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Influenza Vaccine Effectiveness for Prevention of Severe Influenza-Associated Illness Among Adults in the United States, 2019–2020: A Test-Negative Study

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Background. Influenza vaccine effectiveness (VE) against a spectrum of severe disease, including critical illness and death, remains poorly characterized.

Methods. We conducted a test-negative study in an intensive care unit (ICU) network at 10 US hospitals to evaluate VE for preventing influenza-associated severe acute respiratory infection (SARI) during the 2019–2020 season, which was characterized by circulation of drifted A/H1N1 and B-lineage viruses. Cases were adults hospitalized in the ICU and a targeted number outside the ICU (to capture a spectrum of severity) with laboratory-confirmed, influenza-associated SARI. Test-negative controls were frequency-matched based on hospital, timing of admission, and care location (ICU vs non-ICU). Estimates were adjusted for age, comorbidities, and other confounders.

Results. Among 638 patients, the median (interquartile) age was 57 (44–68) years; 286 (44.8%) patients were treated in the ICU and 42 (6.6%) died during hospitalization. Forty-five percent of cases and 61% of controls were vaccinated, which resulted in an overall VE of 32% (95% CI: 2–53%), including 28% (−9% to 52%) against influenza A and 52% (13–74%) against influenza B. VE was higher in adults 18–49 years old (62%; 95% CI: 27–81%) than those aged 50–64 years (20%; −48% to 57%) and ≥65 years old (−3%; 95% CI: −97% to 46%) ($P = .0789$ for interaction). VE was significantly higher against influenza-associated death (80%; 95% CI: 4–96%) than nonfatal influenza illness.

Conclusions. During a season with drifted viruses, vaccination reduced severe influenza-associated illness among adults by 32%. VE was high among young adults.

Keywords. influenza; vaccine effectiveness; critical illness; vaccination; immunization.

In the United States, influenza vaccination is recommended annually for everyone at least 6 months old without a contraindication to vaccination [1–3]. Because influenza viruses continue to evolve, influenza disease burden and the effectiveness of seasonal influenza vaccination vary from season to season [4]. Prior studies have consistently demonstrated the effectiveness of influenza vaccination for preventing influenza infection among ambulatory and hospitalized patients [3, 5–8]. Previous reports from small studies suggest that seasonal influenza vaccination may provide greater protection against intensive care unit (ICU) admissions than non-ICU hospital admissions, as well as shorten the length of ICU stay [9–11]. However, the effectiveness of influenza vaccination for preventing the most severe manifestations of influenza infection remains poorly characterized.

The 2019–2020 US influenza season started earlier than usual, was severe, and was characterized by intense early circulation of influenza B-Victoria lineage viruses, with cocirculation of influenza A(H1N1)pdm09 viruses [12, 13]. Studies have reported limited antigenic similarity (ie, "drift") between the seasonal vaccine viruses used during the 2019–2020 season and the circulating influenza B and some subclades of A(H1N1)pdm09 viruses [14–16]. Available estimates suggest modest vaccine effectiveness (VE) (~39%) for prevention of ambulatory visits and hospitalizations in this season with circulation of 2 drifted viruses, but the VE for prevention of critical influenza illness has

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not been explored [16]. In an ICU network of 10 US hospitals, we evaluated the effectiveness of influenza vaccination for the prevention of severe influenza-associated illness among adults during the 2019–2020 influenza season.

METHODS

We conducted a prospective observational study using a test-negative design to estimate influenza VE for preventing severe influenza-associated illness, including hospitalization, ICU admission, acute organ failure, and death [17–21]. The study was conducted by the Influenza and Other Viruses in the Acutely Ill (IVY) Network, a multicenter network funded by the Centers for Disease Control and Prevention (CDC). The study protocol was approved by the Institutional Review Board at Vanderbilt University Medical Center. Written informed consent was obtained from each patient or a legally authorized representative.

Study Population

We enrolled hospitalized adults with signs and symptoms of severe acute respiratory infection (SARI) from 10 October 2019 to 28 February 2020 at 10 hospitals in 9 US states. Detailed eligibility criteria are shown in Supplementary Table 1. The enrollment strategy, which is detailed in Supplementary Table 2, prioritized enrollment of critically ill influenza cases and test-negative controls, while also enrolling representative samples of hospitalized, non–critically ill cases and controls.

Study Procedures

After enrollment, trained study personnel interviewed patients (or surrogate informants if the patient was unable to answer questions) to collect data, including self-report of influenza vaccination for the current (2019–2020) and prior (2018–2019) season. Study personnel collected a midturbinate nasal and oropharyngeal swab for viral testing. Study personnel also abstracted data from the medical record, including death, ICU admission, and development of acute organ failure, defined as receipt of invasive or noninvasive mechanical ventilation, vasopressor support, new renal replacement therapy, or extracorporeal membrane oxygenation.

