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Supplemental information

**FDA-authorized mRNA COVID-19 vaccines are
effective per real-world evidence synthesized
across a multi-state health system**

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Supplementary Material

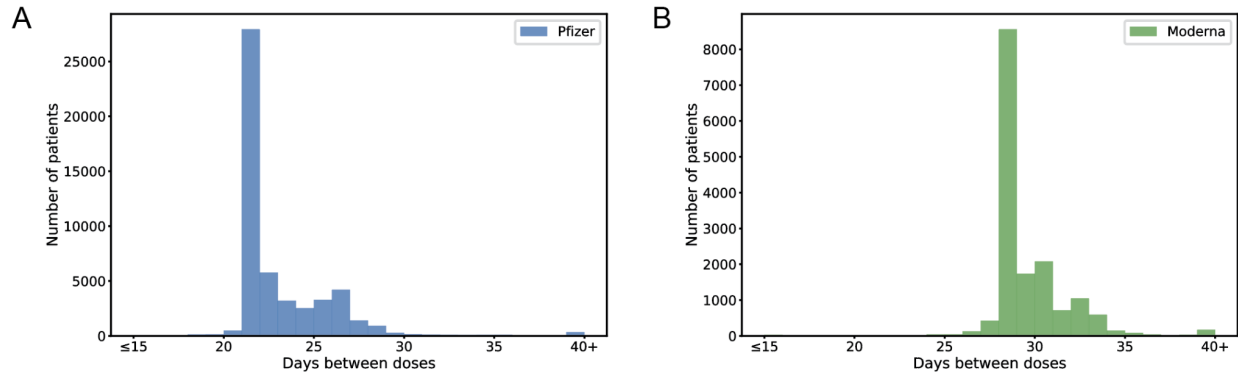


Figure S1. Distribution of time between first and second vaccine doses for all individuals receiving two doses of BNT162b2 or mRNA-1273, related to STAR Methods. (A) Distribution of time between doses for individuals receiving BNT162b2. It is recommended that the second dose is administered 21 days following the first. (B) Distribution of time between doses for individuals receiving mRNA-1273. It is recommended that the second dose is administered 28 days following the first. Consistent with these recommendations, the median and mode of time between doses among the analyzed individuals in the Mayo Clinic health system are 21 and 28 days for BNT162b2 and mRNA-1273, respectively.

