

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

Anna Ostroplets <sup>1</sup>, George Hripcsak<sup>1,2</sup>

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<sup>1</sup>Department of Biomedical Informatics, Columbia University Irving Medical Center, New York, New York, USA

<sup>2</sup>Medical Informatics Services, New York-Presbyterian Hospital, New York, New York, USA

## Correspondence to

Professor George Hripcsak;  
gh13@cumc.columbia.edu

## 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 Irving Medical Center data linked to state and city immunisation 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 hospitalisation). We conducted manual chart review of cases in week 1 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 6 effectiveness approximating 84% (95% CI 72% to 91%) for COVID-19 infection and 86% (95% CI 69% to 95%) for COVID-19-associated hospitalisation. When analysing unexpectedly high effectiveness in week 1, 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 International Classification of Diseases, Tenth Revision, Clinical Modification diagnosis, the influence of excluding patients with prior COVID-19 infection and anchoring in the unexposed group. Long-term vaccine effectiveness in fully vaccinated patients matched the results of the randomised trials.

**Conclusions** For vaccine effectiveness studies, observational data need to be scrutinised to ensure compared groups exhibit similar health-seeking behaviour 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 patients' baseline characteristics, indirect comparison of vaccines may produce biased results.

## BACKGROUND

Randomised clinical phase III trials have demonstrated high efficacy for the four most commonly used COVID-19 vaccines against

## 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) accompanied by manual chart review of the cases in week 1.
- ⇒ 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.

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.<sup>1-4</sup> Their rapid approval and widespread use require robust postmarketing 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 randomised clinical trials (RCTs) across the globe, both test negative and cohort,<sup>5-12</sup> followed by studies across different patient populations, variants and number of doses.<sup>13-17</sup>

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.<sup>18</sup> For COVID-19 vaccines, questions associated with vaccine status misclassification,<sup>19</sup> matching vaccinated and unvaccinated populations,<sup>6</sup> addressing disease risk factor confounding and ascertainment bias<sup>20 21</sup> and others were raised.

One of such questions is COVID-19 vaccine effectiveness during the first 2 weeks following

the first dose. Studies have shown contradicting results for Pfizer-BioNTech vaccine with effectiveness ranging from moderate effectiveness of 52%<sup>3</sup> to very high effectiveness of 92.6%.<sup>22</sup> Similarly, a recent study showed an unexplained high effectiveness of Janssen vaccine during week 1.<sup>23</sup> Other studies simply excluded the first week(s) from the time at risk.<sup>9 13 24–26</sup> While week 1 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.<sup>9</sup>

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 bias and leveraged a range of secondary analyses as well as manual review of the COVID-19 infection cases in week 1 to examine the health-seeking behaviour of vaccinated and unvaccinated patients.

## METHODS

### Main design

For this retrospective observational cohort study, we used electronic health records (EHR) from the Columbia University Irving Medical Center (CUIMC) database (online supplemental 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.<sup>27</sup>

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 PCR assay) or a diagnostic code of COVID-19 and (b) COVID-19 hospitalisation defined as an inpatient visit associated with a COVID-19 positive test or diagnosis within 30 days prior or during the visit. On further examination of the results, we added two other outcomes: (a) COVID-19 positive test only and (b) COVID-19

hospitalisation associated with a positive COVID-19 test. Design overview is provided in online supplemental appendix 2; code lists and links to phenotype definitions are provided in online supplemental 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 1 following the first dose, we conducted a chart review for patients with a COVID-19-positive test recorded in the above-mentioned period. We reviewed all cases for the vaccinated population as well as a random sample of the cases in the unvaccinated population and extracted the 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,<sup>28 29</sup> 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 in 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 scores and match patients in each exposed and unexposed group with a 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-term period (prior year) and short-term period (prior month).<sup>30 31</sup>

For each outcome, we fitted a Cox proportional hazards model to estimate HRs and constructed Kaplan-Meier plots. Empirical calibration based on the negative control outcomes was used to identify and minimise any potential residual confounding by calibrating HRs and 95% confidence intervals (CIs).<sup>32 33</sup> Vaccine effectiveness was calculated as  $100\% \times (1 - \text{HR})$ .

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 regularised regression<sup>34</sup> 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.<sup>35</sup> 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.<sup>35</sup> 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 standardised difference of means of all covariates after propensity score matching was less than 0.1.<sup>36</sup>

For negative control calibration, we used 93 negative controls (online supplemental 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.<sup>37</sup> We assessed residual bias from the negative control estimates.

## Patient and public involvement

No patient was involved.

## RESULTS

### Patient characteristics

In total, we identified 179 666 patients with at least one dose of COVID-19 vaccine in January to May 2021: 121 771 patients for Pfizer-BioNTech, 52 728 for Moderna and 5167 for Janssen (table 1). The sample included patients from all age groups, with or without comorbidities captured in inpatient and outpatient settings.

