Real-world performance of the concurrent comparator

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Background

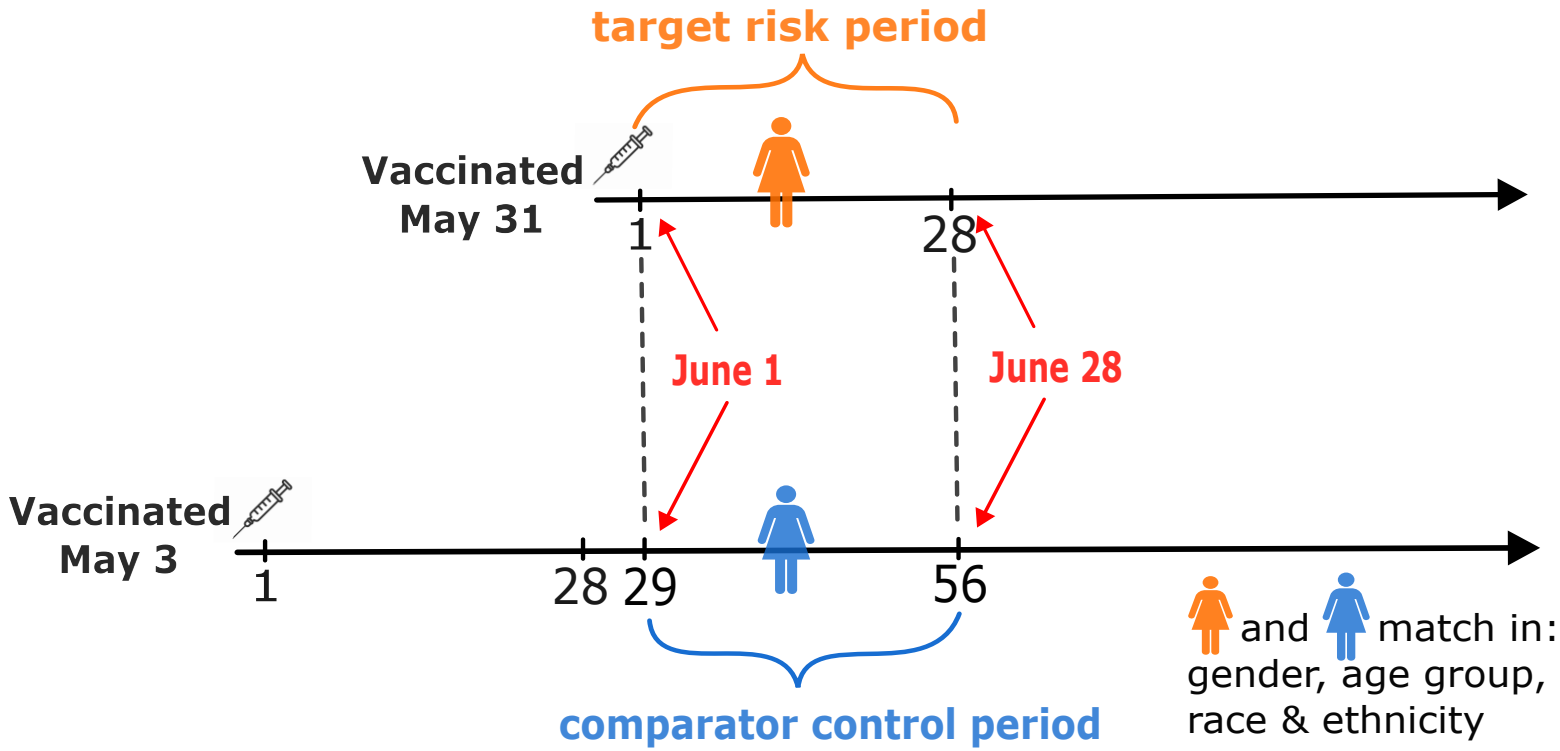
- Earlier work* carried out large-scale comparative evaluation of existing state-of-the-art methods for vaccine safety surveillance.
- These methods may produce biased estimates based on differences in patient preference, regarding (1) whether they receive the vaccine and/or (2) when they receive the vaccine.
- Klein et al. (2021)** proposed a new method called **concurrent comparator**, which aims to control for this bias.
- Q: How does the concurrent comparator perform based on real-world observational health data?

