Effectiveness of SARS-CoV-2 mRNA Vaccines for Preventing Covid-19 Hospitalizations in the United States

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For the Influenza and Other Viruses in the Acutely Ill (IVY) Network**

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Summary: From March–May 2021, full vaccination using authorized mRNA products was associated with 87.1% (95% CI: 80.7 to 91.3%) protection against Covid-19 hospitalization among US adults. Vaccine effectiveness was lower in adults with versus without immunosuppression (62.9% versus 91.3%).

ABSTRACT

Background: As SARS-CoV-2 vaccination coverage increases in the United States (US), there is a need to understand the real-world effectiveness against severe Covid-19 and among people at increased risk for poor outcomes.

Methods: In a multicenter case-control analysis of US adults hospitalized March 11-May 5, 2021, we evaluated vaccine effectiveness to prevent Covid-19 hospitalizations by comparing odds of prior vaccination with an mRNA vaccine (Pfizer-BioNTech or Moderna) between cases hospitalized with Covid-19 and hospital-based controls who tested negative for SARS-CoV-2.

Results: Among 1212 participants, including 593 cases and 619 controls, median age was 58 years, 22.8% were Black, 13.9% were Hispanic, and 21.0% had immunosuppression. SARS-CoV-2 lineage B.1.1.7 (Alpha) was the most common variant (67.9% of viruses with lineage determined). Full vaccination (receipt of two vaccine doses ≥14 days before illness onset) had been received by 8.2% of cases and 36.4% of controls. Overall vaccine effectiveness was 87.1% (95% CI: 80.7 to 91.3%). Vaccine effectiveness was similar for Pfizer-BioNTech and Moderna vaccines, and highest in adults aged 18-49 years (97.4%; 95% CI: 79.3 to 99.7%). Among 45 patients with vaccine-breakthrough Covid hospitalizations, 44 (97.8%) were ≥50 years old and 20 (44.4%) had immunosuppression. Vaccine effectiveness was lower among patients with immunosuppression (62.9%; 95% CI: 20.8 to 82.6%) than without immunosuppression (91.3%; 95% CI: 85.6 to 94.8%).

Conclusion: During March–May 2021, SARS-CoV-2 mRNA vaccines were highly effective for preventing Covid-19 hospitalizations among US adults. SARS-CoV-2 vaccination was beneficial for patients with immunosuppression, but effectiveness was lower in the immunosuppressed population.

Key Words:
COVID-19; vaccine effectiveness; mRNA vaccines; hospitalized; immunocompromised.

INTRODUCTION

Over 2.3 million hospitalizations and 600,000 deaths related to coronavirus disease 2019 (Covid-19) occurred in the United States (US) through July 2021.[1] In December 2020, the Food and Drug Administration granted Emergency Use Authorization (EUA) for two messenger RNA (mRNA) vaccines (from Pfizer-BioNTech and Moderna) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] Widespread public health initiatives resulted in over 65% of the US adult population receiving at least one dose of a SARS-CoV-2 vaccine by the end of July 2021.[1] Among those vaccinated, the mRNA vaccines have been the predominate (>95%) SARS-CoV-2 vaccine products used in the US.[1]

Phase 3 clinical trials of mRNA vaccines found a 94–95% reduction in Covid-19 illness and near 100% protection against severe Covid-19.[3, 4] However, these clinical trials had few cases of hospitalized Covid-19, and limited power to assess efficacy among persons with underlying illnesses who are at high risk for severe Covid-19. Observational vaccine effectiveness evaluations are important to understand how well the vaccines protect against Covid-19 in real-world settings across diverse populations, including immunocompromised hosts. The Centers for Disease Control and Prevention (CDC) collaborates with the Influenza and Other Viruses in the Acutely Ill (IVY) Network to monitor the effectiveness of SARS-CoV-2 vaccines for the prevention of Covid-19 hospitalizations among US adults. In this analysis, we evaluated the effectiveness of SARS-CoV-2 mRNA vaccines for preventing Covid-19 hospitalizations by vaccine product, by age group, and by underlying medical conditions.[5]

METHODS

Design

We conducted a prospective observational case-control evaluation of vaccine effectiveness by comparing the odds of antecedent SARS-CoV-2 vaccination in hospitalized case-patients with Covid-19 versus control-patients without Covid-19. We included two control groups: 1) "test-negative" controls were hospitalized with signs or symptoms of an acute respiratory illness but tested negative for SARS-CoV-2; and 2) "syndrome-negative" controls were hospitalized without signs or symptoms of an acute respiratory illness and tested negative for SARS-CoV-2. Test-negative controls are commonly used in hospital-based vaccine effectiveness evaluations;[6-9] in the test-negative design, utilizing a comparison group with the same clinical syndrome and similar level of acuity as cases reduces bias due to differential healthcare seeking behavior. Because of the potential for misclassification of true cases as test-negative controls due to false-negative tests, particularly for those presenting late in the course of illness, we included the second control group of hospitalized patients without an acute respiratory illness. [10][11]

Setting

This surveillance activity included patients hospitalized from March 11 through May 5, 2021 at 18 US hospitals within the IVY Network.[6, 12] This activity was conducted consistent with applicable federal law and CDC policy (Supplementary Appendix B).