Test-Positive Cases and Test-Negative Controls

The results of all clinically obtained influenza reverse transcription–polymerase chain reaction (RT-PCR) tests completed between 72 hours before and 72 hours after hospital presentation were recorded. Additionally, all respiratory samples collected for the study were shipped to the study laboratory at Vanderbilt for RT-PCR influenza testing using CDC primers and protocols. Test results with a cycle threshold of 40 or less were considered positive for influenza and with a cycle threshold of 40 or greater were considered indeterminate. Influenza-positive specimens were further tested to determine A subtypes (H1N1pdm09 and H3N2) and B lineages (Victoria and Yamagata).

Study patients with SARI who tested positive for influenza by either a clinically obtained RT-PCR or central laboratory RT-PCR test were classified as cases. Patients with SARI who tested negative for influenza by all tests were classified as controls. Patients with indeterminate influenza status (cycle threshold ≥40) by RT-PCR were not included in VE analyses.

Genetic Characterization of Detected Influenza Viruses

Influenza-positive specimens with a cycle threshold value of less than 30 underwent further genetic characterization at CDC, including whole-genome sequencing [22]. Phylogenetic analysis was conducted to determine hemagglutinin (HA) genetic clades and subclades in sequenced influenza A viruses [12, 13, 23].

Influenza Vaccination Verification

Research personnel conducted a systematic search of electronic medical records and state vaccination registries, and contacted relevant pharmacies, clinics (eg, primary care providers), payors, and other venues for evidence of influenza vaccination. Research personnel called patients/surrogates to clarify discordant information between initial self/surrogate-report of vaccination and results of systematic searches. Patients with verified receipt of an influenza vaccine more than 13 days prior to illness onset for the current season were classified as vaccinated. Patients without verified receipt of vaccination or vaccination after illness onset for the current season were classified as unvaccinated. Patients who had verified vaccination 0–13 days prior to illness onset were excluded from the VE analyses.

Study Covariates

Covariates, identified a priori, included study site, age, sex, race/ethnicity, calendar time (categorized as tertiles generated based on site-specific influenza activity using disease-onset dates of influenza cases) [24], insurance status, enrollment location (ICU vs non-ICU), days from illness onset to specimen collection for influenza testing, chronic medical conditions (including cardiovascular and pulmonary diseases; kidney and gastrointestinal diseases; neurological, psychiatric, and gastrointestinal diseases; malignancies; and hematological, autoimmune, and other immunosuppressive conditions), and frailty (assessed using a questionnaire derived from Fried and colleagues [25]) [7, 26].

Statistical Analyses

We summarized patients' characteristics by influenza infection status (influenza cases vs test-negative controls) and verified vaccination status (vaccinated vs unvaccinated). Influenza VE within the full study population (ie, for the prevention of influenza-associated SARI) was calculated as follows: (1 − adjusted odds ratio of cases compared with

controls for being vaccinated) × 100%. The adjusted odds ratio was calculated using multivariable unconditional logistic regression that modeled the association between vaccination and influenza status, while adjusting for the study covariates listed above. Vaccine effectiveness was reported in percentages with 95% confidence intervals (CIs). Missing data for covariates (including 4 variables with up to 13 missing values, ~2% of total observations) were imputed using multiple imputation with chained equations and 20 imputed datasets were generated for multivariable regression analyses [27].

Several planned secondary analyses were conducted to estimate influenza VE in prespecified subgroups, including the following: (1) age groups (18–49, 50–64, and ≥65 years), (2) influenza-associated ICU admission, (3) influenza-associated acute organ failure, and (4) influenza-associated death. For these assessments, we added corresponding interaction terms with vaccination status to the main regression model, and VE estimates were derived from the multivariable regression coefficients. A post hoc subgroup assessment of VE by race/ethnicity was also conducted. Vaccine effectiveness was also estimated by influenza virus type (A and B) and the most common subtype/lineage by restricting influenza cases to those from the specific type/lineage [5]. Exploratory VE estimates by the most common vaccine types (quadrivalent and trivalent high-dose) were provided.

Because previous reports suggest that vaccination in previous years could influence VE for the current season, we also conducted separate estimates incorporating verified vaccination information for the previous season (2018–2019) [5, 28]. This and other sensitivity analyses are detailed in Supplementary Table 3.

Statistical significance for effectiveness estimates was defined as a 95% CI excluding the null value. For assessing differences in VE by subgroups, we considered *P* values less than .15 as statistically significant, which is sufficient for interpreting interaction between 2 dichotomous variables when effect size is expected to be moderate to high (eg, absolute difference in VE >25%) [29, 30]. Analyses were conducted in R version 4.0.3 (http://www.r-project.org) and Stata version 16.1 (StataCorp, College Station, TX).

RESULTS

Study Patients

From 10 October 2019 through 28 February 2020, 998 eligible patients were approached for participation in the study; 725 of these patients consented for participation and 6 later withdrew from the study. Of the 719 enrolled patients who did not withdraw from the study, 81 were excluded from primary analysis due to indeterminate influenza infection status (n = 9), inability to verify vaccination status (n = 65), or verified vaccination within 13 days prior to symptom onset (n = 7) (Figure 1 and Supplementary Figure 1). Among 638 patients included in the primary analysis, the median (interquartile range) age was 57 years (44–68 years) and 336 (52.7%) were female. In this study sample enriched with ICU patients, 286 (44.8%) patients were treated in the ICU, 254 (39.8%) experienced acute organ failure, and 42 (6.6%) died during hospitalization.

