



Evaluating real-world COVID-19 vaccine effectiveness using a test-negative case–control design

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Aim: It is important to assess if clinical trial efficacy translates into real-world effectiveness for COVID-19 vaccines. **Materials & methods:** We conducted a modified test-negative design (TND) to evaluate the real-world effectiveness of three COVID-19 vaccines. We defined cases in two ways: self-reported COVID-19-positive tests, and self-reported positive tests with ≥ 1 moderate/severe COVID-19 symptom. **Results:** Any vaccination was associated with a 95% reduction in subsequently reporting a positive COVID-19 test, and a 71% reduction in reporting a positive test and ≥ 1 moderate/severe symptom. **Conclusion:** We observed high effectiveness across all three marketed vaccines, both for self-reported positive COVID-19 tests and moderate/severe COVID-19 symptoms. This innovative TND approach can be implemented in future COVID-19 vaccine and treatment real-world effectiveness studies. **Clinicaltrials.gov identifier:** NCT04368065.

Tweetable abstract: Evaluating real-world COVID-19 vaccine effectiveness. #COVID19 #Vaccines #TND #PRO #patientreportedoutcomes

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Large-scale clinical trials evaluating the currently approved COVID-19 vaccines demonstrated robust efficacy in controlled settings, but there are limited data on their effectiveness under real-world conditions and in particular, their effectiveness at preventing more severe symptoms associated with infection [1–3]. Establishing the real-world effectiveness of COVID-19 vaccines may help promote vaccine uptake by allaying concerns about the unprecedented speed at which the vaccines were developed and launched, especially as new variants continue to emerge [4].

An efficient method of evaluating vaccine effectiveness is the test-negative case–control study design [5–8], often used for studying influenza vaccines where clinical trials may not be ethical or feasible, and formal testing is not routinely conducted [9–12]. Test-negative designs (TNDs) have also recently been used for COVID-19 vaccine effectiveness research since these types of studies have been shown to provide reliable estimates of vaccine effectiveness without being subject to confounding by healthcare seeking behavior [13–16]. These designs differ from traditional case–control study designs in that the study subjects are selected from those who present for COVID-19 testing whether such testing was the result of having COVID-19-like symptoms, possible exposure to COVID-19, or was a requirement for work or travel. Cases are those who test positive and controls are those who test negative. TND case–control studies are useful tools that can inform both regulatory and public health policy, especially since much of the initial post-marketing US data on the COVID-19 vaccine effectiveness comes from ecological reporting and observational studies in healthcare workers, with somewhat limited information on their effectiveness in community-dwelling, nonhealthcare-affiliated adults [17–22].

We used a modified version of the TND using direct-to-patient survey data (using community reporting via internet volunteers as opposed to traditional site-based recruitment) to estimate vaccine effectiveness of the Moderna (mRNA-1273, US FDA approval: 31 January 2022), Pfizer (BNT162b2, US FDA approval: 23 August 2021), and Janssen (JNJ-78436735, US FDA Emergency Use Authorization approval: 27 February 2021) [23] vaccines in the general population, including their effectiveness at preventing moderate to severe COVID-19 symptoms.

Materials & methods

This study used self-reported data from the COVID-19 Active Research Experience (CARE) registry's US community-based on-line registry, first launched in March, 2020 to study COVID-19 symptoms and severity outside of the hospital setting and to identify what factors, if any, mitigated the risk from COVID-19 (www.helpstopCOVID19.com) [24,25]. The protocol and survey were updated in January 2021 to include information on vaccination, regardless of whether participants had ever contracted COVID-19.

At enrollment, community-based participants report demographics, COVID-19 test results, medical history, presence and severity of COVID-19-like symptoms, as well as use of medications (prescription and non-prescription) and dietary supplements. COVID-19 test results included both PCR tests and antigen tests. Severity of COVID-19-like symptoms were self-defined by the participant using a four-point scale. In January 2021, questions were added regarding COVID-19 vaccination including dates of administrations and manufacturer for each vaccination [26]. Confirmation of vaccination and COVID-19 test results were not independently obtained.

COVID-19-related symptoms were assembled from the core FDA list [27] with some additions resulting from common free-text write-in responses from the surveys. These symptoms included fever, chills, cough, shortness of breath/difficulty breathing, nasal congestion, sore throat, nausea, diarrhea, fatigue, headache, aches and pains, runny nose, decreased sense of smell, decreased sense of taste, decreased appetite, vomiting, persistent pain or pressure in the chest, trouble waking up after sleeping, anxiety, feeling disoriented or having trouble thinking, depression and insomnia or trouble sleeping. Participants reported symptom severity using a 4-point scale to indicate very mild, mild, moderate or severe.

We used a modified TND to evaluate the effectiveness of the COVID-19 vaccines. In contrast to a traditional TND that is site-based and prospectively tests all participants at the point of care, this study employs online self-reporting of COVID-19 vaccines, COVID-19-testing, results, COVID-19 symptoms and severity. While this is a diversion from the traditional TND approach, these participants have more direct and immediate access to the relevant COVID-19-testing than to testing for other infectious diseases like influenza. To ensure that the study population had the potential for vaccination, we restricted these analyses to participants who reported a COVID-19-test result between 1 March through 16 September 2021, a time-period during which vaccines were widely available in US.