We observed that unexposed patients (table 1) were on average younger and had fewer comorbidities and less exposure to various drugs prior to matching. We were able to achieve balance on all covariates (up to 54 987 covariates, standardised 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 with anchoring patients on a visit.

Patients vaccinated with Pfizer-BioNTech had a similar distribution of baseline characteristics compared with the patients vaccinated with Moderna but differed from the patients vaccinated with Janssen. On average, the latter group was younger, had more patients with race recorded

as Black and had more comorbidities 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 two doses of Pfizer-BioNTech and 42 384 (80%) patients had two doses of Moderna. We found 344 and 291 patients with three 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 postobservation.

### 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 with 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 1 was characterised by unexpectedly high effectiveness (58%; 95% CI 45% to 69% against COVID-19 infection and 72%; 95% CI 57% to 83% against COVID-19-associated hospitalisation), we observed plausible increasing effectiveness beginning week 2 with the effectiveness on week 6 approximating 84% (95% CI 72% to 91%) for COVID-19 infection and 86% (95% CI 69% to 95%) for COVID-19-associated hospitalisation.

We then looked at the week 1 COVID-19 infection cases to explain high effectiveness (figure 4). A chart review of week 1 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 with only 61% of vaccinated patients. Initial healthcare encounters in vaccinated population were oftentimes related to other medical reasons such as comorbid conditions or surgeries (39% compared with 14% in unvaccinated population, online supplemental 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 1 after the index date, we observed that the unvaccinated cohort had a higher proportion of asymptomatic cases (39% compared with 18% in the vaccinated cohort) 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 (online supplemental Appendices 6-8). We observed

**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

Characteristic	Before matching			After matching		
	Vaccinated	Unvaccinated	Standardised difference	Vaccinated	Unvaccinated	Standardised difference
<b>Pfizer-BioNTech COVID-19 vaccine</b>						
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)						
Positive COVID-19 test (n)				822	1355	
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 (%)						
Asian	3.8	2.6	0.07	3.5	3.4	0.01
Black or African American	12.4	14.2	–0.05	12.6	12.2	0.01
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
HIV infection	1.4	1.1	0.03	1.1	1	0
Hyperlipidaemia	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

Continued



**Table 1** Continued

	Before matching			After matching		
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
<b>Moderna COVID-19 vaccine</b>						
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)						
Positive COVID-19 test (n)				382	786	
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 (%)						
Asian	4.2	2.8	0.07	4.2	4.4	-0.01
Black or African American	8.7	14.2	-0.17	9	8.4	0.02
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
HIV infection	0.9	1.2	-0.03	0.8	0.8	0
Hyperlipidaemia	14.9	8.9	0.19	13	12.6	0.01

Continued

Table 1 Continued

	Before matching			After matching		
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
<b>Janssen COVID-19 vaccine</b>						
Patients (n)	5167	52 643		5031	5031	
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	
<b>Age group (%)</b>						
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
<b>Gender (%)</b>						
Female	63.4	63.2	0.01	63.5	61.1	0.05
<b>Race (%)</b>						
Asian	3.6	1.7	0.12	3.7	3.6	0.01
Black or African American	15.9	15.5	0.01	15.7	15.5	0
White	37.4	35.7	0.03	37.4	37.5	0
<b>Medical history (%)</b>						
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

Continued

**Table 1** Continued

	Before matching			After matching		
Diabetes mellitus	10.3	6.2	0.15	9.5	10.2	-0.02
HIV infection	1.7	1.4	0.02	1.6	1.8	-0.01
Hyperlipidaemia	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 arrhythmias, heart valve disorders, coronary arteriosclerosis, heart failure, cardiomyopathies, etc.

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 hospitalisation, while Janssen vaccine exhibited a wide range of effectiveness (online supplemental 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 online supplemental Appendices 10 and 11).