Participants

Sites screened hospitalized adults ≥18 years old for potential eligibility through daily review of hospital admission logs and electronic medical records. Detailed eligibility criteria are shown in Supplementary Appendix B. Covid-19 cases included patients hospitalized with a clinical syndrome consistent with acute Covid-19 (≥1 of the following: fever; cough; shortness of breath; loss of taste; loss of smell; use of respiratory support for the acute illness; or new pulmonary findings on chest

imaging consistent with pneumonia) and a positive test for SARS-CoV-2 within 10 days following symptom onset.[13-15] Test-negative controls were hospitalized with a clinical syndrome consistent with acute Covid-19 and tested negative for SARS-CoV-2. Syndrome-negative controls were hospitalized without a clinical syndrome consistent with Covid-19 and tested negative for SARS-CoV-2. Individual matching between cases and controls was not performed. Sites attempted to capture all cases admitted to the hospital during the surveillance period and targeted a case: control ratio of approximately 1:1. Information on vaccination status was not collected until after patients were included.

Data Collection

Participants (or their proxies) were interviewed by trained personnel to collect data on demographics, medical conditions, SARS-CoV-2 vaccination, and other patient characteristics. Additional information on underlying medical conditions and SARS-CoV-2 clinical testing was obtained through standardized medical record review.

Laboratory Analysis

Upper respiratory specimens (nasal swabs or saliva) were collected, frozen, and shipped to a central laboratory at Vanderbilt University Medical Center (Nashville, Tennessee). Specimens underwent reverse transcription polymerase chain reaction (RT-PCR) testing for the SARS-CoV-2 nucleocapsid gene using standardized methods and interpretive criteria.[16] Specimens positive for SARS-CoV-2 with a cycle threshold <32 were shipped to the University of Michigan (Ann Arbor, Michigan) for viral whole genome sequencing using the ARTIC Network version 3 protocol on an Oxford Nanopore Technologies instrument (Supplementary Appendix B).[17] SARS-CoV-2 lineages were assigned with >80% coverage using Pangolin genomes.[18]

Classification of Case-Control Status

Final classification of case-control status was determined with consideration of both clinical SARS-CoV-2 testing completed at local hospital laboratories and RT-PCR testing completed at the central laboratory. Cases tested positive for SARS-CoV-2 by a clinical test or central laboratory RT-PCR test. Cases with SARS-CoV-2 detected by RT-PCR with a cycle threshold >32 were included in the analysis, but viral sequencing information was not available for these cases. Test-negative and syndrome negative controls tested negative for SARS-CoV-2 by all clinical and central laboratory testing.

Classification of Vaccination Status

Details of SARS-CoV-2 vaccination, including dates and location of vaccination, vaccine product, and lot number, were ascertained through a systematic process including patient or proxy interview and source verification. Sources of documentation included vaccination card, hospital records, state vaccine registries which were searched at the time of interview and again approximately 28 days later, and vaccine records requested from clinics and pharmacies. Vaccine doses were classified as administered if source documentation was identified or if the patient/proxy reported a vaccine dose with a plausible date and location of vaccination.

The SARS-CoV-2 mRNA vaccines are administered as a two-dose series; participants were considered fully vaccinated 14 days after receipt of the second vaccine dose.[19] Vaccination status was classified based on the number of mRNA vaccine doses received before a reference date, which was the date of symptom onset for cases and test-negative controls and date of hospital admission for syndrome-negative controls. Participants were classified as: unvaccinated if they had received no vaccine doses prior to the reference date; partially vaccinated if they received one dose ≥14 days before the reference date; and fully vaccinated if they received both doses ≥14 days before the reference date. As protective immunity from SARS-CoV-2 vaccines is not expected immediately after the first dose,[12] patients who received a first dose <14 days before the reference date were

excluded from the analysis. Patients who received a SARS-CoV-2 vaccine that had not been authorized in the US were excluded. Due to recent introduction of the Janssen (Johnson & Johnson) SARS-CoV-2 vaccine following its EUA in February 2021,[2] patients who received this vaccine were also excluded.

Statistical Analysis

Vaccine effectiveness and 95% confidence intervals (95% CI) were determined by comparing the odds of prior SARS-CoV-2 vaccination in case-patients and control-patients, calculated as: vaccine effectiveness = (1 – odds ratio) × 100%.[20]

Primary vaccine effectiveness estimates were calculated in adults of all ages for full vaccination versus unvaccinated and for partial vaccination versus unvaccinated. Unadjusted odds ratios were calculated with simple logistic regression and then a model building approach was applied to estimate adjusted vaccine effectiveness accounting for potential confounders. Prespecified covariates in base multivariable logistic regression models included calendar time in biweekly intervals, US Department of Health and Human Services region, age, sex, and self-reported race and Hispanic ethnicity. We repeated the regression by adding health status indicators (such as number of chronic conditions and prior hospitalizations in the past year) and SARS-CoV-2 exposure variables (such as mask use and attending large gatherings) potentially associated with the likelihood of vaccination and risk of Covid-19 hospitalization (detailed in Supplementary Appendix B). An absolute change in the odds ratio of vaccination of more than 5% in either direction was used as a pre-specified cutoff for inclusion of additional variables to the base model. Potential effect modification of prior SARS-CoV-2 infection (at least 14 days prior to the current illness) was assessed using a likelihood ratio test (with a P-value <0.15 suggestive of effect modification).[21]

Separate assessments were initially performed using the test-negative control and the syndrome-negative control groups to assess comparability of estimates. Effectiveness estimates

were very similar using the test-negative and syndrome-negative control groups. Therefore, control groups were combined to improve precision.