We approached our analysis in two ways. Our first analysis (COVID-19 case positivity) defines cases as those participants who were tested for any reason and reported a positive COVID-19 test result, and controls as those participants who were tested for any reason and reported a negative COVID-19 result. When participants reported both positive and negative test results in that time interval, we selected the positive result and classified them as a case as of that date. When they reported multiple positive tests, we randomly selected one of the results as the study test result; similarly, if a participant reported multiple negative results, we selected a random result. We used random selection to ensure that there was no bias implemented by always taking earlier or later tests, knowing that access to vaccination increased over time starting early in 2021.

A second analysis incorporates the severity of self-reported COVID-19-like symptoms. In this analysis, we defined cases as participants who reported a positive COVID-19 test result and also reported at least one moderate or severe COVID-19 symptom within ± 7 days of that test result. We conducted a sensitivity analyses using those who reported a positive COVID-19 test result and also at least one COVID-19 symptom, regardless of severity. Controls included all participants who reported a negative COVID-19 test result as well as those who reported a positive test result but did not report any moderate/severe symptoms within ± 7 days of that test result. We queried symptoms from participants at the time of positive or negative test report; when multiple surveys were available within ± 7 days of the reported COVID-19-test, we chose the survey with the largest number of moderate/severe symptoms reported to assure we identified the highest severity of symptoms reported.

We used self-reported vaccination status, which was subsequently characterized as unvaccinated, partially vaccinated, or fully vaccinated at the time of the reported COVID-19 test result. Unvaccinated participants had not received any vaccine at the time of the COVID-19 test result (Figure 1). We classified participants as 'fully

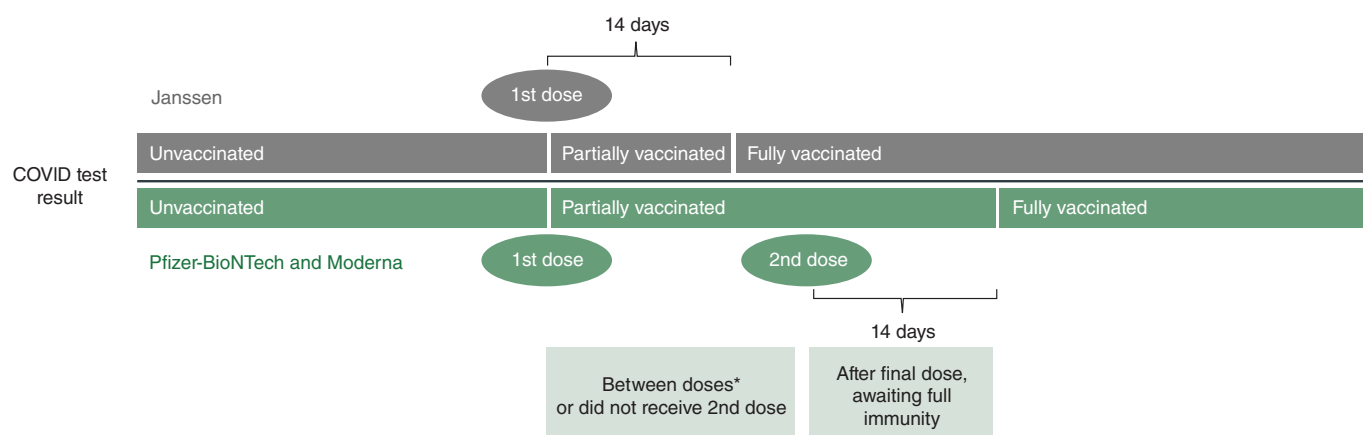


Figure 1. Vaccination status determination at time of COVID-19 testing for single- and two-dose vaccines.

Table 1. Access proxy defined as matrix of availability and vaccine administration rate.

	High vaccination rate (admin per 100,000 on 6/1 [†])	Low vaccination rate (admin per 100,000 on 6/1 [†])
Early availability (March 10–April 4 2021)	AZ, CO, CT, IL, KS, MN, MT, ND, NH, OH, UT (>79,938) Count: 11	AL, AR, GA, IN, LA, MS, OK, SC, TX, WV, WY (<79,938) Count: 11
Late availability (April 5–April 19 2021)	CA, DC, DE, HI, MA, MD, ME, NJ, NM, NY, PA, RI, VA, VT, WA (>96,910) Count: 15	AK, FL, IA, ID, KY, MI, MO, NC, NE, NV, OR, SD, TN, WI (<96,910) Count: 14

[†] 1 June 2021.

vaccinated' at 14 days post-second dose of Moderna or Pfizer vaccine or 14 days after their receipt of the Janssen vaccine. We classified participants as 'partially' vaccinated if they had only received their first dose of Pfizer or Moderna but not the second dose, or if they had received two doses of Pfizer or Moderna vaccine, but were not yet 14 days post-second dose, or had received Janssen but were not yet 14 days post-vaccination. We treated the five participants who reported receiving doses from different manufacturers as 'fully vaccinated' using the same time intervals described previously, but they were excluded from the manufacturer-specific analysis. If participants noted vaccination prior to 1 December 2020 ($n = 10$) or reported vaccination with a COVID-19 vaccine other than Janssen, Pfizer or Moderna, they were excluded from this study ($n = 6$). We also excluded those who reported the same date for their first and second vaccine doses for Moderna and Pfizer ($n = 8$). Boosters were largely unavailable at the time these data were collected and are not considered in this study.

