Estimating degree of leaky vaccine-induced protection from COVID-19 vaccines against SARS-CoV-2 infections in California state prisons

Pre-analysis Plan

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Original date: 12/5/23
Last updated: 1/30/24

Objective: Estimate vaccine effectiveness of COVID-19 vaccination and boosters in California state prisons against Omicron SARS-CoV-2 infection under different forces of infection.

Hypothesis: COVID-19 booster vaccines provide leaky protection, defined as being less effective against infection in high incidence settings compared to low incidence settings.

Study outcome: Omicron SARS-CoV-2 infection

Background:

Vaccination is thought to provide protection against infection through one of two (or a combination of both) mechanisms: "all-or-nothing" protection, which provides full protection for a fraction of individuals and no protection for others, and "leaky protection", in which vaccine effectiveness is dependent on reducing risk of infection given exposure. Here, we propose a study within California prisons that will characterize the degree of leaky protection of COVID-19 vaccines, especially boosters, to inform future vaccine policy specifically designed to improve the health of this population. Given the carceral setting is a high-risk environment for transmission, this study's findings are most relevant for informing customized vaccine policy for this population, especially during future surges.

Methods:

We will conduct a retrospective vaccine effectiveness study among residents of California prisons, under different levels of infection incidence, to evaluate whether COVID-19 vaccines demonstrate leaky protection against Omicron SARS-CoV-2 infection (i.e., lower vaccine effectiveness in high incidence compared to low incidence periods). In brief, we will retrospectively identify a cohort of residents and follow SARS-CoV-2 outcomes. Residents will be matched based on their vaccine status and other key demographic and COVID-19 related characteristics. Comparing matched residents over the same time period, we will use variation in incidence at a building level to assess leaky vaccine protection by quantifying differences in vaccine effectiveness and waning over time given different background incidence.

Study period

The study period will be from December 15, 2021-March 1, 2023. This corresponds to genomic surveillance data suggesting circulation of Omicron lineage and similar testing practices. We will also use historical data from the entire pandemic on prior infection and vaccination history of residents.

Study design

Vaccine status exposures

We will use multiple definitions of vaccine status to evaluate leaky effects. We will assess:

1. Absolute vaccine effectiveness and leaky protection of vaccines
    a. Unvaccinated residents (Reference)
    b. Vaccinated residents (excluding partially vaccinated residents)

    We will also define exposure groups by time since last vaccine (see Additional Analyses)

2. Relative vaccine effectiveness and leaky protection from booster vaccines
    a. Vaccinated residents that completed only their primary series (Reference)
    b. Vaccinated residents that received at least 1 booster

Subvariant periods

We will separately analyze survival and leaky vaccination during four subvariant periods. However, since this analysis relies on adequate power from infection events and variability in background force of infection across buildings. If sample size and variability in incidence are not large enough in later variant periods, we will focus our analysis on the first subvariant period, which reflects the first and largest Omicron wave (December 15, 2021 - May 14, 2022).

The four periods and dominant subvariants of the study period are as follows broadly based on genomic surveillance:

1. December 15, 2021 – May 14, 2022 (Omicron BA.1 and BA.2)
2. May 15, 2022 – August 14, 2022 (Omicron BA.4 and BA.5)
3. August 15, 2022 – December 14, 2022 (Omicron BA.5)
4. December 15, 2022 – March 1, 2023 (Omicron XBB)

Inclusion criteria

We will evaluate the eligibility of residents at the start of each variant period. For inclusion, residents must:

- Have been incarcerated since March 2020 to ensure more complete reporting of prior SARS-CoV-2 infection and vaccination
- Have not had an infection within 90 days of the start of the variant period
- Be unvaccinated or have completed a primary vaccine series

Censoring criteria

Eligible residents will be censored in the subvariant period if they:

- Have a positive SARS-CoV-2 test
- Receive a new vaccine dose (only if they switch vaccine status exposure)
- Move buildings
- Released

In this fixed matching approach, we may often censor residents frequently within a subvariant period solely due to movement between buildings. If sample size with this study design is

inadequate for this reason, we will switch to a rolling matching approach (see Rolling Matching), which will allow for the continuous rematching of residents throughout the study period.

Matching

We will match residents based on vaccine exposure groups at the start of each subvariant period. Residents in different exposure groups will be matched by:

- Age (numeric in years)
- Risk score (0, 1, 2+)
- Sex (exactly)
- Prior SARS-CoV-2 infection (exactly)
    - 0: no prior infection
    - 1: most recent infection within 1 year
    - 2: most recent infection between 1-2 years
    - 3: most recent infection >2 years
- Room type (exactly)
    - Cell (<3 people)
    - Dorm (3+ people)
- Building (exactly)

Additional matching variables

- Vaccine status of roommate(s)

Survival analysis

We will fit time-varying Cox frailty models to estimate the hazard of SARS-CoV-2 infection by vaccine status. We will stratify the analysis by variant period since baseline hazards may vary by variant. We will incorporate a frailty term for each pair of matched residents. We will incorporate interactions between vaccine status, time of last vaccine dose, and background force of infection (measured by a rolling window of cumulative building incidence in the previous 3-9 days) to assess a leaky mode of vaccine protection (see specific analyses for details).

