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

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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.

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5 For the time-at-risk, we selected six consecutive 7-day intervals after the first dose until an outcome, end
6 of observation period or death, whichever came earlier. Additionally, given the results for vaccine
7 effectiveness during week 1 following the first dose, we conducted chart review for patients with a
8 COVID-19 positive test recorded in the abovementioned period. We reviewed all cases for the vaccinated
9 population as well a random sample of the cases in the unvaccinated population.
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13 14 ***Sensitivity analyses*** 15

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17 Along with studying granular weekly intervals, we assessed overall absolute vaccine effectiveness in
18 patients with at least one dose of a COVID-19 vaccine and in fully vaccinated patients. The latter was
19 defined as 14 days after the second dose of Pfizer-BioNTech or Moderna vaccines or first dose of Janssen
20 vaccine. For each comparison we estimated hazard ratios (HRs) and constructed Kaplan-Meier plots as
21 described below.
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26 Given that the published studies focused on patients without prior COVID-19 infection, our second
27 sensitivity analysis included all eligible patients regardless of their previous COVID-19 status. Finally, as
28 the strategy for unvaccinated group index date selection (anchoring) has been reported to influence
29 incidence of outcomes (17), we additionally tested an unvaccinated comparator indexed on a healthcare
30 encounter matching the index date of one of the target group participants within 3 days corridor, with at
31 least 365 days of prior observation located at New York.
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39 ***Statistical methods*** 40

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42 For each analysis, we fitted a lasso regression model to calculate propensity score and match patients in
43 each target and comparator group with 1:1 ratio. For propensity model we used all demographic
44 information, index year and month, as well as the number of visits, condition and drug groups,
45 procedures, device exposures, laboratory and instrumental tests and other observations over long (prior
46 year) and short-term period (prior month).
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51 For each outcome, we fitted a Cox proportional hazards models to estimate HRs and constructed Kaplan-
52 Meier plots. Empirical calibration based on the negative control outcomes was used to identify and
53 minimize any potential residual confounding by calibrating HRs and 95% confidence intervals (CIs)
54 (18,19). Vaccine effectiveness was calculated as $100\% \times (1 - \text{hazard ratio})$.
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3 All analyses were supported by the OHDSI Infrastructure (CohortMethod package, available
4 at <https://ohdsi.github.io/CohortMethod/>, FeatureExtraction available at
5 <https://ohdsi.github.io/FeatureExtraction/> and the Cyclops package for large-scale regularized regression
6 (20) available at <https://ohdsi.github.io/Cyclops>).

10 ***Diagnostics***

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

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

34 **Patient and public involvement**

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37 No patient involved

42 **RESULTS**

46 ***Patient characteristics***

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

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53 Among vaccinated patients, 68% received Pfizer-BioNTech vaccine, 29% received Moderna and 3%
54 received Janssen vaccine. When investigating the vaccination pathways, we discovered that 112,963
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3 patients (93% of patients with at least one dose of Pfizer-BioNTech) had 2 doses of Pfizer-BioNTech and
4 42,384 (80%) patients had 2 doses of Moderna. We found 344 and 291 patients with 3 doses of the
5 corresponding vaccines and 440 patients having mixed Pfizer-BioNTech, Moderna and Janssen vaccines
6 in different combinations.
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11 Within our database, Moderna was administered early on with a peak in January 2021 (Figure 1), while
12 Pfizer-BioNTech and Janssen vaccinations peaked in April. It was reflected in the follow-up time with
13 Moderna patients having on average longer follow-up with some individuals having up to 5.8 months of
14 post-observation.
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19 We observed that unvaccinated comparator patients (Table 1) were on average younger and had fewer co-
20 morbidities and less exposure to various drugs prior to matching. We were able to achieve balance on all
21 covariates (up to 54,987 covariates, standardized difference of means less than 0.1) with propensity score
22 matching. Figure 2 presents the covariate balance and propensity score balance plots showing that
23 anchoring unvaccinated patients on a date allowed us to achieve better balance compared to anchoring
24 patients on a visit.
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30 Patients vaccinated with Pfizer-BioNTech had a similar distribution of baseline characteristics compared
31 to the patients vaccinated with Moderna but differed from the patients vaccinated with Janssen. On
32 average, the latter group was older, had more patients with race recorded as Black, and had more co-
33 morbidities such as diabetes mellitus or hypertensive disorder (Table 1).
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37 38 ***Main week-by-week absolute effectiveness analysis*** 39

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41 Figure 3, A shows week-by-week estimates for patients vaccinated with at least one dose of Pfizer-
42 BioNTech or Moderna. Due to the small sample size, we were not able to obtain stable week-by-week
43 estimates for Janssen. While week one was characterized by unexpectedly high effectiveness (58%, 95%
44 CI 45-69% against COVID-19 infection and 72%, 95% CI 57-83% against COVID-19 associated
45 hospitalization), we observed plausible increasing effectiveness beginning week 2 with the effectiveness
46 on week 6 approximating 84% (95% CI 72-91%) for COVID-19 infection and 86% (95% CI 69-95) for
47 COVID-19-associated hospitalization.
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54 We then looked at the week one COVID-19 infection cases to explain high effectiveness. A chart review
55 of week one positive COVID-19 tests revealed a high proportion of unvaccinated patients seeking care
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3 related to COVID-19 symptoms or COVID-19 exposure (85% in total) compared to only 69% of
4 vaccinated patients. Initial healthcare encounters in vaccinated population were oftentimes related to other
5 medical reasons such as co-morbid conditions or surgeries (39% compared to 21% in unvaccinated
6 population, Appendix 5). Moreover, an observed gap between symptom onset and an initial healthcare
7 encounter was more pronounced in the vaccinated cohort as the patients attributed their symptoms to
8 temporal vaccine side effects as opposed to COVID-19 infection.
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14 When looking at the severity of COVID-19 symptoms at the initial encounter during week one after the
15 index date, we observed that the unvaccinated cohort had a higher proportion of asymptomatic cases
16 (39% compared to 11%) while the vaccinated population had more severe or mild cases (34% and 48%
17 respectively).
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22 ***Sensitivity analysis***

23 *Overall effectiveness*

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25 As cohort analysis allows us to construct Kaplan-Meier curves to assess effectiveness over time, we also
26 looked at the effectiveness during the year after the first dose (Figure 4). We observed similar trends with
27 all three vaccines being less effective during the first month after the first dose. After that, Pfizer-
28 BioNTech and Moderna were highly effective against both COVID-19 infection and COVID-19
29 associated hospitalization, while Janssen vaccine exhibited a wide range of effectiveness (Appendix 6).
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38 The results for fully vaccinated patients with time-at-risk starting at the full vaccination matched the
39 results of the clinical trials for corresponding vaccines (detailed estimates are provided in Appendix 7 and
40 8).
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44 Our initial design included a positive COVID-19 test or a diagnostic code as an outcome. Upon further
45 case examination, we discovered that COVID-19 diagnostic codes in the CUIMC data were partially
46 assigned to the patients with negative COVID-19 tests on or immediately following the date of diagnosis.
47 In that case, ICD10CM code U07.1 “Disease caused by Severe acute respiratory syndrome coronavirus 2”
48 was entered in the system for billing purposes (COVID-19 molecular or antibody tests) or for COVID-19
49 sequelae. We, therefore, focused on positive COVID-19 test only for our primary outcome, which led to
50 higher effectiveness for all vaccines compared to using both positive test and diagnosis (Appendix 6).
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3 Finally, exclusion of patients with prior COVID-19 infection in our main analysis resulted in higher
4 absolute effectiveness. Inclusion of patients regardless of their prior COVID-19 status led to a small
5 decrease in observed effectiveness (Appendix 9) for both COVID-19 infection and hospitalization in
6 patients vaccinated with Moderna or Janssen.
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10 11 **DISCUSSION** 12 13

14 In this retrospective cohort study, we examined the weekly effectiveness of COVID-19 mRNA vaccines
15 as well as the overall effectiveness of three COVID-19 vaccines commonly used in the US. COVID-19
16 mRNA vaccines were highly effective against both COVID-19 infection and COVID-19 associated
17 hospitalization. Our findings support the RCTs and previously published post-marketing studies for all
18 three vaccines. Larger sample size for patients vaccinated with COVID-19 mRNA vaccines allowed us to
19 have more power, which resulted in overlapping yet narrower confidence intervals compared to the RCTs.
20 On the other hand, our study had fewer patients with the Janssen vaccine, which resulted in wider yet
21 overlapping intervals compared to the Janssen's vaccine RCT (1,2,7).
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28 Our study complemented previous studies by examining and comparing disparate design choices such as
29 studying both COVID-19-associated hospitalization and COVID-19 infection, different outcome
30 definitions and broad age group (4,5). We scrutinized the effectiveness of the mRNA vaccines following
31 the first dose and confirmed the findings of moderate vaccine effectiveness during the first two weeks.
32 For week one following the first dose we discovered previously uncaptured differential biases in
33 vaccinated and unvaccinated populations. Vaccination directly influenced the attitude of patients towards
34 their symptoms, causing a delay in seeking care and a higher symptom severity threshold needed to seek
35 care. In unvaccinated patients, mild COVID-19 related symptoms were the reason to seek care; in
36 vaccinated patients such cases were mainly captured upon seeking outpatient and inpatient care for other
37 conditions. Such a difference may affect any observational vaccine study that uses hospitalization as a
38 surrogate for COVID-19 severity.
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46 Previous research suggested that vaccinated patients do not have an increase in the number of cases
47 immediately following vaccination as they are unlikely to get vaccinated if sick (10). Our review of the
48 cases in week one supplements this assumption by showing that vaccinated patients are more likely to
49 attribute their symptoms to common vaccine side effects and, therefore, are less likely to seek care.
50 Nevertheless, even when this differential bias is present, the estimates of the COVID-19 vaccine
51 effectiveness in subsequent weeks still match the results of the RCTs. This indicates that high
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3 effectiveness during week one following vaccination does not necessarily undermine the estimates of
4 subsequent vaccine effectiveness.
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8 Our sensitivity analyses discovered several challenges and potential biases that must be accounted for
9 when conducting vaccine effectiveness studies on observational data. First, we observed that outcome
10 definitions are prone to measurement error, which has not been studied thoroughly. The specifics of data
11 capture and billing processes were associated with some patients having assigned COVID-19 diagnosis
12 codes for billing for tests rather than as an indicator of active disease. Another reason for assigning the
13 code was COVID-19 sequela, where the actual date of COVID-19 infection could have been anywhere
14 from 6 months to a couple of weeks in the past. Such index date misclassification can be present in other
15 healthcare institutions and therefore should be scrutinized to make valid inferences.
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22 Second, inclusion or exclusion of patients with prior COVID-infection influenced estimated effectiveness.
23 We observed that inclusion of patients with prior COVID-19 leads to lower effectiveness for all vaccines
24 regardless of the outcome definition.
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28 If absolute effectiveness is studied, an appropriate index event (anchor) for the unvaccinated cohort must
29 be chosen. In our study, we observed that an arbitrary date represents a better counterfactual than a
30 medical visit for COVID-19 vaccination, which is reflected in propensity score balance and covariate
31 balance. Nevertheless, other institutions may have different vaccination pathways such as vaccination on
32 discharge, which can make a visit a better counterfactual for vaccination. More generally, completeness
33 of vaccination data capture is a crucial feature that influences the robustness of the study. While CUIMC
34 data ensures complete exposure capture by linking EHR to the City and State Registries, the researchers
35 should exhibit caution with conducting studies on the data sources with unknown vaccination capture.
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42 We obtained similar results to RCTs, which strengthens the conclusions about the high effectiveness of
43 vaccines against COVID-19 infection in the broad age group. While these RCTs allowed us to make such
44 comparisons for absolute effectiveness, there are other research questions for which RCTs may not be
45 feasible or readily available. The US and international booster campaigns raise the question of vaccine
46 comparative effectiveness to prioritize vaccination. An indirect comparison may not be accurate due to
47 the differences in the populations we observed in our study. First, patients vaccinated with Janssen were
48 substantially different from mRNA patients: on average, they were older, had a higher proportion of
49 patients with race recorded as Black and had more comorbidities. Therefore, comparative effectiveness
50 studies of Janssen and mRNA vaccines require robust techniques such as large-scale propensity matching
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3 to ensure valid comparison. Second, while Moderna and Pfizer patients had similar baseline
4 characteristics, the temporal distribution of vaccinations in CUIMC data differ. Moderna vaccine was
5 administered early on in 2021 with the peak in January, while Pfizer vaccination peaked in April. Given
6 the varying baseline COVID-19 prevalence, a comparison of mRNA vaccines requires matching patients
7 on calendar month to account for this potential bias. These vaccines also had different administration
8 pathways in our system. As opposed to Pfizer vaccine, which was administered at Columbia University
9 Irving Medical Center/New York-Presbyterian sites to all patients over a prolonged period, Moderna
10 vaccination was performed elsewhere and recorded for actively observed patients. Such patients were
11 more likely to get tested or receive care outside of our healthcare system.
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19 **LIMITATIONS**

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

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

53 **Author contributions**

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5 GH designed and supervised the study. All co-authors contributed to interpretation of the results and writing
6 the manuscript, approved the final version and had final responsibility for the decision to submit for
7 publication.
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15 Initiative (75F40120D00039).
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18 19 **Declaration of interests**

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22 All authors have completed the ICMJE disclosure form (available on request from the corresponding
23 author). GH and AO receive funding from the US National Institutes of Health (NIH) and the US Food and
24 Drug Administration.
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28 29 **Ethical approval**

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32 The protocol for this research was approved by the Columbia University Institutional Review Board
33 (AAAO7805).
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36 37 **Data sharing**

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40 Patient-level data cannot be shared without approval from data custodians due to local information
41 governance and data protection regulations.
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44 45 **Transparency declaration**

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48 The lead authors affirms that this manuscript is an honest, accurate, and transparent account of the study
49 being reported; that no important aspects of the study have been omitted; and that any discrepancies from
50 the study as planned (and, if relevant, registered) have been explained.
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53 54 **Acknowledgment**

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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.

