

## Background

The cohort method is one of the most common methods in comparative effectiveness and safety studies. In a cohort study, we compare rates of events during time-at-risk in target and comparator groups. Such rates are, therefore, dependent on the choice of starting point for time-at-risk or, as we call it, anchoring. Choice of anchoring may influence both the rates of observed outcomes and baseline patient characteristics, which are subsequently used in propensity score models or outcome models.

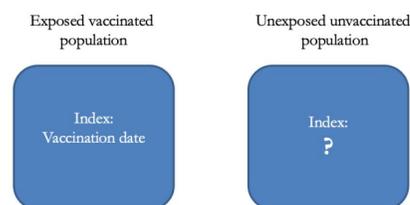


Figure 1. What is the index date for the unexposed population?

When the cohort method is applied in vaccine safety studies, a vaccinated population is compared to an unvaccinated population. The latter cohort does not have a clear index date, which is left up to researchers' judgment.

**In this study, we investigate how the choice of the index date (anchor) influences patient baseline characteristics and baseline incidence rates.**

## Methods

We investigated the influence of anchoring unvaccinated population on incidence rates of 15 adverse events occurring during different time-at-risk windows (A). Additionally, we investigated its impact on baseline patient characteristics in unvaccinated and vaccinated populations (B).

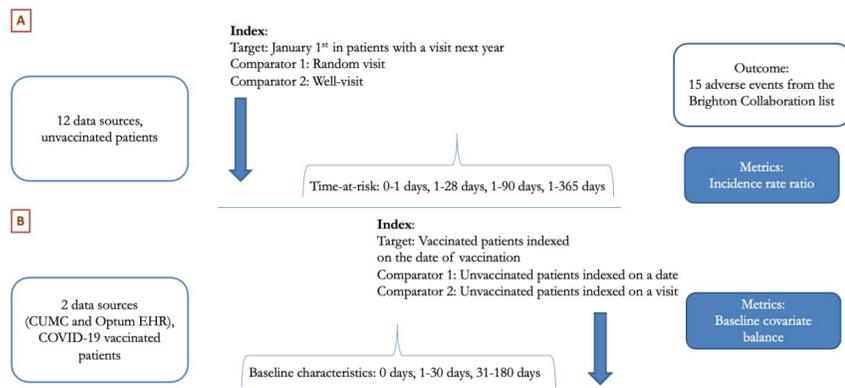


Figure 2. Two study designs used in this study, A – Background incidence rate evaluation and B – baseline characteristics assessment.

For the *first* study, we modified the study design described in the paper by Li et al. (2021). Briefly, we used 12 data sources to study incidence rates of 15 adverse events of special interest in unvaccinated population in 2017-2020 in a number of time-at-risk intervals. We calculated incidence rate ratios (IRR) of incidence rates in two pairs of cohorts with different index dates (“anchors”): a visit and a well visit, defined as a visit associated with preventive visit CPT4 codes. We performed random-effect meta-analysis across data sources. In the *second* study, we compared baseline characteristics of patients vaccinated with COVID-19 and unvaccinated patients in CUMC and Optum EHR.

The latter were anchored on a) a date matched to the index date of one of the target group, b) a visit matched to the index date of one of the target group. Additionally, each target and comparator groups were matched on age and sex.