Vaccine effectiveness estimates were stratified by age group (18–49, 50–64, or ≥65 years), SARS-CoV-2 vaccine product (Pfizer-BioNTech or Moderna), SARS-CoV-2 variant, and underlying medical conditions with a prevalence ≥20% in the population, including immunocompromising conditions[6], diabetes mellitus, chronic lung disease, chronic cardiovascular disease, and obesity (definitions provided in Supplementary Appendix B). Sensitivity analyses are described in Supplementary Appendix B. Stata Version 16 (College Station, TX) and SAS 9.4 (Cary, NC) were used for statistical analysis.

RESULTS

Participants

We included 1212 patients (593 cases, 334 test-negative controls, and 285 syndrome-negative controls) (Figure S1) enrolled from 18 clinical sites (Figure 1) over the course of 51 days (Figure S2). Overall, median age was 58 years, 276 (22.8%) were non-Hispanic Black, 168 (13.9%) were Hispanic, and 254 (21.0%) had an immunocompromising condition (Table 1, Table S1). Among the 593 case patients, 32.2% were admitted to an intensive care unit (ICU) and 8.3% died during the hospitalization.

After excluding 75 patients with a first vaccine dose 0-13 days before the reference date, full SARS-CoV-2 vaccination had been received by 45 (8.2%) cases, 115 (36.7%) test-negative controls, and 100 (36.0%) syndrome-negative controls (Figure 2); 456 (83.5%) cases were unvaccinated. Among fully vaccinated patients, median time between the last vaccine dose and onset of Covid-like symptoms was 44 days (interquartile range [IQR] 25 to 54 days) for cases and 42 days (IQR 27 to 60 days) for test-negative controls. Among fully vaccinated patients, 251 (96.5%) had source verification

of vaccine doses. SARS-CoV-2 whole genome sequencing with lineage determination was available for 234 cases, with variant of concern B.1.1.7 (Alpha) the most common lineage (159/234, 67.9%) (Table 2).

Vaccine effectiveness

The base vaccine effectiveness model was used as additional variables that were considered did not change the odds ratio of vaccination by the pre-specified cutoff of more than 5%. Vaccine effectiveness results for full vaccination were very similar using the test-negative control group (86.6%, 95% CI: 79.0–91.4%) and syndrome-negative control group (87.0%, 95% CI: 79.0–91.9%) (Figure S3 and Figure S4). Thus, we combined the test negative and syndrome negative control groups. After combining control groups and comparing fully vaccinated versus unvaccinated status, 45/501 (9.0%) cases and 215/488 (44.1%) controls were fully vaccinated; SARS-CoV-2 vaccine effectiveness for full vaccination to prevent Covid-19 hospitalizations was 87.1% (95% CI: 80.7–91.3%) (Figure 3). Vaccine effectiveness for full vaccination was similar for Pfizer-BioNTech (84.4%, 95% CI: 74.9–90.4%) and Moderna (90.1%, 95% CI: 82.3–94.5) vaccines. Point estimates were higher for people aged 18–49 years (97.4%, 95% CI: 79.3–99.7%) than aged 50–64 years (75.2%, 95% CI: 48.3–88.1%) and aged ≥65 years (87.3%, 95% CI: 77.8–92.7%). Among adults aged ≥65 years, vaccine effectiveness was similar in those 65-74 years (88.3%, 95% CI: 74.8–94.5%) and ≥75 years (90.5%, 95% CI: 73.2–96.7%). Vaccine effectiveness against SARS-CoV-2 B.1.1.7 (Alpha) lineage was 92.4% (95% CI: 83.6–96.5%).

Vaccine effectiveness was significantly reduced for patients with immunocompromising conditions (62.9%, 95% CI: 20.8–82.6%) compared to individuals without an immunocompromising condition (91.3%, 95% CI: 85.6-94.8%) (Figure 3). Restricted to immunocompromised patients with an active solid organ or hematologic malignancy or solid organ transplant, vaccine effectiveness was 51.2% (95% CI: -30.7–81.8%). Vaccine effectiveness point estimates were lower for patients with underlying cardiovascular disease (83.0%, 95% CI: 72.6–89.4%), chronic lung disease (82.1%, 95% CI:

60.3–91.9%), and diabetes mellitus (82.5%, 95% CI: 66.4–90.9%) compared to patients without these underlying conditions but 95% confidence limits overlapped.

Partial vaccination had a vaccine effectiveness of 76.1% (95% CI: 64.0–84.2%). Evidence of effect modification by prior laboratory-confirmed SARS-CoV-2 infection was not observed (likelihood ratio test p-value = 0.59). Sensitivity analyses produced results similar to the primary analysis (Table S2).

