Department of Biostatistics, Epidemiology and Informatics

Is Documented SARS-CoV-2 Infection within 14 days after Vaccination a Negative Control Outcome of COVID-19 Vaccine?

--Findings from Sequential Target Trial Emulations

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Background

- **Negative control outcome (NCO)** experiments have become an important tool for addressing residual bias such as unmeasured confounders and systematic bias in real-world data (RWD)

  - Diagnosis – report and check
  - Calibration – bias correction

- During the COVID-19 pandemic, **comparative effective research (CER)** and **target trial emulation (TTE)** studies on vaccine effectiveness have been particularly critical

- An important ongoing debate: whether infections occurring within the first week(s) after COVID vaccination should be considered as negative controls

COVID-19 and Flu Updated 2024-2025 Vaccines

RSV Immunization to Protect Babies

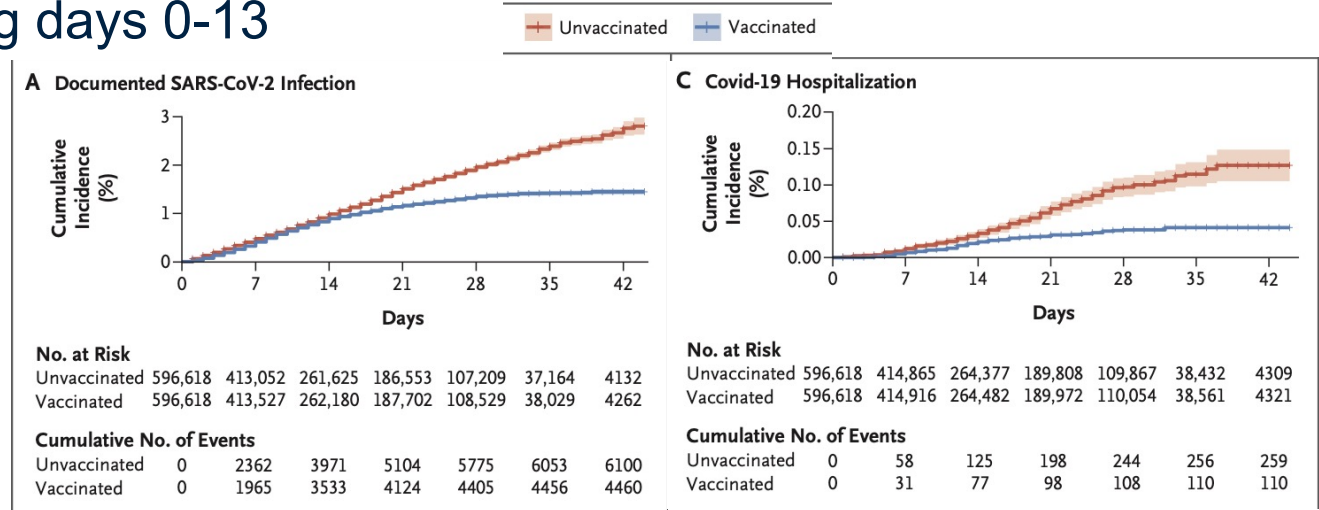**RSV Vaccine for Older Adults**

An Ongoing Debate

▸ Paper A (NEJM): the risk was similar during days 0-13

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting

Noa Dagan, M.D., Noam Barda, M.D., Eldad Kepten, Ph.D., Oren Miron, M.A., Shay Perchik, M.A., Mark A. Katz, M.D., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Ben Reis, Ph.D., and Ran D. Balicer, M.D.
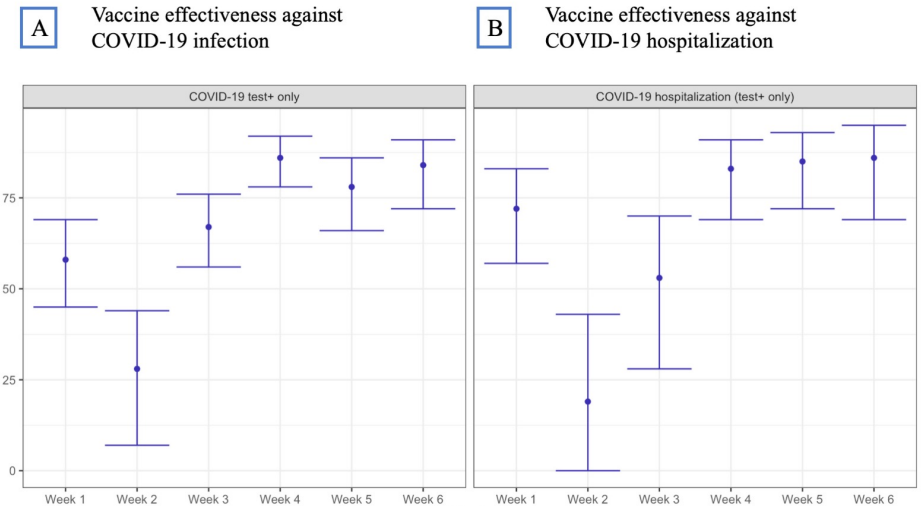
Unvaccinated   Vaccinated

A Documented SARS-CoV-2 Infection

Cumulative Incidence (%) vs Days

No. at Risk

Unvaccinated	596,618	413,052	261,625	186,553	107,209	37,164	4132
Vaccinated	596,618	413,527	262,180	187,702	108,529	38,029	4262

Cumulative No. of Events

Unvaccinated	0	2362	3971	5104	5775	6053	6100
Vaccinated	0	1965	3533	4124	4405	4456	4460

C Covid-19 Hospitalization

Cumulative Incidence (%) vs Days

No. at Risk

Unvaccinated	596,618	414,865	264,377	189,808	109,867	38,432	4309
Vaccinated	596,618	414,916	264,482	189,972	110,054	38,561	4321

Cumulative No. of Events

Unvaccinated	0	58	125	198	244	256	259
Vaccinated	0	31	77	98	108	110	110

▸ Paper B (BMJ Open): week 1 had high effectiveness

**Open access** **Original research**

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

Anna Ostropolets [1] George Hripcsak[1,2]

A Vaccine effectiveness against COVID-19 infection

B Vaccine effectiveness against COVID-19 hospitalization

COVID-19 test+ only

COVID-19 hospitalization (test+ only)

