COVID-19 Correlates of Protection Analysis Report $$\operatorname{mock}$$ Study

USG COVID-19 Response Biostatistics Team

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CoP: Correlates of Vaccine Efficacy

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CoP: Controlled Vaccine Efficacy

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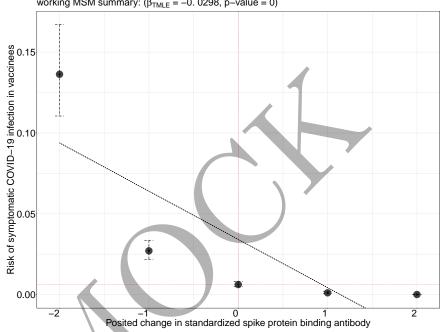
Stochastic Interventional Risk and Vaccine Efficacy Effects

We estimate the counterfactual mean of symptomatic COVID-19 infection under posited shifts in the measured activity levels of each of 4 candidate mechanistic correlates of protection (mCoP) biomarkers. By shifting the standardized biomarker activity levels by standard unit shifts along the grid $\{-2, -1, 0, 1, 2\}$, we can assess the degree to which vaccines that modulate mCoP biomarker activity to these levels could mitigate symptomatic COVID-19 infection in terms of counterfactual stochastic interventional risk and vaccine efficacy (VE).

3.1 Figures with estimates and confidence intervals for Day 57

3.1.1 Stochastic interventional risk: spike protein binding antibody

Estimated counterfactual risk of symptomatic COVID–19 infection at Day 57 working MSM summary: ($\hat{\beta}_{TMLE}$ = -0. 0298, p-value = 0)

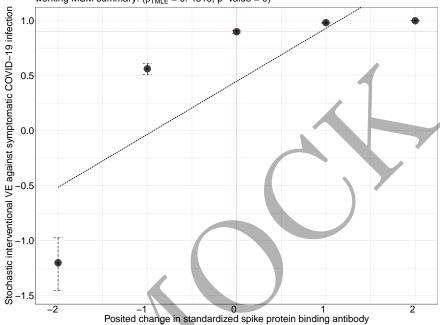


Mean counterfactual COVID-19 infection risk across standardized shifts in spike protein binding antibody levels, summarized by projection of causal dose–response curve onto a linear working model.

$3.1.\,$ FIGURES WITH ESTIMATES AND CONFIDENCE INTERVALS FOR DAY 5715

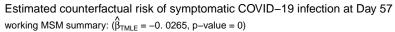
3.1.2 Stochastic interventional VE: spike protein binding antibody

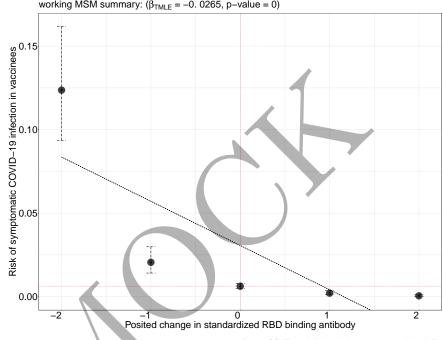
Estimated vaccine efficacy v. symptomatic COVID–19 infection at Day 57 working MSM summary: ($\hat{\beta}_{TMLE}$ = 0. 4818, p–value = 0)



Stochastic interventional vaccine efficacy v. COVID-19 infection across standardized shifts in spike protein binding antibody levels, summarized by projection of causal dose-response curve on a linear working model.

3.1.3 Stochastic interventional risk: RBD binding antibody



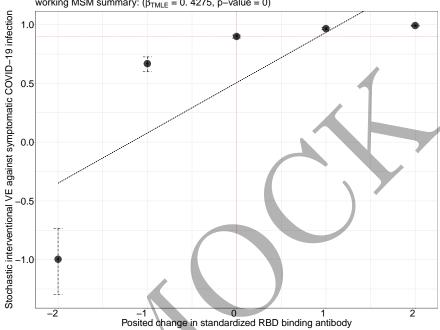


Mean counterfactual COVID-19 infection risk across standardized shifts in RBD binding antibody levels, summarized by projection of causal dose-response curve onto a linear working model.