Among the 638 patients included in the analyses, 309 (48.4%) were influenza cases, including 207 influenza A cases [166 A(H1N1)pdm09, 14 A(H3N2), 27 A without a subtype determined], 100 influenza B cases (77 B/Victoria, 3 B/Yamagata, 20 B without lineage determined), and 2 influenza cases with co-detections of A(H1N1)pdm09 and B/Victoria. A total of 339 (53.1%) patients were vaccinated for the current (2019–2020) season, including 138 (44.7%) of 309 influenza cases and 201 (61.1%) of 329 controls.

Compared with controls, influenza cases were younger, more likely to be Hispanic, and had fewer healthcare encounters during the prior year, lower frailty scores, and fewer comorbidities (Table 1). Compared with unvaccinated patients, patients who were vaccinated were older, more likely to be White non-Hispanic, more likely to have government insurance, and had more healthcare encounters during the prior year, higher frailty scores, and more comorbidities.

Genetic Characterization of Influenza Viruses

Among 309 influenza cases, 120 had viruses characterized by whole-genome sequencing, including 70 A(H1N1)pdm09, 4 A(H3N2), 43 B/Victoria, and 3 B/Yamagata. All sequenced A(H1N1)pdm09 viruses belonged to the hemagglutinin 6B.1A group. Eighteen A(H1N1)pdm09 viruses belonged to subclade 5A viruses with additional amino acid changes in K130N, N156K, L161I, V250A, and E506D (5A + 156K viruses); 43 belonged to subclade 5A viruses with additional amino acid substitutions D187A and Q189E in the HA protein (5A + 187A, 189E viruses); and 9 belonged to other subclades. All sequenced A(H3N2) viruses belonged to the 3C.2a1b group. Of the 43 B/Victoria viruses sequenced, 42 viruses belonged to clade V1A.3 and 1 belonged to clade V1A.1. All sequenced B/Yamagata viruses belonged to clade Y3 [14, 15, 31]. Recent assessments have shown that A(H1N1)pdm09 5A + 156K viruses were poorly matched by the 2019–2020 influenza vaccine formulation. Moreover, the V1A.3 B/Victoria viruses showed limited similarity with the vaccine formulation components [1, 12, 13].

Vaccine Effectiveness

In the primary multivariable analytical model, VE for the prevention of influenza-associated SARI was 32% (2% to 53%). Vaccine effectiveness was higher among adults aged 18–49 years old (62%; 95% CI: 27% to 81%) than those aged 50–64 years old (20%; 95% CI: −48% to 57%) and those aged 65 years or older (−3%; 95% CI: −97% to 46%) (*P* value for interaction = .0789) (Table 2).

