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Lack of Evidence for Vaccine-Associated Enhanced Disease From COVID-19 Vaccines Among Adults in the Vaccine Safety Datalink

Thomas G. Boyce[1], **David L. McClure**[1], **Kayla E. Hanson**[1], **Matthew F. Daley**[2], **Malini B. DeSilva**[3], **Stephanie A. Irving**[4], **Lisa A. Jackson**[5], **Nicola P. Klein**[6], **Bruno Lewin**[7], **Joshua T. B. Williams**[8], **Jonathan Duffy**[9], **Michael M. McNeil**[9], **Eric S. Weintraub**[9], **Edward A. Belongia**[1]

[1]Center for Clinical Epidemiology and Population Health, Marshfield Clinic Research Institute, Marshfield, Wisconsin, USA

[2]Institute for Health Research, Kaiser Permanente Colorado, Aurora, Colorado, USA

[3]HealthPartners Institute, Bloomington, Minnesota, USA

[4]Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon, USA

[5]Kaiser Permanente Washington Health Research Institute, Seattle, Washington, USA

[6]Vaccine Study Center, Kaiser Permanente Northern California, Oakland, California, USA

[7]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California, USA

[8]Center for Health Systems Research, Denver Health & Hospital Authority, Denver, Colorado, USA

[9]Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Abstract

Correspondence: Thomas G. Boyce (boyce.thomas@marshfieldclinic.org).

Author Contributions

Dr. Thomas G. Boyce had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: All. Acquisition, analysis, and interpretation of data: Thomas G. Boyce, Edward A. Belongia, David L. McClure, and Kayla E. Hanson. Drafting of the manuscript: Thomas G. Boyce and David L. McClure. Critical revision of the manuscript for important intellectual content: All. Statistical analysis: David L. McClure. Obtained funding: Edward A. Belongia and Kayla E. Hanson. Administrative, technical, or material support: Kayla E. Hanson, David L. McClure, Jonathan Duffy, Michael M. McNeil, and Eric S. Weintraub.

Disclosure

The findings and conclusions in this paper are those of the authors and do not necessarily represent the official position of the CDC. Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC.

Ethics Statement

This study was approved by the institutional review boards at all participating sites, including a waiver of informed consent, and was conducted consistent with federal law and CDC policy.

Conflicts of Interest

NPK reports research support from Pfizer for COVID-19 vaccine clinical trials and from Merck, Sanofi, GlaxoSmithKline and Pfizer for unrelated studies. No other authors report conflicts of interest.

Purpose: Vaccine-associated enhanced disease (VAED) is a theoretical concern with new vaccines, although trials of authorized vaccines against SARS-CoV-2 have not identified markers for VAED. The purpose of this study was to detect any signals for VAED among adults vaccinated against coronavirus disease 2019 (COVID-19).

Methods: In this cross-sectional study, we assessed COVID-19 severity as a proxy for VAED among 400 adults hospitalized for COVID-19 from March through October 2021 at eight US healthcare systems. Primary outcomes were admission to an intensive care unit (ICU) and severe illness (score ≥6 on the World Health Organization [WHO] Clinical Progression Scale). We compared the risk of outcomes among those who had completed a COVID-19 vaccine primary series versus those who were unvaccinated. We incorporated inverse propensity weights for vaccination status in a doubly robust regression model to estimate the causal average treatment effect.

Results: The causal risk ratio in vaccinated versus unvaccinated was 0.36 (95% confidence interval [CI], 0.15–0.94) for ICU admission and 0.46 (95% CI, 0.25–0.76) for severe illness.

Conclusion: Among hospitalized patients, reduced disease severity in those vaccinated against COVID-19 supports the absence of VAED.

Keywords

COVID-19 vaccines; SARS-CoV-2; vaccine-associated enhanced disease; vaccine safety

1 | Introduction

Vaccine-associated enhanced disease (VAED) occurs when persons previously vaccinated against a pathogen develop more severe disease upon subsequent infection with that pathogen relative to unvaccinated persons [1]. VAED was first identified in the 1960s in children who developed severe respiratory syncytial virus (RSV) disease after administration of an investigational formalin-inactivated RSV vaccine [2]. An inactivated measles vaccine administered in the United States from 1963 to 1967 was also associated with VAED [3]. Both vaccines resulted in altered symptoms and greater severity compared with disease in unvaccinated individuals. More recently, a tetravalent dengue vaccine was associated with increased risk for severe dengue in children without prior dengue antigen exposure [4].