$3.1.\,$ FIGURES WITH ESTIMATES AND CONFIDENCE INTERVALS FOR DAY 5717

3.1.4 Stochastic interventional VE: RBD binding antibody

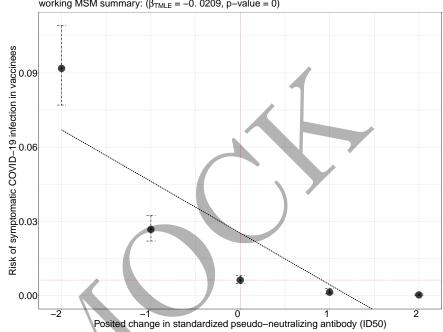
Estimated vaccine efficacy v. symptomatic COVID–19 infection at Day 57 working MSM summary: ($\hat{\beta}_{TMLE}$ = 0. 4275, p–value = 0)



Stochastic interventional vaccine efficacy v. COVID-19 infection across standardized shifts in RBD binding antibody levels, summarized by projection of causal dose–response curve on a linear working model.

3.1.5 Stochastic interventional risk: pseudo-neutralizing antibody (ID50)

Estimated counterfactual risk of symptomatic COVID–19 infection at Day 57 working MSM summary: ($\hat{\beta}_{TMLE}$ = -0. 0209, p-value = 0)

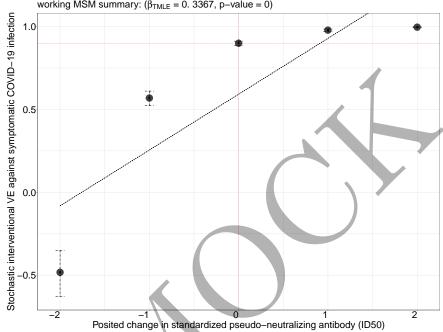


Mean counterfactual COVID-19 infection risk across standardized shifts in pseudo-neutralizing antibody (ID50) levels, summarized by projection of causal dose-response curve onto a linear working model.

$3.1. \; FIGURES \; WITH \; ESTIMATES \; AND \; CONFIDENCE \; INTERVALS \; FOR \; DAY \; 5719$

3.1.6 Stochastic interventional VE: pseudo-neutralizing antibody (ID50)

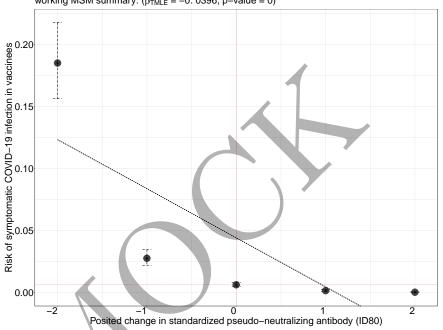
Estimated vaccine efficacy v. symptomatic COVID–19 infection at Day 57 working MSM summary: ($\hat{\beta}_{TMLE}$ = 0. 3367, p–value = 0)



Stochastic interventional vaccine efficacy v. COVID-19 infection across standardized shifts in pseudo-neutralizing antibody (ID50) levels, summarized by projection of causal dose-response curve on a linear working model.

3.1.7 Stochastic interventional risk: pseudo-neutralizing antibody (ID80)

Estimated counterfactual risk of symptomatic COVID–19 infection at Day 57 working MSM summary: ($\hat{\beta}_{TMLE}$ = -0. 0396, p-value = 0)

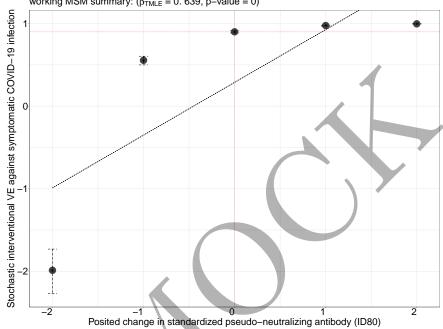


Mean counterfactual COVID-19 infection risk across standardized shifts in pseudo-neutralizing antibody (ID80) levels, summarized by projection of causal dose-response curve onto a linear working model.

