COVID-19 Outcomes After mRNA SARS-CoV-2 Vaccine

Authors:

Sameh N. Saleh, MD

Madison Pickering, MS

Dimpy P. Shah, MD, PhD

Pankil K. Shah, MD, MSPH

Christoph U. Lehmann, MD

Richard J. Medford, MD

Corresponding Author:

Sameh N. Saleh, MD

Keywords:

COVID-19, SARS-CoV-2, vaccine, vaccine effectiveness, vaccine breakthrough infection, outcomes research, COVID-19 hospitalization, BNT162b2, mRNA-1273

Abstract

Introduction

Breakthrough COVID-19 in fully vaccinated individuals have been reported. We determined clinical outcomes in partially or fully vaccinated (BNT162b2 or mRNA-1273) patients with subsequent breakthrough COVID-19 versus unvaccinated individuals with COVID-19.

Methods

We conducted a retrospective cohort study of adult patients with or without COVID-19 vaccination, who were diagnosed with COVID-19 for the first time between December 11th, 2020, and March 1st, 2021, in the Optum® de-identified COVID-19 Electronic Health Record dataset of ~4.5 million patients. Groups 1A and 1B included patients who developed COVID-19 after one or two doses of vaccine. Group 1C included patients who contracted COVID-19 ≥14 days after the second vaccination. Group 2 included patients who had COVID-19 but never received any vaccination. The primary outcome was 30-day all-cause mortality and secondary outcomes included 30-day emergency room visits, hospitalizations, and intensive care unit stays.

Results

The dataset contained 4,478,451 patients, who were predominately female (56.4%), Caucasian (72.6%), and non-Hispanic (78.7%) with a mean age of 50.2 years. We identified 177,483 patients (4.0% of all patients) with COVID-19 by diagnosis code or by test results (PCR or antigen). Of those, 2,592 (1.5%) and 522 (0.3%) patients developed COVID-19 after one or two vaccine doses, respectively, while 174,369 (98.2%) patients were unvaccinated. Fully vaccinated patients had approximately one-third the odds of an ED visit (odds ratio, 0.39; 95% confidence interval [CI] 0.22-0.63) or a hospitalization (odds ratio, 0.30; 95% CI, 0.12-0.58) compared to being unvaccinated. Receiving one dose had an odds ratio of 0.26 (95% CI, 0.16-0.39) for ICU

stays and 0.31 (95% CI, 0.20-0.46) for death when compared to lack of vaccination. Two doses had odds ratios of 0.16 (95% CI, 0.02-0.57) and 0.04 (95% CI, 0.00-0.31) for ICU stay and death, respectively.

Discussion

We conducted the first nationwide United States study to evaluate real-world effectiveness of COVID-19 vaccination on outcomes of breakthrough infections. Vaccination with either mRNA COVID-19 vaccine was consistently associated with significantly lower rates of ED visits, hospitalizations, ICU stay, and death. Two vaccine doses had a stronger association than one dose for all outcomes.

Introduction

With the continued global spread of the COVID-19 pandemic, the morbidity and mortality caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus has been devastating. There were 200 million cases and 4.5 million deaths (case fatality rate of 2.1%) globally as of August 4, 2021[1]. Despite an early start at vaccination, the United States has been disproportionately affected with approximately 17.6% of cases and 14.5% of all deaths worldwide despite only representing 4.3% of the world's population by the same date. Large-scale deployment of the SARS-CoV-2 vaccines is crucial to curtail further spread of the virus and its more dangerous variants[2]. The three vaccines currently approved for administration in the US—Pfizer's BNT162b2, Moderna's mRNA-1273, and Johnson and Johnson's Ad26.COV2.S—have shown high efficacy in preventing severe COVID-19, including hospitalizations, and intensive care unit (ICU) utilization in randomized control trials[3,4].

However, there have been reports of breakthrough COVID-19 in a small subset of fully vaccinated individuals[4–7]. As early as May 2021, the CDC reported more than 10,000 cases of breakthrough infections after at least one dose of vaccine. Infections were predominately in females (63%) with 10% of patients requiring hospitalization and 2% dying[5]. In June 2021, the CDC redefined definitions of breakthrough infection to include only people who developed COVID-19 ≥14 days after the completion of all recommended doses. This reduced the number of reported breakthrough infections to 4,115 with 608 (15%) deaths related to COVID-19[7]. A recent study from Israel comparing the effectiveness of the BNT162b2 vaccine in individuals 14 to 20 days after vaccination demonstrated an estimated 72% (95% CI, 19 to 100) effectiveness preventing death from Covid-19[8]. Estimating the number of breakthrough infections, severity of outcomes, and the

identification of patients at risk for developing breakthrough infections are crucial to the development of preventive strategies. In this study, we determined the rate of clinical outcomes in patients that have been partially or fully vaccinated with BNT162b2 or mRNA-1273 compared to unvaccinated individuals using a US database of individuals tested for COVID-19. Due to the nature of our data source, we were able to explore factors associated with emergency department (ED) visits, hospitalization, ICU use, and death.