VAED is a theoretical safety concern for all new vaccines, especially those that utilize novel platforms [1]. In an animal model, an experimental vaccine using modified vaccinia Ankara (MVA) virus encoding full-length SARS-CoV glycoprotein S against SARS-CoV-1 was associated with more severe subsequent disease and with an increase in Th2-type cytokines [5], a hallmark of VAED. In contrast, trials of mRNA COVID-19 vaccines did not identify clinical or immune markers for VAED [6-8]. When COVID-19 vaccines were initially authorized, the number of severe COVID-19 illnesses and available follow-up time were insufficient to fully assess the risk of VAED. Confirmation of VAED is challenging without immunologic markers or histopathology, neither of which are routinely clinically available. However, the absence of VAED can be inferred when vaccination reduces the risk of severe illness caused by the target pathogen. To identify a potential signal for VAED, we

conducted a cross-sectional study of COVID-19 severity among hospitalized adults in the Vaccine Safety Datalink (VSD).

2 | Methods

2.1 | Study Design and Participants

VSD is a collaboration between the Centers for Disease Control and Prevention (CDC) and nine integrated healthcare systems that conducts vaccine safety evaluations [9]. For this cross-sectional study, eight VSD sites contributed data for persons aged ≥18 years who were hospitalized for COVID-19 from March through October 2021. The analysis was restricted to individuals with ≥12 months of continuous VSD enrollment prior to admission to ensure complete capture of relevant past medical history.

2.2 | Outcomes

Potential COVID-19 hospitalizations were identified from ICD-10 diagnosis codes (U07.1, J12.82, or M35.81) in the inpatient setting. Medical record review was used to confirm that COVID-19 contributed to hospital admission. Our pre-specified primary outcomes were admission to an intensive care unit (ICU) and severe illness defined as a score ≥6 on the World Health Organization (WHO) Clinical Progression Scale (Table A1) [10]. We also performed post hoc analyses assessing death prior to discharge and a composite endpoint of ICU admission or death. All outcomes were adjudicated by a physician (TGB).

2.3 | Exposures

Persons were classified according to their COVID-19 vaccination status as of admission. Specifically, persons were considered to have completed a primary series if they had received two doses of mRNA vaccine (Pfizer-BioNTech or Moderna) or one dose of Janssen vaccine at least 14 days before hospitalization. Persons were considered partially vaccinated if they had started but not completed the primary series or if their most recent primary series dose was <14 days before hospitalization. We conducted medical record reviews for all sampled patients to confirm COVID-19 vaccination status and to collect additional information on reason for admission, treatment, severity, and disposition.

2.4 | Exclusions

We excluded individuals who were partially vaccinated, because there were insufficient cases to analyze partial vaccination as a separate exposure group. Individuals with a prior inpatient diagnosis of COVID-19, those who had received COVID-19 antiviral or monoclonal antibody therapy prior to admission, and those who were admitted for reasons other than COVID-19 were also excluded from analyses. Excluded patients were not replaced, because study power remained sufficient for primary outcomes.

2.5 | Covariates

Two-hundred patients who completed the primary series were sampled and frequency matched to 200 unvaccinated patients in strata based on month of admission, site, and age group (18–49, 50–64, ≥65 years). Covariates included site, age group, sex,

race, and Hispanic ethnicity, history of prior SARS-CoV-2 infection more than 90 days prior to admission (based on a positive laboratory test or diagnosis code), receipt of influenza vaccine in the previous 2 years, tobacco smoking status, and 10 high-risk conditions for COVID-19 in the 12 months prior to hospitalization as outlined by CDC: cancer, cardiovascular disease, cerebrovascular disease, dementia, diabetes mellitus, immune compromise, chronic kidney disease, chronic lung disease, obesity, and substance use disorder. Four additional high-risk conditions (sickle cell disease, Down syndrome, chronic liver disease, and organ transplant) were assessed but could not be included in analyses due to complete or quasi-complete separation of the data. All covariates were ascertained from electronic data except for tobacco smoking status, which was collected during medical record review.

2.6 | Statistical Methods and Data Analysis

We compared the distribution of characteristics and the risk of severe outcomes among hospitalized patients who had completed a primary series versus those who were unvaccinated at the time admission. We used doubly robust regression models to estimate the causal average treatment effect (ATE) [11, 12]. This method relies on four assumptions: (1) untreated (unvaccinated) patients represent the unobserved “untreated” status of the vaccinated patients (i.e., no unmeasured confounding); (2) the probability of being vaccinated can be determined (i.e., propensity to be fully vaccinated); (3) treatment exposures are precisely defined, and there are no hidden variations of treatments (e.g., exclusion of partially vaccinated individuals); and (4) absence of interference (outcomes are not affected by vaccination status of other patients).