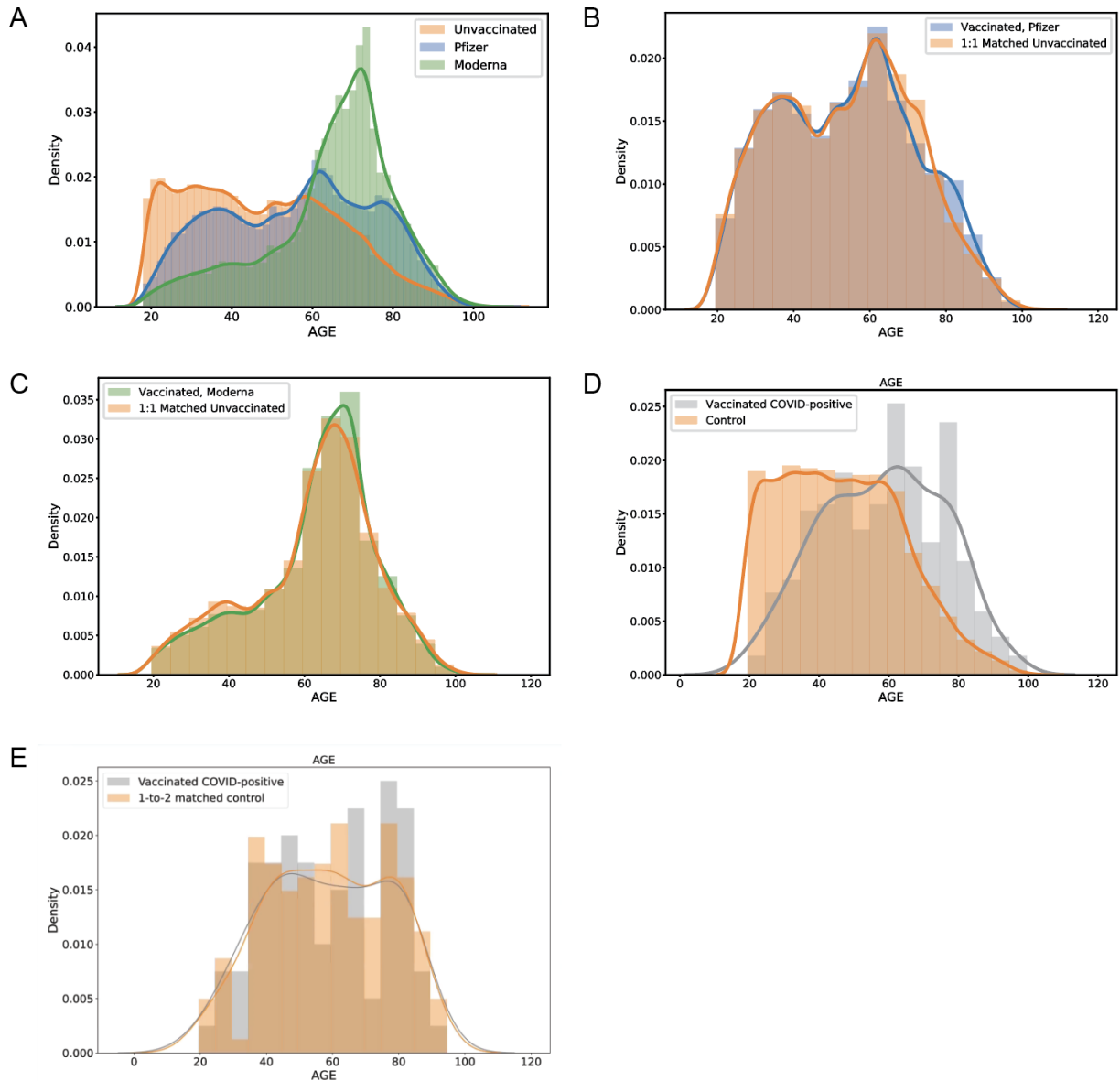


Figure S2. Age distributions for vaccinated and unvaccinated cohorts before and after propensity matching, related to STAR Methods. (A) Distribution of ages for vaccinated individuals and unvaccinated individuals before 1-to-1 matching. (B) Distribution of ages for individuals vaccinated with BNT162b2 and 1-to-1 matched unvaccinated individuals. (C) Distribution of ages for individuals vaccinated with mRNA-1273 and 1-to-1 matched unvaccinated individuals. These matched cohorts were used to assess vaccine effectiveness in preventing a positive SARS-CoV-2 PCR test. (D) Distribution of ages for vaccinated COVID-19 patients who were diagnosed at least 14 days after their second dose and unvaccinated COVID-19 patients, before 1-to-2 propensity score matching. (E) Distribution of ages for vaccinated COVID-19 patients who were diagnosed at least 14 days after their second dose and unvaccinated COVID-19 patients, after 1-to-2 propensity score matching. These matched cohorts were used to assess the effect of vaccination on COVID-19 disease severity.

