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Original Article

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Updated Bivalent COVID-19 Vaccines Reduce Risk of Hospitalization and Severe Outcomes in Adults: An Observational Cohort Study

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Abstract

Background: This study evaluates the real-world effectiveness of updated bivalent coronavirus disease 2019 (COVID-19) vaccines in adults, as the virus evolves and the need for new vaccinations increases.

Methods: In this observational, retrospective, multi-center, cohort analysis, we examined emergency care encounters with COVID-19 in metro Detroit, Michigan, from January 1, 2022, to March 9, 2023. Patients were categorized by vaccination status: unvaccinated, fully vaccinated, fully vaccinated and boosted (FV&B), or fully vaccinated and bivalent boosted (FV&BB). The primary outcome was to assess the impact of bivalent COVID-19 vaccinations on the risk of composite severe outcomes (intensive care unit (ICU) admission, mechanical ventilation, or death) among patients presenting to a hospital with a primary diagnosis of COVID-19.

Results: A total of 21,439 encounters met inclusion criteria: 9,630 (44.9%) unvaccinated, 9,223 (43.0%) vaccinated, 2,180 (10.2%) FV&B, and 406 (1.9%) FV&BB. The average age was 48.8, with 59.6% female; 61.1% were White, 32.8% Black, and 6.0% other races. Severe disease affected 5.5% overall: 5.0% unvaccinated, 5.7% vaccinated, 7.0% FV&B, and 4.7% FV&BB (P = 0.001). Severe disease rates among admitted patients were 13.3% unvaccinated, 11.9% vaccinated, 12.2% boosted, and 8.1% FV&BB (P = 0.052). The FV&BB group showed a 4.0% (P = 0.0369) lower risk of severe disease compared to FV&B and a 5.1% (P = 0.0203) lower probability of hospitalization.

Conclusions: As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to mutate and evolve, updated vaccines are necessary to better combat COVID-19. In a real-world hospital-based population, this investigation demonstrates the incremental benefit of the bivalent booster vaccine in reducing the risk of hospitalization and severe outcomes in those diagnosed with COVID-19 compared to all other forms of vaccination.

Keywords: COVID-19; SARS-CoV-2; Booster dose; Vaccination; Hospitalization; Severe illness; Mortality; Death

Introduction

The coronavirus disease 2019 (COVID-19) virus has proved to be one of the deadliest viruses to date, as the death toll approaches 7,000,000 people and nearly 800,000,000 confirmed infections in just 3 years [1, 2]. This disease has quickly become one of the top causes of death in the USA, next to heart disease and cancer [3].

Fortunately, a variety of therapeutics have been identified or developed to combat this virulent pathogen. For active infection, anti-inflammatories, monoclonal antibodies, and antivirals have resulted in improved outcomes in some patient populations [4-7]. However, infection control and prevention remain the most effective method of reducing mortality. After the first rollout of vaccines in early 2021, nearly 644.7 million vaccinations were distributed in the USA within 1 year [8]. The original monovalent vaccine was developed using mRNA to produce the spike protein found on the surface of the virus [9]. Both the primary series of two vaccines, plus the rollout of booster shots 1 year later, quickly demonstrated significant reductions in COVID-19-related hospitalizations and in-hospital deaths [10, 11].

Unfortunately, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to evolve, and changes in its genetic code diminish the effectiveness of targeted vaccinations. mRNA viruses like SARS-CoV-2 mutate five times faster than DNA viruses, therefore, it is not surprising to ob-

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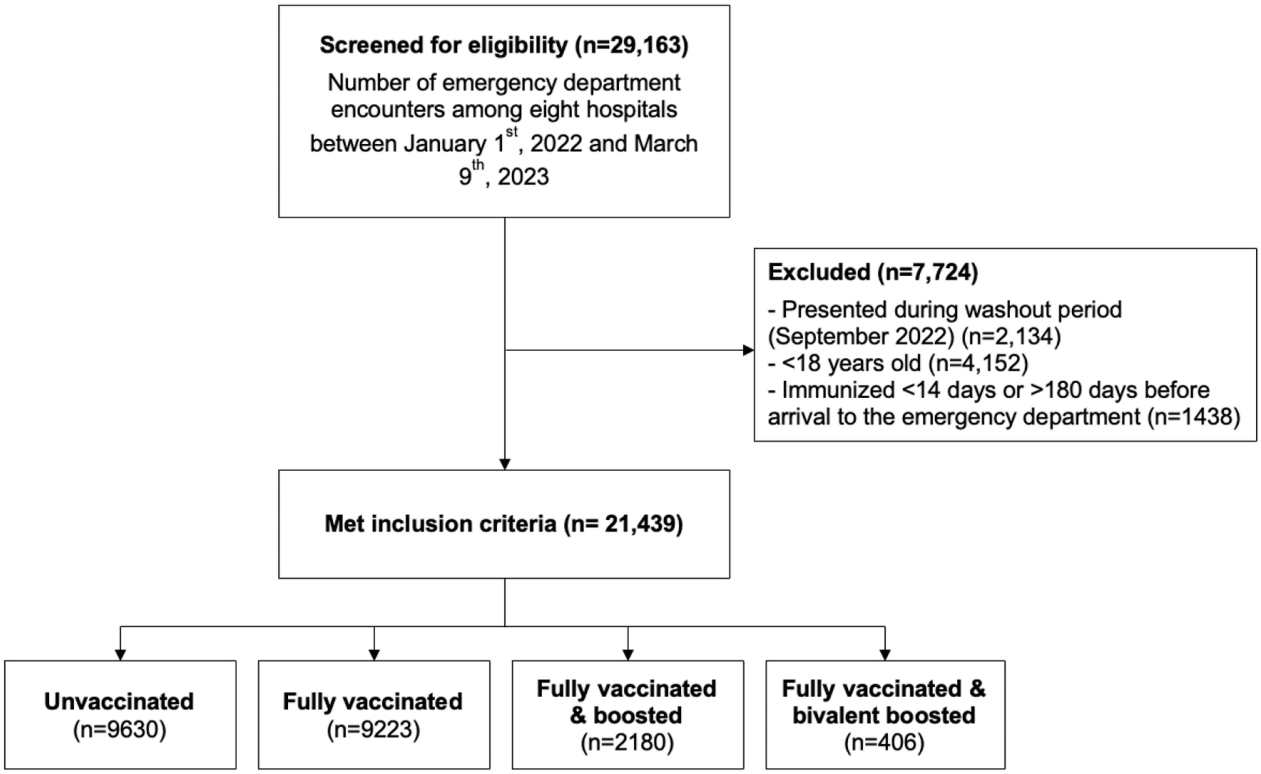