Breakthrough vaccine Covid-19 hospitalizations

Forty-five Covid-19 case patients were fully vaccinated before symptom onset (Table S3). Among these, median age was 68 years (IQR 62–77 years), median time between the final vaccine dose and symptom onset was 44 days (IQR: 25 to 54 days), and 20 (44.4%) had an immunocompromising condition, including active solid organ or hematologic malignancy (n=9), or prior solid organ transplant (n=7). Of vaccine breakthrough cases with SARS-CoV-2 lineage determined, 9/20 (45.0%) had B.1.1.7 (Alpha) variant viruses. Admission to an ICU occurred in 9/45 (20.0%) breakthrough cases versus 153/455 (33.6%) unvaccinated cases (p=0.06); in-hospital death occurred in 2/45 (4.4%) breakthrough cases versus 42/455 (9.2%) unvaccinated cases (p=0.28).

DISCUSSION

In this prospective observational surveillance program conducted at 18 geographically dispersed sites in the US during the early phase of the SARS-CoV-2 vaccination program, the two mRNA vaccines authorized for use in the US were approximately 87% effective for preventing Covid-19 hospitalizations, with similar effectiveness observed for the Pfizer BioNTech and Moderna products. This analysis adds to early real-world evaluations that demonstrated high vaccine effectiveness against Covid-19 in groups prioritized for early vaccination, such as healthcare workers.[22, 23]

These results also add to a limited body of evidence that the SARS-CoV-2 mRNA vaccines are highly effective for preventing Covid-19 hospitalizations.

These results expand upon findings of high efficacy for SARS-CoV-2 mRNA vaccines reported from phase 3 clinical trials.[3, 4] The trials included patient populations healthier at baseline than those commonly hospitalized with Covid-19 and were not powered to evaluate the protective benefits of vaccination for preventing severe outcomes, such as hospitalization. The design of this surveillance analysis with concurrent inclusion of patients hospitalized with Covid-19 and two separate control groups enabled a robust evaluation of vaccine effectiveness for the prevention of severe Covid-19, including among patients with multiple and serious medical comorbidities. Vaccination coverage in the two control groups was very similar to one another and to vaccine uptake in the US during the surveillance period for this analysis,[1] adding confidence to our vaccine effectiveness results. The findings of high vaccine effectiveness in the US adult population and across subgroups defined by age, demographics, and comorbidities suggest that the mRNA vaccines are broadly effective for the prevention of severe Covid-19, including in populations at high risk of severe illness.

The protective benefits of any vaccination require an immune response to the vaccine. A history of solid organ transplant and other immunocompromising conditions have been associated with reduced cell-mediated and humoral immune responses to SARS-CoV-2 vaccines.[24, 25] Our results suggested substantial clinical benefit from vaccination in immunosuppressed people, with a vaccine effectiveness of about 60% for the prevention of Covid-19 hospitalizations in this population. However, vaccine effectiveness was significantly lower in patients with immunocompromising conditions compared to those without immunocompromising conditions. Among patients with vaccine breakthrough Covid-19 hospitalizations in this analysis, almost one-half had an immunocompromising condition, most commonly a history of solid organ transplantation or an actively treated malignancy. Immunosuppressive conditions affect millions of adults in the United

States.[26] This highlights the need for continued focus on prompt diagnosis and treatment of Covid-19 in the immunocompromised population, even among those who have been vaccinated. Future work is needed to understand vaccine effectiveness among people with specific immunocompromising conditions and the durability of protection in this population.

During implementation of the national SARS-CoV-2 vaccination program in Israel between December 2020 and February 2021, the Pfizer BioNTech vaccine product demonstrated 87% vaccine effectiveness for the prevention of Covid-19 hospitalizations with a mean follow-up of 15 days.[27] Results of our US analysis in a population with a higher burden of comorbidities demonstrated similar vaccine effectiveness for both the Pfizer BioNTech and Moderna mRNA vaccines with longer follow-up time (median 43 days and maximum 113 days). Evaluating the duration of protection from SARS-CoV-2 vaccines will require additional evaluation with longer follow-up time.

This analysis had certain limitations. While we included control groups that were likely to reduce bias from differential healthcare seeking behavior, there was potential for residual confounding. People who chose to be vaccinated may have been more likely to engage in other behaviors to reduce their risk for Covid-19, such as mask use and avoiding large crowds. However, adjusting for self-reported variables on non-vaccine preventive measures did not substantively change vaccine effectiveness estimates suggesting this was not a major confounder. Race and Hispanic ethnicity differed between case and control groups; this likely represented underlying differences in the incidence of SARS-CoV-2 infection by race and ethnicity in the US and models were adjusted for race and ethnicity.[28] Different immunocompromising conditions are likely associated with varying severity of immunosuppression; more severe immunosuppression may be associated with lower vaccine effectiveness, but this analysis was not powered to look at vaccine effectiveness among subgroups of immunocompromising conditions. In an effort to capture all COVID-19 cases admitted to participating hospitals during a period of high community transmission, enrollment of cases and controls was not matched on a day-to-day basis; however, all cases and controls were

enrolled within a 51-day period and vaccine effectiveness models were adjusted for calendar time. As hospitalized adults frequently had multiple chronic medical conditions that may impact effectiveness of vaccines, findings from this analysis may not be broadly generalizable to populations with lower burden of chronic medical conditions. Lastly, most sequenced viruses in this analysis were B.1.1.7 (Alpha) variants, which represented the majority of circulating viruses in the US during this time period;[1] vaccine effectiveness against other emerging variants will require additional study.