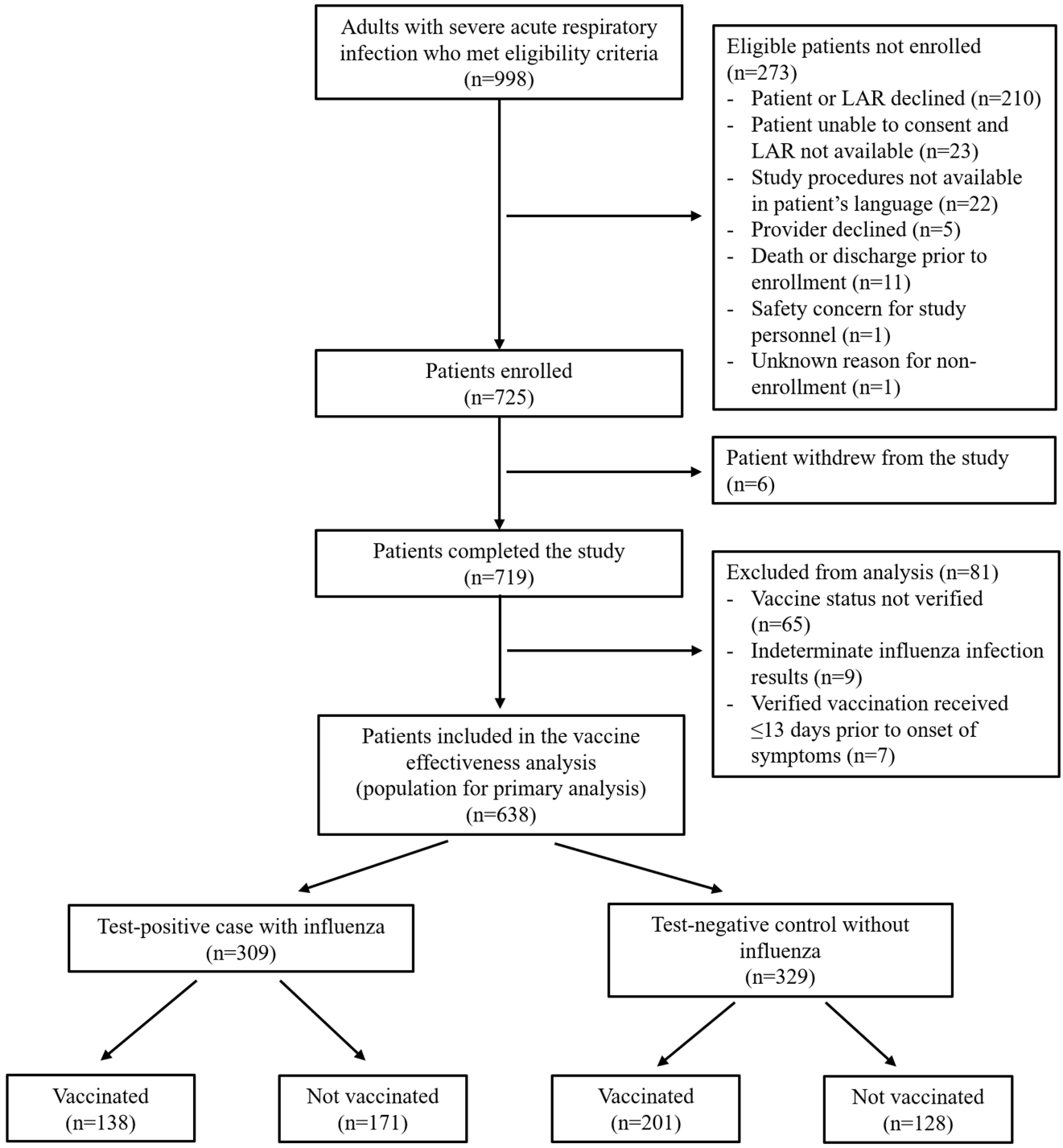

Figure 1. Flow diagram of patient enrollment. Abbreviation: LAR, legally authorized representative.

In subgroup analysis, VE was higher for the prevention of influenza-associated death than for prevention of nonfatal influenza ($P = .1136$). The estimated VE for the prevention of influenza-associated death was 80% (4% to 96%). Most of the 21 patients with influenza who died were young or middle-aged adults (median age: 53 years) as compared with the 21 test-negative control patients who died (median age: 68 years) (Supplementary Tables 4 and 5). No significant differences in VE were observed among subgroups defined by race/ethnicity, ICU admission, or acute organ failure (Table 2).

Vaccine effectiveness for preventing SARI caused by influenza A was 28% (−9% to 52%) and by influenza B was 52% (13% to 74%), with similar estimates for the most frequently detected subtype/lineage. Similar to the pattern observed in the

Table 1. Characteristics of Study Participants by Case-Control and Vaccination Status