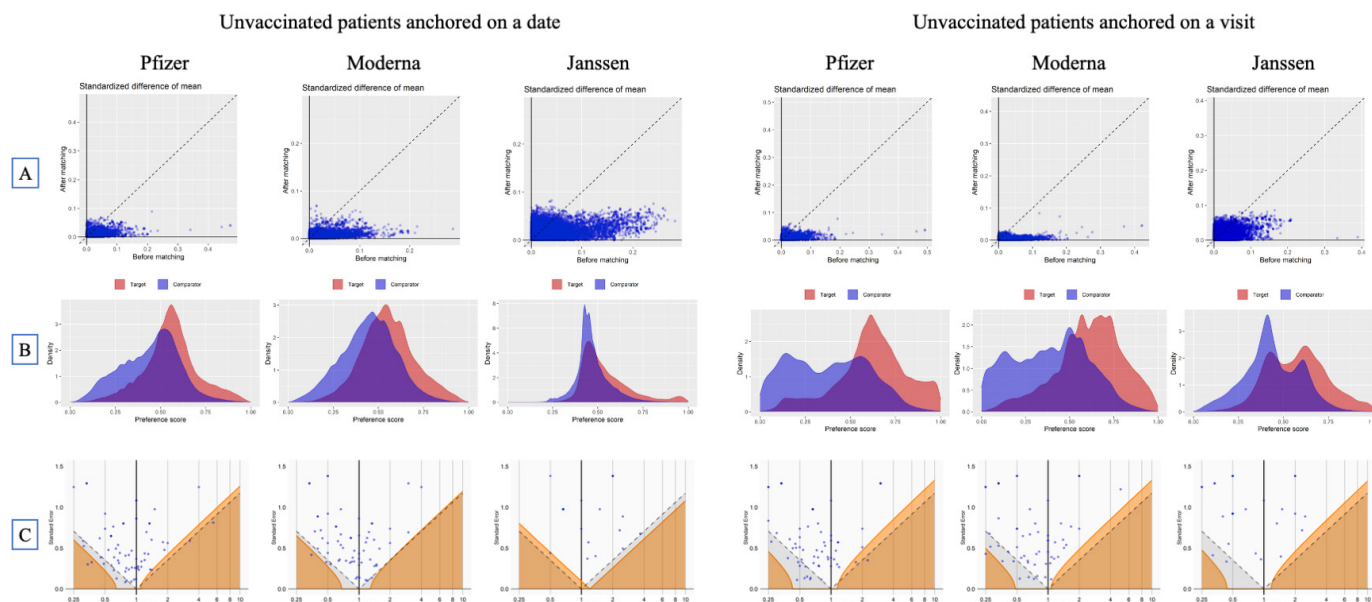
Our initial design included a positive COVID-19 test or a diagnostic code as an outcome. On further case examination, we discovered that COVID-19 diagnostic codes in the CUIMC data were partially assigned to the patients with negative COVID-19 tests on or immediately following the date of diagnosis. In that case, International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) 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 with using both positive test and diagnosis (online supplemental 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 (online supplemental appendix 12) for both COVID-19 infection and hospitalisation 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 scrutinised the effectiveness of the mRNA vaccines following the first dose and confirmed the findings of moderate vaccine effectiveness during the first 2 weeks. For week 1 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 utilisation such as number of visits before baseline, comorbidities or prior vaccination behaviour.<sup>6 13 24</sup> Nevertheless, the confounding we observed remains even on 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 with unvaccinated.<sup>20 38</sup> This indicates that patients' attitude towards risk of infection and testing may vary geographically and



**Figure 1** 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 SE. In (A), each dot represents the standardised 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  $p < 0.05$ .

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 on seeking outpatient and inpatient care for other conditions.

For example, vaccinated patients could be hospitalised 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<sup>39</sup> and may affect any observational study that uses hospitalisation as a surrogate for COVID-19 severity as it can be hard to accurately identify the main reason for hospitalisation 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.<sup>9 40</sup> Our review of the cases in week 1 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.