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3 **Figure 2.** Diagnostics for the absolute effectiveness study comparing the cohort vaccinated with at least
4 one dose of Pfizer, Moderna or Janssen COVID-19 vaccines and unvaccinated cohort anchored on a date
5 or on a visit: (A) covariate balance before and after propensity score matching, (B) preference score
6 balance and (C) effect of negative control calibration displaying effect estimate and standard error.
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8 In (A), each dot represents the standardized difference of the means for a single covariate before and after
9 stratification on the propensity score.
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11 In (C), each blue dot is a negative control. The area below the dashed line indicates estimates with $p < 0.05$
12 and the orange area indicates estimates with calibrated $p < 0.05$.
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19 **Figure 3.** Week-by-week estimates of vaccine effectiveness of Pfizer-BioNTech and Moderna after 1st
20 dose, % and 95% CI for COVID-19 infection (A) and COVID-19 hospitalization (B). Chart review of
21 COVID-19 cases (defined as a positive COVID-19 test) during week 1, vaccinated and unvaccinated
22 patients (C).
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28 **Figure 4.** Kaplan-Meier curves for absolute effectiveness of COVID-19 vaccines for time-at-risk of 1 day
29 – 365 days after the first dose compared to the unvaccinated patients residing in New York City.
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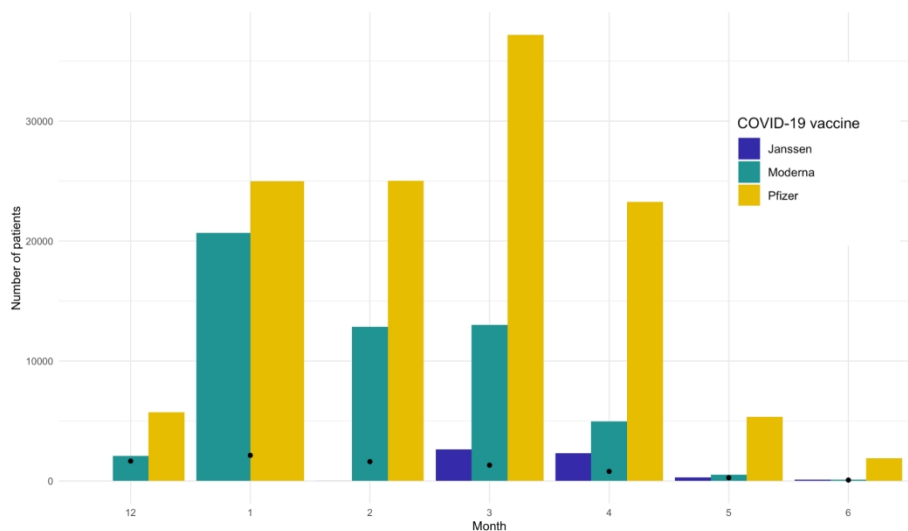
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Table 1. Patient baseline characteristics for patients with at least one dose of a COVID-19 vaccine and the comparator unvaccinated patients, before and after propensity score matching.

Characteristic	Before matching									After matching								
	Pfizer			Moderna			Janssen			Pfizer			Moderna			Janssen		
	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 (79-140)	107 (79-140)		126 (102-153)	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	0.03	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	0.00	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

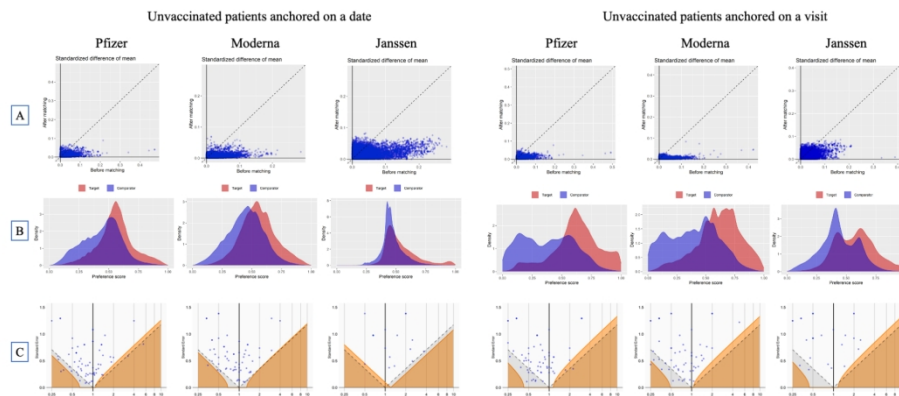
75-84	11.3	8.9	0.08	15.4	10	0.16	7.6	7.9	0.01	10.6	10.7	0	14.6	14.6	0.00	7.2	7.9	0.03
>84	4.1	3.8	0.02	5.8	4.8	0.04	4.3	4.3	0.00	4.2	4.1	0.01	5.6	5.6	0.00	4.2	4	0.01
Gender, %																		
Female	63.7	57.8	0.12	64.4	58.7	0.12	63.4	63.2	0.01	61.4	62	0.01	64.2	64.7	0.01	63.5	61.1	0.05
Race, %																		
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	0.0 3	0.9	1.2	- 0.0 3	1.7	1.4	0.0 2	1.1	1	0	0.8	0.8	0	1.6	1.8	- 0.0 1
Hyperlipidemia	12. 9	8.1	0.1 6	14. 9	8.9	0.1 9	14. 3	10.2	0.1 3	10. 2	9.5	0.0 2	13	12.6	0.0 1	13. 4	14.3	- 0.0 3
Hypertensive disorder	16	11.3	0.1 4	16	12.4	0.1	21. 4	13.8	0.2	13. 1	12.2	0.0 3	14. 7	13.9	0.0 2	20. 1	21.7	- 0.0 4
Obesity	5.1	4.9	0.0 1	4	4.4	- 0.0 2	7.3	5.9	0.0 6	4.4	4.1	0.0 2	3.8	3.6	0.0 1	6.8	7.8	- 0.0 4
Osteoarthritis	7.3	4.7	0.1 1	7.7	5.3	0.1	8.4	6.2	0.0 8	5.8	5.3	0.0 2	6.8	6.5	0.0 1	7.8	8.8	- 0.0 4
Renal impairment	3.7	3	0.0 4	3.5	3.3	0.0 1	6.6	3.3	0.1 5	2.9	2.7	0.0 1	3.3	3	0.0 1	5.3	5.9	- 0.0 2
Cerebrovascular disease	1.7	1.4	0.0 2	2.2	1.6	0.0 5	2.7	1.7	0.0 7	1.5	1.4	0.0 1	2	1.8	0.0 2	2.3	2.4	- 0.0 1
Heart disease	8.6	7.1	0.0 6	10. 1	7.6	0.0 9	11. 8	8	0.1 3	7.5	7.1	0.0 2	9.2	8.7	0.0 2	10. 3	11.7	- 0.0 4
Malignant neoplastic disease	5.3	4.5	0.0 4	6.5	5	0.0 7	5	4.9	0	4.7	4.3	0.0 2	5.9	5.5	0.0 2	4.8	5.2	- 0.0 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.

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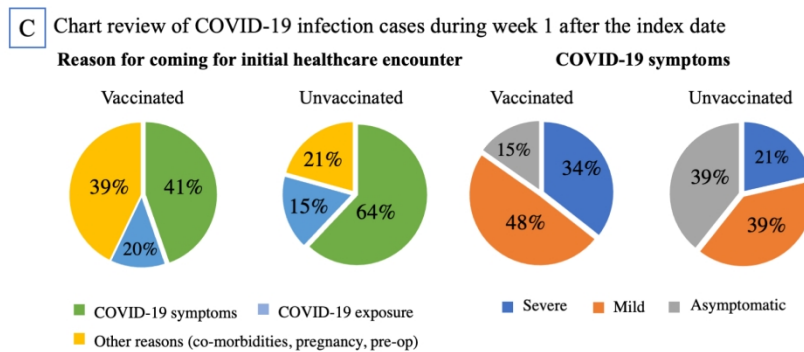
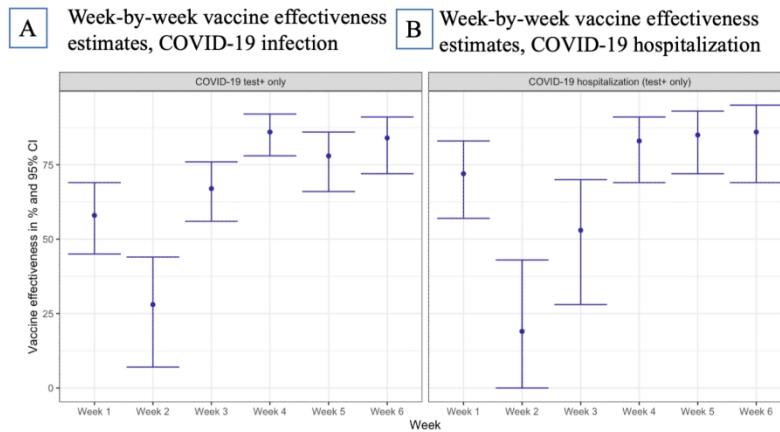


23 Diagnostics for the absolute effectiveness study comparing the cohort vaccinated with at least one dose of
 24 Pfizer, Moderna or Janssen COVID-19 vaccines and unvaccinated cohort anchored on a date or on a visit:
 25 (A) covariate balance before and after propensity score matching, (B) preference score balance and (C)
 26 effect of negative control calibration displaying effect estimate and standard error.

27 In (A), each dot represents the standardized difference of the means for a single covariate before and after
 28 stratification on the propensity score.

29 In (C), each blue dot is a negative control. The area below the dashed line indicates estimates with $p < 0.05$
 30 and the orange area indicates estimates with calibrated $p < 0.05$.

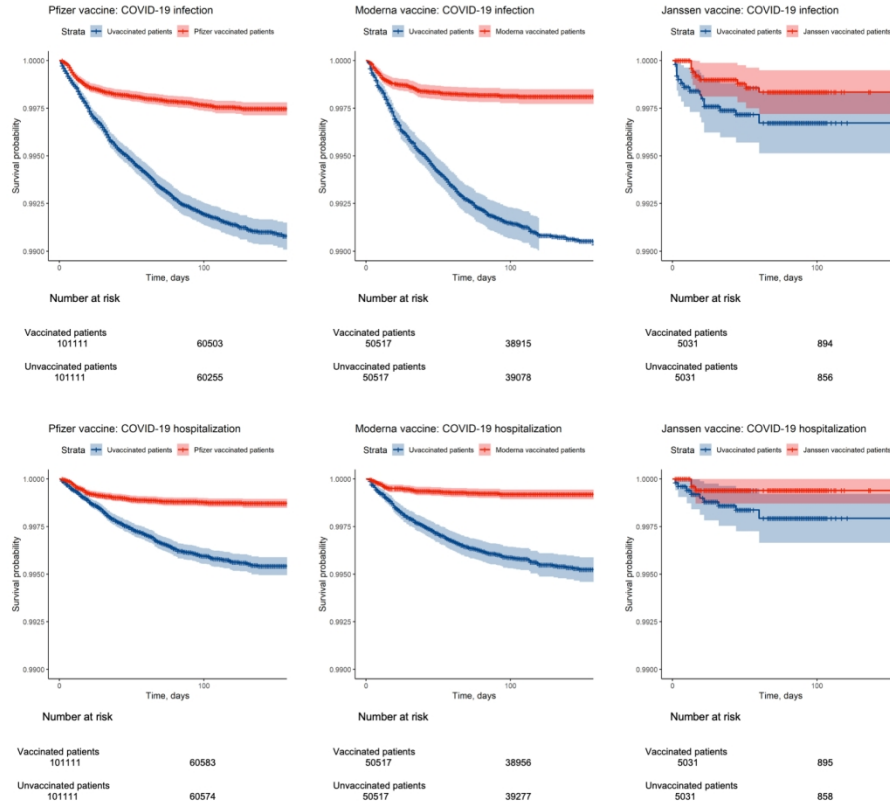
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Week-by-week estimates of vaccine effectiveness of Pfizer-BioNTech and Moderna after 1st dose, % and 95% CI for COVID-19 infection (A) and COVID-19 hospitalization (B). Chart review of COVID-19 cases (defined as a positive COVID-19 test) during week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

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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.

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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.

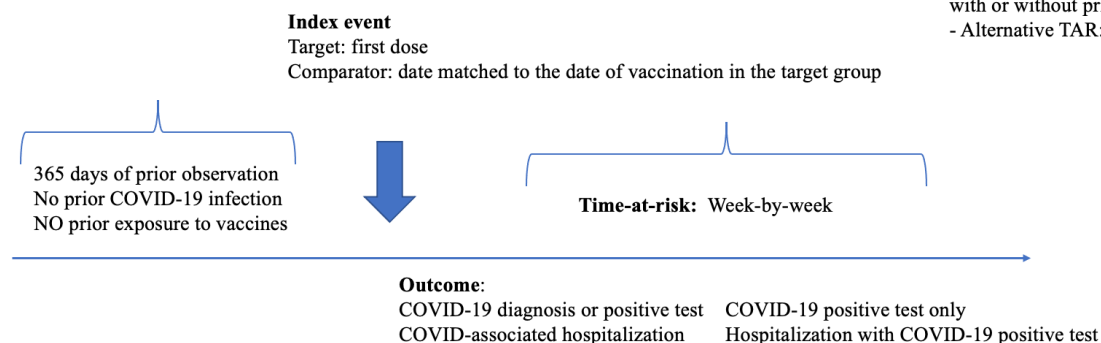
Appendix 2. Retrospective cohort COVID-19 vaccine effectiveness study design overview.

Main analysis

Target: patients with at least one dose (Ad26.COVID.S BNT162b2 and mRNA-1273) located in NYC
Comparator: unvaccinated patients matched on the date of vaccination located in NYC

Sensitivity analyses

- Alternative comparator: Patients matched on the visit
- Alternative target: fully vaccinated patients
- Alternative target and comparator: patients with or without prior COVID-19
- Alternative TAR: 1 day– 365 days



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	<p>Target cohorts were defined as patients with at least one dose of the corresponding vaccine (Pfizer, 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"> - 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 <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>Links:</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/498</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/494</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/497</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/418</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/417</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/420</p>
Comparator cohorts	<p>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.</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 sensitivity analysis we applied the abovementioned criteria with adding COVID-19 diagnosis as an alternative for positive COVID-19 test.</p> <p>Links:</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/425</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/422</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

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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 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

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%)

<i>Type of initial healthcare encounter</i>				
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%)

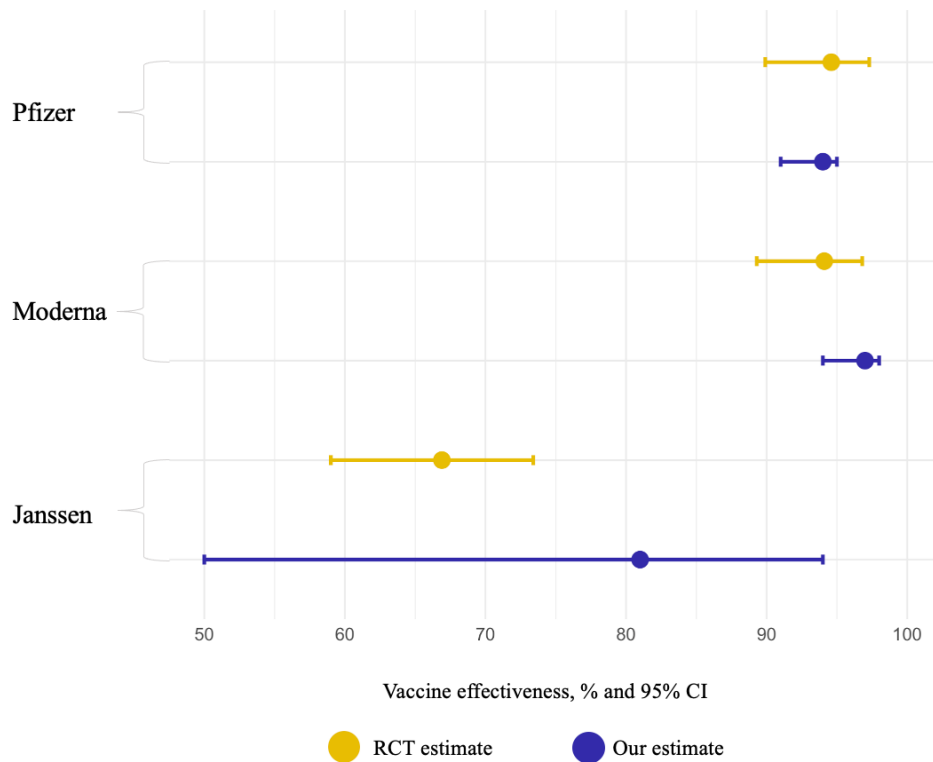
Appendix 6. Estimates for absolute effectiveness of COVID-19 vaccines for time-at-risk of 1 day – 365 days after the first dose in the vaccinated patients without prior COVID-19 infection compared to unvaccinated patients residing in NYC.