We first calculated inverse propensity weights for vaccination status (primary series completed vs. unvaccinated). The propensity score model included the covariates listed in Table A2. Site, calendar time as month of admission, and receipt of influenza vaccine in the previous 2 years were excluded in the propensity model due to failed convergence or extreme/unstable weights.

For each endpoint, we performed outcome regression modeling including the inverse propensity score weights. Additional covariates were included in each model to increase the precision of ATE estimates and to control for residual confounding. All outcome models included age group, month of admission, influenza vaccination, cardiovascular disease, and diabetes mellitus. Site was excluded due to failed convergence.

Causal ATE risk ratios (aRR) with 95% confidence intervals (CIs) were calculated from potential outcome means and their 10 000 bootstrap-sampled 95% CIs using the method of variance estimates recovery [13]. Using this method, aRR <1.0 indicates that vaccination is associated with protection from a severe outcome. We postulated that an aRR >1.0, with a 95% CI excluding 1.0, would signal possible VAED. In a post hoc analysis, we performed a *t*-test to compare the mean time interval from most recent vaccination to hospital admission in patients with high (≥6) and low (<6) severity scores. All analyses were two-sided and were conducted in SAS 9.4/STAT 15.1 (Cary, NC).

3 | Results

3.1 | Characteristics of Participants

From March 1, 2021 through October 31, 2021, 21 177 persons in VSD were hospitalized with a diagnosis of COVID-19. Of the original sample of 400 patients (200 vaccinated and 200 unvaccinated), 185 (46.3%) were excluded after medical record review: 152 (38.0%) were ineligible because the patient was not hospitalized for treatment of COVID-19 or COVID-19-related complications, 17 (4.3%) were reclassified as partially vaccinated, 12 (3.0%) had received COVID-19 antiviral or monoclonal antibody therapy prior to hospitalization, 2 (<1%) were duplicate records, and 2 (<1%) had uncertain vaccination status. The remaining 215 patients were included in analyses, of which 92 (42.8%) were fully vaccinated. Fifty patients received Pfizer-BioNTech, 19 received Moderna, and 23 received Janssen for their primary series. None had received a booster dose; the study period preceded the recommendation of booster doses for all adults. Baseline characteristics with unweighted and weighted standardized mean differences by vaccination status are shown in Table A2. Most co-morbid conditions were more common in the vaccinated group.

3.2 | Severity Outcome Analysis

In the doubly robust regression models, vaccination was associated with decreased severity of COVID-19 illness (Figure 1). Twenty-eight (30.4%) of 92 vaccinated patients had a score ≥ 6 on the WHO Clinical Progression Scale as compared with 59 (48.0%) of 123 unvaccinated patients (aRR 0.46 [95% CI, 0.25–0.76]). Ten vaccinated patients (10.9%) were admitted to an ICU versus 21 unvaccinated patients (17.1%) (aRR 0.36 [95% CI, 0.15–0.94]). Six vaccinees (6.5%) died as compared with 17 unvaccinated patients (13.8%) (aRR 0.22 [95% CI, 0.03–0.56]). Eleven vaccinees (12.0%) were admitted to ICU or died during hospitalization, versus 27 unvaccinated patients (22.0%) (aRR 0.32 [95% CI, 0.14–0.78]). The mean interval from vaccine receipt to hospital admission was similar for hospitalized patients with severity score ≥6 and those with severity score <6 ($p = 0.73$).

4 | Discussion

Multiple COVID-19 vaccine effectiveness studies have assessed hospitalization as a severity endpoint, but few have examined severity among patients already hospitalized for COVID-19. In this US study, completion of a COVID-19 primary vaccine series was associated with reduced illness severity among patients hospitalized for COVID-19 using four different outcomes: WHO Clinical Progression Scale, ICU admission, in-hospital death, and a composite of ICU admission or death. For each outcome, the adjusted risk ratio was significantly <1.0 in vaccinated versus unvaccinated individuals, consistent with vaccine-induced protection against serious hospital outcomes and consistent with an absence of VAED.