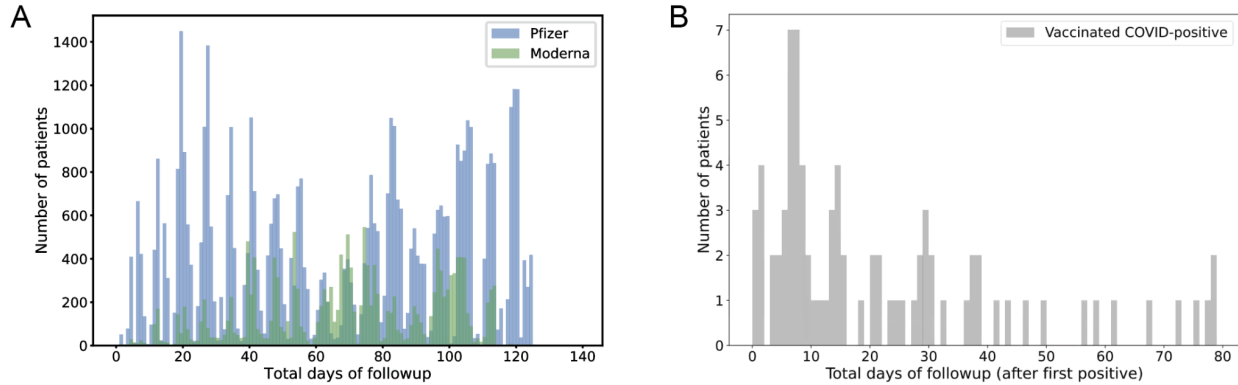


Figure S3. Distributions of total available follow-up time for study cohorts of interest, related to STAR Methods. (A) Total available follow-up time (days) for the 68,266 individuals who received a COVID-19 vaccine, did not have a positive SARS-CoV-2 test before their first vaccine dose, and were adequately matched to an unvaccinated individual for inclusion in the vaccine effectiveness analyses. Total available follow-up time is defined as the number of days from first vaccine to the final study date (April 20, 2021), including days after COVID-19 diagnosis or death, if applicable. (B) Total available follow-up time (days) for the 81 individuals who tested positive for SARS-CoV-2 by PCR at least 14 days after their second dose of a COVID-19 vaccine. Total available follow-up time is defined as the number of days from diagnosis (date of positive SARS-CoV-2 test) to the final study date (April 20, 2020), including days after COVID-19 diagnosis or death, if applicable.

