 subgroup of the influenza A(H3N2) 3C.2a1b subclade that predominated was antigenically different from the vaccine strain.

Methods. To understand the effectiveness of the 2021–2022 vaccine against hospitalized influenza illness, a multistate sentinel surveillance network enrolled adults aged ≥18 years hospitalized with acute respiratory illness and tested for influenza by a molecular assay. Using the test-negative design, vaccine effectiveness (VE) was measured by comparing the odds of current-season influenza vaccination in influenza-positive case-patients and influenza-negative, SARS-CoV-2–negative controls, adjusting for confounders. A separate analysis was performed to illustrate bias introduced by including SARS-CoV-2–positive controls.

Results. A total of 2334 patients, including 295 influenza cases (47% vaccinated), 1175 influenza- and SARS-CoV-2–negative controls (53% vaccinated), and 864 influenza-negative and SARS-CoV-2–positive controls (49% vaccinated), were analyzed. Influenza VE was 26% (95% CI: −14% to 52%) among adults aged 18–64 years, −3% (−54% to 31%) among adults aged ≥65 years, and 50% (15–71%) among adults aged 18–64 years without immunocompromising conditions. Estimated VE decreased with inclusion of SARS-CoV-2–positive controls.

Conclusions. During a season where influenza A(H3N2) was antigenically different from the vaccine virus, vaccination was associated with a reduced risk of influenza hospitalization in younger immunocompetent adults. However, vaccination did not provide protection in adults ≥65 years of age. Improvements in vaccines, antivirals, and prevention strategies are warranted.

Keywords. influenza; vaccine effectiveness; antigenic drift; SARS-CoV-2.

The coronavirus disease 2019 (COVID-19) pandemic resulted in dramatic declines in global influenza virus circulation. The 2019–2020 US influenza season was characterized by early predominance of influenza B/Victoria lineage viruses from a newly emerged V1A.3 subclade [1], followed by an antigenically drifted A(H1N1)pdm09 virus [2]. During the early COVID-19 pandemic, the adoption of nonpharmaceutical interventions intended to reduce the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was associated with historically low influenza circulation, which continued through the 2020–2021 influenza season [3].

Some increase in circulation of influenza was observed during the 2021–2022 US influenza season, although circulation remained low compared with pre-pandemic years [4]. Most viruses belonged to the 2a.2 subgroup of the influenza A(H3N2) 3C.2a1b subclade [5]. This subgroup of A(H3N2) viruses is genetically similar to, but antigenically distinct from, the

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Northern Hemisphere 2021–2022 vaccine strain, which contains a 2a.1-like A(H3N2) component [6]. Influenza A(H3N2) viruses have typically been associated with reduced vaccine effectiveness (VE) due to antigenic mismatch, egg-adaptive mutations in the vaccine component, and age cohort effects in which older persons may have less protection against A(H3N2) viruses due to early exposures to non–A(H3N2) influenza viruses [7, 8].

Interim estimates of 2021–2022 influenza VE in the US Influenza Vaccine Effectiveness Network found low VE against medically attended influenza illness in outpatient settings due to these emerging H3N2 viruses [9]. However, subsequent evaluations have shown that, during periods of increased SARS-CoV-2 circulation, VE studies that enroll test-negative controls with acute respiratory illness (ARI) due to SARS-CoV-2 infection are likely to underestimate VE because use of these SARS-CoV-2–positive patients as controls may introduce bias due to the correlated likelihood of receiving influenza and SARS-CoV-2 vaccination [10, 11].

The Influenza and Other Viruses in the Acutely Ill (IVY) Network is a multistate network of hospitals that enrolls adults hospitalized with ARI to evaluate the effectiveness of influenza and COVID-19 vaccines. The objectives of this analysis were to evaluate the effectiveness of the 2021–2022 influenza vaccine against hospitalized influenza illness with the use of SARS-CoV-2–negative controls and to explore potential bias in VE associated with the use of SARS-CoV-2–positive controls.