Our findings mirror those from a multicenter case-control study of 1197 patients hospitalized for COVID-19 in the United States [14]. In that study, death or invasive mechanical ventilation was associated with decreased likelihood of vaccination (12.0% vs. 24.7%, adjusted odds ratio 0.33 [95% CI, 0.19–0.58]). Other studies have demonstrated

that booster doses continued to provide a high level of protection against COVID-19 hospitalization and death during the Omicron period [15-18].

Strengths of this study include a racially and geographically diverse patient population and medical record review confirmation of COVID-19 hospitalization and severity. There were also several limitations. The relatively small sample size precluded subgroup analyses, and children were not included in the analysis since COVID-19 hospitalizations in that age group are much less common. The mean follow-up time from vaccination to hospitalization was relatively short (approximately 4 months), and it is possible that risk for VAED could vary by time from vaccination due to declining antibody titers. Finally, the study period ended prior to the emergence of the Omicron variant and the availability of booster doses for all adults.

A substantial body of evidence supports the absence of VAED after the primary series and Omicron boosters [15-18]. However, the immunologic risk factors for VAED are not fully understood and the risk may change with emergence of major new variants that are antigenically distinct. In the historical instances of VAED, the risk was greatest in immunologically naive individuals who were vaccinated for the first time. Future studies of VAED associated with COVID-19 vaccines should therefore include children receiving a primary series. In addition, the potential for VAED should be assessed following emergence of new variants that represent major antigenic shifts. In both scenarios, measurement of immunologic markers for VAED will be important to distinguish vaccine-enhanced disease from vaccine failure.

4.1 | Plain Language Summary

Vaccine-associated enhanced disease (VAED) is a theoretical risk from COVID-19 vaccines. We assessed COVID-19 severity as a proxy for VAED among hospitalized adults. Primary outcomes were admission to an intensive care unit (ICU) and severe illness (score ≥6 on the World Health Organization [WHO] Clinical Progression Scale). We compared the risk of outcomes among those who had completed a COVID-19 vaccine primary series versus those who were unvaccinated. The adjusted risk for both ICU admission and for severe illness based on WHO Clinical Progression Scale was significantly lower in vaccinated versus unvaccinated patients. Reduced severity among vaccinated COVID-19 patients supports the absence of VAED.

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APPENDIX A

TABLE A1 |

World Health Organization (WHO) Clinical Progression Scale for COVID-19.[a]

Patient state	Descriptor	Score[b]
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized; moderate disease	Hospitalized; no oxygen therapy	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized; severe disease	Hospitalized; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation, pO_2/FiO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation, pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Death	Death	10

Abbreviations: ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; NIV = noninvasive ventilation; pO_2 = partial pressure of oxygen; SpO_2 = oxygen saturation.

[a] From: WHO Working Group on the Clinical Characterization and Management of COVID-19 Infection. A Minimal Common Outcome Measure Set for COVID-19 Clinical Research. *Lancet Infectious Diseases* 2020;20:e192–e197. doi: 10.1016/S1473-3099(20)30483-7.

[b] Our study assessed outcomes among hospitalized patients and thus was restricted to scores from four through 10.

TABLE A2 |

Characteristics of eligible hospitalized patients with COVID-19 in the Vaccine Safety Datalink by COVID-19 vaccination status at the time of admission, March 1, 2021 through October 31, 2021.

	Completed COVID-19 vaccine primary series				Unvaccinated against COVID-19				Standardized Mean Differences	
Characteristic[a]	Number	Column Percent	Unweighted Mean (SD)	Weighted Mean (SD)	Number	Column Percent	Unweighted Mean (SD)	Weighted Mean (SD)	Unweighted	Weighte
Total	92	100			123	100			N/A	N/A
Vaccine product										
Pfizer-BioNTech	50	54.3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Moderna	19	20.7	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Janssen	23	25.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Age at the time of admission										
18–49 years[b]	11	12	0.88 (0.32)	0.86 (0.34)	22	17.9	0.82 (0.38)	0.86 (0.34)	0.17	−0.01