Figure 1. Flow figure of inclusion and exclusion criteria. Flow figure of encounters screened for eligibility, encounters excluded from the study, and vaccination categorization.

serve significant changes to the virus's genome over the course of several years [12]. Emerging in India in late 2020, the delta variant was highly contagious and was an early real-world example of how viral variants could reduce vaccine efficacy [12, 13]. Subsequently, the omicron variant, first detected in November 2021, proved to be even more infectious with an even greater ability to infect vaccinated individuals [14, 15]. In order to combat these variants, a new series of bivalent boosters was developed. These boosters targeted a component of the original SARS-CoV-2 strain and a shared component of the BA.4/BA.5 lineages of the omicron variant. These vaccines were disseminated to the American public in September 2022 [16]. Early trials showed additional efficacy in preventing infection when compared to the monovalent vaccines [17]. However, there is still a lack of data regarding the efficacy of these vaccines in a real-world population, particularly in patients requiring hospital-level care. Thus, the primary aim of this study was to investigate the impact of the bivalent SARS-CoV-2 vaccinations compared to their monovalent counterparts in preventing severe outcomes among hospitalized patients.

Materials and Methods

Study design

This study was an observational, retrospective, multi-center cohort analysis of patient encounters extracted from electronic health records (EHRs). Eight distinct hospitals, ranging from small community hospitals to a large, academic, tertiary care center in Southeast Michigan, USA, comprised the study setting.

Selection of participants

Encounters of patients with a principal diagnosis (laboratory confirmed at time of the emergency department (ED) presentation) of COVID-19 (U07.1), among patients who were 18 or older at the time of the encounter and presented to one of Corewell Health East's ED between January 1, 2022, and March 9, 2023, met inclusion criteria. Any patients with laboratory-verified positive COVID-19 test within the preceding 28 days were excluded, as this was likely not an acute infection but rather a persistent one (Fig. 1). The Corewell Health Institutional Review Board (IRB) approved this (IRB #2022-266); given the retrospective nature of the study, a waiver for written informed consent was granted. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Measurements

All data were extracted from the EHR system (Epic, Verona,

Wisconsin). These data included demographic, clinical, laboratory, and outcomes variables, including age, sex, ethnicity, past medical history, vaccination status, initial vital signs, in-hospital therapies, and outcomes of interest, such as the need for care in the intensive care unit (ICU), mechanical ventilation, death, and hospital length of stay. Comorbidities were assessed using the Agency for Healthcare Research and Quality (AHRQ) Elixhauser Comorbidity Index [18]. Immunocompromised individuals were identified based on the International Classification of Diseases, 10th Revision (ICD-10) codes per the AHRQ definition, such as autoimmune diseases, organ transplants, nutritional deficiencies, certain genetic conditions, certain chronic diseases, and human immunodeficiency virus disease [19]. The vaccination status for SARS-CoV-2 of patients was confirmed through the EHR at the institution, connected with the Michigan Care Improvement Registry (MCIR) [20]. This integration ensured that even those who received their vaccinations outside the Corewell Health System had updated vaccination data. The MCIR keeps detailed records of SARS-CoV-2 vaccinations for people immunized in Michigan, including the specific type of vaccine received and the date it was administered.

Definitions

Vaccination status was grouped into four categories: unvaccinated, vaccinated, boosted, and bivalent boosted. The unvaccinated group consisted of patients with no records of vaccination. The vaccinated category consisted of patients who received the primary two-dose monovalent mRNA vaccination series (Pfizer, Moderna) or received one viral vector vaccine (Janssen). The fully vaccinated and boosted (FV&B) cohort consisted of patients who met criteria of the vaccinated category and received at least one additional vaccine before September 1, 2022. The fully vaccinated and bivalent boosted (FV&BB) cohort consisted of patients who met criteria of the FV&B category and received one of the bivalent boosted vaccines between October 1, 2022, and March 9, 2023. A washout period (September 2022) was utilized. All data were queried on March 31, 2023. For all vaccination groups, the immunization date must be at least 14 days after vaccination administration, which is consistent with previous studies [21, 22]. Safety information regarding potential side effects is monitored and reported by the Centers for Disease Control and Prevention (CDC) [23].