	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 (b) For matched studies, give matching criteria and number of exposed and unexposed	5
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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	6-7 6-7 - NA 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (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- 20 8, 18
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

1	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	8, supplementary materials
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
4	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
5	Discussion			
6	Key results	18	Summarise key results with reference to study objectives	10
7	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
8	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
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
10	Other information			
11	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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6 3 **COVID-19 vaccination effectiveness rates by week and sources of bias: a retrospective cohort study**
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34 **ABSTRACT**

36 **Objective**

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

40 **Design and setting**

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

44 **Outcomes and measures**

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

51 **Results**

52 The study included 179,666 patients. We observed increasing effectiveness after the first dose of mRNA
53 vaccines with week six effectiveness approximating 84% (95% CI 72-91%) for COVID-19 infection and
54 86% (95% CI 69-95) for COVID-19-associated hospitalization. When analyzing unexpectedly high
55 effectiveness in week one, chart review revealed that vaccinated patients are less likely to seek care after
56 vaccination and are more likely to be diagnosed with COVID-19 during the encounters for other
57 conditions. Sensitivity analyses highlighted potential outcome misclassification for ICD10-CM diagnosis,
58 the influence of excluding patients with prior COVID-19 infection and anchoring in the unexposed group.
59 Overall vaccine effectiveness in fully vaccinated patients matched the results of the randomized trials.

61 **Conclusions**

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

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2
3 **68 Strengths and limitations of this study**
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6 69 - This study thoroughly investigates weekly COVID-19 vaccine effectiveness using methods to reduce
7 70 potential confounding (large-scale propensity score matching, negative control calibration) and
8 71 accompanied by manual chart review of the cases in week one
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12 72 - The study includes a range of sensitivity analyses for different patient populations, anchoring strategies
13 73 and outcome definitions.
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15

16 74 - The study was carried out using routinely collected clinical practice data, which represents real-world
17 75 patients, but also implies a risk of misclassification.
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20 76 **Word count:** 3179
21

22 77 **Keywords:** COVID-19, Epidemiology, Health Informatics, Bias
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99 BACKGROUND

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

107
108 There have been recent observational studies, which have shown effectiveness similar to the randomized
109 clinical trials (RCTs) across the globe, both test-negative and cohort (5–12), followed by studies across
110 different patient populations, variants and number of doses (13–17).

111
112 Nevertheless, the challenges associated with the use of observational data such as incomplete data
113 capture, outcome misclassification and appropriate comparator sampling can undermine the results of the
114 studies if such biases are not accounted for (18). For COVID-19 vaccines, questions associated with
115 vaccine status misclassification (19), matching vaccinated and unvaccinated populations (6), addressing
116 disease risk factor confounding and ascertainment bias (20,21) and others were raised.

117
118 One of such questions is COVID-19 vaccine effectiveness during the first two weeks following the first
119 dose. Studies have shown contradicting results for Pfizer–BioNTech vaccine with effectiveness ranging
120 from moderate effectiveness of 52% (3) to very high effectiveness of 92.6% (22). Similarly, a recent
121 study showed an unexplained high effectiveness of Janssen vaccine during week one (23). Other studies
122 simply excluded the first week(s) from the time-at-risk (9,13,24–26). While week one lack of
123 effectiveness has been suggested as a metric for lack of confounding in the long-term vaccine
124 effectiveness studies, the reasons for high effectiveness and its impact on the validity of the conclusions
125 regarding the overall effectiveness remain unclear (9).

126
127 The goal of this study was to examine COVID-19 vaccine effectiveness over six 7-day intervals after the
128 first dose to assess underlying bias associated with the use of observational data for short-term vaccine
129 effectiveness and its impact on long-term vaccine effectiveness estimates . We employed large-scale
130 propensity score matching and many negative controls to reduce and assess bias and leveraged a range of
131 sensitivity analyses as well as manual review of the COVID-19 infection cases in week one to examine
132 health-seeking behavior of vaccinated and unvaccinated patients.

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3 1334 134 **METHODS**5 135
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8 138 *Main design*9 139
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11 138 For this retrospective observational cohort study, we used electronic health records from the Columbia
12 139 University Irving Medical Center (CUIMC) database (Appendix 1), which has an ongoing automated
13 140 connection to New York City and State public health department vaccine registries and includes all
14 141 within-state vaccinations for our population. The data were translated to the OMOP Common Data Model
15 142 version 5 and was previously used in multiple studies (27).
16 143

17 144

18 144 For our main analysis, we studied two mRNA vaccines (Pfizer-BioNTech or Moderna). The exposed
19 145 group included patients indexed on the first dose of one of the corresponding vaccines with no prior
20 146 COVID-19 infection and no previous exposure to other COVID-19 vaccines. For the unexposed group,
21 147 we selected unvaccinated patients and set their index date to a date (not necessarily with any medical
22 148 event) that matched the index date of one of the exposed group participants. Both the exposed and
23 149 unexposed groups had at least 365 days of prior observation and primarily resided in New York City
24 150 according to their zip code. Patients who did not reside in New York were excluded from the study to
25 151 ensure reliable vaccination data capture.
26 152

27 153

28 153 Outcomes of interest included a) COVID-19 infection defined as a positive COVID-19 test (reverse-
29 154 transcriptase–polymerase-chain-reaction assay) or a diagnostic code of COVID-19 and b) COVID-19
30 155 hospitalization defined as an inpatient visit associated with a COVID-19 positive test or diagnosis within
31 156 30 days prior or during the visit. Upon further examination of the results, we added two other outcomes:
32 157 a) COVID-19 positive test only and b) COVID-19 hospitalization associated with a positive COVID-19
33 158 test. Design overview is provided in Appendix 2; code lists and links to phenotype definitions are
34 159 provided in Appendix 3.
35 160

36 161

37 161 We calculated vaccine effectiveness during six consecutive 7-day intervals after the first dose. Within
38 162 each interval, patients were followed-up until an outcome, end of the period or death, whichever came
39 163 earlier. Additionally, given the results for vaccine effectiveness during week one following the first dose,
40 164 we conducted chart review for patients with a COVID-19 positive test recorded in the abovementioned
41 165 period. We reviewed all cases for the vaccinated population as well a random sample of the cases in the
42 166 unvaccinated population and extracted main complaint, COVID-19 history, including symptoms (fever,
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3 167 shortness of breath, sore throat, cough etc.), severity, time from the first symptom to encounter and
4 168 COVID-19 exposure.

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8 170 ***Secondary analyses***

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11 172 We also conducted a set of secondary analyses. First, given that the published studies focused on patients
12 173 without prior COVID-19 infection, we studied all eligible patients regardless of their previous COVID-19
13 174 status.

14 175
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16 176 As the strategy for unvaccinated group index date selection (anchoring) has been reported to influence
17 177 incidence of outcomes and baseline characteristics (28,29), we additionally tested unexposed patients
18 178 indexed on a healthcare encounter matching the index date of one of the exposed group participants
19 179 within 3 days corridor, with at least 365 days of prior observation located at New York.

20 180
21
22 181 Finally, we assessed vaccine effectiveness in patients with at least one dose of a COVID-19 vaccine and
23 182 in fully vaccinated patients over all available follow-up to compare the estimates to the results of the
24 183 RCTs. The latter was defined as 14 days after the second dose of Pfizer-BioNTech or Moderna vaccines
25 184 or first dose of Janssen vaccine. For each comparison we estimated hazard ratios (HRs) and constructed
26 185 Kaplan-Meier plots as described below.

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31 187 ***Statistical methods***

32 188 For each analysis, we fitted a lasso regression model to calculate propensity score and match patients in
33 189 each exposed and unexposed group with 1:1 ratio. For large-scale propensity score model we used all
34 190 demographic information, index year and month, as well as the number of visits, condition and drug
35 191 groups, procedures, device exposures, laboratory and instrumental tests and other observations over long
36 192 (prior year) and short-term period (prior month) (30,31).

37
38
39 193 For each outcome, we fitted a Cox proportional hazards models to estimate HRs and constructed Kaplan-
40 194 Meier plots. Empirical calibration based on the negative control outcomes was used to identify and
41 195 minimize any potential residual confounding by calibrating HRs and 95% confidence intervals (CIs)
42 196 (32,33). Vaccine effectiveness was calculated as $100\% \times (1 - \text{hazard ratio})$.

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3 197 All analyses were supported by the OHDSI Infrastructure (CohortMethod package, available
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5 198 at <https://ohdsi.github.io/CohortMethod/>, FeatureExtraction available at
6
7 199 <https://ohdsi.github.io/FeatureExtraction/> and the Cyclops package for large-scale regularized regression
8
9 200 (34) available at <https://ohdsi.github.io/Cyclops>).

10 201 ***Diagnostics***

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12
13 202 We used multiple sources of diagnostics to estimate potential bias and confounding following best
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15 203 practices for evidence generation (35). First, we examined covariate and propensity score balance prior to
16
17 204 proceeding with outcome modelling and effect estimation to ensure that we have enough sample size and
18
19 205 to control for potential observed confounding (35). We plotted propensity scores to investigate the
20
21 206 overlap in patient populations at the baseline and examined the balance of all baseline characteristics to
22
23 207 determine if the exposed and unexposed cohorts were imbalanced at the baseline and after propensity
24
25 208 score matching. Exposed and unexposed cohorts were said to be balanced if the standardized difference of
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27 209 means of all covariates after propensity score matching was less than 0.1 (36).

28
29 210 For negative control calibration, we used 93 negative controls (Appendix 4) with no known causal
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31 211 relationship with the COVID-19 vaccines. Negative controls were selected based on a review of existing
32
33 212 literature, product labels and spontaneous reports and were reviewed by clinicians (37). We assessed
34
35 213 residual bias from the negative control estimates.

36 214 **Patient and public involvement**

37 215
38 216 No patient involved

39 217
40 218

41 219 **RESULTS**

42 220 43 221 ***Patient characteristics***

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45
46 223 In total, we identified 179,666 patients with at least one dose of COVID-19 vaccine in January-May 2021:
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48 224 121,771 patients for Pfizer-BioNTech, 52,728 for Moderna and 5,167 for Janssen (Table 1). The sample
49
50 225 included patients from all age groups, with or without co-morbidities captured in inpatient and outpatient
51
52 226 settings.

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2
3 227 We observed that unexposed patients (Table 1) were on average younger and had fewer co-morbidities
4 228 and less exposure to various drugs prior to matching. We were able to achieve balance on all covariates
5 229 (up to 54,987 covariates, standardized difference of means less than 0.1) with propensity score matching.
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8 230 Figure 1 presents the covariate balance and propensity score balance plots showing that anchoring
9 231 unvaccinated patients on a date allowed us to achieve better balance compared to anchoring patients on a
10 232 visit.
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14 234 Patients vaccinated with Pfizer-BioNTech had a similar distribution of baseline characteristics compared
15 235 to the patients vaccinated with Moderna but differed from the patients vaccinated with Janssen. On
16 236 average, the latter group was older, had more patients with race recorded as Black, and had more co-
17 237 morbidities such as diabetes mellitus or hypertensive disorder (Table 1).
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21 238
22 239 When investigating the vaccination pathways, we discovered that 112,963 patients (93% of patients with
23 240 at least one dose of Pfizer-BioNTech) had 2 doses of Pfizer-BioNTech and 42,384 (80%) patients had 2
24 241 doses of Moderna. We found 344 and 291 patients with 3 doses of the corresponding vaccines and 440
25 242 patients having mixed Pfizer-BioNTech, Moderna and Janssen vaccines in different combinations.
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30 244 Within our database, Moderna was administered early on with a peak in January 2021 (Figure 2), while
31 245 Pfizer-BioNTech and Janssen vaccinations peaked in April. It was reflected in the follow-up time with
32 246 Moderna patients having on average longer follow-up with some individuals having up to 5.8 months of
33 247 post-observation.
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37 249 *Main week-by-week effectiveness analysis*

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40
41 251 Figure 3 shows vaccine effectiveness over six 7-day intervals for patients vaccinated with at least one
42 252 dose of Pfizer-BioNTech or Moderna (160,114 patients) compared to unvaccinated patients (115,689).
43 253 Due to the small sample size, we were not able to obtain stable week-by-week estimates for Janssen.
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45

46 254

47 255 While week one was characterized by unexpectedly high effectiveness (58%, 95% CI 45-69% against
48 256 COVID-19 infection and 72%, 95% CI 57-83% against COVID-19 associated hospitalization), we
49 257 observed plausible increasing effectiveness beginning week 2 with the effectiveness on week 6
50 258 approximating 84% (95% CI 72-91%) for COVID-19 infection and 86% (95% CI 69-95) for COVID-19-
51 259 associated hospitalization.
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3 261 We then looked at the week one COVID-19 infection cases to explain high effectiveness (Figure 4). A
4 262 chart review of week one positive COVID-19 tests revealed a high proportion of unvaccinated patients
5 263 seeking care related to COVID-19 symptoms or COVID-19 exposure (85% in total) compared to only
6 264 69% of vaccinated patients. Initial healthcare encounters in vaccinated population were oftentimes related
7 265 to other medical reasons such as co-morbid conditions or surgeries (39% compared to 21% in
8 266 unvaccinated population, Appendix 5). Moreover, an observed gap between symptom onset and an initial
9 267 healthcare encounter was more pronounced in the vaccinated cohort as the patients attributed their
10 268 symptoms to temporal vaccine side effects as opposed to COVID-19 infection.
11 269