Methods

Data Source

We analyzed the Optum® de-identified COVID-19 Electronic Health Record (EHR) dataset, a national low-latency data pipeline that leverages EHR data generated by providers across the continuum of care, including acute inpatient stays and outpatient visits. Optum's COVID-19-specific database captures approximately 4.5 million patients to date sourced from Optum's longitudinal EHR repository, which is derived from dozens of healthcare provider organizations in the United States, including more than 700 hospitals and 7,000 clinics. The data are certified as de-identified by an independent statistical expert following HIPAA statistical de-identification rules and managed according to Optum® customer data use agreements. The COVID-19 dataset incorporates a wide swath of raw clinical data, including new, unmapped COVID-specific clinical data points from both inpatient and ambulatory EHRs, practice management systems, and numerous other internal systems. The COVID-19 data capture point of care diagnostics specific to the COVID-19 patient during initial presentation, acute illness, and convalescence, with over 500 mapped labs and bedside observations, including COVID-19 specific testing.

The Optum® COVID-19 data elements include demographics, encounter information, laboratory results, vital signs and measurements, diagnoses, procedures, and information derived from unstructured clinical notes using natural language processing. The data are comprised of multiple tables linked by a common patient identifier (anonymous, randomized string of characters). The COVID-19 EHR database includes patients who have a documented clinical care encounter as early as January 2007 through the most current monthly data release (latest data released through April 1, 2021) with a documented diagnosis of COVID-19 after February 1, 2020, or documented SARS-CoV-2 polymerase chain reaction (PCR) or antigen testing result. Further details about the database have been previously published[9].

Study Design and Populations

We conducted an EHR-based retrospective cohort study of adult patients (18 years or older) with or without COVID-19 vaccination, who were diagnosed with COVID-19 for the first time between December 11th, 2020, and March 1st, 2021. March 1st, 2021, was chosen as the cutoff date to allow for a 30-day follow-up period after infection as April 1st, 2021, was the final date for which the current database version contained data. As the dataset was deidentified without the option to identify any individuals who contributed data, this study is not considered human subject research and thus did not require IRB approval.

We categorized a case of COVID-19 as the first instance of a COVID-19-specific ICD-10 diagnosis (Appendix A1) or the first positive SARS-CoV-2 PCR or antigen test (Appendix A2) for a patient. We identified the first administration date of a COVID-19 vaccine as the date of the first dose and the second administration date (if one existed) of a COVID-19 vaccine ≥14 days

from the first dose for a given patient as the date of the second dose. To avoid including adult vaccine trial patients, we only included vaccinations on or after December 10th, 2020, the date of the Food and Drug Administration's first Emergency Use Authorization in the United States[10]. All the patients in this group study received either BNT162b2 (Pfizer) or mRNA-1273 (Moderna) vaccine except for one patient who instead received the Ad26.COV2.S (Johnson and Johnson) vaccine and was excluded from analysis.

Patient Groups and Characteristics

We categorized patients into four groups. Group 1A included individuals who developed COVID-19 after only a single dose of vaccine. Group 1B included individuals who developed COVID-19 after completing their two-dose mRNA immunization series but were diagnosed with COVID-19 <14 days from the second dose. Group 1C includes patients who were diagnosed with COVID-19 ≥14 days after the second dose of vaccination and were considered fully vaccinated per CDC definition[7]. Group 2 included patients who had COVID-19 but never received any vaccination. For each group we compared demographic data including age, sex, race, ethnicity, race, insurance status, body mass index (BMI), and comorbidities according to the Charlson Comorbidity Index (CCI)[11]. The International Classification of Diseases (ICD) diagnosis codes used for determining the subcomponents of the CCI are included in Appendix B. We also evaluated the first value of the laboratory assays C-reactive protein (CRP), D-dimer, and ferritin post-infection, if present.

Main Outcomes

The main outcome of interest was all-cause mortality within 30 days from documented infection. Secondary outcomes included all-cause emergency department visits, hospitalizations, and intensive care unit admissions within 30 days from documented infection. For each visit type, we

evaluated percentage of occurrence for each group as well as the number of visits and days from COVID-19 diagnosis to visit.