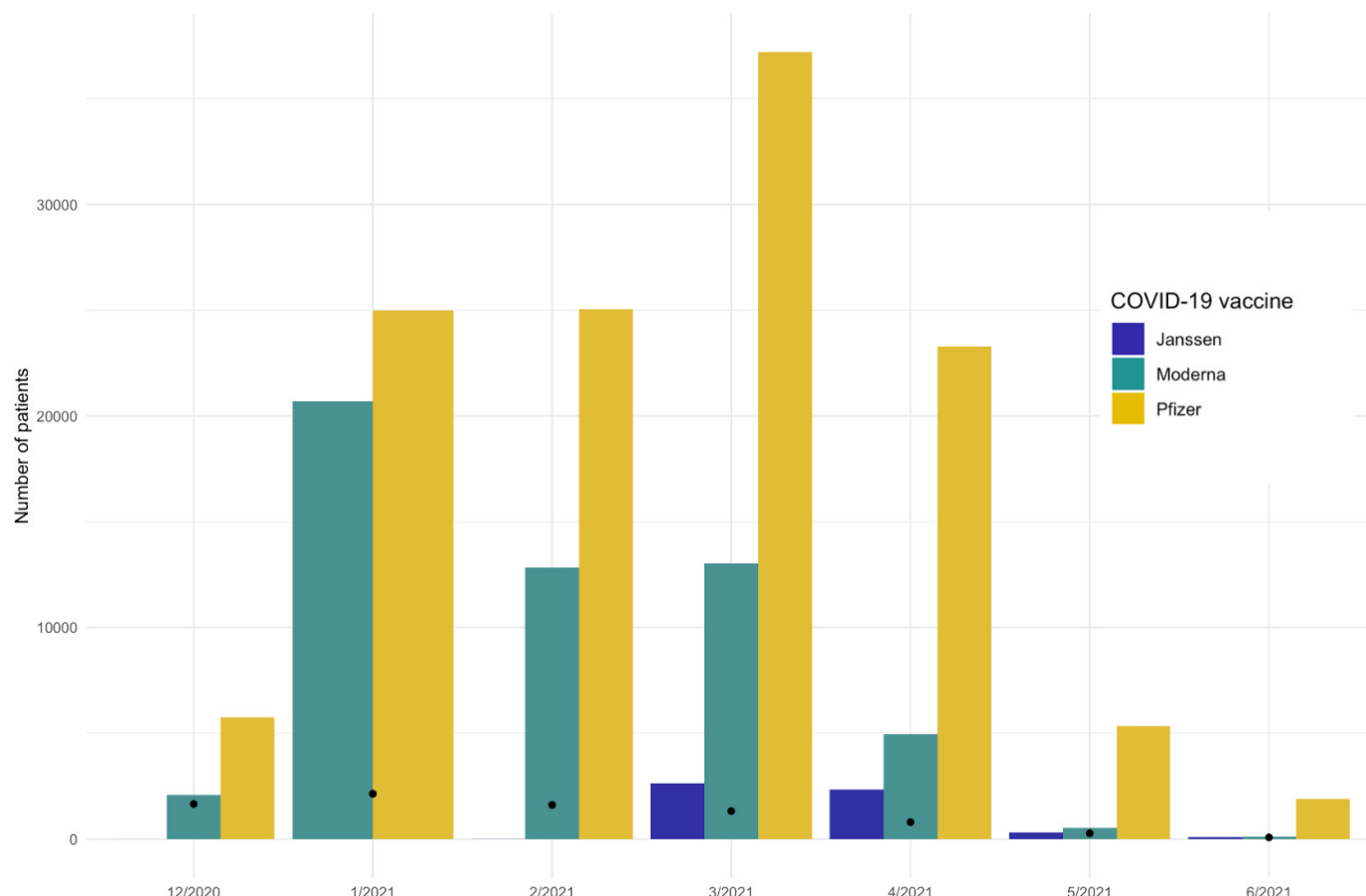
Nevertheless, even when this differential bias is present, the estimates of the COVID-19 vaccine effectiveness in subsequent weeks still match the results of the RCTs. This indicates that high effectiveness during week 1 following vaccination does not necessarily undermine the estimates of subsequent 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.<sup>41</sup>

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.<sup>42–44</sup> 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 scrutinised in each institution participating in the analysis to make valid inferences.<sup>45 46</sup>

Second, inclusion or exclusion of patients with prior COVID-19 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.