12 270 When looking at the severity of COVID-19 symptoms at the initial encounter during week one after the
13 271 index date, we observed that the unvaccinated cohort had a higher proportion of asymptomatic cases
14 272 (39% compared to 11%) while the vaccinated population had more severe or mild cases (34% and 48%
15 273 respectively).
16 274

17 275 *Secondary analysis*

18 276

19 277 As cohort analysis allows us to construct Kaplan-Meier curves to assess effectiveness over time, we also
20 278 looked at the effectiveness during the year after the first dose (Appendix 6-8). We observed similar trends
21 279 with all three vaccines being less effective during the first month after the first dose. After that, Pfizer-
22 280 BioNTech and Moderna were highly effective against both COVID-19 infection and COVID-19
23 281 associated hospitalization, while Janssen vaccine exhibited a wide range of effectiveness (Appendix 9).
24 282

25 283 The results for fully vaccinated patients with time-at-risk starting at the full vaccination matched the
26 284 results of the clinical trials for corresponding vaccines (detailed estimates are provided in Appendix 10
27 285 and 11).
28 286

29 287 Our initial design included a positive COVID-19 test or a diagnostic code as an outcome. Upon further
30 288 case examination, we discovered that COVID-19 diagnostic codes in the CUIMC data were partially
31 289 assigned to the patients with negative COVID-19 tests on or immediately following the date of diagnosis.
32 290 In that case, ICD10CM code U07.1 “Disease caused by Severe acute respiratory syndrome coronavirus 2”
33 291 was entered in the system for billing purposes (COVID-19 molecular or antibody tests) or for COVID-19
34 292 sequelae. We, therefore, focused on positive COVID-19 test only for our primary outcome, which led to
35 293 higher effectiveness for all vaccines compared to using both positive test and diagnosis (Appendix 9).
36 294

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3 295 Finally, exclusion of patients with prior COVID-19 infection in our main analysis resulted in higher
4 296 effectiveness. Inclusion of patients regardless of their prior COVID-19 status led to a small decrease in
5
6 297 observed effectiveness (Appendix 12) for both COVID-19 infection and hospitalization in patients
7
8 298 vaccinated with Moderna or Janssen.

9 299

10 300 **DISCUSSION**

11 301

12 302 In this retrospective cohort study, we examined the effectiveness of COVID-19 mRNA vaccines over six
13
14 303 7-day intervals after the first dose. We scrutinized the effectiveness of the mRNA vaccines following the
15
16 304 first dose and confirmed the findings of moderate vaccine effectiveness during the first two weeks. For
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18 305 week one following the first dose we discovered previously uncaptured differential biases in vaccinated
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20 306 and unvaccinated populations resulting in high vaccine effectiveness. Other researchers suggested that the
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22 307 difference between vaccinated and unvaccinated groups can be mitigated by adjusting for previous
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24 308 healthcare utilization such as number of visits before baseline, co-morbidities or prior vaccination
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26 309 behavior (6,13,24). Nevertheless, the confounding we observed remains even upon controlling for a large
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28 310 number of covariates including those above.

29 311

30 312 Vaccination directly influenced the attitude of patients towards their symptoms, causing a delay in
31
32 313 seeking care and a higher symptom severity threshold needed to seek care or get tested. On contrary,
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34 314 vaccinated patients in other studies had higher rates of testing compared to unvaccinated (20,38). This
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36 315 indicates that patients' attitude toward risk of infection and testing may vary geographically and over
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38 316 time. Similarly, frequency of testing may depend on local policies and practices.

39 317

40 318 In unvaccinated patients, mild COVID-19 related symptoms were the reason to seek care; in vaccinated
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42 319 patients such cases were mainly captured upon seeking outpatient and inpatient care for other conditions.
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44 320 For example, vaccinated patients could be hospitalized for elective surgery or delivery and be tested
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46 321 positive for COVID-19 on the day of admission or later on. Differential symptom severity was previously
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48 322 reported for other vaccines (39) and may affect any observational study that uses hospitalization as a
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50 323 surrogate for COVID-19 severity as it can be hard to accurately identify the main reason for
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52 324 hospitalization in structured data.

53 325

54 326 Previous research suggested that vaccinated patients do not have an increase in the number of cases
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56 327 immediately following vaccination as they are unlikely to get vaccinated if sick (9,40). Our review of the

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3 328 cases in week one adds to ‘healthy vaccinee’ effect by showing that vaccinated patients are more likely to
4 329 attribute their symptoms to common vaccine side effects and, therefore, are less likely to seek care.

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8 331 Nevertheless, even when this differential bias is present, the estimates of the COVID-19 vaccine
9 332 effectiveness in subsequent weeks still match the results of the RCTs. This indicates that high
10 333 effectiveness during week one following vaccination does not necessarily undermine the estimates of
11 334 subsequent vaccine effectiveness. On the other hand, we argue against using estimates of vaccine
12 335 effectiveness within a short period after the vaccination as a negative control as the differences between
13 336 the groups observed in this study are likely to be time-variant and may diminish over time (41).

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16 338 Our secondary analyses discovered several challenges and potential biases that must be accounted for
17 339 when conducting vaccine effectiveness studies on observational data. First, we observed that outcome
18 340 definitions are prone to measurement error, which has not been studied thoroughly. Some of the published
19 341 studies used ICD-10 or ICD-10(CM) codes to identify COVID-19 outcomes (42–44). We found that the
20 342 specifics of data capture and billing processes were associated with some patients having assigned
21 343 COVID-19 diagnosis codes for billing for tests rather than as an indicator of active disease. Another
22 344 reason for assigning the code was COVID-19 sequela, where the actual date of COVID-19 infection could
23 345 have been anywhere from 6 months to a couple of weeks in the past. Some researchers have previously
24 346 reported high positive predictive value of ICD-10 diagnostic codes for COVID-19, which points out that
25 347 index date misclassification should be scrutinized in each institution participating in the analysis to make
26 348 valid inferences (45,46).

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29 350 Second, inclusion or exclusion of patients with prior COVID-infection influenced estimated effectiveness.
30 351 We observed that inclusion of patients with prior COVID-19 leads to lower effectiveness for all vaccines
31 352 regardless of the outcome definition.

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34 354 Third, an appropriate index event (anchor) for the unvaccinated cohort must be chosen to represent a
35 355 counterfactual for vaccination (29,47). In our study, we confirmed that an arbitrary date represents a
36 356 better counterfactual than a medical visit for COVID-19 vaccination, which is reflected in propensity
37 357 score balance and covariate balance. Nevertheless, other institutions may have different vaccination
38 358 pathways such as vaccination on discharge, which can make a visit a better counterfactual for vaccination.
39 359 More generally, completeness of vaccination data capture is a crucial feature that influences the
40 360 robustness of the study. While CUIMC data ensures complete exposure capture by linking EHR to the

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3 361 City and State Registries, the researchers should exhibit caution with conducting studies on the data
4 362 sources with unknown vaccination capture.

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7 364 In general, our findings support the RCTs and previously published post-marketing studies for all three
8 365 vaccines. Larger sample size for patients vaccinated with COVID-19 mRNA vaccines allowed us to have
9 366 more power, which resulted in overlapping yet narrower confidence intervals compared to the RCTs. On
10 367 the other hand, our study had fewer patients with the Janssen vaccine, which resulted in wider yet
11 368 overlapping intervals compared to the Janssen's vaccine RCT (1,2,7). Nevertheless, an indirect
12 369 comparison of these vaccines may not be accurate due to the differences in the populations we observed
13 370 in our study. First, patients vaccinated with Janssen were substantially different from mRNA patients: on
14 371 average, they were older, had a higher proportion of patients with race recorded as Black and had more
15 372 comorbidities. Therefore, comparative effectiveness studies of Janssen and mRNA vaccines require
16 373 robust techniques such as large-scale propensity matching to ensure valid comparison. Second, while
17 374 Moderna and Pfizer patients had similar baseline characteristics, the temporal distribution of vaccinations
18 375 in CUIMC data differ. Moderna vaccine was administered early on in 2021 with the peak in January,
19 376 while Pfizer vaccination peaked in April. Given the varying baseline COVID-19 prevalence, a
20 377 comparison of mRNA vaccines requires matching patients on calendar month to account for this potential
21 378 bias. These vaccines also had different administration pathways in our system. As opposed to Pfizer
22 379 vaccine, which was administered at Columbia University Irving Medical Center/New York-Presbyterian
23 380 sites to all patients over a prolonged period, Moderna vaccination was performed elsewhere and recorded
24 381 for actively observed patients. Such patients were more likely to get tested or receive care outside of our
25 382 healthcare system.

26 383

27 384 **LIMITATIONS**

28 385

29 386 Due to observational nature of the study, the data sources may not have complete capture of patient
30 387 conditions as the patients could seek care outside of the hospital system. While our outcome phenotype
31 388 algorithms may be subject to measurement error, we provided additional analyses with alternative
32 389 outcome definitions. Exposure misclassification was mitigated by having free and available COVID-19
33 390 testing and COVID-19 vaccination in Columbia University Irving Medical Center/New York-
34 391 Presbyterian sites as well as by having data capture from New York City and State Immunization
35 392 Registries. Along with availability of testing, COVID-19 baseline infection rate difference was mitigated
36 393 by matching the exposed and unexposed groups on the index date and using the index month as a
37 394 covariate in propensity score model. We attempted to address potential differences between exposed and

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3 395 unexposed groups by selecting a large number of covariates in our propensity score model such as
4 396 number of visits, procedure and drug utilization, prior vaccine behavior, race and others. Nevertheless, we
5 397 did not have data for social interactions, adherence to preventive measures and policies, which could
6 398 affect likelihood of COVID-19 infection and testing.
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11 400 The results of the study may not be generalizable to other countries or settings with different vaccine
12 401 administration practices and policies. Finally, the study period did not allow us to stratify the results by
13 402 COVID-19 variants, which limits generalizability of findings to other variants.
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19 405 **CONCLUSIONS**

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22 407 Observational data can be used to ascertain vaccine effectiveness if potential biases such as exposure and
23 408 outcome misclassification are accounted for, and appropriate anchoring event is selected. When analyzing
24 409 vaccine effectiveness researchers need to scrutinize the data to ensure that compared groups exhibit
25 410 similar health seeking behavior and are equally likely to be captured in the data and report their findings.
26 411 Specifically for COVID-19 vaccines, an arbitrary date for the index date in unvaccinated patients
27 412 represents a better counterfactual for vaccination than a healthcare encounter. Effectiveness over the first
28 413 week(s) after the vaccination should be reported even though low or high effectiveness immediately after
29 414 the vaccination may not invalidate study findings. Given the difference in temporal trends of vaccine
30 415 exposure and baseline characteristics, there is a need for large-scale direct comparison of vaccines to
31 416 examine comparative effectiveness.
38 417

39 418 **DECLARATION**

41 419 42 420 **Author contributions**

44 421
45 422 GH designed and supervised the study. AO executed the study, interpreted the results, and drafted the
46 423 manuscript. GH and AO reviewed the manuscript, approved the final version and had final responsibility
47 424 for the decision to submit for publication.
50 425

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8 431 **Declaration of interests**

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11 433 All authors have completed the ICMJE disclosure form (available on request from the corresponding
12 434 author). GH and AO receive funding from the US National Institutes of Health (NIH) and the US Food and
13 435 Drug Administration.
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17 437 **Ethical approval**

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20 439 The protocol for this research was approved by the Columbia University Institutional Review Board
21 440 (AAAO7805).
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25 442 **Data sharing**

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28 444 Patient-level data cannot be shared without approval from data custodians due to local information
29 445 governance and data protection regulations.
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33 447 **Transparency declaration**

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36 449 The lead authors affirms that this manuscript is an honest, accurate, and transparent account of the study
37 450 being reported; that no important aspects of the study have been omitted; and that any discrepancies from
38 451 the study as planned (and, if relevant, registered) have been explained.
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42 453 **Acknowledgment**

43
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5 617 **Figure 1.** Distribution of vaccination month for COVID-19 vaccines. Black dots represent the number of
6 618 incident COVID-19 cases (defined as a positive test) in each month.
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9 620 **Figure 2.** Diagnostics for the effectiveness study comparing the cohort vaccinated with at least one dose
10 621 of Pfizer, Moderna or Janssen COVID-19 vaccines and unvaccinated cohort anchored on a date or on a
11 622 visit: (A) covariate balance before and after propensity score matching, (B) preference score balance and
12 623 (C) effect of negative control calibration displaying effect estimate and standard error.

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14 624 In (A), each dot represents the standardized difference of the means for a single covariate before and after
15 625 stratification on the propensity score.