In conclusion, the SARS-CoV-2 mRNA vaccines were highly effective for preventing Covid-19 hospitalizations among US adults in March through May 2021. Widespread vaccination can be expected to have a major beneficial impact on Covid-19 hospitalizations and associated outcomes, such as death and post-Covid complications.[29, 30] Continued efforts are needed to address vaccine hesitancy and access and improve population coverage. While SARS-CoV-2 mRNA vaccines appear to provide substantial benefit to immunocompromised people, effectiveness is lower in this population than in the immunocompetent population. It will be crucial to understand the benefit of additional preventive measures, such as vaccine boosters and continued masking, in patients at highest risk for vaccine breakthrough.

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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TABLES

Table 1. Characteristics of hospitalized Covid-19 case and control patients — IVY Network, United States, March–May 2021.

Characteristic	**Covid-19 Cases (N = 593)**	**Combined Test-negative and Syndrome-negative Controls (N = 619)**	**Test-negative Controls (N = 334)**	**Syndrome-negative Controls (N = 285)**
Median age (IQR*) – years	56 (44 – 65)	61 (47 – 70)	62 (48 – 71)	59 (47 – 70)
Age category – no./total no. (%)				
18-49 years	213/593 (35.9)	177/619 (28.6)	90/334 (27.0)	87/285 (30.5)
50-64 years	221/593 (37.3)	185/619 (29.9)	99/334 (29.6)	86/285 (30.2)
≥65 years	159/593 (26.8)	257/619 (41.5)	145/334 (43.4)	112/285 (39.3)
Female sex – no./total no. (%)	283/593 (47.7)	314/619 (50.7)	166/334 (49.7)	148/285 (51.9)
Race/ethnicity – no./total no. (%)†				
Non-Hispanic White	275/593 (46.4)	414/619 (66.9)	204/334 (61.1)	210/285 (73.7)
Non-Hispanic Black	150/593 (25.3)	126/619 (20.4)	80/334 (24.0)	46/285 (16.1)
Hispanic, any race	110/593 (18.6)	58/619 (9.4)	37/334 (11.1)	21/285 (7.4)
Non-Hispanic, all other races	48/593 (8.1)	19/619 (3.1)	12/334 (3.6)	7/285 (2.5)
Unknown	10/593 (1.7)	2/619 (0.3)	1/334 (0.3)	1/285 (0.4)
U.S. Census region – no./total no. (%)				
East	105/593 (17.7)	114/619 (18.4)	63/334 (18.9)	51/285 (17.9)
South	196/593 (33.1)	235/619 (38.0)	121/334 (36.2)	114/285 (40.0)
Midwest	141/593 (23.8)	174/619 (28.1)	86/334 (25.8)	88/285 (30.9)
West	151/593 (25.5)	96/619 (15.5)	64/334 (19.2)	32/285 (11.2)

Residence in long-term care facility – no./total no. (%) ‡	12/588 (2.0)	42/613 (6.9)	22/330 (6.7)	20/283 (7.1)
Health insurance – no./total no. (%)	544/593 (91.7)	597/619 (96.5)	322/334 (96.4)	275/285 (96.5)
Employed – no./total no. (%)	210/478 (43.9)	178/568 (31.3)	89/311 (28.6)	89/257 (34.6)
Healthcare worker – no./total no. (%)	33/478 (6.9)	33/568 (5.8)	15/311 (4.8)	18/257 (7.0)
Education level: attended some college or more – no./total no. (%)	202/413 (48.9)	333/547 (60.9)	173/300 (57.7)	160/247 (64.8)
Reported always wearing mask when around others in public – no./total no. (%)	315/433 (72.8)	429/538 (79.7)	236/290 (81.4)	193/248 (77.8)
Reported attending ≥1 gathering with more than 10 people in past 2 weeks – no./total no. (%)	167/443 (37.7)	145/551 (26.3)	62/303 (20.5)	83/248 (33.5)
Number of medications – median (IQR)	6 (2 – 11)	9 (4 – 14)	10 (5 – 14)	8 (4 – 13)
Reported ≥1 hospital admission in past year – no./total no. (%)	155/543 (28.6)	322/588 (54.8)	193/324 (59.6)	129/264 (48.9)
Underlying medical conditions – no./total no. (%) §				
Chronic cardiovascular disease	320/593 (54.0)	393/619 (63.5)	231/334 (69.2)	162/285 (56.8)
Chronic lung disease	122/593 (20.6)	204/619 (33.0)	128/334 (38.3)	76/285 (26.7)
Diabetes mellitus	187/593 (31.5)	201/619 (32.5)	122/334 (36.5)	79/285 (27.7)
Immunocompromising condition	99/593 (16.7)	155/619 (25.0)	93/334 (27.8)	62/285 (21.8)
Obesity by body-mass index	329/586 (56.1)	276/618 (44.7)	159/334 (47.6)	117/284 (41.2)
Self-reported prior laboratory-confirmed SARS-CoV-2 infection	15/593 (2.5)	58/618 (9.4)	31/334 (9.3)	27/284 (9.5)
SARS-CoV-2 vaccination status – no./total no. (%)¶				
Unvaccinated	456/593 (76.9)	273/619 (44.1)	144/334 (43.1)	129/285 (45.3)
First vaccine dose within 0-13 days	47/593 (7.9)	28/619 (4.5)	21/334 (6.3)	7/285 (2.5)
Partially vaccinated	45/593 (7.6)	103/619 (16.6)	54/334 (16.2)	49/285 (17.2)
Fully vaccinated	45/593 (7.6)	215/619 (34.7)	115/334 (34.4)	100/285 (35.1)
Among fully vaccinated patients, vaccine product received – no./total no. (%)				
Moderna two doses	17/45 (37.8)	93/215 (43.3)	46/115 (40.0)	47/100 (47.0)
Pfizer-BioNTech two doses	28/45 (62.2)	122/215 (56.7)	69/115 (60.0)	53/100 (53.0)

