## Title

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BRIEF REPORT

# Effectiveness of mRNA Vaccines Against COVID-19 Hospitalization by Age and Chronic Medical Conditions Burden Among Immunocompetent US Adults, March-August 2021

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Vaccine effectiveness (VE) against COVID-19 hospitalization was evaluated among immunocompetent adults (≥18 years) during March–August 2021 using a case-control design. Among 1669 hospitalized COVID-19 cases (11% fully vaccinated) and 1950 RT-PCR–negative controls (54% fully vaccinated), VE was 96% (95% confidence interval [CI], 93%–98%) among patients with no chronic medical conditions and 83% (95% CI, 76%–88%) among patients with ≥ 3 categories of conditions. VE was similar between those aged 18–64 years versus ≥65 years ($P$ > .05). VE against severe COVID-19 was very high among adults without chronic conditions and lessened with increasing comorbidity burden.

**Keywords.** chronic medical conditions; COVID-19; preexisting conditions; vaccine effectiveness.

Through October 2021, the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in more than 2.3 million hospitalizations and 690 000 deaths in the United States [1]. In December 2020, the US Food and Drug Administration granted emergency use authorization for 2 messenger RNA (mRNA) COVID-19 vaccines, BNT162b2 from Pfizer-BioNTech and mRNA-1273 from Moderna [1].

mRNA COVID-19 vaccines elicit immunity against the SARS-CoV-2 spike protein [2] and have been shown in clinical trials [3, 4] and observational studies [5–7] to be effective in preventing severe COVID-19 requiring hospitalization. Real-world evaluations of vaccine effectiveness (VE) against COVID-19 hospitalization frequently pool multiple age groups and persons with and without preexisting chronic medical conditions. VE estimates by age group and comorbidity burden can complement large pooled VE analyses using heterogenous populations. Identifying the heterogeneity of VE against severe COVID-19 can also potentially inform decisions about targeting preventive measures to populations most likely to benefit from them.

Prior work has identified heterogeneity of VE by immunocompromised state, age, variants, and time since vaccination [5–7], leading to decisions in the United States to provide a third vaccine dose to immunocompromised persons and a booster dose to adults generally [8]. Despite some evidence that mRNA VE could differ by factors such as burden of chronic medical conditions, race/ethnicity, sex, and obesity (body mass index [BMI] ≥ 30 kg/m$^2$) [9], these factors have not often been studied in detail. Therefore, we evaluated the effectiveness of mRNA vaccines against COVID-19 hospitalizations stratified by burden of chronic conditions, age, and other demographics.

## METHODS

The Centers for Disease Control and Prevention (CDC) collaborates with the Influenza and Other Viruses in the Acutely Ill (IVY) Network to monitor effectiveness of COVID-19 vaccines against COVID-19 hospitalization. As previously described [5, 6], we prospectively enrolled adults ≥ 18 years of age at 21 IVY Network hospitals during 11 March to 15 August 2021. We have reported VE during this surveillance period [5, 6], but did not assess VE by burden of chronic conditions or other

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characteristics presented here. Using a case-control design, we assessed mRNA VE against COVID-19 hospitalization by comparing odds of prior vaccination in hospitalized case patients with COVID-19 versus control patients without COVID-19. We restricted analysis to immunocompetent persons because our objective was to inform VE within the general population.

Case or control status was determined by clinical testing results as well as centralized reverse transcription polymerase chain reaction (RT-PCR) testing of upper respiratory samples at Vanderbilt University Medical Center (Nashville, TN). Cases were hospitalized with a COVID-19-like illness (≥1 of fever, cough, shortness of breath, loss of taste or smell, use of respiratory support for the acute illness, pulmonary findings on chest imaging consistent with pneumonia) and had a positive RT-PCR or antigen test for SARS-CoV-2 within 10 days following symptom onset. Two hospitalized control groups that tested negative for SARS-CoV-2 by RT-PCR were enrolled: (1) test-negative controls with COVID-19-like illness and (2) syndrome-negative controls without COVID-19-like illness. The second control group was included due to imperfect diagnostic accuracy of SARS-CoV-2 tests, which could lead to misclassification of cases. Vaccination coverage and VE estimates were highly similar for individual control groups [7], and therefore these groups were combined to improve statistical power. Sites attempted a 1:1 enrollment ratio of cases to controls in each group, with controls admitted within 2 weeks of cases, although individual matching was not performed.