$3.1. \;\; FIGURES \; WITH \; ESTIMATES \; AND \; CONFIDENCE \; INTERVALS \; FOR \; DAY \; 5721$

3.1.8 Stochastic interventional VE: pseudo-neutralizing antibody (ID80)

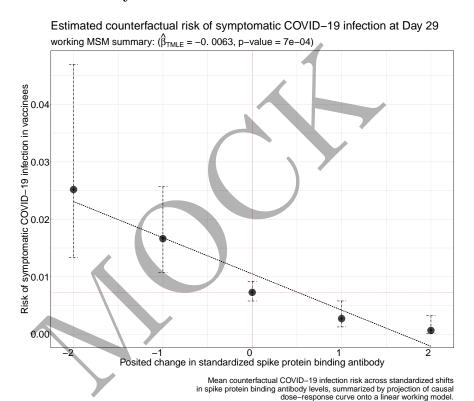
Estimated vaccine efficacy v. symptomatic COVID–19 infection at Day 57 working MSM summary: ($\hat{\beta}_{TMLE}$ = 0. 639, p-value = 0)



Stochastic interventional vaccine efficacy v. COVID-19 infection across standardized shifts in pseudo-neutralizing antibody (ID80) levels, summarized by projection of causal dose-response curve on a linear working model.

3.2 Figures with estimates and confidence intervals for Day 29

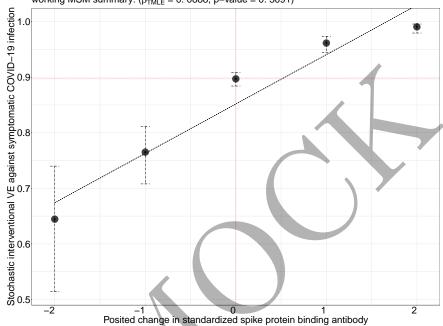
3.2.1 Stochastic interventional risk: spike protein binding antibody



$3.2.\ FIGURES\ WITH\ ESTIMATES\ AND\ CONFIDENCE\ INTERVALS\ FOR\ DAY\ 2923$

3.2.2 Stochastic interventional VE: spike protein binding antibody

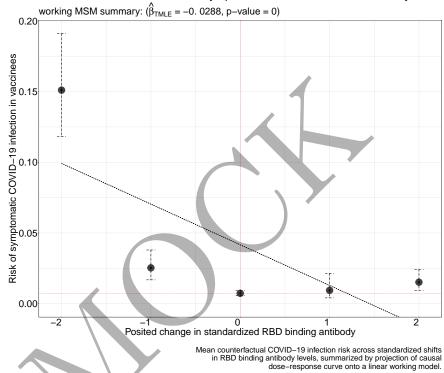
Estimated vaccine efficacy v. symptomatic COVID-19 infection at Day 29 working MSM summary: ($\hat{\beta}_{TMLE}$ = 0. 0888, p-value = 0. 3091)



Stochastic interventional vaccine efficacy v. COVID-19 infection across standardized shifts in spike protein binding antibody levels, summarized by projection of causal dose–response curve on a linear working model.

3.2.3 Stochastic interventional risk: RBD binding antibody

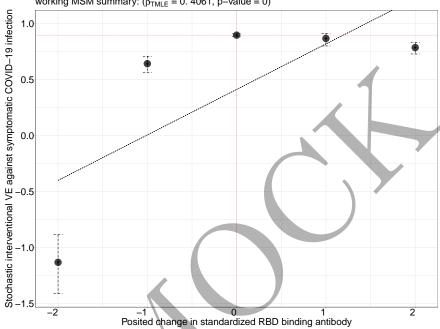




$3.2.\ FIGURES\ WITH\ ESTIMATES\ AND\ CONFIDENCE\ INTERVALS\ FOR\ DAY\ 2925$

3.2.4 Stochastic interventional VE: RBD binding antibody

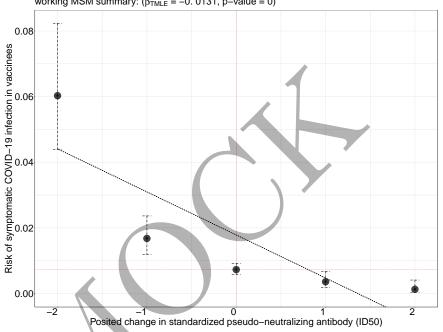
Estimated vaccine efficacy v. symptomatic COVID–19 infection at Day 29 working MSM summary: ($\hat{\beta}_{TMLE}$ = 0. 4061, p–value = 0)



Stochastic interventional vaccine efficacy v. COVID-19 infection across standardized shifts in RBD binding antibody levels, summarized by projection of causal dose-response curve on a linear working model.