The core analyses aimed to compare the exposure of vaccinated (fully or partially) versus unvaccinated, but also included sensitivity analyses separately for those that were fully vaccinated versus unvaccinated and partially vaccinated versus unvaccinated. Further, we examined each vaccine manufacturer separately for effectiveness using the primary study vaccine exposure definition (fully or partially vaccinated vs unvaccinated).

We accounted for participants' initial geographical access to vaccination by using a proxy variable defined by the timing of availability in a given state (e.g., before or after 5 April 2021), and the state-specific administration rate among those 16 years and older on 1 June 2021. We defined high and low administration rates per 100,000 population for each state and DC according to CDC data [28] using the median state's rate as the cut-off to determine high and low. We deemed 1 June 2021 as date where the majority of the US population would have an opportunity to be vaccinated. (Table 1).

We calculated crude and adjusted odds ratios (95% confidence intervals) via multivariate logistic regression models to examine vaccine effectiveness. In multivariable models we adjusted for the following: race (White, other); gender (female, male, other [including male, transgender, not disclosed and other]); age (continuous); education (some college or less, 4-year college degree, >4 year college degree); ethnicity of Hispanic or Latino (yes, no); access to COVID-19 vaccine proxy (early availability, high vaccination rate; early availability, low vaccination rate; late availability, high vaccination rate; late availability, low vaccination rate); and medical conditions including

anxiety, autoimmune disorder, blood disorder, cardiovascular disorder, depression, diabetes, hypertension, insomnia or trouble sleeping, kidney disorder and lung disorder (yes, no).

Results

Participant characteristics

Of the 2481 participants who reported testing and vaccination status, 695 (28.0%) individuals reported a positive COVID-19 test result and 1786 (72.0%) individuals reported a negative test result. Among these participants, 1211 (48.8%) were fully vaccinated, 354 (14.3%) were partially vaccinated and 916 (36.9%) were unvaccinated (Table 2). Most participants (80.2%) reported not having any moderate/severe symptoms; 6.2% having at least one moderate to severe symptom, and 13.6% having two or more such symptoms. Among participants that reported a positive COVID-19 test, 38.0% of cases reported at least one moderate/severe symptom as compared with 12.7% of those reporting a negative test. Of the 695 positive COVID-19 participants, 12 (1.7%) reported a hospitalization related to COVID-19. Study participants had a mean age of 46.4 years (standard deviation [SD] = 15.1) and were predominately female (82.8%), well educated (61.9% $\geq$ 4-year college) and White (87.1%). Both cases and controls were similar with regard to age (mean age: 46.7 years [SD = 15.3] versus 46.3 years [SD = 15.0]), gender (female 80.7% vs 83.7%) and race (White: 89.5% vs 86.2%), but the case population (52.5% $\geq$ 4-year college) reported slightly lower education than controls (65.6% $\geq$ 4-year college). A notable proportion of the study participants reported having anxiety (38.5%), depression (32.5%), insomnia or trouble sleeping (29.8%) and/or hypertension (22.6%) at their baseline survey, which were comparable across both cases and controls.

Test-negative design analysis

When looking at vaccine effectiveness against self-reported COVID-19-positive tests only, 124 cases (17.8% of 695) reported being fully or partially vaccinated at the time of their positive COVID-19 test, while 1441 controls (80.6% of 1786) reported being fully or partially vaccinated at the time of their negative COVID-19 test (Table 2). This resulted in an unadjusted odds ratio of 0.05 (95% CI: 0.04, 0.07) and adjusted odds ratio (aOR) of 0.05 (95% CI: 0.04, 0.06), indicating that being vaccinated was associated with a 95% reduction in the odds of having a self-reported positive COVID-19 test.

When looking at vaccine effectiveness against at least one moderate/severe COVID-19 symptom in COVID-19-positive cases (165 cases and 2316 controls) (Table 3), 57 cases reported being fully or partially vaccinated at the time of their positive COVID-19 test with at least one moderate/severe symptom, while 1,547 control patients reported being fully or partially vaccinated at the time of their negative COVID-19 test with at least one moderate/severe symptom. This resulted in an unadjusted odds ratio of 0.26 (95% CI: 0.19, 0.37) and aOR of 0.29 (95% CI: 0.20, 0.40), indicating a 71% reduction in the odds of having a self-reported positive COVID-19 test and at least one moderate/severe symptom. As a sensitivity analysis, we examined vaccine effectiveness against any COVID symptoms regardless of reported severity and we observed an aOR of 0.22 (95% CI: 0.16, 0.31) for fully vaccinated and 0.37 (0.24, 0.58) for those partially vaccinated.

When examining the effects of covariates on reporting a positive test for COVID-19, male gender (aOR 1.50; 95% CI: 1.10, 2.06), White (aOR = 2.33; 95% CI: 1.64, 3.32), reporting a blood disorder, (including a history of blood clots, sickle cell disease, thalassemia, thrombocytopenia or other blood disease) (aOR = 3.01; 95% CI: 1.56, 5.83) and reporting a lung disorder (aOR = 0.55; 95% CI: 0.37, 0.81) were significant predictors in the adjusted model. While not statistically significant, low vaccination rates in the state of the participant, regardless of timing of vaccine availability were greater than one (early availability/low access: aOR = 1.24; 95% CI: 0.74, 2.09; and late availability/low access: aOR = 1.26; 95% CI 0.79, 2.02).