Vaccination status was determined primarily by review of electronic medical records (EMRs), state vaccine registries, provider or pharmacy records, and available CDC vaccination cards, with patient or proxy self-report of vaccination (including known date and location) during enrollment interviews considered as vaccinated in the absence of source documentation. Vaccination status was classified based on vaccine receipt before a reference date, defined as the date of symptom onset for cases and test-negative controls and days prior to admission for syndrome-negative controls. Participants were either unvaccinated or were fully vaccinated if 2 doses of a mRNA vaccine were received ≥ 14 days before the reference date; patients were excluded if they received ≥ 1 vaccine doses but were not fully vaccinated, received a non-mRNA vaccine, or received multiple COVID-19 vaccine products.

Trained personnel obtained information on participants' preexisting chronic medical conditions associated with severe COVID-19 [10] through EMR review [7] using a standardized case report form (Supplementary Table 1). Individual conditions were grouped into 7 categories: cardiovascular, neurologic, pulmonary, gastrointestinal, endocrine, renal, and hematologic. Participants were classified by the number of categories in which conditions were documented (0, 1, 2 or ≥ 3).

Logistic regression models, with COVID-19 case status as the outcome and vaccination status as the predictor, were used to estimate overall VE adjusted for date of admission (biweekly intervals), age (continuous), sex, self-reported race and ethnicity, burden of underlying conditions (0, 1, 2, or ≥ 3 categories), and US Health and Human Services region of the admitting hospital. VE was calculated as: VE = (1 − adjusted odds ratio) × 100.

Interaction terms were introduced into the main VE model to evaluate VE by primary characteristics of interest: age group (18–64 years or ≥ 65 years) and number of chronic medical condition categories (0, 1, 2, or ≥ 3). Additional exploratory models were constructed with interaction terms between vaccination status and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, all other races non-Hispanic, unknown), sex (female or male), and obesity (obese or not obese). To estimate VE by condition category within each age category, an additional regression model was fit to include the 3-way interaction among vaccination status, age group, and conditions category along with each 2-way interaction. Likelihood ratio $\chi^2$ tests were used to estimate whether differences in VE across groups were significant at a threshold of $P < .05$.

Older adults and those with certain chronic medical conditions were targeted for early priority vaccination after mRNA vaccines became available and may be affected more by waning effectiveness than other groups that were vaccinated later, resulting in potentially lower VE. Therefore, we performed a sensitivity analysis that restricted vaccinated patients to those with a reference date within 120 days of their second vaccine dose, a period during which significant waning against severe COVID-19 is not expected [6]. An additional sensitivity analysis was included to explore differences in VE by conditions burden restricted to cases with hypoxemia ($O_2$ saturation < 92% or supplemental oxygen support) within 24 hours of admission to account for the possibility of patients with multimorbidity being more likely to be hospitalized for mild illness (ie, admission bias).

This activity was conducted as a public health surveillance activity, with waiver of informed consent, consistent with applicable federal law and CDC policy, eg, 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.

## RESULTS

After excluding participants who did not meet inclusion criteria, 3619 immunocompetent adults (1669 case patients, 11% fully vaccinated; 1950 control patients, 54% fully vaccinated) were included. Fully vaccinated patients (compared with unvaccinated) were older (median age, 67 vs 53 years), and more likely to report being non-Hispanic white (63% vs 48%), have been hospitalized ≥ 1 time during the past year (48% vs 35%), and have ≥ 1 chronic medical condition (88% vs 69%), including cardiovascular disease (75% vs 52%), endocrine disease including diabetes (44% vs 30%), pulmonary disease (30% vs 22%), and renal disease (21% vs 10%), but were less commonly obese (45% vs 53%) (Table 1). A similar proportion of cases

