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| **Title** | CRIUS  (Comparative-effectiveness Research on Immunization Used for SARS-CoV-2) |
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**RATIONALE AND BACKGROUND**

COVID-19 vaccines shown effectiveness in preventing COVID-19 infection and complications in randomized clinical trials. Further studies on large and heterogeneous populations are required to establish vaccine effectiveness in real-world settings.

Initial research on a limited sample size (<400 patients aged ≥65 years) was performed by CDC (1) and showed adjusted vaccine effectiveness of 94% (95% CI = 49%–99%) for Pfizer-BioNTech and Moderna vaccines. In this work, we will extend the study of the abovementioned vaccines to a larger population and other age groups and examine effectiveness of the other COVID-19 vaccines used in the United States (Janssen).

We will also study the impact of COVID-19 vaccination on COVID-19 hospitalization.

**STUDY OBJECTIVES**

1. Estimating absolute effectiveness of COVID-19 vaccines

Do patients vaccinated with Pfizer-BioNTech, Moderna or Janssen COVID-19 vaccine have a different risk of COVID-19 infection or COVID-19 related hospitalization compared to unvaccinated patients?

1. Estimating comparative effectiveness of COVID-19 vaccines

Do patients vaccinated with different COVID-19 vaccines have a different risk of COVID-19 infection or COVID-19 related hospitalization compared to the other COVID vaccines?

**RESEARCH METHODS**

**Study design and settings**

This study will follow a retrospective, observational, comparative cohort design (2). We define ‘retrospective’ to mean the study will be conducted using data already collected prior to the start of the study. We define ‘observational’ to mean there is no intervention or treatment assignment imposed by the study. We define ‘cohort’ to mean a set of subjects satisfying one or more inclusion criteria for a duration of time. We define ‘comparative cohort design’ to mean the formal comparison between two cohorts, a target cohort and comparator cohort, for the risk of an outcome during a defined time-period after cohort entry.

**Data Sources**

1. Columbia University Irving Medical Center (CUIMC)

Columbia University Irving Medical Center (CUIMC) has an anonymized electronic health record data from the Columbia University Irving Medical Center and New York-Presbyterian Hospital clinical transaction-based data repository. The data are derived from a mixture of inpatient and outpatient visits, span a time period of 4 decades (1980s-present), and represent a population of 4 million patients.

All data sources have been standardized to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) (3), version 5.3. The OMOP CDM includes a standard representation of health care experiences (such as information related to drug utilization and condition occurrences), common vocabularies for coding clinical concepts, and enables consistent application of analysis across multiple disparate data (3). The completed specification for the OMOP CDM is available at: <https://github.com/OHDSI/CommonDataModel>.

**Study Populations**

1. Absolute effectiveness

The target cohorts (patients vaccinated with a) Pfizer-BioNTech, b) Moderna or c) Janssen COVID-19 vaccine) and the comparator cohorts (unvaccinated patients anchored on a) date and b) visit) as well as the outcome cohorts ( a) COVID-19 infection and b) COVID-19 hospitalization) are described in further detail below.

1. Comparative effectiveness

Target and comparator cohorts (patients vaccinated with a) Pfizer-BioNTech, b) Moderna or c) Janssen COVID-19 vaccine) for pairwise vaccine comparison are described below under numbers 1-3.

**Target Cohorts**

1. **Persons fully vaccinated with Moderna COVID-19 vaccine** (<https://atlas.ohdsi.org/#/cohortdefinition/417>)

Persons indexed on a drug exposure of Moderna COVID-19 vaccine with

* At least one drug exposure of Moderna COVID-19 vaccine within 14-56 days after the index date
* At least 14 days of observation after the index date
* No drug exposures of other COVID-19 vaccines with 120 days prior or after the index date
* persons with location in New York City, to ensure that city immunization registry record does not exist

1. **Persons fully vaccinated with Pfizer COVID-19 vaccine** (<https://atlas.ohdsi.org/#/cohortdefinition/418>)

Persons indexed on a drug exposure of Pfizer COVID-19 vaccine with

* At least one drug exposure of Pfizer COVID-19 vaccine within 14-56 days after the index date
* At least 14 days of observation after the index date
* No drug exposures of other COVID-19 vaccines with 120 days prior or after the index date
* persons with location in New York City, to ensure that city immunization registry record does not exist

1. **Persons fully vaccinated with Janssen COVID-19 vaccine:**

(<https://atlas.ohdsi.org/#/cohortdefinition/420>)

Persons indexed on a drug exposure of Janssen COVID-19 vaccine with

* At least 14 days of observation after the index date
* No drug exposures of other COVID-19 vaccines with 120 days prior or after the index date
* persons with location in New York City, to ensure that city immunization registry record does not exist