3.2.5 Stochastic interventional risk: pseudo-neutralizing antibody (ID50)

Estimated counterfactual risk of symptomatic COVID-19 infection at Day 29 working MSM summary: ($\hat{\beta}_{TMLE} = -0.0131$, p-value = 0)

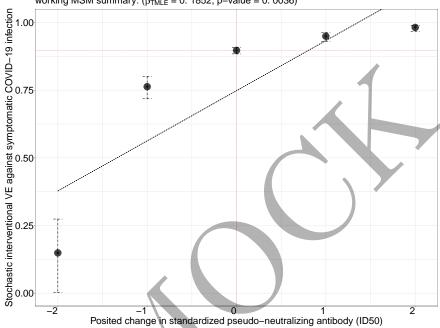


Mean counterfactual COVID-19 infection risk across standardized shifts in pseudo-neutralizing antibody (ID50) levels, summarized by projection of causal dose-response curve onto a linear working model.

3.2. FIGURES WITH ESTIMATES AND CONFIDENCE INTERVALS FOR DAY 2927

3.2.6 Stochastic interventional VE: pseudo-neutralizing antibody (ID50)

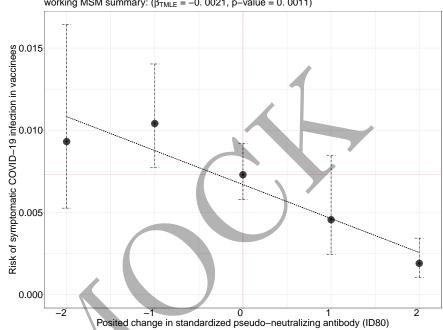
Estimated vaccine efficacy v. symptomatic COVID-19 infection at Day 29 working MSM summary: ($\hat{\beta}_{TMLE}$ = 0. 1852, p-value = 0. 0036)



Stochastic interventional vaccine efficacy v. COVID-19 infection across standardized shifts in pseudo-neutralizing antibody (ID50) levels, summarized by projection of causal dose-response curve on a linear working model.

3.2.7 Stochastic interventional risk: pseudo-neutralizing antibody (ID80)

Estimated counterfactual risk of symptomatic COVID–19 infection at Day 29 working MSM summary: ($\hat{\beta}_{TMLE}$ = -0. 0021, p-value = 0. 0011)

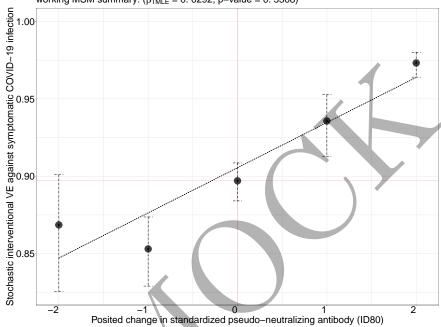


Mean counterfactual COVID-19 infection risk across standardized shifts in pseudo-neutralizing antibody (ID80) levels, summarized by projection of causal dose-response curve onto a linear working model.

$3.2.\ FIGURES\ WITH\ ESTIMATES\ AND\ CONFIDENCE\ INTERVALS\ FOR\ DAY\ 2929$

3.2.8 Stochastic interventional VE: pseudo-neutralizing antibody (ID80)

Estimated vaccine efficacy v. symptomatic COVID–19 infection at Day 29 working MSM summary: ($\hat{\beta}_{TMLE}$ = 0. 0292, p-value = 0. 5308)



Stochastic interventional vaccine efficacy v. COVID-19 infection across standardized shifts in pseudo-neutralizing antibody (ID80) levels, summarized by projection of causal dose-response curve on a linear working model.



Mediators of Vaccine Efficacy

Table 4.1: Table of mediation effect estimates for quantitative markers with 95% confidence intervals.