Among fully vaccinated patients, days between second vaccine dose and symptom onset (or hospital admission for syndrome-negative control group) – median (IQR)	44 (25 – 54)	43 (26 – 65)	42 (27 – 60)	47 (24 – 66.5)

***** IQR denotes interquartile range

† Race and ethnic groups were reported by the patient or proxy

‡ Long-term care facility included reporting living in a nursing home, assisted living home, or rehab hospital / other sub-acute or chronic facility before the hospital admission

§ Chronic medical condition categories were obtained through medical chart review by trained personnel

¶ Vaccination status was classified based on the number of mRNA vaccine doses received before a reference date, which was the date of symptom onset for cases and test-negative controls and date of hospital admission for syndrome-negative controls. Unvaccinated patients received no doses of vaccine before the reference date, partially vaccinated patients received one of two doses of mRNA vaccine ≥14 days before the reference date or both doses with the second dose received <14 days before the reference date, and fully vaccinated patients received both doses of vaccine ≥14 days before the reference date.

Table 2. SARS-CoV-2 lineages identified by whole genome sequencing of upper respiratory specimens collected from Covid-19 cases — IVY Network, United States, March–May 2021.*

SARS CoV-2 lineage	Patients hospitalized with Covid-19 and SARS CoV-2 sequencing completed				
	Fully vaccinated cases (n =24)	Partially vaccinated cases (n=21)	First vaccine dose 0-13 days before symptom onset (n=18)	Unvaccinated cases (n=200)	All cases with sequencing completed (n=263)
Variants of concern					
B.1.1.7	9	14	14	122	159
P.1	2	2	0	10	14
B.1.429	0	0	0	10	10
B.1.351	1	0	1	2	4
Variants of interest					
B.1.526.1	1	1	0	6	8
B.1.526	2	0	0	4	6
B.1.525	0	1	0	2	3
Other variants					
B.1.1.519	0	0	1	6	7
B.1.2	2	0	0	3	5
B.1	1	0	1	1	3
B.1.621	0	0	0	3	3
B.1.526.2	1	0	0	2	3
B.1.526.3	0	0	0	2	2
B.1.623	0	0	0	2	2
R.1	0	0	0	1	1
B.1.612	0	0	0	1	1
B.1.361	0	0	0	1	1
B.1.517	0	0	0	1	1
C.37	1	0	0	0	1
Sequencing completed but lineage could not be assigned	4	3	1	21	29

*Specimens with SARS-CoV-2 detection by RT-PCR with cycle threshold <32 for at least one of two nucleocapsid gene targets tested underwent whole genome sequencing. SARS-CoV-2 lineages were assigned with >80% coverage using Pangolin genomes; 263/593 (44.4%) Covid-19 cases had samples with complete sequencing. Of these 263 samples with complete sequencing, 234 (89.0%) had a lineage assigned.

FIGURE LEGENDS AND FOOTNOTES

Figure 1. Map of continental United States with incidence of Covid-19 hospitalizations by state in April 2021 indicated by color (red). Participating sites are shown on the map with circles; the size of each circle represents the number of Covid-19 cases included from each site in this analysis -- IVY Network, United States, March–May 2021.*

Figure 1 footnote:

***** Sources of state Covid-19 hospitalization data and population census data were HealthData.gov and United States Census Bureau. [31, 32]

Figure 2. Vaccination status of case patients (N=546), test-negative controls (N=313), and syndrome-negative controls (N=278) — IVY Network, United States, March–May 2021.*****

Figure 2 footnote:

* Vaccination status was classified based on the number of mRNA vaccine doses received before a reference date, which was the date of symptom onset (for cases and test-negative controls) or date of hospital admission (for syndrome-negative controls). Unvaccinated patients received no doses of mRNA vaccine before the reference date, partially vaccinated patients received one of two doses of mRNA vaccine ≥14 days before the reference date or both doses with the second dose received <14 days before the reference date, and fully vaccinated patients received both doses of vaccine ≥14 days before the reference date. Patients who received the first dose of a SARS-CoV-2 vaccine 0-13 days before the reference date (47 cases; 21 test-negative controls; 7 syndrome-negative controls) were excluded from this analysis.

