Causal evaluation of vaccine efficacy in COVID-19 trials with stochastic interventional effects (SER 2021)

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

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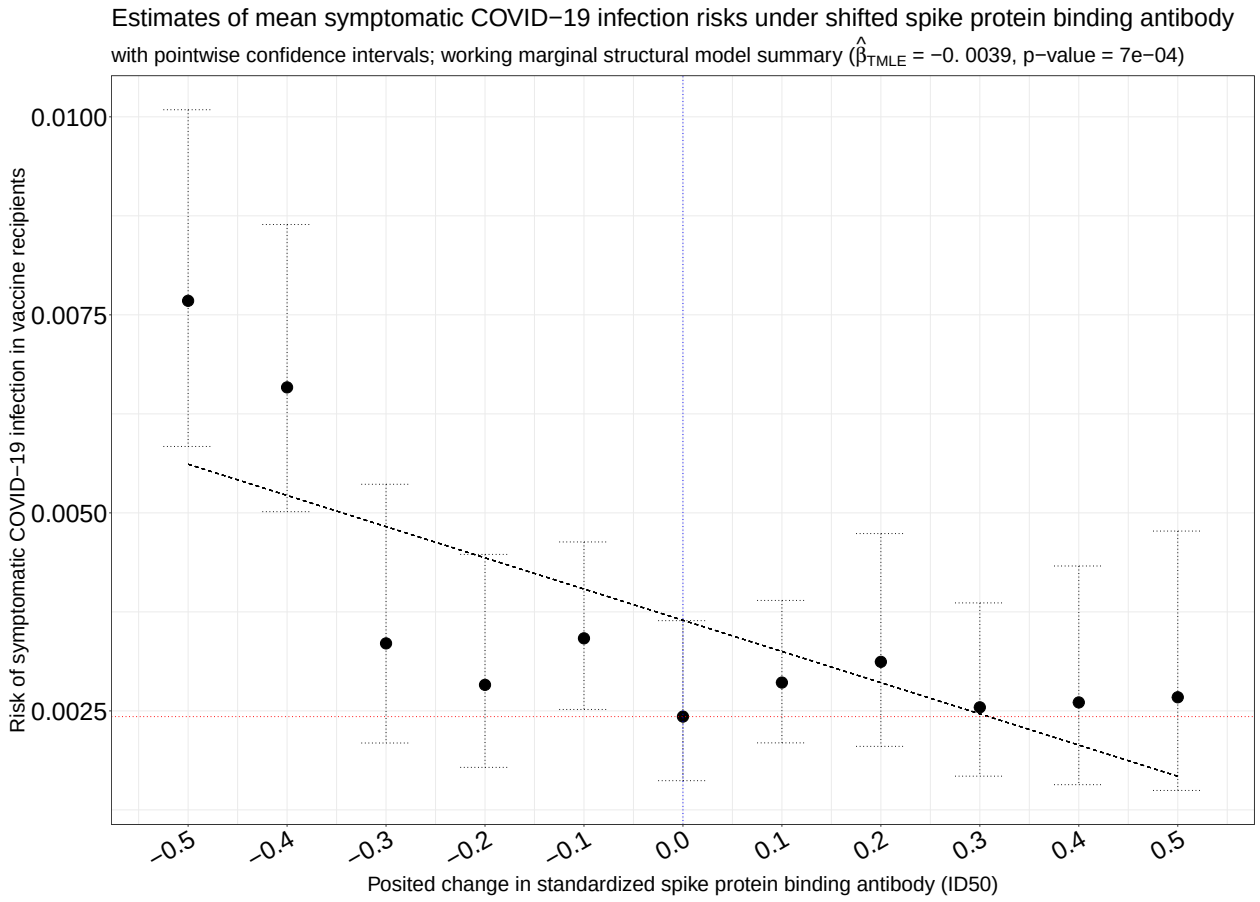
Promising initial efficacy assessments of vaccine candidates for COVID-19 have made for a promising start to curbing the pandemic. A critical next step is identifying immune correlates of protection, and their use in the development of future (protective) vaccine candidates. Deploying the tools of statistical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

We present a novel framework for evaluating vaccine efficacy through immune correlates of protection: nonparametric-efficient, multiply robust estimators of *causal* vaccine efficacy based on stochastic interventional effects, which treat immune correlates as mediators of the effect of vaccination on disease. Our effect definitions quantify how disease risk would change across (counterfactual) shifts in the observed immunogenicity levels of immune correlates, similar, in principal, to a dose-response analysis. Our framework readily incorporates corrections for two-phase sampling and right-censoring of disease endpoints, and conveniently defines vaccine efficacy by comparing counterfactual risks in the vaccine versus placebo arms. Using example data from the COVID-19 Vaccine Prevention Network, we illustrate how our proposed analysis facilitates the evaluation of candidate correlates of protection in terms of the impacts of posited shifts in post-vaccination immunogenicity on disease risk.


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)