**Figure 2** 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.

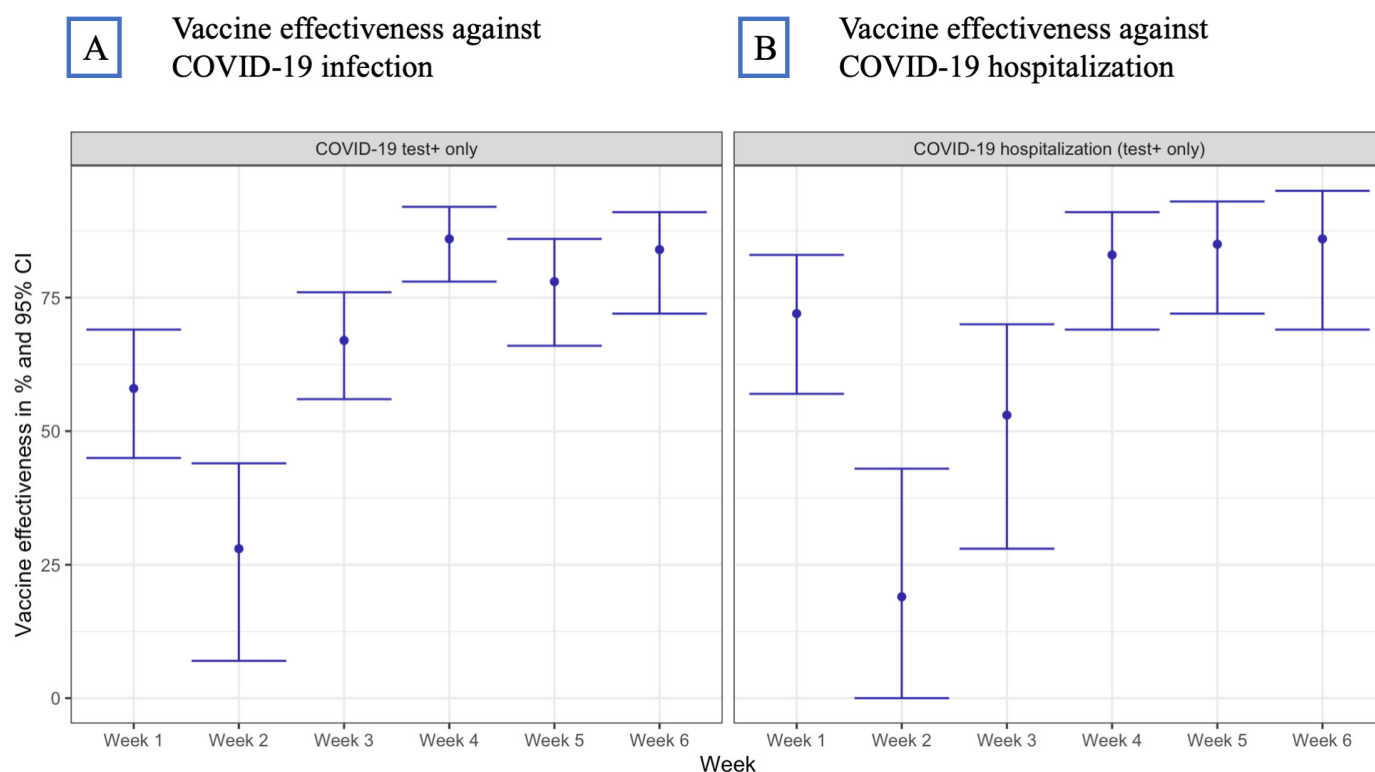
Third, an appropriate index event (anchor) for the unvaccinated cohort must be chosen to represent a counterfactual for vaccination.<sup>29 47</sup> In our study, we confirmed that an arbitrary date represents a better counterfactual than a medical visit for COVID-19 vaccination, which is reflected in 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 ensure 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 postmarketing 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 CIs compared with the RCTs. On the other hand, our study had fewer patients with the Janssen vaccine, which resulted in wider yet overlapping intervals compared with the Janssen's vaccine RCT.<sup>12 7</sup> 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 younger, 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 Moderna and Pfizer patients had similar baseline characteristics, the temporal distribution of vaccinations in CUIMC data differed. 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 the CUIMC/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

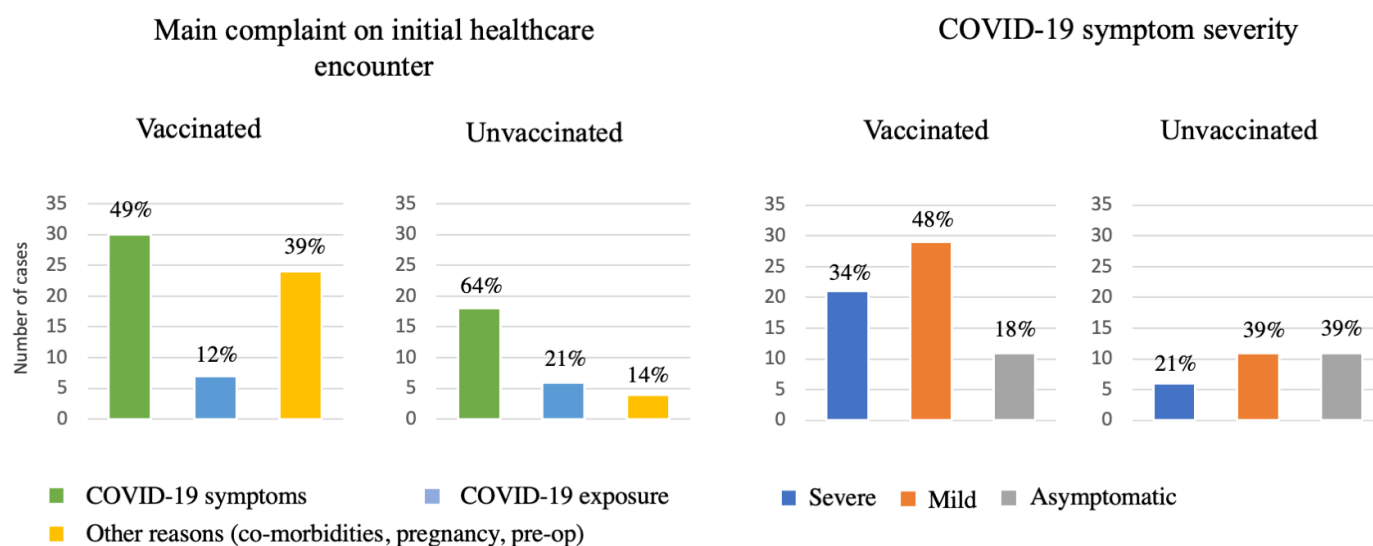
Due to observational nature of the study, the data sources may not have complete capture of patient conditions



**Figure 3** Effectiveness of Pfizer-BioNTech and Moderna vaccines over six 7-day intervals after first dose; % and 95% CI for COVID-19 infection (A) and COVID-19 hospitalisation (B).