Direct VE = VE comparing vaccine vs. placebo with marker set to distribution in placebo.

Indirect VE = VE in vaccinated comparing observed marker vs. hypothetical marker under placebo.

Prop. mediated = fraction of total risk reduction from vaccine attributed to antibody response.

| Time | Assay | Direct VE | Indirect VE | Prop. mediated |
|--------|------------------------------|----------------------------|----------------------------|----------------------------|
| Day 57 | Binding Antibody to Spike | NA | NA | NA |
| Day 57 | Binding Antibody to RBD | NA | NA | NA |
| Day 57 | PsV Neutralization 50% Titer | NA | NA | NA |
| Day 57 | PsV Neutralization 80% Titer | NA | NA | NA |
| Day 29 | Binding Antibody to Spike | NA | NA | NA |
| Day 29 | Binding Antibody to RBD | NA | NA | NA |
| Day 29 | PsV Neutralization 50% Titer | $0.205 \ (0.142, \ 0.262)$ | $0.856 \ (0.823, \ 0.883)$ | $0.894 \ (0.927, \ 0.861)$ |
| Day 29 | PsV Neutralization 80% Titer | $0.823 \ (0.729, \ 0.884)$ | 0.352 (-0.032, 0.593) | 0.200 (0.408, -0.007) |

^a NA denotes insufficient overlap in antibody response between vaccinated and control participants.

Table 4.2: Table of mediation effect estimates for tertile markers with 95% confidence intervals.

Direct VE = VE comparing vaccine vs. placebo with marker set to distribution in placebo.

Indirect VE = VE in vaccinated comparing observed marker vs. hypothetical marker under placebo.

Prop. mediated = fraction of total risk reduction from vaccine attributed to antibody response.

| Time | Assay | Direct VE | Indirect VE | Prop. mediated |
|--------|------------------------------|----------------------------|----------------------------|----------------------------|
| Day 57 | Binding Antibody to Spike | 0.865 (0.723, 0.934) | 0.157 (-0.577, 0.549) | 0.078 (0.369, -0.212) |
| Day 57 | Binding Antibody to RBD | $0.777 \ (0.677, \ 0.846)$ | $0.487 \ (0.305, \ 0.622)$ | $0.308 \ (0.450, \ 0.166)$ |
| Day 57 | PsV Neutralization 50% Titer | $0.736\ (0.643,\ 0.805)$ | $0.568 \ (0.485, \ 0.637)$ | 0.386 (0.480, 0.293) |
| Day 57 | PsV Neutralization 80% Titer | $0.742\ (0.646,\ 0.812)$ | $0.557 \ (0.460, \ 0.637)$ | $0.375 \ (0.479, \ 0.272)$ |
| Day 29 | Binding Antibody to Spike | 0.890 (0.784, 0.944) | -0.047 (-0.927, 0.431) | -0.021 (0.260, -0.303) |
| Day 29 | Binding Antibody to RBD | $0.940 \ (0.701, \ 0.988)$ | -0.909 (-7.917, 0.591) | -0.299 (0.407, -1.004) |
| Day 29 | PsV Neutralization 50% Titer | 0.917 (0.700, 0.977) | -0.388 (-3.702, 0.590) | -0.151 (0.409, -0.712) |
| Day 29 | PsV Neutralization 80% Titer | $0.905 \ (0.809, \ 0.953)$ | -0.208 (-1.262, 0.355) | -0.087 (0.201, -0.376) |

Appendix

- This report was built from the CoVPN/correlates_reporting repository with commit hash a6650c62ba971b13ba484300063447e3737ff1cb. A diff of the changes introduced by that commit may be viewed at https://github.com/CoVPN/correlates_reporting/commit/a6650c62ba971b13ba484300063447e3737ff1cb
- The sha256 hash sum of the raw input file, "COVID_VEtrial_practicedata_primarystage1.csv": 2353971c2e14399ede55ef6ba0d4e624626433dc15ec507c2482bb886210019a
- \bullet The sha256 hash sum of the processed file, "practice_data.csv": 6250066f886245b78f7aa29fefc615ba5d10118448f298c39ec2b601b2a5049f