Statistical Analysis

We performed descriptive data analyses of demographic and medical characteristics and the outcome variables for the four groups. We then fit unadjusted and multivariable logistic regression models for the primary outcome and each secondary outcome, adjusting for age, sex, race/ethnicity group, insurance status, geographic region, BMI, and CCI. Model covariates were selected a priori based on clinical relevance. Supplemental Table 1 includes details for each variable included. Only BMI had missing values (33.8%); we used multiple imputation with a k-nearest neighbors method (k set for each integer from 2 to 7) to fill missing values. We applied Firth's Penalized Likelihood to mitigate bias of the model given the low prevalence of certain outcome events in our dataset. We also fit unadjusted and multivariable logistic regression models for the subgroup of patients with a comorbidity of malignancy. The α level of significance was set a priori at 0.05, and all hypothesis testing was 2-sided. We presented model results as odds ratios with 95% confidence interval and visualized them using forest plots. Statistical analyses were performed using Python Statistical Software version 3.8.8 (Python Software Foundation) and R version 4.1.0 (R Foundation for Statistical Computing).

Results

The COVID-19 Optum dataset contained data for 4,478,451 patients, who were predominately female (56.4%), Caucasian (72.6%), and non-Hispanic (78.7%) with a mean age of 50.2 years. The largest group of patients were from the Midwest (44.7%), followed by the Northeast (25.4%), South (18%), and West (8.4%) (Supplemental Table 1D). Of the 3,903,787 patients tested by a

PCR or antigen test, 607,249 (15.6%) had a positive test; when restricted to the study dates, 176,971 (15.6%) of 1,134,273 patients had a positive test. Overall, 365,640 (8.2%) patients had received at least one dose and 235,575 (5.3%) had received both doses of the COVID-19 vaccine. By region, 13.9% of patients in the Northeast, 8.9% in the Midwest, 8.4% in the West, and 4.1% in the South had received at least one COVID-19 vaccination (Supplemental Table 2).

We identified 177,483 patients (4.0% of all patients) with COVID-19 by diagnosis code or by testing through PCR or antigen that met our inclusion criteria. Of those identified, 2,592 (1.5%) and 522 (0.3%) patients developed COVID-19 after one or two vaccine doses, respectively, while 174,369 (98.2%) patients were unvaccinated.

Table 1 shows the demographic, regional, and insurance characteristics of these groups. Vaccinated groups had proportionally more women (1A, 69.8%; 1B, 64.5%; 1C, 72.1% vs. 2, 55.4%) than in the unvaccinated group. The percentage of patients of Asian race (1A, 4.1%; 1B, 7.2%; 1C, 6.4% vs. 2, 1.8%) was higher in vaccinated groups than in the unvaccinated group, but the percentage of patients of Black race (1A, 4.7%; 1B, 5.3%; 1C, 5.4% vs. 2, 9.8%) was lower. Compared to the unvaccinated group, the vaccinated groups also had proportionally more patients in the West (1A, 10.8%; 1B, 26.1%; 1C, 29.9% vs. 2, 4.3%) and fewer patients in the South (1A, 15.6%; 1B, 8.5%; 1C, 4.9% vs. 2, 29.3%). Vaccinated groups had higher prevalence of patients with malignancy (1A, 10.8%; 1B, 13.4%; 1C, 9.8% vs 2, 7.8%) compared to the unvaccinated group. Fully vaccinated patients in 1C had a larger prevalence of patients without reported comorbidities (1A, 52.1%; 1B, 50.6%; 2, 51.0% vs 1C, 59.3%). Where obtained, patients who were unvaccinated had a higher median ferritin (1A, 339.5 [136.8-621.0]; 1B, 360.0 [87.8-964.0];

1C, 223.5 [154-319.3] vs 2, 434.0 [193.0-913.0]) and D-dimer (1A, 2.0 [136.8-621.0]; 1B, 1.86 [87.8-964.0]; 1C, 0.69 [154-319.3] vs 2, 5.48 [193.0-913.0]) on admission than patients from the vaccinated groups.