Outcomes

The primary outcome of this study was to assess the impact of bivalent COVID-19 vaccinations on the risk reduction of composite severe outcomes among patients presenting to a hospital with a primary diagnosis of COVID-19. Severe outcomes included admission to the ICU, mechanical ventilation, or death, as first described by the CDC [24]. The secondary outcome evaluated the need for hospitalization following initial ED evaluation. Of note, mechanically ventilated patients required an ICU level of care per institutional policy. Additional outcome measures included need for oxygen therapy, and hospital length of stay.

Data analyses

First, descriptive statistics were used to summarize patient characteristics based on their COVID-19 vaccination status. Continuous variables were expressed as means, standard deviation of the mean, median, and interquartile range. Categorical variables were reported as frequencies and percentages. Differences in the characteristics based on vaccination status were tested using Pearson's Chi-square test for categorical variables, and Kruskal-Wallis test for continuous variables.

Next, three logistic regression models were fit to evaluate the effect of vaccination status on the above-mentioned composite outcome: 1) unadjusted model did not control for any additional covariate; 2) partially adjusted model controlled for age and Elixhauser comorbidity index; 3) fully adjusted model, controlled for age, Elixhauser comorbidity index, sex, race pre-existing end-stage renal disease and if the patient was immunocompromised. Following each estimated regression model, average marginal effects of vaccination status on composite outcome were calculated. Using these marginal effects, analysis of variance contrast tests was used to estimate the differences in predicted probabilities (along with 95% confidence intervals) of composite outcome between vaccination status groups using the boosted as the reference category. The same steps were followed for the secondary outcome. The contrasts test results are presented in figures for ease of visual inspection and assessment. All the statistical analysis was performed using Stata 17.0 [25].

Results

Between January 1, 2022, and March 9, 2023, 21,439 patient encounters met inclusion criteria: 9,630 (44.9%) were unvaccinated, 9,223 (43.0%) were vaccinated, 2,180 (10.2%) were boosted, and 406 (1.9%) were bivalent boosted. The average age was 48.8 years old, 59.6% (n = 12,777) of the population was female, and 61.1% (n = 13,109) identified as White, 32.8% (7,034) identified as Black, and 6.0% (n = 1,296) identified with a race other than Black or White. Immunocompromised state was present in 12.8% of the population, with the largest proportion among boosted patients (18.5%) and the lowest proportion among the unvaccinated patients (9.5%; $P < 0.001$). The bivalent boosted group comprised the highest proportion requiring oxygen therapy (37.2%), compared to the boosted, vaccinated, and unvaccinated groups (32.7%, 28.4%, and 22.1%, respectively. $P < 0.001$). Overall, 5.5% (n = 1,178) of the population experienced composite severe disease; 5.0% (n = 477) unvaccinated, 5.7% (n = 530) vaccinated, 7.0% (n = 152) boosted, and 4.7% (n = 19) bivalent boosted ($P = 0.001$). The average length of stay was longest in the unvaccinated cohort (183.0 h) and shortest in the bivalent boosted cohort (147.0 h) (Table 1).

In a subgroup analysis of patients admitted to the hospi-

Table 1. Demographics, Comorbidities, Initial Vital Signs, In-Hospital Therapies, and Outcomes of All Patients