	Completed COVID-19 vaccine primary series				Unvaccinated against COVID-19				Standardized Mean Differences	
Characteristic[a]	Number	Column Percent	Unweighted Mean (SD)	Weighted Mean (SD)	Number	Column Percent	Unweighted Mean (SD)	Weighted Mean (SD)	Unweighted	Weighte
50–64 years[b]	29	31.5	0.68 (0.46)	0.75 (0.43)	31	25.2	0.75 (0.43)	0.77 (0.42)	−0.14	−0.04
≥65 years[b]	52	56.5	0.43 (0.50)	0.39 (0.49)	70	56.9	0.43 (0.50)	0.37 (0.48)	0.01	0.04
Sex										
Female	40	43.5	0.57 (0.50)	0.48 (0.50)	66	53.7	0.46 (0.50)	0.54 (0.50)	−0.20	0.12
Male[b]	52	56.5	0.43 (0.50)	0.52 (0.50)	57	46.3	0.54 (0.50)	0.46 (0.50)	0.20	−0.12
Race and Hispanic ethnicity										
Black, non-Hispanic	10	10.9	0.53 (0.50)	0.5 (0.50)	18	14.6	0.54 (0.50)	0.59 (0.49)	0.11	0.25
Hispanic/ Latino	30	32.6	0.89 (0.31)	0.93 (0.26)	31	25.2	0.85 (0.35)	0.84 (0.36)	−0.16	−0.30
Other including unknown	9	9.8	0.67 (0.47)	0.67 (0.47)	18	14.6	0.75 (0.43)	0.81 (0.39)	0.15	0.42
White, non-Hispanic[b]	43	46.7	0.90 (0.30)	0.90 (0.30)	56	45.5	0.85 (0.35)	0.76 (0.43)	−0.02	−0.17
High-risk co-morbid conditions in the 12 months prior to hospitalization										
Any	85	92.4	0.08 (0.27)	0.19 (0.39)	88	71.5	0.28 (0.45)	0.2 (0.4)	−0.56	−0.02
Cancer[b]	11	12	0.88 (0.32)	0.94 (0.24)	4	3.3	0.97 (0.18)	0.96 (0.19)	−0.33	−0.09
Cardiovascular disease[b]	57	62	0.38 (0.49)	0.46 (0.50)	59	48	0.52 (0.50)	0.52 (0.50)	−0.28	−0.12
Cerebrovascular disease[b]	5	5.4	0.95 (0.23)	0.95 (0.22)	7	5.7	0.94 (0.23)	0.95 (0.22)	0.01	0.01
Dementia[b]	5	5.4	0.95 (0.23)	0.95 (0.21)	12	9.8	0.90 (0.30)	0.93 (0.25)	0.16	0.09
Diabetes mellitus[b]	51	55.4	0.45 (0.5)	0.57 (0.49)	38	30.9	0.69 (0.46)	0.57 (0.50)	−0.51	0.01
Down syndrome	0	0	N/A	N/A	0	0	N/A	N/A	N/A	N/A
Immune compromised[b]	31	33.7	0.66 (0.47)	0.83 (0.37)	5	4.1	0.96 (0.20)	0.82 (0.39)	−0.82	0.05
Chronic kidney disease[b]	38	41.3	0.59 (0.49)	0.76 (0.43)	20	16.3	0.84 (0.37)	0.73 (0.44)	−0.58	0.06
Chronic liver disease	14	15.2	0.85 (0.36)	0.89 (0.31)	5	4.1	0.96 (0.20)	0.96 (0.20)	−0.38	−0.22
Chronic lung disease[b]	22	23.9	0.76 (0.43)	0.81 (0.39)	16	13	0.87 (0.34)	0.86 (0.34)	−0.28	−0.13
Obesity[b]	39	42.4	0.58 (0.49)	0.69 (0.46)	31	25.2	0.75 (0.43)	0.73 (0.44)	−0.37	−0.09
Organ transplant	12	13	N/A	N/A	0	0	N/A	N/A	N/A	N/A