## Results

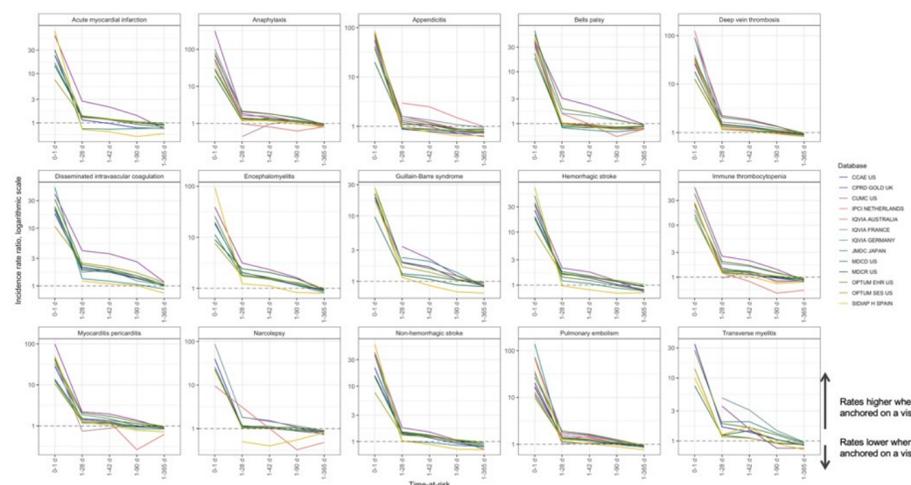


Figure 3. Incidence rate ratio of incidence rate of outcomes when entering the cohort on a random visit versus entering on January 1<sup>st</sup> in patients with a visit in the next year, time-at-risk 0-1 day, 1-28 days, 1-42 days, 1-90 days and 1-365 days.

### Influence of anchoring on the background incidence rates

Incidence rates of all adverse events across all data sources and all conditions were highly sensitive to the choice of anchoring. For a short time-at-risk (0-1 day) anchoring on a visit was associated with up to a 100-fold increase in incidence when compared to anchoring on January 1<sup>st</sup> (pooled IRR 26.8 (95% CI 21.9-32.8)). Acute conditions such as anaphylaxis were impacted the most (pooled IRR 47.6 (95% CI 32.8 – 69.1)). The effect was attenuated for longer times at risk (Figure 3) but was still present. For example, for 1 – 28 days window, pooled IRR was 1.4 (95% CI 1.3-1.5).

We observed similar trends for anchoring on a well visit with the pooled IRR of 1.21 (95% CI 1.11-1.31). Overall, anchoring on a well visit was associated with higher incidence rates with several conditions (such as Bell’s palsy or narcolepsy) being highly sensitive.

### Influence of anchoring on baseline characteristics

When looking at the baseline characteristics, unvaccinated population had more events (measurements, conditions, procedures, observations) on day 0 than vaccinated population regardless of the anchoring event (Figure 4). Similarly, the effect attenuated with increased lookback window but was still present.

Vaccinated patients had fewer lab tests (such as body weight, blood pressure or respiratory rate), co-morbidities (diabetes, hyperlipidemia, dyspnea etc.) and visits on day 0 when compared to a random date or a random visit in unvaccinated population. In patients vaccinated with an influenza vaccine (not shown here) compared to patients not vaccinated with influenza vaccine the opposite trend was observed: the former had more lab tests and co-morbidities on day 0 than unvaccinated patients.

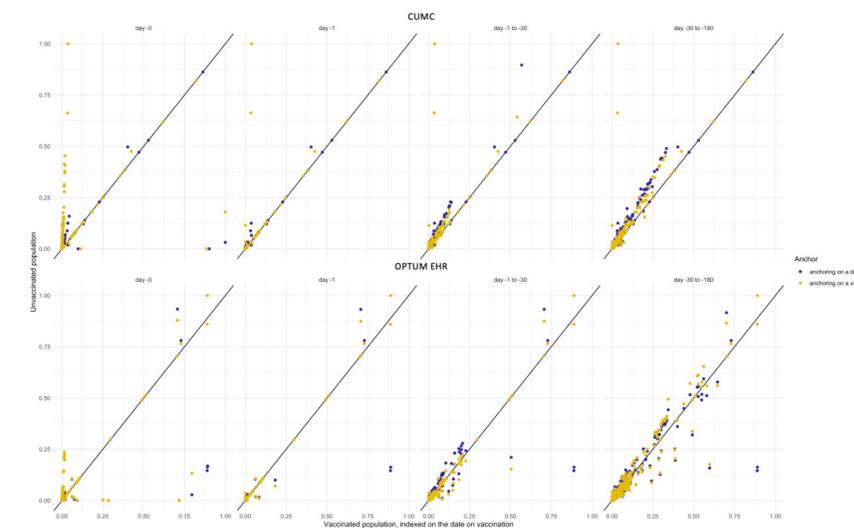


Figure 4. Comparison of baseline characteristics in unvaccinated versus COVID-19 vaccinated patients in CUMC and Optum EHR. Each dot represents one covariate, blue – unvaccinated patients anchored on a date, yellow – unvaccinated patients anchored on a visit.

## Conclusions

1. Anchoring influences both baseline patient characteristics and incidence rates of conditions observed after the index date.
2. It is crucial to select an anchoring that represents the target index date best based on the knowledge of the target (e.g. vaccination settings) or empirical comparison of multiple options.
3. Balance on visit on day 0 should be assessed in any cohort study.