Variables[a]	All	Unvaccinated	Vaccinated	Boosted	Bivalent boosted	P value
N	21,439	9,630 (44.9%)	9,223 (43.0%)	2,180 (10.2%)	406 (1.9%)	
Demographics						
Age, years						
Mean	48.8 (26.6)	37.8 (26.5)	58.9 (21.3)	66.2 (18.7)	72.3 (14.3)	< 0.001
Median	52 (29, 71)	35 (17, 59)	62 (43, 76)	70 (56, 80)	73 (65, 82)	
Sex						
Female	12,777 (59.6)	5,762 (59.8)	5,562 (60.3)	1,248 (57.2)	205 (50.5)	< 0.001
Male	8,662 (40.4)	3,868 (40.2)	3,661 (39.7)	932 (42.8)	201 (49.5)	
Race						
Black or African American	7,034 (32.8)	3,927 (40.8)	2,533 (27.5)	498 (22.8)	76 (18.7)	< 0.001
White or Caucasian	13,109 (61.1)	5,182 (53.8)	6,063 (65.7)	1,553 (71.2)	311 (76.6)	
Other	1,296 (6.0)	521 (5.4)	627 (6.8)	129 (5.9)	19 (4.7)	
Body mass index, kg/m^2						
Mean	29.5 (8.4)	29.4 (8.9)	29.8 (8.1)	29.0 (7.4)	29.0 (8.3)	< 0.001
Median	28.2 (23.6, 34)	28.1 (23.1, 34.1)	28.4 (24.1, 34.1)	27.6 (23.7, 33.1)	27.5 (23.5, 3.5)	
Comorbidities						
Immunocompromised	2,749 (12.8)	917 (9.5)	1,365 (14.8)	404 (18.5)	63 (15.5)	< 0.001
Pre-existing end-stage renal disease	694 (3.2)	194 (2.0)	358 (3.9)	133 (6.1)	9 (2.2)	< 0.001
Elixhauser weighted score						
Mean	3.17 (3.3)	2.2 (2.9)	4.0 (3.5)	4.8 (3.6)	5.1 (3.5)	< 0.001
Median	2 (0,5)	1 (0,3)	3 (1,6)	4 (2,7)	5 (2,8)	
Elixhauser, category						
0	3,947 (18.4)	2,438 (25.3)	1,284 (13.9)	202 (9.3)	23 (5.7)	< 0.001
1 to 2	6,192 (28.9)	3,192 (33.1)	2,425 (26.3)	481 (22.1)	94 (23.2)	
3 to 4	4,279 (20.0)	1,744 (18.1)	1,968 (21.3)	486 (22.3)	81 (20.0)	
≥ 5	7,021 (32.7)	2,256 (23.4)	3,546 (38.4)	1,011 (46.4)	208 (51.2)	
Initial vital signs						
Respiratory rate, breaths per minute						
< 30	21,041 (98.2)	9,467 (98.4)	9,042 (98.1)	2,134 (97.9)	398 (98.0)	0.282
≥ 30	381 (1.8)	153 (1.6)	175 (1.9)	45 (2.1)	8 (2.0)	
Pulse, beats per minute						
< 90	10,451 (48.8)	4,304 (44.7)	4,656 (50.5)	1,237 (56.8)	254 (62.6)	< 0.001
≥ 90	10,976 (51.2)	5,318 (55.3)	4,564 (49.5)	942 (43.2)	152 (37.4)	
Systolic blood pressure, mm Hg						

Table 1. Demographics, Comorbidities, Initial Vital Signs, In-Hospital Therapies, and Outcomes of All Patients - *(continued)*

Variables[a]	All	Unvaccinated	Vaccinated	Boosted	Bivalent boosted	P value
< 90	261 (1.2)	87 (0.9)	127 (1.4)	42 (1.9)	5 (1.2)	< 0.001
≥ 90	21,161 (98.8)	9,533 (99.1)	9,090 (98.6)	2,137 (98.1)	401 (98.8)	
Temperature, °C						
< 36	442 (2.1)	159 (1.7)	229 (2.5)	48 (2.2)	6 (1.5)	< 0.001
36 - 38	19,033 (89.0)	8,502 (88.4)	8,177 (88.9)	1,991 (91.5)	363 (89.6)	
> 38	1,921 (9.0)	952 (9.9)	796 (8.7)	137 (6.3)	36 (8.9)	
Blood oxygen saturation, %						
< 90	588 (2.7)	277 (2.9)	247 (2.7)	56 (2.6)	8 (2.0)	0.582
≥ 90	20,836 (97.3)	9,345 (97.1)	8,970 (97.3)	2,123 (97.4)	398 (98.0)	
In-hospital therapies						
O_2 therapy	5,618 (26.2)	2,131 (22.1)	2,623 (28.4)	713 (32.7)	151 (37.2)	< 0.001
Nasal cannula/non-rebreather	4,008 (18.7)	1,463 (15.2)	1,922 (20.8)	506 (23.2)	117 (28.8)	< 0.001
High-flow O_2	556 (2.6)	255 (2.6)	231 (2.5)	57 (2.6)	13 (3.2)	0.801
Non-mechanical ventilation	593 (2.8)	211 (2.2)	276 (3.0)	94 (4.3)	12 (3.0)	< 0.001
Vasopressor	598 (2.8)	230 (2.4)	269 (2.9)	84 (3.9)	15 (3.7)	0.001
Primary outcome						
Composite severe disease	1,178 (5.5)	477 (5.0)	530 (5.7)	152 (7.0)	19 (4.7)	0.001
ICU-level care	1,015 (4.7)	405 (4.2)	453 (4.9)	139 (6.4)	18 (4.4)	< 0.001
Mechanical ventilation	461 (2.2)	202 (2.1)	194 (2.1)	56 (2.6)	9 (2.2)	0.563
Death	416 (1.9)	178 (1.8)	183 (2.0)	48 (2.2)	7 (1.7)	0.705
Secondary outcomes						
Hospital admission	9,390 (43.8)	3,543 (36.8)	4,366 (47.3)	1,246 (57.2)	235 (57.9)	< 0.001
Length of stay, h						
Mean	172.1 (170.0)	183.0 (176.2)	167.3 (170.0)	171.2 (164.3)	147.0 (128.7)	< 0.001
Median	122 (72, 212)	127, (76, 233)	121 (71, 200)	121 (71, 216)	101 (64, 171)	

[a]For continuous variables, medians (interquartile ranges (IQRs)) and means (standard deviation (SD)) were presented. For categorical variables, frequencies (percentage) were presented. ICU: intensive care unit.