16 626 In (C), each blue dot is a negative control. The area below the dashed line indicates estimates with $p < 0.05$
17 627 and the orange area indicates estimates with calibrated $p < 0.05$.
18 628

19 629 **Figure 3.** Effectiveness of Pfizer-BioNTech and Moderna vaccines over six 7-day intervals after 1st dose,
20 630 % and 95% CI for COVID-19 infection (A) and COVID-19 hospitalization (B).
21 631

22 632 **Figure 4.** Chart review of COVID-19 cases (defined as a positive COVID-19 test) during week one,
23 633 vaccinated and unvaccinated patients.
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25 635

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		
	Target	Comparator	Std. diff	Target	Comparator	Std. diff
<i>Pfizer-BioNTech COVID-19 vaccine</i>						
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	
<i>Age group, %</i>						
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
<i>Gender, %</i>						
Female	63.7	57.8	0.12	61.4	62	-0.01
<i>Race, %</i>						
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
<i>Medical history, %</i>						
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

<i>Race, %</i>						
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
<i>Medical history, %</i>						
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
<i>Janssen COVID-19 vaccine</i>						
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	
<i>Age group, %</i>						

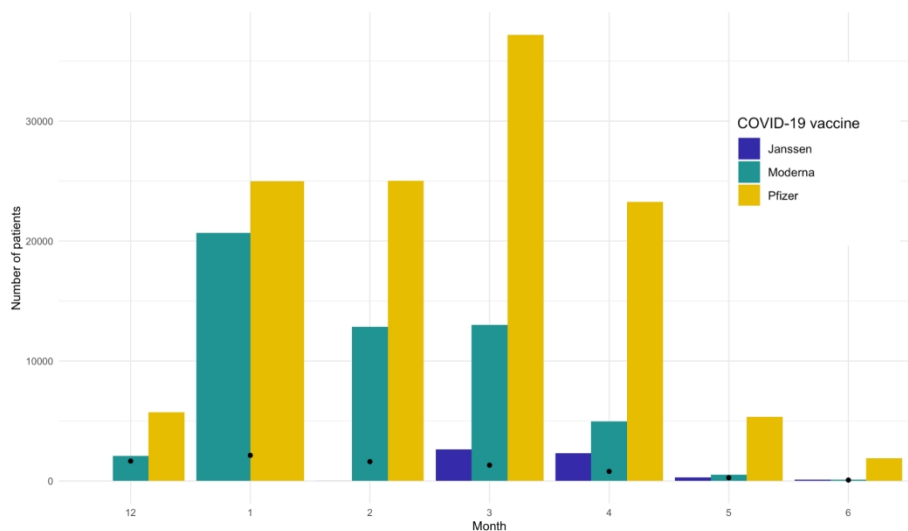
10-19	0.8	0.8	0.00	0.8	0.8	0.00
20-49	43.9	43	0.02	44.2	43.9	0.01
50-64	31.7	31.7	0.00	31.8	31.3	0.01
65-74	11.6	12.2	-0.02	11.5	12	-0.02
75-84	7.6	7.9	-0.01	7.2	7.9	-0.03
>84	4.3	4.3	0.00	4.2	4	0.01
<i>Gender, %</i>						
Female	63.4	63.2	0.01	63.5	61.1	0.05
<i>Race, %</i>						
race = Asian	3.6	1.7	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
<i>Medical history, %</i>						
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

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Influenza vaccination within a year prior	12.5	8.0	0.15	10.1	11.4	-0.04
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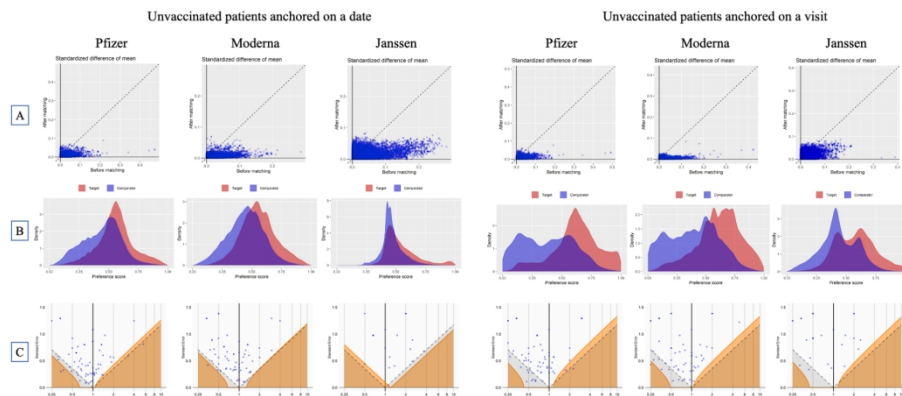
- * Hypertensive disorder includes primary and secondary hypertension
- ** Renal impairment includes acute and chronic renal failure (prerenal and renal);
- *** Heart disease includes cardiac arrhythmias, heart valve disorders, coronary arteriosclerosis, heart failure, cardiomyopathies, etc.

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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)

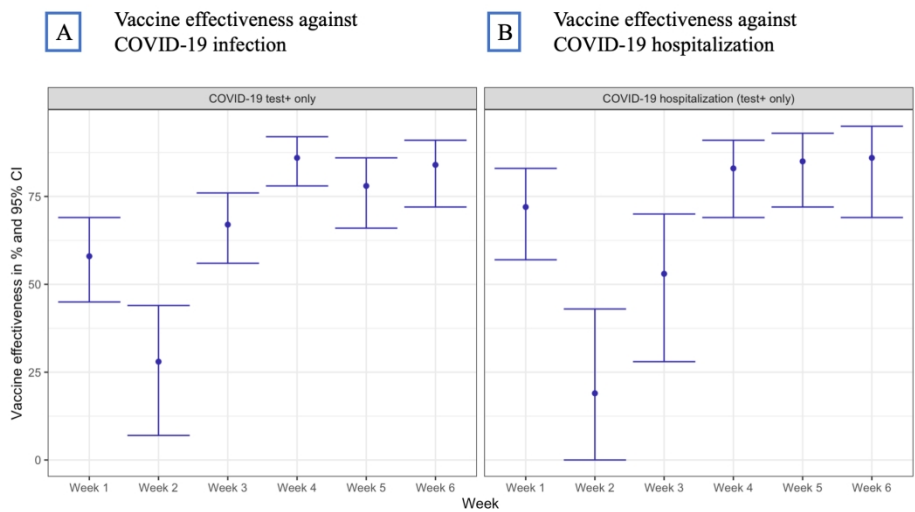


23 Diagnostics for the absolute effectiveness study comparing the cohort vaccinated with at least one dose of
 24 Pfizer, Moderna or Janssen COVID-19 vaccines and unvaccinated cohort anchored on a date or on a visit:
 25 (A) covariate balance before and after propensity score matching, (B) preference score balance and (C)
 26 effect of negative control calibration displaying effect estimate and standard error.

27 In (A), each dot represents the standardized difference of the means for a single covariate before and after
 28 stratification on the propensity score.

29 In (C), each blue dot is a negative control. The area below the dashed line indicates estimates with $p < 0.05$
 30 and the orange area indicates estimates with calibrated $p < 0.05$.

31 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)

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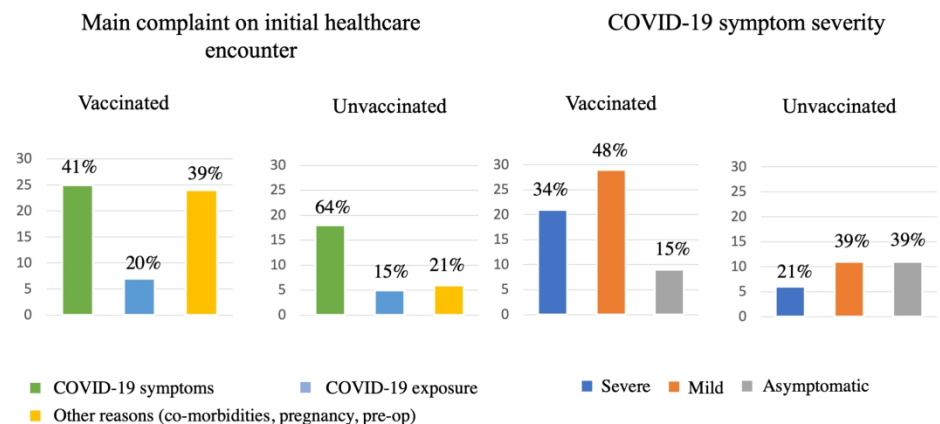


Chart review of COVID-19 cases (defined as a positive COVID-19 test) during week one, vaccinated and unvaccinated patients.

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.

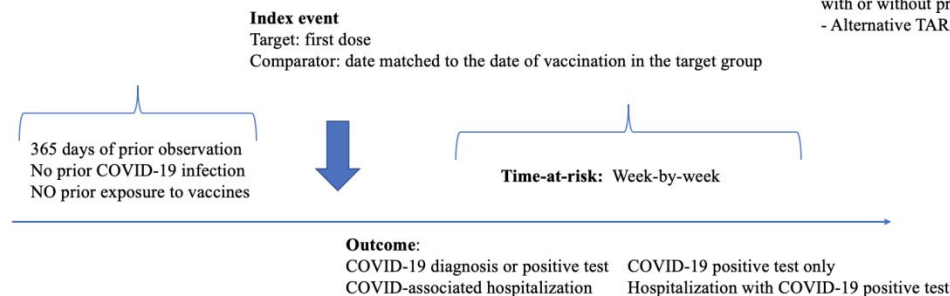
Appendix 2. Retrospective cohort COVID-19 vaccine effectiveness study design overview.

Main analysis

Target: patients with at least one dose (Ad26.COV2.S BNT162b2 and mRNA-1273) located in NYC
Comparator: unvaccinated patients matched on the date of vaccination located in NYC

Sensitivity analyses

- Alternative comparator: Patients matched on the visit
- Alternative target: fully vaccinated patients
- Alternative target and comparator: patients with or without prior COVID-19
- Alternative TAR: 1 day– 365 days



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	<p>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:</p> <ul style="list-style-type: none"> - 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 <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>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</p>
Comparator cohorts	<p>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.</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 sensitivity analysis we applied the abovementioned criteria with adding COVID-19 diagnosis as an alternative for positive COVID-19 test.</p> <p>Links:</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/425</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/422</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

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 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

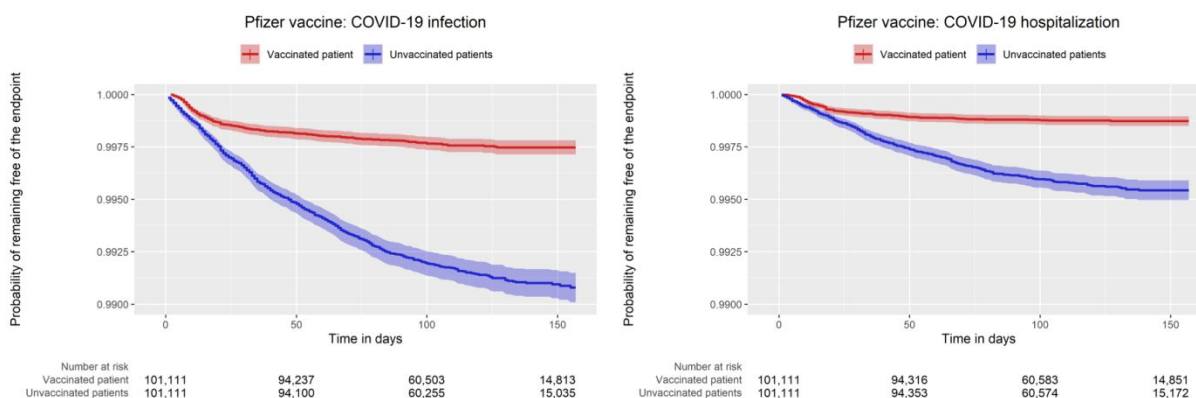
Link to the original list of negative controls used in EUMAEUS study: https://ohdsi-studies.github.io/Eumaeus/Protocol.html#8_Research_Methods

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.

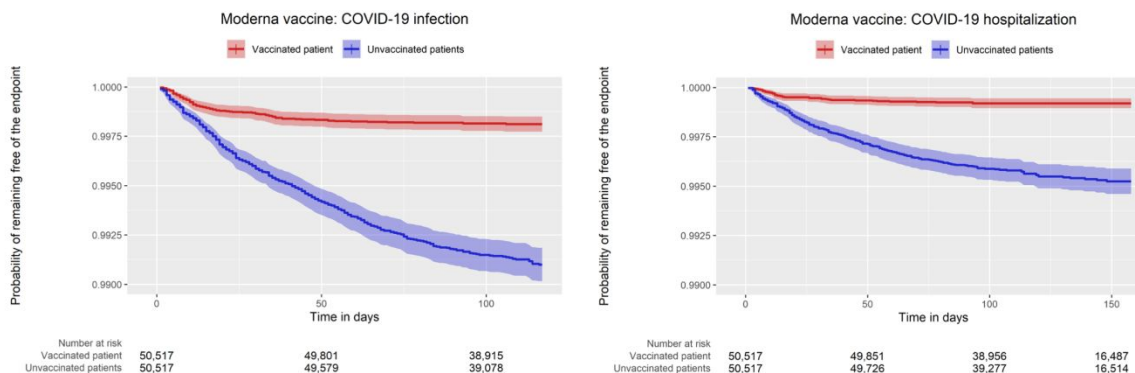
	Pfizer-BioNTech	Moderna	Pfizer-BioNTech and Moderna	Unvaccinated patients
Total	36	25	61	28
Average age	65	67.8	65.8	58
<i>COVID-19 symptoms</i>				
Severe	14 (39%)	7 (28%)	21 (34%)	6 (21%)
Mild	18 (50%)	11 (44%)	29 (48%)	11 (39%)
Asymptomatic	2 (6%)	7 (28%)	9 (15%)	11 (39%)
<i>Reason for coming for initial healthcare encounter</i>				
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%)

<i>Type of initial healthcare encounter</i>				
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%)

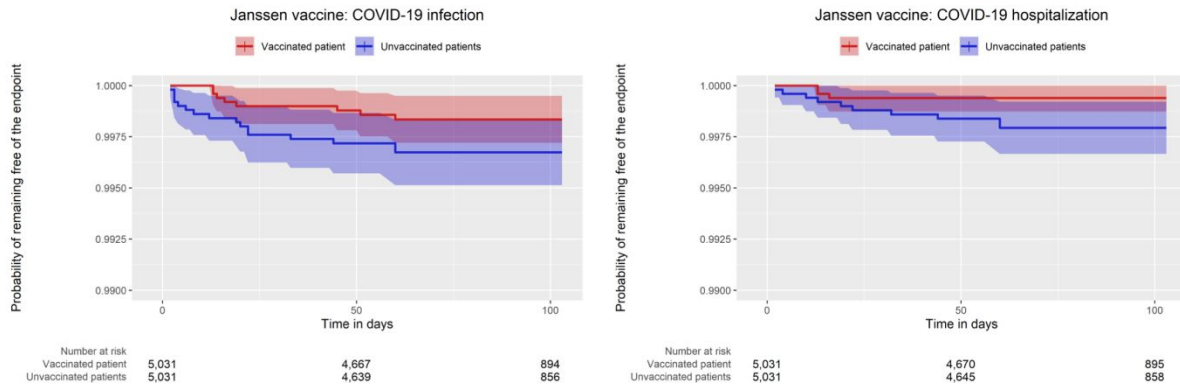
Appendix 6. Kaplan-Meier curves for effectiveness of COVID-19 Pfizer-BioNTech vaccine for time-at-risk of 1 day – 365 days after the first dose compared to the unvaccinated patients residing in New York City.



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.