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 at the CUIMC/New York-Presbyterian sites as well as by having data capture from New York City and state immunisation 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 utilisation, prior vaccine behaviour, race and others. Nevertheless, we did not have data for social interactions, adherence to preventive measures and policies, which could affect the likelihood of COVID-19 infection and testing.



**Figure 4** Chart review of COVID-19 cases (defined as a positive COVID-19 test) during week 1, vaccinated and unvaccinated patients.

The results of the study may not be generalisable 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 the generalisability 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 analysing vaccine effectiveness researchers need to scrutinise the data to ensure that compared groups exhibit similar health-seeking behaviour 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.

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**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** The protocol for this research was approved by the Columbia University Institutional Review Board (AAA07805). The study used deidentified data.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information. Patient-level data cannot be shared without approval from data custodians due to local information governance and data protection regulations.

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## ORCID iD

Anna Ostropelets <http://orcid.org/0000-0002-0847-6682>

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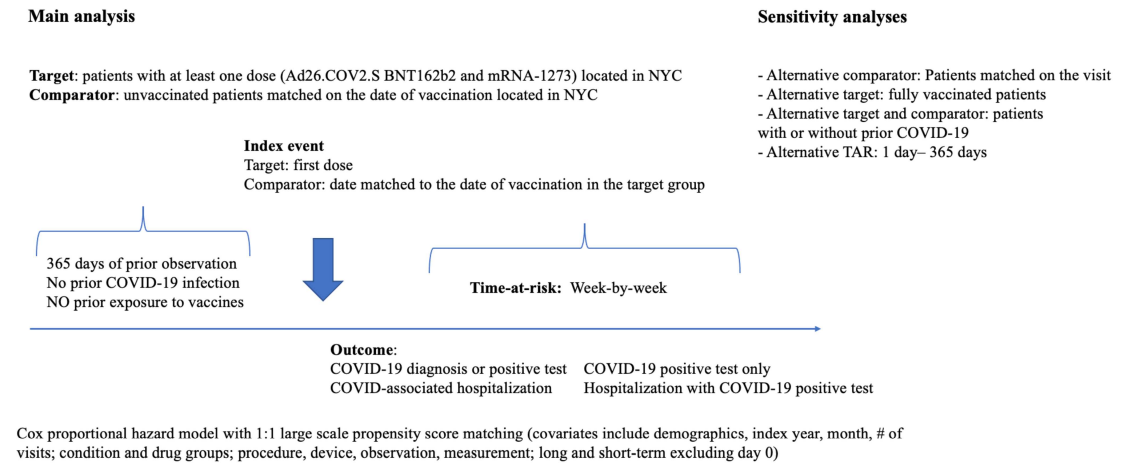


Supplementary materials

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 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	<p>Vaccinated patients were defined as patients with at least one dose of the corresponding vaccine (Pfizer BioNTech, Moderna, Janssen)</p> <p>Index event: first exposure to the corresponding vaccine</p> <p>Inclusion and exclusion criteria:</p> <ul style="list-style-type: none"> <li>- 365 days of prior observation</li> <li>- no other COVID-19 vaccine exposure in 120 days prior and 120 days after the index date</li> <li>- no prior COVID-19 infection (diagnosis code of COVID-19 or positive test)</li> <li>- residence in New York City determined by the zip code recorded</li> </ul> <p>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).</p> <p><b>Links:</b></p> <p><a href="https://atlas.ohdsi.org/#/cohortdefinition/498">https://atlas.ohdsi.org/#/cohortdefinition/498</a></p> <p><a href="https://atlas.ohdsi.org/#/cohortdefinition/494">https://atlas.ohdsi.org/#/cohortdefinition/494</a></p> <p><a href="https://atlas.ohdsi.org/#/cohortdefinition/497">https://atlas.ohdsi.org/#/cohortdefinition/497</a></p> <p><a href="https://atlas.ohdsi.org/#/cohortdefinition/418">https://atlas.ohdsi.org/#/cohortdefinition/418</a></p> <p><a href="https://atlas.ohdsi.org/#/cohortdefinition/417">https://atlas.ohdsi.org/#/cohortdefinition/417</a></p> <p><a href="https://atlas.ohdsi.org/#/cohortdefinition/420">https://atlas.ohdsi.org/#/cohortdefinition/420</a></p>
Unvaccinated cohorts	<p>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.</p>