METHODS

Participants and Sites

IVY is a surveillance network of 21 hospitals in 18 states that estimates VE against influenza and COVID-19 [12]. IVY sites enrolled hospitalized adults aged 18 years and older who met a prespecified ARI definition of having 1 or more of the following: fever, cough, shortness of breath, use of respiratory support for the acute illness, or new pulmonary findings on chest imaging consistent with pneumonia. Sites with 5 or more enrolled, laboratory-confirmed influenza cases during the 2021–2022 influenza season surveillance period contributed to this analysis and surveillance personnel at all sites were trained and followed a common surveillance protocol. From daily reviews of hospital admissions logs or electronic medical records, patients with ARI who received clinical testing for SARS-CoV-2 and/or influenza using a molecular or antigen assay were enrolled. Research upper respiratory specimens were also collected and shipped to Vanderbilt University Medical Center (Nashville, TN) for central reverse transcription–polymerase chain reaction (RT-PCR) testing for influenza and SARS-CoV-2 and respiratory syncytial virus (RSV). We included patients who received clinical testing within 10 days of illness onset and were admitted to the hospital within 14 days of illness onset. Enrollment began 31 January 2022, when RT-PCR testing was expanded in the surveillance protocol from exclusively SARS-CoV-2 to include influenza.

Case-patients were those with ARI who tested positive for influenza by molecular or antigen assay through clinical or molecular assay through research central laboratory testing. Control-patients had ARI and tested negative for influenza on all tests performed. Sites attempt to enroll all case-patients and target an enrollment ratio of test-positive cases (influenza, SARS-CoV-2, and/or RSV) to test-negative controls of 1:1, with randomly selected control-patients enrolled within 2 weeks of case-patients. Other than enrollment date and site, cases and controls were not matched based on individual characteristics.

At enrollment, information on patient demographics, clinical characteristics including symptoms and date of illness onset, and receipt of current season influenza vaccination was collected through patient or proxy interviews and in-depth reviews of medical records. Current-season influenza vaccination status was determined by electronic medical record and local Immunization Information System (IIS) searches performed around the time of patient enrollment or by plausible self-report that included the date and location of vaccine receipt. A patient was considered vaccinated if they received influenza vaccination on or after 1 August 2021, with a date of administration 14 days or more before illness onset. A patient was considered unvaccinated if they received no influenza vaccine doses between 1 August 2021 and the date of illness onset.

We excluded patients who (1) withdrew from the program; (2) did not receive influenza testing; (3) had an illness-onset date after admission (to exclude possible nosocomial cases) or more than 14 days before admission date; (4) received influenza testing before illness-onset date or more than 10 days after onset date for the index illness; (5) had influenza and SARS-CoV-2 coinfection; (6) were enrolled at a site that enrolled 5 or fewer patients with influenza during the surveillance period; (7) were enrolled as controls with testing before the first influenza case or after the last influenza case at a site; (8) had incomplete influenza vaccination status documentation; (9) received an influenza vaccine 0–13 days after illness onset; (10) had a reported history of influenza vaccine receipt by self-report only (ie, without verification through source documentation) and without an exact or approximate date and/or known location of vaccination; or (11) were missing covariate data on age, sex, or race/ethnicity used in VE models.

Laboratory Analysis

Standardized protocols were used for centralized pathogen RT-PCR testing at Vanderbilt University Medical Center and influenza virus sequencing at the University of Michigan (Supplementary Appendix B).

Statistical Analysis

We described demographic and clinical characteristics of influenza case-patients and test-negative controls, as well as vaccinated and unvaccinated patients, using counts and percentages or medians and interquartile ranges. Case versus control and vaccinated versus unvaccinated groups were compared using the Pearson's chi-square test for categorical variables or Wilcoxon rank-sum testing for continuous variables.