Figure 3. Vaccine effectiveness of SARS-CoV-2 mRNA vaccines for the prevention of Covid-19 hospitalizations overall and by subgroups — IVY Network, United States, March–May 2021.*

Figure 3 footnote:

* The analysis included case patients with Covid-19-like illness who tested positive for SARS-CoV-2 infection and control patients combined from two groups, including a (1) test-negative control group with Covid-19-like illness and negative SARS-CoV-2 testing and (2) a syndrome-negative control group without Covid-19-like illness and negative for SARS-CoV-2. Vaccine effectiveness models were adjusted for calendar time in biweekly intervals, US Department of Health and Human Services region, age in years, sex, race and ethnicity. Vaccination status was classified based on the number of mRNA vaccine doses received before a reference date, which was defined as the date of symptom onset for cases and test-negative controls and date of hospital admission for syndrome-negative controls. Unvaccinated patients received no doses of vaccine before the reference date, partially vaccinated patients received one of two doses of vaccine ≥14 days before the reference date or both doses with the second dose received <14 days before the reference date, and fully vaccinated patients received both doses of vaccine ≥14 days before the reference date.

Figure 1

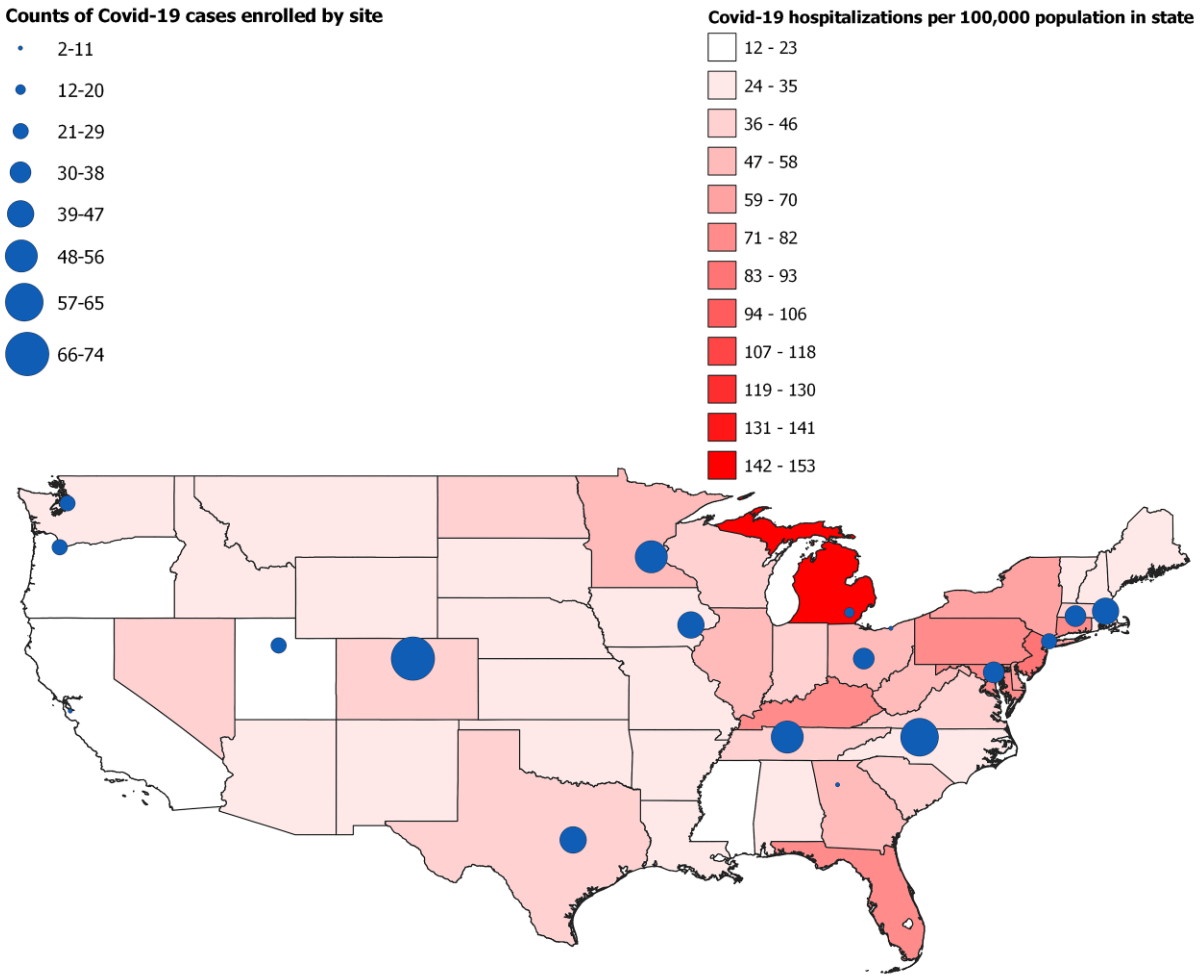

Figure 2

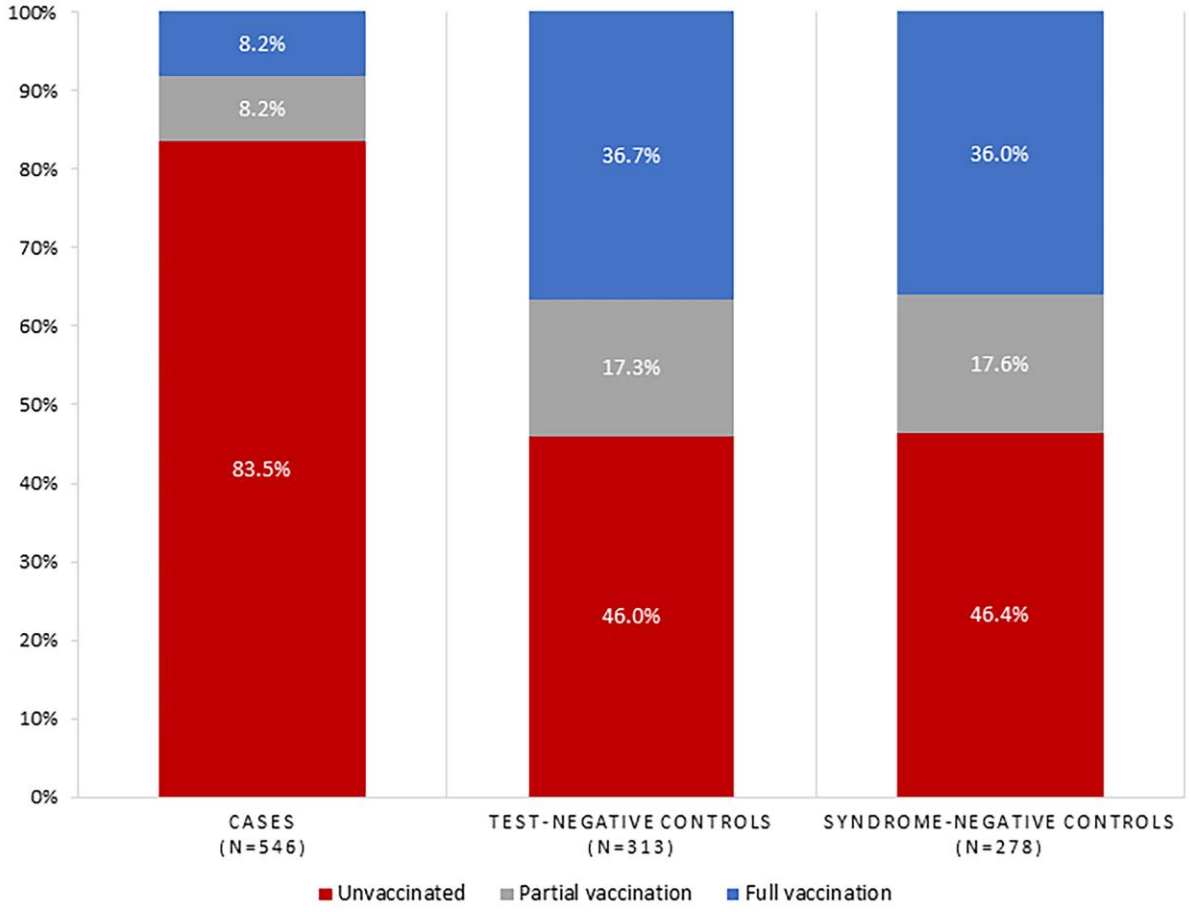

