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COVID-19 vaccination effectiveness rates by week and sources of bias

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ABSTRACT

Objective

To examine granular weekly COVID-19 vaccine effectiveness and assess the feasibility of using observational data for vaccine effectiveness studies.

Design and setting

Retrospective cohort study using Columbia University Medical Center data linked to State and City Immunization Registries.

Outcomes and measures

We used propensity score matching with up to 54,987 covariates and fitted Cox proportional hazards models to estimate hazard ratios and constructed Kaplan-Meier plots for two main outcomes (COVID-19 infection and COVID-19-associated hospitalization). We conducted manual chart review of cases in week one in both groups along with a set of sensitivity analyses for Pfizer- BioNTech, Moderna and Janssen vaccines.

Results

The study included 179,666 patients. We observed increasing effectiveness after the first dose of mRNA vaccines with week six effectiveness approximating 84% (95% CI 72-91%) for COVID-19 infection and 86% (95% CI 69-95) for COVID-19-associated hospitalization. When analyzing unexpectedly high effectiveness in week one, chart review revealed that vaccinated patients are less likely to seek care after vaccination and are more likely to be diagnosed with COVID-19 during the encounters for other conditions. Sensitivity analyses highlighted potential outcome misclassification for ICD10-CM diagnosis, the influence of excluding patients with prior COVID-19 infection and anchoring in the unexposed group. Overall vaccine effectiveness in fully vaccinated patients matched the results of the randomized trials.

Conclusions

Observational data can be used to ascertain vaccine effectiveness if potential biases are accounted for. The data need to be scrutinized to ensure compared groups exhibit similar health seeking behavior and are equally likely to be captured in the data. Given the difference in temporal trends of vaccine exposure and baseline characteristics, indirect comparison of vaccines may produce biased results.

Strengths and limitations of this study

- This study thoroughly investigates weekly COVID-19 vaccine effectiveness using methods to reduce potential confounding (large-scale propensity score matching, negative control calibration) and accompanied by manual chart review of the cases in week one

- The study includes a range of sensitivity analyses for different patient populations, anchoring strategies and outcome definitions.

- The study was carried out using routinely collected clinical practice data, which represents real-world patients, but also implies a risk of misclassification.

Word count: 3179

Keywords: COVID-19, Epidemiology, Health Informatics

BACKGROUND

Randomized clinical phase-3 trials have demonstrated high efficacy for the three US-authorized COVID-19 vaccines against symptomatic COVID-19 infection, ranging from 66.9% for Ad26.COV2.S (Johnson & Johnson–Janssen) to 94.1% and 94.6% for BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) vaccines (1–3). Their fast approval and widespread use require robust post-marketing studies that leverage large sample size, heterogeneous populations, and longer follow-up available in observational data.

There have been several recent observational studies, which have shown effectiveness similar to the randomized clinical trials (RCTs). Thompson et al. used a test-negative design to examine the effectiveness of Pfizer–BioNTech and Moderna vaccines with respect to COVID-19 hospitalization across a network of institutions (4). The cohort study by Tartof et al. examined the effectiveness of Pfizer–BioNTech against COVID-19 infection and hospitalization in fully vaccinated patients, reporting the limitations of matching the vaccinated and unvaccinated populations (5). Another cohort study by Polinski et al. used a large population to assess the effectiveness of Ad26.COV2.S and obtained similar results despite the fact that the data source did not allow to ascertain vaccination status for all patients (6). There were several non-US studies showing similar overall effectiveness, which nevertheless may not be generalizable to the US population due to differences in patient populations, COVID-19 variants spread and baseline COVID-19 prevalence (7–11).

While the existing observational studies matched randomized clinical trial results, there is a growing number of pressing questions related to COVID-19 vaccine effectiveness such as effectiveness against new variants and vaccine durability, for which trials may not be readily available (12). Moreover, the challenges associated with the use of observational data such as incomplete data capture, outcome misclassification and appropriate comparator sampling can undermine the results of the studies if such biases are not accounted for (13). Such biases are illustrated in the estimates of vaccine effectiveness during the first two weeks following the first dose. Studies have shown contradicting results for Pfizer–BioNTech vaccine with effectiveness ranging from moderate effectiveness of 52% (3) to very high effectiveness of 92.6% (14). Similarly, a recent study showed an unexplained high effectiveness of Janssen vaccine during week one (15). While week one lack of effectiveness has been suggested as a metric for lack of confounding in the long-term vaccine effectiveness studies, the reasons for high

effectiveness and its impact on the validity of the conclusions regarding the overall effectiveness remain unclear (10).

The goal of this study was to examine granular weekly effectiveness estimates and uncover underlying biases and challenges associated with the use of observational data for vaccine effectiveness studies. We employed large-scale propensity score matching and many negative controls to reduce and assess bias, and leveraged a range of sensitivity analyses as well as manual review of the COVID-19 infection cases during the first week after vaccination.

METHODS

Main design

For this retrospective observational cohort study, we used electronic health records from the Columbia University Irving Medical Center (CUIMC) database (Appendix 1), which has an ongoing automated connection to New York City and State public health department vaccine registries and includes all within-state vaccinations for our population. The data were translated to the OMOP Common Data Model version 5 and was previously used in multiple studies (16).

We studied the three main US COVID-19 vaccines separately. Three target cohorts included patients indexed on the first dose of one of the corresponding vaccines with no prior COVID-19 infection and no previous exposure to other COVID-19 vaccines. Our comparator group was unvaccinated patients who were indexed on a date selected from the unvaccinated patient's history (not necessarily with any medical event) such that it matched the index date of one of the target group participants. Both the target and comparator groups had at least 365 days of prior observation and primarily resided in New York.

Outcomes of interest included a) COVID-19 infection defined as a positive COVID-19 test (e.g., reverse-transcriptase–polymerase-chain-reaction assays) or a diagnostic code of COVID-19 and b) COVID-19 hospitalization defined as an inpatient visit associated with a COVID-19 positive test or diagnosis within 30 days prior or during the visit. Upon further examination of the results, we added two other outcomes: a) COVID-19 positive test only and b) COVID-19 hospitalization associated with a positive COVID-19 test. Design overview is provided in Appendix 2; code lists and links to phenotype definitions are provided in Appendix 3.

For the time-at-risk, we selected six consecutive 7-day intervals after the first dose until an outcome, end of observation period or death, whichever came earlier. Additionally, given the results for vaccine effectiveness during week 1 following the first dose, we conducted chart review for patients with a COVID-19 positive test recorded in the abovementioned period. We reviewed all cases for the vaccinated population as well a random sample of the cases in the unvaccinated population.

Sensitivity analyses

Along with studying granular weekly intervals, we assessed overall absolute vaccine effectiveness in patients with at least one dose of a COVID-19 vaccine and in fully vaccinated patients. The latter was defined as 14 days after the second dose of Pfizer-BioNTech or Moderna vaccines or first dose of Janssen vaccine. For each comparison we estimated hazard ratios (HRs) and constructed Kaplan-Meier plots as described below.

Given that the published studies focused on patients without prior COVID-19 infection, our second sensitivity analysis included all eligible patients regardless of their previous COVID-19 status. Finally, as the strategy for unvaccinated group index date selection (anchoring) has been reported to influence incidence of outcomes (17), we additionally tested an unvaccinated comparator indexed on a healthcare encounter matching the index date of one of the target group participants within 3 days corridor, with at least 365 days of prior observation located at New York.

Statistical methods

For each analysis, we fitted a lasso regression model to calculate propensity score and match patients in each target and comparator group with 1:1 ratio. For propensity model we used all demographic information, index year and month, as well as the number of visits, condition and drug groups, procedures, device exposures, laboratory and instrumental tests and other observations over long (prior year) and short-term period (prior month).

For each outcome, we fitted a Cox proportional hazards models to estimate HRs and constructed Kaplan-Meier plots. Empirical calibration based on the negative control outcomes was used to identify and minimize any potential residual confounding by calibrating HRs and 95% confidence intervals (CIs) (18,19). Vaccine effectiveness was calculated as 100% × (1−hazard ratio).

All analyses were supported by the OHDSI Infrastructure (CohortMethod package, available at https://ohdsi.github.io/CohortMethod/, FeatureExtraction available at https://ohdsi.github.io/FeatureExtraction/ and the Cyclops package for large-scale regularized regression (20) available at https://ohdsi.github.io/Cyclops).

Diagnostics

We used multiple sources of diagnostics to estimate potential bias and confounding following best practices for evidence generation (21). First, we examined covariate and propensity score balance prior to proceeding with outcome modelling and effect estimation to ensure that we have enough sample size and to control for potential observed confounding (21). We plotted propensity scores to investigate the overlap in patient populations at the baseline and examined the balance of all baseline characteristics to determine if the target and comparator cohorts were imbalanced at the baseline and after propensity score matching. Target and comparator cohorts were said to be balanced if the standardized difference of means of all covariates after propensity score matching was less than 0.1 (22).

For negative control calibration, we used 93 negative controls (Appendix 4) with no known causal relationship with the COVID-19 vaccines. Negative controls were selected based on a review of existing literature, product labels and spontaneous reports and were reviewed by clinicians (23). We assessed residual bias from the negative control estimates.

Patient and public involvement

No patient involved

RESULTS

Patient characteristics

In total, we identified 179,666 patients with at least one dose of COVID-19 vaccine: 121,771 patients for Pfizer-BioNTech, 52,728 for Moderna and 5,167 for Janssen (Table 1).

Among vaccinated patients, 68% received Pfizer-BioNTech vaccine, 29% received Moderna and 3% received Janssen vaccine. When investigating the vaccination pathways, we discovered that 112,963

patients (93% of patients with at least one dose of Pfizer-BioNTech) had 2 doses of Pfizer-BioNTech and 42,384 (80%) patients had 2 doses of Moderna. We found 344 and 291 patients with 3 doses of the corresponding vaccines and 440 patients having mixed Pfizer-BioNTech, Moderna and Janssen vaccines in different combinations.

Within our database, Moderna was administered early on with a peak in January 2021 (Figure 1), while Pfizer-BioNTech and Janssen vaccinations peaked in April. It was reflected in the follow-up time with Moderna patients having on average longer follow-up with some individuals having up to 5.8 months of post-observation.

We observed that unvaccinated comparator patients (Table 1) were on average younger and had fewer co-morbidities and less exposure to various drugs prior to matching. We were able to achieve balance on all covariates (up to 54,987 covariates, standardized difference of means less than 0.1) with propensity score matching. Figure 2 presents the covariate balance and propensity score balance plots showing that anchoring unvaccinated patients on a date allowed us to achieve better balance compared to anchoring patients on a visit.

Patients vaccinated with Pfizer-BioNTech had a similar distribution of baseline characteristics compared to the patients vaccinated with Moderna but differed from the patients vaccinated with Janssen. On average, the latter group was older, had more patients with race recorded as Black, and had more co-morbidities such as diabetes mellitus or hypertensive disorder (Table 1).

Main week-by-week absolute effectiveness analysis

Figure 3, A shows week-by-week estimates for patients vaccinated with at least one dose of Pfizer-BioNTech or Moderna. Due to the small sample size, we were not able to obtain stable week-by-week estimates for Janssen. While week one was characterized by unexpectedly high effectiveness (58%, 95% CI 45-69% against COVID-19 infection and 72%, 95% CI 57-83% against COVID-19 associated hospitalization), we observed plausible increasing effectiveness beginning week 2 with the effectiveness on week 6 approximating 84% (95% CI 72-91%) for COVID-19 infection and 86% (95% CI 69-95) for COVID-19-associated hospitalization.

We then looked at the week one COVID-19 infection cases to explain high effectiveness. A chart review of week one positive COVID-19 tests revealed a high proportion of unvaccinated patients seeking care

related to COVID-19 symptoms or COVID-19 exposure (85% in total) compared to only 69% of vaccinated patients. Initial healthcare encounters in vaccinated population were oftentimes related to other medical reasons such as co-morbid conditions or surgeries (39% compared to 21% in unvaccinated population, Appendix 5). Moreover, an observed gap between symptom onset and an initial healthcare encounter was more pronounced in the vaccinated cohort as the patients attributed their symptoms to temporal vaccine side effects as opposed to COVID-19 infection.

When looking at the severity of COVID-19 symptoms at the initial encounter during week one after the index date, we observed that the unvaccinated cohort had a higher proportion of asymptomatic cases (39% compared to 11%) while the vaccinated population had more severe or mild cases (34% and 48% respectively).

Sensitivity analysis

Overall effectiveness

As cohort analysis allows us to construct Kaplan-Meier curves to assess effectiveness over time, we also looked at the effectiveness during the year after the first dose (Figure 4). We observed similar trends with all three vaccines being less effective during the first month after the first dose. After that, Pfizer-BioNTech and Moderna were highly effective against both COVID-19 infection and COVID-19 associated hospitalization, while Janssen vaccine exhibited a wide range of effectiveness (Appendix 6).

The results for fully vaccinated patients with time-at-risk starting at the full vaccination matched the results of the clinical trials for corresponding vaccines (detailed estimates are provided in Appendix 7 and 8).

Our initial design included a positive COVID-19 test or a diagnostic code as an outcome. Upon further case examination, we discovered that COVID-19 diagnostic codes in the CUIMC data were partially assigned to the patients with negative COVID-19 tests on or immediately following the date of diagnosis. In that case, ICD10CM code U07.1 “Disease caused by Severe acute respiratory syndrome coronavirus 2” was entered in the system for billing purposes (COVID-19 molecular or antibody tests) or for COVID-19 sequelae. We, therefore, focused on positive COVID-19 test only for our primary outcome, which led to higher effectiveness for all vaccines compared to using both positive test and diagnosis (Appendix 6).

Finally, exclusion of patients with prior COVID-19 infection in our main analysis resulted in higher absolute effectiveness. Inclusion of patients regardless of their prior COVID-19 status led to a small decrease in observed effectiveness (Appendix 9) for both COVID-19 infection and hospitalization in patients vaccinated with Moderna or Janssen.

DISCUSSION

In this retrospective cohort study, we examined the weekly effectiveness of COVID-19 mRNA vaccines as well as the overall effectiveness of three COVID-19 vaccines commonly used in the US. COVID-19 mRNA vaccines were highly effective against both COVID-19 infection and COVID-19 associated hospitalization. Our findings support the RCTs and previously published post-marketing studies for all three vaccines. Larger sample size for patients vaccinated with COVID-19 mRNA vaccines allowed us to have more power, which resulted in overlapping yet narrower confidence intervals compared to the RCTs. On the other hand, our study had fewer patients with the Janssen vaccine, which resulted in wider yet overlapping intervals compared to the Janssen's vaccine RCT (1,2,7).

Our study complemented previous studies by examining and comparing disparate design choices such as studying both COVID-19-associated hospitalization and COVID-19 infection, different outcome definitions and broad age group (4,5). We scrutinized the effectiveness of the mRNA vaccines following the first dose and confirmed the findings of moderate vaccine effectiveness during the first two weeks. For week one following the first dose we discovered previously uncaptured differential biases in vaccinated and unvaccinated populations. Vaccination directly influenced the attitude of patients towards their symptoms, causing a delay in seeking care and a higher symptom severity threshold needed to seek care. In unvaccinated patients, mild COVID-19 related symptoms were the reason to seek care; in vaccinated patients such cases were mainly captured upon seeking outpatient and inpatient care for other conditions. Such a difference may affect any observational vaccine study that uses hospitalization as a surrogate for COVID-19 severity.

Previous research suggested that vaccinated patients do not have an increase in the number of cases immediately following vaccination as they are unlikely to get vaccinated if sick (10). Our review of the cases in week one supplements this assumption by showing that vaccinated patients are more likely to attribute their symptoms to common vaccine side effects and, therefore, are less likely to seek care. Nevertheless, even when this differential bias is present, the estimates of the COVID-19 vaccine effectiveness in subsequent weeks still match the results of the RCTs. This indicates that high

effectiveness during week one following vaccination does not necessarily undermine the estimates of subsequent vaccine effectiveness.

Our sensitivity analyses discovered several challenges and potential biases that must be accounted for when conducting vaccine effectiveness studies on observational data. First, we observed that outcome definitions are prone to measurement error, which has not been studied thoroughly. The specifics of data capture and billing processes were associated with some patients having assigned COVID-19 diagnosis codes for billing for tests rather than as an indicator of active disease. Another reason for assigning the code was COVID-19 sequela, where the actual date of COVID-19 infection could have been anywhere from 6 months to a couple of weeks in the past. Such index date misclassification can be present in other healthcare institutions and therefore should be scrutinized to make valid inferences.

Second, inclusion or exclusion of patients with prior COVID-infection influenced estimated effectiveness. We observed that inclusion of patients with prior COVID-19 leads to lower effectiveness for all vaccines regardless of the outcome definition.

If absolute effectiveness is studied, an appropriate index event (anchor) for the unvaccinated cohort must be chosen. In our study, we observed that an arbitrary date represents a better counterfactual than a medical visit for COVID-19 vaccination, which is reflected in propensity score balance and covariate balance. Nevertheless, other institutions may have different vaccination pathways such as vaccination on discharge, which can make a visit a better counterfactual for vaccination. More generally, completeness of vaccination data capture is a crucial feature that influences the robustness of the study. While CUIMC data ensures complete exposure capture by linking EHR to the City and State Registries, the researchers should exhibit caution with conducting studies on the data sources with unknown vaccination capture.

We obtained similar results to RCTs, which strengthens the conclusions about the high effectiveness of vaccines against COVID-19 infection in the broad age group. While these RCTs allowed us to make such comparisons for absolute effectiveness, there are other research questions for which RCTs may not be feasible or readily available. The US and international booster campaigns raise the question of vaccine comparative effectiveness to prioritize vaccination. An indirect comparison may not be accurate due to the differences in the populations we observed in our study. First, patients vaccinated with Janssen were substantially different from mRNA patients: on average, they were older, had a higher proportion of patients with race recorded as Black and had more comorbidities. Therefore, comparative effectiveness studies of Janssen and mRNA vaccines require robust techniques such as large-scale propensity matching

to ensure valid comparison. Second, while Modena and Pfizer patients had similar baseline characteristics, the temporal distribution of vaccinations in CUIMC data differ. Moderna vaccine was administered early on in 2021 with the peak in January, while Pfizer vaccination peaked in April. Given the varying baseline COVID-19 prevalence, a comparison of mRNA vaccines requires matching patients on calendar month to account for this potential bias. These vaccines also had different administration pathways in our system. As opposed to Pfizer vaccine, which was administered at Columbia University Irving Medical Center/New York-Presbyterian sites to all patients over a prolonged period, Moderna vaccination was performed elsewhere and recorded for actively observed patients. Such patients were more likely to get tested or receive care outside of our healthcare system.

LIMITATIONS

Due to observational nature of the study, the data sources may not have complete capture of patient conditions, which was mitigated by having free and available COVID-19 testing in Columbia University Irving Medical Center/New York-Presbyterian sites as well as by having data capture from New York City and State Immunization Registries. Along with availability of testing, COVID-19 baseline infection rate difference was mitigated by matching the target and comparator groups on the index date and using the index month as a covariate in propensity score model. While our outcome phenotype algorithms may be subject to measurement error, we provided additional sensitivity analyses with alternative outcome definitions.

CONCLUSIONS

Observational data can be used to ascertain vaccine effectiveness if potential biases such as exposure and outcome misclassification are accounted for, and appropriate anchoring event is selected. When analyzing granular vaccine effectiveness researchers need to scrutinize the data to ensure that compared groups exhibit similar health seeking behavior and are equally likely to be captured in the data. Given the difference in temporal trends of vaccine exposure and baseline characteristics, there is a need for large-scale direct comparison of vaccines to examine comparative effectiveness.

DECLARATION

Author contributions

GH designed and supervised the study. All co-authors contributed to interpretation of the results and writing the manuscript, approved the final version and had final responsibility for the decision to submit for publication.

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Declaration of interests

All authors have completed the ICMJE disclosure form (available on request from the corresponding author). GH and AO receive funding from the US National Institutes of Health (NIH) and the US Food and Drug Administration.

Ethical approval

The protocol for this research was approved by the Columbia University Institutional Review Board (AAAO7805).

Data sharing

Patient-level data cannot be shared without approval from data custodians due to local information governance and data protection regulations.

Transparency declaration

The lead authors affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure 1. Distribution of vaccination month for COVID-19 vaccines. Black dots represent the number of incident COVID-19 cases (defined as a positive test) in each month.

Figure 2. Diagnostics for the absolute effectiveness study comparing the cohort vaccinated with at least one dose of Pfizer, Moderna or Janssen COVID-19 vaccines and unvaccinated cohort anchored on a date or on a visit: (A) covariate balance before and after propensity score matching, (B) preference score balance and (C) effect of negative control calibration displaying effect estimate and standard error.
In (A), each dot represents the standardized difference of the means for a single covariate before and after stratification on the propensity score.
In (C), each blue dot is a negative control. The area below the dashed line indicates estimates with $p<0.05$ and the orange area indicates estimates with calibrated $p<0.05$.