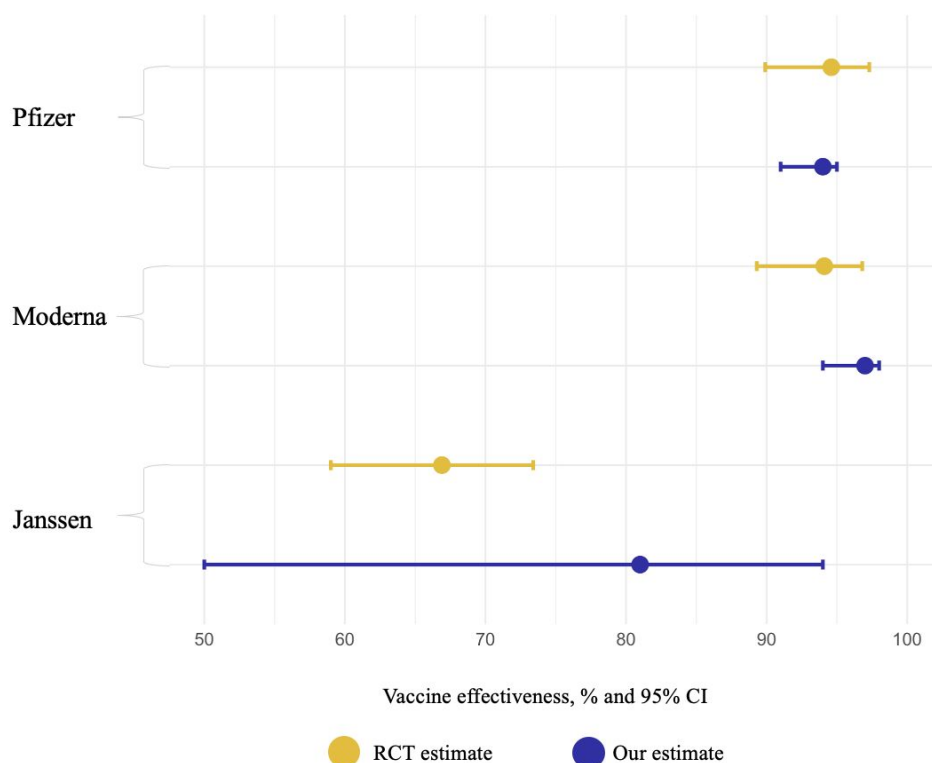
	COVID-19 infection		COVID-19 hospitalization		COVID-19 positive test only		COVID-19 positive test only hospitalization	
	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value	VE (95% CI), %	P-value
Pfizer-BioNTech	42 (37 – 47)	<0.01	63 (56–70)	<0.01	71 (66 – 75)	<0.01	69 (62 – 75)	<0.01
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

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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 (b) For matched studies, give matching criteria and number of exposed and unexposed	5
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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	6-7 6-7 - NA 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (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- 20 8, 18
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

1	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	8, supplementary materials
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
4	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
5	Discussion			
6	Key results	18	Summarise key results with reference to study objectives	10
7	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
8	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
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
10	Other information			
11	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.

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6 3 **COVID-19 vaccination effectiveness rates by week and sources of bias: a retrospective cohort study**
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34 **ABSTRACT**

36 **Objective**

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

40 **Design and setting**

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

44 **Outcomes and measures**

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

50 **Results**

51 The study included 179,666 patients. We observed increasing effectiveness after the first dose of mRNA
52 vaccines with week six effectiveness approximating 84% (95% CI 72-91%) for COVID-19 infection and
53 86% (95% CI 69-95) for COVID-19-associated hospitalization. When analyzing unexpectedly high
54 effectiveness in week one, chart review revealed that vaccinated patients are less likely to seek care after
55 vaccination and are more likely to be diagnosed with COVID-19 during the encounters for other
56 conditions. Secondary analyses highlighted potential outcome misclassification for ICD10-CM diagnosis,
57 the influence of excluding patients with prior COVID-19 infection and anchoring in the unexposed group.
58 Overall vaccine effectiveness in fully vaccinated patients matched the results of the randomized trials.

60 **Conclusions**

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

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3 **68 Strengths and limitations of this study**
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6 **69** - This study thoroughly investigates weekly COVID-19 vaccine effectiveness using methods to reduce
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8 **70** potential confounding (large-scale propensity score matching, negative control calibration) and
9
10 **71** accompanied by manual chart review of the cases in week one

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12 **72** - The study includes a range of secondary analyses for different patient populations, anchoring strategies
13
14 **73** and outcome definitions.

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16 **74** - The study was carried out using routinely collected clinical practice data, which represents real-world
17
18 **75** patients, but also implies a risk of misclassification.

19
20 **76** **Word count:** 3483

21
22 **77** **Keywords:** COVID-19, Epidemiology, Health Informatics, Bias
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99 BACKGROUND

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

107
108 There have been recent observational studies, which have shown effectiveness similar to the randomized
109 clinical trials (RCTs) across the globe, both test-negative and cohort (5–12), followed by studies across
110 different patient populations, variants and number of doses (13–17).

111
112 Nevertheless, the challenges associated with the use of observational data such as incomplete data
113 capture, outcome misclassification and appropriate comparator sampling can undermine the results of the
114 studies if such biases are not accounted for (18). For COVID-19 vaccines, questions associated with
115 vaccine status misclassification (19), matching vaccinated and unvaccinated populations (6), addressing
116 disease risk factor confounding and ascertainment bias (20,21) and others were raised.

117
118 One of such questions is COVID-19 vaccine effectiveness during the first two weeks following the first
119 dose. Studies have shown contradicting results for Pfizer–BioNTech vaccine with effectiveness ranging
120 from moderate effectiveness of 52% (3) to very high effectiveness of 92.6% (22). Similarly, a recent
121 study showed an unexplained high effectiveness of Janssen vaccine during week one (23). Other studies
122 simply excluded the first week(s) from the time-at-risk (9,13,24–26). While week one lack of
123 effectiveness has been suggested as a metric for lack of confounding in the long-term vaccine
124 effectiveness studies, the reasons for high effectiveness and its impact on the validity of the conclusions
125 regarding the overall effectiveness remain unclear (9).

126
127 The goal of this study was to examine COVID-19 vaccine effectiveness over six 7-day intervals after the
128 first dose to assess underlying bias associated with the use of observational data for short-term vaccine
129 effectiveness and its impact on long-term vaccine effectiveness estimates . We employed large-scale
130 propensity score matching and many negative controls to reduce and assess bias and leveraged a range of
131 secondary analyses as well as manual review of the COVID-19 infection cases in week one to examine
132 health-seeking behavior of vaccinated and unvaccinated patients.

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3 1334 134 **METHODS**5 135
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8 138 *Main design*9 139
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11 138 For this retrospective observational cohort study, we used electronic health records from the Columbia
12 139 University Irving Medical Center (CUIMC) database (Appendix 1), which has an ongoing automated
13 140 connection to New York City and State public health department vaccine registries and includes all
14 141 within-state vaccinations for our population. The data were translated to the OMOP Common Data Model
15 142 version 5 as was used in multiple studies (27).
16 143

17 144

18 144 For our main analysis, we studied two mRNA vaccines (Pfizer-BioNTech or Moderna). The exposed
19 145 group included patients indexed on the first dose of one of the corresponding vaccines with no prior
20 146 COVID-19 infection and no previous exposure to other COVID-19 vaccines. For the unexposed group,
21 147 we selected unvaccinated patients and set their index date to a date (not necessarily with any medical
22 148 event) that matched the index date of one of the exposed group participants. Both the exposed and
23 149 unexposed groups had at least 365 days of prior observation and primarily resided in New York City
24 150 according to their zip code. Patients who did not reside in New York were excluded from the study to
25 151 ensure reliable vaccination data capture.
26 152

27 153

28 153 Outcomes of interest included a) COVID-19 infection defined as a positive COVID-19 test (reverse-
29 154 transcriptase–polymerase-chain-reaction assay) or a diagnostic code of COVID-19 and b) COVID-19
30 155 hospitalization defined as an inpatient visit associated with a COVID-19 positive test or diagnosis within
31 156 30 days prior or during the visit. Upon further examination of the results, we added two other outcomes:
32 157 a) COVID-19 positive test only and b) COVID-19 hospitalization associated with a positive COVID-19
33 158 test. Design overview is provided in Appendix 2; code lists and links to phenotype definitions are
34 159 provided in Appendix 3.
35 160

36 161

37 161 We calculated vaccine effectiveness during six consecutive 7-day intervals after the first dose. Within
38 162 each interval, patients were followed-up until an outcome, end of the period or death, whichever came
39 163 earlier. Additionally, given the results for vaccine effectiveness during week one following the first dose,
40 164 we conducted chart review for patients with a COVID-19 positive test recorded in the abovementioned
41 165 period. We reviewed all cases for the vaccinated population as well a random sample of the cases in the
42 166 unvaccinated population and extracted main complaint, COVID-19 history, including symptoms (fever,
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3 167 shortness of breath, sore throat, cough etc.), severity, time from the first symptom to encounter and
4 168 COVID-19 exposure.

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8 170 ***Secondary analyses***

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11 172 We also conducted a set of secondary analyses. First, given that the published studies focused on patients
12 173 without prior COVID-19 infection, we studied all eligible patients regardless of their previous COVID-19
13 174 status.

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16 176 As the strategy for unvaccinated group index date selection (anchoring) has been reported to influence
17 177 incidence of outcomes and baseline characteristics (28,29), we additionally tested unexposed patients
18 178 indexed on a healthcare encounter matching the index date of one of the exposed group participants
19 179 within 3 days corridor, with at least 365 days of prior observation located at New York.

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22 181 Finally, we assessed vaccine effectiveness in patients with at least one dose of a COVID-19 vaccine and
23 182 in fully vaccinated patients over all available follow-up to compare the estimates to the results of the
24 183 RCTs. The latter was defined as 14 days after the second dose of Pfizer-BioNTech or Moderna vaccines
25 184 or first dose of Janssen vaccine. For each comparison we estimated hazard ratios (HRs) and constructed
26 185 Kaplan-Meier plots as described below.

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31 187 ***Statistical methods***

32 188 For each analysis, we fitted a lasso regression model to calculate propensity score and match patients in
33 189 each exposed and unexposed group with 1:1 ratio. For large-scale propensity score model we used all
34 190 demographic information, index year and month, as well as the number of visits, condition and drug
35 191 groups, procedures, device exposures, laboratory and instrumental tests and other observations over long
36 192 (prior year) and short-term period (prior month) (30,31).

37
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39 193 For each outcome, we fitted a Cox proportional hazards models to estimate HRs and constructed Kaplan-
40 194 Meier plots. Empirical calibration based on the negative control outcomes was used to identify and
41 195 minimize any potential residual confounding by calibrating HRs and 95% confidence intervals (CIs)
42 196 (32,33). Vaccine effectiveness was calculated as $100\% \times (1 - \text{hazard ratio})$.

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3 197 All analyses were supported by the OHDSI Infrastructure (CohortMethod package, available
4 198 at <https://ohdsi.github.io/CohortMethod/>, FeatureExtraction available at
5
6 199 <https://ohdsi.github.io/FeatureExtraction/> and the Cyclops package for large-scale regularized regression
7
8 200 (34) available at <https://ohdsi.github.io/Cyclops/>.

201 ***Diagnostics***

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

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

214 **Patient and public involvement**

215
216 No patient involved

217
218

219 **RESULTS**

221 ***Patient characteristics***

222
223 In total, we identified 179,666 patients with at least one dose of COVID-19 vaccine in January-May 2021:
224 121,771 patients for Pfizer-BioNTech, 52,728 for Moderna and 5,167 for Janssen (Table 1). The sample
225 included patients from all age groups, with or without co-morbidities captured in inpatient and outpatient
226 settings.

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3 227 We observed that unexposed patients (Table 1) were on average younger and had fewer co-morbidities
4 228 and less exposure to various drugs prior to matching. We were able to achieve balance on all covariates
5 229 (up to 54,987 covariates, standardized difference of means less than 0.1) with propensity score matching.
6 230 Figure 1 presents the covariate balance and propensity score balance plots showing that anchoring
7 231 unvaccinated patients on a date allowed us to achieve better balance compared to anchoring patients on a
8 232 visit.
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14 234 Patients vaccinated with Pfizer-BioNTech had a similar distribution of baseline characteristics compared
15 235 to the patients vaccinated with Moderna but differed from the patients vaccinated with Janssen. On
16 236 average, the latter group was older, had more patients with race recorded as Black, and had more co-
17 237 morbidities such as diabetes mellitus or hypertensive disorder (Table 1).
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22 239 When investigating the vaccination pathways, we discovered that 112,963 patients (93% of patients with
23 240 at least one dose of Pfizer-BioNTech) had 2 doses of Pfizer-BioNTech and 42,384 (80%) patients had 2
24 241 doses of Moderna. We found 344 and 291 patients with 3 doses of the corresponding vaccines and 440
25 242 patients having mixed Pfizer-BioNTech, Moderna and Janssen vaccines in different combinations.
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30 244 Within our database, Moderna was administered early on with a peak in January 2021 (Figure 2), while
31 245 Pfizer-BioNTech and Janssen vaccinations peaked in April. It was reflected in the follow-up time with
32 246 Moderna patients having on average longer follow-up with some individuals having up to 5.8 months of
33 247 post-observation.
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36 249 *Main week-by-week effectiveness analysis*

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41 251 Figure 3 shows vaccine effectiveness over six 7-day intervals for patients vaccinated with at least one
42 252 dose of Pfizer-BioNTech or Moderna (160,114 patients) compared to unvaccinated patients (115,689).
43 253 Due to the small sample size, we were not able to obtain stable week-by-week estimates for Janssen.
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46
47 255 While week one was characterized by unexpectedly high effectiveness (58%, 95% CI 45-69% against
48 256 COVID-19 infection and 72%, 95% CI 57-83% against COVID-19 associated hospitalization), we
49 257 observed plausible increasing effectiveness beginning week 2 with the effectiveness on week 6
50 258 approximating 84% (95% CI 72-91%) for COVID-19 infection and 86% (95% CI 69-95) for COVID-19-
51 259 associated hospitalization.
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3 261 We then looked at the week one COVID-19 infection cases to explain high effectiveness (Figure 4). A
4 262 chart review of week one positive COVID-19 tests revealed a high proportion of unvaccinated patients
5 263 seeking care related to COVID-19 symptoms or COVID-19 exposure (85% in total) compared to only
6 264 69% of vaccinated patients. Initial healthcare encounters in vaccinated population were oftentimes related
7 265 to other medical reasons such as co-morbid conditions or surgeries (39% compared to 21% in
8 266 unvaccinated population, Appendix 5). Moreover, an observed gap between symptom onset and an initial
9 267 healthcare encounter was more pronounced in the vaccinated cohort as the patients attributed their
10 268 symptoms to temporal vaccine side effects as opposed to COVID-19 infection.
11 269

12 270 When looking at the severity of COVID-19 symptoms at the initial encounter during week one after the
13 271 index date, we observed that the unvaccinated cohort had a higher proportion of asymptomatic cases
14 272 (39% compared to 11%) while the vaccinated population had more severe or mild cases (34% and 48%
15 273 respectively).
16 274

17 275 *Secondary analysis*

18 276

19 277 As cohort analysis allows us to construct Kaplan-Meier curves to assess effectiveness over time, we also
20 278 looked at the effectiveness during the year after the first dose (Appendix 6-8). We observed similar trends
21 279 with all three vaccines being less effective during the first month after the first dose. After that, Pfizer-
22 280 BioNTech and Moderna were highly effective against both COVID-19 infection and COVID-19
23 281 associated hospitalization, while Janssen vaccine exhibited a wide range of effectiveness (Appendix 9).
24 282

25 283 The results for fully vaccinated patients with time-at-risk starting at the full vaccination matched the
26 284 results of the clinical trials for corresponding vaccines (detailed estimates are provided in Appendix 10
27 285 and 11).
28 286

29 287 Our initial design included a positive COVID-19 test or a diagnostic code as an outcome. Upon further
30 288 case examination, we discovered that COVID-19 diagnostic codes in the CUIMC data were partially
31 289 assigned to the patients with negative COVID-19 tests on or immediately following the date of diagnosis.
32 290 In that case, ICD10CM code U07.1 “Disease caused by Severe acute respiratory syndrome coronavirus 2”
33 291 was entered in the system for billing purposes (COVID-19 molecular or antibody tests) or for COVID-19
34 292 sequelae. We, therefore, focused on positive COVID-19 test only for our primary outcome, which led to
35 293 higher effectiveness for all vaccines compared to using both positive test and diagnosis (Appendix 9).
36 294

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3 295 Finally, exclusion of patients with prior COVID-19 infection in our main analysis resulted in higher
4 296 effectiveness. Inclusion of patients regardless of their prior COVID-19 status led to a small decrease in
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6 297 observed effectiveness (Appendix 12) for both COVID-19 infection and hospitalization in patients
7
8 298 vaccinated with Moderna or Janssen.