Figure 3

Subgroup	Vaccinated case patients / total case patients (%)	Vaccinated control patients / total control patients (%)	Vaccine effectiveness (95% confidence interval)
Full vaccination			
Overall	45/501 (9.0)	215/488 (44.1)	87.1 (80.7 to 91.3)
18 to 49 yr	1/186 (0.5)	25/139 (18.0)	97.4 (79.3 to 99.7)
50 to 64 yr	14/186 (7.5)	39/136 (28.7)	75.2 (48.3 to 88.1)
≥65 yr	30/129 (23.3)	151/213 (70.9)	87.3 (77.8 to 92.7)
Covid-19 vaccine product			
Pfizer-BioNTech	28/484 (5.8)	122/395 (30.9)	84.4 (74.9 to 90.4)
Moderna	17/473 (3.6)	93/366 (25.4)	90.1 (82.3 to 94.5)
B.1.1.7 variant lineage	9/131 (6.9)	215/488 (44.1)	92.4 (83.6 to 96.5)
Underlying medical condition			
Chronic cardiovascular disease	38/264 (14.4)	150/311 (48.2)	83.0 (72.6 to 89.4)
No chronic cardiovascular disease	7/237 (3.0)	65/177 (36.7)	95.5 (88.8 to 98.2)
Chronic lung disease	14/98 (14.3)	72/158 (45.6)	82.1 (60.3 to 91.9)
No chronic lung disease	31/403 (7.7)	143/330 (43.3)	89.4 (82.7 to 93.5)
Diabetes mellitus	19/153 (12.4)	73/162 (45.1)	82.5 (66.4 to 90.9)
No diabetes mellitus	26/348 (7.5)	142/326 (43.6)	89.9 (83.0 to 94.0)
Immunocompromising condition	20/82 (24.4)	59/119 (49.6)	62.9 (20.8 to 82.6)
No immunocompromising condition	25/419 (6.0)	156/369 (42.3)	91.3 (85.6 to 94.8)
Obesity	21/291 (7.2)	95/215 (44.2)	89.1 (80.3 to 93.9)
No obesity	24/204 (11.8)	120/272 (44.1)	84.8 (73.2 to 91.4)
Partial vaccination			
Overall	45/501 (9.0)	103/376 (27.4)	76.1 (64.0 to 84.2)