Figure 3. Week-by-week estimates of vaccine effectiveness of Pfizer-BioNTech and Moderna after 1st dose, % and 95% CI for COVID-19 infection (A) and COVID-19 hospitalization (B). Chart review of COVID-19 cases (defined as a positive COVID-19 test) during week 1, vaccinated and unvaccinated patients (C).

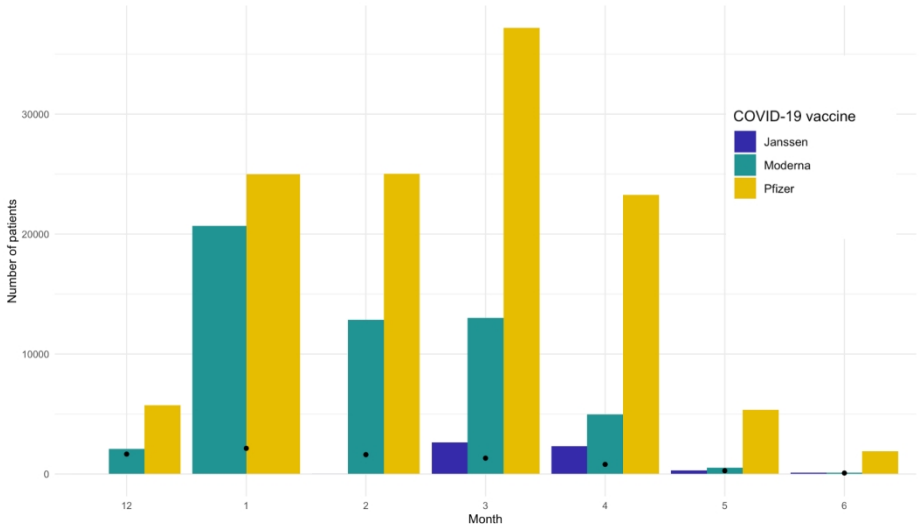
Figure 4. Kaplan-Meier curves for absolute effectiveness of COVID-19 vaccines for time-at-risk of 1 day – 365 days after the first dose compared to the unvaccinated patients residing in New York City.

Table 1. Patient baseline characteristics for patients with at least one dose of a COVID-19 vaccine and the comparator unvaccinated patients, before and after propensity score matching.

	Before matching									After matching								
	Pfizer			Moderna			Janssen			Pfizer			Moderna			Janssen		
Characteristic	**Target**	**Comparator**	**Std. diff**	**Target**	**Comparator**	**Std. diff**	**Target**	**Comparator**	**Std. diff**	**Target**	**Comparator**	**Std. diff**	**Target**	**Comparator**	**Std. diff**	**Target**	**Comparator**	**Std. diff**
Patients, n	121,771	164,997		52,728	148,795		5,167	52,643		101,109	101,111		50,517	50,517		5,031	5,031	
Follow-up, days. Median (IQR)	107 (80–137)	104 (71-137)		127 (102–153)	123 (99-153)		79 (72-95)	79 (72-95)		107 (78-149)	107 (79-140)		126 (101-153)	126 (102-153)		79 (72-95)	79 (72-95)	
Age group, %																		
10-19	4.2	10.8	-0.25	0.5	1.7	-0.12	0.8	0.8	0.00	4.8	4.3	0.02	0.5	0.4	0.01	0.8	0.8	0.00
20-49	37.2	42.6	-0.11	35.7	45.7	-0.20	43.9	43	0.02	40.3	40.1	0	36.9	37.4	-0.01	44.2	43.9	0.01
50-64	23.9	20.3	0.09	21.2	23.3	-0.05	31.7	31.7	0.00	23.6	23.7	0	21.7	21.4	0.01	31.8	31.3	0.01
65-74	18.8	12.6	0.17	21.3	14.4	0.18	11.6	12.2	-0.02	15.8	16.6	-0.02	20.6	20.5	0.00	11.5	12	-0.02

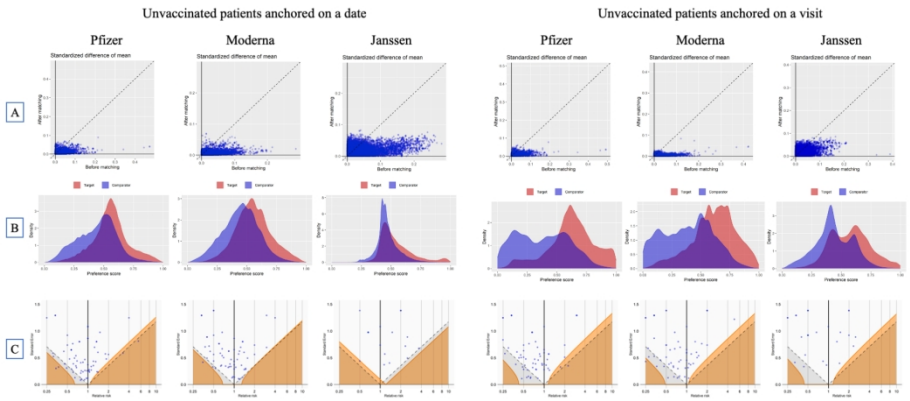
75-84	11.3	8.9	0.08	15.4	10	0.16	7.6	7.9	-0.01	10.6	10.7	0	14.6	14.6	0.00	7.2	7.9	-0.03
>84	4.1	3.8	0.02	5.8	4.8	0.04	4.3	4.3	0.00	4.2	4.1	0.01	5.6	5.6	0.00	4.2	4	0.01
Gender, %																		
Female	63.7	57.8	0.12	64.4	58.7	0.12	63.4	63.2	0.01	61.4	62	-0.01	64.2	64.7	-0.01	63.5	61.1	0.05
Race, %																		
race = Asian	3.8	2.6	0.07	4.2	2.8	0.07	3.6	1.7	0.12	3.5	3.4	0.01	4.2	4.4	-0.01	3.7	3.6	0.01
race = Black or African American	12.4	14.2	-0.05	8.7	14.2	-0.17	15.9	15.5	0.01	12.6	12.2	0.01	9	8.4	0.02	15.7	15.5	0
race = White	40.5	35.1	0.11	48.3	34.4	0.29	37.4	35.7	0.03	39.3	39.5	0	46.9	47.9	-0.02	37.4	37.5	0
Medical history, %																		
Chronic liver disease	0.6	0.6	0	0.5	0.6	-0.02	1.1	0.7	0.05	0.5	0.5	0	0.5	0.5	0	1	1.2	-0.02
Chronic obstructive lung disease	1.3	1	0.02	1.4	1.1	0.02	2.4	1.3	0.09	1	1	0.01	1.2	1.2	0	2	2.2	-0.01
Dementia	1.2	1.1	0	1	1.2	-0.02	2.6	1.1	0.11	1.1	1	0.01	1	0.9	0.01	2.2	2.2	0
Depressive disorder	5.3	4	0.06	4.7	3.9	0.04	8	4.8	0.13	4	3.7	0.02	4.2	4	0.01	7.1	8	-0.03
Diabetes mellitus	7.1	5.2	0.08	6.6	5.6	0.04	10.3	6.2	0.15	5.7	5.4	0.01	6.2	5.8	0.02	9.5	10.2	-0.02

Human immunodeficiency virus infection	1.4	1.1	0.03	0.9	1.2	-0.03	1.7	1.4	0.02	1.1	1	0	0.8	0.8	0	1.6	1.8	-0.01
Hyperlipidemia	12.9	8.1	0.16	14.9	8.9	0.19	14.3	10.2	0.13	10.2	9.5	0.02	13	12.6	0.01	13.4	14.3	-0.03
Hypertensive disorder	16	11.3	0.14	16	12.4	0.1	21.4	13.8	0.2	13.1	12.2	0.03	14.7	13.9	0.02	20.1	21.7	-0.04
Obesity	5.1	4.9	0.01	4	4.4	-0.02	7.3	5.9	0.06	4.4	4.1	0.02	3.8	3.6	0.01	6.8	7.8	-0.04
Osteoarthritis	7.3	4.7	0.11	7.7	5.3	0.1	8.4	6.2	0.08	5.8	5.3	0.02	6.8	6.5	0.01	7.8	8.8	-0.04
Renal impairment	3.7	3	0.04	3.5	3.3	0.01	6.6	3.3	0.15	2.9	2.7	0.01	3.3	3	0.01	5.3	5.9	-0.02
Cerebrovascular disease	1.7	1.4	0.02	2.2	1.6	0.05	2.7	1.7	0.07	1.5	1.4	0.01	2	1.8	0.02	2.3	2.4	-0.01
Heart disease	8.6	7.1	0.06	10.1	7.6	0.09	11.8	8	0.13	7.5	7.1	0.02	9.2	8.7	0.02	10.3	11.7	-0.04
Malignant neoplastic disease	5.3	4.5	0.04	6.5	5	0.07	5	4.9	0	4.7	4.3	0.02	5.9	5.5	0.02	4.8	5.2	-0.02



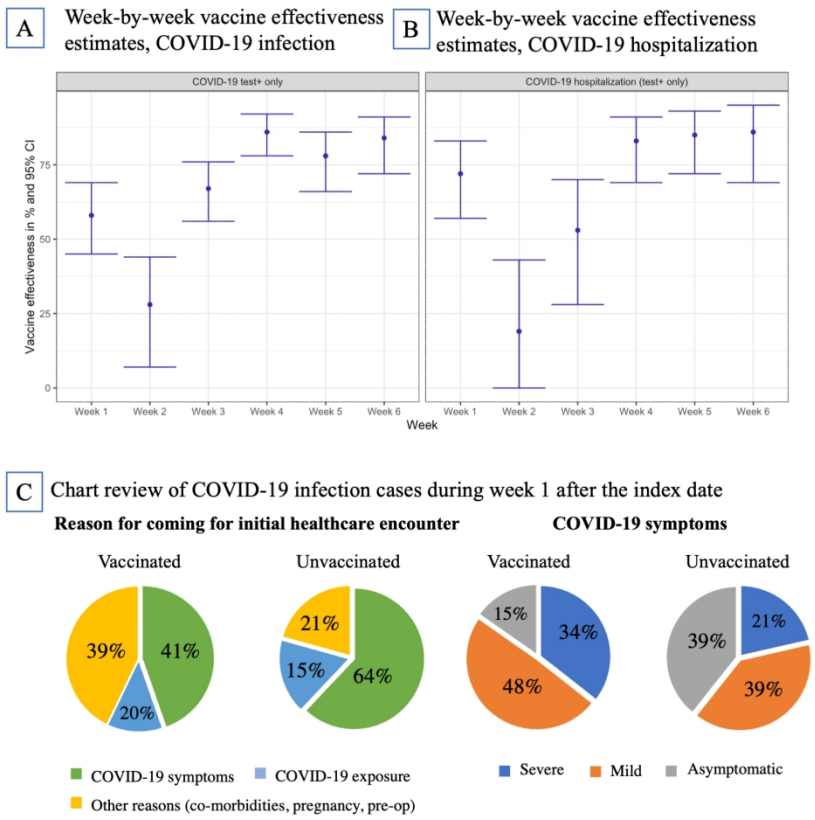
Distribution of vaccination month for COVID-19 vaccines. Black dots represent the number of incident COVID-19 cases (defined as a positive test) in each month.

338x190mm (144 x 144 DPI)



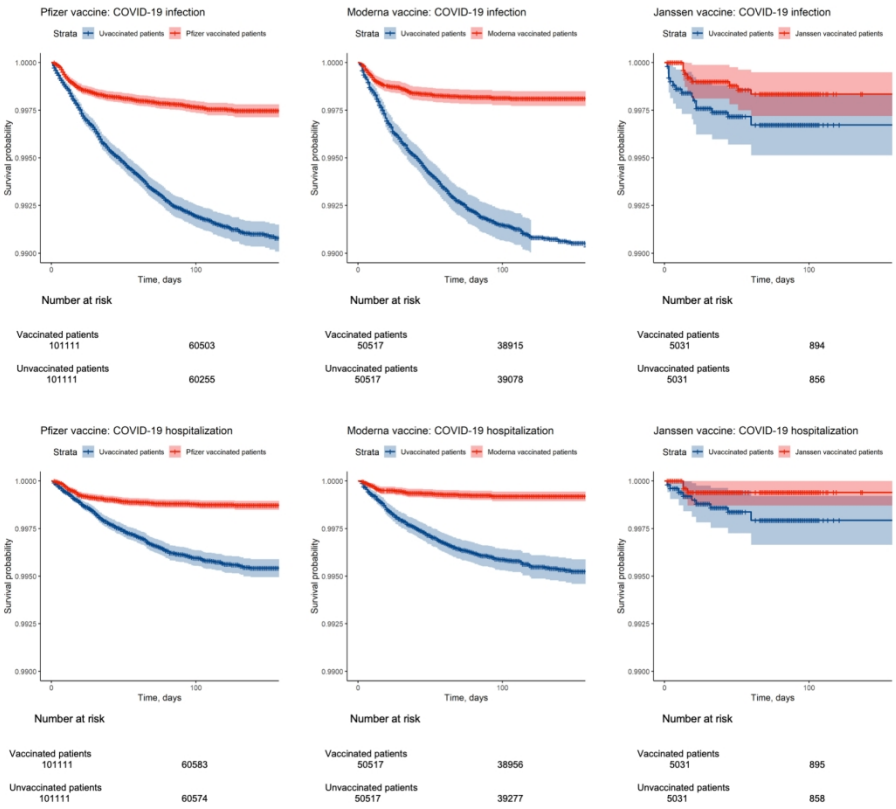
Diagnostics for the absolute effectiveness study comparing the cohort vaccinated with at least one dose of Pfizer, Moderna or Janssen COVID-19 vaccines and unvaccinated cohort anchored on a date or on a visit: (A) covariate balance before and after propensity score matching, (B) preference score balance and (C) effect of negative control calibration displaying effect estimate and standard error.
In (A), each dot represents the standardized difference of the means for a single covariate before and after stratification on the propensity score.
In (C), each blue dot is a negative control. The area below the dashed line indicates estimates with $p<0.05$ and the orange area indicates estimates with calibrated $p<0.05$.

625x313mm (78 x 78 DPI)



Week-by-week estimates of vaccine effectiveness of Pfizer-BioNTech and Moderna after 1st dose, % and 95% CI for COVID-19 infection (A) and COVID-19 hospitalization (B). Chart review of COVID-19 cases (defined as a positive COVID-19 test) during week 1, vaccinated and unvaccinated patients (C).

262x241mm (186 x 186 DPI)



Kaplan-Meier curves for absolute effectiveness of COVID-19 vaccines for time-at-risk of 1 day – 365 days after the first dose compared to the unvaccinated patients residing in New York City.

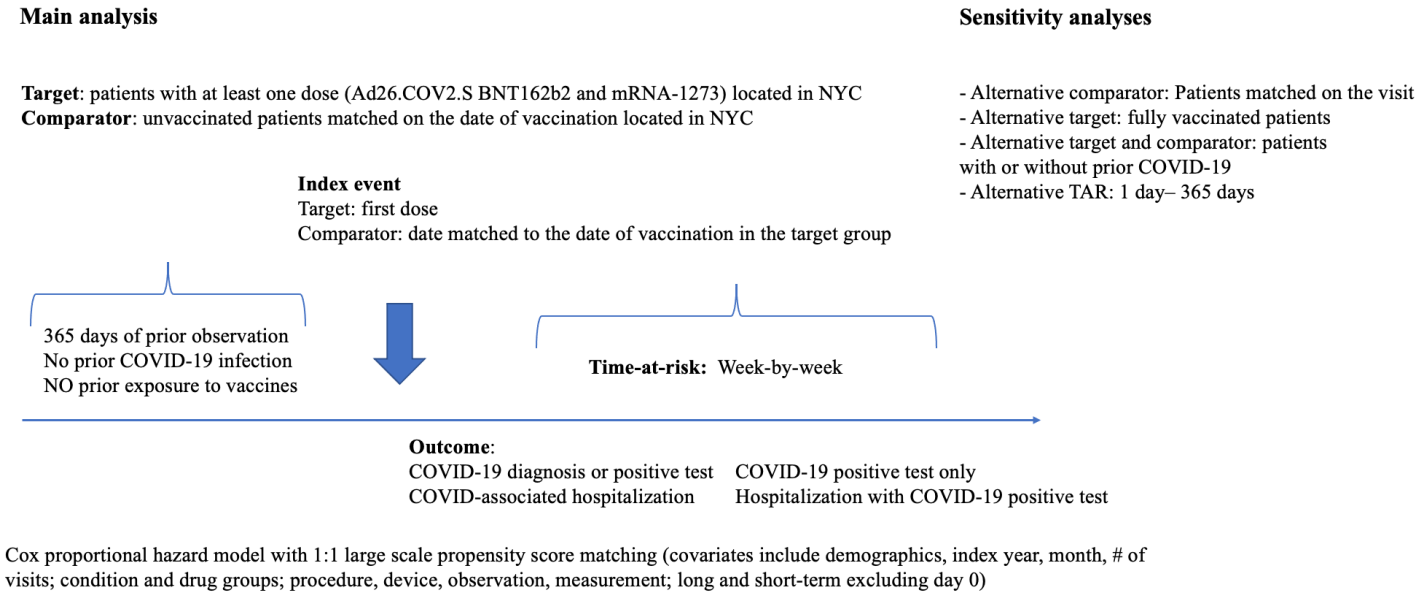
262x241mm (186 x 186 DPI)

Supplementary materials

Appendix 1. Data source description

The Columbia University Irving Medical Center (CUIMC) database comprises electronic health records on more than 6 million patients, with data collection starting in 1985. CUIMC is a Northeast US quaternary care center with primary care practices in northern Manhattan and surrounding areas, and the database includes inpatient and outpatient care. The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions (billing diagnoses and problem lists), drugs (outpatient prescriptions and inpatient orders and administrations), devices, measurements (laboratory tests and vital signs), and other observations (symptoms). The data sources include current and previous electronic health record systems (homegrown Clinical Information System, homegrown WebCIS, Allscripts Sunrise Clinical Manager, Allscripts TouchWorks, Epic Systems), administrative systems (IBM PCS-ADS, Eagle Registration, IDX Systems, Epic Systems), and ancillary systems (homegrown LIS, Sunquest, Cerner Laboratory). Additionally, it contains the information on vaccination from New York City and State immunization registries.

Appendix 2. Retrospective cohort COVID-19 vaccine effectiveness study design overview.



Appendix 3. Cohort definitions and codes for the absolute COVID-19 vaccine effectiveness study

3.1 Cohort definitions for target comparator and outcome cohorts for studying absolute effectiveness of COVID-19 vaccines.

	Definition and link to the public repository
Target cohorts	Target cohorts were defined as patients with at least one dose of the corresponding vaccine (Pfizer, Moderna, Janssen) Index event: first exposure to the corresponding vaccine Inclusion and exclusion criteria: - 365 days of prior observation - no other COVID-19 vaccine exposure in 120 days prior and 120 days after the index date - no prior COVID-19 infection (diagnosis code of COVID-19 or positive test) - residence in New York City determined by the zip code recorded For the analysis on fully vaccinated patients, we applied the same criteria and required patients to have a) the second dose of Pfizer or Moderna vaccine (if applicable) within 14 to 56 days after the first dose b) at least 14 days of observation after the second dose (one dose of Janssen). **Links:** https://atlas.ohdsi.org/#/cohortdefinition/498 https://atlas.ohdsi.org/#/cohortdefinition/494 https://atlas.ohdsi.org/#/cohortdefinition/497 https://atlas.ohdsi.org/#/cohortdefinition/418 https://atlas.ohdsi.org/#/cohortdefinition/417 https://atlas.ohdsi.org/#/cohortdefinition/420
Comparator cohorts	Comparator cohorts were created separately for each target cohort by selecting patients with no COVID-19 vaccination in their record (any vaccine), 365 days of prior observation and New York City residence. The patients were matched on the index date of one of the target group participants for the comparator anchored on a date and on the date of a healthcare encounter within 3-day corridor for the comparator anchored on a visit.

