

Comparative performance of the concurrent comparator design with existing vaccine safety surveillance approaches on real-world observational health data

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Background

It is of critical public health concern to identify safety signals originating from wide-scale immunization efforts. Such safety signals may be identified from spontaneous reports and other data sources. Although some work has been done on the best methods for vaccine safety surveillance, there is a scarcity of information on how these perform in analyses of real-world data.

Recent work¹ revealed extensive differences in the performance characteristics of different designs based on the choice in comparison groups that depend on the context in which a vaccine is administered, such as in a pharmacy or during a healthcare visit. Consequently, there is residual confounding even after standard adjustments are carried out as implemented in existing designs, leading to further bias when detecting safety signals or obtaining risk estimates.

Motivated by the need to address concerns with residual bias due to preferences of individuals receiving the vaccine, Klein et al.² recently

proposed the concurrent comparator design. Although the recently proposed concurrent comparator approach has been used to detect safety signals in observational health data³, there is a research gap in the evaluation of the overall statistical performance characteristics of the concurrent comparator and comparative assessment with existing methods. In this paper, we compare the performance characteristics of the concurrent comparator to other state-of-the-art designs considered in Schuemie et al.⁴ on real-world observational data. To the best of our knowledge, our work provides the first such open-source implementation that builds upon the OHDSI tool stack.

Methods

We use four administrative claims databases and one electronic health record (EHR) database to evaluate the operating characteristics of the recently proposed concurrent comparator, self-controlled case series, historical comparator and case-control epidemiological designs for vaccine safety, using negative control outcomes (unrelated to the vaccine), imputed positive control outcomes, and one real-world positive control outcome (myocarditis or pericarditis) for COVID-19. In this evaluation, we consider vaccine exposures for COVID-19, 2017-2018 seasonal influenza, H1N1pdm flu, Human Papillomavirus (HPV), and Varicella-Zoster. The methods are compared based on type 1 error, power of association detection, and proportion of non-finite association estimates produced.

Figure 1 provides a schematic illustration of the concurrent comparator cohort construction.

Results

All methods exhibit systematic error, leading to type 1 errors that are greater than the nominal ($=0.05$) threshold, often by a substantial amount. To restore near-nominal type 1 error, we carry out empirical calibration based on the large set of negative controls. Post-empirical calibration, the

self-controlled case series designs had the highest power overall, closely followed by the concurrent comparator designs. However, concurrent comparator analyses often produced a higher proportion of non-finite estimates.

Figure 2 plots type 1 errors of different designs evaluated over a surveillance period of 9 months, with negative control outcomes and data from an electronic health record database. With the same database and surveillance period, Figure 3 plots the power for these designs with imputed positive control outcomes with risk ratio = 2.

Conclusion

Our results indicate that there remains non-negligible systematic error under the concurrent comparator design. In terms of statistical performance, the concurrent comparator designs show promising results in some scenarios, regularly outperforming the historical comparator and case-control designs, but often producing non-finite estimates. Future work building on the concurrent comparator design is required to construct more efficient designs with lower systematic error.