Characteristic	Cases[a] (n = 309)	Controls[a] (n = 329)	Vaccinated[b] (n = 339)	Not Vaccinated[b] (n = 299)
Vaccinated for influenza,[b] n (%)	138 (45)	201 (61)	…	…
Age, median (IQR), years	56 (41–65)	59 (46–70)	62 (52–72)	51 (36–62)
Age group, n (%)				
18–49 years	117 (38)	95 (29)	71 (21)	141 (47)
50–64 years	109 (35)	99 (30)	113 (33)	95 (32)
≥65 years	83 (27)	135 (41)	155 (46)	63 (21)
Male sex, n (%)	152 (49)	150 (46)	152 (45)	150 (50)
Race/ethnicity, n (%)				
Black non-Hispanic	76 (25)	84 (26)	78 (23)	82 (27)
White non-Hispanic	170 (55)	206 (63)	222 (65)	154 (52)
Hispanic	46 (15)	30 (9)	33 (10)	43 (14)
Other race, non-Hispanic	17 (6)	9 (3)	6 (2)	20 (7)
Site, n (%)				
Baystate Medical Center	23 (7)	22 (7)	27 (8)	18 (6)
Beth Israel Deaconess	11 (4)	9 (3)	12 (4)	8 (<1)
Hennepin County Medical Center	21 (7)	23 (7)	23 (7)	21 (7)
Intermountain Medical Center	24 (8)	16 (5)	19 (6)	21 (7)
Montefiore Medical Center	36 (12)	45 (14)	35 (10)	46 (15)
Ohio State Medical Center	22 (7)	20 (6)	23 (7)	19 (6)
Oregon Health and Sciences	34 (11)	35 (11)	32 (9)	37 (12)
University of Colorado	29 (9)	28 (9)	27 (8)	30 (10)
Vanderbilt University	76 (25)	101 (31)	100 (29)	77 (26)
Wake Forest	33 (11)	30 (9)	41 (12)	22 (7)
Insurance, n (%)				
Government	185 (60)	214 (65)	230 (68)	169 (57)
Private	98 (32)	102 (31)	106 (31)	94 (31)
None	26 (8)	13 (4)	3 (<1)	36 (12)
Healthcare visits in past year, n (%)				
0	43 (14)	29 (9)	17 (5)	55 (19)
1	20 (7)	25 (8)	22 (6)	23 (8)
≥2	237 (79)	271 (83)	294 (88)	214 (73)
ED visits past year, n (%)				
0	106 (35)	99 (30)	95 (28)	110 (38)
1	58 (19)	71 (22)	72 (21)	57 (20)
≥2	136 (45)	155 (48)	168 (50)	123 (42)
Hospital admissions in past year, n (%)				
0	141 (47)	125 (38)	122 (36)	144 (49)
1	57 (19)	73 (22)	73 (22)	57 (20)
≥2	103 (34)	128 (39)	140 (42)	91 (31)
Frailty score,[c] median (IQR)	1 (0–3)	2 (1–3)	2 (1–3)	1 (0–3)
Time between symptom onset and first				
RT-PCR influenza test, median (IQR), days	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–4)
Smoking/vaping history, n (%)	181 (59)	192 (58)	192 (57)	181 (61)
Tertile of seasonal influenza Activity[d]				
1 (Initial one-third of season)	105 (34)	88 (27)	91 (27)	102 (34)
2 (Middle one-third of season)	97 (31)	87 (26)	99 (29)	85 (28)
3 (Last one-third of season)	107 (35)	154 (47)	149 (44)	112 (37)
Comorbidities, n (%)				
Cardiovascular/pulmonary	218 (71)	266 (81)	289 (85)	195 (65)
Endocrine/kidney	130 (42)	183 (56)	207 (61)	106 (35)
Immunosuppressive condition	100 (32)	163 (50)	158 (47)	105 (35)
Neurologic/psychiatric/gastrointestinal	126 (41)	136 (41)	159 (47)	103 (34)
Enrollment in ICU, n (%)	129 (42)	157 (48)	150 (44)	136 (45)
Influenza infection,[a] n (%)	309 (100)	-	171 (57)	138 (41)
Influenza A,[a] n (%)	207 (67)		99 (30)	108 (36)
A(H1N1)pdm09	166 (54)		83 (24)	83 (28)
H3N2	14 (5)		4 (1)	10 (3)

Table 1. Continued

Characteristic	Cases[a] (n = 309)	Controls[a] (n = 329)	Vaccinated[b] (n = 339)	Not Vaccinated[b] (n = 299)
Influenza B,[a] n (%)	100 (32)		38 (12)	62 (21)
Victoria	77 (25)		30 (9)	47 (16)
Yamagata	3 (1)		2 (1)	1 (<1)

Abbreviations: IQR, interquartile range; ED, emergency department; ICU, intensive care unit; RT-PCR, reverse transcription-polymerase chain reaction.

[a]Participants who tested positive for influenza by RT-PCR were classified as cases, while those who tested negative were classified as controls. Counts may not add up to totals due to incomplete typing or subtyping.

[b]Participants who had verified receipt of an influenza vaccine for the 2019–2020 season at least 13 days before illness onset were classified as vaccinated, while those who did not have verified receipt of an influenza vaccine for the 2019–2020 season were classified as unvaccinated. Patients with vaccine receipt 0–13 days prior to illness onset were excluded from the analysis.

[c]The frailty score ranged from 0 (not frail) to 5 (very frail) according to the classification described by Fried and colleagues [25].

[d]Tertile of seasonal influenza activity divided the 2019–2020 influenza season into the initial one-third of the season, middle one-third of the season, and last one-third of the season for each site based on local influenza activity [4].

main analysis, VE against influenza A and B estimates tended to be higher, but not significantly different, among younger compared with older adults (Figure 2 and Supplementary Table 6); VE estimates by vaccine types were consistent with the main findings (Supplementary Table 6). Compared with patients who were not vaccinated in either the current or previous influenza season, patients vaccinated only during the current season or during both current and previous season had similar VE estimates—49% (19% to 67%) and 44% (9% to 66%), respectively (Figure 3 and Supplementary Table 6).

Sensitivity Analyses

When age was modeled with a flexible spline function, VE for the prevention of SARI varied significantly with age (P = .0242), with higher VE again observed among younger adults (Supplementary Figure 2*A*). Higher VE among younger adults was also observed for the prevention of ICU admission and acute organ failure (Supplementary Figure 2*B*, 2*C*). There were no significant differences in estimates based on presence of cardiopulmonary or immunosuppressive conditions, although the VE estimates for patients with immunosuppressive conditions was only 17% (−44% to 52%) (Supplementary Table 7).

The alternate analysis that summarized relevant covariates through calculation of vaccination propensity scores and stabilized inverse probability of treatment weighting yielded VE results for the prevention of SARI (35%; 6% to 55%) that were nearly identical to those from the primary analysis (Figure 3 and Supplementary Table 7). Supplementary Figure 3 displays the standardized mean differences between cases and controls before and after weighting, indicating that the distribution of covariates was well balanced after weighting. Last, influenza vaccination was not significantly associated with lower odds of death among influenza-negative controls, but it was associated with lower odds of death among influenza-positive cases (P-interaction = .035) (Supplementary Table 7).