Logistic regression models were constructed to examine the association between influenza vaccination (primary exposure) and case status (outcome). Vaccine effectiveness was estimated by comparing the odds of vaccination in cases versus controls adjusting for prespecified potential confounders, calculated as VE = (1− adjusted odds ratio) × 100%. Potential confounders included age group (18–49, 50–64, ≥ 65 years), sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic of any race, other or unknown), admitting hospital, and calendar time of admission (monthly intervals). In the primary VE model, we excluded SARS-CoV-2–positive controls due to the association between influenza and COVID-19 vaccine receipt [11]. To examine the influence of including SARS-CoV-2–positve controls, we also generated secondary VE estimates including both SARS-CoV-2–positive and SARS-CoV-2–negative controls. The primary analysis included patients who had vaccination status available by source documentation or self-report. In a sensitivity analysis, the population was restricted to patients with both source documentation and self-reported information for influenza vaccination. Furthermore, models were stratified by age group (18–64 and ≥65 years), presence of immunocompromising conditions, and time since vaccination. For time since vaccination, separate models were constructed comparing unvaccinated patients with patients vaccinated at 14–150 days before illness onset and unvaccinated patients with patients vaccinated more than 150 days before illness onset, with models adjusted for calendar month and other covariates in the primary VE model. Those without immunocompromising conditions were further stratified by age group. VE models stratified by age groups were adjusted for continuous age in years.

Finally, we examined in-hospital outcomes for influenza case-patients, including intensive care unit (ICU) admission, receipt of respiratory support including low-flow supplemental oxygen, high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation (IMV), and in-hospital death in vaccinated and unvaccinated patients. In-hospital outcomes were censored at 28 days from the date of admission if the patient was still hospitalized. Analyses were conducted using Stata version 16 (StataCorp, College Station, TX) [13]. This analysis was determined to be a public health surveillance activity by the Centers for Disease Control and Prevention (CDC) and each participating site and conducted in a manner consistent with applicable federal law and CDC policy.

RESULTS

Overall, 4732 patients were enrolled during the surveillance period between 31 January 2022 and 15 June 2022 (Figure 1). Of these, 2398 (51%) were excluded from the analysis, with the most common reasons being enrolled as a control before the first or after the last influenza case at the site (n = 1180), 5 or fewer cases of influenza observed at the site (n = 579), or not receiving testing within the 10 days following illness onset (n = 291) (Figure 1). A total of 2334 patients were included in the analysis from 16 hospitals in 14 states (295 influenza cases, 1175 influenza- and SARS-CoV-2–negative controls, and 864 influenza-negative and SARS-CoV-2–positive controls for the secondary bias exploration analysis).

For the primary analysis excluding SARS-CoV-2–positive patients (Table 1), the median age was 64 years, 756 (51%) patients were female, 829 (56%) non-Hispanic White, 303 (21%) non-Hispanic Black, 243 (17%) Hispanic of any race, and 1376 (94%) had 1 or more chronic underlying condition including 337 (23%) with an immunocompromising condition; 813 (55%) had 1 or more hospitalization in the prior year. Among influenza case-patients enrolled during the surveillance period, all cases (202) with subtype information were A(H3N2) viruses; 129 influenza A viruses were processed for sequencing, 114 (88%) of which yielded hemagglutinin sequences of sufficient quality for clade identification. All of these were A(H3N2) viruses within the 2a.2 subgroup of A(H3N2) 3C.2a1b viruses. The median number of influenza case-patients contributed by site in the analysis was 13.5 (interquartile range: 9.5–24.5).

Current-season influenza vaccination was received by 139 of 295 (47%) influenza case-patients, 622 of 1175 (53%) influenza- and SARS-CoV-2–negative controls, and 424 of 864 (49%) influenza-negative but SARS-CoV-2–positive controls. Restricting patients to influenza cases and primary controls (both influenza- and SARS-CoV-2–negative) (Table 2), the median time from influenza vaccination to illness onset among those who received vaccination was 166 days (interquartile range: 129–200 days). Cases and controls were similar with respect to most baseline characteristics but differed in race and ethnicity distribution ($P = .003$) and had slightly longer delays from illness onset to hospital admission and influenza testing ($P < .05$ for both). Among cases and controls combined, those who received influenza vaccination were older (median age: 67 vs 61 years; $P < .001$), more likely to be non-Hispanic White (65% vs 48%; $P < .001$ for race/ethnicity distribution), more likely to have 1 or more underlying medical condition (96% vs 91%; $P < .001$) including immunocompromising conditions (27% vs 18%; $P < .001$), and more likely to have 1 or more hospitalization in the prior year (61% vs 49%; $P < .001$) (Table 1).