*Schuemie MJ, Arshad F, Pratt N, *et al.* Vaccine safety surveillance using routinely collected healthcare Data—An empirical evaluation of epidemiological designs. *Frontiers in Pharmacology*. 2022;13.

**Klein NP, Lewis N, Goddard K, *et al.* Surveillance for adverse events after COVID-19 mRNA vaccination. *JAMA: The Journal of the American Medical Association*. 2021;326:1390–9.

Concurrent comparator

- The concurrent comparator **predefines a risk interval** and matches each vaccinated patient for whom an outcome is observed during their **target risk period**, with a vaccinated patient in their **comparator control period** on the same calendar day.
- This matching is done based on gender, age group, race, and ethnicity.



- Estimation of risk ratio is carried out using a conditional Poisson regression.

Objectives of the study

- **Goal:** compare performance characteristics of the concurrent comparator with existing methods in the context of vaccine safety based on real-world observational data.

- Comparison is based on the metrics and methods on right.

Statistical metrics and detection rule:

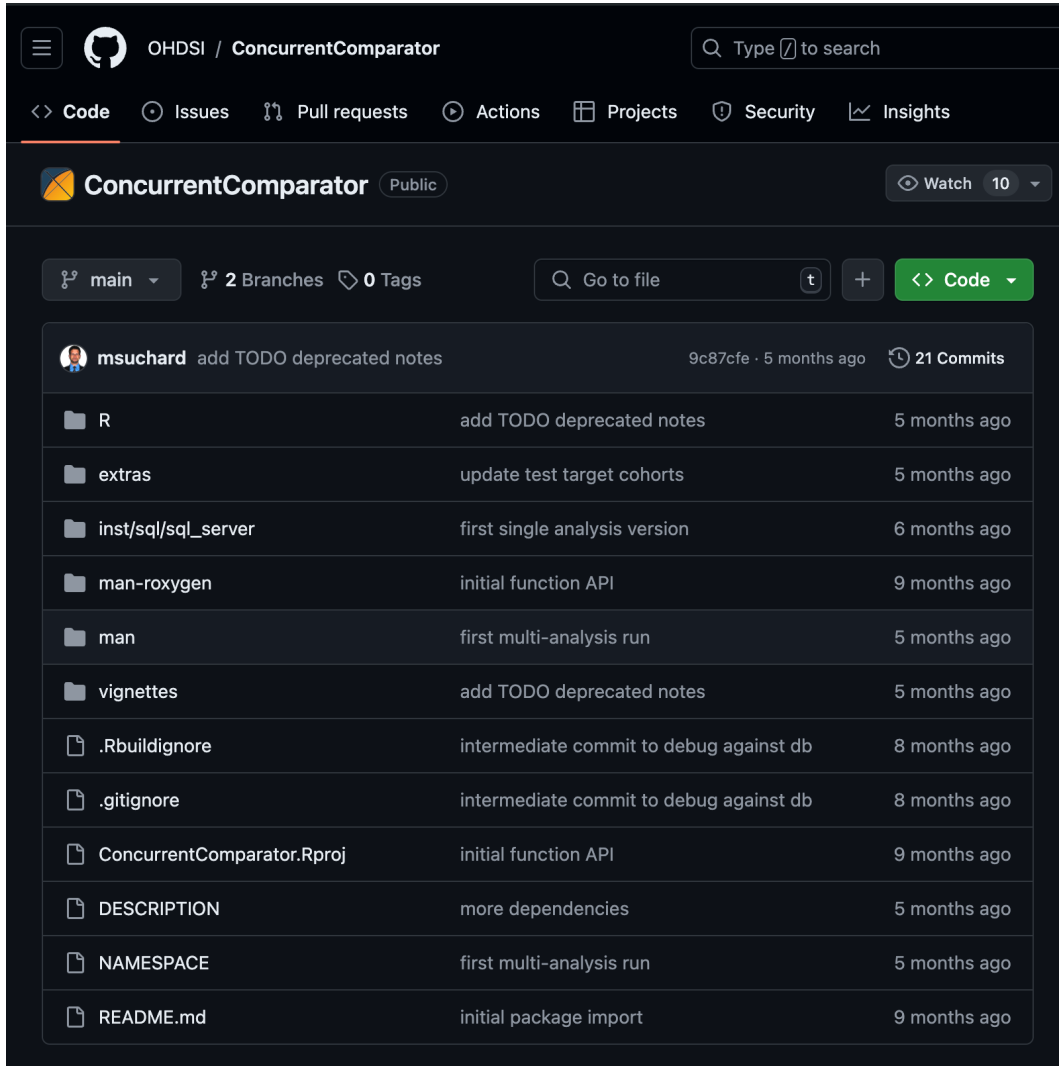
- Type 1 error (across time)
- Power of detection (across time)
- Proportion of non-finite estimates
- We use the MaxSPRT rule to detect a safety signal.