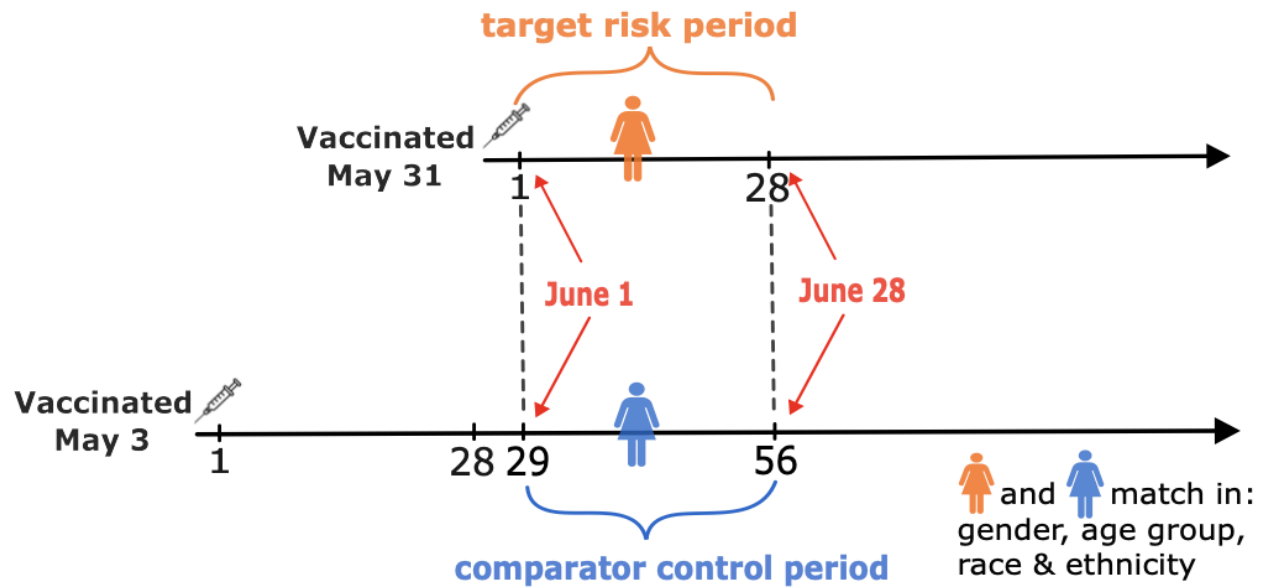


Figure 1: The concurrent comparator approach. The individual (in orange) with an outcome during their target TAR (1-28 days post-vaccination) is matched to another vaccinated individual (in blue) in their comparator control period (29-56 days post-vaccination), based on gender, age group, race, and ethnicity.

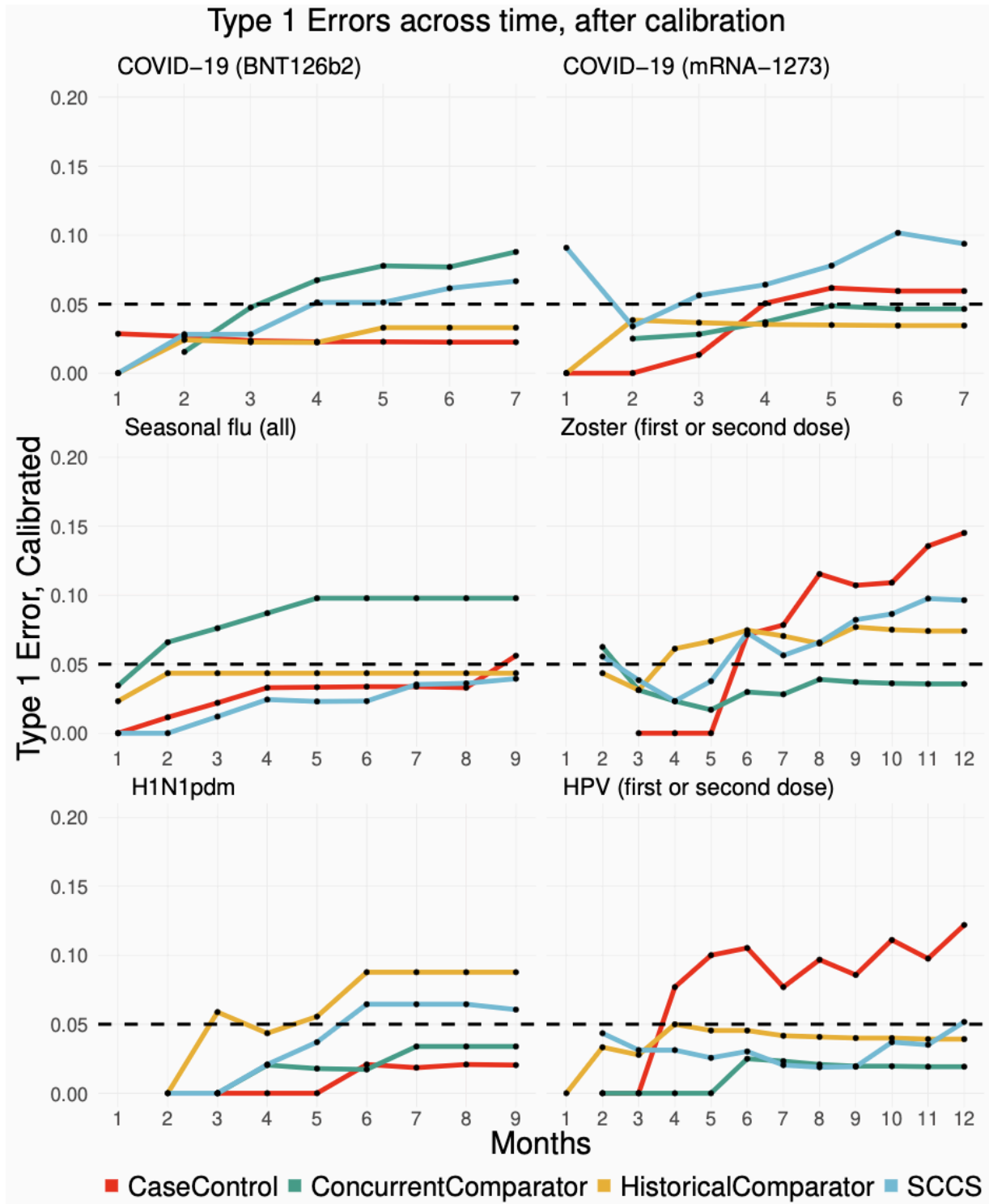


Figure 2: Calibrated type 1 errors of methods as a function of time, across different exposures for the Optum EHR data source.