When examining the effectiveness of full vaccination (versus being unvaccinated) and partial vaccination (at least one dose, but not having achieved full potential immunity) versus being unvaccinated, full vaccination was more protective (aOR = 0.03; 95% CI: 0.03, 0.05) when compared with partial vaccination (versus being unvaccinated) (aOR = 0.08; 95% CI: 0.06, 0.12) (Table 4). In the symptom-based analysis, fully vaccination (aOR = 0.28; 95% CI: 0.19, 0.41) resulted in slightly higher effectiveness than those with partial vaccination (aOR = 0.29; 95% CI: 0.16, 0.53).

When examining COVID-19 test positivity alone, vaccine effectiveness results were similar across manufacturers (Table 5 & Figure 2); Moderna had the highest effectiveness of 97% (aOR = 0.03; 95% CI: 0.02, 0.04), followed closely by Janssen at 96% (aOR = 0.04; 95% CI: 0.02, 0.09), and Pfizer at 94% (aOR = 0.06; 95% CI: 0.04, 0.07). When examining by the symptom severity case definition, Moderna showed the highest effectiveness at

Table 2. Participant characteristics.

	Cases COVID-19 test positive	Controls COVID-19 test negative	Cases COVID-19 test positive with >1 moderate to severe COVID symptoms	Controls COVID-19 test positive with <1 moderate to severe COVID symptoms and COVID-19 test negative	Total
Vaccination status (n)	695	1786	165	2316	2481
Fully vaccinated, n (%)	76 (10.9)	1135 (63.6)	42 (25.5)	1199 (51.8)	1211 (48.8)
Partially vaccinated, n (%)	48 (6.9)	306 (17.1)	15 (9.1)	348 (15.0)	354 (14.3)
Unvaccinated, n (%)	571 (82.2)	345 (19.3)	108 (65.5)	769 (33.2)	916 (36.9)
Moderate/severe symptoms (n)					
None, n (%)	431 (62.0)	1559 (87.3)	0 (0)	1991 (85.9)	1990 (80.2)
One, n (%)	87 (12.5)	67 (3.8)	54 (32.7)	99 (4.3)	154 (6.2)
Two or more, n (%)	177 (25.5)	160 (8.9)	111 (67.3)	226 (9.8)	337 (13.6)
Age, years (n)	695	1786	165	2316	2481
Mean (SD)	46.7 (15.3)	46.3 (15.0)	46.7 (15.2)	46.3 (15.1)	46.4 (15.1)
Median (IQR)	46 (34–60)	45 (34–59)	46 (34–59)	45 (34–59)	45 (34–59)
Age group, n (years)	695	1786	19 (11.5)	322 (13.9)	2481
18–29, n (%)	93 (13.4)	248 (13.9)	35 (21.2)	573 (24.7)	341 (13.7)
30–39, n (%)	164 (23.6)	444 (24.8)	27 (16.4)	433 (18.7)	608 (24.5)
40–49, n (%)	123 (17.7)	337 (18.9)	45 (27.3)	416 (17.9)	460 (18.5)
50–59, n (%)	139 (20.0)	322 (18.0)	39 (23.6)	572 (24.7)	461 (18.6)
≥ 60, n (%)	176 (25.3)	435 (24.4)	19 (11.5)	322 (13.9)	611 (24.6)
Gender (n)	695	1786	165	2316	2481
Female, n (%)	561 (80.7)	1495 (83.7)	135 (81.8)	1921 (82.9)	2056 (82.8)
Male, n (%)	118 (16.9)	244 (13.7)	25 (15.2)	337 (14.6)	362 (14.6)
Transgender, n (%)	7 (1.0)	26 (1.5)	2 (1.2)	31 (1.3)	33 (1.3)
Other, n (%)	9 (1.3)	20 (1.5)	3 (1.8)	26 (1.1)	29 (1.2)
Not disclosed, n (%)	0 (0)	1 (0.1)	0 (0)	1 (0.04)	1 (0.04)
Education (n)	695	1784	165	2314	2479
Some college or less, n (%)	330 (47.5)	614 (34.4)	88 (53.3)	856 (37.0)	944 (38.1)
4-year college degree, n (%)	157 (22.6)	491 (27.5)	36 (21.8)	612 (26.4)	648 (26.1)
>4-year college degree, n (%)	208 (29.9)	679 (38.1)	41 (24.9)	846 (36.5)	887 (35.8)
Race (n)	692	1783	1 (0.6)	53 (2.3)	2481
Asian, n (%)	5 (0.7)	49 (2.8)	2 (1.2)	81 (3.5)	54 (2.2)
Black or African-American, n (%)	24 (3.5)	59 (3.3)	143 (86.7)	2013 (86.9)	83 (3.4)
White, n (%)	619 (89.5)	1537 (86.2)	18 (10.9)	164 (7.1)	2156 (87.1)
Other [†] , n (%)	44 (6.4)	138 (7.7)	1 (0.6)	5 (0.2)	182 (7.4)
Ethnicity					
Hispanic or Latino, n (%)	73 (10.6)	154 (8.7)	14 (8.5)	213 (9.2)	227 (9.2)
Medical condition					
Anxiety, n (%)	289 (41.5)	666 (37.3)	84 (50.9)	871 (37.6)	955 (38.5)
Autoimmune disease, n (%)	90 (13.0)	214 (11.9)	27 (16.3)	277 (11.9)	304 (12.3)
Blood disorder, n (%)	30 (4.3)	36 (2.0)	54 (2.3)	12 (7.3)	66 (2.7)
Cardiovascular disease, n (%)	39 (5.6)	100 (5.6)	14 (8.5)	125 (5.4)	139 (5.6)
Depression, n (%)	239 (34.4)	567 (31.8)	69 (41.8)	737 (31.8)	806 (32.5)
Diabetes, n (%)	65 (9.4)	151 (8.5)	15 (9.1)	201 (8.7)	216 (8.7)
Hypertension, n (%)	158 (22.7)	402 (22.5)	40 (24.2)	520 (22.5)	560 (22.6)
Insomnia or trouble sleeping, n (%)	225 (32.4)	515 (28.8)	72 (43.6)	668 (28.8)	740 (29.8)

[†] The race category of other includes: 13 American-Indians or Alaskans, 3 Hawaiian or Pacific Islander, 77 who selected multiple races and 89 who selected 'other'.