1. **Persons fully or partially vaccinated with Moderna COVID-19 vaccine**

Persons indexed on the first drug exposure of Moderna COVID-19 vaccine with

* No drug exposures of other COVID-19 vaccines with 120 days prior or after the index date
* persons with location in New York City, to ensure that city immunization registry record does not exist

1. **Persons fully or partially vaccinated with Pfizer COVID-19 vaccine**

Persons indexed on the first drug exposure of Pfizer COVID-19 vaccine with

* No drug exposures of other COVID-19 vaccines with 120 days prior or after the index date
* persons with location in New York City, to ensure that city immunization registry record does not exist

1. **Persons fully or partially vaccinated with Janssen COVID-19 vaccine**

Persons indexed on the first drug exposure of Janssen COVID-19 vaccine with

* No drug exposures of other COVID-19 vaccines with 120 days prior or after the index date
* persons with location in New York City, to ensure that city immunization registry record does not exist

**Comparator Cohorts**

***Absolute effectiveness estimation***

There is no established index date for unvaccinated comparators. In this study, we approximate the start date for every comparator person by selecting a visit or a date matching the date of vaccination in the target group. Alternative approaches will be explored.

1. Persons not exposed to any COVID-19 vaccine indexed on a visit

- index visit matched to the date of vaccination in patients in a target group as well as on their age and sex

- >=365 days of prior observation

- persons with location in New York City, to ensure that city immunization registry record does not exist

1. Persons not exposed to any COVID-19 vaccine indexed on a random date

- index date matched to the date of vaccination in patients in a target group as well as on their age and sex

- >=365 days of prior observation

- persons with location in New York City, to ensure that city immunization registry record does not exist

***Comparative effectiveness estimation***

Pairwise comparison of COVID-19 vaccines

**Outcomes of Interest**

Both absolute and comparative effectiveness estimations use two outcome cohorts:

1. Episodes with observed COVID-19 (COVID-19 diagnosis or a positive SARS-CoV-2 test): (<https://atlas.ohdsi.org/#/cohortdefinition/422>)

Persons indexed on observed diagnosis or positive test for COVID-19 after 2019-12-01

1. Hospitalizations with observed COVID-19 in 30d prior (diagnosis or a positive SARS-CoV-2 test):

(<https://atlas.ohdsi.org/#/cohortdefinition/425>)

Persons indexed on an inpatient or emergency room visit after 2019-12-01 with

* A diagnosis of COVID-19 within 30 days prior to the index date OR
* A positive test for COVID-19 within 30 days prior to the index date

**Time-at-risk**

***Absolute effectiveness estimation***

1. For fully vaccinated patients:

1.1 Cohort end (14d from last vaccination) -- cohort end + 365 days, end of observation period, outcome or death whichever comes earlier

1. For fully and partially vaccinated patients:
   1. One week time-at-risk interval starting after the first dose and ending with the second dose, end of observation period, outcome or death (1- 7 days, 8 – 14 days, 15 – 21 days etc.)
   2. One week time-at-risk interval starting after the first dose and ending with the end of observation period, outcome or death (no truncation at the second dose, 1- 7 days, 8 – 14 days, 15 – 21 days etc.)
   3. One week time-at-risk interval starting after the second dose and ending with the end of observation period, outcome or death (1- 7 days, 8 – 14 days, 15 – 21 days etc.)

***Comparative effectiveness estimation***

One week time-at-risk interval starting after the first dose and ending with the end of observation period, outcome or death (no truncation at the second dose, 1- 7 days, 8 – 14 days, 15 – 21 days etc.)

**Negative Controls**

We will a sample of 93 outcomes known to not be associated with COVID vaccines to allow for estimation of residual bias and empirical calibration from EUMAEUS (<https://ohdsi-studies.github.io/Eumaeus/Protocol.html>)

**Propensity score model**

Propensity scores (PS) will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates (4). The PS is the probability of a subject being classified in the target cohort versus the comparator cohort, given a set of observed covariates.

The types of baseline covariates used to fit the propensity score model will be:

* Demographics
  + Gender
  + Age group (5-year bands)
  + Index year
  + Index month
* Time Bound Era Covariates
  + Condition group concepts both 365 days and 30 days on or prior to cohort index
  + Drug groups both 365 days and 30 days on or prior to cohort index
* Time Bound Covariates
  + Procedure occurrence concept and any of its descendants both 365 days and 30 days on or prior to cohort index
  + The occurrence of a measurement concept and any of its descendants both 365 days and 30 days on or prior to cohort index
  + The occurrence of an observation concept and any of its descendants both 365 days and 30 days on or prior to cohort index
  + Device concept and any of its descendants both 365 days and 30 days on or prior to cohort index
  + Number of visits observed both 365 days and 30 days on or prior to cohort index
* Index Score Covariates
  + CHADS2, CHA2DS2-VASc, Charlson Index, DCSI

Note: covariates on the index date itself are excluded from the analysis

Specific drug exposure concepts that define the target and comparator cohorts will be excluded from the propensity score model fitting.