**Table 1. Characteristics of Participants by Cases (Hospitalized With COVID-19) vs Control (Hospitalized Without COVID-19) Status and by COVID-19 Vaccination Status—21 Hospitals[a] in 18 US States, March–August 2021**

| Characteristic[b] | Case Patients (n = 1669) | Control Patients (n = 1950) | Unvaccinated Participants (n = 2379) | Vaccinated[c] Participants (n = 1240) |
|---|---|---|---|---|
| COVID-19 case | 1669 (100.0) | 0 (0.0) | 1481 (62.3) | 188 (15.2) |
| Fully vaccinated | 188 (11.3) | 1052 (53.9) | 0 (0.0) | 1240 (100.0) |
| Hypoxemia[d] | 1239/1662 (74.5) | 617/1049 (58.8) | 1398/1980 (70.6) | 458/731 (62.7) |
| Admitted to ICU | 970/1645 (59.0) | 823/1930 (42.6) | 1246/2345 (53.1) | 547/1230 (44.5) |
| Median age, y (IQR) | 54 (41–66) | 62 (47–72) | 53 (40–64) | 67 (57–76) |
| Age group, ≥65 y | 462 (27.7) | 845 (43.3) | 580 (24.4) | 727 (58.6) |
| Sex, female | 815 (48.8) | 931 (47.7) | 1133 (47.6) | 613 (49.4) |
| Race/ethnicity[e] | | | | |
| White, non-Hispanic | 733 (43.9) | 1188 (60.9) | 1135 (47.7) | 786 (63.4) |
| Black, non-Hispanic | 427 (25.6) | 425 (21.8) | 624 (26.2) | 228 (18.4) |
| Any race, Hispanic | 391 (23.4) | 242 (12.4) | 468 (19.7) | 165 (13.3) |
| All other races, non-Hispanic | 82 (4.9) | 76 (3.9) | 108 (4.5) | 50 (4.0) |
| Unknown | 36 (2.2) | 19 (1.0) | 44 (1.8) | 11 (0.9) |
| US census region[f] | | | | |
| Northeast | 245 (14.7) | 291 (14.9) | 343 (14.4) | 193 (15.6) |
| South | 737 (44.2) | 761 (39.0) | 1035 (43.5) | 463 (37.3) |
| Midwest | 305 (18.3) | 505 (25.9) | 489 (20.6) | 321 (25.9) |
| West | 382 (22.9) | 393 (20.2) | 512 (21.5) | 263 (21.2) |
| Residence in long-term care facility[g] | 34/1602 (2.1) | 118/1861 (6.3) | 54/2276 (2.4) | 98/1187 (8.3) |
| Has health insurance | 1473/1668 (88.3) | 1807/1950 (92.7) | 2074/2379 (87.2) | 1206/1239 (97.3) |
| Employed | 611/1300 (47.0) | 480/1651 (29.1) | 794/1885 (42.1) | 297/1066 (27.9) |
| Health care worker | 83/1300 (6.4) | 92/1651 (5.6) | 108/1885 (5.7) | 67/1066 (6.3) |
| Attended some college or more | 557/1147 (48.6) | 758/1494 (50.7) | 740/1673 (44.2) | 575/968 (59.4) |
| ≥1 hospital admission in past year | 371/1506 (24.6) | 955/1831 (52.2) | 764/2172 (35.2) | 562/1165 (48.2) |
| Self-reported prior laboratory-confirmed SARS-CoV-2 infection | 51 (3.1) | 163 (8.4) | 136 (5.7) | 78 (6.3) |
| No. of categories of underlying medical conditions[h] | | | | |
| 0 | 546 (32.7) | 332 (17.0) | 727 (30.6) | 151 (12.2) |
| 1 | 489 (29.3) | 498 (25.5) | 686 (28.8) | 301 (24.3) |
| 2 | 365 (21.9) | 540 (27.7) | 532 (22.4) | 373 (30.1) |
| ≥3 | 269 (16.1) | 580 (29.7) | 434 (18.2) | 415/1240 (33.5) |
| Specific underlying medical conditions | | | | |
| Cardiovascular disease | 848 (50.8) | 1307 (67.0) | 1224 (51.5) | 931 (75.1) |
| Hypertension | 774 (46.4) | 1141 (58.5) | 1098 (46.2) | 817 (65.9) |
| Endocrine disease (including diabetes) | 500 (30.0) | 757 (38.8) | 715 (30.1) | 542 (43.7) |
| Diabetes | 435 (26.1) | 638 (32.7) | 620 (26.1) | 453 (36.5) |
| Pulmonary disease | 332 (19.9) | 565 (29.0) | 524 (22.0) | 373 (30.1) |
| COPD | 117 (7.0) | 293 (15.0) | 210 (8.8) | 200 (16.1) |
| Renal disease | 154 (9.2) | 342 (17.5) | 236 (9.9) | 260 (21.0) |
| Hematologic disease | 114 (6.8) | 244 (12.5) | 209 (8.8) | 149 (12.0) |
| Neurological disease | 127 (7.6) | 217 (11.1) | 193 (8.1) | 151 (12.2) |