9 299

10 300 **DISCUSSION**

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14 302 In this retrospective cohort study, we examined the effectiveness of COVID-19 mRNA vaccines over six
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16 303 7-day intervals after the first dose. We scrutinized the effectiveness of the mRNA vaccines following the
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18 304 first dose and confirmed the findings of moderate vaccine effectiveness during the first two weeks. For
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20 305 week one following the first dose we discovered previously uncaptured differential biases in vaccinated
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22 306 and unvaccinated populations resulting in high vaccine effectiveness. Other researchers suggested that the
23
24 307 difference between vaccinated and unvaccinated groups can be mitigated by adjusting for previous
25
26 308 healthcare utilization such as number of visits before baseline, co-morbidities or prior vaccination
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28 309 behavior (6,13,24). Nevertheless, the confounding we observed remains even upon controlling for a large
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30 310 number of covariates including those above.

31 311

32 312 Vaccination directly influenced the attitude of patients towards their symptoms, causing a delay in
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34 313 seeking care and a higher symptom severity threshold needed to seek care or get tested. On contrary,
35
36 314 vaccinated patients in other studies had higher rates of testing compared to unvaccinated (20,38). This
37
38 315 indicates that patients' attitude toward risk of infection and testing may vary geographically and over
39
40 316 time. Similarly, frequency of testing may depend on local policies and practices.

41 317

42 318 In unvaccinated patients, mild COVID-19 related symptoms were the reason to seek care; in vaccinated
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44 319 patients such cases were mainly captured upon seeking outpatient and inpatient care for other conditions.
45
46 320 For example, vaccinated patients could be hospitalized for elective surgery or delivery and be tested
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48 321 positive for COVID-19 on the day of admission or later on. Differential symptom severity was previously
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50 322 reported for other vaccines (39) and may affect any observational study that uses hospitalization as a
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52 323 surrogate for COVID-19 severity as it can be hard to accurately identify the main reason for
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54 324 hospitalization in structured data.

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56 326 Previous research suggested that vaccinated patients do not have an increase in the number of cases
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58 327 immediately following vaccination as they are unlikely to get vaccinated if sick (9,40). Our review of the

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3 328 cases in week one adds to ‘healthy vaccinee’ effect by showing that vaccinated patients are more likely to
4 329 attribute their symptoms to common vaccine side effects and, therefore, are less likely to seek care.

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8 331 Nevertheless, even when this differential bias is present, the estimates of the COVID-19 vaccine
9 332 effectiveness in subsequent weeks still match the results of the RCTs. This indicates that high
10 333 effectiveness during week one following vaccination does not necessarily undermine the estimates of
11 334 subsequent vaccine effectiveness. On the other hand, we argue against using estimates of vaccine
12 335 effectiveness within a short period after the vaccination as a negative control as the differences between
13 336 the groups observed in this study are likely to be time-variant and may diminish over time (41).

14 337
15
16 338 Our secondary analyses discovered several challenges and potential biases that must be accounted for
17 339 when conducting vaccine effectiveness studies on observational data. First, we observed that outcome
18 340 definitions are prone to measurement error, which has not been studied thoroughly. Some of the published
19 341 studies used ICD-10 or ICD-10(CM) codes to identify COVID-19 outcomes (42–44). We found that the
20 342 specifics of data capture and billing processes were associated with some patients having assigned
21 343 COVID-19 diagnosis codes for billing for tests rather than as an indicator of active disease. Another
22 344 reason for assigning the code was COVID-19 sequela, where the actual date of COVID-19 infection could
23 345 have been anywhere from 6 months to a couple of weeks in the past. Some researchers have previously
24 346 reported high positive predictive value of ICD-10 diagnostic codes for COVID-19, which points out that
25 347 index date misclassification should be scrutinized in each institution participating in the analysis to make
26 348 valid inferences (45,46).

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28
29 350 Second, inclusion or exclusion of patients with prior COVID-infection influenced estimated effectiveness.
30 351 We observed that inclusion of patients with prior COVID-19 leads to lower effectiveness for all vaccines
31 352 regardless of the outcome definition.

32 353
33
34 354 Third, an appropriate index event (anchor) for the unvaccinated cohort must be chosen to represent a
35 355 counterfactual for vaccination (29,47). In our study, we confirmed that an arbitrary date represents a
36 356 better counterfactual than a medical visit for COVID-19 vaccination, which is reflected in propensity
37 357 score balance and covariate balance. Nevertheless, other institutions may have different vaccination
38 358 pathways such as vaccination on discharge, which can make a visit a better counterfactual for vaccination.
39 359 More generally, completeness of vaccination data capture is a crucial feature that influences the
40 360 robustness of the study. While CUIMC data ensures complete exposure capture by linking EHR to the

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3 361 City and State Registries, the researchers should exhibit caution with conducting studies on the data
4 362 sources with unknown vaccination capture.

5 363
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8 364 In general, our findings support the RCTs and previously published post-marketing studies for all three
9 365 vaccines. Larger sample size for patients vaccinated with COVID-19 mRNA vaccines allowed us to have
10 366 more power, which resulted in overlapping yet narrower confidence intervals compared to the RCTs. On
11 367 the other hand, our study had fewer patients with the Janssen vaccine, which resulted in wider yet
12 368 overlapping intervals compared to the Janssen's vaccine RCT (1,2,7). Nevertheless, an indirect
13 369 comparison of these vaccines may not be accurate due to the differences in the populations we observed
14 370 in our study. First, patients vaccinated with Janssen were substantially different from mRNA patients: on
15 371 average, they were older, had a higher proportion of patients with race recorded as Black and had more
16 372 comorbidities. Therefore, comparative effectiveness studies of Janssen and mRNA vaccines require
17 373 robust techniques such as large-scale propensity matching to ensure valid comparison. Second, while
18 374 Moderna and Pfizer patients had similar baseline characteristics, the temporal distribution of vaccinations
19 375 in CUIMC data differ. Moderna vaccine was administered early on in 2021 with the peak in January,
20 376 while Pfizer vaccination peaked in April. Given the varying baseline COVID-19 prevalence, a
21 377 comparison of mRNA vaccines requires matching patients on calendar month to account for this potential
22 378 bias. These vaccines also had different administration pathways in our system. As opposed to Pfizer
23 379 vaccine, which was administered at Columbia University Irving Medical Center/New York-Presbyterian
24 380 sites to all patients over a prolonged period, Moderna vaccination was performed elsewhere and recorded
25 381 for actively observed patients. Such patients were more likely to get tested or receive care outside of our
26 382 healthcare system.

27 383

28 384 **LIMITATIONS**

29 385

30 386 Due to observational nature of the study, the data sources may not have complete capture of patient
31 387 conditions as the patients could seek care outside of the hospital system. While our outcome phenotype
32 388 algorithms may be subject to measurement error, we provided additional analyses with alternative
33 389 outcome definitions. Exposure misclassification was mitigated by having free and available COVID-19
34 390 testing and COVID-19 vaccination in Columbia University Irving Medical Center/New York-
35 391 Presbyterian sites as well as by having data capture from New York City and State Immunization
36 392 Registries. Along with availability of testing, COVID-19 baseline infection rate difference was mitigated
37 393 by matching the exposed and unexposed groups on the index date and using the index month as a
38 394 covariate in propensity score model. We attempted to address potential differences between exposed and

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3 395 unexposed groups by selecting a large number of covariates in our propensity score model such as
4 396 number of visits, procedure and drug utilization, prior vaccine behavior, race and others. Nevertheless, we
5 397 did not have data for social interactions, adherence to preventive measures and policies, which could
6 398 affect likelihood of COVID-19 infection and testing.
9 399

11 400 The results of the study may not be generalizable to other countries or settings with different vaccine
12 401 administration practices and policies. Finally, the study period did not allow us to stratify the results by
13 402 COVID-19 variants, which limits generalizability of findings to other variants.
16 403
17 404

19 405 **CONCLUSIONS**

20 406
22 407 Observational data can be used to ascertain vaccine effectiveness if potential biases such as exposure and
23 408 outcome misclassification are accounted for, and appropriate anchoring event is selected. When analyzing
24 409 vaccine effectiveness researchers need to scrutinize the data to ensure that compared groups exhibit
25 410 similar health seeking behavior and are equally likely to be captured in the data and report their findings.
26 411 Specifically for COVID-19 vaccines, an arbitrary date for the index date in unvaccinated patients
27 412 represents a better counterfactual for vaccination than a healthcare encounter. Effectiveness over the first
28 413 week(s) after the vaccination should be reported even though low or high effectiveness immediately after
29 414 the vaccination may not invalidate study findings. Given the difference in temporal trends of vaccine
30 415 exposure and baseline characteristics, there is a need for large-scale direct comparison of vaccines to
31 416 examine comparative effectiveness.
38 417

39 418 **DECLARATION**

40 419
42 420 **Author contributions**

44 421
45 422 GH designed and supervised the study. AO executed the study, interpreted the results, and drafted the
46 423 manuscript. GH and AO reviewed the manuscript, approved the final version and had final responsibility
47 424 for the decision to submit for publication.
50 425

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8 431 **Declaration of interests**

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11 433 All authors have completed the ICMJE disclosure form (available on request from the corresponding
12 434 author). GH and AO receive funding from the US National Institutes of Health (NIH) and the US Food and
13 435 Drug Administration.
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17 437 **Ethical approval**

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20 439 The protocol for this research was approved by the Columbia University Institutional Review Board
21 440 (AAA07805).
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25 442 **Data sharing**

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28 444 Patient-level data cannot be shared without approval from data custodians due to local information
29 445 governance and data protection regulations.
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33 447 **Transparency declaration**

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36 449 The lead authors affirms that this manuscript is an honest, accurate, and transparent account of the study
37 450 being reported; that no important aspects of the study have been omitted; and that any discrepancies from
38 451 the study as planned (and, if relevant, registered) have been explained.
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5 616 **Figure 1.** Distribution of vaccination month for COVID-19 vaccines. Black dots represent the number of
6 617 incident COVID-19 cases (defined as a positive test) in each month.
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9 619 **Figure 2.** Diagnostics for the effectiveness study comparing the cohort vaccinated with at least one dose
10 620 of Pfizer, Moderna or Janssen COVID-19 vaccines and unvaccinated cohort anchored on a date or on a
11 621 visit: (A) covariate balance before and after propensity score matching, (B) preference score balance and
12 622 (C) effect of negative control calibration displaying effect estimate and standard error.

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14 623 In (A), each dot represents the standardized difference of the means for a single covariate before and after
15 624 stratification on the propensity score.

16 625 In (C), each blue dot is a negative control. The area below the dashed line indicates estimates with $p < 0.05$
17 626 and the orange area indicates estimates with calibrated $p < 0.05$.
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19 628 **Figure 3.** Effectiveness of Pfizer-BioNTech and Moderna vaccines over six 7-day intervals after 1st dose,
20 629 % and 95% CI for COVID-19 infection (A) and COVID-19 hospitalization (B).
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22 631 **Figure 4.** Chart review of COVID-19 cases (defined as a positive COVID-19 test) during week one,
23 632 vaccinated and unvaccinated patients.
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25 634

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	Std. diff	Vaccinated	Unvaccinated	Std. diff
<i>Pfizer-BioNTech COVID-19 vaccine</i>						
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	
<i>Age group, %</i>						
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
<i>Gender, %</i>						
Female	63.7	57.8	0.12	61.4	62	-0.01
<i>Race, %</i>						
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
<i>Medical history, %</i>						
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
<i>Medical history, %</i>						
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
<i>Janssen COVID-19 vaccine</i>						
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	
<i>Age group, %</i>						
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
<i>Gender, %</i>						
Female	63.4	63.2	0.01	63.5	61.1	0.05
<i>Race, %</i>						
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
<i>Medical history, %</i>						
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

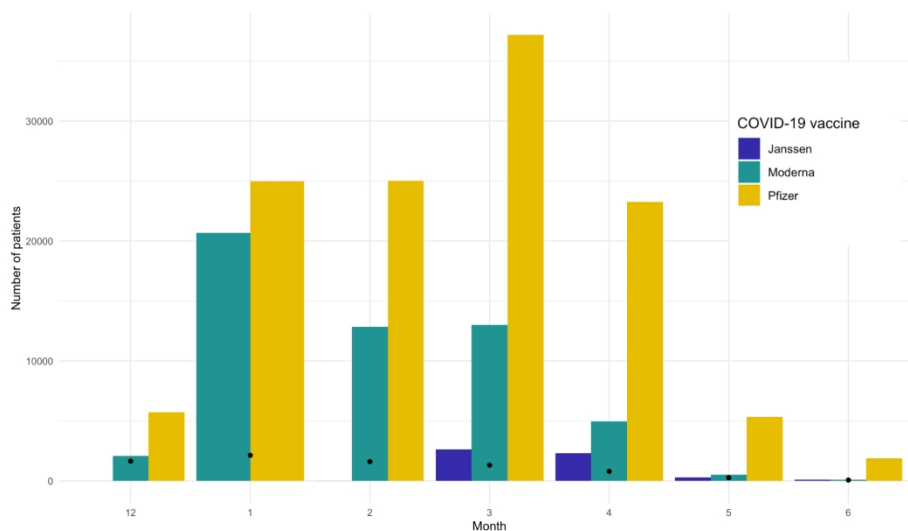
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* Hypertensive disorder includes primary and secondary hypertension

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

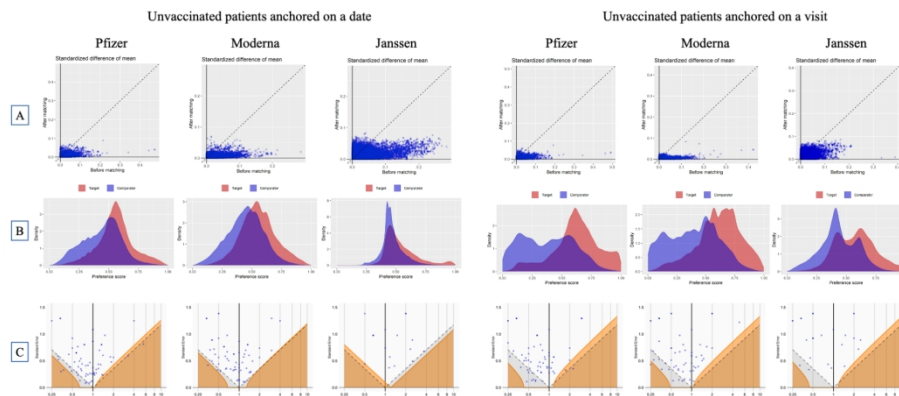
*** Heart disease includes cardiac arrhythmias, heart valve disorders, coronary arteriosclerosis, heart failure, cardiomyopathies, etc.