tal (n = 9,390), 54.3% (5,101) of the subgroup was female, with 24.8% (n = 2,325) identifying as Black, 69.9% (6,567) identifying as White, and 5.3% (n = 498) identifying with a race other than Black or White. Immunocompromised state was present in 20.5% (n = 1,922) of the population, and 52.1% (4,888) had an Elixhauser score of ≥ 5. Thirty-seven point seven percent (n = 3,543) were unvaccinated, 46.5% (n = 4,366) were vaccinated, 13.3% (n = 1,246) were boosted, and 2.5% (n = 235) were bivalent boosted. There was no difference in the proportion of the need for oxygen therapy (bivalent boosted = 59.6%, boosted = 55.5%, unvaccinated = 56.9%, and vaccinated = 56.8%; P = 0.645). For the primary outcome, 13.3% (n = 472) of the unvaccinated patients experienced composite severe disease, compared to 11.9% of vaccinated patients, 12.2% of boosted patients, and 8.1% of bivalent boosted patients (P = 0.052) (Table 2). The risk of severe disease among the FV&BB cohort of admitted patients was 4.0% lower compared to the FV&B cohort of admitted patients (P = 0.0369) (Fig. 2a).

The difference in the probability of requiring hospital admission, after adjusting for age, sex, race, Elixhauser comorbidity index, pre-existing end-stage renal disease, and immunocompromised state was 2.9% (P = 0.0351) greater in the unvaccinated group, compared to the FV&B group. There was no difference in the contrast of predictions for the vaccinated versus the boosted groups (P > 0.05). The probability of requiring hospitalization was 5.1% higher in the FV&B group compared to the FV&BB group (P = 0.0203) (Fig. 2b) (Supplementary Material 1, www.jocmr.org).

Discussion

This study serves as one of the first to investigate the real-world effectiveness of the bivalent formulations for the mRNA vaccines. After adjusting for baseline risk factors, we observed a reduced rate of hospital admission as well as a reduction in the rate of severe outcomes amongst patients who had received the bivalent booster as compared to all other groups. While fully vaccinated and FV&B demonstrated a significant reduction in these risks when compared to unvaccinated individuals, bivalent boosted patients demonstrated an even greater reduction in these risks. Additionally, despite the bivalent boosted population being the oldest and highest risk for inpatient mortality, as predicted by the Elixhauser index, we observed the lowest absolute mortality and composite severe outcome rate in this group. Further, after adjusting for age, sex, race, and comorbidities, the bivalent mRNA booster patients had the lowest rates of composite severe disease, shortest hospital length of stay, and lowest probability of requiring hospitalization when compared to all other groups. These findings align with other similar previous studies [26-30]. These results not only re-enforce the known efficacy of the bivalent boosters but demonstrate a significant reduction in morbidity and mortality among the highest-risk population in our cohort.

Unfortunately, reception and distribution of the vaccines have decreased over the past year despite COVID-19 remaining one of the highest causes of morbidity and mortality in the USA [31]. It is notable that the unvaccinated cohort still comprises the highest burden to hospitals. In Oakland County, Michigan, 25.4% of residents were unvaccinated during the study period, however they comprised 44.9% of all patients hospitalized for COVID-19 [32]. This represents an ongoing and significant burden to the hospital systems across the country which is potentially avoidable with wider adoption of vaccines. Looking specifically at the most vulnerable individuals, while we observed a trend towards older individuals with higher levels of comorbidities being higher on the vaccination status ladder, our overall population of bivalent boosted individuals was still small. Current data report that in Oakland County, 18% of residents are older than 65. However, only 8% of Oakland County residents have received the bivalent booster [2]. These numbers suggest that even in a best-case scenario, we would still expect that at least 10% of individuals older than 65 have not yet received their bivalent booster.

It is important for individuals with elevated baseline risk to understand that there is an added layer of protection with the bivalent vaccine formulation, even compared to the very effective monovalent boosted cohort. Furthermore, when compared to other common upper respiratory viruses like influenza and respiratory syncytial virus, COVID-19 infection comprises higher rates of hospitalization and death overall [33]. Given the significant added protection from the bivalent boosters we observed in our study, it is critical that older, higher-risk individuals receive these vaccinations prior to SARS-CoV-2 exposure to reduce the risk of severe outcomes. Overall, our findings demonstrate the need for individuals to stay up to date on their COVID-19 vaccinations according to current guidelines per the CDC.

This investigation had some limitations. One limitation was the inability to identify the precise viral variant causing each infection. While specific variant data could further eliminate confounding variables, our study has the benefit of observing a real-world population for patient-centered outcomes. Therefore, we feel that our results demonstrate real-world efficacy despite our lack of specific variant data. In addition, Figure 3 visually demonstrates the number of cases meeting inclusion criteria group by predominant COVID-19 variant in the region per CDC genomic surveillance [34]. Another factor that limits the strength of our results is the small sample size of the bivalent boosted cohort. While this is a limitation, we still observed statistically significant results for our outcomes of interest, suggesting that the impact of bivalent vaccines is large enough to overcome this limitation. Next, there is a small chance that who tested positive for COVID-19 on admission to the hospital did not remain positive during the entirety of their hospitalization. Additionally, we did not have data on whether patients had previously tested positive for SARS-CoV-2 prior to vaccination, and therefore were unable to evaluate for the effects of innate immunity within our cohort. There is also a possibility that varying time between initial vaccinations and booster doses may have an effect on immunity, and this is not something that we evaluated. Finally, the retrospective nature of our study design may have caused issues with data collection and review. However, we have spent a significant amount of time validating our dataset over the course of the COVID-19 pandemic and believe that our collection methods retain the highest level of accuracy and integrity possible. Additionally,