Overall VE against influenza-associated hospitalizations in the primary analysis (ie, excluding SARS-CoV-2–positive

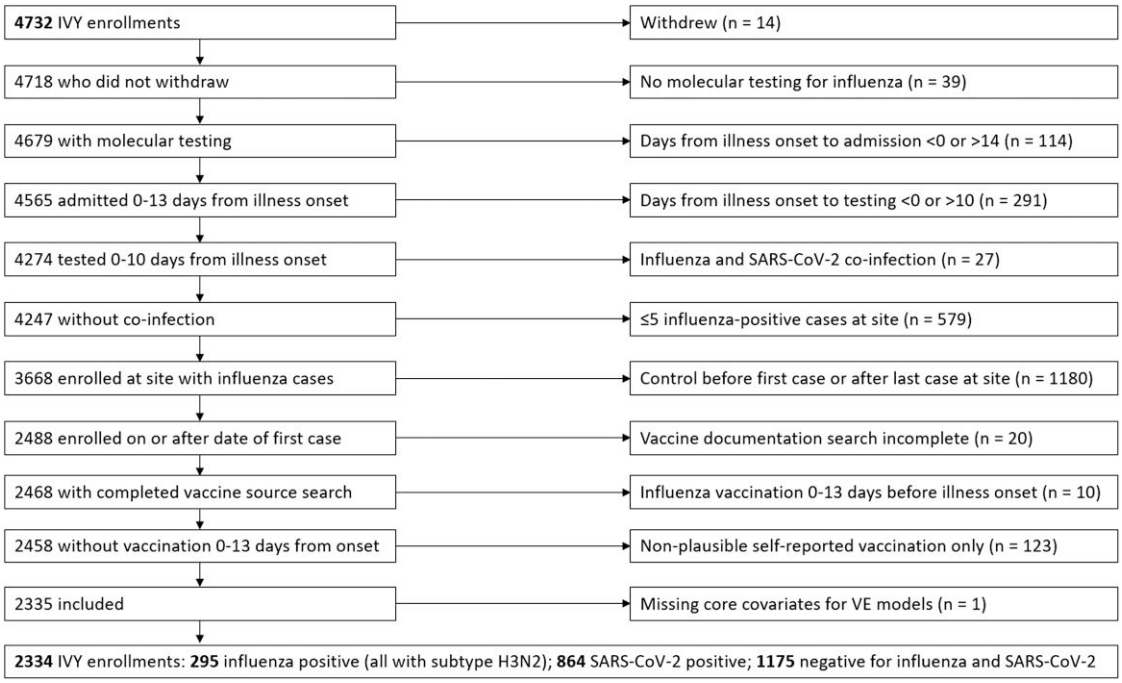

Figure 1. Exclusion flowchart. Abbreviations: IVY, Influenza and Other Viruses in the Acutely Ill; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness.

patients) was 11% (95% confidence interval [CI]: −19% to 33%). In stratified analyses, VE was 26% (95% CI: −14% to 52%) among all adults aged 18–64 years and −3% (95% CI: −54% to 31%) among adults 65 years of age and older. Vaccine effectiveness was 18% (95% CI: −13% to 41%) among all patients without immunocompromising conditions and −24% (95% CI: −145% to 37%) among patients with immunocompromising conditions (Figure 2). In contrast, VE was 50% (95% CI: 15% to 71%) among younger adults (18–64 years) without immunocompromising conditions. No evidence of waning vaccine protection was observed during the season, with VE similar for those vaccinated 14–150 days and more than 150 days prior to illness onset. Post hoc analyses found similar findings restricted to patients tested for influenza within 5 days of illness onset (overall VE: 10%; 95% CI: −23% to 34%) and adjusting for calendar week rather than calendar month (overall VE: 10%; 95% CI: −20% to 32%).