**Table 1. Continued**

| Characteristic[b] | Case Patients (n = 1669) | Control Patients (n = 1950) | Unvaccinated Participants (n = 2379) | Vaccinated[c] Participants (n = 1240) |
|---|---|---|---|---|
| Gastrointestinal disease | 52 (3.1) | 139 (7.1) | 114 (4.8) | 77 (6.2) |
| BMI-based obesity (≥30 kg/m$^2$) | 970/1645 (59.0) | 823/1930 (42.6) | 1246/2345 (53.1) | 547/1230 (44.5) |

Data are No./total No. (%) except where indicated.

Abbreviations: BMI, body-mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Hospitals by region were Northeast: Baystate Medical Center (Springfield, MA), Beth Israel Deaconess Medical Center (Boston, MA), Montefiore Medical Center (Bronx, NY); South: Vanderbilt University Medical Center (Nashville, TN), University of Miami Medical Center (Miami, FL), Emory University Medical Center (Atlanta, GA), Johns Hopkins Hospital (Baltimore, MD), Wake Forest University Baptist Medical Center (Winston-Salem, NC), Baylor Scott and White Health (Temple, TX); Midwest: University of Iowa Hospitals and Clinics (Iowa City, IA), University of Michigan Hospital (Ann Arbor, MI), Hennepin County Medical Center (Minneapolis, MN), Barnes-Jewish Hospital (St Louis, MO), Cleveland Clinic (Cleveland, OH), Ohio State University Wexner Medical Center (Columbus, OH); West: Stanford University Medical Center (Stanford, CA), UCLA Medical Center (Los Angeles, CA), UCHealth University of Colorado Hospital (Aurora, CO), Oregon Health and Science University Hospital (Portland, OR), Intermountain Medical Center (Murray, UT), University of Washington (Seattle, WA).

[b]Data are not complete for all characteristics in the table; denominators are included in the table for characteristics in which data is missing.

[c]Fully vaccinated with mRNA COVID-19 vaccines defined as ≥ 14 days from dose 2.

[d]Hypoxemia defined as needing $O_2$ support or having blood $O_2$ levels below 92% within first 24 hours of admission. Information to assess hypoxemia was collected for case patients and test-negative controls but not for patients in the syndrome-negative control group.

[e]Racial and ethnic groups were reported by the patient or proxy.

[f]Northeast: Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; Midwest: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin; South: Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia; West: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming.

[g]Long-term care facility included reporting living in a nursing home, assisted living home, or rehabilitation hospital, or other subacute or chronic facility before the hospital admission.

[h]Chronic medical conditions were obtained through medical chart review by trained personnel and classified by condition category specified in the table; a full list of conditions is included in Supplementary Table 1.

met our definition of hypoxemia across underlying condition categories (77%, 73%, 77%, and 71% for 0, 1, 2, and ≥ 3 condition categories, respectively).

