Evaluation of causal vaccine efficacy under stochastic interventional shifts of an immunologic marker in COVID-19 vaccine efficacy trials

Keywords: causal inference, stochastic interventions, mediation analysis, interventional effects, two-phase sampling, immune correlate of protection, vaccine efficacy, COVID-19

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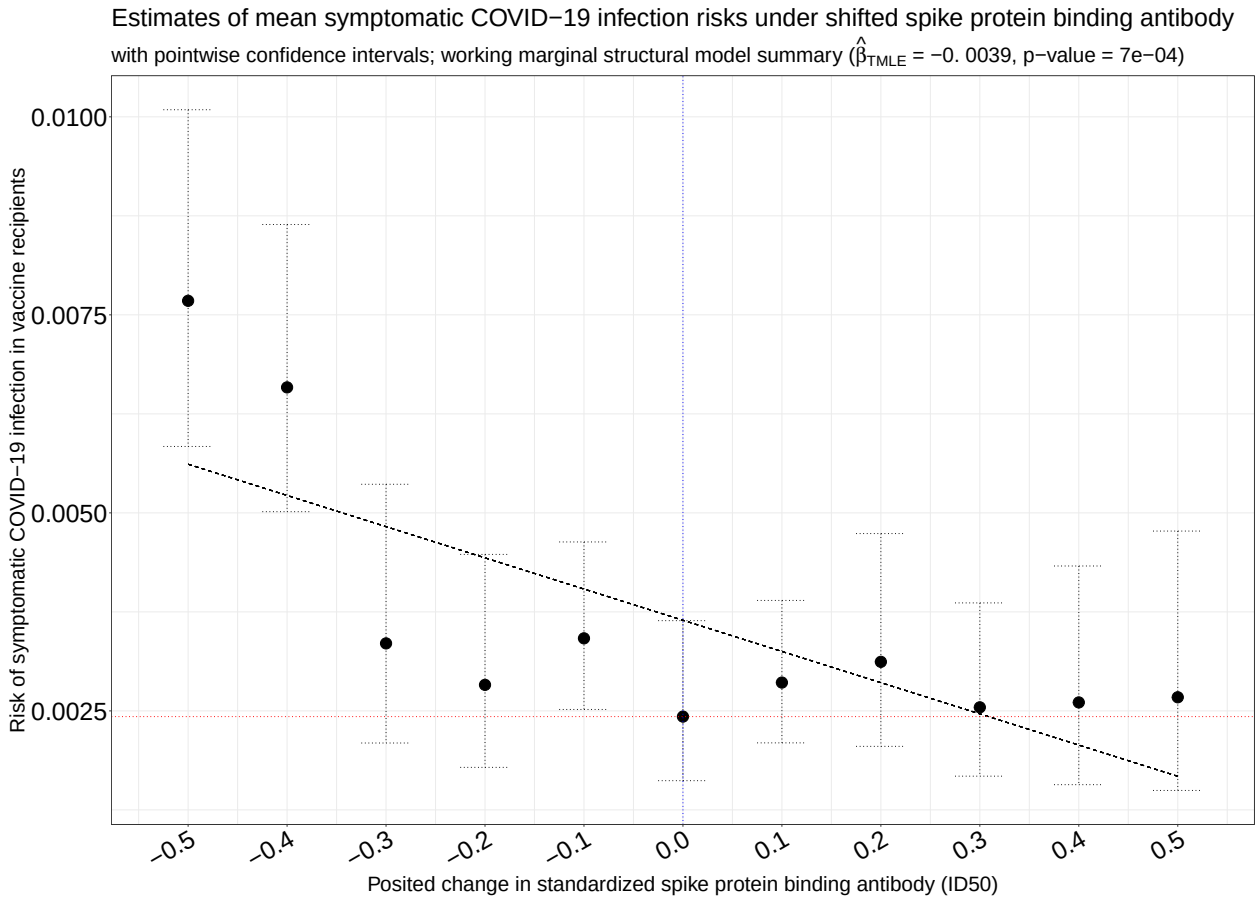
Initial efficacy assessments of vaccine candidates for COVID-19 have made for a promising start to curbing the pandemic. A critical next step is identifying immune correlates of protection, and their use in the development of next-generation protective vaccine candidates. Deploying the tools of causal inference in service of such goals is obstructed by the historical focus of the field on static interventions, which cannot be applied to *quantitative* immunologic marker measurements without simplifying assumptions. Stochastic interventions, which define the target parameter as the mean counterfactual outcome under hypothetically shifted versions of the observed immunologic marker distribution, hold promise for circumventing such difficulties. Complicating analytic efforts further, vaccine efficacy trials regularly employ two-phase sampling of immunologic markers, necessitating careful adjustment for formal statistical inference.

We present a novel framework for evaluating *causal* vaccine efficacy under stochastic interventional shifts of immunologic markers, with multiply robust, nonparametric-efficient estimators utilizing state-of-the-art machine learning in nuisance parameter estimation. Our effect definitions quantify how disease risk would change across counterfactual shifts of the observed immunogenicity of immunologic markers modulated by vaccination, similar to a dose-response analysis. Our framework incorporates corrections for two-phase sampling and right-censoring of disease endpoints, and defines vaccine efficacy by comparing counterfactual risks in vaccine and placebo arms. The approach, appearing in the correlates statistical analysis plan (https://doi.org/10.6084/m9.figshare.13198595) of the COVID-19 Prevention Network, is applied to mock data inspired by real-world vaccine efficacy trials to demonstrate how candidate correlates of protection may be evaluated by the impacts on disease risk of posited post-vaccination immunogenicity shifts.


Estimates of mean symptomatic COVID−19 infection risks under shifted spike protein binding antibody
with pointwise confidence intervals; working marginal structural model summary ($\hat{\beta}_{TMLE}$ = −0. 0039, p−value = 7e−04)
Risk of symptomatic COVID−19 infection in vaccine recipients
0.0100
0.0075
0.0050
0.0025
−0.5
−0.4
−0.3
−0.2
−0.1
0.0
0.1
0.2
0.3
0.4
0.5
Posited change in standardized spike protein binding antibody (ID50)