In a secondary analysis evaluating the magnitude of potential bias associated with including SARS-CoV-2–positive patients as controls (representing 864/2039 [42%] of potential influenza-negative controls), we observed a downward bias in estimated overall VE compared with the primary analysis (4% vs 11%) among patients aged 18–64 years (19% vs 26%) and among patients aged 65 years and older (−14% vs −3%).

Among 291 of 295 (99%) influenza case-patients with available in-hospital outcomes, 38 (13%) were admitted to the ICU, 176 (60%) received any supplemental oxygen support including 12 (4%) receiving IMV, and 6 (2%) died in-hospital within 28 days of admission (Table 3). A lower proportion of vaccinated compared with unvaccinated case-patients required ICU admission (9% vs 17%; $P = .045$).

DISCUSSION

During the 2021–2022 season when a subclade of A(H3N2) viruses predominated that were antigenically distinct from the vaccine virus, we found no significant effectiveness of seasonal influenza vaccine against influenza hospitalization among older adults and adults with immunocompromising conditions. However, modest VE was observed among younger (18–64 years), non-immunocompromised adults, even in the setting of drifted A(H3N2) viruses. These findings highlight heterogeneity across adult populations and limits to the generalizability of pooled VE estimates to the broader population. They also suggest a general need for improved influenza vaccines and therapeutics as well as a potential role for nonpharmaceutical prevention strategies during periods of high influenza circulation.

Our findings align with repeated observations of relatively low VE against influenza A(H3N2) virus infection [14, 15] and hospitalization [16] during recent influenza seasons. Low overall VE against A(H3N2) may be due to the vaccine strain being antigenically distinct from the clade of the subsequently circulating virus [17], as well as possibly ongoing egg

Table 1. Characteristics of Patients Vaccinated and Unvaccinated With Influenza Vaccines: IVY Network

	Overall	Influenza Vaccinated[a]	Influenza Unvaccinated	*P*[b]
No. (%)	1470 (100)	761 (52)	709 (48)	
Census region				
Northeast	439 (30)	212 (28)	227 (32)	<.001
South	420 (29)	199 (26)	221 (31)	
Midwest	322 (22)	199 (26)	123 (17)	
West	289 (20)	151 (20)	138 (19)	
Baseline characteristics				
Demographics and behavioral risk factors				
Age, median (IQR), years	64 (53–74)	67 (58–77)	61 (47–70)	<.001
Age group				
18–49 years	311 (21)	115 (15)	196 (28)	<.001
50–64 years	452 (31)	213 (28)	239 (34)	
65+ years	707 (48)	433 (57)	274 (39)	
Female	756 (51)	418 (55)	338 (48)	.005
Race/ethnicity				
White, non-Hispanic	829 (56)	491 (65)	338 (48)	<.001
Black, non-Hispanic	303 (21)	149 (20)	154 (22)	
Hispanic, any race	243 (17)	78 (10)	165 (23)	
Other race, non-Hispanic	69 (5)	34 (4)	35 (5)	
Unknown	26 (2)	9 (1)	17 (2)	
Insured	1422 (97)	755 (99)	667 (94)	<.001
Current tobacco smoking	261/1331 (20)	97/697 (14)	164/634 (26)	<.001
Health status indicators[c]				
≥1 Underlying chronic medical condition	1376 (94)	731 (96)	645 (91)	<.001
Chronic respiratory condition	615 (42)	360 (47)	255 (36)	<.001
Chronic immunocompromising condition[d]	337 (23)	207 (27)	130 (18)	<.001
≥1 Hospitalization in prior year	813/1469 (55)	467/760 (61)	346/709 (49)	<.001
Admission characteristics				
Days from illness onset to testing, median (IQR)	2 (1–4)	2 (1–4)	2 (0–4)	.025
Days from illness onset to hospitalization, median (IQR)	2 (0–3)	2 (0–4)	1 (0–3)	.016

Data are presented as n (%) unless otherwise indicated. Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; IVY, Influenza and Other Viruses in the Acutely Ill.