DISCUSSION

During the 2019–2020 influenza season in the United States, characterized by unusually early and intense influenza B activity as well as circulation of drifted A(H1N1)pdm and B/Victoria viruses [12, 13], influenza vaccination was associated with a 32% reduction in the odds of severe, hospitalized, laboratory-confirmed influenza disease. Vaccine effectiveness against influenza A was 28% (−9% to 52%) and against influenza B was 52% (13% to 74%). In a season with a relatively poor match between vaccine strains and circulating viruses [12, 13], influenza vaccination was modestly protective against the most severe manifestations of influenza infection.

Influenza VE varied with age, with high effectiveness against severe outcomes among young adults. Although this study was designed to enroll patients with SARI, and included a large subset of patients who were treated in an ICU, the median age of influenza-positive cases was only 56 years. Furthermore, among patients with laboratory-confirmed influenza infection who died, the median age was only 53 years. The vast majority of those fatal cases had no major underlying comorbidities, suggesting that their outcome could have been prevented if they did not develop influenza disease. Compared with previous VE studies [6, 7, 9], this study included younger patients with a higher mortality rate, suggesting that the effort to target enrollment of severely ill patients with critical illness caused by influenza was successful.

Although VE for the prevention of influenza-associated death was based on only 42 deaths, it is noteworthy that the estimated VE point estimate was higher (~80%) than the effectiveness estimates against other study outcomes. The higher level of protection against deaths when adjusted for age and other potential confounders reflected the markedly lower vaccination rates (14%) among patients with influenza-associated death than test-negative controls overall (61%) and test-negative controls who died (62%). Thus, we suspect that the observed influenza-associated deaths were potentially preventable with vaccination. Additional studies of severe influenza illness, possibly combining data across multiple seasons to increase sample size, will be important to conclusively estimate VE against death. These observations contribute to the accumulating body of evidence supporting the effectiveness of influenza vaccines for the prevention of influenza-associated death [32, 33].

Table 2. Vaccine Effectiveness for the Prevention of Influenza-Associated Severe Outcomes, Including Severe Acute Respiratory Infection, Intensive Care Unit Admission, Organ Failure, and Death

	Influenza Cases, n [n Vaccinated (% Vaccinated)]	Noninfluenza Controls, n [n Vaccinated (% Vaccinated)]	Unadjusted OR for Vaccination (95% CI)[a]	Adjusted OR for Vaccination (95% CI)[b]	Vaccine Effectiveness,[c] % (95% CI)	*P* Value for Interaction
Severe acute respiratory infection (full population)	309 [138 (44.7%)]	329 [201 (61.1%)]	.51 (.37–.7)	.68 (.47–.98)	32 (2–53)	
Age groups (years)						
18–49	117 [26 (22.2%)]	95 [45 (47.4%)]	.32 (.18–.57)	.38 (.20–.73)	62 (27–81)	.0789
50–64	109 [53 (48.6%)]	99 [60 (60.6%)]	.62 (.35–1.07)	.8 (.43–1.48)	20 (−48 to 57)	
≥65	83 [59 (71.1%)]	135 [96 (71.1%)]	1 (.55–1.83)	1.03 (.54–1.97)	−3 (−97 to 46)	
Race/ethnicity[d]						
Black non-Hispanic	76 [32 (42.1%)]	84 [46 (54.8%)]	.6 (.32–1.12)	.67 (.34–1.33)	33 (−33 to 66)	.9083
White non-Hispanic	170 [86 (50.6%)]	206 [136 (66%)]	.53 (.35–.8)	.7 (.44–1.12)	30 (−12 to 56)	
Other race/Hispanic	63 [20 (31.7%)]	39 [19 (48.7%)]	.49 (.22–1.11)	.56 (.23–1.38)	44 (− 38 to 77)	
ICU admission						
Non-ICU admission	180 [79 (43.9%)]	172 [110 (64%)]	.44 (.29–.68)	.54 (.33–.87)	46 (13–67)	.1612
ICU admission	129 [59 (45.7%)]	157 [91 (58%)]	.61 (.38–.98)	.88 (.51–1.51)	12 (−51 to 49)	
Acute organ failure[e]						
No acute organ failure	199 [87 (43.7%)]	185 [118 (63.8%)]	.44 (.29–.66)	.59 (.37–.94)	41 (6–63)	.3582
Acute organ failure	110 [51 (46.4%)]	144 [83 (57.6%)]	.64 (.39–1.05)	.82 (.47–1.43)	18 (−43 to 53)	
In-hospital death						
No death	288 [135 (46.9%)]	308 [188 (61.0%)]	.56 (.41–.78)	.73 (.5–1.07)	27 (−7 to 50)	.1136
Death	21 [3 (14.3%)]	21 [13 (61.9%)]	.10 (.02–.46)	.20 (.04–.97)	80 (4–96)	
Virus type and main subtype/lineage						
Influenza A	207 [99 (47.8%)]	329 [201 (61.1%)]	.58 (.41–.83)	.72 (.48–1.09)	28 (−9 to 52)	…
A(H1N1)pdm09	166 [83 (50%)]	329 [201 (61.1%)]	.64 (.44–0.93)	.83 (.53–1.31)	17 (−31 to 47)	…
Influenza B	100 [38 (38%)]	329 [201 (61.1%)]	.39 (.25–0.62)	.48 (.27–.87)	52 (13–74)	…
Victoria	77 [30 (39%)]	329 [201 (61.1%)]	.41 (.24–.68)	.55 (.28–1.09)	45 (−9 to 72)	…