Table 2. Participant characteristics (cont.).

	Cases COVID-19 test positive	Controls COVID-19 test negative	Cases COVID-19 test positive with >1 moderate to severe COVID symptoms	Controls COVID-19 test positive with <1 moderate to severe COVID symptoms and COVID-19 test negative	Total
Kidney disease, n (%)	21 (3.0)	53 (3.0)	6 (3.6)	68 (2.9)	74 (3.0)
Lung disease, n (%)	63 (9.1)	204 (11.4)	21 (12.7)	246 (10.6)	267 (10.7)
Organ transplant, n (%)	2 (0.3)	3 (0.2)	1 (0.6)	4 (0.2)	5 (0.2)
On treatment for cancer, n (%)	692	1777			2469
Yes, n (%)	10 (1.5)	22 (1.2)	5 (3.0)	27 (1.2)	32 (1.3)

†The race category of other includes: 13 American-Indians or Alaskans, 3 Hawaiian or Pacific Islander, 77 who selected multiple races and 89 who selected 'other'.

Table 3. Multivariate model for vaccine effectiveness at preventing cases of COVID-19.

Covariates	Odds of having a COVID-19-positive test	Odds of having a COVID-19-positive test with ≥ 1 moderate/severe symptom
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Vaccination status		
Unvaccinated	(ref)	(ref)
Fully or partially vaccinated	0.05 (0.04, 0.06)	0.29 (0.20, 0.40)
Anxiety	1.27 (0.96, 1.69)	1.46 (0.97, 2.21)
Autoimmune disorder	1.22 (0.86, 1.74)	1.15 (0.72, 1.85)
Blood disorder	3.01 (1.56, 5.83)	2.60 (1.28, 5.28)
Cardiovascular disorder	0.89 (0.53, 1.50)	1.47 (0.76, 2.81)
Depression	1.00 (0.74, 1.33)	1.07 (0.71, 1.61)
Diabetes	1.23 (0.81, 1.86)	0.87 (0.48, 1.58)
Hypertension	0.89 (0.66, 1.20)	0.85 (0.55, 1.32)
Insomnia or trouble sleeping	1.09 (0.84, 1.42)	1.57 (1.09, 2.25)
Kidney Disorder	1.19 (0.60, 2.36)	0.95 (0.38, 2.42)
Lung Disorder	0.55 (0.37, 0.81)	0.90 (0.54, 1.52)
Education		
Some college or less	(ref)	(ref)
4-year college degree	0.73 (0.55, 0.97)	0.71 (0.46, 1.08)
>4-year college degree	0.97 (0.74, 1.27)	0.68 (0.45, 1.02)
Race		
Other	(ref)	(ref)
White	2.33 (1.64, 3.32)	1.09 (0.65, 1.82)
Age (per 1 year increment)	1.00 (0.99, 1.01)	1.01 (0.99, 1.02)
Gender		
Female	(ref)	(ref)
Male	1.50 (1.10, 2.06)	1.26 (0.79, 2.01)
Other	1.35 (0.63, 2.91)	1.29 (0.48, 3.47)
Ethnicity (Hispanic Latino vs not)		
Not Hispanic	(ref)	(ref)
Hispanic	0.99 (0.68, 1.46)	0.84 (0.45, 1.54)
Vaccination access (proxy)		
Early availability, high vaccination rate	(ref)	(ref)
Early availability, low vaccination rate	0.87 (0.60, 1.26)	1.24 (0.74, 2.09)
Late availability, high vaccination rate	0.63 (0.46, 0.86)	0.72 (0.44, 1.16)
Late availability, low vaccination rate	1.15 (0.83, 1.60)	1.26 (0.79, 2.02)

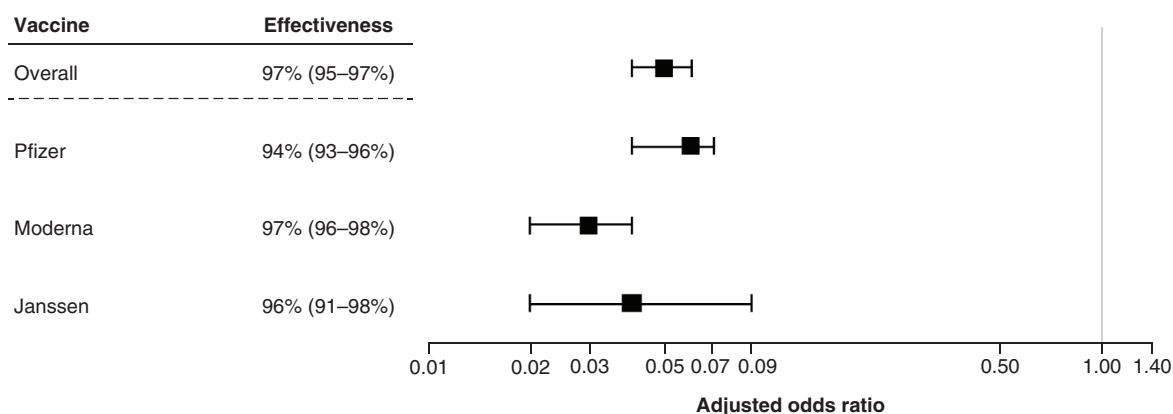
If a referent category is not listed, then the comparison is yes vs no (referent group).