Outcome cohorts	<p>For the main analysis COVID-19 infection was defined as a COVID-19 test with the result 'Positive' or 'Detected'.</p> <p>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.</p> <p>For a secondary analysis we applied the abovementioned criteria with adding COVID-19 diagnosis as an alternative for positive COVID-19 test.</p> <p>Links:</p> <p><a href="https://atlas.ohdsi.org/#/cohortdefinition/425">https://atlas.ohdsi.org/#/cohortdefinition/425</a></p> <p><a href="https://atlas.ohdsi.org/#/cohortdefinition/422">https://atlas.ohdsi.org/#/cohortdefinition/422</a></p>
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### 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

<b>SNOMED concept id</b>	<b>SNOMED concept name</b>
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 osteoarthritis 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

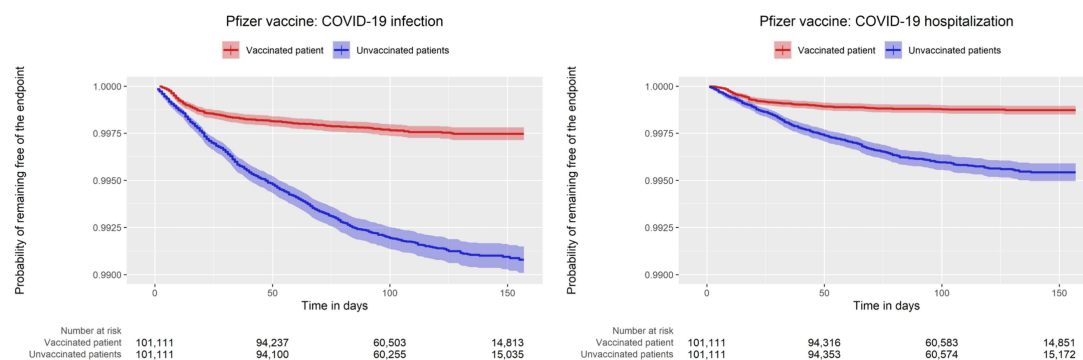
Link to the original list of negative controls used in EUMAEUS study: [https://ohdsi-studies.github.io/Eumaeus/Protocol.html#8\\_Research\\_Methods](https://ohdsi-studies.github.io/Eumaeus/Protocol.html#8_Research_Methods)



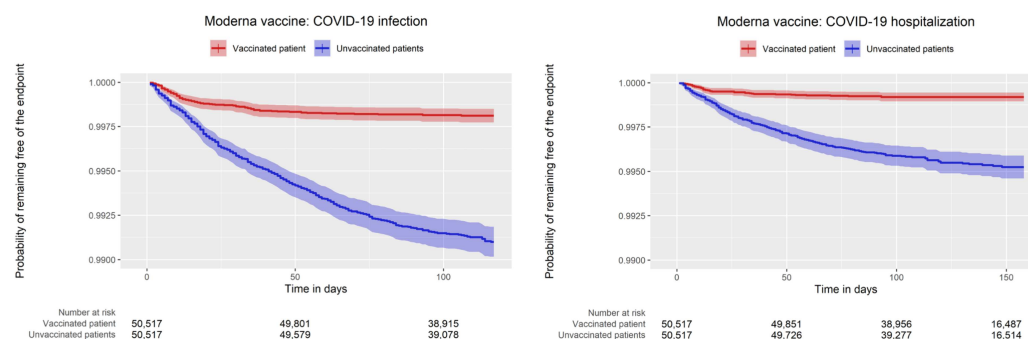
**Appendix 5.** Summary of manual chart review of COVID-19 infection cases during week 1 after the index date, patients vaccinated with mRNA vaccines and unvaccinated patients.

	<b>Pfizer-BioNTech</b>	<b>Moderna</b>	<b>Pfizer-BioNTech and Moderna</b>	<b>Unvaccinated patients</b>
Total	36	25	61	28
Average age	65.0	67.8	65.8	58.0
<b>COVID-19 symptoms</b>				
Severe	14 (39%)	7 (28 %)	21 (34%)	6 (21%)
Mild	18 (50%)	11 (44%)	29 (48%)	11 (39%)
Asymptomatic	4 (11%)	7 (28%)	11 (18%)	11 (39%)
<b>Reason for coming for initial healthcare encounter</b>				
COVID-19 symptoms	18 (50%)	12 (48%)	30 (49%)	18 (64%)
Exposure to COVID-19	3 (8%)	4 (16%)	7 (12%)	6 (21%)
For other reason (co-morbidities, procedures etc.)	15 (42%)	9 (36%)	24 (39%)	4 (14%)
<b>Type of initial healthcare encounter</b>				
Telehealth/phone	5 (14%)	6 (24%)	11 (18%)	3 (11%)
Test only	3 (8%)	2 (8%)	5 (8%)	6 (21%)
Outpatient visit	4 (11%)	3 (12%)	7 (12%)	1 (4%)
Emergency room or inpatient visit	24 (67%)	14 (56%)	38 (62%)	18 (64%)