Table 1. Group demographics

	1A	1B	1C	2
	COVID-19 AFTER 1st Dose Received (n = 2,592)	**COVID-19 Infection AFTER Both Doses Received (<14d from 2nd dose) (n=318)**	**COVID-19 Infection AFTER Fully Vaccinated (>=14d from 2nd dose) (n=204)**	**COVID-19 WITHOUT Vaccination* (n = 174,369)**
Age, median (IQR)	51 (37 - 64)	52 (39-65)	48 (36-60)	50 (34 - 64)
Gender, n (%)				
Female	1,808 (69.8)	205 (64.5)	147 (72.1)	96,546 (55.4)
Male	777 (30.0)	112 (35.2)	57 (27.9)	77,615 (44.5)
Other/Unknown	7 (0.3)	1 (0.3)	0 (0)	208 (0.1)
Race, n (%)				
Black	122 (4.7)	17 (5.3)	11 (5.4)	17,035 (9.8)
Asian	105 (4.1)	23 (7.2)	13 (6.4)	3,183 (1.8)
White	1,983 (76.5)	204 (64.2)	134 (65.7)	129642 (74.3)
Other/Unknown	382 (14.7)	74 (23.2)	46 (22.5)	24,509 (14.1)
Ethnicity, n (%)				
Hispanic	123 (4.7)	15 (4.7)	15 (7.4)	17,405 (10.0)
Not Hispanic	2,119 (81.8)	234 (73.6)	154 (75.5)	137,978 (79.1)
Other/Unknown	350 (13.5)	69 (21.7)	35 (17.2)	18,986 (10.9)
Region, n (%)				
Midwest	1,020 (39.4)	88 (27.7)	53 (26.0)	70,626 (40.5)
Northeast	832 (32.1)	118 (37.1)	75 (36.8)	38,718 (22.2)
South	405 (15.6)	27 (8.5)	10 (4.9)	51,076 (29.3)
West	280 (10.8)	83 (26.1)	61 (29.9)	7,461 (4.3)
Other/Unknown	55 (2.1)	2 (0.6)	5 (2.5)	6,488 (3.7)
Insurance, n (%)				
Commercial	1,776 (68.5)	191 (60.1)	137 (67.2)	92,711 (53.2)
Medicaid	69 (2.7)	5 (1.6)	1 (0.4)	17,115 (9.8)
Medicare	525 (20.3)	64 (20.1)	17 (8.3)	31,911 (18.3)
Uninsured	15 (0.6)	0 (0)	0 (0)	5,594 (3.2)
Other Payer/Unknown	554 (21.4)	81 (25.5)	43 (21.1)	29,814 (17.1)
Null/no entry	340 (13.1)	76 (23.9)	51 (25.0)	34,960 (20.0)
Month				
December 11-Dec 31st	557 (21.5)	0 (0)	0 (0)	66,953 (38.4)
January 1 - 31	1,425 (55.0)	173 (54.4)	34 (16.7)	75,554 (43.3)
February 1 - Mar 1	610 (23.5)	145 (45.6)	170 (83.3)	31,862 (18.3)

Charlson Comorbidity Index, median (IQR)*	0 (0-2)	0 (0-2)	0 (0-1)	0 (0-2)
Charlson Comorbidity Index, mean (std)*	1.6 (2.6)	1.8 (2.8)	1.2 (2.4)	1.6 (2.6)
Cerebrovascular Disease	221 (8.5)	31 (9.7)	11 (5.4)	14,118 (8.1)
Congestive Heart Failure	228 (8.8)	30 (9.4)	11 (5.4)	14,616 (8.4)
COPD	599 (23.1)	74 (23.3)	43 (21.1)	41,715 (23.9)
Dementia	76 (2.9)	10 (3.1)	4 (2.0)	5,512 (3.2)
Diabetes Mellitus (complicated)	200 (7.7)	23 (7.2)	4 (2.0)	14,880 (8.5)
Diabetes Mellitus (uncomplicated)	436 (16.8)	55 (17.3)	12 (5.9)	31,743 (18.2)
Hemiplegia/Paraplegia	32 (1.2)	5 (1.6)	1 (0.5)	2,695 (1.5)
HIV/AIDS	6 (0.2)	0 (0)	0 (0)	592 (0.3)
Kidney Disease	236 (9.1)	34 (10.7	13 (6.4)	16,644 (9.5)
Liver Disease (mild)	211 (8.1)	24 (7.5)	17 (8.3)	12,151 (7.0)
Liver Disease (moderate/severe)	10 (0.4)	2 (0.6)	2 (1.0)	992 (0.6)
Malignancy	280 (10.8)	50 (15.7)	20 (9.8)	13,572 (7.8)
Metastatic Solid Tumor	42 (1.6)	6 (1.9)	6 (2.9)	2,967 (1.7)
Myocardial Infarction	144 (5.6)	17 (5.3)	10 (4.9)	11,026 (6.3)
Peptic Ulcer Disease	61 (2.4)	9 (2.8)	6 (2.9)	4,044 (2.3)
Peripheral Vascular Disease	223 (8.6)	29 (9.1)	6 (2.9)	12,163 (7.0)
Rheumatic Disease	97 (3.7)	15 (4.7)	4 (2.0)	5,217 (3.0)
No Comorbidities	1,351 (52.1)	161 (50.6)	121 (59.3)	88,979 (51.0)
Obesity[+‡]	739 (45.7)	77 (42.3)	50 (43.9)	56,283 (48.7)
Body Mass Index (BMI)[+]	29.1 (25.2-34.6)	29.0 (25.0-33.1)	28.4 (24.2-33.1)	29.7 (25.4-35.2)

* The lack of diagnoses recorded in the database was assumed to mean absence of the conditions. All patients had at least one diagnosis recorded in the database.
+Variables with missing data have a denominator shown.
‡ BMI was reported based on the most recent observation within the previous 180 days prior to COVID-19 diagnosis, if present. Obesity was determined by a BMI of ≥30.