[a]Vaccination defined as documented and/or plausible self-report of influenza vaccine received 1 August 2021 or later.

[b]*P* value for test of difference across case and control groups based on chi-square statistic for categorical variables and Wilcoxon rank-sum test for continuous variables.

[c]Health indicators obtained through chart review and included chronic cardiovascular, neurological, pulmonary, gastrointestinal, endocrine, renal, hematologic, autoimmune, or immunocompromising conditions.

[d]Immunocompromising conditions include any of the following: active solid-organ cancer, active hematologic cancer, solid-organ transplant, bone marrow/stem cell transplant, HIV infection, congenital immunodeficiency syndrome, use of an immunosuppressive medication within the past 30 days, splenectomy, graft-versus-host disease (currently or in the past), or any other condition that causes moderate or severe immunosuppression.

adaptation mutations in A(H3N2) during vaccine manufacturing, such that the vaccine strain may elicit antibodies to sites that are unavailable in circulating viruses [17, 18]. In addition, we found moderate VE in younger adults without immunocompromising conditions but null VE for persons aged 65 years and older that cannot be explained by differences in virus subtype since nearly all infections were related to the same 2a.2 subclade. This finding could be related to factors that affect A(H3N2)-specific immune response to vaccination among younger versus older adults. The concept of original antigenic sin suggests that the human body will condition, or "imprint," antibody response to the first influenza virus infection that one experiences in life [19]. Older adults were imprinted with A(H1N1) since it was the only subtype circulating in humans from 1918–1957; consequently, their immune response may be biased toward A(H1N1) and away from A(H3N2) viruses, which emerged in 1968 [8]. In contrast, younger adults were more likely to have been imprinted by A(H3N2) viruses. Other factors for the lower VE in older adults might be related to immune senescence [20], "inflamm-aging" [21] (ie, a chronic low-level state of inflammation from multiple underlying conditions and frailty suspected to impair immune responses), and diminished effects of repeated vaccination that might occur among older adults [22]. Differences in vaccine type are unlikely to explain lower VE in older US adults who typically receive high-dose inactivated influenza vaccine as compared with younger US adults who largely receive the standard-dose vaccine [23].

This study examined VE both with and without the inclusion of patients with SARS-CoV-2 as controls. A recent simulation

Table 2. Characteristics of Influenza-Positive Patients (Cases) and Influenza-Negative Patients (Controls): IVY Network

	Overall	Influenza-Positive	Influenza-Negative	*P*[a]
No. (%)	1470 (100)	295	1175	
Census region				
Northeast	439 (30)	81 (27)	358 (30)	.29
South	420 (29)	79 (27)	341 (29)	
Midwest	322 (22)	66 (22)	256 (22)	
West	289 (20)	69 (23)	220 (19)	
Baseline characteristics				
Demographics and behavioral risk factors				
Age, median (IQR), years	64 (53–74)	66 (51–76)	64 (53–73)	.28
Age group				
18–49 years	311 (21)	70 (24)	241 (21)	.009
50–64 years	452 (31)	69 (23)	383 (33)	
65+ years	707 (48)	156 (53)	551 (47)	
Female	756 (51)	157 (53)	599 (51)	.49
Race/ethnicity				
White, non-Hispanic	829 (56)	142 (48)	687 (58)	.003
Black, non-Hispanic	303 (21)	63 (21)	240 (20)	
Hispanic, any race	243 (17)	63 (21)	180 (15)	
Other race, non-Hispanic	69 (5)	22 (7)	47 (4)	
Unknown	26 (2)	5 (2)	21 (2)	
Insured	1422 (97)	282 (96)	1140 (97)	.22
Current tobacco smoking	261/1331 (20)	54/269 (20)	207/1062 (19)	.83
Health status indicators[b]				
≥1 Underlying chronic medical condition	1376 (94)	275 (93)	1101 (94)	.76
Chronic respiratory condition	615 (42)	124 (42)	491 (42)	.94
Chronic immunocompromising condition[c]	337 (23)	62 (21)	275 (23)	.38
≥1 Hospitalization in prior year	813/1469 (55)	149/295 (51)	664/1174 (57)	.062
Admission characteristics				
Days from illness onset to testing, median (IQR)	2 (1–4)	2 (1–4)	2 (0–4)	.023
Days from illness onset to hospitalization, median (IQR)	2 (0–3)	2 (1–4)	1 (0–3)	<.001