Outcome cohorts	For the main analysis COVID-19 infection was defined as a COVID-19 test with the result 'Positive' or 'Detected'. COVID-19 associated hospitalization was defined as an inpatient, emergency department or intensive care unit admission with a positive COVID-19 test recorded within 30 days prior or during hospitalization. For a sensitivity analysis we applied the abovementioned criteria with adding COVID-19 diagnosis as an alternative for positive COVID-19 test. Links: https://atlas.ohdsi.org/#/cohortdefinition/425 https://atlas.ohdsi.org/#/cohortdefinition/422

3.2 Codes used in the study.

1. **Pfizer vaccine:**

RxNorm 2468235 SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension

2. **Moderna vaccine:**

RxNorm 2470234 SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension

3. **Janssen vaccine:**

CVX 212 SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-Ad26, preservative free, 0.5 mL

4. **COVID-19 diagnosis:**

ICD10-CM U07.1 Emergency use of U07.1 | COVID-19

5. **COVID-19 test:**

LOINC 94500-6 SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA with probe detection
LOINC 94558-4 SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay

Appendix 4. Negative controls

SNOMED concept id	SNOMED concept name
438945	Accidental poisoning by benzodiazepine-based tranquilizer
434455	Acquired claw toes
316211	Acquired spondylolisthesis
201612	Alcoholic liver damage
438730	Alkalosis
441258	Anemia in neoplastic disease
432513	Animal bite wound
4171556	Ankle ulcer
4098292	Antiphospholipid syndrome
77650	Aseptic necrosis of bone
4239873	Benign neoplasm of ciliary body
23731	Benign neoplasm of larynx
199764	Benign neoplasm of ovary
195500	Benign neoplasm of uterus
4145627	Biliary calculus
4108471	Burn of digit of hand
75121	Burn of lower leg
4284982	Calculus of bile duct without obstruction
434327	Cannabis abuse
78497	Cellulitis and abscess of toe
4001454	Cervical spine ankylosis
4068241	Chronic instability of knee
195596	Chronic pancreatitis
4206338	Chronic salpingitis
4058397	Claustrophobia
74816	Contusion of toe
73302	Curvature of spine
4151134	Cyst of pancreas
77638	Displacement of intervertebral disc without myelopathy
195864	Diverticulum of bladder
201346	Edema of penis
200461	Endometriosis of uterus
377877	Esotropia
193530	Follicular cyst of ovary
4094822	Foreign body in respiratory tract
443421	Gallbladder and bile duct calculi

4299408	Gouty tophus
135215	Hashimoto thyroiditis
442190	Hemorrhage of colon
43020475	High risk heterosexual behavior
194149	Hirschsprung's disease
443204	Human ehrlichiosis
4226238	Hyperosmolar coma due to diabetes mellitus
4032787	Hyperosmolarity
197032	Hyperplasia of prostate
140362	Hypoparathyroidism
435371	Hypothermia
138690	Infestation by Pediculus
4152376	Intentional self poisoning
192953	Intestinal adhesions with obstruction
196347	Intestinal parasitism
137977	Jaundice
317510	Leukemia
765053	Lump in right breast
378165	Nystagmus
434085	Obstruction of duodenum
4147016	Open wound of buttock
4129404	Open wound of upper arm
438120	Opioid dependence
75924	Osteodystrophy
432594	Osteomalacia
30365	Panhypopituitarism
4108371	Peripheral gangrene
440367	Plasmacytosis
439233	Poisoning by antidiabetic agent
442149	Poisoning by bee sting
4314086	Poisoning due to sting of ant
4147660	Postural kyphosis
434319	Premature ejaculation
199754	Primary malignant neoplasm of pancreas
4311499	Primary malignant neoplasm of respiratory tract
436635	Primary malignant neoplasm of sigmoid colon
196044	Primary malignant neoplasm of stomach
433716	Primary malignant neoplasm of testis
133424	Primary malignant neoplasm of thyroid gland

194997	Prostatitis
80286	Prosthetic joint loosening
443274	Psychostimulant dependence
314962	Raynaud's disease
37018294	Residual osteitis
4288241	Salmonella enterica subspecies arizonae infection
45757269	Sclerosing mesenteritis
74722	Secondary localized osteoarthrosis of pelvic region
200348	Secondary malignant neoplasm of large intestine
43020446	Sedative withdrawal
74194	Sprain of spinal ligament
4194207	Tailor's bunion
193521	Tropical sprue
40482801	Type II diabetes mellitus uncontrolled
74719	Ulcer of foot
196625	Viral hepatitis A without hepatic coma
197494	Viral hepatitis C
4284533	Vitamin D-dependent rickets

Link to the original list of negative controls used in EUMAEUS study: https://ohdsi-studies.github.io/Eumaeus/Protocol.html#8_Research_Methods

Appendix 5. Summary of manual chart review of COVID-19 infection cases during week 1 after the index date, patients vaccinated with mRNA vaccines and unvaccinated patients.

	Pfizer-BioNTech	**Moderna**	**Pfizer-BioNTech and Moderna**	**Unvaccinated patients**
Total	36	25	61	28
Average age	65	67.8	65.8	58
COVID-19 symptoms				
Severe	14 (39%)	7 (28%)	21 (34%)	6 (21%)
Mild	18 (50%)	11 (44%)	29 (48%)	11 (39%)
Asymptomatic	2 (6%)	7 (28%)	9 (15%)	11 (39%)
Reason for coming for initial healthcare encounter				
COVID-19 symptoms	17 (47%)	8 (32%)	25 (41%)	18 (64%)
Exposure to COVID-19	3 (8%)	4 (16%)	7 (11%)	5 (18%)
For other reason (co-morbidities, procedures etc.)	13 (36%)	11 (44%)	24 (39%)	6 (21%)

Type of initial healthcare encounter				
Telehealth/phone	5 (14%)	6 (24%)	11 (18%)	3 (11%)
Test only	3 (8%)	2 (8%)	5 (8%)	6 (21%)
OP	4 (11%)	3 (12%)	7 (11%)	1 (4%)
ED or IP	24 (67%)	14 (56%)	38 (62%)	18 (64%)

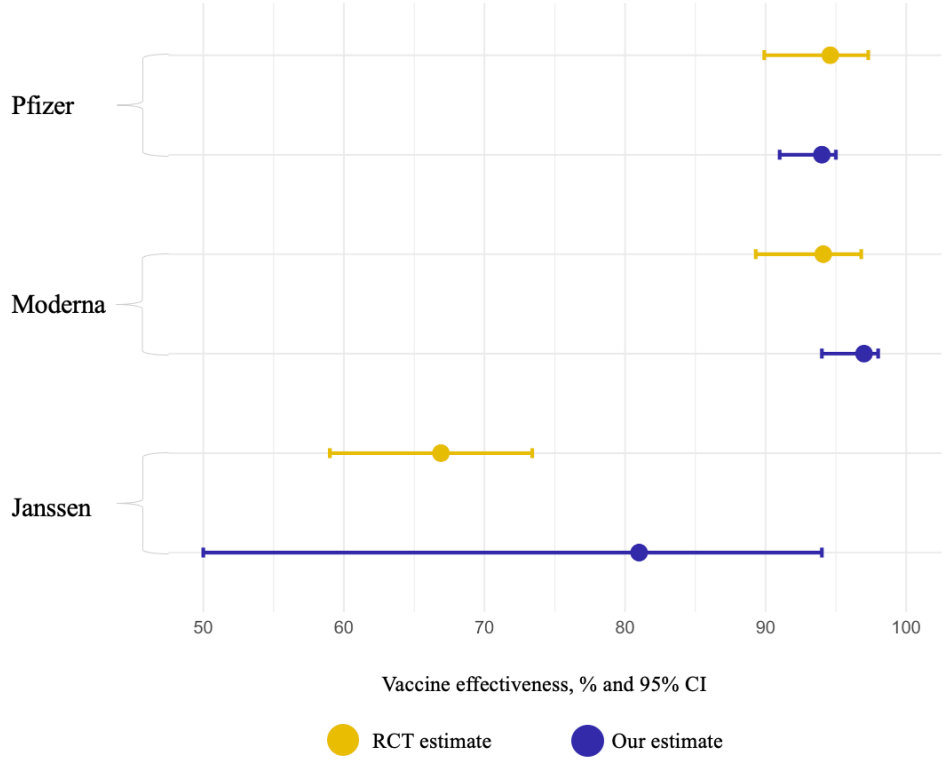
Appendix 6. Estimates for absolute effectiveness of COVID-19 vaccines for time-at-risk of 1 day – 365 days after the first dose in the vaccinated patients without prior COVID-19 infection compared to unvaccinated patients residing in NYC.

	COVID-19 infection		**COVID-19 hospitalization**		**COVID-19 positive test only**		**COVID-19 positive test only hospitalization**	
	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value
Pfizer-BioNTech	42 (37 – 47)	<0.01	63 (56-70)	<0.01	71 (66 - 75)	<0.01	69 (62 - 75)	<0.01
Moderna	54 (48 – 60)	<0.01	76 (69 – 82)	<0.01	78 (73 – 83)	<0.01	81 (74 – 87)	<0.01
Janssen	24 (0-55)	0.31	64 (0.1 – 1.06)	0.09	53 (0 – 82)	0.1	70 (2 – 93)	0.08

Appendix 7. Estimates for absolute effectiveness of COVID-19 vaccines for time-at-risk of 1 day – 365 days after full vaccination in fully vaccinated patients without prior COVID-19 infection compared to unvaccinated patients residing in NYC.

	COVID-19 positive test only		**COVID-19 positive test only hospitalization**		**COVID-19 infection**		**COVID-19 hospitalization**	
	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value
Pfizer-BioNTech	94 (91-95)	<0.01	95 (92-97)	<0.01	70 (66-74)	<0.01	88 (84-92)	<0.01
Moderna	97 (94-98)	<0.01	96 (92-99)	<0.01	72 (66 – 77)	<0.01	92 (87-95)	<0.01
Janssen	81 (50-94)	<0.01	92 (58-100)	0.03	55 (23 – 75)	0.01	87 (56-98)	0.01

Appendix 8. Comparison of the absolute effectiveness estimates in fully vaccinated patients obtained in our study and those from the randomized clinical trials of the corresponding vaccines.



Appendix 9. Estimates for absolute effectiveness of COVID-19 vaccines for time-at-risk of 1 day – 365 days after the first dose in the vaccinated patients with or without prior COVID-19 infection compared to unvaccinated patients residing in NYC.

	COVID-19 infection		**COVID-19 hospitalization**		**COVID-19 positive test only**		**COVID-19 positive test only hospitalization**	
	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value
Pfizer-BioNTech	43 (38-48)	<0.01	64 (57-70)	<0.01	71 (66-75)	<0.01	71(64-76)	<0.01
Moderna	51 (45-57)	<0.01	71 (63-78)	<0.01	76 (71-81)	<0.01	81 (73-86)	<0.01
Janssen	15 (0-49)	0.52	60 (2-86)	0.06	45 (0-75)	0.12	63 (0-90)	0.09

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	6-7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, 18-20
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	8, 18
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8, supplementary materials
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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COVID-19 vaccination effectiveness rates by week and sources of bias: a retrospective cohort study

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Primary Subject Heading:	Health informatics
Secondary Subject Heading:	Epidemiology, Infectious diseases, Public health
Keywords:	COVID-19, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, EPIDEMIOLOGY

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COVID-19 vaccination effectiveness rates by week and sources of bias: a retrospective cohort study

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ABSTRACT

Objective

To examine COVID-19 vaccine effectiveness over six 7-day intervals after the first dose and assess underlying bias in observational data.

Design and setting

Retrospective cohort study using Columbia University Medical Center data linked to State and City Immunization Registries.

Outcomes and measures

We used large-scale propensity score matching with up to 54,987 covariates and fitted Cox proportional hazards models to estimate hazard ratios and constructed Kaplan-Meier plots for two main outcomes (COVID-19 infection and COVID-19-associated hospitalization). We conducted manual chart review of cases in week one in both groups along with a set of secondary analyses for other index date, outcome and population choices.

Results

The study included 179,666 patients. We observed increasing effectiveness after the first dose of mRNA vaccines with week six effectiveness approximating 84% (95% CI 72-91%) for COVID-19 infection and 86% (95% CI 69-95) for COVID-19-associated hospitalization. When analyzing unexpectedly high effectiveness in week one, chart review revealed that vaccinated patients are less likely to seek care after vaccination and are more likely to be diagnosed with COVID-19 during the encounters for other conditions. Sensitivity analyses highlighted potential outcome misclassification for ICD10-CM diagnosis, the influence of excluding patients with prior COVID-19 infection and anchoring in the unexposed group. Overall vaccine effectiveness in fully vaccinated patients matched the results of the randomized trials.

Conclusions

For vaccine effectiveness studies, observational data need to be scrutinized to ensure compared groups exhibit similar health seeking behavior and are equally likely to be captured in the data. Effectiveness in the first week(s) after the vaccination should be reported even though low or high effectiveness immediately after the vaccination may not invalidate study findings. Given the difference in temporal trends of vaccine exposure and baseline characteristics, indirect comparison of vaccines may produce biased results.

Strengths and limitations of this study

- This study thoroughly investigates weekly COVID-19 vaccine effectiveness using methods to reduce potential confounding (large-scale propensity score matching, negative control calibration) and accompanied by manual chart review of the cases in week one

- The study includes a range of sensitivity analyses for different patient populations, anchoring strategies and outcome definitions.

- The study was carried out using routinely collected clinical practice data, which represents real-world patients, but also implies a risk of misclassification.

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Keywords: COVID-19, Epidemiology, Health Informatics, Bias

BACKGROUND

Randomized clinical phase-3 trials have demonstrated high efficacy for the four most commonly used COVID-19 vaccines against symptomatic COVID-19 infection, ranging from 66.9% and 70.4% for Ad26.COV2.S (Johnson & Johnson–Janssen) and ChAdOx1 (Astrazeneca) to 94.1% and 94.6% for BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) vaccines (1–4). Their rapid approval and widespread use require robust post-marketing studies that leverage large sample size, heterogeneous populations, and longer follow-up available in observational data.

There have been recent observational studies, which have shown effectiveness similar to the randomized clinical trials (RCTs) across the globe, both test-negative and cohort (5–12), followed by studies across different patient populations, variants and number of doses (13–17).

Nevertheless, the challenges associated with the use of observational data such as incomplete data capture, outcome misclassification and appropriate comparator sampling can undermine the results of the studies if such biases are not accounted for (18). For COVID-19 vaccines, questions associated with vaccine status misclassification (19), matching vaccinated and unvaccinated populations (6), addressing disease risk factor confounding and ascertainment bias (20,21) and others were raised.

One of such questions is COVID-19 vaccine effectiveness during the first two weeks following the first dose. Studies have shown contradicting results for Pfizer–BioNTech vaccine with effectiveness ranging from moderate effectiveness of 52% (3) to very high effectiveness of 92.6% (22). Similarly, a recent study showed an unexplained high effectiveness of Janssen vaccine during week one (23). Other studies simply excluded the first week(s) from the time-at-risk (9,13,24–26). While week one lack of effectiveness has been suggested as a metric for lack of confounding in the long-term vaccine effectiveness studies, the reasons for high effectiveness and its impact on the validity of the conclusions regarding the overall effectiveness remain unclear (9).

The goal of this study was to examine COVID-19 vaccine effectiveness over six 7-day intervals after the first dose to assess underlying bias associated with the use of observational data for short-term vaccine effectiveness and its impact on long-term vaccine effectiveness estimates . We employed large-scale propensity score matching and many negative controls to reduce and assess bias and leveraged a range of sensitivity analyses as well as manual review of the COVID-19 infection cases in week one to examine health-seeking behavior of vaccinated and unvaccinated patients.

METHODS

Main design

For this retrospective observational cohort study, we used electronic health records from the Columbia University Irving Medical Center (CUIMC) database (Appendix 1), which has an ongoing automated connection to New York City and State public health department vaccine registries and includes all within-state vaccinations for our population. The data were translated to the OMOP Common Data Model version 5 and was previously used in multiple studies (27).

For our main analysis, we studied two mRNA vaccines (Pfizer-BioNTech or Moderna). The exposed group included patients indexed on the first dose of one of the corresponding vaccines with no prior COVID-19 infection and no previous exposure to other COVID-19 vaccines. For the unexposed group, we selected unvaccinated patients and set their index date to a date (not necessarily with any medical event) that matched the index date of one of the exposed group participants. Both the exposed and unexposed groups had at least 365 days of prior observation and primarily resided in New York City according to their zip code. Patients who did not reside in New York were excluded from the study to ensure reliable vaccination data capture.

Outcomes of interest included a) COVID-19 infection defined as a positive COVID-19 test (reverse-transcriptase–polymerase-chain-reaction assay) or a diagnostic code of COVID-19 and b) COVID-19 hospitalization defined as an inpatient visit associated with a COVID-19 positive test or diagnosis within 30 days prior or during the visit. Upon further examination of the results, we added two other outcomes: a) COVID-19 positive test only and b) COVID-19 hospitalization associated with a positive COVID-19 test. Design overview is provided in Appendix 2; code lists and links to phenotype definitions are provided in Appendix 3.

We calculated vaccine effectiveness during six consecutive 7-day intervals after the first dose. Within each interval, patients were followed-up until an outcome, end of the period or death, whichever came earlier. Additionally, given the results for vaccine effectiveness during week one following the first dose, we conducted chart review for patients with a COVID-19 positive test recorded in the abovementioned period. We reviewed all cases for the vaccinated population as well a random sample of the cases in the unvaccinated population and extracted main complaint, COVID-19 history, including symptoms (fever,

shortness of breath, sore throat, cough etc.), severity, time from the first symptom to encounter and COVID-19 exposure.

Secondary analyses

We also conducted a set of secondary analyses. First, given that the published studies focused on patients without prior COVID-19 infection, we studied all eligible patients regardless of their previous COVID-19 status.

As the strategy for unvaccinated group index date selection (anchoring) has been reported to influence incidence of outcomes and baseline characteristics (28,29), we additionally tested unexposed patients indexed on a healthcare encounter matching the index date of one of the exposed group participants within 3 days corridor, with at least 365 days of prior observation located at New York.

Finally, we assessed vaccine effectiveness in patients with at least one dose of a COVID-19 vaccine and in fully vaccinated patients over all available follow-up to compare the estimates to the results of the RCTs. The latter was defined as 14 days after the second dose of Pfizer-BioNTech or Moderna vaccines or first dose of Janssen vaccine. For each comparison we estimated hazard ratios (HRs) and constructed Kaplan-Meier plots as described below.

Statistical methods

For each analysis, we fitted a lasso regression model to calculate propensity score and match patients in each exposed and unexposed group with 1:1 ratio. For large-scale propensity score model we used all demographic information, index year and month, as well as the number of visits, condition and drug groups, procedures, device exposures, laboratory and instrumental tests and other observations over long (prior year) and short-term period (prior month) (30,31).

For each outcome, we fitted a Cox proportional hazards models to estimate HRs and constructed Kaplan-Meier plots. Empirical calibration based on the negative control outcomes was used to identify and minimize any potential residual confounding by calibrating HRs and 95% confidence intervals (CIs) (32,33). Vaccine effectiveness was calculated as 100% × (1−hazard ratio).

All analyses were supported by the OHDSI Infrastructure (CohortMethod package, available at https://ohdsi.github.io/CohortMethod/, FeatureExtraction available at https://ohdsi.github.io/FeatureExtraction/ and the Cyclops package for large-scale regularized regression (34) available at https://ohdsi.github.io/Cyclops).

Diagnostics

We used multiple sources of diagnostics to estimate potential bias and confounding following best practices for evidence generation (35). First, we examined covariate and propensity score balance prior to proceeding with outcome modelling and effect estimation to ensure that we have enough sample size and to control for potential observed confounding (35). We plotted propensity scores to investigate the overlap in patient populations at the baseline and examined the balance of all baseline characteristics to determine if the exposed and unexposed cohorts were imbalanced at the baseline and after propensity score matching. Exposed and unexposed cohorts were said to be balanced if the standardized difference of means of all covariates after propensity score matching was less than 0.1 (36).

For negative control calibration, we used 93 negative controls (Appendix 4) with no known causal relationship with the COVID-19 vaccines. Negative controls were selected based on a review of existing literature, product labels and spontaneous reports and were reviewed by clinicians (37). We assessed residual bias from the negative control estimates.

Patient and public involvement

No patient involved

RESULTS

Patient characteristics

In total, we identified 179,666 patients with at least one dose of COVID-19 vaccine in January-May 2021: 121,771 patients for Pfizer-BioNTech, 52,728 for Moderna and 5,167 for Janssen (Table 1). The sample included patients from all age groups, with or without co-morbidities captured in inpatient and outpatient settings.

We observed that unexposed patients (Table 1) were on average younger and had fewer co-morbidities and less exposure to various drugs prior to matching. We were able to achieve balance on all covariates (up to 54,987 covariates, standardized difference of means less than 0.1) with propensity score matching. Figure 1 presents the covariate balance and propensity score balance plots showing that anchoring unvaccinated patients on a date allowed us to achieve better balance compared to anchoring patients on a visit.

Patients vaccinated with Pfizer-BioNTech had a similar distribution of baseline characteristics compared to the patients vaccinated with Moderna but differed from the patients vaccinated with Janssen. On average, the latter group was older, had more patients with race recorded as Black, and had more co-morbidities such as diabetes mellitus or hypertensive disorder (Table 1).

When investigating the vaccination pathways, we discovered that 112,963 patients (93% of patients with at least one dose of Pfizer-BioNTech) had 2 doses of Pfizer-BioNTech and 42,384 (80%) patients had 2 doses of Moderna. We found 344 and 291 patients with 3 doses of the corresponding vaccines and 440 patients having mixed Pfizer-BioNTech, Moderna and Janssen vaccines in different combinations.

Within our database, Moderna was administered early on with a peak in January 2021 (Figure 2), while Pfizer-BioNTech and Janssen vaccinations peaked in April. It was reflected in the follow-up time with Moderna patients having on average longer follow-up with some individuals having up to 5.8 months of post-observation.

Main week-by-week effectiveness analysis

Figure 3 shows vaccine effectiveness over six 7-day intervals for patients vaccinated with at least one dose of Pfizer-BioNTech or Moderna (160,114 patients) compared to unvaccinated patients (115,689). Due to the small sample size, we were not able to obtain stable week-by-week estimates for Janssen.