Of the COVID-19 patients who were unvaccinated, 20.8% (n=38,413) were seen in the emergency department (ED), compared to 13.5% (n=350), 7.9% (n=25), 7.4% (n=15) in the 1A, 1B, and 1C vaccinated groups, respectively (Table 2). While 13.0% (n=22,750) of unvaccinated patients (i.e., group 2) with COVID-19 were admitted to the hospital, 7.3% (n=188) were hospitalized in the 1-dose vaccine group 1A, 6.0% (n=19) in the 2-dose group 1B, and 3.9% (n=8) in the fully vaccinated group 1C. There was a decreasing trend in median (IQR) LOS with increasing number of vaccination doses: unvaccinated, 5 (3-9) days; single dose, 4 (3-8) days; both doses, 3 (1-5) days. The limited hospitalizations in the fully vaccinated 1C group had a higher LOS with a median

(IQR) of 6 (2.6-9) days. An ICU stay occurred in 2.7% (n=4,647) in the unvaccinated COVID-19 patients compared to 0.7% (n=18), 0.6% (n=1), and 0.7% (n=2) in the vaccinated groups 1A, 1B, and 1C, respectively. Of unvaccinated COVID-19 patients, 2.3% (n=4,038) died compared to 0.9% (n=23) in the 1-dose 1A group. Groups 1B and 1C both had zero deaths.

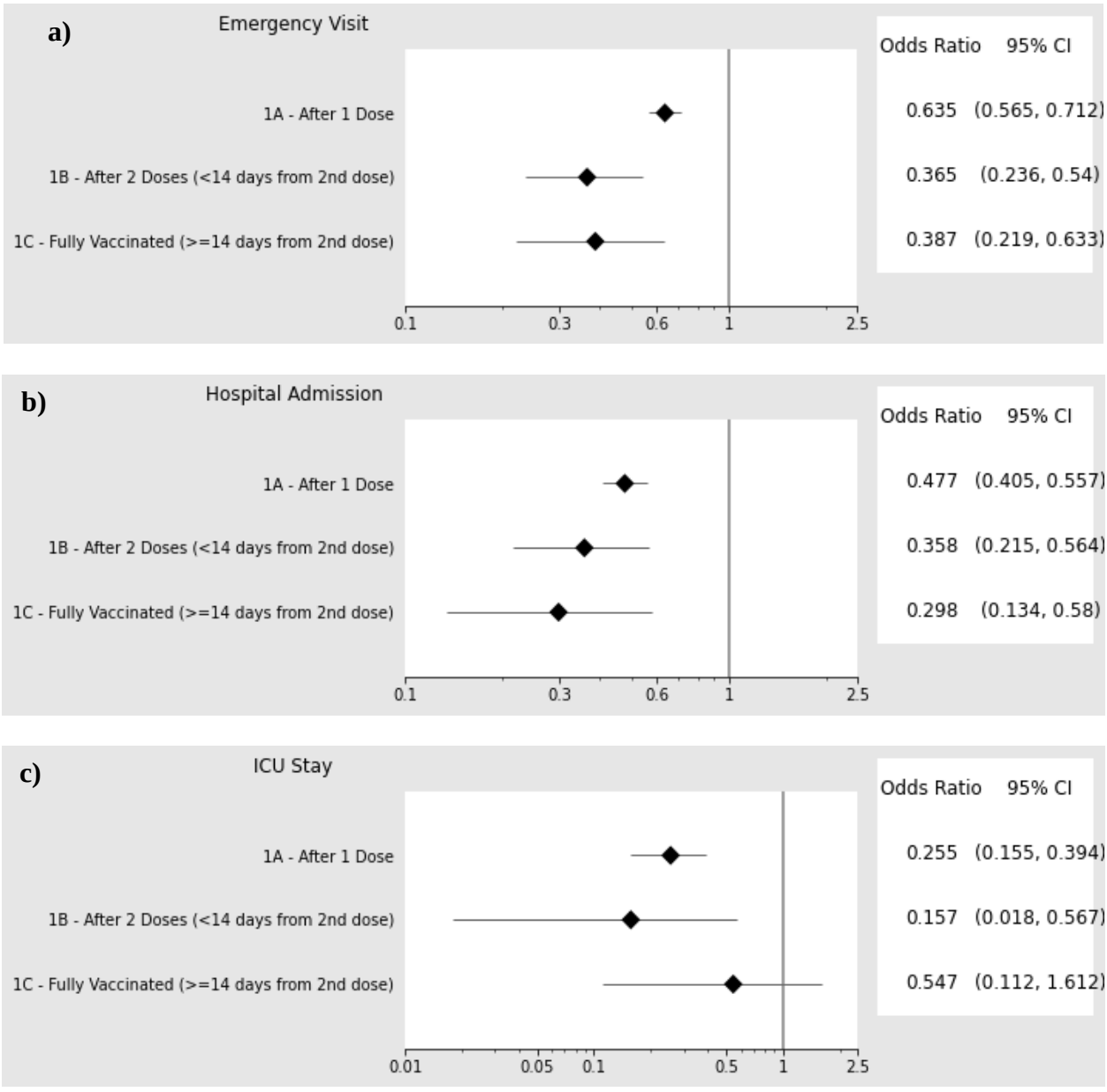
Table 2. Group clinical outcomes for COVID-19 compared after partial vaccination, complete vaccination, and without vaccination. All outcomes are within 30 days of the date of the COVID-19 diagnosis (either by diagnosis code or initial positive test).