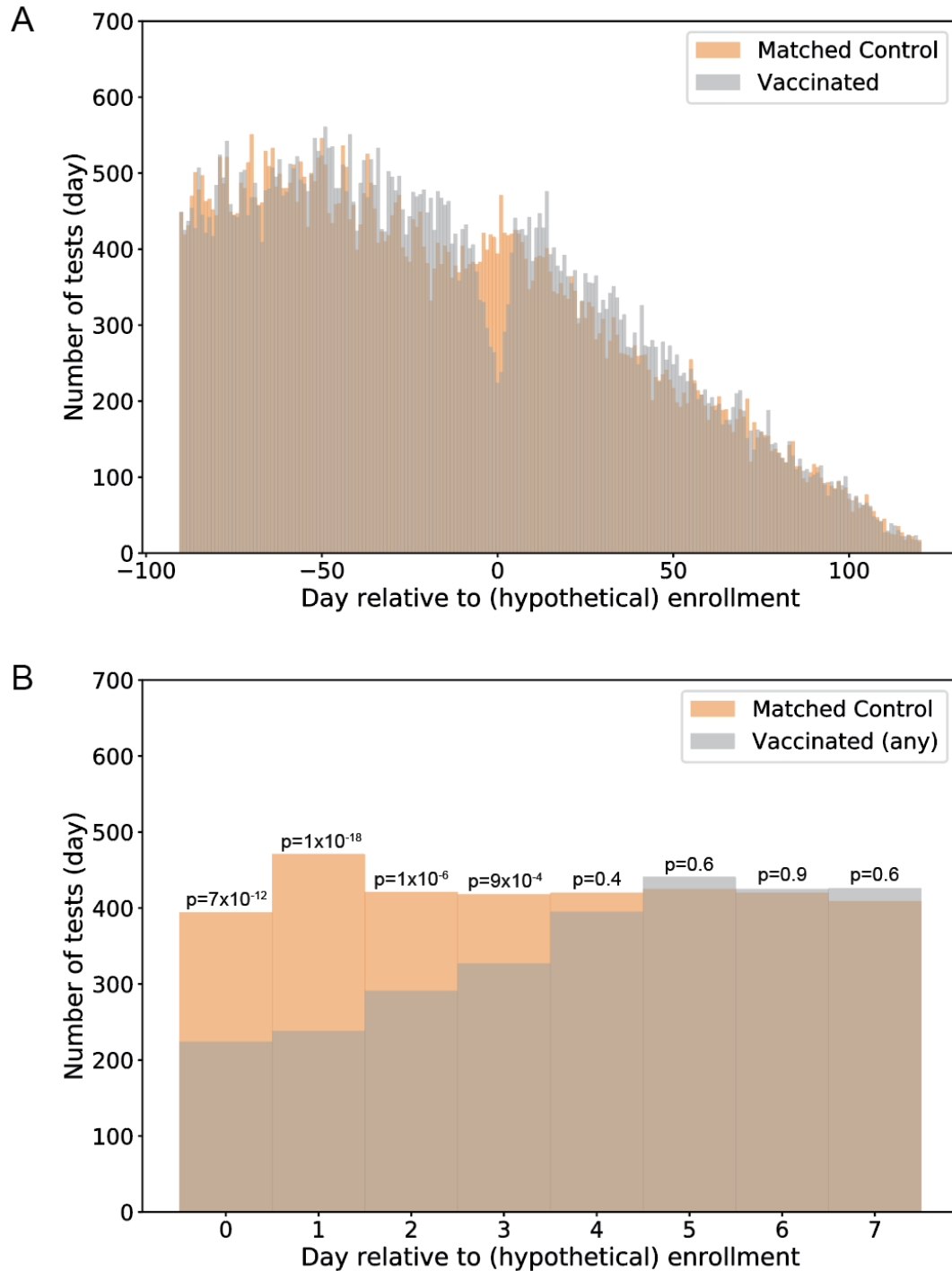


Figure S4. Daily number of SARS-CoV-2 PCR tests for the propensity matched vaccinated and unvaccinated cohorts, related to STAR Methods. The x-axis corresponds to the number of days relative to the study enrollment date. For the vaccinated cohort, the study enrollment date is the date of the first vaccine dose. For the unvaccinated cohort, the study enrollment date is defined as the date of the first vaccine dose for the matched vaccinated individual. (A) Number of tests from Day -90 to Day 120. (B) Number of tests from Day 0 to Day 7. To determine when the testing rates became similar again after vaccination, statistical significance was assessed using the Fisher exact test, and individual (uncorrected) p-values are shown for each day.

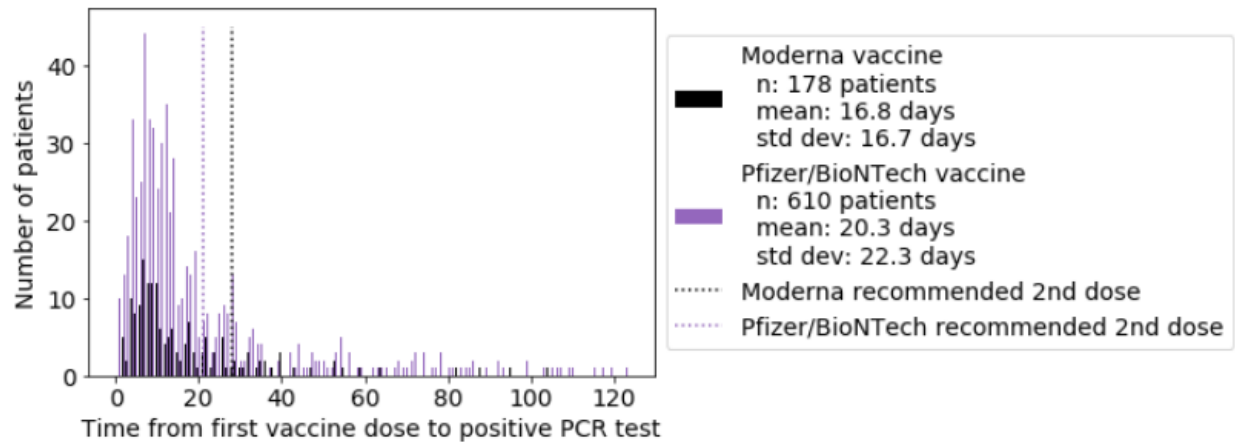
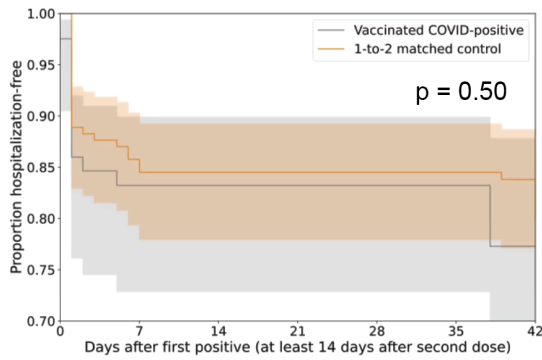


Figure S5. Distribution of the time from first vaccine dose to first positive SARS-CoV-2 PCR test, for the individuals with at least one positive test following vaccination, related to Table 3. Patient counts for mRNA-1273 (Moderna vaccine) are shown in black, and patient counts for BNT162b2 (Pfizer/BioNTech vaccine) are shown in purple. For mRNA-1273, the mean time to positive PCR test following the first dose is 16.8 days (standard deviation: 16.7 days), and for BNT162b2, the mean time to positive PCR test following the first dose is 20.3 days (standard deviation: 22.3 days).