While week one was characterized by unexpectedly high effectiveness (58%, 95% CI 45-69% against COVID-19 infection and 72%, 95% CI 57-83% against COVID-19 associated hospitalization), we observed plausible increasing effectiveness beginning week 2 with the effectiveness on week 6 approximating 84% (95% CI 72-91%) for COVID-19 infection and 86% (95% CI 69-95) for COVID-19-associated hospitalization.

We then looked at the week one COVID-19 infection cases to explain high effectiveness (Figure 4). A chart review of week one positive COVID-19 tests revealed a high proportion of unvaccinated patients seeking care related to COVID-19 symptoms or COVID-19 exposure (85% in total) compared to only 69% of vaccinated patients. Initial healthcare encounters in vaccinated population were oftentimes related to other medical reasons such as co-morbid conditions or surgeries (39% compared to 21% in unvaccinated population, Appendix 5). Moreover, an observed gap between symptom onset and an initial healthcare encounter was more pronounced in the vaccinated cohort as the patients attributed their symptoms to temporal vaccine side effects as opposed to COVID-19 infection.

When looking at the severity of COVID-19 symptoms at the initial encounter during week one after the index date, we observed that the unvaccinated cohort had a higher proportion of asymptomatic cases (39% compared to 11%) while the vaccinated population had more severe or mild cases (34% and 48% respectively).

Secondary analysis

As cohort analysis allows us to construct Kaplan-Meier curves to assess effectiveness over time, we also looked at the effectiveness during the year after the first dose (Appendix 6-8). We observed similar trends with all three vaccines being less effective during the first month after the first dose. After that, Pfizer-BioNTech and Moderna were highly effective against both COVID-19 infection and COVID-19 associated hospitalization, while Janssen vaccine exhibited a wide range of effectiveness (Appendix 9).

The results for fully vaccinated patients with time-at-risk starting at the full vaccination matched the results of the clinical trials for corresponding vaccines (detailed estimates are provided in Appendix 10 and 11).

Our initial design included a positive COVID-19 test or a diagnostic code as an outcome. Upon further case examination, we discovered that COVID-19 diagnostic codes in the CUIMC data were partially assigned to the patients with negative COVID-19 tests on or immediately following the date of diagnosis. In that case, ICD10CM code U07.1 “Disease caused by Severe acute respiratory syndrome coronavirus 2” was entered in the system for billing purposes (COVID-19 molecular or antibody tests) or for COVID-19 sequelae. We, therefore, focused on positive COVID-19 test only for our primary outcome, which led to higher effectiveness for all vaccines compared to using both positive test and diagnosis (Appendix 9).

Finally, exclusion of patients with prior COVID-19 infection in our main analysis resulted in higher effectiveness. Inclusion of patients regardless of their prior COVID-19 status led to a small decrease in observed effectiveness (Appendix 12) for both COVID-19 infection and hospitalization in patients vaccinated with Moderna or Janssen.

DISCUSSION

In this retrospective cohort study, we examined the effectiveness of COVID-19 mRNA vaccines over six 7-day intervals after the first dose. We scrutinized the effectiveness of the mRNA vaccines following the first dose and confirmed the findings of moderate vaccine effectiveness during the first two weeks. For week one following the first dose we discovered previously uncaptured differential biases in vaccinated and unvaccinated populations resulting in high vaccine effectiveness. Other researchers suggested that the difference between vaccinated and unvaccinated groups can be mitigated by adjusting for previous healthcare utilization such as number of visits before baseline, co-morbidities or prior vaccination behavior (6,13,24). Nevertheless, the confounding we observed remains even upon controlling for a large number of covariates including those above.

Vaccination directly influenced the attitude of patients towards their symptoms, causing a delay in seeking care and a higher symptom severity threshold needed to seek care or get tested. On contrary, vaccinated patients in other studies had higher rates of testing compared to unvaccinated (20,38). This indicates that patients' attitude toward risk of infection and testing may vary geographically and over time. Similarly, frequency of testing may depend on local policies and practices.

In unvaccinated patients, mild COVID-19 related symptoms were the reason to seek care; in vaccinated patients such cases were mainly captured upon seeking outpatient and inpatient care for other conditions. For example, vaccinated patients could be hospitalized for elective surgery or delivery and be tested positive for COVID-19 on the day of admission or later on. Differential symptom severity was previously reported for other vaccines (39) and may affect any observational study that uses hospitalization as a surrogate for COVID-19 severity as it can be hard to accurately identify the main reason for hospitalization in structured data.

Previous research suggested that vaccinated patients do not have an increase in the number of cases immediately following vaccination as they are unlikely to get vaccinated if sick (9,40). Our review of the

cases in week one adds to 'healthy vaccinee' effect by showing that vaccinated patients are more likely to attribute their symptoms to common vaccine side effects and, therefore, are less likely to seek care.

Nevertheless, even when this differential bias is present, the estimates of the COVID-19 vaccine effectiveness in subsequent weeks still match the results of the RCTs. This indicates that high effectiveness during week one following vaccination does not necessarily undermine the estimates of subsequent vaccine effectiveness. On the other hand, we argue against using estimates of vaccine effectiveness within a short period after the vaccination as a negative control as the differences between the groups observed in this study are likely to be time-variant and may diminish over time (41).

Our secondary analyses discovered several challenges and potential biases that must be accounted for when conducting vaccine effectiveness studies on observational data. First, we observed that outcome definitions are prone to measurement error, which has not been studied thoroughly. Some of the published studies used ICD-10 or ICD-10(CM) codes to identify COVID-19 outcomes (42–44). We found that the specifics of data capture and billing processes were associated with some patients having assigned COVID-19 diagnosis codes for billing for tests rather than as an indicator of active disease. Another reason for assigning the code was COVID-19 sequela, where the actual date of COVID-19 infection could have been anywhere from 6 months to a couple of weeks in the past. Some researchers have previously reported high positive predictive value of ICD-10 diagnostic codes for COVID-19, which points out that index date misclassification should be scrutinized in each institution participating in the analysis to make valid inferences (45,46).

Second, inclusion or exclusion of patients with prior COVID-infection influenced estimated effectiveness. We observed that inclusion of patients with prior COVID-19 leads to lower effectiveness for all vaccines regardless of the outcome definition.

Third, an appropriate index event (anchor) for the unvaccinated cohort must be chosen to represent a counterfactual for vaccination (29,47). In our study, we confirmed that an arbitrary date represents a better counterfactual than a medical visit for COVID-19 vaccination, which is reflected in propensity score balance and covariate balance. Nevertheless, other institutions may have different vaccination pathways such as vaccination on discharge, which can make a visit a better counterfactual for vaccination. More generally, completeness of vaccination data capture is a crucial feature that influences the robustness of the study. While CUIMC data ensures complete exposure capture by linking EHR to the

City and State Registries, the researchers should exhibit caution with conducting studies on the data sources with unknown vaccination capture.

In general, our findings support the RCTs and previously published post-marketing studies for all three vaccines. Larger sample size for patients vaccinated with COVID-19 mRNA vaccines allowed us to have more power, which resulted in overlapping yet narrower confidence intervals compared to the RCTs. On the other hand, our study had fewer patients with the Janssen vaccine, which resulted in wider yet overlapping intervals compared to the Janssen's vaccine RCT (1,2,7). Nevertheless, an indirect comparison of these vaccines may not be accurate due to the differences in the populations we observed in our study. First, patients vaccinated with Janssen were substantially different from mRNA patients: on average, they were older, had a higher proportion of patients with race recorded as Black and had more comorbidities. Therefore, comparative effectiveness studies of Janssen and mRNA vaccines require robust techniques such as large-scale propensity matching to ensure valid comparison. Second, while Modena and Pfizer patients had similar baseline characteristics, the temporal distribution of vaccinations in CUIMC data differ. Moderna vaccine was administered early on in 2021 with the peak in January, while Pfizer vaccination peaked in April. Given the varying baseline COVID-19 prevalence, a comparison of mRNA vaccines requires matching patients on calendar month to account for this potential bias. These vaccines also had different administration pathways in our system. As opposed to Pfizer vaccine, which was administered at Columbia University Irving Medical Center/New York-Presbyterian sites to all patients over a prolonged period, Moderna vaccination was performed elsewhere and recorded for actively observed patients. Such patients were more likely to get tested or receive care outside of our healthcare system.

LIMITATIONS

Due to observational nature of the study, the data sources may not have complete capture of patient conditions as the patients could seek care outside of the hospital system. While our outcome phenotype algorithms may be subject to measurement error, we provided additional analyses with alternative outcome definitions. Exposure misclassification was mitigated by having free and available COVID-19 testing and COVID-19 vaccination in Columbia University Irving Medical Center/New York-Presbyterian sites as well as by having data capture from New York City and State Immunization Registries. Along with availability of testing, COVID-19 baseline infection rate difference was mitigated by matching the exposed and unexposed groups on the index date and using the index month as a covariate in propensity score model. We attempted to address potential differences between exposed and

unexposed groups by selecting a large number of covariates in our propensity score model such as number of visits, procedure and drug utilization, prior vaccine behavior, race and others. Nevertheless, we did not have data for social interactions, adherence to preventive measures and policies, which could affect likelihood of COVID-19 infection and testing.

The results of the study may not be generalizable to other countries or settings with different vaccine administration practices and policies. Finally, the study period did not allow us to stratify the results by COVID-19 variants, which limits generalizability of findings to other variants.

CONCLUSIONS

Observational data can be used to ascertain vaccine effectiveness if potential biases such as exposure and outcome misclassification are accounted for, and appropriate anchoring event is selected. When analyzing vaccine effectiveness researchers need to scrutinize the data to ensure that compared groups exhibit similar health seeking behavior and are equally likely to be captured in the data and report their findings. Specifically for COVID-19 vaccines, an arbitrary date for the index date in unvaccinated patients represents a better counterfactual for vaccination than a healthcare encounter. Effectiveness over the first week(s) after the vaccination should be reported even though low or high effectiveness immediately after the vaccination may not invalidate study findings. Given the difference in temporal trends of vaccine exposure and baseline characteristics, there is a need for large-scale direct comparison of vaccines to examine comparative effectiveness.

DECLARATION

Author contributions

GH designed and supervised the study. AO executed the study, interpreted the results, and drafted the manuscript. GH and AO reviewed the manuscript, approved the final version and had final responsibility for the decision to submit for publication.

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Declaration of interests

All authors have completed the ICMJE disclosure form (available on request from the corresponding author). GH and AO receive funding from the US National Institutes of Health (NIH) and the US Food and Drug Administration.

Ethical approval

The protocol for this research was approved by the Columbia University Institutional Review Board (AAAO7805).

Data sharing

Patient-level data cannot be shared without approval from data custodians due to local information governance and data protection regulations.

Transparency declaration

The lead authors affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure 1. Distribution of vaccination month for COVID-19 vaccines. Black dots represent the number of incident COVID-19 cases (defined as a positive test) in each month.

Figure 2. Diagnostics for the effectiveness study comparing the cohort vaccinated with at least one dose of Pfizer, Moderna or Janssen COVID-19 vaccines and unvaccinated cohort anchored on a date or on a visit: (A) covariate balance before and after propensity score matching, (B) preference score balance and (C) effect of negative control calibration displaying effect estimate and standard error.
In (A), each dot represents the standardized difference of the means for a single covariate before and after stratification on the propensity score.
In (C), each blue dot is a negative control. The area below the dashed line indicates estimates with $p<0.05$ and the orange area indicates estimates with calibrated $p<0.05$.

Figure 3. Effectiveness of Pfizer-BioNTech and Moderna vaccines over six 7-day intervals after 1st dose, % and 95% CI for COVID-19 infection (A) and COVID-19 hospitalization (B).

Figure 4. Chart review of COVID-19 cases (defined as a positive COVID-19 test) during week one, vaccinated and unvaccinated patients.

Table 1. Patient baseline characteristics for patients with at least one dose of a COVID-19 vaccine and the unexposed patients, before and after propensity score matching.

	Before matching			After matching		
Characteristic	**Target**	**Comparator**	**Std. diff**	**Target**	**Comparator**	**Std. diff**
Pfizer-BioNTech COVID-19 vaccine						
Patients, n	121,771	164,997		101,109	101,111	
Follow-up, days. Median (IQR)	107 (80 – 137)	104 (71-137)		107 (78-149)	107 (79-140)	
COVID-19 diagnosis or positive COVID-19 test, n				822	1355	
Positive COVID-19 test, n				231	786	
Age group, %						
10-19	4.2	10.8	-0.25	4.8	4.3	0.02
20-49	37.2	42.6	-0.11	40.3	40.1	0
50-64	23.9	20.3	0.09	23.6	23.7	0
65-74	18.8	12.6	0.17	15.8	16.6	-0.02
75-84	11.3	8.9	0.08	10.6	10.7	0
>84	4.1	3.8	0.02	4.2	4.1	0.01
Gender, %						
Female	63.7	57.8	0.12	61.4	62	-0.01
Race, %						
race = Asian	3.8	2.6	0.07	3.5	3.4	0.01
race = Black or African American	12.4	14.2	-0.05	12.6	12.2	0.01
race = White	40.5	35.1	0.11	39.3	39.5	0
Medical history, %						
Chronic liver disease	0.6	0.6	0	0.5	0.5	0
Chronic obstructive lung disease	1.3	1	0.02	1	1	0.01
Dementia	1.2	1.1	0	1.1	1	0.01

Depressive disorder	5.3	4	0.06	4	3.7	0.02
Diabetes mellitus	7.1	5.2	0.08	5.7	5.4	0.01
Human immunodeficiency virus infection	1.4	1.1	0.03	1.1	1	0
Hyperlipidemia	12.9	8.1	0.16	10.2	9.5	0.02
Hypertensive disorder*	16	11.3	0.14	13.1	12.2	0.03
Obesity	5.1	4.9	0.01	4.4	4.1	0.02
Osteoarthritis	7.3	4.7	0.11	5.8	5.3	0.02
Renal impairment**	3.7	3	0.04	2.9	2.7	0.01
Cerebrovascular disease	1.7	1.4	0.02	1.5	1.4	0.01
Heart disease***	8.6	7.1	0.06	7.5	7.1	0.02
Malignant neoplastic disease	5.3	4.5	0.04	4.7	4.3	0.02
Charlson comorbidity index, mean (SD)	1.75 (3.18)	1.69 (3.09)	-0.01	1.70 (3.11)	1.63 (3.03)	-0.01
Influenza vaccination within a year prior	10.9	7.9	0.10	7.5	6.9	0.02
Moderna COVID-19 vaccine						
Patients, n	52,728	148,795		50,517	50,517	
Follow-up, days. Median (IQR)	127 (102 – 153)	123 (99-153)		126 (101- 153)	126 (102-153)	
COVID-19 diagnosis or positive COVID-19 test, n				382	786	
Positive COVID-19 test, n				94	447	
Age group, %						
10-19	0.5	1.7	-0.12	0.5	0.4	0.01
20-49	35.7	45.7	-0.20	36.9	37.4	-0.01
50-64	21.2	23.3	-0.05	21.7	21.4	0.01
65-74	21.3	14.4	0.18	20.6	20.5	0.00
75-84	15.4	10	0.16	14.6	14.6	0.00
>84	5.8	4.8	0.04	5.6	5.6	0.00
Gender, %						
Female	64.4	58.7	0.12	64.2	64.7	-0.01

Race, %						
race = Asian	4.2	2.8	0.07	4.2	4.4	-0.01
race = Black or African American	8.7	14.2	-0.17	9	8.4	0.02
race = White	48.3	34.4	0.29	46.9	47.9	-0.02
Medical history, %						
Chronic liver disease	0.5	0.6	-0.02	0.5	0.5	0
Chronic obstructive lung disease	1.4	1.1	0.02	1.2	1.2	0
Dementia	1	1.2	-0.02	1	0.9	0.01
Depressive disorder	4.7	3.9	0.04	4.2	4	0.01
Diabetes mellitus	6.6	5.6	0.04	6.2	5.8	0.02
Human immunodeficiency virus infection	0.9	1.2	-0.03	0.8	0.8	0
Hyperlipidemia	14.9	8.9	0.19	13	12.6	0.01
Hypertensive disorder	16	12.4	0.1	14.7	13.9	0.02
Obesity	4	4.4	-0.02	3.8	3.6	0.01
Osteoarthritis	7.7	5.3	0.1	6.8	6.5	0.01
Renal impairment	3.5	3.3	0.01	3.3	3	0.01
Cerebrovascular disease	2.2	1.6	0.05	2	1.8	0.02
Heart disease	10.1	7.6	0.09	9.2	8.7	0.02
Malignant neoplastic disease	6.5	5	0.07	5.9	5.5	0.02
Charlson comorbidity index, mean (SD)	1.62 (2.81)	1.62 (3.00)	0.00	1.59 (2.80)	1.59 (2.99)	0.00
Influenza vaccination within a year prior	8.4	6.3	0.08	7.2	6.8	0.02
Janssen COVID-19 vaccine						
Patients, n	5,167	52,643		5,031	5,031	
Follow-up, days. Median (IQR)	79 (72-95)	79 (72-95)		79 (72-95)	79 (72-95)	
COVID-19 diagnosis or positive COVID-19 test, n				31	37	
Positive COVID-19 test, n				8	16	
Age group, %						

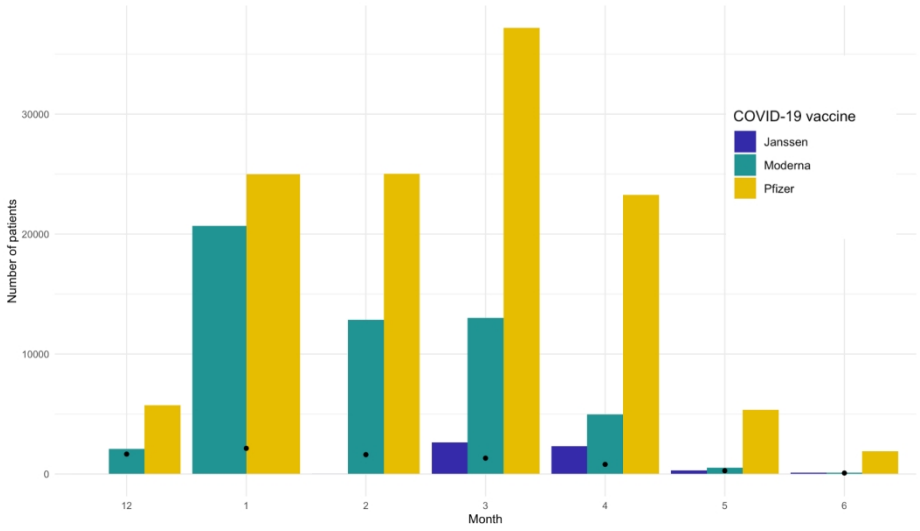
10-19	0.8	0.8	0.00	0.8	0.8	0.00
20-49	43.9	43	0.02	44.2	43.9	0.01
50-64	31.7	31.7	0.00	31.8	31.3	0.01
65-74	11.6	12.2	-0.02	11.5	12	-0.02
75-84	7.6	7.9	-0.01	7.2	7.9	-0.03
>84	4.3	4.3	0.00	4.2	4	0.01
Gender, %						
Female	63.4	63.2	0.01	63.5	61.1	0.05
Race, %						
race = Asian	3.6	1.7	0.12	3.7	3.6	0.01
race = Black or African American	15.9	15.5	0.01	15.7	15.5	0
race = White	37.4	35.7	0.03	37.4	37.5	0
Medical history, %						
Chronic liver disease	1.1	0.7	0.05	1	1.2	-0.02
Chronic obstructive lung disease	2.4	1.3	0.09	2	2.2	-0.01
Dementia	2.6	1.1	0.11	2.2	2.2	0
Depressive disorder	8	4.8	0.13	7.1	8	-0.03
Diabetes mellitus	10.3	6.2	0.15	9.5	10.2	-0.02
Human immunodeficiency virus infection	1.7	1.4	0.02	1.6	1.8	-0.01
Hyperlipidemia	14.3	10.2	0.13	13.4	14.3	-0.03
Hypertensive disorder	21.4	13.8	0.2	20.1	21.7	-0.04
Obesity	7.3	5.9	0.06	6.8	7.8	-0.04
Osteoarthritis	8.4	6.2	0.08	7.8	8.8	-0.04
Renal impairment	6.6	3.3	0.15	5.3	5.9	-0.02
Cerebrovascular disease	2.7	1.7	0.07	2.3	2.4	-0.01
Heart disease	11.8	8	0.13	10.3	11.7	-0.04
Malignant neoplastic disease	5	4.9	0	4.8	5.2	-0.02
Charlson comorbidity index, mean (SD)	1.84 (3.34)	1.55 (2.96)	-0.07	1.56 (3.04)	1.43 (2.79)	-0.03

Influenza vaccination within a year prior	12.5	8.0	0.15	10.1	11.4	-0.04

* Hypertensive disorder includes primary and secondary hypertension

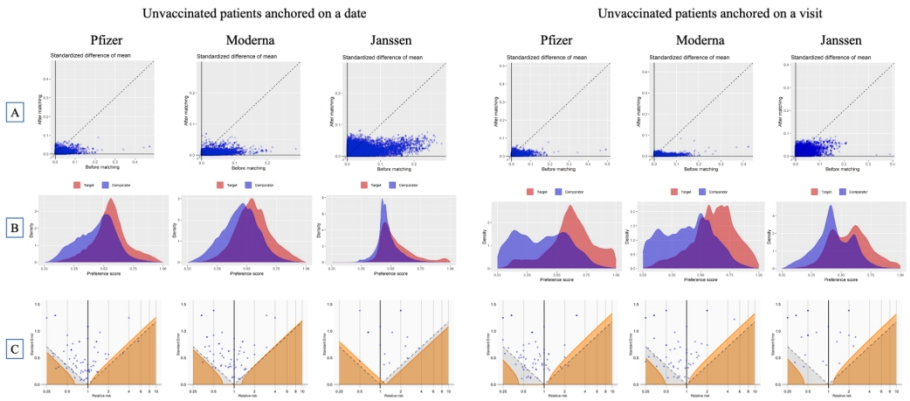
** Renal impairment includes acute and chronic renal failure (prerenal and renal);

*** Heart disease includes cardiac arrythmias, heart valve disorders, coronary arteriosclerosis, heart failure, cardiomyopathies, etc.