	1A	**1B**	**1C**	**2**
	COVID-19 Infection AFTER 1st Dose Received (n = 2,592)	**COVID-19 Infection AFTER Both Doses Received (<14d from 2nd dose) (n=318)**	**COVID-19 Infection AFTER Fully Vaccinated (>=14d from 2nd dose) (n=204)**	**COVID-19 Infection WITHOUT Vaccination (n = 174,369)**
Days from first vaccination to infection, median (IQR)	9 (6-14)	28 (24 -32)	48 (42-56)	N/A
ED visit, n (%)	350 (13.5)	25 (7.9)	15 (7.4)	38,413 (20.8)
Hospitalization, n (%)	188 (7.3)	19 (6.0)	8 (3.9)	22,750 (13.0)
Length of stay in days, median (IQR)	4 (3-8)	3 (1-5)	6 (2.6-9)	5 (3-9)
ICU stay, n (%)	18 (0.7)	1 (0.5)	2 (0.6)	4,647 (2.7)
Mortality, n (%)	23 (0.9)	0 (0.0)	0 (0.0)	4,038 (2.3)

Table 3. Unadjusted and adjusted odds ratios for each outcome compared to the unvaccinated group 2. Odds ratios are derived through Firth penalized logistic regression adjusted for age, gender, region, race/ethnicity, insurance, BMI, and CCI (shown in Supplement Table 4).

Reference = Group 2	**Adjusted Odds Ratio (95% CI)**						**Unadjusted Odds Ratio (95% CI)**		
	1A	**p**	**1B**	**p**	**1C**	**p**	**1A**	**1B**	**1C**
ED visit	0.64 (0.57-0.71)	<0.001	0.37 (0.24-0.54)	<0.001	0.39 (0.22-0.63)	<0.001	0.60 (0.53-0.67)	0.33 (0.22-0.49)	0.31 (0.18-0.51)
Hospitalization	0.48 (0.41-0.56)	<0.001	0.36 (0.22-0.56)	<0.001	0.30 (0.12-0.58)	<0.001	0.52 (0.45-0.61)	0.44 (0.27-0.67)	0.29 (0.14-0.54)
ICU stay	0.26 (0.16-0.39)	<0.001	0.16 (0.02-0.57)	0.002	0.55 (0.11-1.61)	0.31	0.26 (0.16-0.40)	0.18 (0.02-0.62)	0.46 (0.10-1.29)
Mortality	0.31 (0.20-0.46)	<0.001	0.04 (0.00-0.31)	<0.001	0.10 (0.00-0.73)	0.02	0.39 (0.25-0.57)	0.07 (0.00-0.45)	0.10 (0.00-0.71)

Figure 1. Forest plot for a) emergency visits, b) hospitalizations, c) ICU stays, and d) all-cause mortality.