A



B

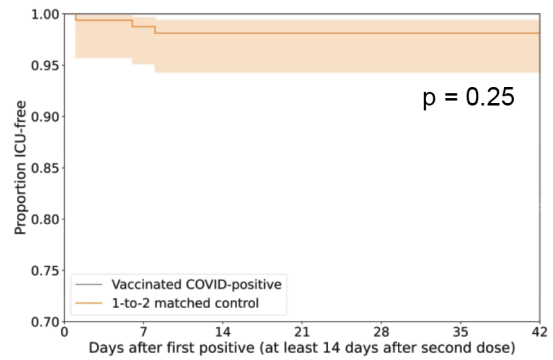


Figure S6. Kaplan Meier analyses to assess hospitalization and ICU admission rates between fully vaccinated (breakthrough) and unvaccinated COVID-19 patients, related to STAR Methods. (A) Hospitalization-free survival comparison between patients who tested positive for SARS-CoV-2 at least 14 days after their second vaccine dose ($n = 81$) versus 1:2 propensity-matched patients who tested positive for SARS-CoV-2 and were not previously vaccinated ($n = 162$). A log-rank test fails to reject the null hypothesis of equal hazard rates with a p-value of 0.50. (B) ICU-free survival comparison between the same cohorts as in panel (A). A log-rank test fails to reject the null hypothesis of equal hazard rates with a p-value of 0.25.

Table S1. Follow-up, dosing, and PCR testing information for the vaccinated and 1-to-1 propensity matched unvaccinated cohorts, related to Tables 1-2. For the vaccinated cohort, descriptive statistics on the number of doses received and the number of days of follow-up from the first and second vaccine doses are provided. In the summary of “Number of vaccine doses”, the valid time window for the second dose is defined as 17 to 28 days after the first dose for BNT162b2 and 24 to 35 days after the first dose for mRNA-1273. For both cohorts, the number of individuals with PCR tests taken after the enrollment date are provided. For the vaccinated cohort, the enrollment date corresponds to the date of the first vaccine dose. For the unvaccinated cohort, the enrollment date corresponds to the date of the first vaccine dose for the matched vaccinated individual.

	Vaccinated cohort	1-to-1 Propensity-matched unvaccinated cohort
Total number of individuals	68,266	68,266
Number of vaccine doses <ul style="list-style-type: none"> - 1 dose - 2 doses <ul style="list-style-type: none"> - No positive SARS-CoV-2 PCR test before second dose AND received second dose within valid time window 	15,848 (23%) 52,418 (77%) 50,909 (75%)	
Number of days follow-up from first vaccine dose <ul style="list-style-type: none"> - Mean - Standard deviation - Median - IQR (25th quantile, 75th quantile) - Range (minimum, maximum) 	67.1 34.2 70 (39, 98) (1, 139)	
Number of days follow-up from second vaccine dose, among patients included in the second dose analysis <ul style="list-style-type: none"> - Mean - Standard deviation - Median - IQR (25th quantile, 75th quantile) - Range (minimum, maximum) 	53.2 29.6 58 (27, 78) (0, 120)	
Number of individuals with PCR tests taken after enrollment date <ul style="list-style-type: none"> - 1 or more PCR tests - No PCR tests 	18,377 (26.9%) 49,889 (73.1%)	17,497 (25.6%) 50,769 (74.4%)

Table S2. Clinical characteristics of vaccinated COVID-19 patients who first tested positive at least 14 days after the second vaccine dose and their 1-to-2 propensity matched unvaccinated controls, related to STAR Methods. The SARS-CoV-2 positive vaccinated cohort includes all patients who received at least one dose of a COVID-19 vaccine and then subsequently received a positive PCR test at least 14 days following their second vaccination dose. The control cohort is a 1:2 propensity-matched cohort derived from the set of unvaccinated patients with a positive PCR test on or after December 1, 2020. Demographics and comorbidities are presented for each cohort, and number of doses is presented for the vaccinated cohort. Comorbidities were determined via neural network models applied to clinical notes for each patient between December 1, 2015 and November 30, 2020. Highly balanced covariates with Standardized Mean Difference (SMD) < 0.1 are indicated with ***. Moderately balanced covariates with SMD < 0.25 are indicated with *.

