Evaluating vaccine efficacy in COVID-19 trials with stochastic interventional effects (SER 2021)

Keywords: causal inference, stochastic interventions, vaccine efficacy, two-phase sampling, COVID-19

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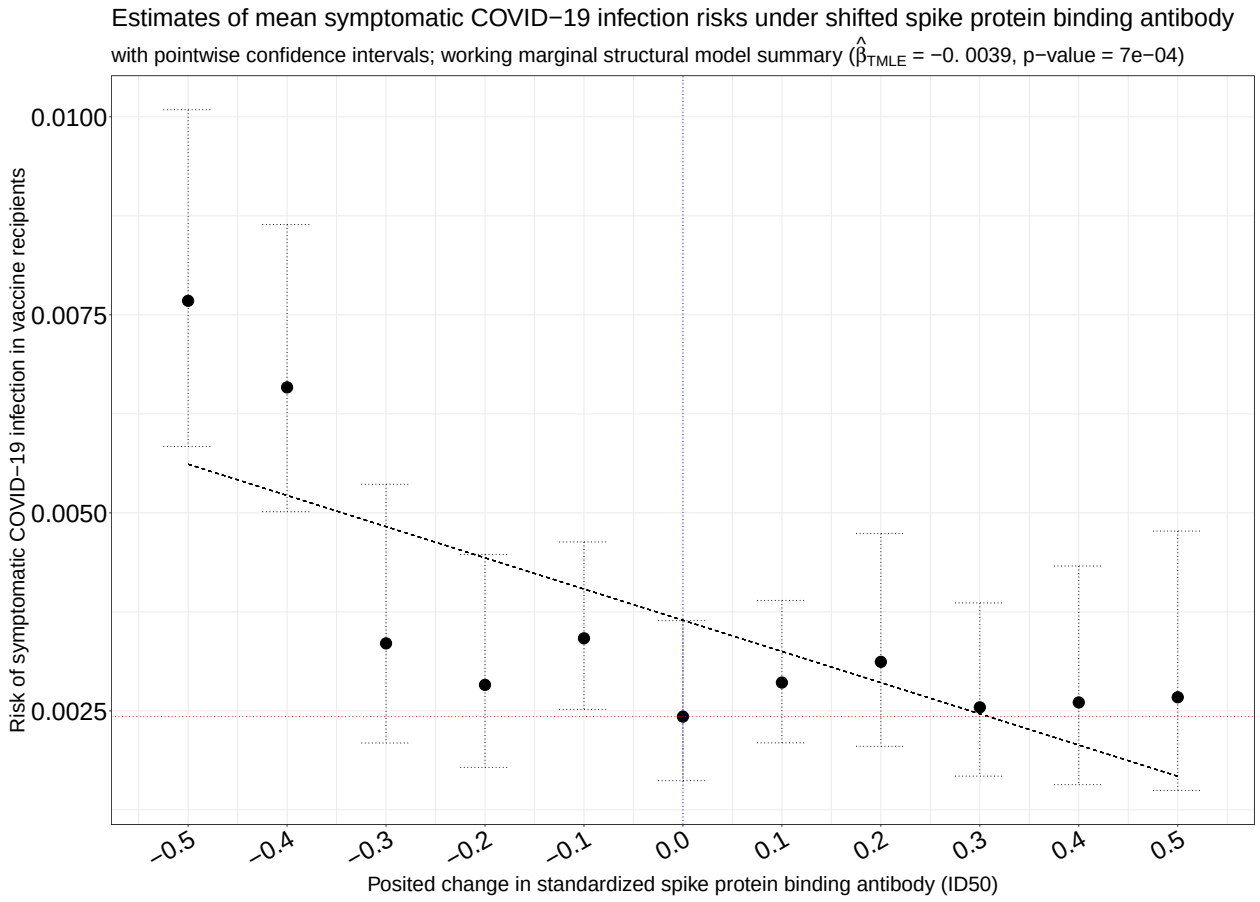
While promising vaccine efficacy assessments have softened the critical landscape surrounding the COVID-19 pandemic, many critical open questions remain. In order to elucidate the mechanisms by which existing vaccines have achieved remarkable protection against symptomatic and significant COVID-19 infection, and to better align the development of next-generation (protective) vaccines, careful study of immune correlates of protection is imperative. As measurements of the post-vaccination levels of such immune markers are quantitative, the most common tools of statistical causal inference, which require binary exposures and TODO, cannot be readily utilized. To complicate such analyses further, vaccine efficacy trials generally employ two-phase sampling of such immune markers, necessitating careful downstream adjustment for formal statistical inference. Stochastic shift interventions define the target parameter as the mean counterfactual outcome under hypothetically shifted versions of the observed immune correlates activity distribution.

We present a novel framework for use in evaluating vaccine efficacy: nonparametric-efficient, multiply robust estimators of causal vaccine efficacy effects based on stochastic shift interventions, augmented to two-phase sampling. Our effect definitions open the door to asking how the risk for symptomatic disease would change across various (counterfactual) levels of activity of immune correlates of protection, similar, in principal, to a dose-response analysis. Our proposed methodology incorporates corrections for censored outcomes in the vaccine arm of the trial and, unlike prior proposals, defines effects by comparing risk in the vaccine arm to that in the control arm. We demonstrate our proposed immune correlates analysis using data produced by the COVID-19 Vaccine Prevention Network, illustrating how the post-vaccination immunogenicity of XYZ may be quantified across a grid of possible 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)