We will evaluate assumptions of linearity in our survival model for all covariates and factors of interest. We will conduct sensitivity analyses that allow for fitting of nonlinear relationships between covariates and survival. We will also evaluate all assumptions of Cox models to assess suitability and revise the model to address any violations.

Absolute vaccine effectiveness and leaky protection

We will assess leaky protection of vaccines by including an interaction between vaccine status (binary) and incidence (time-varying) in the described survival model. We will also adjust for the number of vaccine doses. The model equation is as follows:

$$\frac{h_v(t|Z(t))}{h_{v0}(t|Z(t))} \sim \exp(binaryvaccine * incidence + priorinfection + age + riskscore + sex + roomtype + institution + frailty(matchgroup) + strata(v))$$

$$Z(t) \sim incidence + priorinfection$$

- *v*: variant period (stratifies analysis by variant, which allows the baseline hazard to vary for different Omicron subvariants)
- *matchgroup*: match id group
- $Z(t)$ reflects covariates that are time-varying and will be updated daily

<u>Relative vaccine effectiveness and leaky protection</u>

We will conduct the analyses with the following interaction terms:

- Interaction between vaccine status (booster) and incidence (time-varying) and interaction between vaccine status (booster) and time since most recent vaccine (time-varying)

$$\frac{h_v(t|Z(t))}{h_{v0}(t|Z(t))} \sim \exp(boostervaccine * incidence + boostervaccine * timesincevaccine + priorinfection + age + roomtype + riskscore + sex + institution + frailty(matchgroup) + strata(v))$$

$$Z(t) \sim incidence + timesincevaccine + priorinfection$$

- Interaction between time since most recent vaccine (time-varying) and incidence (time-varying) and interaction between vaccine status (booster) and time since most recent vaccine

$$\frac{h_v(t|Z(t))}{h_{v0}(t|Z(t))} \sim \exp(timesincevaccine * incidence + boostervaccine * timesincevaccine + priorinfection + age + riskscore + sex + roomtype + institution + frailty(matchgroup) + strata(v))$$

$$Z(t) \sim timesincevaccine + incidence + priorinfection$$

- Interaction between vaccine status (booster) and incidence, interaction between time since most recent vaccine (time-varying) and incidence (time-varying), and interaction between vaccine status (booster) and time since most recent vaccine (time-varying)

$$\frac{h_v(t|Z(t))}{h_{v0}(t|Z(t))} \sim \exp(boostervaccine * incidence + timesincevaccine * incidence + boostervaccine * timesincevaccine + priorinfection + age + riskscore + sex + roomtype + institution + frailty(matchgroup) + strata(v))$$

$$Z(t) \sim incidence + timesincevaccine + priorinfection$$

Additional analyses

Additional analyses for absolute leaky protection

We will also plan an analysis that categorize vaccine status by doses (No vaccine, primary series, booster) and by time (i.e. No vaccine, vaccine within 3 months, vaccine within 6 months, vaccine within 1 year, vaccine 1+years). Exposure categories will depend on sample sizes of subgroups. The statistical model will include an interaction between vaccine status by time and incidence.

Additional analyses for relative leaky protection

Based on convergence and feasibility, we will also consider more parsimonious interactions:

- Interaction with vaccine status (booster) and incidence (time-varying)
- Interaction with time since most recent vaccine and incidence (time-varying)

Rolling matching approach

This approach will be considered to improve sample size from the fixed matching approach, which may censor residents frequently due to movement between buildings.

We will use rolling matching[1] to match residents based on their vaccine status and exposure definitions. Residents will be rematched on a rolling basis when they move buildings. Recently infected individuals or individuals are eligible for matching 90 days after infection. We allow residents with multiple recurrent events during the study period to be included (though they are censored for 90 days after an infection). Residents that receive a vaccine during the study period are also censored but eligible thereafter with their updated vaccine status.

Residents will be matched by variant period, prior infection (exactly), and building (exactly) and by propensity score of other matching characteristics. Rolling matching will occur within a 30-day window during the same variant period. All other aspects of the survival analysis will remain the same.

Leaky protection from SARS-CoV-2 infection

We will evaluate leaky protection from prior SARS-CoV-2 infection. We will use prior SARS-CoV-2 infection as the exposure of interest in matching and in survival analysis.

Sensitivity analyses

In addition to the alternative analyses already outlined, we will conduct various sensitivity analyses of study design and analytical decisions. For example, we recognize that residents may be matched that co-reside in the same room. We will conduct a sensitivity analysis of such that matches cannot be from the same room. We will consider matching residents by the vaccine status of their roommates. We will assess leaky effects with a Cox model without frailty terms. We will also use a Cox model with frailty term for resident since residents may be eligible at multiple subvariant periods.

Ethics

This study is approved by the Stanford University IRB. The data used in this study has no direct identifiers. This study is a retrospective analysis of data collected for operational purposes for COVID-19 control and routine testing; no interventions were applied in this study.

References

1. Jones K, Chew R, Witman A, Liu Y. The R Journal: rollmatch: An R Package for Rolling Entry Matching. *R J*. 2019;11(2):243-253. doi:10.32614/RJ-2019-005