This study will be designed using OHDSI tools (specifically the Population-Level Estimation tools) and run with R [19].

**Sample Size and Study Power**

The sample size of the cohorts is reported in Table 1. These patient counts represent the initial population, prior to statistical adjustment, so provide an upper bound of exposure available for each analysis. For population-level effect estimation, where our aim is to produce an unbiased estimate of the average treatment effect, the precision we will achieve will vary by the incidence rate of each outcome. Because our focus is to estimate the magnitude of the effect, it is acceptable to be underpowered for the analyses, recognizing that this will manifest as wider confidence intervals that account for the random sampling error inherent to the analysis. Smaller sample size for specific comparisons may be associated with larger statistical uncertainty. Small samples may also limit the ability to fit adequate propensity models and thus limit our ability to control confounding.

There is no a priori hypothesis testing for this study, therefore there is no prespecified requirement of sample sizes for the comparative analyses. After all design specifications have been implemented for each pairwise comparison, the minimum detectable hazard ratio will be calculated. The calculation includes a targeted type I error rate (alpha) of 0.05 (2-sided) and a type II error rate (beta) of 0.20 (power=80%) and reports the minimum hazard ratio detectable given the final target and comparator patient count, outcome event count, and TAR (5).

**Table 1.** Initial pre-matching sample size for target, comparator and outcome cohorts in CUMC data.

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| --- | --- | --- | --- |
|  | Target | Comparator (anchored on a date) | Comparator (anchored on a visit) |
| Patients fully vaccinated with Pfizer-BioNTech | 96,383 | 93,284 | 73,848 |
| Patients fully vaccinated with Moderna | 35,168 | 66,582 | 41,458 |
| Patients fully vaccinated with Janssen vaccine | 4,023 | 8,046 | 7,290 |
| Patients partially and fully vaccinated with Pfizer-BioNTech | 116,646 | 148,580 | 83,137 |
| Patients partially and fully vaccinated with Moderna | 48,904 | 65,937 | 55,137 |
| Patients partially and fully vaccinated with Janssen vaccine | 4,059 | 7,958 | 5,525 |
| COVID-19 infection episodes | 58,759 |  |  |
| COVID-19 hospitalization | 11,455 |  |  |

**Study Diagnostics**

For each population-level effect estimate generated by the study, i.e. each target-comparator-outcome-analysis-database combination, we will report diagnostics to assess its potential for bias and threats to its valid interpretation. The diagnostics include both propensity score distribution and covariate balance before and after propensity score matching.

**Propensity Score Distribution**

Once the PS model is fit for each pairwise comparison, the PS distribution for the target and comparator cohort will be plotted to evaluate the comparability, as a proxy for exchange ability, of the two cohorts before matching. The plot will be scaled to the preference score, which normalizes for initial cohort size imbalance. If the proportion of subjects in clinical equipoise, i.e. the patients with a preference score between 0.3 and 0.718, is less than 50%, then the estimate will not be reported.

**Covariate balance before and after propensity score matching**

Covariate balance will be evaluated by plotting the standardized mean difference (SMD) of each covariate before against the SMD after propensity score matching. After matching SMDs with values of <0.1 are asserted to indicate negligible group differences.

**Study Output**

The final outcome model, a conditional Cox proportional hazards model, will be summarized by providing the hazards ratio and associated 95% confidence interval. The number of persons, amount of time-at-risk, and number of outcomes in each cohort will also be reported along with the characteristics of the subjects.

Covariate balance before and after matching will be summarized in tabular form by showing the mean value for all baseline covariates in the target and comparator cohort, with the associated standardized mean difference computed for each covariate.

Once the propensity score model is fit, we will plot the propensity score distribution of the target and comparator cohorts to evaluate the comparability of the two cohorts. The plot will be scaled to the preference score, normalizing for any imbalance in cohort size. The covariates selected within the propensity score model, with associated coefficients will also be reported.

Covariate balance will be evaluated by plotting the standardized mean difference of each covariate before propensity score stratification against the standardized mean difference for each covariate after propensity score stratification.

An attrition diagram will be provided to detail the loss of subjects from the original target cohort and comparator cohort to the subpopulations that remain after all design considerations have been applied.

**Limitations**

There may be residual bias due to unmeasured or mis-specified confounders. COVID-19 episodes may be subject to outcome misclassification due to out-of-system testing. Nevertheless, propensity score matching allows balancing on many baseline potential confounders and use of negative and positive control outcomes allows for evaluating the study design in terms of residual bias. Causality between drug exposure and any given event cannot be drawn for individual cases.

**Protection of Human Subjects**

The study is the subject to the relevant Institutional Review Board approval. All study reports will contain aggregate data only and will not identify individual subjects or physicians.

**REFERENCES**

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