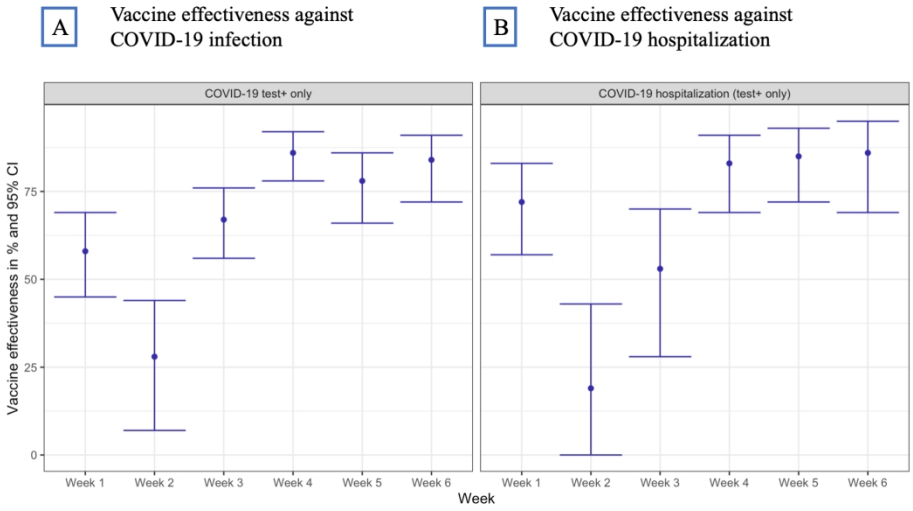
Distribution of vaccination month for COVID-19 vaccines. Black dots represent the number of incident COVID-19 cases (defined as a positive test) in each month.

338x190mm (144 x 144 DPI)



Diagnostics for the absolute effectiveness study comparing the cohort vaccinated with at least one dose of Pfizer, Moderna or Janssen COVID-19 vaccines and unvaccinated cohort anchored on a date or on a visit: (A) covariate balance before and after propensity score matching, (B) preference score balance and (C) effect of negative control calibration displaying effect estimate and standard error.
In (A), each dot represents the standardized difference of the means for a single covariate before and after stratification on the propensity score.
In (C), each blue dot is a negative control. The area below the dashed line indicates estimates with $p<0.05$ and the orange area indicates estimates with calibrated $p<0.05$.

625x313mm (78 x 78 DPI)



Effectiveness of Pfizer-BioNTech and Moderna vaccines over six 7-day intervals after 1st dose, % and 95% CI for COVID-19 infection (A) and COVID-19 hospitalization (B).

272x152mm (226 x 226 DPI)

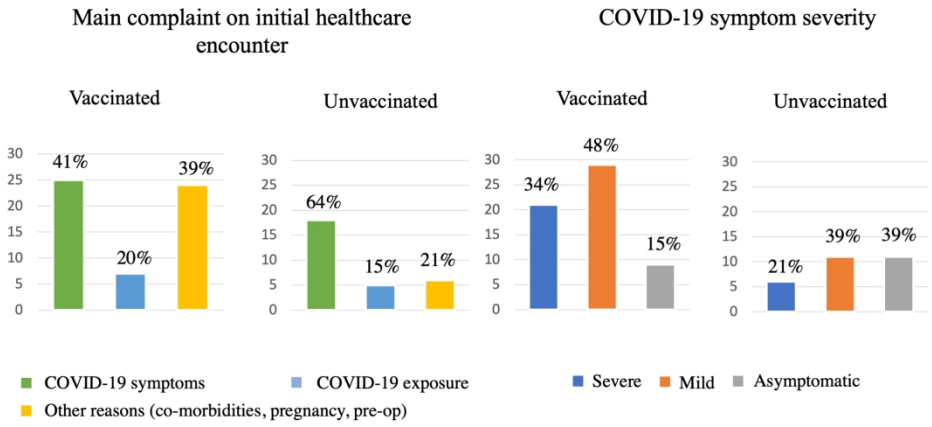


Chart review of COVID-19 cases (defined as a positive COVID-19 test) during week one, vaccinated and unvaccinated patients.

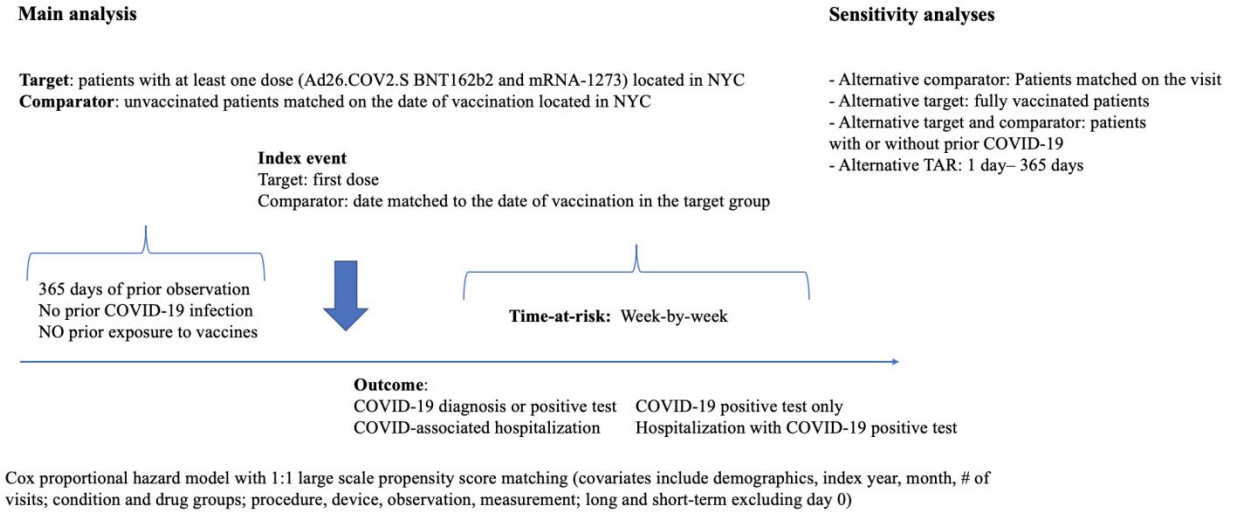
272x152mm (226 x 226 DPI)

Supplementary materials

Appendix 1. Data source description

The Columbia University Irving Medical Center (CUIMC) database comprises electronic health records on more than 6 million patients, with data collection starting in 1985. CUIMC is a Northeast US quaternary care center with primary care practices in northern Manhattan and surrounding areas, and the database includes inpatient and outpatient care. The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions (billing diagnoses and problem lists), drugs (outpatient prescriptions and inpatient orders and administrations), devices, measurements (laboratory tests and vital signs), and other observations (symptoms). The data sources include current and previous electronic health record systems (homegrown Clinical Information System, homegrown WebCIS, Allscripts Sunrise Clinical Manager, Allscripts TouchWorks, Epic Systems), administrative systems (IBM PCS-ADS, Eagle Registration, IDX Systems, Epic Systems), and ancillary systems (homegrown LIS, Sunquest, Cerner Laboratory). Additionally, it contains the information on vaccination from New York City and State immunization registries.

Appendix 2. Retrospective cohort COVID-19 vaccine effectiveness study design overview.



Cox proportional hazard model with 1:1 large scale propensity score matching (covariates include demographics, index year, month, # of visits; condition and drug groups; procedure, device, observation, measurement; long and short-term excluding day 0)

Appendix 3. Cohort definitions and codes for the absolute COVID-19 vaccine effectiveness study

3.1 Cohort definitions for target comparator and outcome cohorts for studying absolute effectiveness of COVID-19 vaccines.

	Definition and link to the public repository
Target cohorts	Target cohorts were defined as patients with at least one dose of the corresponding vaccine (Pfizer BioNTech, Moderna, Janssen) Index event: first exposure to the corresponding vaccine Inclusion and exclusion criteria: - 365 days of prior observation - no other COVID-19 vaccine exposure in 120 days prior and 120 days after the index date - no prior COVID-19 infection (diagnosis code of COVID-19 or positive test) - residence in New York City determined by the zip code recorded For the analysis on fully vaccinated patients, we applied the same criteria and required patients to have a) the second dose of Pfizer or Moderna vaccine (if applicable) within 14 to 56 days after the first dose b) at least 14 days of observation after the second dose (one dose of Janssen). **Links:** https://atlas.ohdsi.org/#/cohortdefinition/498 https://atlas.ohdsi.org/#/cohortdefinition/494 https://atlas.ohdsi.org/#/cohortdefinition/497 https://atlas.ohdsi.org/#/cohortdefinition/418 https://atlas.ohdsi.org/#/cohortdefinition/417 https://atlas.ohdsi.org/#/cohortdefinition/420
Comparator cohorts	Comparator cohorts were created separately for each target cohort by selecting patients with no COVID-19 vaccination in their record (any vaccine), 365 days of prior observation and New York City residence. The patients were matched on the index date of one of the target group participants for the comparator anchored on a date and on the date of a healthcare encounter within 3-day corridor for the comparator anchored on a visit.

Outcome cohorts	For the main analysis COVID-19 infection was defined as a COVID-19 test with the result 'Positive' or 'Detected'. COVID-19 associated hospitalization was defined as an inpatient, emergency department or intensive care unit admission with a positive COVID-19 test recorded within 30 days prior or during hospitalization. For a sensitivity analysis we applied the abovementioned criteria with adding COVID-19 diagnosis as an alternative for positive COVID-19 test. Links: https://atlas.ohdsi.org/#/cohortdefinition/425 https://atlas.ohdsi.org/#/cohortdefinition/422

3.2 Codes used in the study.

1. **Pfizer vaccine:**

RxNorm 2468235 SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension

2. **Moderna vaccine:**

RxNorm 2470234 SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension

3. **Janssen vaccine:**

CVX 212 SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-Ad26, preservative free, 0.5 mL

4. **COVID-19 diagnosis:**

ICD10-CM U07.1 Emergency use of U07.1 | COVID-19

5. **COVID-19 test:**

LOINC 94500-6 SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA with probe detection
LOINC 94558-4 SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay

Appendix 4. Negative controls

SNOMED concept id	SNOMED concept name
438945	Accidental poisoning by benzodiazepine-based tranquilizer
434455	Acquired claw toes
316211	Acquired spondylolisthesis
201612	Alcoholic liver damage
438730	Alkalosis
441258	Anemia in neoplastic disease
432513	Animal bite wound
4171556	Ankle ulcer
4098292	Antiphospholipid syndrome
77650	Aseptic necrosis of bone
4239873	Benign neoplasm of ciliary body
23731	Benign neoplasm of larynx
199764	Benign neoplasm of ovary
195500	Benign neoplasm of uterus
4145627	Biliary calculus
4108471	Burn of digit of hand
75121	Burn of lower leg
4284982	Calculus of bile duct without obstruction
434327	Cannabis abuse
78497	Cellulitis and abscess of toe
4001454	Cervical spine ankylosis
4068241	Chronic instability of knee
195596	Chronic pancreatitis
4206338	Chronic salpingitis
4058397	Claustrophobia
74816	Contusion of toe
73302	Curvature of spine
4151134	Cyst of pancreas
77638	Displacement of intervertebral disc without myelopathy
195864	Diverticulum of bladder
201346	Edema of penis
200461	Endometriosis of uterus
377877	Esotropia
193530	Follicular cyst of ovary
4094822	Foreign body in respiratory tract
443421	Gallbladder and bile duct calculi

4299408	Gouty tophus
135215	Hashimoto thyroiditis
442190	Hemorrhage of colon
43020475	High risk heterosexual behavior
194149	Hirschsprung's disease
443204	Human ehrlichiosis
4226238	Hyperosmolar coma due to diabetes mellitus
4032787	Hyperosmolarity
197032	Hyperplasia of prostate
140362	Hypoparathyroidism
435371	Hypothermia
138690	Infestation by Pediculus
4152376	Intentional self poisoning
192953	Intestinal adhesions with obstruction
196347	Intestinal parasitism
137977	Jaundice
317510	Leukemia
765053	Lump in right breast
378165	Nystagmus
434085	Obstruction of duodenum
4147016	Open wound of buttock
4129404	Open wound of upper arm
438120	Opioid dependence
75924	Osteodystrophy
432594	Osteomalacia
30365	Panhypopituitarism
4108371	Peripheral gangrene
440367	Plasmacytosis
439233	Poisoning by antidiabetic agent
442149	Poisoning by bee sting
4314086	Poisoning due to sting of ant
4147660	Postural kyphosis
434319	Premature ejaculation
199754	Primary malignant neoplasm of pancreas
4311499	Primary malignant neoplasm of respiratory tract
436635	Primary malignant neoplasm of sigmoid colon
196044	Primary malignant neoplasm of stomach
433716	Primary malignant neoplasm of testis
133424	Primary malignant neoplasm of thyroid gland

194997	Prostatitis
80286	Prosthetic joint loosening
443274	Psychostimulant dependence
314962	Raynaud's disease
37018294	Residual osteitis
4288241	Salmonella enterica subspecies arizonae infection
45757269	Sclerosing mesenteritis
74722	Secondary localized osteoarthrosis of pelvic region
200348	Secondary malignant neoplasm of large intestine
43020446	Sedative withdrawal
74194	Sprain of spinal ligament
4194207	Tailor's bunion
193521	Tropical sprue
40482801	Type II diabetes mellitus uncontrolled
74719	Ulcer of foot
196625	Viral hepatitis A without hepatic coma
197494	Viral hepatitis C
4284533	Vitamin D-dependent rickets

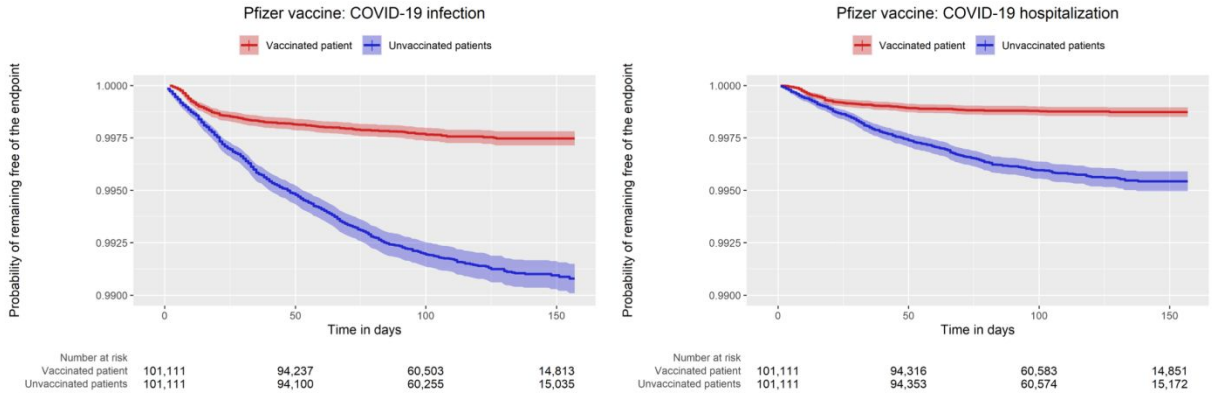
Link to the original list of negative controls used in EUMAEUS study: https://ohdsi-studies.github.io/Eumaeus/Protocol.html#8_Research_Methods

Appendix 5. Summary of manual chart review of COVID-19 infection cases during week 1 after the index date, patients vaccinated with mRNA vaccines and unvaccinated patients.

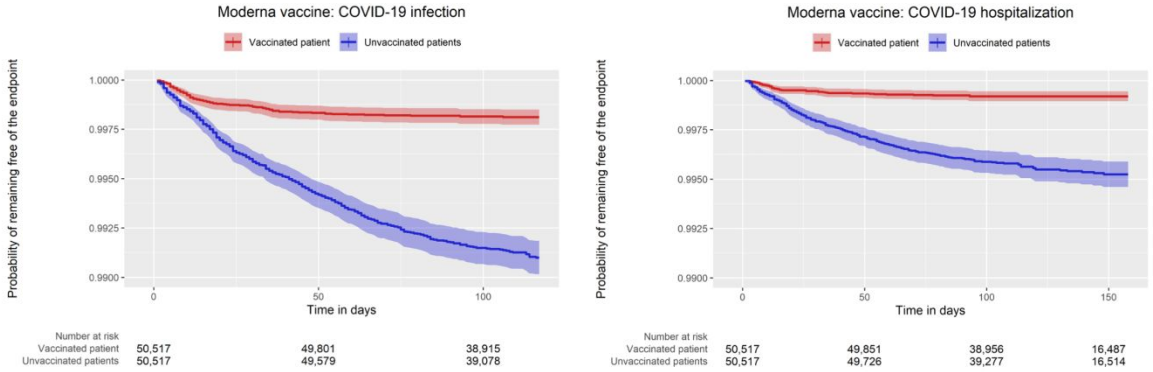
	Pfizer-BioNTech	**Moderna**	**Pfizer-BioNTech and Moderna**	**Unvaccinated patients**
Total	36	25	61	28
Average age	65	67.8	65.8	58
COVID-19 symptoms				
Severe	14 (39%)	7 (28%)	21 (34%)	6 (21%)
Mild	18 (50%)	11 (44%)	29 (48%)	11 (39%)
Asymptomatic	2 (6%)	7 (28%)	9 (15%)	11 (39%)
Reason for coming for initial healthcare encounter				
COVID-19 symptoms	17 (47%)	8 (32%)	25 (41%)	18 (64%)
Exposure to COVID-19	3 (8%)	4 (16%)	7 (11%)	5 (18%)
For other reason (co-morbidities, procedures etc.)	13 (36%)	11 (44%)	24 (39%)	6 (21%)

Type of initial healthcare encounter				
Telehealth/phone	5 (14%)	6 (24%)	11 (18%)	3 (11%)
Test only	3 (8%)	2 (8%)	5 (8%)	6 (21%)
OP	4 (11%)	3 (12%)	7 (11%)	1 (4%)
ED or IP	24 (67%)	14 (56%)	38 (62%)	18 (64%)

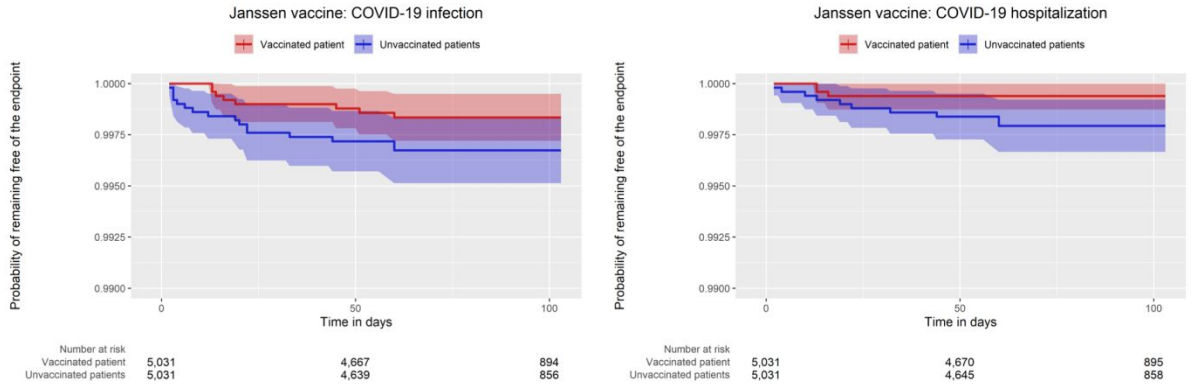
Appendix 6. Kaplan-Meier curves for effectiveness of COVID-19 Pfizer-BioNTech vaccine for time-at-risk of 1 day – 365 days after the first dose compared to the unvaccinated patients residing in New York City.



Appendix 7. Kaplan-Meier curves for effectiveness of COVID-19 Moderna vaccine for time-at-risk of 1 day – 365 days after the first dose compared to the unvaccinated patients residing in New York City.



Appendix 8. Kaplan-Meier curves for effectiveness of COVID-19 Janssen vaccine for time-at-risk of 1 day – 365 days after the first dose compared to the unvaccinated patients residing in New York City.