VE differed by number of condition categories in a gradient, from persons with 0 categories of conditions (VE, 96%; 95% CI, 93%–98%) to persons with ≥ 3 (VE, 83%; 95% CI, 76%–88%; $P < .001$) (Figure 1); results were similar when restricted to hypoxemic cases (Supplementary Figure 1). VE was not statistically different for patients aged ≥ 65 years compared with patients aged 18–64 years (VE, 88% [95% CI, 84%–91%] vs 91% [95% CI, 88%–93%]; $P = .142$). The relationship between VE and number of chronic medical condition categories did not vary by age group ($P = .903$).

Exploratory analyses showed that VE differed by sex (male, 88% [95% CI, 84%–91%] vs female, 92% [95% CI, 89%–94%]; $P = .037$) but not across race/ethnicity groups ($P = .415$) or by obesity status (obese, 91% [95% CI, 89%–94%] vs not obese, 88% [95% CI, 85%–91%]; $P = .105$; Supplementary Table 2). Results were similar in a sensitivity analysis limiting the analytical population to patients with illness onset within 120 days of full vaccination.

## DISCUSSION

This analysis suggests COVID-19 mRNA vaccines are highly effective for preventing COVID-19 hospitalizations for heterogeneous immunocompetent adults, with some decline in VE with increasing burden of chronic medical conditions. VE was very high (96%), including among adults ≥ 65 years old (95%), among people without conditions, which make up half the US population [11]. In addition, adults aged 18–64 years have accounted for the majority of cumulative US COVID-19 hospitalizations, with hospitalization rates among the unvaccinated > 10 times those of the fully vaccinated [1]; they also tend to have lower vaccination coverage [12] and fewer conditions and compared with adults aged ≥ 65 years. As efforts continue to increase vaccination coverage in the United States, these data suggest that vaccinating younger persons without chronic medical conditions will substantially reduce COVID-19 hospitalizations.

Our findings also suggest that VE against COVID-19–associated hospitalization decreases roughly proportionally to the number of chronic medical conditions, both overall and stratified by age. The conditions included in our analysis align closely with those identified as risk factors for severe COVID-19 in the prevaccination era [10], suggesting that the same chronic conditions placing a person at high risk for severe COVID-19 are also associated with COVID-19 hospitalization among vaccinated persons. Prior studies have suggested that antibody response and immune protection after vaccination could be attenuated for persons with severe chronic medical conditions, including both immunocompromising conditions [13]