Table 4. Test-negative analysis (odds of a positive COVID-19 test or a positive COVID-19 test and at least one moderate to severe symptom by vaccination status).

	Vaccination status	Cases COVID-19 test positive (n)	Controls COVID-19 test negative (n)	OR (95% CI)	aOR (95% CI)
Test-negative analysis based on COVID-19 test results	Fully vaccinated	76	1135	0.04 (0.03, 0.05)	0.03 (0.03, 0.05)
	Unvaccinated	571	345		
	Partially vaccinated	48	306	0.10 (0.07, 0.13)	0.08 (0.06, 0.12)
	Unvaccinated	571	345		
	Vaccination status	Cases COVID-19 test positive with >1 moderate to severe COVID symptoms (n)	Controls COVID-19 test positive without moderate to severe COVID symptoms and COVID-19 test negative (n)	OR (95% CI)	aOR (95% CI)
Test-negative analysis based on COVID-19 test results and requiring at least one moderate to severe symptom	Fully vaccinated	42	1199	0.25 (0.17, 0.36)	0.28 (0.19, 0.41)
	Unvaccinated	108	769		
	Partially vaccinated	15	348	0.31 (0.18, 0.53)	0.29 (0.16, 0.53)
	Unvaccinated	108	769		

Table 5. Vaccine effectiveness at preventing cases of COVID-19 by vaccine manufacturer and vaccination status for both test-negative analysis results.

	Manufacturer	Vaccination status	Cases COVID-19 test positive (n)	Controls COVID-19 test negative (n)	OR (95% CI)	aOR (95% CI)
Test-negative analysis based on COVID-19 test results	Pfizer	Fully or partially vaccinated	80	732	0.06 (0.05, 0.09)	0.06 (0.04, 0.07)
		Unvaccinated	571	345		
	Moderna	Fully or partially vaccinated	37	611	0.04 (0.03, 0.05)	0.03 (0.02, 0.04)
		Unvaccinated	571	345		
	Janssen	Fully or partially vaccinated	7	93	0.05 (0.02, 0.09)	0.04 (0.02, 0.09)
		Unvaccinated	571	345		
	Manufacturer	Vaccination status	Cases COVID-19 test positive with >1 moderate to severe COVID symptoms (n)	Controls COVID-19 test positive without moderate to severe COVID symptoms and COVID-19 test negative (n)	OR (95% CI)	aOR (95% CI)
Test-negative analysis based on COVID-19 test results and requiring at least one moderate to severe symptom	Pfizer	Fully or partially vaccinated	30	620	0.35 (0.23, 0.52)	0.38 (0.24, 0.58)
		Unvaccinated	108	769		
	Moderna	Fully or partially vaccinated	9	495	0.13 (0.07, 0.26)	0.14 (0.07, 0.28)
		Unvaccinated	108	769		
	Janssen	Fully or partially vaccinated	3	83	0.26 (0.08, 0.83)	0.35 (0.11, 1.15)
		Unvaccinated	108	769		

**Figure 2. Vaccine effectiveness of preventing cases of COVID-19 among those with at least one vaccination versus unvaccinated, overall and by manufacturer (primary analysis based on COVID-19 test results).**

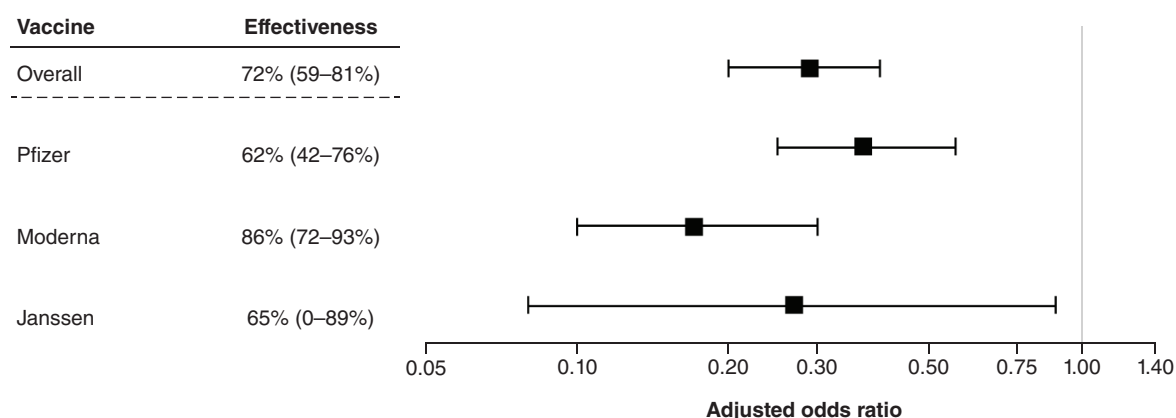


Figure 3. Vaccine effectiveness of preventing cases of COVID-19 among those with at least one vaccination versus unvaccinated, overall and by manufacturer (secondary analysis based on test results and requiring at least one moderate to severe symptom).

preventing symptomatic cases with an 86% effectiveness (aOR = 0.14; 95% CI: 0.07, 0.28), followed by Janssen at 65% (aOR = 0.35; 95% CI: 0.11, 1.15) and Pfizer at 62% (aOR = 0.38; 95% CI: 0.24, 0.58) (Figure 3).