Appendix 9. Estimates for absolute effectiveness of COVID-19 vaccines for time-at-risk of 1 day – 365 days after the first dose in the vaccinated patients without prior COVID-19 infection compared to unvaccinated patients residing in NYC.

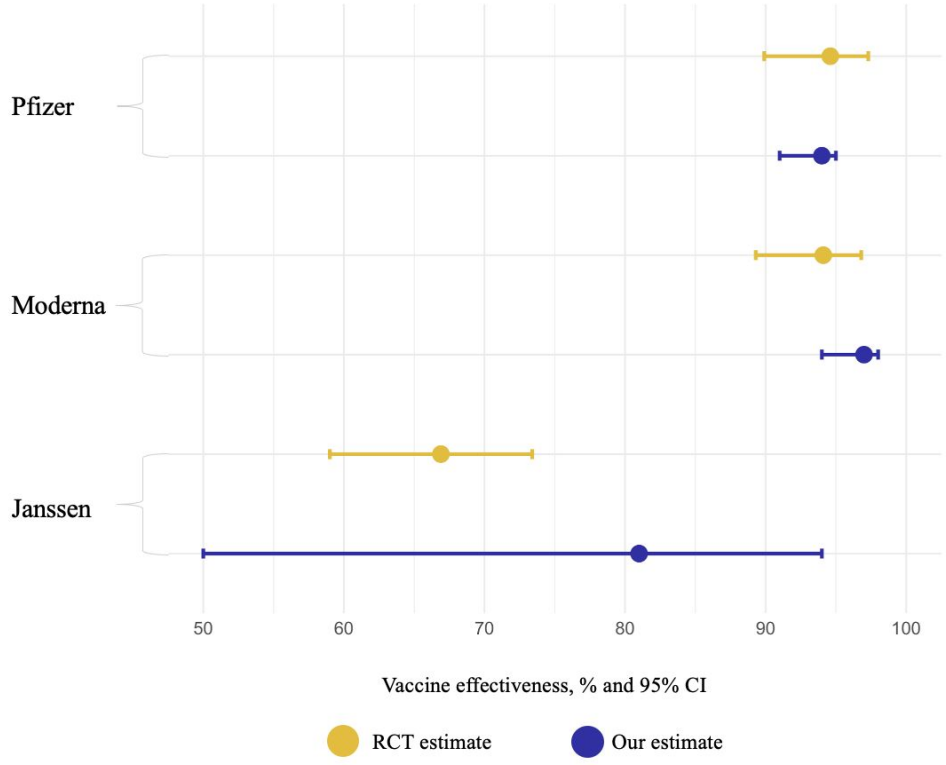
	COVID-19 infection		**COVID-19 hospitalization**		**COVID-19 positive test only**		**COVID-19 positive test only hospitalization**	
	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value
Pfizer-BioNTech	42 (37 – 47)	<0.01	63 (56-70)	<0.01	71 (66 - 75)	<0.01	69 (62 - 75)	<0.01
Moderna	54 (48 – 60)	<0.01	76 (69 – 82)	<0.01	78 (73 – 83)	<0.01	81 (74 – 87)	<0.01
Janssen	24 (0-55)	0.31	64 (0.1 – 1.06)	0.09	53 (0 – 82)	0.1	70 (2 – 93)	0.08

Appendix 10. Estimates for absolute effectiveness of COVID-19 vaccines for time-at-risk of 1 day – 365 days after full vaccination in fully vaccinated patients without prior COVID-19 infection compared to unvaccinated patients residing in NYC.

	COVID-19 positive test only		**COVID-19 positive test only hospitalization**		**COVID-19 infection**		**COVID-19 hospitalization**	
	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value

Pfizer-BioNTech	94 (91-95)	<0.01	95 (92-97)	<0.01	70 (66-74)	<0.01	88 (84-92)	<0.01
Moderna	97 (94-98)	<0.01	96 (92-99)	<0.01	72 (66 – 77)	<0.01	92 (87-95)	<0.01
Janssen	81 (50-94)	<0.01	92 (58-100)	0.03	55 (23 – 75)	0.01	87 (56-98)	0.01

Appendix 11. Comparison of the absolute effectiveness estimates in fully vaccinated patients obtained in our study and those from the randomized clinical trials of the corresponding vaccines.



Appendix 12. Estimates for absolute effectiveness of COVID-19 vaccines for time-at-risk of 1 day – 365 days after the first dose in the vaccinated patients with or without prior COVID-19 infection compared to unvaccinated patients residing in NYC.

	COVID-19 infection		**COVID-19 hospitalization**		**COVID-19 positive test only**		**COVID-19 positive test only hospitalization**	
	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value

Pfizer-BioNTech	43 (38-48)	<0.01	64 (57-70)	<0.01	71 (66-75)	<0.01	71(64-76)	<0.01
Moderna	51 (45-57)	<0.01	71 (63-78)	<0.01	76 (71-81)	<0.01	81 (73-86)	<0.01
Janssen	15 (0-49)	0.52	60 (2-86)	0.06	45 (0-75)	0.12	63 (0-90)	0.09

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	6-7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, 18-20
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	8, 18
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8, supplementary materials
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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COVID-19 vaccination effectiveness rates by week and sources of bias: a retrospective cohort study

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COVID-19 vaccination effectiveness rates by week and sources of bias: a retrospective cohort study

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ABSTRACT

Objective

To examine COVID-19 vaccine effectiveness over six 7-day intervals after the first dose and assess underlying bias in observational data.

Design and setting

Retrospective cohort study using Columbia University Medical Center data linked to State and City Immunization Registries.

Outcomes and measures

We used large-scale propensity score matching with up to 54,987 covariates, fitted Cox proportional hazards models and constructed Kaplan-Meier plots for two main outcomes (COVID-19 infection and COVID-19-associated hospitalization). We conducted manual chart review of cases in week one in both groups along with a set of secondary analyses for other index date, outcome and population choices.

Results

The study included 179,666 patients. We observed increasing effectiveness after the first dose of mRNA vaccines with week six effectiveness approximating 84% (95% CI 72-91%) for COVID-19 infection and 86% (95% CI 69-95) for COVID-19-associated hospitalization. When analyzing unexpectedly high effectiveness in week one, chart review revealed that vaccinated patients are less likely to seek care after vaccination and are more likely to be diagnosed with COVID-19 during the encounters for other conditions. Secondary analyses highlighted potential outcome misclassification for ICD10-CM diagnosis, the influence of excluding patients with prior COVID-19 infection and anchoring in the unexposed group. Overall vaccine effectiveness in fully vaccinated patients matched the results of the randomized trials.

Conclusions

For vaccine effectiveness studies, observational data need to be scrutinized to ensure compared groups exhibit similar health seeking behavior and are equally likely to be captured in the data. While we found that studies may be capable of accurately estimating long-term effectiveness despite bias in early weeks, the early week results should be reported in every study so that we may gain a better understanding of the biases. Given the difference in temporal trends of vaccine exposure and baseline characteristics, indirect comparison of vaccines may produce biased results.

Strengths and limitations of this study

- This study thoroughly investigates weekly COVID-19 vaccine effectiveness using methods to reduce potential confounding (large-scale propensity score matching, negative control calibration) and accompanied by manual chart review of the cases in week one

- The study includes a range of secondary analyses for different patient populations, anchoring strategies and outcome definitions.

- The study was carried out using routinely collected clinical practice data, which represents real-world patients, but also implies a risk of misclassification.

Word count: 3483

Keywords: COVID-19, Epidemiology, Health Informatics, Bias

BACKGROUND

Randomized clinical phase-3 trials have demonstrated high efficacy for the four most commonly used COVID-19 vaccines against symptomatic COVID-19 infection, ranging from 66.9% and 70.4% for Ad26.COV2.S (Johnson & Johnson–Janssen) and ChAdOx1 (Astrazeneca) to 94.1% and 94.6% for BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) vaccines (1–4). Their rapid approval and widespread use require robust post-marketing studies that leverage large sample size, heterogeneous populations, and longer follow-up available in observational data.

There have been recent observational studies, which have shown effectiveness similar to the randomized clinical trials (RCTs) across the globe, both test-negative and cohort (5–12), followed by studies across different patient populations, variants and number of doses (13–17).

Nevertheless, the challenges associated with the use of observational data such as incomplete data capture, outcome misclassification and appropriate comparator sampling can undermine the results of the studies if such biases are not accounted for (18). For COVID-19 vaccines, questions associated with vaccine status misclassification (19), matching vaccinated and unvaccinated populations (6), addressing disease risk factor confounding and ascertainment bias (20,21) and others were raised.

One of such questions is COVID-19 vaccine effectiveness during the first two weeks following the first dose. Studies have shown contradicting results for Pfizer–BioNTech vaccine with effectiveness ranging from moderate effectiveness of 52% (3) to very high effectiveness of 92.6% (22). Similarly, a recent study showed an unexplained high effectiveness of Janssen vaccine during week one (23). Other studies simply excluded the first week(s) from the time-at-risk (9,13,24–26). While week one lack of effectiveness has been suggested as a metric for lack of confounding in the long-term vaccine effectiveness studies, the reasons for high effectiveness and its impact on the validity of the conclusions regarding the overall effectiveness remain unclear (9).

The goal of this study was to examine COVID-19 vaccine effectiveness over six 7-day intervals after the first dose to assess underlying bias associated with the use of observational data for short-term vaccine effectiveness and its impact on long-term vaccine effectiveness estimates . We employed large-scale propensity score matching and many negative controls to reduce and assess bias and leveraged a range of secondary analyses as well as manual review of the COVID-19 infection cases in week one to examine health-seeking behavior of vaccinated and unvaccinated patients.

METHODS

Main design

For this retrospective observational cohort study, we used electronic health records from the Columbia University Irving Medical Center (CUIMC) database (Appendix 1), which has an ongoing automated connection to New York City and State public health department vaccine registries and includes all within-state vaccinations for our population. The data were translated to the OMOP Common Data Model version 5 as was used in multiple studies (27).

For our main analysis, we studied two mRNA vaccines (Pfizer-BioNTech or Moderna). The exposed group included patients indexed on the first dose of one of the corresponding vaccines with no prior COVID-19 infection and no previous exposure to other COVID-19 vaccines. For the unexposed group, we selected unvaccinated patients and set their index date to a date (not necessarily with any medical event) that matched the index date of one of the exposed group participants. Both the exposed and unexposed groups had at least 365 days of prior observation and primarily resided in New York City according to their zip code. Patients who did not reside in New York were excluded from the study to ensure reliable vaccination data capture.

Outcomes of interest included a) COVID-19 infection defined as a positive COVID-19 test (reverse-transcriptase–polymerase-chain-reaction assay) or a diagnostic code of COVID-19 and b) COVID-19 hospitalization defined as an inpatient visit associated with a COVID-19 positive test or diagnosis within 30 days prior or during the visit. Upon further examination of the results, we added two other outcomes: a) COVID-19 positive test only and b) COVID-19 hospitalization associated with a positive COVID-19 test. Design overview is provided in Appendix 2; code lists and links to phenotype definitions are provided in Appendix 3.

We calculated vaccine effectiveness during six consecutive 7-day intervals after the first dose. Within each interval, patients were followed-up until an outcome, end of the period or death, whichever came earlier. Additionally, given the results for vaccine effectiveness during week one following the first dose, we conducted chart review for patients with a COVID-19 positive test recorded in the abovementioned period. We reviewed all cases for the vaccinated population as well a random sample of the cases in the unvaccinated population and extracted main complaint, COVID-19 history, including symptoms (fever,

shortness of breath, sore throat, cough etc.), severity, time from the first symptom to encounter and COVID-19 exposure.

Secondary analyses

We also conducted a set of secondary analyses. First, given that the published studies focused on patients without prior COVID-19 infection, we studied all eligible patients regardless of their previous COVID-19 status.

As the strategy for unvaccinated group index date selection (anchoring) has been reported to influence incidence of outcomes and baseline characteristics (28,29), we additionally tested unexposed patients indexed on a healthcare encounter matching the index date of one of the exposed group participants within 3 days corridor, with at least 365 days of prior observation located at New York.

Finally, we assessed vaccine effectiveness in patients with at least one dose of a COVID-19 vaccine and in fully vaccinated patients over all available follow-up to compare the estimates to the results of the RCTs. The latter was defined as 14 days after the second dose of Pfizer-BioNTech or Moderna vaccines or first dose of Janssen vaccine. For each comparison we estimated hazard ratios (HRs) and constructed Kaplan-Meier plots as described below.

Statistical methods

For each analysis, we fitted a lasso regression model to calculate propensity score and match patients in each exposed and unexposed group with 1:1 ratio. For large-scale propensity score model we used all demographic information, index year and month, as well as the number of visits, condition and drug groups, procedures, device exposures, laboratory and instrumental tests and other observations over long (prior year) and short-term period (prior month) (30,31).

For each outcome, we fitted a Cox proportional hazards models to estimate HRs and constructed Kaplan-Meier plots. Empirical calibration based on the negative control outcomes was used to identify and minimize any potential residual confounding by calibrating HRs and 95% confidence intervals (CIs) (32,33). Vaccine effectiveness was calculated as 100% × (1−hazard ratio).

All analyses were supported by the OHDSI Infrastructure (CohortMethod package, available at https://ohdsi.github.io/CohortMethod/, FeatureExtraction available at https://ohdsi.github.io/FeatureExtraction/ and the Cyclops package for large-scale regularized regression (34) available at https://ohdsi.github.io/Cyclops).

Diagnostics

We used multiple sources of diagnostics to estimate potential bias and confounding following best practices for evidence generation (35). First, we examined covariate and propensity score balance prior to proceeding with outcome modelling and effect estimation to ensure that we have enough sample size and to control for potential observed confounding (35). We plotted propensity scores to investigate the overlap in patient populations at the baseline and examined the balance of all baseline characteristics to determine if the exposed and unexposed cohorts were imbalanced at the baseline and after propensity score matching. Exposed and unexposed cohorts were said to be balanced if the standardized difference of means of all covariates after propensity score matching was less than 0.1 (36).

For negative control calibration, we used 93 negative controls (Appendix 4) with no known causal relationship with the COVID-19 vaccines. Negative controls were selected based on a review of existing literature, product labels and spontaneous reports and were reviewed by clinicians (37). We assessed residual bias from the negative control estimates.

Patient and public involvement

No patient involved

RESULTS

Patient characteristics

In total, we identified 179,666 patients with at least one dose of COVID-19 vaccine in January-May 2021: 121,771 patients for Pfizer-BioNTech, 52,728 for Moderna and 5,167 for Janssen (Table 1). The sample included patients from all age groups, with or without co-morbidities captured in inpatient and outpatient settings.

We observed that unexposed patients (Table 1) were on average younger and had fewer co-morbidities and less exposure to various drugs prior to matching. We were able to achieve balance on all covariates (up to 54,987 covariates, standardized difference of means less than 0.1) with propensity score matching. Figure 1 presents the covariate balance and propensity score balance plots showing that anchoring unvaccinated patients on a date allowed us to achieve better balance compared to anchoring patients on a visit.

Patients vaccinated with Pfizer-BioNTech had a similar distribution of baseline characteristics compared to the patients vaccinated with Moderna but differed from the patients vaccinated with Janssen. On average, the latter group was older, had more patients with race recorded as Black, and had more co-morbidities such as diabetes mellitus or hypertensive disorder (Table 1).

When investigating the vaccination pathways, we discovered that 112,963 patients (93% of patients with at least one dose of Pfizer-BioNTech) had 2 doses of Pfizer-BioNTech and 42,384 (80%) patients had 2 doses of Moderna. We found 344 and 291 patients with 3 doses of the corresponding vaccines and 440 patients having mixed Pfizer-BioNTech, Moderna and Janssen vaccines in different combinations.

Within our database, Moderna was administered early on with a peak in January 2021 (Figure 2), while Pfizer-BioNTech and Janssen vaccinations peaked in April. It was reflected in the follow-up time with Moderna patients having on average longer follow-up with some individuals having up to 5.8 months of post-observation.

Main week-by-week effectiveness analysis

Figure 3 shows vaccine effectiveness over six 7-day intervals for patients vaccinated with at least one dose of Pfizer-BioNTech or Moderna (160,114 patients) compared to unvaccinated patients (115,689). Due to the small sample size, we were not able to obtain stable week-by-week estimates for Janssen.

While week one was characterized by unexpectedly high effectiveness (58%, 95% CI 45-69% against COVID-19 infection and 72%, 95% CI 57-83% against COVID-19 associated hospitalization), we observed plausible increasing effectiveness beginning week 2 with the effectiveness on week 6 approximating 84% (95% CI 72-91%) for COVID-19 infection and 86% (95% CI 69-95) for COVID-19-associated hospitalization.

We then looked at the week one COVID-19 infection cases to explain high effectiveness (Figure 4). A chart review of week one positive COVID-19 tests revealed a high proportion of unvaccinated patients seeking care related to COVID-19 symptoms or COVID-19 exposure (85% in total) compared to only 69% of vaccinated patients. Initial healthcare encounters in vaccinated population were oftentimes related to other medical reasons such as co-morbid conditions or surgeries (39% compared to 21% in unvaccinated population, Appendix 5). Moreover, an observed gap between symptom onset and an initial healthcare encounter was more pronounced in the vaccinated cohort as the patients attributed their symptoms to temporal vaccine side effects as opposed to COVID-19 infection.

When looking at the severity of COVID-19 symptoms at the initial encounter during week one after the index date, we observed that the unvaccinated cohort had a higher proportion of asymptomatic cases (39% compared to 11%) while the vaccinated population had more severe or mild cases (34% and 48% respectively).

Secondary analysis

As cohort analysis allows us to construct Kaplan-Meier curves to assess effectiveness over time, we also looked at the effectiveness during the year after the first dose (Appendix 6-8). We observed similar trends with all three vaccines being less effective during the first month after the first dose. After that, Pfizer-BioNTech and Moderna were highly effective against both COVID-19 infection and COVID-19 associated hospitalization, while Janssen vaccine exhibited a wide range of effectiveness (Appendix 9).

The results for fully vaccinated patients with time-at-risk starting at the full vaccination matched the results of the clinical trials for corresponding vaccines (detailed estimates are provided in Appendix 10 and 11).

Our initial design included a positive COVID-19 test or a diagnostic code as an outcome. Upon further case examination, we discovered that COVID-19 diagnostic codes in the CUIMC data were partially assigned to the patients with negative COVID-19 tests on or immediately following the date of diagnosis. In that case, ICD10CM code U07.1 “Disease caused by Severe acute respiratory syndrome coronavirus 2” was entered in the system for billing purposes (COVID-19 molecular or antibody tests) or for COVID-19 sequelae. We, therefore, focused on positive COVID-19 test only for our primary outcome, which led to higher effectiveness for all vaccines compared to using both positive test and diagnosis (Appendix 9).

Finally, exclusion of patients with prior COVID-19 infection in our main analysis resulted in higher effectiveness. Inclusion of patients regardless of their prior COVID-19 status led to a small decrease in observed effectiveness (Appendix 12) for both COVID-19 infection and hospitalization in patients vaccinated with Moderna or Janssen.

DISCUSSION

In this retrospective cohort study, we examined the effectiveness of COVID-19 mRNA vaccines over six 7-day intervals after the first dose. We scrutinized the effectiveness of the mRNA vaccines following the first dose and confirmed the findings of moderate vaccine effectiveness during the first two weeks. For week one following the first dose we discovered previously uncaptured differential biases in vaccinated and unvaccinated populations resulting in high vaccine effectiveness. Other researchers suggested that the difference between vaccinated and unvaccinated groups can be mitigated by adjusting for previous healthcare utilization such as number of visits before baseline, co-morbidities or prior vaccination behavior (6,13,24). Nevertheless, the confounding we observed remains even upon controlling for a large number of covariates including those above.

Vaccination directly influenced the attitude of patients towards their symptoms, causing a delay in seeking care and a higher symptom severity threshold needed to seek care or get tested. On contrary, vaccinated patients in other studies had higher rates of testing compared to unvaccinated (20,38). This indicates that patients' attitude toward risk of infection and testing may vary geographically and over time. Similarly, frequency of testing may depend on local policies and practices.

In unvaccinated patients, mild COVID-19 related symptoms were the reason to seek care; in vaccinated patients such cases were mainly captured upon seeking outpatient and inpatient care for other conditions. For example, vaccinated patients could be hospitalized for elective surgery or delivery and be tested positive for COVID-19 on the day of admission or later on. Differential symptom severity was previously reported for other vaccines (39) and may affect any observational study that uses hospitalization as a surrogate for COVID-19 severity as it can be hard to accurately identify the main reason for hospitalization in structured data.

Previous research suggested that vaccinated patients do not have an increase in the number of cases immediately following vaccination as they are unlikely to get vaccinated if sick (9,40). Our review of the

cases in week one adds to 'healthy vaccinee' effect by showing that vaccinated patients are more likely to attribute their symptoms to common vaccine side effects and, therefore, are less likely to seek care.