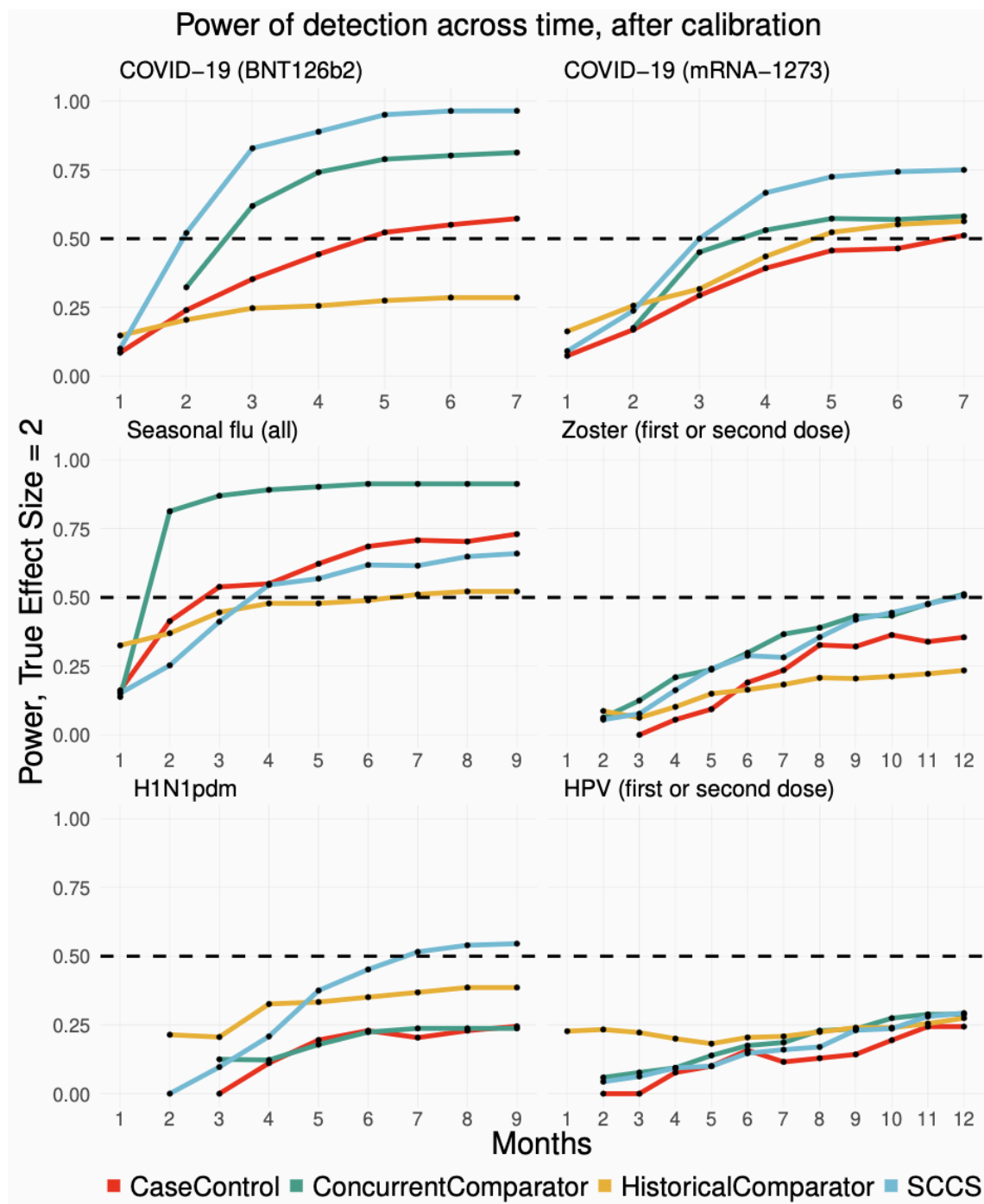


Figure 3: Power of detection for the methods as a function of time, across different exposures for the Optum EHR data source. We assume the true risk ratio = 2.

References

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