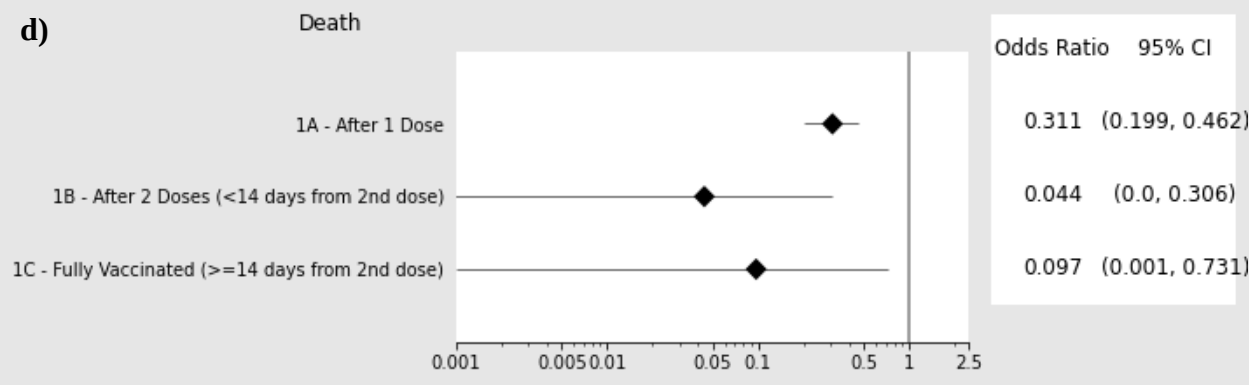


Table 3 shows the unadjusted and adjusted odds ratios of the different outcomes with each vaccination group. Figure 1 displays forest plots for the adjusted odds ratio with confidence intervals. In the adjusted model, infections in vaccinated groups were significantly less likely to have an ED visit or hospitalization within 30 days of COVID-19 diagnosis with an increased association with number of vaccinations. Being fully vaccinated was associated with approximately one-third the odds of an ED visit (odds ratio, 0.39; 95% confidence interval [CI] 0.22-0.63) or a hospitalization (odds ratio, 0.30; 95% CI, 0.12-0.58) compared to being unvaccinated. Receiving 1-dose had an odds ratio of 0.26 (95% CI, 0.16-0.39) for ICU stays and 0.31 (95% CI, 0.20-0.46) when compared to lack of vaccination. Two doses had a stronger association with odds ratios for 0.16 (95% CI, 0.02-0.57) and 0.04 (95% CI, 0.00-0.31) for ICU stays and death, respectively. When evaluating the subgroup of patients with a comorbidity of malignancy, the only significant association across vaccinated groups was a decreased odds of death (Supplemental Table 5).

Discussion

This study explored how immunization with an mRNA vaccine provides protection in patients who subsequently contract COVID-19. To our knowledge, this is the first nationwide study in the United States to evaluate real-world outcomes in breakthrough infections. We leveraged the

Optum® de-identified COVID-19 EHR Dataset, which benefits from national-level data across 700 hospitals and 7,000 clinics that includes nearly 4.5 million patients. Receiving one or two doses of either mRNA COVID-19 vaccine was consistently associated with significantly lower rates of ED visit, hospitalizations, ICU stay, and death. These trends were also seen in the fully vaccinated 1C group. Monitoring and establishing clinical outcomes after vaccination with real-world large-scale data can provide further evidence of vaccine effectiveness across diverse US populations, inform public health and clinical practice, and provide further evidence of vaccine effectiveness to the public.

We observed a disproportionately higher percentage of women in vaccinated groups with breakthrough infection compared to the unvaccinated group. Consistent with recent data from the CDC, women represent a majority (63%) of breakthrough infection[5]. Differences in immunization rate, immunogenicity, vaccine effectiveness, and vaccine administration may all play a role. A recent study notes that men and women had different natural kill cell uptake of lipid nanoparticles in mRNA vaccines that may affect immunogenicity[12]. A 2013 study concluded that the needle length used in IM injections is often too short in overweight and obese females[13]. Women are known to have more subcutaneous fat tissue than men[14] and recommendations suggest selecting needle length based on patient parameters[15]. The standardized use of needle length for all COVID-19 vaccinations may have resulted in more inadvertent subcutaneous injections[16] leading to immunization failures.

The underrepresentation of Black and Hispanic patients and overrepresentation of Asian patients in vaccinated groups seen in this study may be due to immunization rates in these communities.

Asian people are the only group estimated to exceed a 70% vaccination rate while Hispanic people (63%) and Black people (51%) have had much lower immunization rates[17]. Breakthrough infections can only occur if a patient has been vaccinated. These variations in immunization rates likely also account for the disproportionately higher percentage of patients from the West and lower percentage of patients from the South in the vaccinated groups with breakthrough infection. As of June of 2021, the highest vaccination rates were seen in states in the Northeast and West and the lowest in the Midwest and South[18].

While the patient complexity as indicated by the Charlson Comorbidity Index was similar among groups, patients without prior immunization presented with evidence of more severe disease as indicated by higher levels of inflammatory markers Ferritin and D-dimer. In a subgroup analysis, outcomes for patients diagnosed with a malignancy were less favorable than in patients without. This finding may be due to a lowered immune response to the vaccine or higher risk of decompensation after contracting a breakthrough infection. However, the association with vaccination and decreased odds of death remained present for patients with malignancy.

Overall, having partial or completed vaccination was increasingly protective in our patient population against the need for ED visits, hospitalization, and intensive care. Deaths were greatly reduced by vaccination. The data clearly support a strong recommendation for eligible people to become vaccinated against SARS-CoV-2 as soon as possible.

Limitations

This study has several limitations. First, we conducted an observational study of adult patients that precludes determination of causality and may fail to account for some confounding variables.