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

[a]The unadjusted OR was calculated with a logistic regression model with influenza case vs noninfluenza control status as the dependent variable and vaccination status (vaccinated vs unvaccinated) as the independent variable.

[b]The adjusted OR was calculated with a multivariable logistic regression model with influenza case vs noninfluenza control status as the dependent variable, vaccination status (vaccinated vs unvaccinated) as the primary independent variable, and the following covariates: study site, age in years, sex, race/ethnicity, calendar time (categorized as tertiles generated based on site-specific influenza activity using disease-onset dates of influenza cases), insurance status, enrollment location (ICU vs outside the ICU), days from illness onset to specimen collection for influenza testing, chronic medical conditions (including [a] cardiovascular and pulmonary diseases, [b] kidney and gastrointestinal diseases, [c] neurological, psychiatric and gastrointestinal diseases, and [d] hematological, malignancies, autoimmune, and other immunosuppressive conditions), and frailty score (which ranged from 0 [not frail] to 5 [very frail]).

[c]Vaccine effectiveness, reported as a percentage, was calculated as follows: (1 − adjusted OR for vaccination) × 100.

[d]The "Other race" group was combined with the Hispanic group because of low counts in these groups.

[e]Acute organ failure was defined as receipt of any of the following during the hospitalization in which the patient was enrolled: noninvasive or invasive mechanical ventilation, vasopressors, acute renal replacement therapy, or extracorporeal membrane oxygenation.

Results of this study build upon the findings of previous, smaller studies that have also demonstrated influenza VE for preventing severe influenza illness. Among 101 adults hospitalized in the ICU at 2 New Zealand hospitals during 3 consecutive influenza seasons, influenza vaccines were 82% effective in preventing ICU admissions [9]. Similarly, a study conducted among children admitted to the pediatric ICU during 2 consecutive influenza seasons in the United States reported an influenza VE of 74% for the prevention of ICU admission when cases were compared with ICU controls and 82% when compared with community controls [34]. Furthermore, VE for the prevention of influenza-associated ICU admission was 81% among 227 US adult patients during the 2015–2016 season [7]. A recent study from Australia using hospital surveillance data for children and adults from 2010 through 2017 and a test-negative design reported 31% effectiveness in preventing influenza-associated mortality [32].

Acknowledging the widespread use of reliable molecular diagnostics for accurate clinical identification of influenza infections, the current study applied a test-negative design that takes advantage of the rapid availability of clinical test results. This approach, referred to as the "real-time test negative design," can be useful to optimize the case-to-test-negative control ratio and increase study efficiency by supervising the number of enrolled controls [21]. Importantly, all study patients needed to satisfy a clear operational definition of compatible disease (ie, SARI) and have an influenza test performed before they could be enrolled [19, 20, 35]. Although the test-negative design is considered the referent approach for determinations of influenza VE, some elements require careful consideration to ensure the validity of the estimates. As factors that may lead to differential healthcare utilization and influenza testing, we specifically accounted for cardiopulmonary and immunosuppressive conditions in our main analysis and prespecified sensitivity analyses [18, 35].

This study had limitations. First, despite this being the largest US study to date evaluating influenza VE in critically ill ICU patients, the modest sample size resulted in limited precision of some results. Second, although the analysis accounted for several confounding factors identified a priori, and our findings were robust in several prespecified secondary and sensitivity analyses, residual confounding is possible. Other factors, such as the prevaccination immunological status of participants, were not directly measured and accounted for. To examine potential residual confounding in the death analysis, we examined the association between vaccination and death among influenza-negative controls. There was no association between vaccination and death among controls, increasing confidence that the observed association between vaccination and lower odds of influenza-associated death was due to vaccine effects and not residual confounding. Third, viral detections were identified from both clinical and research testing and viral loads