Nevertheless, even when this differential bias is present, the estimates of the COVID-19 vaccine effectiveness in subsequent weeks still match the results of the RCTs. This indicates that high effectiveness during week one following vaccination does not necessarily undermine the estimates of subsequent vaccine effectiveness. On the other hand, we argue against using estimates of vaccine effectiveness within a short period after the vaccination as a negative control as the differences between the groups observed in this study are likely to be time-variant and may diminish over time (41).

Our secondary analyses discovered several challenges and potential biases that must be accounted for when conducting vaccine effectiveness studies on observational data. First, we observed that outcome definitions are prone to measurement error, which has not been studied thoroughly. Some of the published studies used ICD-10 or ICD-10(CM) codes to identify COVID-19 outcomes (42–44). We found that the specifics of data capture and billing processes were associated with some patients having assigned COVID-19 diagnosis codes for billing for tests rather than as an indicator of active disease. Another reason for assigning the code was COVID-19 sequela, where the actual date of COVID-19 infection could have been anywhere from 6 months to a couple of weeks in the past. Some researchers have previously reported high positive predictive value of ICD-10 diagnostic codes for COVID-19, which points out that index date misclassification should be scrutinized in each institution participating in the analysis to make valid inferences (45,46).

Second, inclusion or exclusion of patients with prior COVID-infection influenced estimated effectiveness. We observed that inclusion of patients with prior COVID-19 leads to lower effectiveness for all vaccines regardless of the outcome definition.

Third, an appropriate index event (anchor) for the unvaccinated cohort must be chosen to represent a counterfactual for vaccination (29,47). In our study, we confirmed that an arbitrary date represents a better counterfactual than a medical visit for COVID-19 vaccination, which is reflected in propensity score balance and covariate balance. Nevertheless, other institutions may have different vaccination pathways such as vaccination on discharge, which can make a visit a better counterfactual for vaccination. More generally, completeness of vaccination data capture is a crucial feature that influences the robustness of the study. While CUIMC data ensures complete exposure capture by linking EHR to the

City and State Registries, the researchers should exhibit caution with conducting studies on the data sources with unknown vaccination capture.

In general, our findings support the RCTs and previously published post-marketing studies for all three vaccines. Larger sample size for patients vaccinated with COVID-19 mRNA vaccines allowed us to have more power, which resulted in overlapping yet narrower confidence intervals compared to the RCTs. On the other hand, our study had fewer patients with the Janssen vaccine, which resulted in wider yet overlapping intervals compared to the Janssen's vaccine RCT (1,2,7). Nevertheless, an indirect comparison of these vaccines may not be accurate due to the differences in the populations we observed in our study. First, patients vaccinated with Janssen were substantially different from mRNA patients: on average, they were older, had a higher proportion of patients with race recorded as Black and had more comorbidities. Therefore, comparative effectiveness studies of Janssen and mRNA vaccines require robust techniques such as large-scale propensity matching to ensure valid comparison. Second, while Modena and Pfizer patients had similar baseline characteristics, the temporal distribution of vaccinations in CUIMC data differ. Moderna vaccine was administered early on in 2021 with the peak in January, while Pfizer vaccination peaked in April. Given the varying baseline COVID-19 prevalence, a comparison of mRNA vaccines requires matching patients on calendar month to account for this potential bias. These vaccines also had different administration pathways in our system. As opposed to Pfizer vaccine, which was administered at Columbia University Irving Medical Center/New York-Presbyterian sites to all patients over a prolonged period, Moderna vaccination was performed elsewhere and recorded for actively observed patients. Such patients were more likely to get tested or receive care outside of our healthcare system.

LIMITATIONS

Due to observational nature of the study, the data sources may not have complete capture of patient conditions as the patients could seek care outside of the hospital system. While our outcome phenotype algorithms may be subject to measurement error, we provided additional analyses with alternative outcome definitions. Exposure misclassification was mitigated by having free and available COVID-19 testing and COVID-19 vaccination in Columbia University Irving Medical Center/New York-Presbyterian sites as well as by having data capture from New York City and State Immunization Registries. Along with availability of testing, COVID-19 baseline infection rate difference was mitigated by matching the exposed and unexposed groups on the index date and using the index month as a covariate in propensity score model. We attempted to address potential differences between exposed and

unexposed groups by selecting a large number of covariates in our propensity score model such as number of visits, procedure and drug utilization, prior vaccine behavior, race and others. Nevertheless, we did not have data for social interactions, adherence to preventive measures and policies, which could affect likelihood of COVID-19 infection and testing.

The results of the study may not be generalizable to other countries or settings with different vaccine administration practices and policies. Finally, the study period did not allow us to stratify the results by COVID-19 variants, which limits generalizability of findings to other variants.

CONCLUSIONS

Observational data can be used to ascertain vaccine effectiveness if potential biases such as exposure and outcome misclassification are accounted for, and appropriate anchoring event is selected. When analyzing vaccine effectiveness researchers need to scrutinize the data to ensure that compared groups exhibit similar health seeking behavior and are equally likely to be captured in the data and report their findings. Specifically for COVID-19 vaccines, an arbitrary date for the index date in unvaccinated patients represents a better counterfactual for vaccination than a healthcare encounter. Effectiveness over the first week(s) after the vaccination should be reported even though low or high effectiveness immediately after the vaccination may not invalidate study findings. Given the difference in temporal trends of vaccine exposure and baseline characteristics, there is a need for large-scale direct comparison of vaccines to examine comparative effectiveness.

DECLARATION

Author contributions

GH designed and supervised the study. AO executed the study, interpreted the results, and drafted the manuscript. GH and AO reviewed the manuscript, approved the final version and had final responsibility for the decision to submit for publication.

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Declaration of interests

All authors have completed the ICMJE disclosure form (available on request from the corresponding author). GH and AO receive funding from the US National Institutes of Health (NIH) and the US Food and Drug Administration.

Ethical approval

The protocol for this research was approved by the Columbia University Institutional Review Board (AAAO7805).

Data sharing

Patient-level data cannot be shared without approval from data custodians due to local information governance and data protection regulations.

Transparency declaration

The lead authors affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure 1. Distribution of vaccination month for COVID-19 vaccines. Black dots represent the number of incident COVID-19 cases (defined as a positive test) in each month.

Figure 2. Diagnostics for the effectiveness study comparing the cohort vaccinated with at least one dose of Pfizer, Moderna or Janssen COVID-19 vaccines and unvaccinated cohort anchored on a date or on a visit: (A) covariate balance before and after propensity score matching, (B) preference score balance and (C) effect of negative control calibration displaying effect estimate and standard error.
In (A), each dot represents the standardized difference of the means for a single covariate before and after stratification on the propensity score.
In (C), each blue dot is a negative control. The area below the dashed line indicates estimates with $p<0.05$ and the orange area indicates estimates with calibrated $p<0.05$.

Figure 3. Effectiveness of Pfizer-BioNTech and Moderna vaccines over six 7-day intervals after 1st dose, % and 95% CI for COVID-19 infection (A) and COVID-19 hospitalization (B).

Figure 4. Chart review of COVID-19 cases (defined as a positive COVID-19 test) during week one, vaccinated and unvaccinated patients.

Table 1. Patient baseline characteristics for patients with at least one dose of a COVID-19 vaccine and the unexposed patients, before and after propensity score matching.

	Before matching			After matching		
Characteristic	**Vaccinated**	**Unvaccinated**	**Std. diff**	**Vaccinated**	**Unvaccinated**	**Std. diff**
Pfizer-BioNTech COVID-19 vaccine						
Patients, n	121,771	164,997		101,109	101,111	
Follow-up, days. Median (IQR)	107 (80 – 137)	104 (71-137)		107 (78-149)	107 (79-140)	
COVID-19 diagnosis or positive COVID-19 test, n				822	1355	
Positive COVID-19 test, n				231	786	
Age group, %						
10-19	4.2	10.8	-0.25	4.8	4.3	0.02
20-49	37.2	42.6	-0.11	40.3	40.1	0
50-64	23.9	20.3	0.09	23.6	23.7	0
65-74	18.8	12.6	0.17	15.8	16.6	-0.02
75-84	11.3	8.9	0.08	10.6	10.7	0
>84	4.1	3.8	0.02	4.2	4.1	0.01
Gender, %						
Female	63.7	57.8	0.12	61.4	62	-0.01
Race, %						
race = Asian	3.8	2.6	0.07	3.5	3.4	0.01
race = Black or African American	12.4	14.2	-0.05	12.6	12.2	0.01
race = White	40.5	35.1	0.11	39.3	39.5	0
Medical history, %						
Chronic liver disease	0.6	0.6	0	0.5	0.5	0
Chronic obstructive lung disease	1.3	1	0.02	1	1	0.01
Dementia	1.2	1.1	0	1.1	1	0.01
Depressive disorder	5.3	4	0.06	4	3.7	0.02

Diabetes mellitus	7.1	5.2	0.08	5.7	5.4	0.01
Human immunodeficiency virus infection	1.4	1.1	0.03	1.1	1	0
Hyperlipidemia	12.9	8.1	0.16	10.2	9.5	0.02
Hypertensive disorder*	16	11.3	0.14	13.1	12.2	0.03
Obesity	5.1	4.9	0.01	4.4	4.1	0.02
Osteoarthritis	7.3	4.7	0.11	5.8	5.3	0.02
Renal impairment**	3.7	3	0.04	2.9	2.7	0.01
Cerebrovascular disease	1.7	1.4	0.02	1.5	1.4	0.01
Heart disease***	8.6	7.1	0.06	7.5	7.1	0.02
Malignant neoplastic disease	5.3	4.5	0.04	4.7	4.3	0.02
Charlson comorbidity index, mean (SD)	1.75 (3.18)	1.69 (3.09)	-0.01	1.70 (3.11)	1.63 (3.03)	-0.01
Influenza vaccination within a year prior	10.9	7.9	0.10	7.5	6.9	0.02
Moderna COVID-19 vaccine						
Patients, n	52,728	148,795		50,517	50,517	
Follow-up, days. Median (IQR)	127 (102 – 153)	123 (99-153)		126 (101- 153)	126 (102-153)	
COVID-19 diagnosis or positive COVID-19 test, n				382	786	
Positive COVID-19 test, n				94	447	
Age group, %						
10-19	0.5	1.7	-0.12	0.5	0.4	0.01
20-49	35.7	45.7	-0.20	36.9	37.4	-0.01
50-64	21.2	23.3	-0.05	21.7	21.4	0.01
65-74	21.3	14.4	0.18	20.6	20.5	0.00
75-84	15.4	10	0.16	14.6	14.6	0.00
>84	5.8	4.8	0.04	5.6	5.6	0.00
Gender, %						
Female	64.4	58.7	0.12	64.2	64.7	-0.01
Race, %						

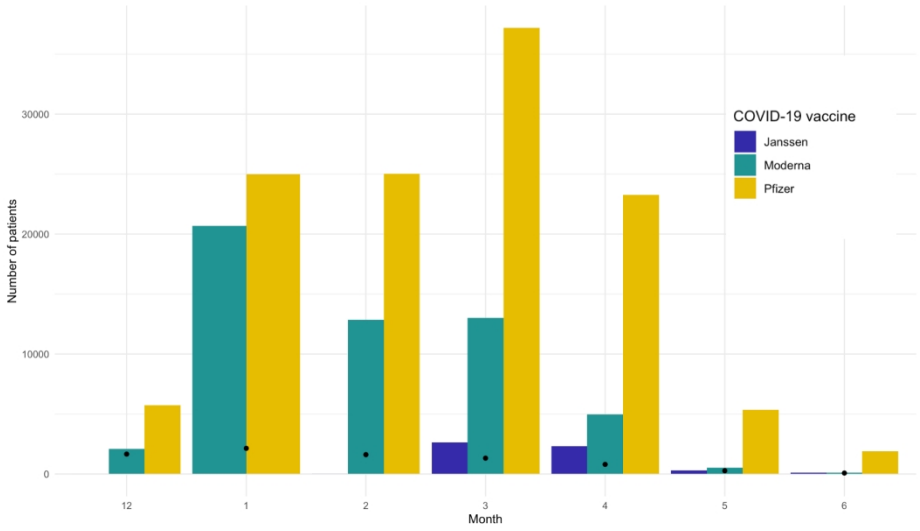
race = Asian	4.2	2.8	0.07	4.2	4.4	-0.01
race = Black or African American	8.7	14.2	-0.17	9	8.4	0.02
race = White	48.3	34.4	0.29	46.9	47.9	-0.02
Medical history, %						
Chronic liver disease	0.5	0.6	-0.02	0.5	0.5	0
Chronic obstructive lung disease	1.4	1.1	0.02	1.2	1.2	0
Dementia	1	1.2	-0.02	1	0.9	0.01
Depressive disorder	4.7	3.9	0.04	4.2	4	0.01
Diabetes mellitus	6.6	5.6	0.04	6.2	5.8	0.02
Human immunodeficiency virus infection	0.9	1.2	-0.03	0.8	0.8	0
Hyperlipidemia	14.9	8.9	0.19	13	12.6	0.01
Hypertensive disorder	16	12.4	0.1	14.7	13.9	0.02
Obesity	4	4.4	-0.02	3.8	3.6	0.01
Osteoarthritis	7.7	5.3	0.1	6.8	6.5	0.01
Renal impairment	3.5	3.3	0.01	3.3	3	0.01
Cerebrovascular disease	2.2	1.6	0.05	2	1.8	0.02
Heart disease	10.1	7.6	0.09	9.2	8.7	0.02
Malignant neoplastic disease	6.5	5	0.07	5.9	5.5	0.02
Charlson comorbidity index, mean (SD)	1.62 (2.81)	1.62 (3.00)	0.00	1.59 (2.80)	1.59 (2.99)	0.00
Influenza vaccination within a year prior	8.4	6.3	0.08	7.2	6.8	0.02
Janssen COVID-19 vaccine						
Patients, n	5,167	52,643		5,031	5,031	
Follow-up, days. Median (IQR)	79 (72-95)	79 (72-95)		79 (72-95)	79 (72-95)	
COVID-19 diagnosis or positive COVID-19 test, n				31	37	
Positive COVID-19 test, n				8	16	
Age group, %						
10-19	0.8	0.8	0.00	0.8	0.8	0.00

20-49	43.9	43	0.02	44.2	43.9	0.01
50-64	31.7	31.7	0.00	31.8	31.3	0.01
65-74	11.6	12.2	-0.02	11.5	12	-0.02
75-84	7.6	7.9	-0.01	7.2	7.9	-0.03
>84	4.3	4.3	0.00	4.2	4	0.01
Gender, %						
Female	63.4	63.2	0.01	63.5	61.1	0.05
Race, %						
race = Asian	3.6	1.7	0.12	3.7	3.6	0.01
race = Black or African American	15.9	15.5	0.01	15.7	15.5	0
race = White	37.4	35.7	0.03	37.4	37.5	0
Medical history, %						
Chronic liver disease	1.1	0.7	0.05	1	1.2	-0.02
Chronic obstructive lung disease	2.4	1.3	0.09	2	2.2	-0.01
Dementia	2.6	1.1	0.11	2.2	2.2	0
Depressive disorder	8	4.8	0.13	7.1	8	-0.03
Diabetes mellitus	10.3	6.2	0.15	9.5	10.2	-0.02
Human immunodeficiency virus infection	1.7	1.4	0.02	1.6	1.8	-0.01
Hyperlipidemia	14.3	10.2	0.13	13.4	14.3	-0.03
Hypertensive disorder	21.4	13.8	0.2	20.1	21.7	-0.04
Obesity	7.3	5.9	0.06	6.8	7.8	-0.04
Osteoarthritis	8.4	6.2	0.08	7.8	8.8	-0.04
Renal impairment	6.6	3.3	0.15	5.3	5.9	-0.02
Cerebrovascular disease	2.7	1.7	0.07	2.3	2.4	-0.01
Heart disease	11.8	8	0.13	10.3	11.7	-0.04
Malignant neoplastic disease	5	4.9	0	4.8	5.2	-0.02
Charlson comorbidity index, mean (SD)	1.84 (3.34)	1.55 (2.96)	-0.07	1.56 (3.04)	1.43 (2.79)	-0.03
Influenza vaccination within a year prior	12.5	8.0	0.15	10.1	11.4	-0.04

* Hypertensive disorder includes primary and secondary hypertension

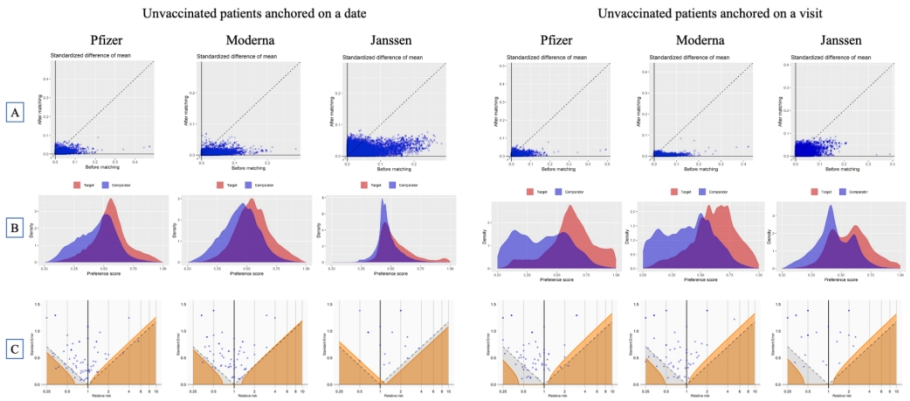
** Renal impairment includes acute and chronic renal failure (prerenal and renal);

*** Heart disease includes cardiac arrythmias, heart valve disorders, coronary arteriosclerosis, heart failure, cardiomyopathies, etc.



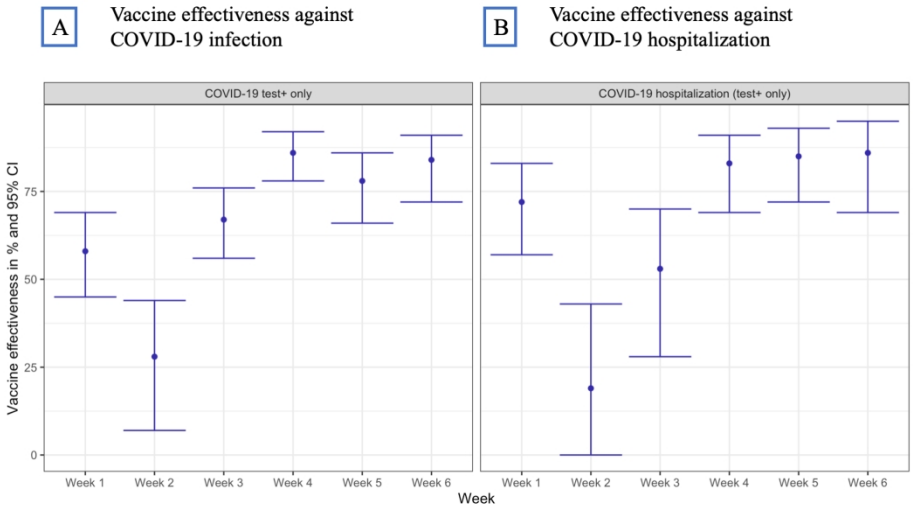
Distribution of vaccination month for COVID-19 vaccines. Black dots represent the number of incident COVID-19 cases (defined as a positive test) in each month.

338x190mm (144 x 144 DPI)



Diagnostics for the effectiveness study comparing the cohort vaccinated with at least one dose of Pfizer, Moderna or Janssen COVID-19 vaccines and unvaccinated cohort anchored on a date or on a visit: (A) covariate balance before and after propensity score matching, (B) preference score balance and (C) effect of negative control calibration displaying effect estimate and standard error.In (A), each dot represents the standardized difference of the means for a single covariate before and after stratification on the propensity score.In (C), each blue dot is a negative control. The area below the dashed line indicates estimates with $p<0.05$ and the orange area indicates estimates with calibrated $p<0.05$.

625x313mm (78 x 78 DPI)



Effectiveness of Pfizer-BioNTech and Moderna vaccines over six 7-day intervals after 1st dose, % and 95% CI for COVID-19 infection (A) and COVID-19 hospitalization (B).

272x152mm (226 x 226 DPI)

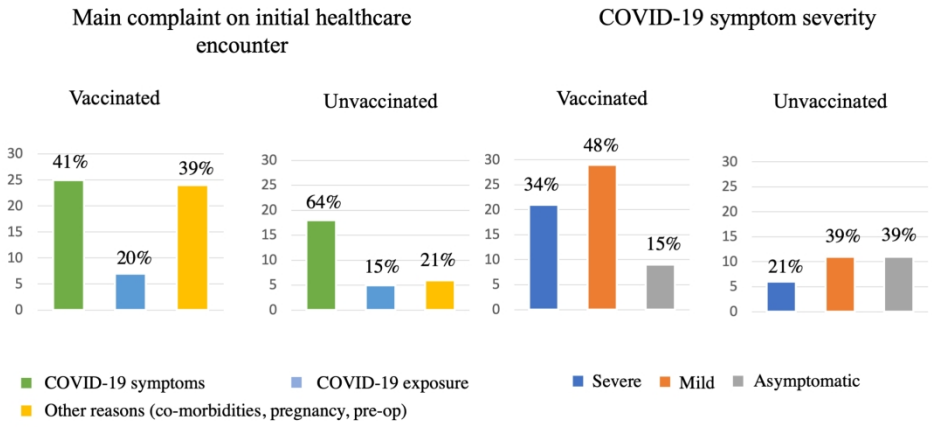


Chart review of COVID-19 cases (defined as a positive COVID-19 test) during week one, vaccinated and unvaccinated patients.