Vaccine effectiveness in % and 95% CI — Week 1 through Week 6

Scientific question

▸ Is documented SARS-CoV-2 infection within 14 days after vaccination a valid negative control outcome (NCO) for COVID-19 vaccines?
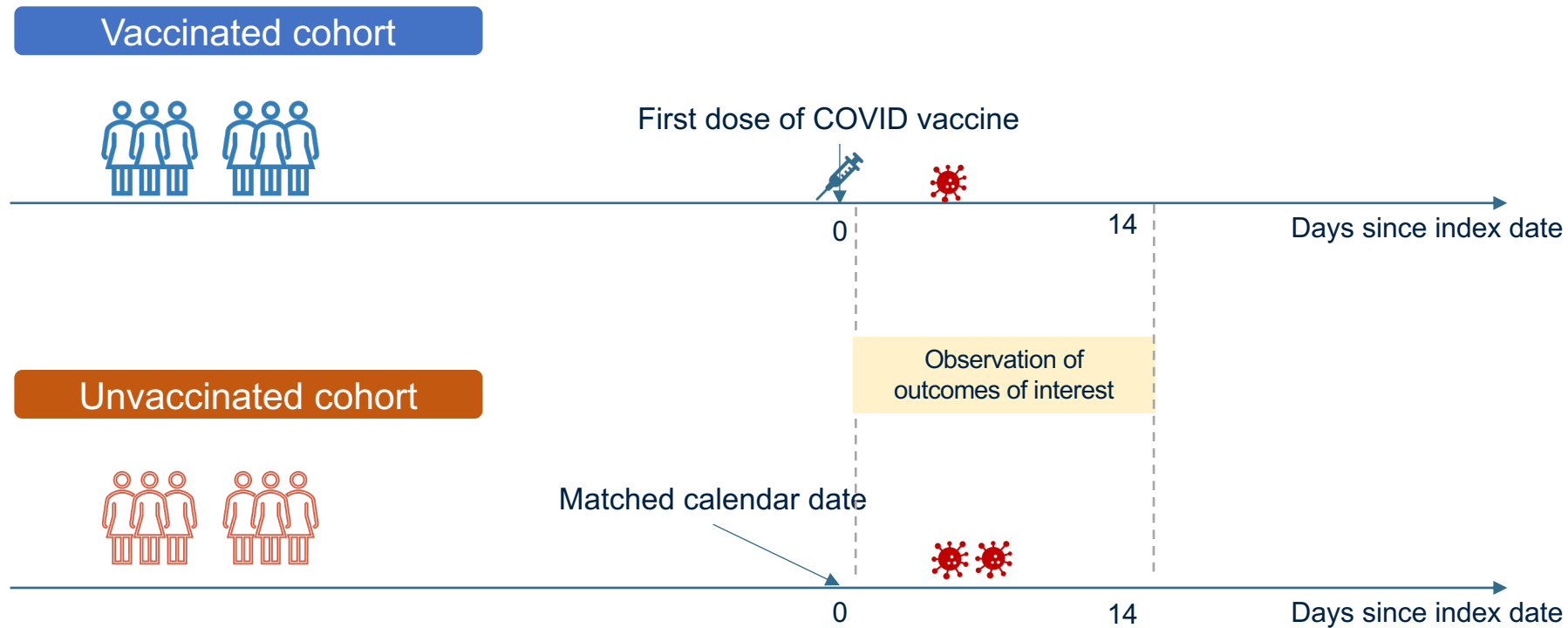
Scientific Setup - PICO

▶ **Database and study period**

- PEDSnet, ~7% US pediatrics population
- Omicron period: 2022-01-01 ~ 2022-11-16

▶ **Selection Criteria**

- Adolescents, age [12, 21)
- No infection or vaccination before trial start