Discussion & Conclusion

While the COVID-19 vaccines were rigorously tested in clinical trials establishing their safety and efficacy, the expedited clinical development coupled with immediate widespread use has brought about scrutiny from the public as to whether the findings would be replicated in the real world. This study was too small to study deaths or serious outcomes, recognizing these are high priority outcomes for patients [29]. Here we show that COVID-19 vaccines manufactured by Pfizer, Janssen and Moderna demonstrated consistent and meaningful real-world effectiveness for protection against moderate to severe COVID-19 symptoms. The results from this community-based registry of US adults are consistent with what has been reported in randomized controlled trials [1–3] as well as other published TND studies from both ambulatory and inpatient settings [13–16]. We observed a 95% reduction in aOR of a self-reported COVID-19-positive test in vaccinated participants, with 94%, 96% and 97% reduction in aOR for Pfizer, Janssen and Moderna, respectively. With respect to vaccine effectiveness at mitigating symptom severity, we observed a 74% reduction in risk of moderate-to-severe symptoms overall among those with self-reported COVID-19 diagnosis. Our results suggest greater protection for those who were fully vaccinated as compared with those partially vaccinated, although the results still show clear protection for patients who only received one mRNA vaccine dose and/or had not completed the full immunity period (i.e., 14 days post-final vaccination). These findings contribute to the evidence supporting COVID-19 vaccine effectiveness at mitigating infection in the community overall and reducing COVID-19 severity among breakthrough infections.

Since their emergency use authorizations, several cohort studies among healthcare workers and among older adults have shown effectiveness of the mRNA vaccines (i.e., Pfizer and Moderna) consistent with the 94–95% efficacy observed phase III studies [17,19,22]. TND studies have also been conducted in similar high-risk groups from the US, UK and Canada, with consistent findings [13–16]. At the same time, there are still limited data on vaccine effectiveness among community-dwelling adults across age groups. Our results generally align with other cohort and case-control studies on vaccine effectiveness in the general population. Of note, our findings for mRNA vaccines specifically are consistent with what was observed in their phase II studies, while our findings for the Janssen vaccine are higher (96.0% effective in this study vs 66.3% in the clinical trial).

Our study also contributes to the broader understanding of vaccine effectiveness at mitigating moderate to severe COVID-19 disease symptoms. While we observed the strongest effectiveness in the context of preventing a self-reported positive test, these COVID-19 vaccines had substantial (~70%) effectiveness in preventing one or more moderate to severe symptoms. It is important to note that the severity of COVID-19 symptoms here requires self-reporting, which may be difficult from a hospital bed or among very sick patients, and had no requirement for or link to healthcare utilization (this study only included 21 participants that reported any hospitalizations during the study period). Our findings show that COVID-19 vaccines protect against moderate-to-severe symptoms that did not necessarily require hospitalization or even interactions with the healthcare system.

While vaccination status is the most important predictor, there were several other variables in the adjusted model that were significant and may provide insight into the bigger picture of COVID-19 risk and vaccine effectiveness. Participants who reported a blood disorder in their baseline medical history were associated with a three-fold risk of testing positive for COVID-19. This blood disorder variable is broad, with our 66 respondents having been prompted by examples that included blood clots, sickle cell disease, thalassemia, thrombocytopenia or other blood disease. Our finding in this heterogeneous group requires some explanation. While it is known that COVID-19 infection may be pro-thrombotic, and this may potentially exacerbate pro-thrombotic blood disorders, our broad and heterogeneous 'blood disorder' group may also have included conditions associated with immunosuppression, or the use of immunosuppressive medications, in turn resulting in decreased viral clearance and more severe disease. This result may highlight another potential at-risk population for increased risk of the COVID-19 infection, and merits further investigation to better define the hematological conditions associated with greater risk. Anaemia has been previously suggested to be an independent risk factor for COVID-19-related mortality, and it would be very likely that our group also included anaemic patients, but their exact contribution to the rather large effect observed is uncertain in our dataset [30,31]. Also, self-reported Caucasian race was associated with a more than a two-fold increased risk of testing COVID-19 positive, but no elevated risk of testing positive and being symptomatic; however, we suspect that self-reported Caucasian race may actually be serving here as a proxy for access to COVID-19 testing rather than having a direct causal relationship, though these data have limited potential to shed much light on the effects of race due to the preponderance of participants who described themselves as Caucasian.

Participants who reported lung disorders were significantly less likely to report a positive for COVID-19 test (aOR = 0.55; 95% CI: 0.37, 0.81). Although it is possible that there may be a common drug/treatment in this group of participants that may be COVID-19 protective, these findings may also have been a result of those at highest risk of severe COVID-19 outcomes either being hospitalized from COVID infection and not able to participate in the study, or that they may have used other methods for preventing COVID-19 infection (e.g., very limited social interaction) that are not explicitly captured as stand-alone variables in our model. These social variables also play an important role in explaining COVID-19 transmission outside of vaccination, and they should be considered in other studies.