Data are presented as n (%) unless otherwise indicated. Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; IVY, Influenza and Other Viruses in the Acutely Ill.

[a] *P* value for test of difference across case and control groups based on chi-square statistic for categorical variables and non-parametric Wilcoxon rank-sum test for continuous variables.

[b] Health indicators obtained through chart review and included chronic cardiovascular, neurological, pulmonary, gastrointestinal, endocrine, renal, hematologic, autoimmune, or immunocompromising conditions.

[c] Immunocompromising conditions include any of the following: active solid-organ cancer, active hematologic cancer, solid-organ transplant, bone marrow/stem cell transplant, HIV infection, congenital immunodeficiency syndrome, use of an immunosuppressive medication within the past 30 days, splenectomy, graft-versus-host disease (currently or in the past), or any other condition that causes moderate or severe immunosuppression.

study has shown that the inclusion of SARS-CoV-2–positive controls can bias influenza VE estimates downwards due to correlation between COVID-19 and influenza vaccination coverage [11]. In test-negative VE studies, including SARS-CoV-2–positive patients among controls for influenza cases may introduce confounding bias when COVID-19 and influenza vaccine receipt are strongly correlated [10]. Because COVID-19 vaccines are protective, controls with COVID-19 are less likely to be vaccinated against COVID-19 compared with the source population. If COVID-19 and influenza vaccination rates are strongly correlated, including patients with COVID-19 as controls in influenza VE studies will enrich the control population with participants who are unvaccinated against influenza compared with the source population from which the cases were generated, and thus bias VE down. Doll et al [10] found that, while this bias was low when patients with COVID-19 represented 10% or less of controls, higher proportions of controls who were SARS-CoV-2–positive likely increased the magnitude of the bias. This analysis provides a practical illustration of this problem, showing a nearly 10% difference in point estimates for VE when SARS-CoV-2–positive patients were included as controls, indicating that investigators should consider excluding SARS-CoV-2–positive controls from future VE analyses.

This analysis was subject to several limitations. First, enrollment did not start until several months into the 2021–2022 influenza season (influenza activity was observed in the United States by October 2021 [24], although activity decreased in December 2021 with the emergence of the SARS-CoV-2 Omicron variant before increasing again in February 2022), the median time from influenza vaccination to illness onset was more than 5 months, and the influenza season was long,