Methods considered:

- Concurrent comparator
- Self-control case series (SCCS)
- Historical comparator
- Case-control

Open-source software

- For implementation of the concurrent comparator approach, our team has created an `R` package called `ConcurrentComparator`.
- The package can be downloaded on GitHub, from: **`https://github.com/OHDSI/ConcurrentComparator`**.
- The package is **open-source, publicly available to download,** and **has been extensively tested.**



Real-world evidence with 118M estimates

Exposures of interest:

- H1N1pdm (`09-`10)
- Seasonal influenza (Fluvirin, `17-`18)
- Seasonal influenza (Fluzone, `17-`18)
- Seasonal influenza (all, `17-`18)
- Zoster (2018, 2 doses)
- HPV (2018, 2 doses)
- Covid-19 (BNT126b2, `20-`21)
- Covid-19 (mRNA-1273, `20-`21)

Data sources:

- CCAE
- MDCR
- MDCD
- Optum EHR
- Optum DOD

Negative control outcomes (93):

- Not related to any of these vaccines
- Similar prevalence and %-inpatient diagnoses (severity) to adverse events
- Clinical expert review

Positive control outcomes:

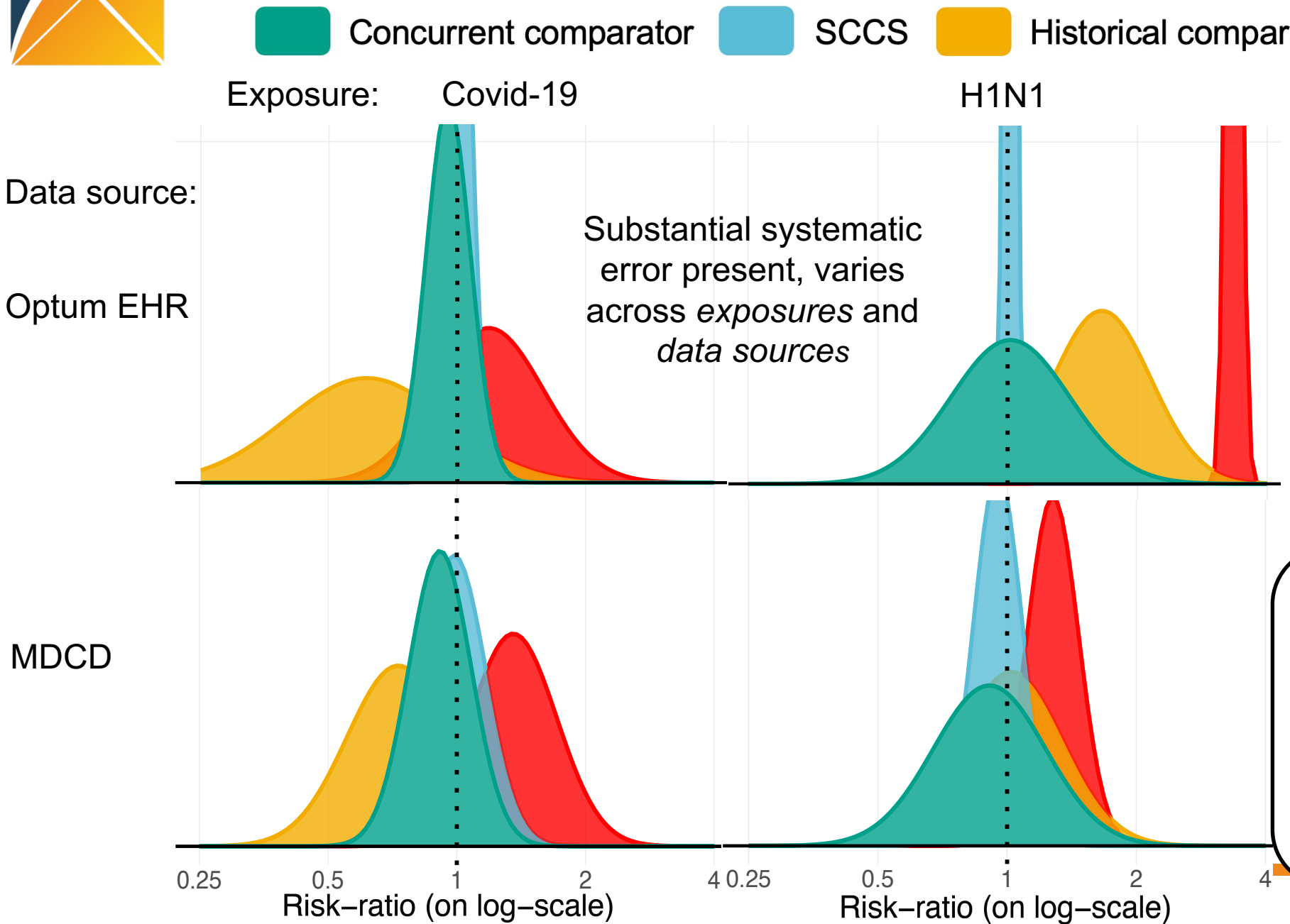
- Imputed from negative controls
- Known effect sizes (1.5, 2, 4 x)

Study protocol link: `https://ohdsi-studies.github.io/Eumaeus/Protocol.html`

Method details & variants for demonstration

- Time-at-risk (TaR) taken to be 1-28 days after exposure to vaccine.
- **Concurrent comparator**
- **Self-control case series (SCCS)**
  - How often did/do events occur in the same patients at different times?
  - Adjust by age and season, excluding pre-vaccination window.
- **Historical rates (Historical comparator)**
  - How often did events occur to other patients in the past?
  - Adjust by age and sex, using TaR after historic visit.
- **Case-control**
  - How often are patients with events vaccinated?
  - Adjust using age and sex matched controls.