Table 2. Demographics, Comorbidities, Initial Vital Signs, In-Hospital Therapies, and Outcomes of Admitted Patients

Variables[a]	All	Unvaccinated	Vaccinated	Boosted	Bivalent boosted	P value
N	9,390	3,543 (37.7%)	4,366 (46.5%)	1,246 (13.3%)	235 (2.5%)	
Demographics						
Age, years						
Mean	67.9 (17.5)	63.0 (18.9)	70.0 (16.3)	72.7 (15.0)	76.6 (11.8)	< 0.001
Median	71 (58, 81)	65 (50, 78)	72 (61, 82)	74 (65, 84)	78 (69, 85)	
Sex						
Female	5,101 (54.3)	1,968 (55.5)	2,359 (54.0)	662 (53.1)	112 (47.7)	0.066
Male	4,289 (45.7)	1,575 (44.5)	2,007 (46.0)	584 (46.9)	123 (52.3)	
Race						
Black or African American	2,325 (24.8)	1,062 (30.0)	965 (22.1)	255 (20.5)	43 (18.3)	< 0.001
White or Caucasian	6,567 (69.9)	2,313 (65.3)	3,147 (72.1)	927 (74.4)	180 (76.6)	
Other	498 (5.3)	168 (4.7)	254 (5.8)	64 (5.1)	12 (5.1)	
Body mass index, kg/m^2						
Mean	29.1 (8.4)	29.6 (8.9)	29.0 (8.3)	28.4 (7.3)	28.2 (7.8)	< 0.004
Median	27.5 (23.4, 33.3)	27.9 (23.4, 34)	27.5 (23.4, 33.1)	27.1 (23.3, 32.4)	26.6 (22.9, 32.1)	
Comorbidities						
Immunocompromised	1,922 (20.5)	608 (17.2)	977 (22.4)	292 (23.4)	45 (19.1)	< 0.001
Pre-existing end-stage renal disease	583 (6.2)	165 (4.7)	299 (6.8)	110 (8.8)	9 (3.8)	< 0.001
Elixhauser weighted score						
Mean	5.2 (3.7)	4.4 (3.6)	5.6 (3.6)	5.8 (3.7)	5.9 (3.6)	< 0.001
Median	5 (2,8)	4 (2,7)	5 (3,8)	6 (3,9)	6 (3,9)	
Elixhauser, category						
0	852 (9.1)	464 (13.1)	296 (6.8)	77 (6.2)	15 (6.4)	< 0.001
1 to 2	1,821 (19.4)	850 (24.0)	751 (17.2)	184 (14.8)	36 (15.3)	
3 to 4	1,829 (19.5)	693 (19.6)	849 (19.4)	247 (19.8)	40 (17.0)	
≥ 5	4,888 (52.1)	1,536 (43.4)	2,470 (56.6)	738 (59.2)	144 (61.3)	
Initial vital signs						
Respiratory rate, breaths per minute						
< 30	9,037 (96.3)	3,398 (95.9)	4,209 (96.4)	1,203 (96.5)	227 (96.6)	0.648
≥ 30	352 (3.7)	144 (4.1)	157 (3.6)	43 (3.5)	8 (3.4)	
Pulse, beats per minute						
< 90	4,849 (51.6)	1,649 (46.6)	2,325 (53.3)	727 (58.3)	148 (63.0)	< 0.001
≥ 90	4,540 (48.4)	1,893 (53.4)	2,041 (46.7)	519 (41.7)	87 (37.0)	
Systolic blood pressure, mm Hg						

Table 2. Demographics, Comorbidities, Initial Vital Signs, In-Hospital Therapies, and Outcomes of Admitted Patients -

Variables[a]	All	Unvaccinated	Vaccinated	Boosted	Bivalent boosted	P value
< 90	233 (2.5)	69 (1.9)	118 (2.7)	41 (3.3)	5 (2.1)	0.036
≥ 90	9,155 (97.5)	3,473 (98.1)	4,247 (97.3)	1,205 (96.7)	230 (97.9)	
Temperature, °C						
< 36	283 (3.0)	97 (2.7)	150 (3.4)	31 (2.5)	5 (2.1)	0.016
36 - 38	8,257 (88.0)	3,097 (87.5)	3,833 (87.8)	1,125 (90.3)	202 (86.0)	
> 38	847 (9.0)	347 (9.8)	382 (8.8)	90 (7.2)	28 (11.9)	
Blood O_2 saturation, %						
< 90	554 (5.9)	264 (7.5)	227 (5.2)	55 (4.4)	8 (3.4)	< 0.001
≥ 90	8,835 (94.1)	3,278 (92.5)	4,139 (94.8)	1,191 (95.6)	227 (96.6)	
In-hospital therapies						
O_2 therapy	5,329 (56.8)	2,016 (56.9)	2,482 (56.8)	691 (55.5)	140 (59.6)	0.645
Nasal cannula/non-rebreather	3,727 (39.7)	1,353 (38.2)	1,784 (40.9)	484 (38.8)	106 (45.1)	0.028
High-flow O_2	556 (5.9)	255 (7.2)	231 (5.3)	57 (4.6)	13 (5.5)	< 0.001
Non-mechanical ventilation	588 (6.3)	207 (5.8)	275 (6.3)	94 (7.5)	12 (5.1)	0.165
Vasopressor	592 (6.3)	228 (6.4)	265 (6.1)	84 (6.7)	15 (6.4)	0.822
Primary outcome						
Composite severe disease	1,164 (12.4)	472 (13.3)	521 (11.9)	152 (12.2)	19 (8.1)	0.052
ICU-level care	1,015 (10.8)	405 (11.4)	453 (10.4)	139 (11.2)	18 (7.7)	0.183
Mechanical ventilation	458 (4.9)	201 (5.7)	192 (4.4)	56 (4.5)	9 (3.8)	0.047
Death	404 (4.3)	174 (4.9)	175 (4.0)	48 (3.9)	7 (3.0)	0.126