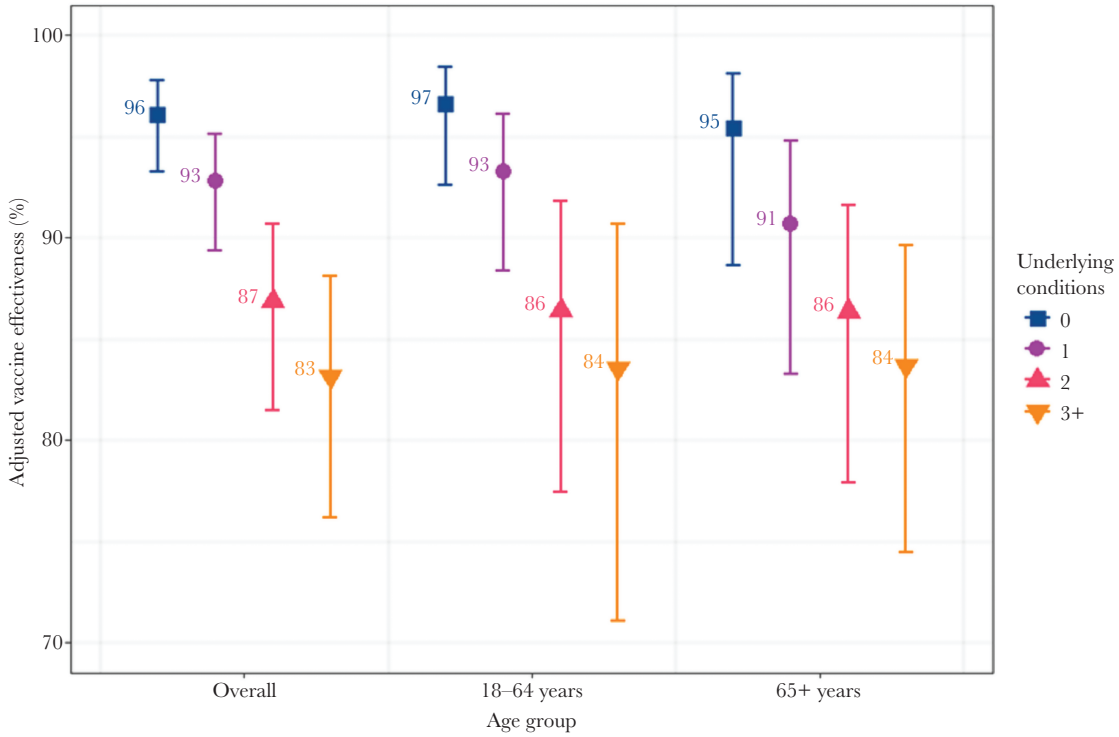


**Figure 1.** Vaccine effectiveness by age group and number of chronic medical conditions. Adjusted vaccine effectiveness (VE) was estimated using logistic regression comparing odds of being fully vaccinated with an mRNA COVID-19 vaccine versus being unvaccinated, in case patients and control patients, using the equation VE = 100 × (1 – odds ratio). Overall VE by number of condition categories documented (0, 1, 2, or ≥ 3) was calculated by including an interaction term between vaccination status and number of condition categories. An additional model including a 3-way interaction between age, conditions, and vaccination status was included to calculate VE by number of condition categories within age groups. Models were additionally adjusted for date of hospital admission (biweekly intervals), US Department of Health and Human Services region of hospital, age (continuous), sex, and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic of any race, non-Hispanic other, or unknown), and number of condition categories. VE point estimates are rounded to the nearest whole number. Error bars represent 95% confidence intervals.

and nonimmunocompromising conditions [14]; however, few show clear associations with lower VE. Our analysis shows that mRNA VE against severe disease is also lessened by chronic medical conditions among immunocompetent adults, independent of age. Booster vaccines for recipients of COVID-19 vaccines are now recommended for persons aged ≥ 18 years [15]. Our findings suggests that persons with a higher burden of chronic medical conditions may experience greater incremental benefit from additional vaccine doses.

Finally, our findings may have implications for interpretation of data from observational COVID-19 VE studies. Our finding of 96% VE against COVID-19 hospitalizations for healthy adults (ie, immunocompetent patients with no preexisting conditions) was similar to VE against severe disease observed in mRNA COVID-19 vaccine clinical trials [3, 4]. This similarity suggests that efficacy estimates from phase 3 COVID-19 clinical trials successfully approximated real-world VE for people without chronic medical conditions but overestimated effectiveness for people with chronic medical comorbidities.

Our findings are subject to some limitations. Enrolling sites were academic medical centers and may have inpatient populations with a higher burden of chronic diseases than community hospitals. While the number of categories of chronic conditions was considered, the severity of conditions within each category was not; for example, hypertension and severe heart failure were both quantified as 1 cardiovascular condition. We had incomplete capture of data for a few variables, such as height and weight used to determine BMI-based obesity (captured for 99% of patients). However, missing information was minimal and unlikely to bias VE estimates. Furthermore, persons with more chronic medical conditions may be more likely to be hospitalized even with milder COVID-19 illness, resulting in lower VE; however, VE was similar restricting analysis to cases with hypoxemia who would have an indication for admission. Multiple comparisons were made in this analysis, with the possibility of type I or type II error.

In conclusion, this analysis provides insight into the heterogeneity of VE by overall health status, beyond immunocompetency alone. Vaccination reduced the risk of COVID-19 hospitalization by > 95% in healthy adults without chronic medical conditions regardless of age, sex, obesity, or race/ethnicity. Continued efforts to vaccinate US adults, aided by the evaluation and reporting of VE for specific subpopulations, will likely have a marked impact on severe COVID-19.

## 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

***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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