	Completed COVID-19 vaccine primary series				Unvaccinated against COVID-19				Standardized Mean Differences	
Characteristic[a]	Number	Column Percent	Unweighted Mean (SD)	Weighted Mean (SD)	Number	Column Percent	Unweighted Mean (SD)	Weighted Mean (SD)	Unweighted	Weighte
Sickle cell disease	0	0	N/A	N/A	0	0	N/A	N/A	N/A	N/A
Substance abuse[b]	9	9.8	0.90 (0.30)	0.94 (0.23)	5	4.1	0.96 (0.20)	0.95 (0.22)	−0.23	−0.04
Smoking status at the time of admission										
Never	51	55.4	0.45 (0.50)	0.43 (0.50)	75	61	0.39 (0.49)	0.48 (0.50)	0.11	−0.10
Past	37	40.2	0.60 (0.49)	0.60 (0.49)	42	34.1	0.66 (0.47)	0.60 (0.49)	−0.13	0.00
Current	4	4.3	0.96 (0.2)	0.97 (0.17)	6	4.9	0.95 (0.22)	0.92 (0.27)	0.03	0.24
Ever (Current or Past)[b]	41	44.6	0.55 (0.5)	0.57 (0.50)	48	39	0.61 (0.51)	0.52 (0.50)	−0.11	0.10
Month of admission in 2021										
March	10	10.9	0.89 (0.31)	0.88 (0.33)	11	8.9	0.91 (0.29)	0.82 (0.38)	−0.06	0.18
April	7	7.6	0.92 (0.27)	0.92 (0.27)	14	11.4	0.89 (0.32)	0.89 (0.32)	0.13	0.12
May	9	9.8	0.90 (0.30)	0.87 (0.34)	9	7.3	0.93 (0.26)	0.94 (0.23)	−0.09	−0.28
June	9	9.8	0.90 (0.30)	0.92 (0.27)	14	11.4	0.89 (0.32)	0.90 (0.30)	0.05	0.07
July	18	19.6	0.80 (0.40)	0.84 (0.36)	18	14.6	0.85 (0.35)	0.86 (0.35)	−0.13	−0.05
August	15	16.3	0.84 (0.37)	0.86 (0.35)	22	17.9	0.82 (0.38)	0.85 (0.36)	0.04	0.03
September	11	12	0.88 (0.32)	0.88 (0.33)	16	13	0.87 (0.34)	0.88 (0.33)	0.03	0.00
October	13	14.1	0.86 (0.35)	0.84 (0.37)	19	15.5	0.85 (0.36)	0.87 (0.34)	0.04	−0.07
Influenza vaccination within 24 months prior to hospitalization	85	92.4	0.08 (0.27)	0.10 (0.30)	58	47.2	0.53 (0.50)	0.55 (0.50)	−1.13	−1.11

Abbreviations: N/A = not applicable; SD = standard deviation.

[a] All characteristics were obtained from electronic data except smoking status, which was obtained from medical record review.

[b] Characteristic included in propensity score model.

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Summary

- Vaccine-associated enhanced disease (VAED) is a theoretical risk after vaccination.
- VAED has not been fully assessed among hospitalized patients with COVID-19.
- We compared COVID-19 severity in hospitalized adults by vaccine status.
- Patients who were vaccinated against COVID-19 had less severe outcomes.
- These results provide further evidence for lack of VAED with COVID-19 vaccines.

Outcome	Number with outcome/total primary series vaccinated (%)	Number with outcome/total unvaccinated (%)	Absolute percent difference (95% CI)	ATE risk ratio* (95% CI)
WHO score ≥6	28/92 (30.4)	59/123 (48.0)	-17.5 (-30.0, -4.6)	0.46 (0.25, 0.76)
ICU admission	10/92 (10.9)	21/123 (17.1)	-6.2 (-3.0, 15.4)	0.36 (0.15, 0.94)
Death	6/92 (6.5)	17/123 (13.8)	-7.3 (-15.2, 0.6)	0.22 (0.03, 0.56)
Death or ICU admission	11/92 (12.0)	27/123 (22.0)	-10.0 (-19.9, -0.1)	0.32 (0.14, 0.78)

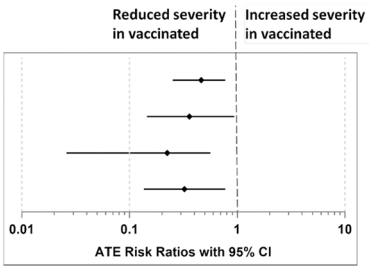

FIGURE 1 |.

Association of severe disease outcomes and vaccination status among adults hospitalized for COVID-19 in the Vaccine Safety Datalink from March 1, 2021 through October 31, 2021. ATE inverse probability treatment weight factors for all outcomes: age group, race and Hispanic ethnicity, sex, tobacco smoking status, and 10 high-risk conditions for COVID-19: cancer, cardiovascular disease, cerebrovascular disease, dementia, diabetes mellitus, immune compromise, kidney disease, lung disease, obesity, and substance use disorder. ATE outcome adjustment factors: age group, month of admission, influenza vaccination, cardiovascular disease, and diabetes mellitus. ATE, average treatment effect; CI, confidence interval; ICU, intensive care unit; WHO, World Health Organization. *An average treatment effect risk ratio less than 1.0 indicated that being unvaccinated against COVID-19 was associated with score ≥6 on the WHO Clinical Progression Scale, ICU admission, or death.