[a]For continuous variables, medians (interquartile ranges (IQRs)) and means (standard deviation (SD)) were presented. For categorical variables, frequencies (percentage) were presented. ICU: intensive care unit.

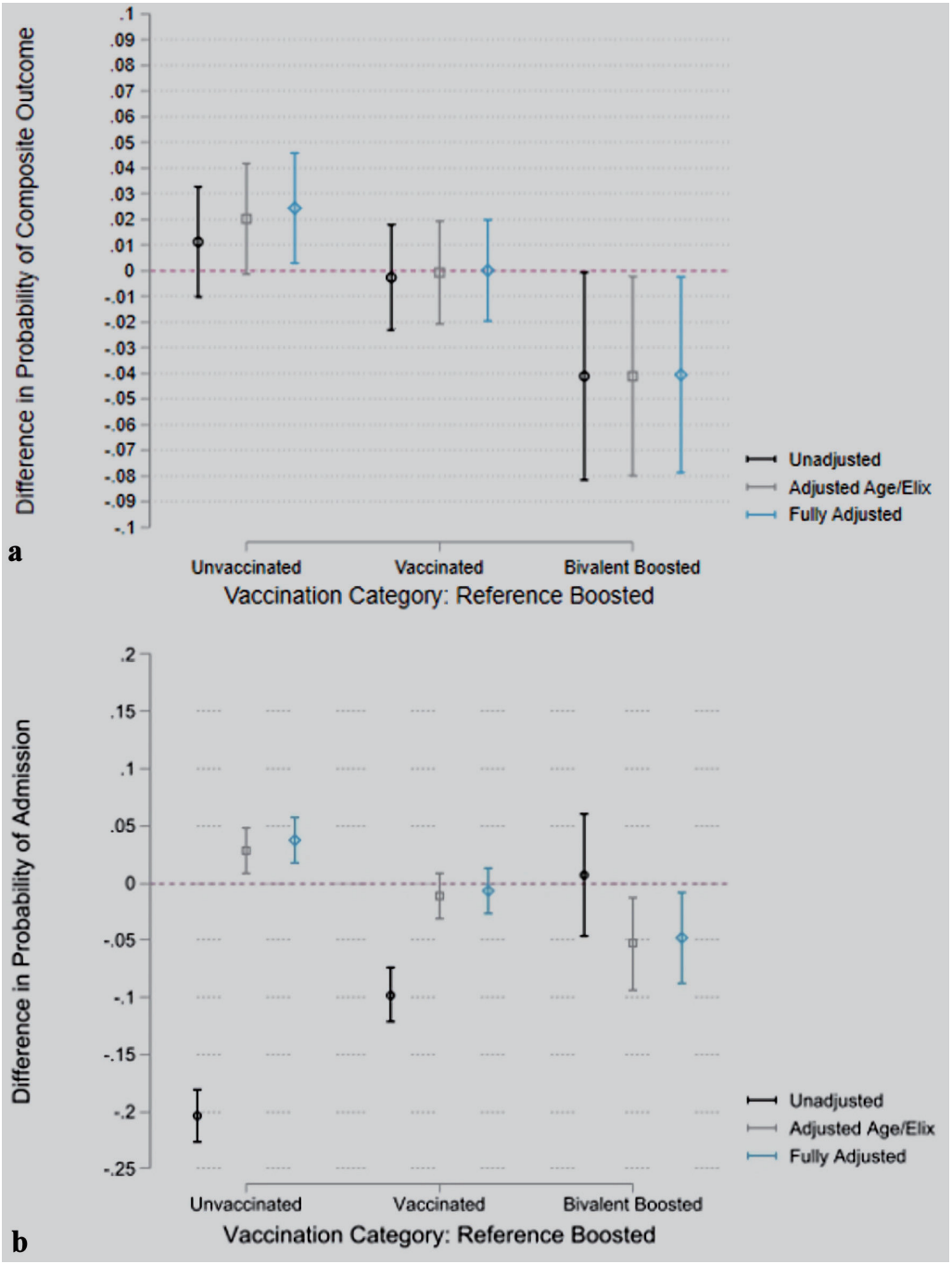

Figure 2. Probability differences in composite outcomes and hospital admission by vaccination status, adjusted for baseline risk factors. Predictions are based on logistic regression models. Unadjusted model does not control for any covariate, adjusted age/Elix controls for age and Elixhauser comorbidity index and fully adjusted further controls for sex, race pre-existing end-stage renal disease and if the patient was immunocompromised. Error bars represent 95% confidence intervals. Point estimates represent the difference in marginal effects of vaccination status on (a) composite outcome with boosted being the reference and (b) probability of hospital admission with boosted being the reference.