- At least one visit 24 months before trial start
- No visit 3 days before trial start

▶ **Intervention**

- First dose of any COVID-19 vaccine versus no receipt of any type of COVID-19 vaccine

▶ **Outcome**

- Documented SARS-CoV-2 infection within 14 days following cohort entry

Statistical Analysis

▸ <u>Step 1:</u> Sequential target trial emulation design to enroll participants with eligibility and matching criteria
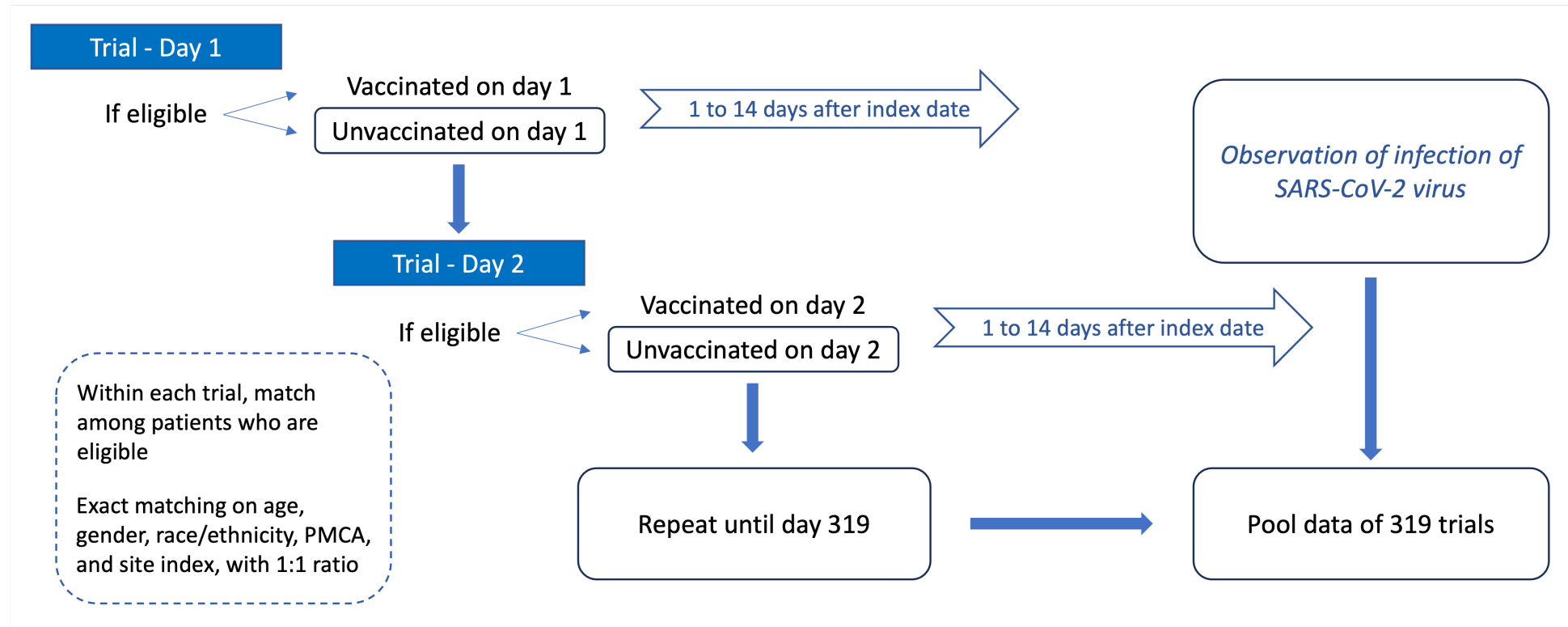
Statistical Analysis