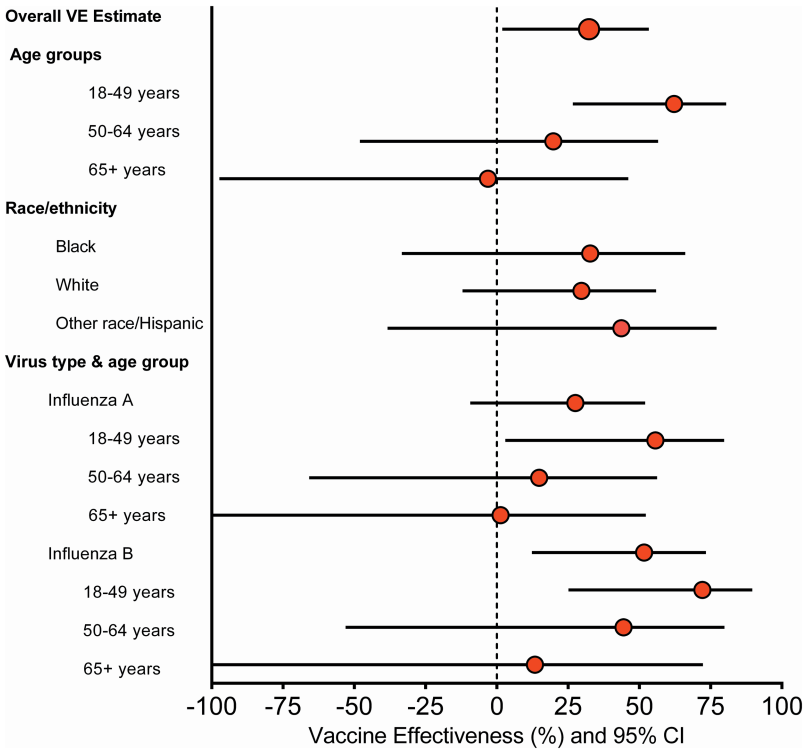

Figure 2. Secondary analyses of influenza VE for the prevention of influenza-associated severe acute respiratory infection. Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

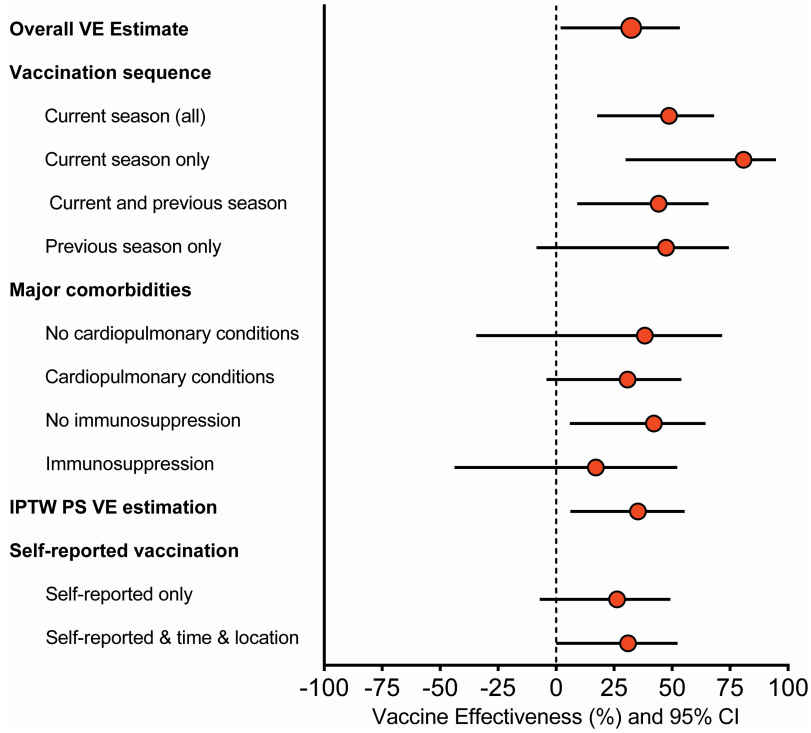

Figure 3. Sensitivity analyses for the assessment of influenza vaccine effectiveness for the prevention of influenza-associated severe acute respiratory infection. These secondary estimates evaluating vaccine sequence were restricted to the subset of patients with verified vaccination for the current and previous season. Note all comparisons used those patients who were not vaccinated in either season as reference. Current season estimates included all participants vaccinated during the current season. Current season only estimates include participants vaccinated during the current season who were not vaccinated during the previous season. Current and previous season estimates include participants who were vaccinated during both seasons. Previous season only estimates include participants who were vaccinated during the previous season; patients vaccinated in the current season were not included in this estimation. Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighting; PS, propensity scores; VE, vaccine effectiveness.

were not evaluated. Fourth, while viral sequencing revealed the circulation of drifted strains, only a fraction of influenza detections were successfully sequenced. Last, although patients were enrolled from 10 locations dispersed across the United States, enrollment occurred at academic medical centers and findings may not be directly applicable to other settings.

In summary, this large, prospective multicenter study demonstrated that during the 2019–2020 influenza season, influenza vaccination was associated with a significant reduction in the risk of hospitalization with severe influenza disease, especially among younger adults. These findings suggest that vaccination decreases the risk of the most severe manifestations of influenza infection.

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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Ethics approval. The conduct of this study was approved by the institutional review board at Vanderbilt University Medical Center, which served as the single institutional review board for the multicenter network.

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