We also observed that while early availability of the vaccine in the participants' home states did not have a notable impact, the level of vaccinations in those states did seem to suggest some association with reporting a positive test. Low vaccination rates in the state of the participant, regardless of timing of vaccine availability, show a modest increased risk of self-reported COVID-19-positive testing (early availability/low access: aOR = 1.24; 95% CI: 0.74, 2.09; and late availability/low access: aOR = 1.26; 95% CI 0.79, 2.02). This suggests that independent of the study participant's personal vaccination status, the vaccination rate in the state they reside may also be potentially important factor in COVID-19 infection risk. Participants who were medically recognized to be highly vulnerable may have sought vaccination with the first available vaccine on the market in the US (Pfizer) and this could explain the slightly lower effectiveness observed with that vaccine.

While the data are reassuring on the effectiveness of the current COVID-19 vaccines, this study was not designed to look at specific variants such as Delta or Omicron and cannot be extrapolated to variants, time periods or regions, nor does it address the efficacy of protecting against severe COVID-19. Coupled with the known possibility of waning immunity from vaccination, additional booster doses are now recommended, particularly for higher risk groups. While cohort studies can be limited when timely data are needed to inform public health measures, the efficiency of a TND or modified TND approach with an unbiased selection of cases and controls are likely one of the best options to study the vaccines in the post-market setting.

Although CARE data rely on self-reported information subject to some information biases, these real-world data have detailed information on participant experiences with respect to COVID-19 and the vaccines. Misclassification of vaccination status can bias TND studies but is unlikely here since participants are likely to know whether they have been vaccinated; further they were encouraged to consult their vaccination cards when reporting manufacturer, lot, and dates. Moreover, person-generated data like this allows for a comprehensive capture of all relevant patient-level clinical and nonclinical data which are often not available in larger real-world data sources.

Nonetheless, it is not always clear whether participants were tested for COVID-19 because they were symptomatic or exposed to someone who tested positive, or if it was mandated for some other reason. It is possible that vaccinated individuals are more likely to take a COVID-19 test out of caution whereas unvaccinated individuals are not concerned about COVID-19, driving their unvaccinated status, and ultimately biasing TND studies if testing

practices were differentially affected by vaccination status. While the study was conducted in a period not affected by the more transmissible Delta and Omicron variants, we chose a period that reflects the circulating virus during the phase III clinical trials to assess consistency of results. This approach, design, and data collection could also be implemented for new and emerging COVID-19 vaccine and treatment effectiveness questions.

It is important to keep in mind that this registry generally reflects reporting from well-educated, middle-aged contributors across the US, with women contributing substantially more than men. The extent to which these findings can be extrapolated to other groups or locations is unknown. That said, the selection factors that influence the decision to join this cohort are unlikely to have biased any comparisons within the cohort. Moreover, it is unlikely that there would have been differential false-negative testing by vaccine manufacturer.

Future perspective

Although voluntary participation from community-dwelling individuals may have resulted in selective participation of those most likely to have sought testing, it is unlikely to have been differential according to vaccine manufacturer. More important, these real-world data add a dimension not often represented in the medical literature, namely reports of the participant experiences that are not commonly found in other health data systems such as electronic health records, medical claims and/or prescription data. For example, while symptom severity may not be clinically reproducible, participants self-reports reflect their perception of their experience and thus, are an important outcome for study. We foresee the evermore expansion of patient-centric approaches and applications to data collection across the pharmaceutical and health industry.

While cohort studies can be limited when timely data are needed to inform public health measures, the efficiency of a TND or modified TND approach with a representative selection of cases and controls are likely one of the best options to study the vaccines in the post-market setting. This approach, design, and data collection could also be implemented for new and emerging COVID-19 vaccine and treatment effectiveness questions.

Summary points

- It is important to assess the extent to which the real-world effectiveness of marketed vaccines is consistent with that observed in the clinical trials, and to characterize how well vaccines prevent COVID-19 symptoms.
- We conducted a modified test-negative design to evaluate the real-world effectiveness of three COVID-19 vaccines by leveraging data from an on-going, US community-based registry. Vaccine effectiveness was examined in two ways: considering cases who (1) self-reported a positive COVID-19 test (695 cases, 1786 controls) and who (2) self-reported a positive test with at least one moderate/severe COVID-19 symptom (165 cases, 2316 controls). Any vaccination (full or partial) was associated with a 95% reduction in the odds of having a self-reported positive COVID-19 test (adjusted odds ratio (aOR) = 0.05; 95% confidence interval [CI] 0.04, 0.06). Full vaccination was associated with an aOR of 0.03 (95% CI 0.03, 0.05) while partial vaccination had an aOR of 0.08 (95% CI 0.06, 0.12). Any vaccination was associated with a 71% reduction in the odds of a self-reported positive COVID-19 test and having at least one moderate/severe symptom (aOR = 0.29; 95% CI 0.20, 0.40). Sensitivity analyses of COVID-19-like symptoms showed similar results.
- We observed high effectiveness across all three vaccine manufacturers both for prevention of self-reported positive COVID-19 test results and prevention of moderate/severe COVID-19 symptoms.

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Ethical conduct of research

The authors have obtained appropriate institutional review board from Advarra Inc. IRB no. Pro00043030. Participants are unpaid, recruited primarily via social media and provide informed consent online. Data collection and study conduct followed all ethical

principles outlined in the Declaration of Helsinki for the conduct of medical research. This study is registered at Clinicaltrials.gov NCT04368065 and EU PAS register EUPAS36240.

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