▸ <u>Step 2:</u> Modified Poisson regression model for binary outcomes to estimate the risk ratios (RRs) between vaccinated and unvaccinated groups for the following outcomes measured within 14 days after cohort entry:

- Documented SARS-CoV-2 infection
- Documented influenza infection
- A list of pre-specified NCOs

$$\log(Pr(Y = 1)|A) = \beta_0 + \beta_1 A$$

Statistical Analysis

▸ <u>Step 3:</u> Hypothesis testing comparing the candidate outcomes, documented SAR-CoV-2 and influenza infection within 14 days following cohort entry, to the empirical distribution of pre-specified NCOs

▸ Known list of NCOs ("OHDSI NCOs")
- e.g., wax in ear, insect bite, injury of right hand, within 14 days after COVID-19 vaccination
- have empirical distribution: $\theta_i \sim N(\mu, \sigma^2)$

▸ New drug-outcome pair: vaccination-documented SARS-CoV-2 infection within 14 days
- Estimated effect $\hat{\eta}$, estimated standard error $\hat{\tau}$
- Test if $\hat{\eta} \sim N(\hat{\mu}, \hat{\sigma}^2 + \hat{\tau}^2)$
- two-sided p value:

$$2 * \min\left\{\Phi\left(\frac{\hat{\eta} - \hat{\mu}}{\sqrt{\hat{\sigma}^2 + \hat{\tau}^2}}\right), 1 - \Phi\left(\frac{\hat{\eta} - \hat{\mu}}{\sqrt{\hat{\sigma}^2 + \hat{\tau}^2}}\right)\right\}$$

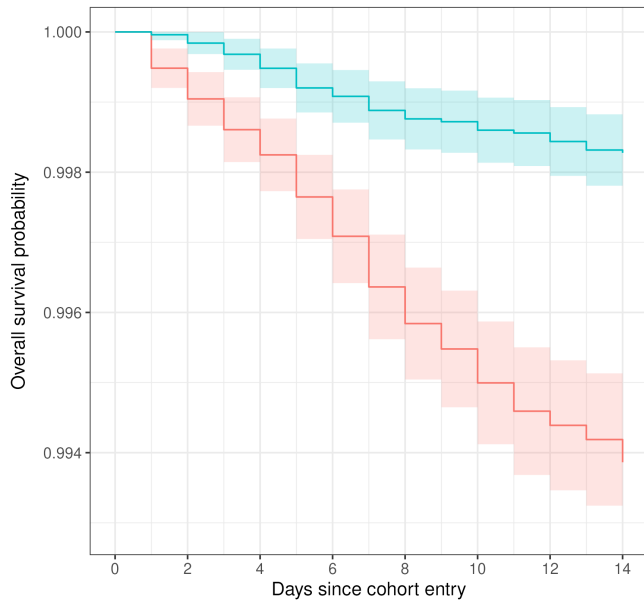Schuemie, Martijn J., et al. "Interpreting observational studies: why empirical calibration is needed to correct p-values." *Statistics in medicine* 33.2 (2014): 209-218.