However, we do not suspect this would change the results significantly. Second, we were limited in determining if a negative outcome was primarily due to COVID-19. However, given that both groups were evaluated under the same conditions, it is reasonable to assume that the contrast in outcomes is most likely associated with COVID-19 vaccination. Third, the Optum database included some variable data quality (e.g., COVID-19 testing without interpretable results or unknown demographics), which could bias usable data. Fourth, misclassification of exposures, diagnoses, and outcomes were possible due to the availability of data in our dataset. But, given the extensive curation and size of the dataset as well as its wide catchment, any misclassifications are not likely to affect observed differences and conclusions. Finally, we used the documentation of an immunization to identify immunized patients and may have missed the recording of vaccinations through other methods. However, this limitation should have weakened the differences between the vaccinated and biased our results toward the null hypothesis.

Conclusions

Inoculation with the BNT162b2 or mRNA-1273 COVID-19 vaccines was associated with reduced odds for ED visits, hospitalizations, ICU utilization, and deaths in patients with new COVID-19. Two vaccine doses had a stronger association than one dose and similar trends were observed in the fully vaccinated group. Patients should be advised that the vaccination has a substantial protective effect on COVID-19 manifestation and clinical outcomes. Further study is needed to assess vaccine effectiveness with the spread of new virus variants.

References

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *The Lancet Infectious Diseases*. 2020;20(5):533-534. doi:10.1016/S1473-3099(20)30120-1
2. Sridhar D, Gurdasani D. Herd immunity by infection is not an option. *Science*. 2021;371(6526):230-231. doi:10.1126/science.abf7921
3. Sadoff J, Gray G, Vandebosch A, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N Engl J Med*. 2021;384(23):2187-2201. doi:10.1056/NEJMoa2101544
4. Tenforde MW, Olson SM, Self WH, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Among Hospitalized Adults Aged ≥65 Years - United States, January-March 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(18):674-679. doi:10.15585/mmwr.mm7018e1
5. CDC COVID-19 Vaccine Breakthrough Case Investigations Team, CDC COVID-19 Vaccine Breakthrough Case Investigations Team, Birhane M, et al. COVID-19 Vaccine Breakthrough Infections Reported to CDC — United States, January 1–April 30, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(21):792-793. doi:10.15585/mmwr.mm7021e3
6. Keehner J, Horton LE, Pfeffer MA, et al. SARS-CoV-2 Infection after Vaccination in Health Care Workers in California. *N Engl J Med*. 2021;384(18):1774-1775. doi:10.1056/NEJMc2101927
7. *COVID-19 Vaccine Breakthrough Case Investigation and Reporting*. Centers for Disease Control and Prevention Accessed June 28, 2021. https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html.

8. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med*. 2021;384(15):1412-1423. doi:10.1056/NEJMoa2101765
9. Incerti D, Rizzo S, Li X, et al. Prognostic model to identify and quantify risk factors for mortality among hospitalised patients with COVID-19 in the USA. *BMJ Open*. 2021;11(4):e047121. doi:10.1136/bmjopen-2020-047121
10. *FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine*. US Food & Drug Administration. Accessed March 30, 2021. https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19
11. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8
12. Vulpis E, Giulimondi F, Digiacomo L, et al. The Possible Role of Sex As an Important Factor in Development and Administration of Lipid Nanomedicine-Based COVID-19 Vaccine. *Mol Pharmaceutics*. 2021;18(6):2448-2453. doi:10.1021/acs.molpharmaceut.1c00291
13. Palma S, Strohfus P. Are IM injections IM in obese and overweight females? A study in injection technique. *Appl Nurs Res*. 2013;26(4):e1-4. doi:10.1016/j.apnr.2013.09.002
14. Westerbacka J, Corn&#65533;r A, Tiikkainen M, et al. Women and men have similar amounts of liver and intra-abdominal fat, despite more subcutaneous fat in women: implications for sex differences in markers of cardiovascular risk. *Diabetologia*. 2004;47(8). doi:10.1007/s00125-004-1460-1

15. *General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)*. Centers for Disease Control and Prevention; 2021. Accessed July 30, 2021. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/administration.html
16. Ng JY. Inadvertent subcutaneous injection of COVID-19 vaccine. *Postgrad Med J*. 2021;97(1148):400-400. doi:10.1136/postgradmedj-2021-139870
17. Reitsma M, Artiga S, Goldhaber-Fiebert J, et al. *Disparities in Reaching COVID-19 Vaccination Benchmarks: Projected Vaccination Rates by Race/Ethnicity as of July 4*. Kaiser Family Foundation; 2021. Accessed July 10, 2021. https://www.kff.org/racial-equity-and-health-policy/issue-brief/disparities-in-reaching-covid-19-vaccination-benchmarks-projected-vaccination-rates-by-race-ethnicity-as-of-july-4/
18. Mathieu E, Ritchie H, Ortiz-Ospina E, et al. A global database of COVID-19 vaccinations. *Nat Hum Behav*. 2021;5(7):947-953. doi:10.1038/s41562-021-01122-8