Clinical covariate	SARS-CoV-2 positive vaccinated cohort	1:2 Propensity-matched SARS-CoV-2 positive unvaccinated cohort	Standardized Mean Difference (SMD)
Total number of patients	81	162	
Age			
- 18-44 years old	22 (27.2%)	43 (26.5%)	0.01***
- 45 - 64 years old	28 (34.6%)	57 (35.2%)	0.01***
- 65-74 years old	9 (11.1%)	19 (11.7%)	0.02***
- >= 75 years old	22 (27.2%)	43 (26.5%)	0.01***
Sex			
- Female	53 (65.4%)	101 (62.3%)	0.06***
- Male	28 (34.6%)	61 (37.7%)	0.06***
- Unknown	0 (0.0%)	0 (0.0%)	N/A
Race			
- Asian	1 (1.2%)	6 (3.7%)	0.15*
- Black / African American	1 (1.2%)	1 (0.6%)	0.07***
- Native American	0 (0%)	0 (0%)	N/A
- White / Caucasian	76 (93.8%)	150 (92.6%)	0.05***
- Other	2 (2.5%)	2 (1.2%)	0.10***
- Unknown	1 (1.2%)	3 (1.9%)	0.05***
Ethnicity			
- Hispanic or Latino	3 (3.7%)	3 (1.9%)	0.12*
- Not Hispanic or Latino	77 (95.1%)	154 (95.1%)	0.00***
- Unknown	1 (1.2%)	5 (3.1%)	0.12*
Comorbidities			
- Asthma	18 (22.2%)	27 (16.7%)	0.14*
- Cancer	37 (45.7%)	69 (42.6%)	0.06***
- Cardiomyopathy	4 (4.9%)	6 (3.7%)	0.06***
- Chronic Kidney Disease	9 (11.1%)	28 (17.3%)	0.17*
- Chronic Obstructive Pulmonary Disease	6 (7.4%)	16 (9.9%)	0.09***
- Coronary Artery Disease	9 (11.1%)	22 (13.6%)	0.07***
- Heart failure	14 (17.3%)	28 (17.3%)	0.00***
- Hypertension	36 (44.4%)	82 (50.6%)	0.12*
- Obesity	14 (17.3%)	39 (24.1%)	0.16*
- Pregnancy	0 (0.0%)	0 (0.0%)	N/A
- Severe Obesity	2 (2.5%)	6 (3.7%)	0.07***
- Sickle Cell Disease	0 (0.0%)	0 (0.0%)	N/A
- Solid Organ Transplant	0 (0.0%)	0 (0.0%)	N/A
- Stroke / Cerebrovascular Disease	6 (7.4%)	4 (2.5%)	0.25*
- Type 2 Diabetes Mellitus	8 (9.9%)	22 (13.6%)	0.11*
Vaccine type			
- Pfizer	73 (90.1%)		
- Moderna	8 (9.9%)		

Table S3. Hospitalization, ICU admission, and mortality rates for vaccinated individuals who contracted COVID-19 at least 14 days after their second dose versus 1-to-2 propensity-matched unvaccinated COVID-19 patients, related to STAR Methods. Patients were considered eligible for analysis if they had at least 21 days (hospitalization, ICU admission) or 28 days (mortality) of follow-up after COVID-19 diagnosis as defined by a positive SARS-CoV-2 PCR test. For each outcome, the relative risk (and its 95% confidence interval) and Fisher exact test p-value are used to compare the rates between vaccinated and unvaccinated patients.

Outcome	Vaccine	Vaccinated COVID positive (81 patients)	Matched unvaccinated, COVID positive (162 patients)	Relative Risk (95% CI)	Fisher Exact test p-value
Number of patients with at least 21 days of follow-up		32	150		
21-Day Hospital admission rate	Overall	5/32 (16%)	25/150 (17%)	0.94 (0.43, 2.3)	1
	Pfizer	5/30 (17%)	23/136 (17%)	0.99 (0.45, 2.4)	1
	Moderna	0/2 (0%)	2/14 (14%)	0 (0, 16)	1
21-Day ICU admission rate	Overall	0/32 (0%)	3/150 (2%)	0 (0, 12)	1
	Pfizer	0/30 (0%)	3/136 (2.2%)	0 (0, 12)	1
	Moderna	0/2 (0%)	0/14 (0%)	N/A	1
Number of patients with at least 28 days of follow-up		26	148		
28-Day Mortality rate	Overall	0/26 (0%)	5/148 (3.4%)	0 (0, 8.8)	1
	Pfizer	0/25 (0%)	5/134 (3.7%)	0 (0, 8.3)	1
	Moderna	0/1 (0%)	0/14 (0%)	N/A	1