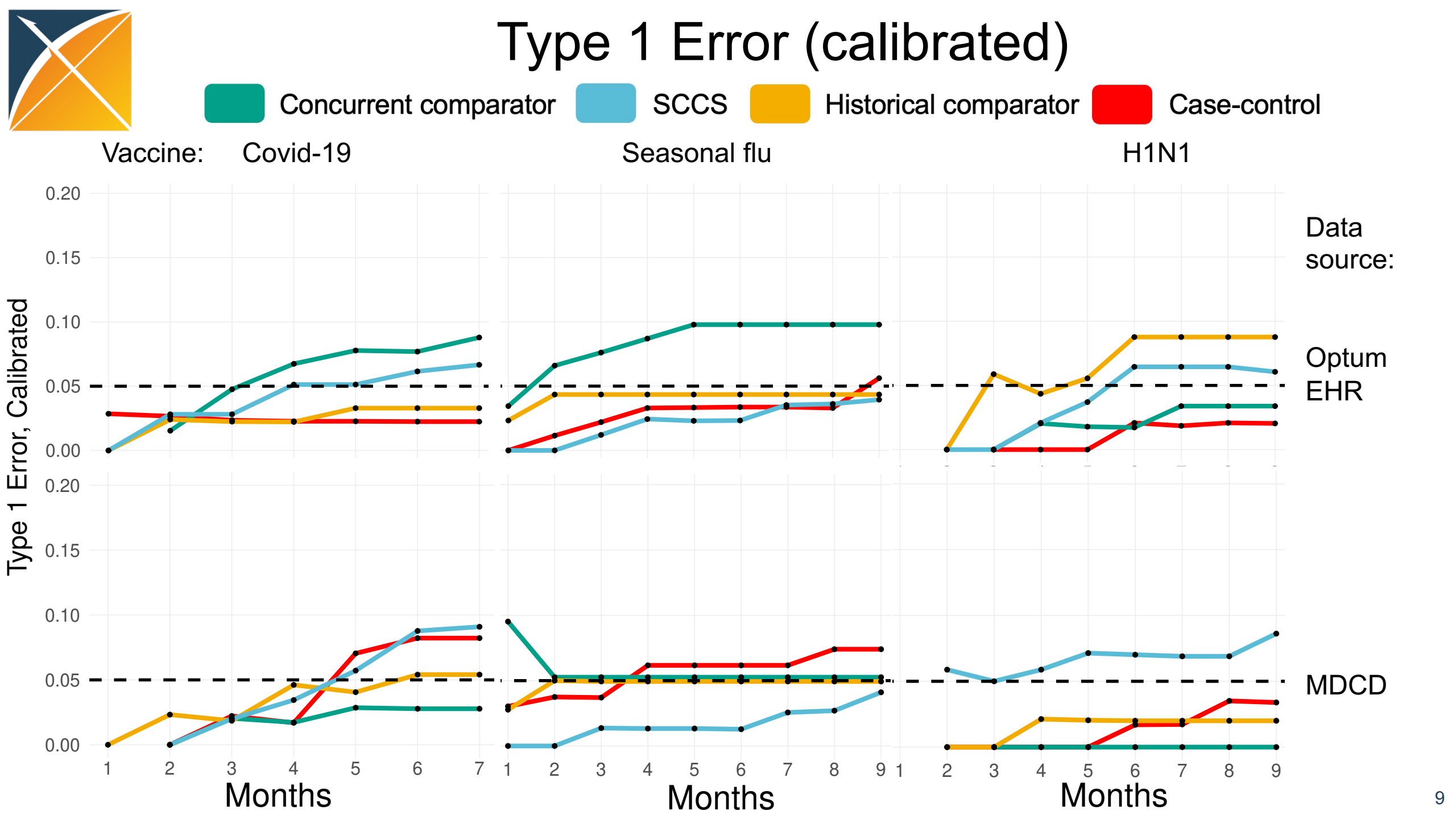
Systematic error



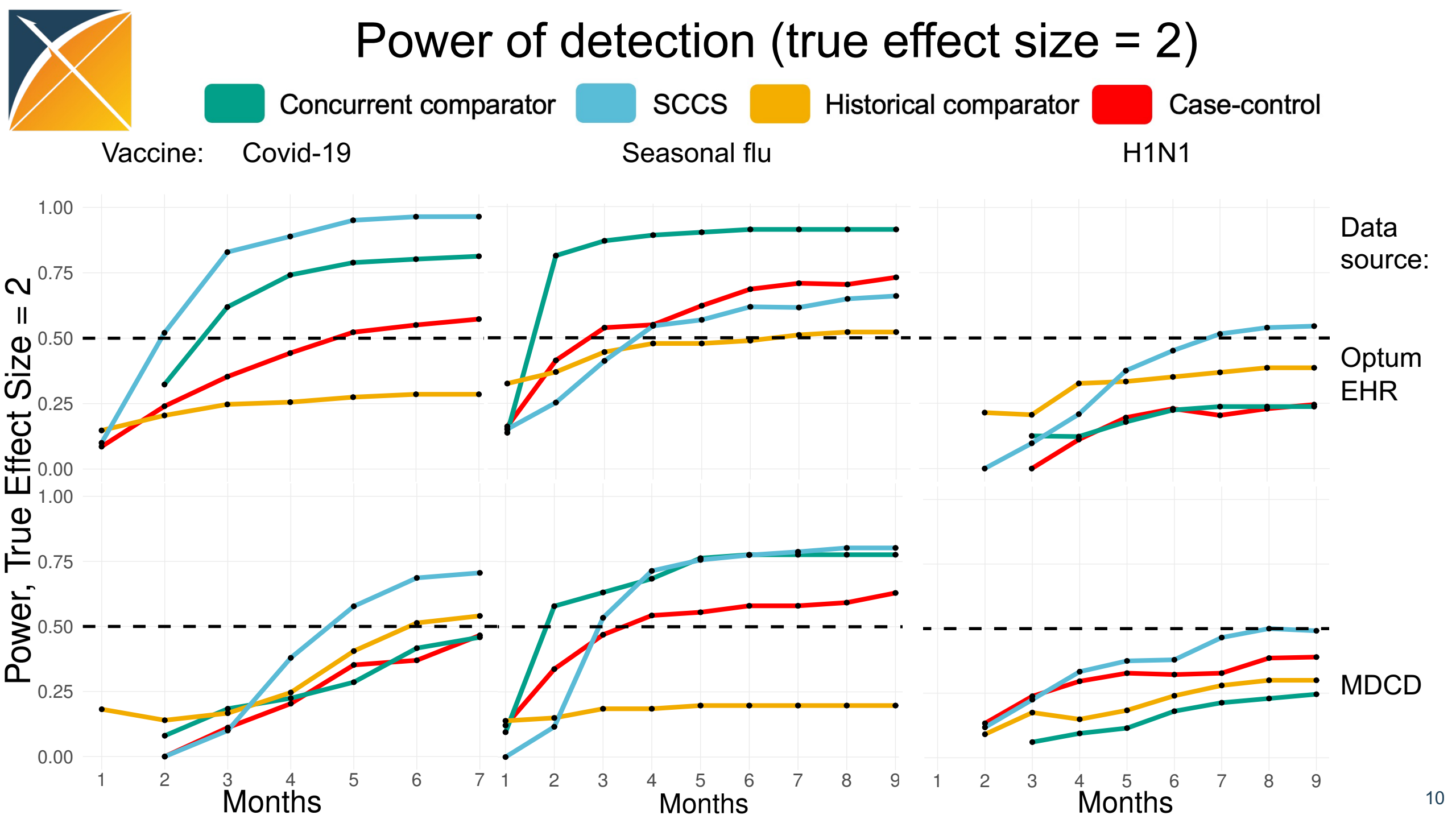
- Type 1 error may deviate from nominal value (= 0.05) due to **systematic error.**
- Overall, we observed systematic error densities of concurrent comparator and SCCS to have centers closer to 1.

To restore type 1 errors to near-nominal values, we carry out **empirical calibration**.

Type 1 Error (calibrated)



Power of detection (true effect size = 2)



Proportion of non-finite estimates

- We also evaluate the methods based on the proportion of non-finite effect size estimates.
- No estimate may be returned if there were no subjects left after propensity score matching.
- Another reason could be that there were no subjects having the outcome.
- Concurrent comparator has a higher proportion than the other methods.

Method	% Non-finite
Case-control	16.95 %
Concurrent comparator	36.56%
Historical comparator	26.88%
SCCS	1.49%

Exposure: H1N1pdm vaccine, Data source: Optum EHR

Method	% Non-finite
Case-control	4.84 %
Concurrent comparator	34.41%
Historical comparator	33.33%
SCCS	0.00%

Exposure: H1N1pdm vaccine, Data source: MDCD

Conclusion

- We compare the concurrent comparator approach with existing methods used in vaccine safety surveillance.
- Our analysis is based on an extensive set of negative controls and imputed positive controls across multiple data sources and vaccines.
- After empirical calibration to restore nominal type 1 error, SCCS performs the best overall, with concurrent comparator close to SCCS in terms of power of detection.
- The relative performance of the concurrent comparator decreases for smaller data sources.
- Compared with other approaches, concurrent comparator produces non-finite estimates more frequently.