Results:
Study population and enrollment process

Adolescents (aged 12-20 y) without any prior infections or vaccinations as of the beginning of the vaccination campaign (January 1, 2022, 319 trials were emulated)
(n=256 501)

Were vaccinated before November 16, 2022
(n=42 641)

Were not vaccinated before November 16, 2022
(n=213 860)

Were excluded according to eligibility criteria, applied dynamically for each trial
1) 7 986 was out of age constraint at trial start
2) 754 had infection or vaccination before trial start
3) 5 571 had no visits 24 months before trial start
4) 2 775 had visits within 3 days before trial start
(n=17 086)

Had same exclusion criteria (1-4) applied dynamically for each trial

Were eligible to be included in the vaccination cohort
(n=25 555)

Were not matched
(n=318)

Were matched, contributing to the vaccinated group, or unvaccinated group, or both
(n=25 237)

Were matched, contributing to the unvaccinated group*
(n=22 652)

Matched as controls before vaccination*
(n=2 494)

Vaccinated group
(n=25 146)

1:1 matching

Unvaccinated group*
(n=25 146)

* person-trial

Penn Medicine

Results:
Cumulative incidence of documented SARS-CoV-2 infection, and documented influenza infection
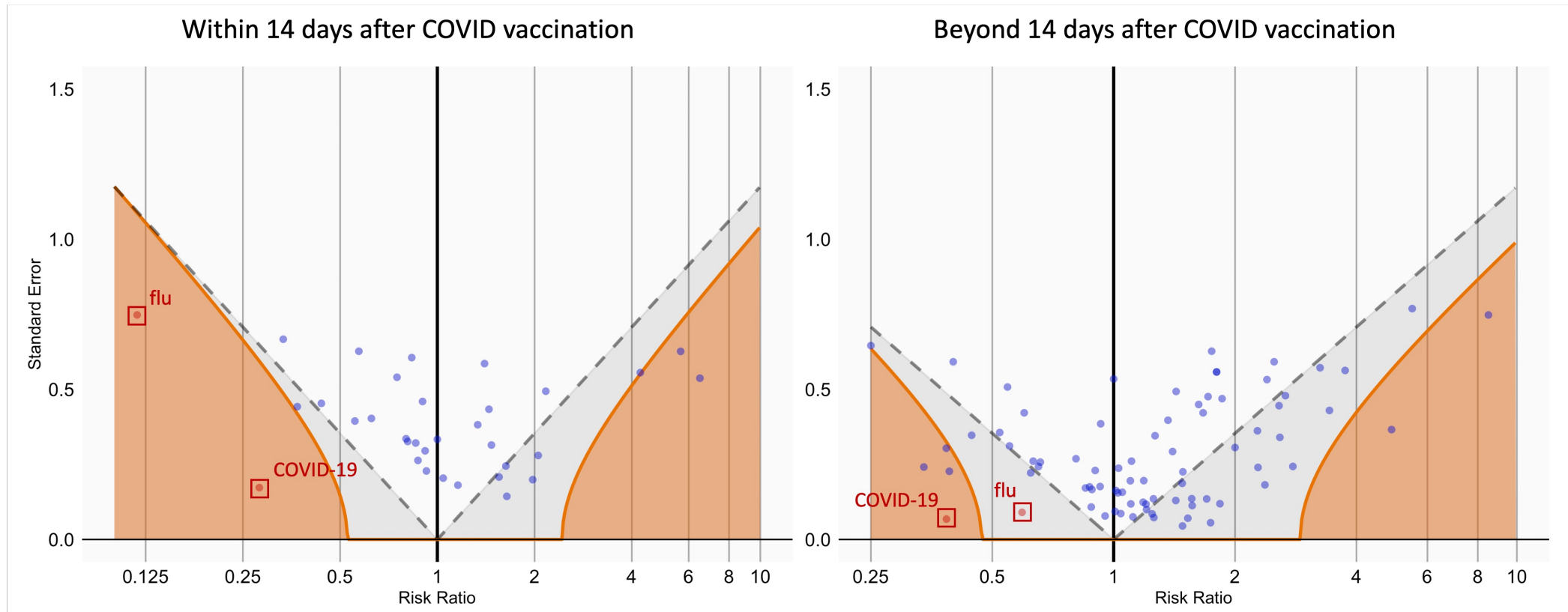
Results:

Forest plot of log relative risk of general NCOs, documented SARS-CoV-2 infection, and documented influenza infection within and beyond 14 days after COVID-19 vaccination
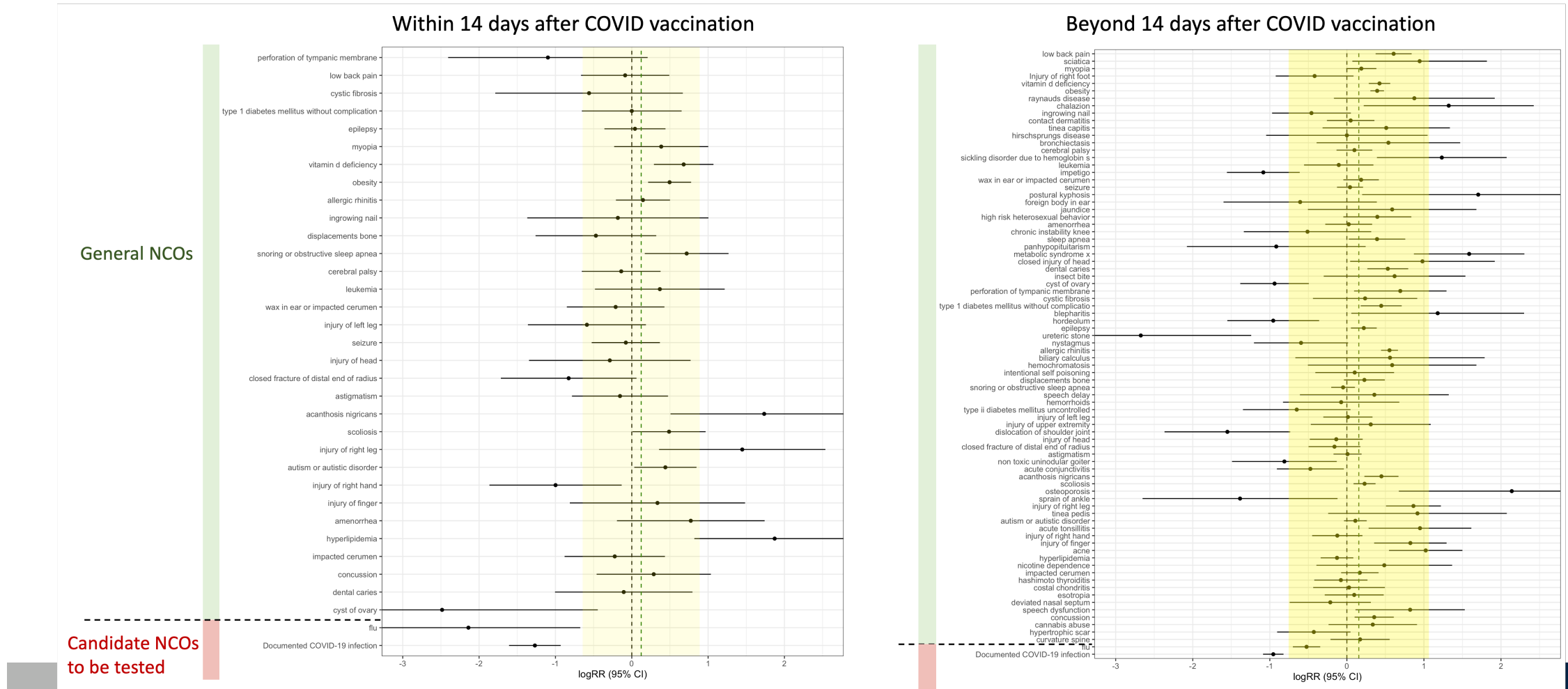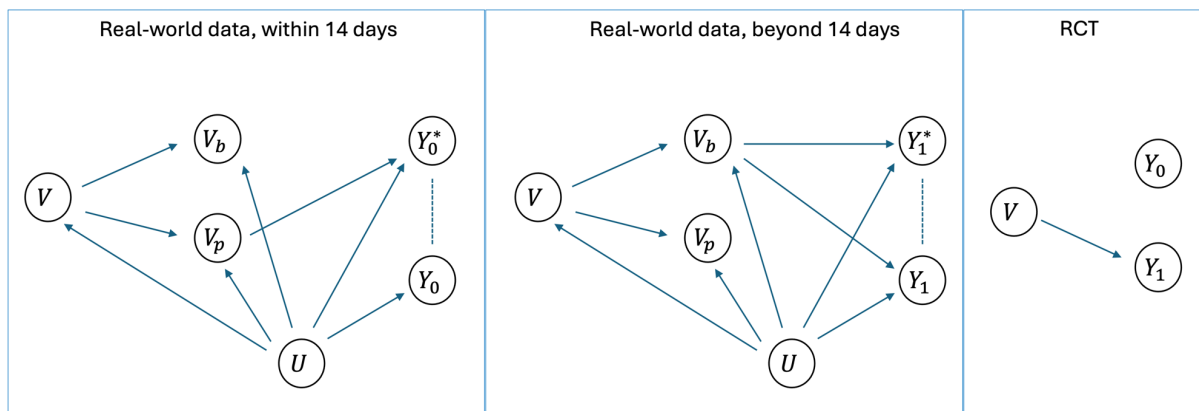
Results:

EASE plot of general NCOs, documented SARS-CoV-2 infection, and documented influenza infection within and beyond 14 days after COVID-19 vaccination

A possible explanation

V: COVID vaccination
V_b: COVID vaccination (biological)
V_p: COVID vaccination (psychological, i.e., telling the patients that they will experience some flu/COVID-like symptoms)
Y_0: True COVID infection within 14 days after COVID vaccination
Y_0^*: Documented COVID infection within 14 days after COVID vaccination
Y_1: True COVID infection beyond 14 days after COVID vaccination
Y_1^*: Documented COVID infection beyond 14 days after COVID vaccination
U: unmeasured confounders, e.g., health seeking behavior

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Check for updates

Conditional Separable Effects

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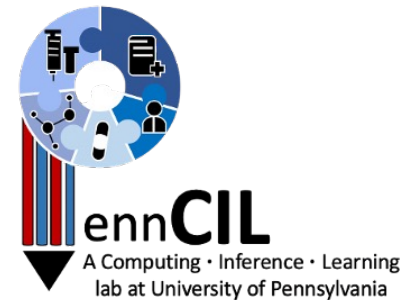
Conclusion

▸ A documented COVID infection within 14 days after vaccination seems not to be "exchangeable" with commonly used NCOs like acute injuries

▸ Potential explanations such as health-seeking behavior for COVID-19 or flu-like symptoms can be impacted by the event of vaccination itself, beyond the biological exposure of the vaccine

▸ A documented influenza infection could be considered as an NCO beyond 14 days, but not within 14 days after COVID vaccination

▸ From Martijn: the utility/relevance of NCO depends on the hypothesis of interest

▸ Comments are welcome!

Acknowledgement

▸ Research Team

- Bingyu Zhang, Qiong Wu, Ting Zhou, Dazheng Zhang, Jiayi Tong, Yuqing Lei, Christopher Forrest, Martijn Schuemie, Jeffrey Morris, Linbo Wang, Patrick Ryan, George Hripcsak