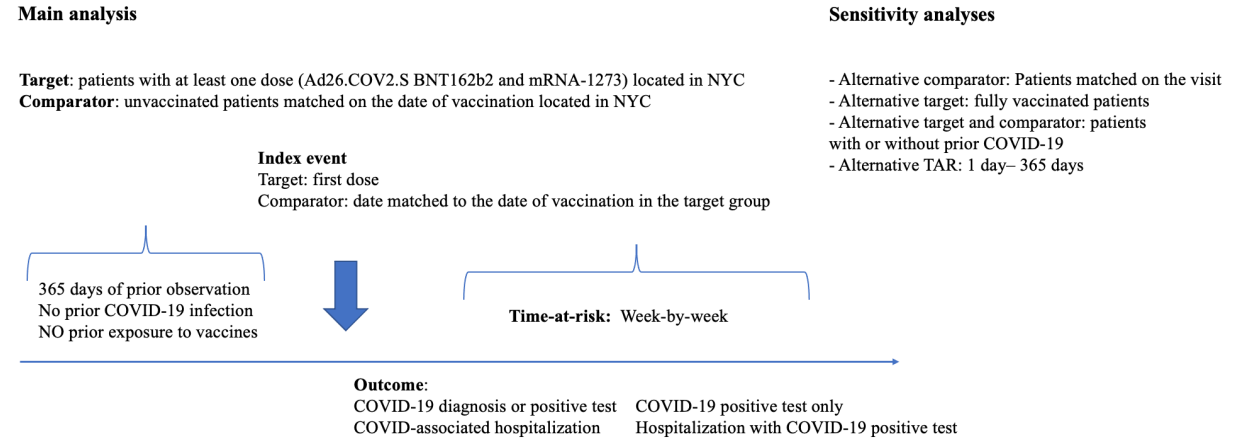
272x152mm (226 x 226 DPI)

Supplementary materials

Appendix 1. Data source description

The Columbia University Irving Medical Center (CUIMC) database comprises electronic health records on more than 6 million patients, with data collection starting in 1985. CUIMC is a Northeast US quaternary care center with primary care practices in northern Manhattan and surrounding areas, and the database includes inpatient and outpatient care. The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions (billing diagnoses and problem lists), drugs (outpatient prescriptions and inpatient orders and administrations), devices, measurements (laboratory tests and vital signs), and other observations (symptoms). The data sources include current and previous electronic health record systems (homegrown Clinical Information System, homegrown WebCIS, Allscripts Sunrise Clinical Manager, Allscripts TouchWorks, Epic Systems), administrative systems (IBM PCS-ADS, Eagle Registration, IDX Systems, Epic Systems), and ancillary systems (homegrown LIS, Sunquest, Cerner Laboratory). Additionally, it contains the information on vaccination from New York City and State immunization registries.

Appendix 2. Retrospective cohort COVID-19 vaccine effectiveness study design overview.



Cox proportional hazard model with 1:1 large scale propensity score matching (covariates include demographics, index year, month, # of visits; condition and drug groups; procedure, device, observation, measurement; long and short-term excluding day 0)

Appendix 3. Cohort definitions and codes for the long-term COVID-19 vaccine effectiveness study

3.1 Cohort definitions for vaccinated, unvaccinated and outcome cohorts for studying effectiveness of COVID-19 vaccines.

	Definition and link to the public repository
Vaccinated cohorts	Vaccinated patients were defined as patients with at least one dose of the corresponding vaccine (Pfizer BioNTech, Moderna, Janssen) Index event: first exposure to the corresponding vaccine Inclusion and exclusion criteria: - 365 days of prior observation - no other COVID-19 vaccine exposure in 120 days prior and 120 days after the index date - no prior COVID-19 infection (diagnosis code of COVID-19 or positive test) - residence in New York City determined by the zip code recorded For the analysis on fully vaccinated patients, we applied the same criteria and required patients to have a) the second dose of Pfizer or Moderna vaccine (if applicable) within 14 to 56 days after the first dose b) at least 14 days of observation after the second dose (one dose of Janssen). **Links:** https://atlas.ohdsi.org/#/cohortdefinition/498 https://atlas.ohdsi.org/#/cohortdefinition/494 https://atlas.ohdsi.org/#/cohortdefinition/497 https://atlas.ohdsi.org/#/cohortdefinition/418 https://atlas.ohdsi.org/#/cohortdefinition/417 https://atlas.ohdsi.org/#/cohortdefinition/420
Unvaccinated cohorts	Unvaccinated cohorts were created separately for each vaccinated cohort by selecting patients with no COVID-19 vaccination in their record (any vaccine), 365 days of prior observation and New York City residence. The patients were matched on the index date of one of the vaccinated group participants for the unvaccinated patients anchored on a date and on the date of a healthcare encounter within 3-day corridor for the unvaccinated patients anchored on a visit.

Outcome cohorts	For the main analysis COVID-19 infection was defined as a COVID-19 test with the result 'Positive' or 'Detected'. COVID-19 associated hospitalization was defined as an inpatient, emergency department or intensive care unit admission with a positive COVID-19 test recorded within 30 days prior or during hospitalization. For a secondary analysis we applied the abovementioned criteria with adding COVID-19 diagnosis as an alternative for positive COVID-19 test. Links: https://atlas.ohdsi.org/#/cohortdefinition/425 https://atlas.ohdsi.org/#/cohortdefinition/422

3.2 Codes used in the study.

1. **Pfizer vaccine:**

RxNorm 2468235 SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension

2. **Moderna vaccine:**

RxNorm 2470234 SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension

3. **Janssen vaccine:**

CVX 212 SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-Ad26, preservative free, 0.5 mL

4. **COVID-19 diagnosis:**

ICD10-CM U07.1 Emergency use of U07.1 | COVID-19

5. **COVID-19 test:**

LOINC 94500-6 SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA with probe detection
LOINC 94558-4 SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay

Appendix 4. Negative controls

SNOMED concept id	SNOMED concept name
438945	Accidental poisoning by benzodiazepine-based tranquilizer
434455	Acquired claw toes
316211	Acquired spondylolisthesis
201612	Alcoholic liver damage
438730	Alkalosis
441258	Anemia in neoplastic disease
432513	Animal bite wound
4171556	Ankle ulcer
4098292	Antiphospholipid syndrome
77650	Aseptic necrosis of bone
4239873	Benign neoplasm of ciliary body
23731	Benign neoplasm of larynx
199764	Benign neoplasm of ovary
195500	Benign neoplasm of uterus
4145627	Biliary calculus
4108471	Burn of digit of hand
75121	Burn of lower leg
4284982	Calculus of bile duct without obstruction
434327	Cannabis abuse
78497	Cellulitis and abscess of toe
4001454	Cervical spine ankylosis
4068241	Chronic instability of knee
195596	Chronic pancreatitis
4206338	Chronic salpingitis
4058397	Claustrophobia
74816	Contusion of toe
73302	Curvature of spine
4151134	Cyst of pancreas
77638	Displacement of intervertebral disc without myelopathy
195864	Diverticulum of bladder
201346	Edema of penis
200461	Endometriosis of uterus
377877	Esotropia
193530	Follicular cyst of ovary
4094822	Foreign body in respiratory tract
443421	Gallbladder and bile duct calculi

4299408	Gouty tophus
135215	Hashimoto thyroiditis
442190	Hemorrhage of colon
43020475	High risk heterosexual behavior
194149	Hirschsprung's disease
443204	Human ehrlichiosis
4226238	Hyperosmolar coma due to diabetes mellitus
4032787	Hyperosmolarity
197032	Hyperplasia of prostate
140362	Hypoparathyroidism
435371	Hypothermia
138690	Infestation by Pediculus
4152376	Intentional self poisoning
192953	Intestinal adhesions with obstruction
196347	Intestinal parasitism
137977	Jaundice
317510	Leukemia
765053	Lump in right breast
378165	Nystagmus
434085	Obstruction of duodenum
4147016	Open wound of buttock
4129404	Open wound of upper arm
438120	Opioid dependence
75924	Osteodystrophy
432594	Osteomalacia
30365	Panhypopituitarism
4108371	Peripheral gangrene
440367	Plasmacytosis
439233	Poisoning by antidiabetic agent
442149	Poisoning by bee sting
4314086	Poisoning due to sting of ant
4147660	Postural kyphosis
434319	Premature ejaculation
199754	Primary malignant neoplasm of pancreas
4311499	Primary malignant neoplasm of respiratory tract
436635	Primary malignant neoplasm of sigmoid colon
196044	Primary malignant neoplasm of stomach
433716	Primary malignant neoplasm of testis
133424	Primary malignant neoplasm of thyroid gland

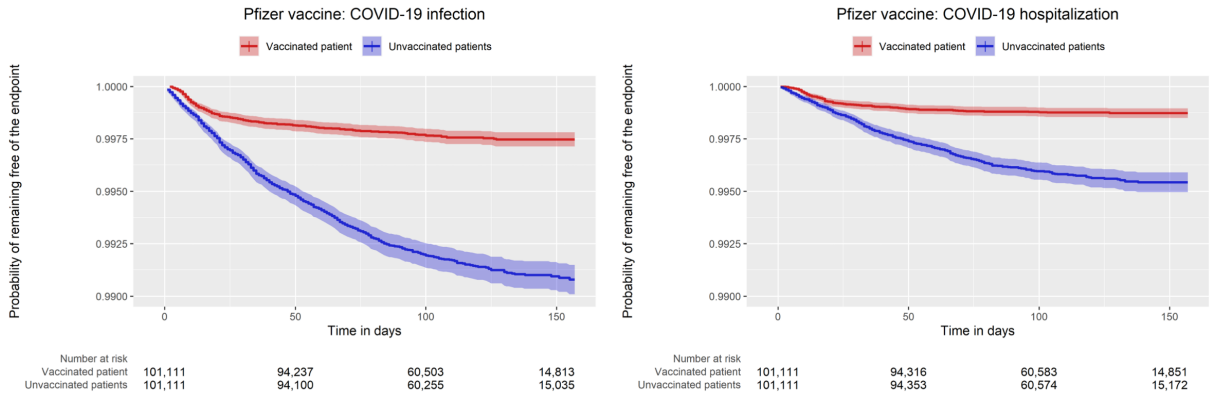
194997	Prostatitis
80286	Prosthetic joint loosening
443274	Psychostimulant dependence
314962	Raynaud's disease
37018294	Residual osteitis
4288241	Salmonella enterica subspecies arizonae infection
45757269	Sclerosing mesenteritis
74722	Secondary localized osteoarthrosis of pelvic region
200348	Secondary malignant neoplasm of large intestine
43020446	Sedative withdrawal
74194	Sprain of spinal ligament
4194207	Tailor's bunion
193521	Tropical sprue
40482801	Type II diabetes mellitus uncontrolled
74719	Ulcer of foot
196625	Viral hepatitis A without hepatic coma
197494	Viral hepatitis C
4284533	Vitamin D-dependent rickets

Link to the original list of negative controls used in EUMAEUS study: https://ohdsi-studies.github.io/Eumaeus/Protocol.html#8_Research_Methods

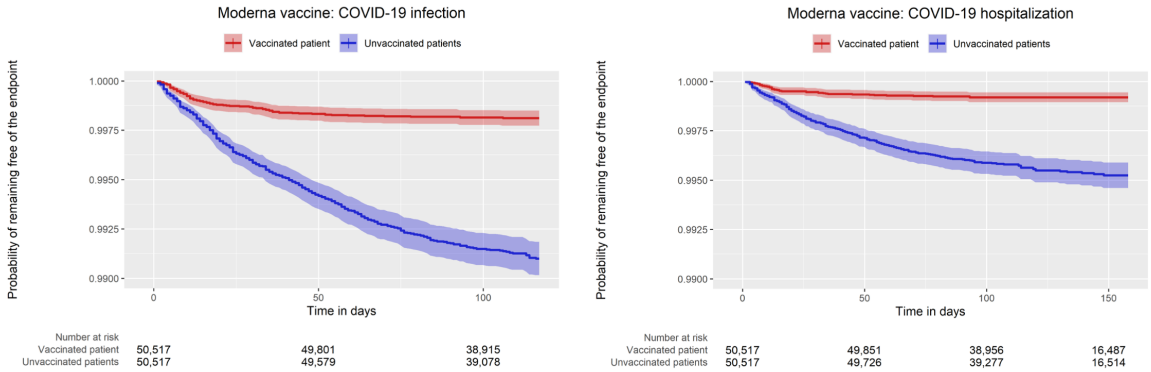
Appendix 5. Summary of manual chart review of COVID-19 infection cases during week 1 after the index date, patients vaccinated with mRNA vaccines and unvaccinated patients.

	Pfizer-BioNTech	**Moderna**	**Pfizer-BioNTech and Moderna**	**Unvaccinated patients**
Total	36	25	61	28
Average age	65	67.8	65.8	58
COVID-19 symptoms				
Severe	14 (39%)	7 (28%)	21 (34%)	6 (21%)
Mild	18 (50%)	11 (44%)	29 (48%)	11 (39%)
Asymptomatic	2 (6%)	7 (28%)	9 (15%)	11 (39%)
Reason for coming for initial healthcare encounter				
COVID-19 symptoms	17 (47%)	8 (32%)	25 (41%)	18 (64%)
Exposure to COVID-19	3 (8%)	4 (16%)	7 (11%)	5 (18%)
For other reason (co-morbidities, procedures etc.)	13 (36%)	11 (44%)	24 (39%)	6 (21%)
Type of initial healthcare encounter				
Telehealth/phone	5 (14%)	6 (24%)	11 (18%)	3 (11%)
Test only	3 (8%)	2 (8%)	5 (8%)	6 (21%)
OP	4 (11%)	3 (12%)	7 (11%)	1 (4%)
ED or IP	24 (67%)	14 (56%)	38 (62%)	18 (64%)

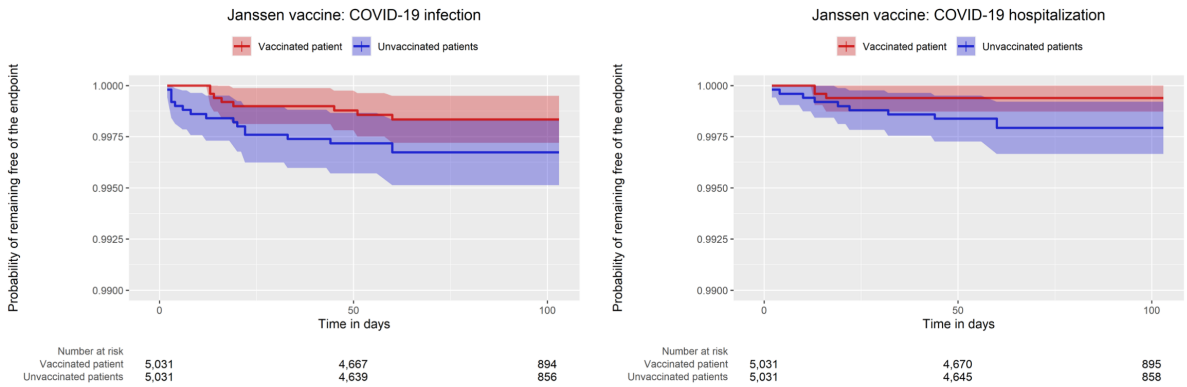
Appendix 6. Kaplan-Meier curves for effectiveness of COVID-19 Pfizer-BioNTech vaccine for time-at-risk of 1 day – 365 days after the first dose compared to the unvaccinated patients residing in New York City.



Appendix 7. Kaplan-Meier curves for effectiveness of COVID-19 Moderna vaccine for time-at-risk of 1 day – 365 days after the first dose compared to the unvaccinated patients residing in New York City.



Appendix 8. Kaplan-Meier curves for effectiveness of COVID-19 Janssen vaccine for time-at-risk of 1 day – 365 days after the first dose compared to the unvaccinated patients residing in New York City.



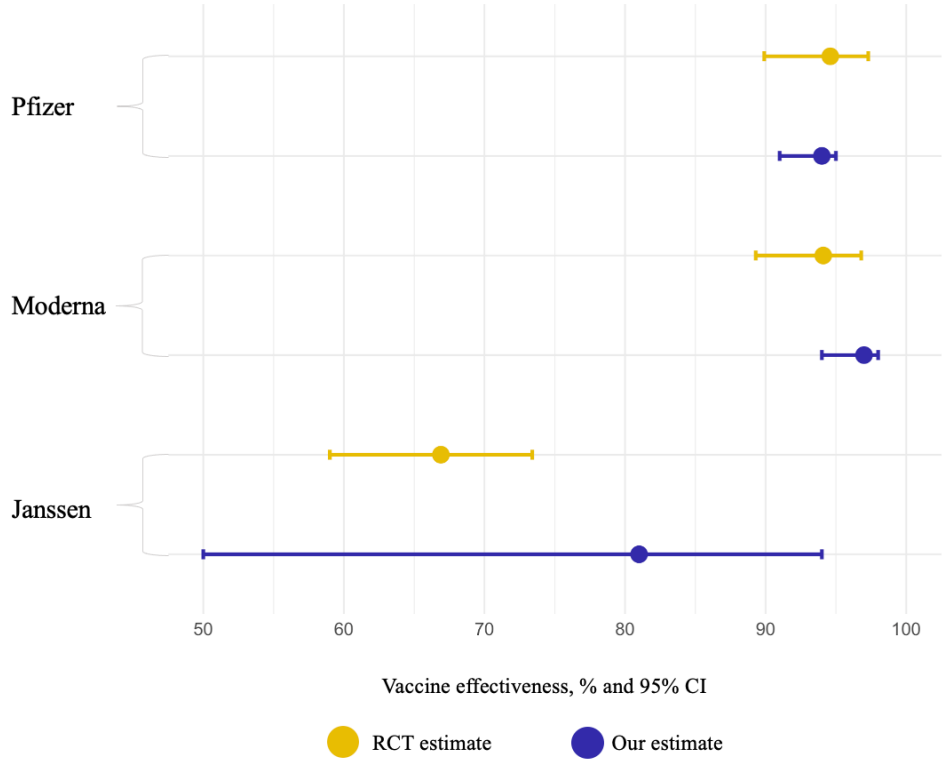
Appendix 9. Estimates for long-term effectiveness of COVID-19 vaccines for time-at-risk of 1 day – 365 days after the first dose in the vaccinated patients without prior COVID-19 infection compared to unvaccinated patients residing in NYC.

	COVID-19 infection		**COVID-19 hospitalization**		**COVID-19 positive test only**		**COVID-19 positive test only hospitalization**	
	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value
Pfizer-BioNTech	42 (37 – 47)	<0.01	63 (56-70)	<0.01	71 (66 - 75)	<0.01	69 (62 - 75)	<0.01
Moderna	54 (48 – 60)	<0.01	76 (69 – 82)	<0.01	78 (73 – 83)	<0.01	81 (74 – 87)	<0.01
Janssen	24 (0-55)	0.31	64 (0.1 – 1.06)	0.09	53 (0 – 82)	0.1	70 (2 – 93)	0.08

Appendix 10. Estimates for effectiveness of COVID-19 vaccines for time-at-risk of 1 day – 365 days after full vaccination in fully vaccinated patients without prior COVID-19 infection compared to unvaccinated patients residing in NYC.

	COVID-19 positive test only		**COVID-19 positive test only hospitalization**		**COVID-19 infection**		**COVID-19 hospitalization**	
	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value
Pfizer-BioNTech	94 (91-95)	<0.01	95 (92-97)	<0.01	70 (66-74)	<0.01	88 (84-92)	<0.01
Moderna	97 (94-98)	<0.01	96 (92-99)	<0.01	72 (66 – 77)	<0.01	92 (87-95)	<0.01
Janssen	81 (50-94)	<0.01	92 (58-100)	0.03	55 (23 – 75)	0.01	87 (56-98)	0.01

Appendix 11. Comparison of the effectiveness estimates in fully vaccinated patients obtained in our study and those from the randomized clinical trials of the corresponding vaccines.



Appendix 12. Estimates for effectiveness of COVID-19 vaccines for time-at-risk of 1 day – 365 days after the first dose in the vaccinated patients with or without prior COVID-19 infection compared to unvaccinated patients residing in NYC.

	COVID-19 infection		**COVID-19 hospitalization**		**COVID-19 positive test only**		**COVID-19 positive test only hospitalization**	
	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value
Pfizer-BioNTech	43 (38-48)	<0.01	64 (57-70)	<0.01	71 (66-75)	<0.01	71(64-76)	<0.01
Moderna	51 (45-57)	<0.01	71 (63-78)	<0.01	76 (71-81)	<0.01	81 (73-86)	<0.01
Janssen	15 (0-49)	0.52	60 (2-86)	0.06	45 (0-75)	0.12	63 (0-90)	0.09

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	6-7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, 18-20
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	8, 18
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8, supplementary materials
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.