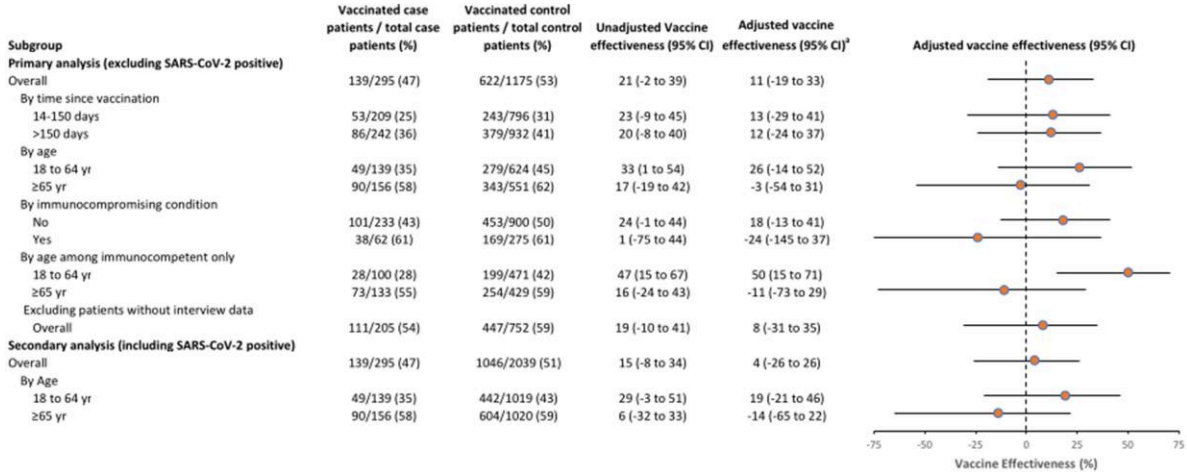

Figure 2. Unadjusted and adjusted influenza vaccine effectiveness, IVY Network. [a]Adjusted for calendar time (in monthly intervals), enrollment site, age, female sex, and race and ethnicity. Abbreviations: CI, confidence interval; IVY, Influenza and Other Viruses in the Acutely Ill; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; yr, years.

with ongoing circulation at many sites through June 2022. This may have led to lower VE in the setting of waning vaccine protection [25], although evidence of waning was not observed. Second, vaccination coverage among hospitalized adults was lower than typically observed in prior influenza seasons [26]. Under-capture of influenza vaccination could lead to VE estimates biased toward the null. However, the COVID-19 pandemic as well as lower influenza activity in the United States since 2020 may have influenced vaccination coverage [11]. Further, among patients with patient or proxy interview data, influenza vaccination coverage was generally similar to that in the full cohort. A sensitivity analysis including only patients with interview data yielded similar VE estimates, lessening concerns about the primary results being heavily biased by underreporting of vaccination coverage. Third, low levels of influenza activity limited statistical power. Fourth, although the analysis controlled for several relevant potential confounders such as calendar time and geographic location, residual confounding is possible. Patients hospitalized with ARI are predominantly older adults and have multiple underlying medical conditions. Therefore, findings may not be generalizable to the entire US population. Finally, influenza clinical testing practice may have varied across participating sites, resulting in a varied number of influenza-positive cases. However, selection bias is not substantial because all patients met ARI criteria and testing is unlikely to be influenced by vaccination status [27]. In addition, all upper respiratory specimens were tested centrally for influenza by RT-PCR.

Table 3. In-Hospital Outcomes of Patients Hospitalized With Influenza Infection (Cases) Who Were Vaccinated and Unvaccinated

Characteristic	Overall (N = 291)	Vaccinated (n = 136)	Unvaccinated (n = 155)	*P*
Intensive care unit admission	38 (13)	12 (9)	26 (17)	.045
Low-flow supplemental oxygen	176 (60)	79 (58)	97 (63)	.43
High-flow nasal cannula	19 (7)	7 (5)	12 (8)	.37
Noninvasive positive-pressure ventilation	28 (10)	14 (10)	14 (9)	.72
Invasive mechanical ventilation	12 (4)	4 (3)	8 (5)	.34
Vasopressor receipt	15 (5)	5 (4)	10 (6)	.29
In-hospital death within 28 days	6 (2)	2 (1)	4 (3)	.51

Data are presented as n (%).

CONCLUSIONS

During a season where circulating influenza A(H3N2) was antigenically different from the vaccine virus, we did not observe significant overall VE against hospitalized influenza, but some protection was seen among younger, non-immunocompromised adults. Vaccine effectiveness was lowest in older adults in whom severe influenza burden is substantially higher, warranting strategies such as improvements in vaccines, antivirals, and other prevention strategies.

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

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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