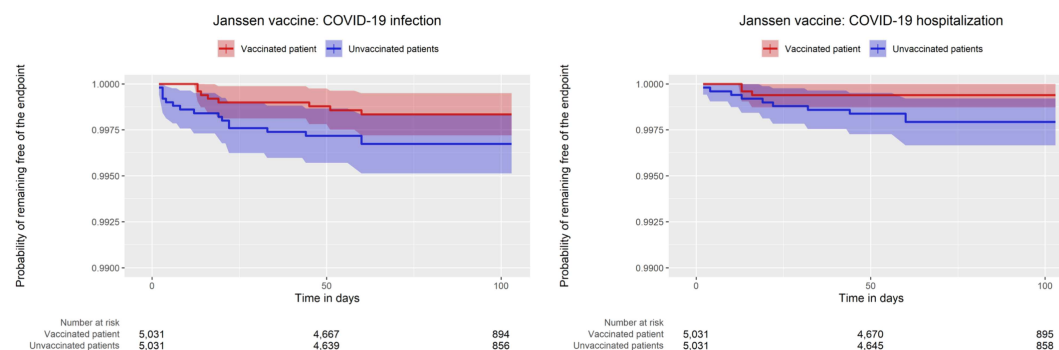
**Appendix 6.** Kaplan-Meier curves for effectiveness of COVID-19 Pfizer-BioNTech vaccine for time-at-risk of 1 day – 365 days after the first dose compared to the unvaccinated patients residing in New York City.



**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.



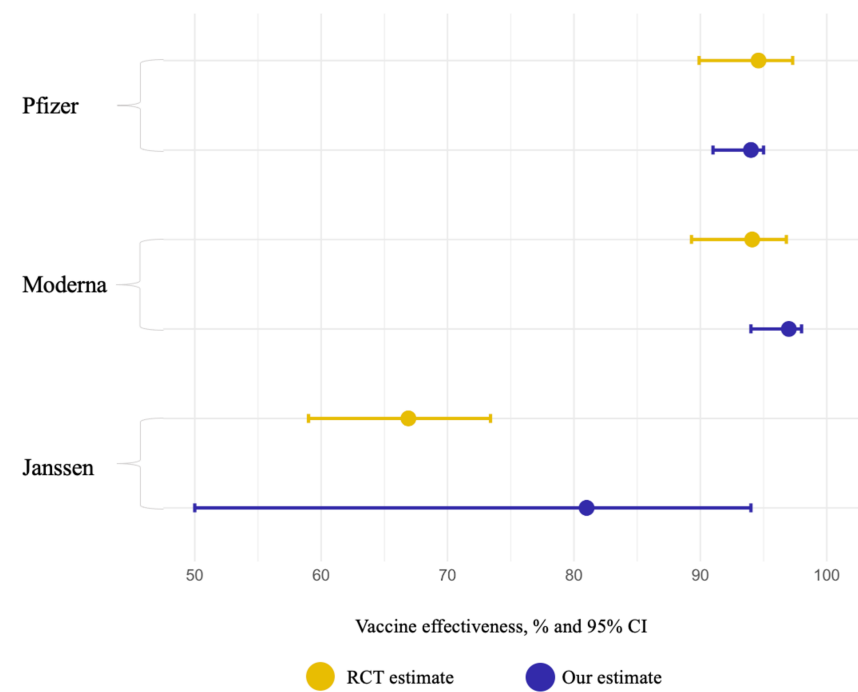
**Appendix 9.** Estimates for long-term effectiveness of COVID-19 vaccines for time-at-risk of 1 day – 365 days after the first dose in the vaccinated patients without prior COVID-19 infection compared to unvaccinated patients residing in NYC.

	<b>COVID-19 infection</b>		<b>COVID-19 hospitalization</b>		<b>COVID-19 positive test only</b>		<b>COVID-19 positive test only hospitalization</b>	
	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value
<b>Pfizer-BioNTech</b>	42 (37 – 47)	<0.01	63 (56–70)	<0.01	71 (66 – 75)	<0.01	69 (62 – 75)	<0.01
<b>Moderna</b>	54 (48 – 60)	<0.01	76 (69 – 82)	<0.01	78 (73 – 83)	<0.01	81 (74 – 87)	<0.01
<b>Janssen</b>	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.

	<b>COVID-19 positive test only</b>		<b>COVID-19 positive test only hospitalization</b>		<b>COVID-19 infection</b>		<b>COVID-19 hospitalization</b>	
	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value
<b>Pfizer-BioNTech</b>	94 (91–95)	<0.01	95 (92–97)	<0.01	70 (66–74)	<0.01	88 (84–92)	<0.01
<b>Moderna</b>	97 (94–98)	<0.01	96 (92–99)	<0.01	72 (66 – 77)	<0.01	92 (87–95)	<0.01
<b>Janssen</b>	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