the retrospective nature did not allow us to standardize the rationale for intubating patients, potentially limiting our ability to use this as a surrogate outcome. However, given that all patients were seen within the same hospital system, we feel that protocols and rationale for intubation were very similar among sites. We were also unable to account for reinfection given the lack of serological information and, therefore, were unable to evaluate this outcome. Several additional manuscripts with similar data acquisition methods have been published by the core investigative team [25, 26, 35].

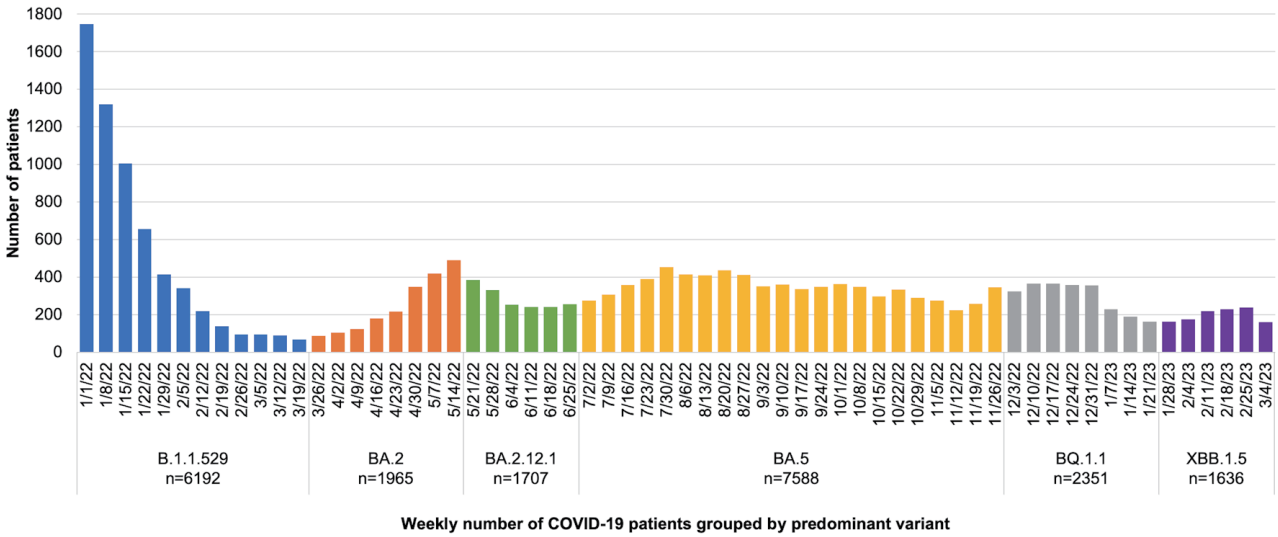

Figure 3. The number of cases meeting inclusion criteria group by predominant coronavirus disease 2019 (COVID-19) variant.

Conclusions

Immunization with the updated bivalent mRNA formulations for the COVID-19 vaccines confer reduced risk of hospitalization and severe outcomes compared to all other groups. Further large-scale real-world research is needed to confirm our findings, particularly with newer variants.

Supplementary Material

Suppl 1. Regression analysis of composite outcome for fully adjusted, partially adjusted, and unadjusted cohorts.

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Financial Disclosure

None to declare.

Conflict of Interest

Amit Bahl, MD, and Steven Johnson, DO, have received grant funding from Moderna. All other authors declare no relevant conflict of interest relevant to this work.

Informed Consent

A Research Waiver of Authorization was granted only for the stipulation of identification/data collection of the specific data variables for this study, given it is not practical or feasible to obtain consent/assent for 10,000+ participants for this chart review. The use of protected health information is necessary to collect study variables/data points in order to achieve the study objectives.

Author Contributions

NM, SJ, CO, and AB designed the study, had full access to the data, and took responsibility for the integrity and accuracy of the data analysis. MT contributed to data and statistical analysis. All authors contributed to the writing and editing of the manuscript. All authors contributed to data acquisition, analysis, and interpretation, and all reviewed and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data Availability

Raw data cannot be shared publicly because protected health information is used in the study. Certain data may be available from the Corewell Health Research Institute (contact via amit.bahl@corewellhealth.org) for researchers who meet the criteria for access to confidential data. Data in tables and supplementary material will be available.

Abbreviations

COVID-19: coronavirus disease 2019; FV&B: fully vaccinated and boosted; FV&BB: fully vaccinated and bivalent boosted; ICU: intensive care unit; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ED: emergency department;

EHR: electronic health record; AHRQ: Agency for Healthcare Research and Quality; ICD-10: International Classification of Diseases, 10th Revision; MCIR: Michigan Care Improvement Registry; CDC: Centers for Disease Control and Prevention; RNA: ribonucleic acid; DNA: deoxyribonucleic acid

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