For peer review only



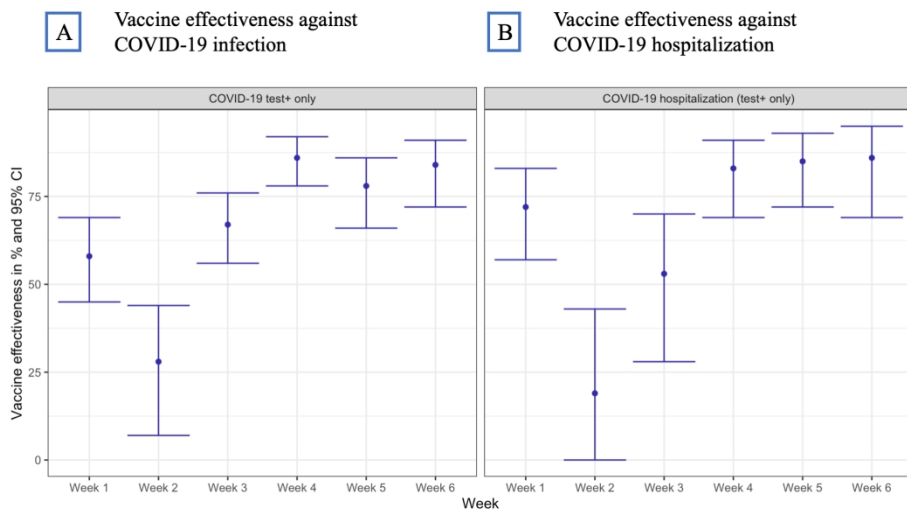
Distribution of vaccination month for COVID-19 vaccines. Black dots represent the number of incident COVID-19 cases (defined as a positive test) in each month.

338x190mm (144 x 144 DPI)



23 Diagnostics for the effectiveness study comparing the cohort vaccinated with at least one dose of Pfizer,
 24 Moderna or Janssen COVID-19 vaccines and unvaccinated cohort anchored on a date or on a visit: (A)
 25 covariate balance before and after propensity score matching, (B) preference score balance and (C) effect of
 26 negative control calibration displaying effect estimate and standard error. In (A), each dot represents the
 27 standardized difference of the means for a single covariate before and after stratification on the propensity
 28 score. In (C), each blue dot is a negative control. The area below the dashed line indicates estimates with
 29 $p < 0.05$ and the orange area indicates estimates with calibrated $p < 0.05$.

30 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)

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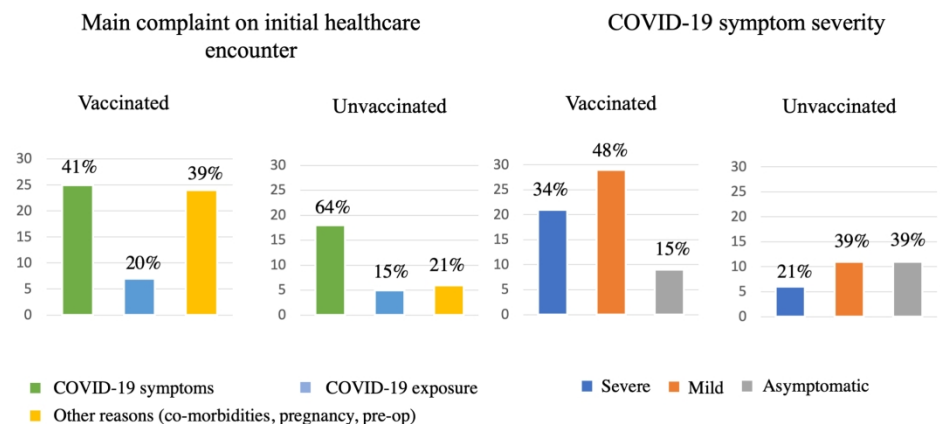


Chart review of COVID-19 cases (defined as a positive COVID-19 test) during week one, vaccinated and unvaccinated patients.

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.

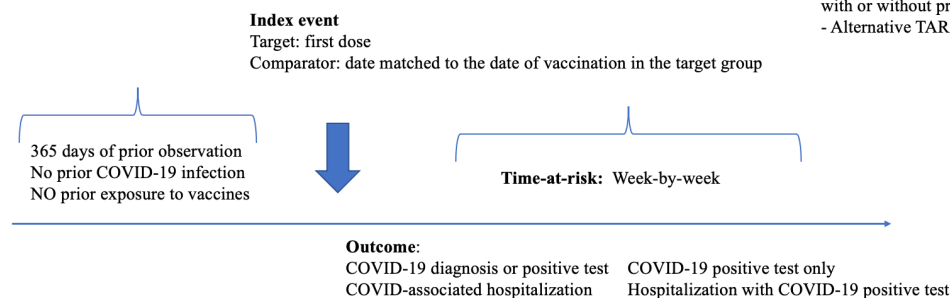
Appendix 2. Retrospective cohort COVID-19 vaccine effectiveness study design overview.

Main analysis

Target: patients with at least one dose (Ad26.COV2.S BNT162b2 and mRNA-1273) located in NYC
Comparator: unvaccinated patients matched on the date of vaccination located in NYC

Sensitivity analyses

- Alternative comparator: Patients matched on the visit
- Alternative target: fully vaccinated patients
- Alternative target and comparator: patients with or without prior COVID-19
- Alternative TAR: 1 day– 365 days



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	<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"> - 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 <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>Links:</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/498</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/494</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/497</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/418</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/417</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/420</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>https://atlas.ohdsi.org/#/cohortdefinition/425</p> <p>https://atlas.ohdsi.org/#/cohortdefinition/422</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

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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

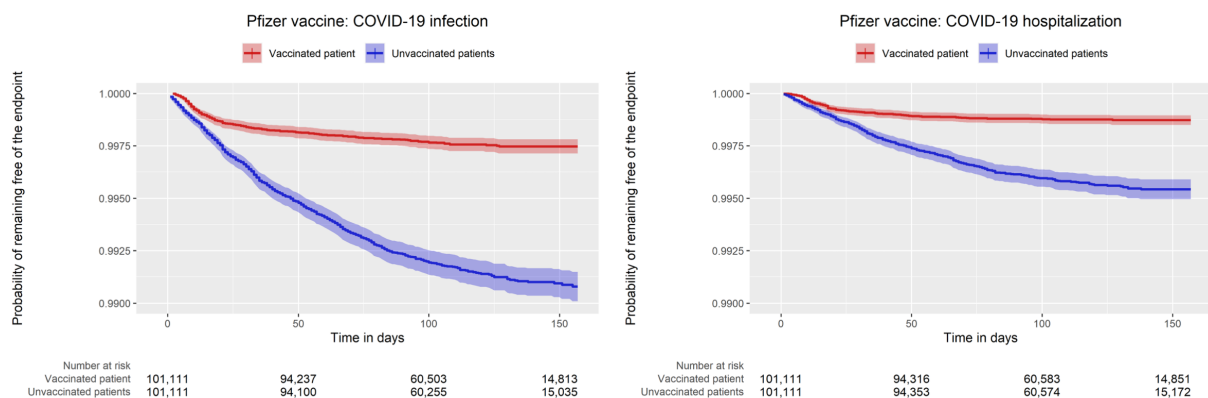
194997	Prostatitis
80286	Prosthetic joint loosening
443274	Psychostimulant dependence
314962	Raynaud's disease
37018294	Residual osteitis
4288241	Salmonella enterica subspecies arizonae infection
45757269	Sclerosing mesenteritis
74722	Secondary localized osteoarthritis of pelvic region
200348	Secondary 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

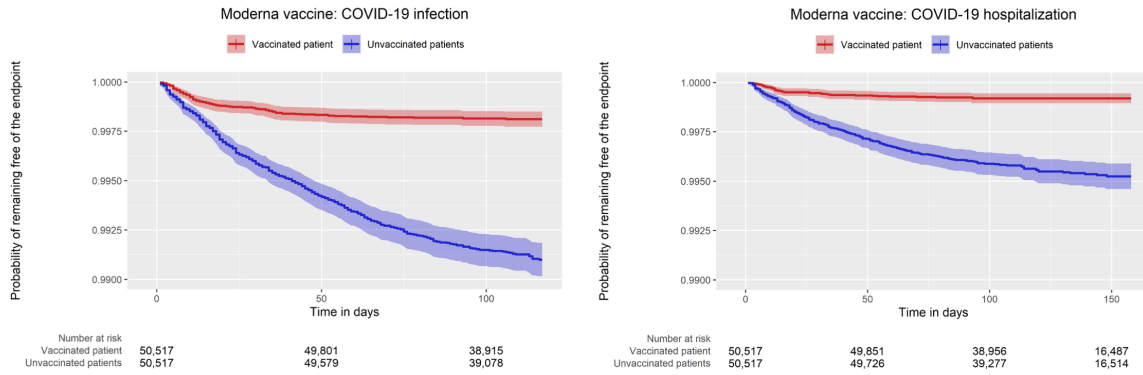
Appendix 5. Summary of manual chart review of COVID-19 infection cases during week 1 after the index date, patients vaccinated with mRNA vaccines and unvaccinated patients.

	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%)

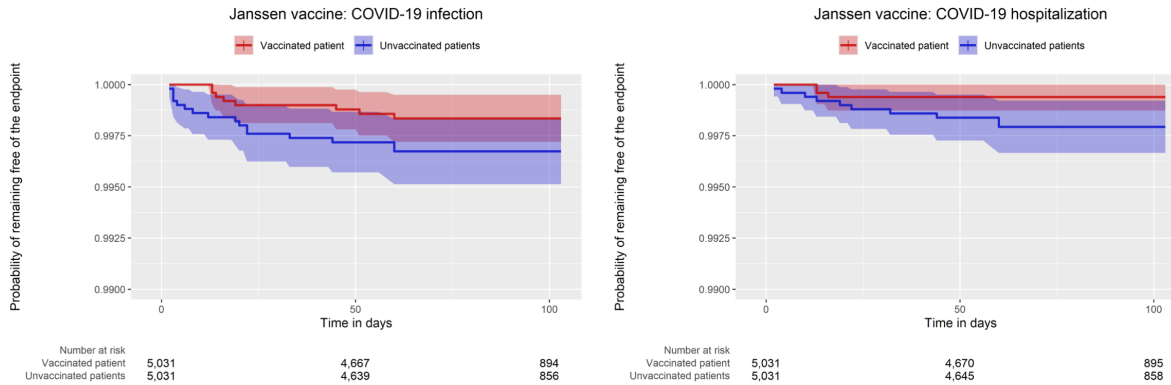
Appendix 6. Kaplan-Meier curves for effectiveness of COVID-19 Pfizer-BioNTech vaccine for time-at-risk of 1 day – 365 days after the first dose compared to the unvaccinated patients residing in New York City.



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.



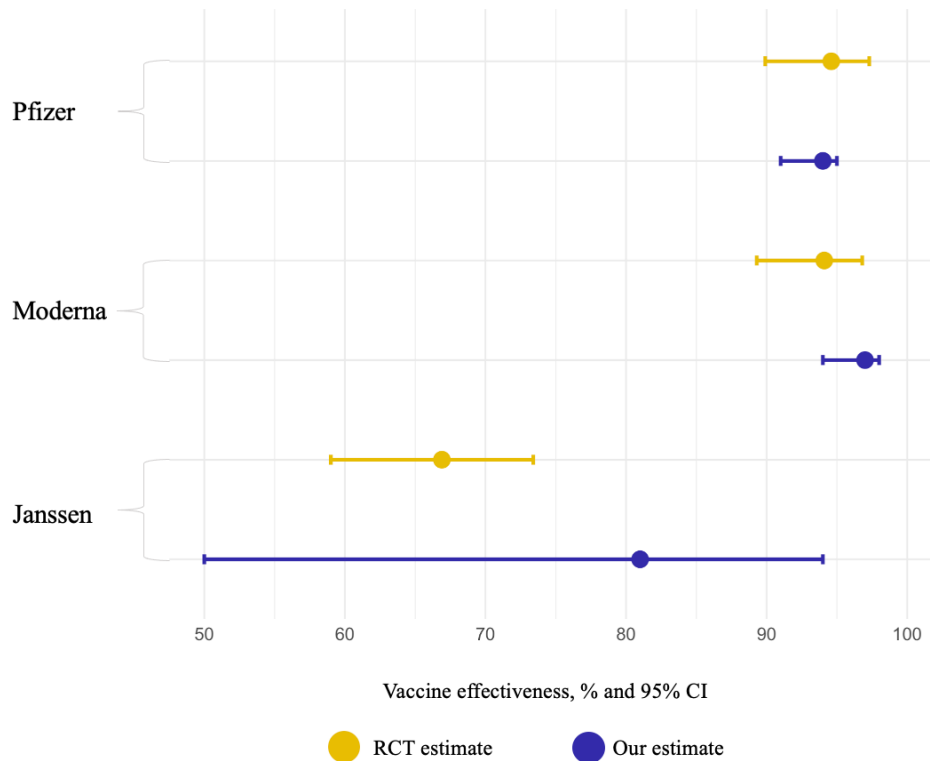
Appendix 9. Estimates for long-term effectiveness of COVID-19 vaccines for time-at-risk of 1 day – 365 days after the first dose in the vaccinated patients without prior COVID-19 infection compared to unvaccinated patients residing in NYC.

	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 (b) For matched studies, give matching criteria and number of exposed and unexposed	5
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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	6-7 6-7 - NA 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (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- 20 8, 18
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

1	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	8, supplementary materials
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
4	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
5	Discussion			
6	Key results	18	Summarise key results with reference to study objectives	10
7	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
8	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
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
10	Other information			
11	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>.