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

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CoP: Correlates of Vaccine Efficacy

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CoP: Controlled Vaccine Efficacy

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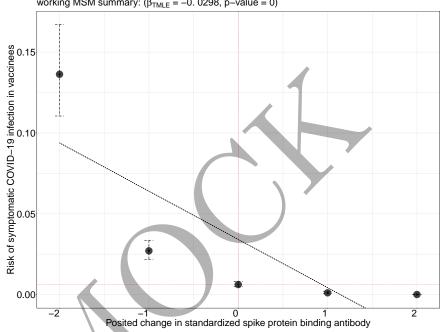
## Stochastic Interventional Risk and Vaccine Efficacy Effects

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)

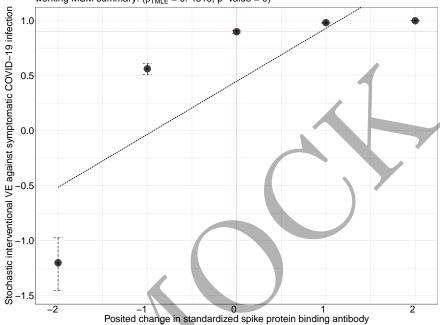


Mean counterfactual COVID-19 infection risk across standardized shifts in spike protein binding antibody levels, summarized by projection of causal dose–response curve onto a linear working model.

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

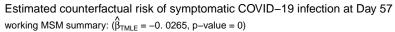
## 3.1.2 Stochastic interventional VE: spike protein binding antibody

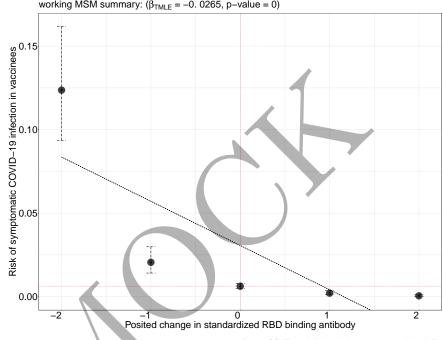
Estimated vaccine efficacy v. symptomatic COVID–19 infection at Day 57 working MSM summary: ( $\hat{\beta}_{TMLE}$  = 0. 4818, p–value = 0)



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



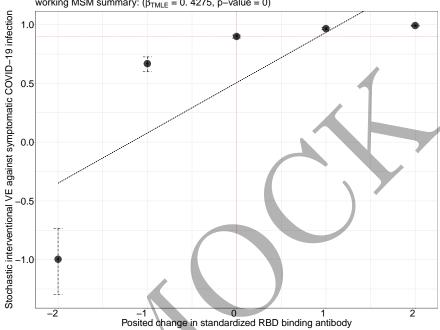


Mean counterfactual COVID-19 infection risk across standardized shifts in RBD binding antibody levels, summarized by projection of causal dose-response curve onto a linear working model.

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

### 3.1.4 Stochastic interventional VE: RBD binding antibody

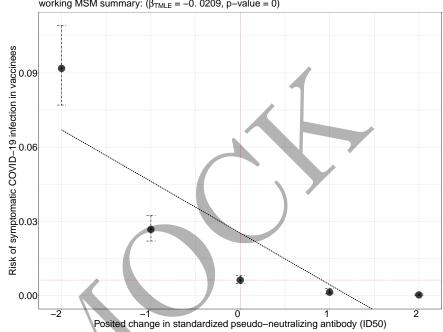
Estimated vaccine efficacy v. symptomatic COVID–19 infection at Day 57 working MSM summary: ( $\hat{\beta}_{TMLE}$  = 0. 4275, p–value = 0)



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)

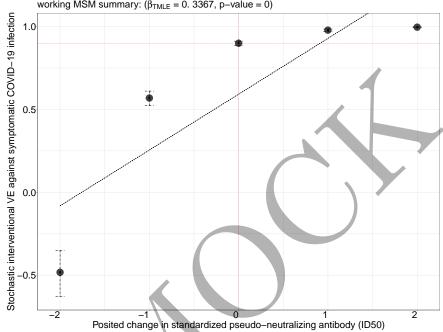


Mean counterfactual COVID-19 infection risk across standardized shifts in pseudo-neutralizing antibody (ID50) levels, summarized by projection of causal dose-response curve onto a linear working model.

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

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

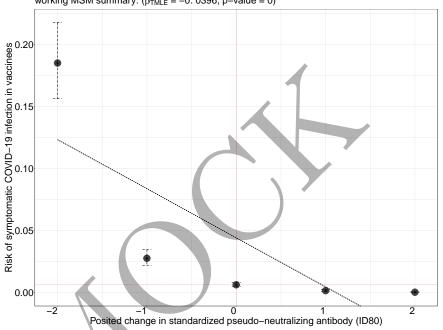
Estimated vaccine efficacy v. symptomatic COVID–19 infection at Day 57 working MSM summary: ( $\hat{\beta}_{TMLE}$  = 0. 3367, p–value = 0)



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)

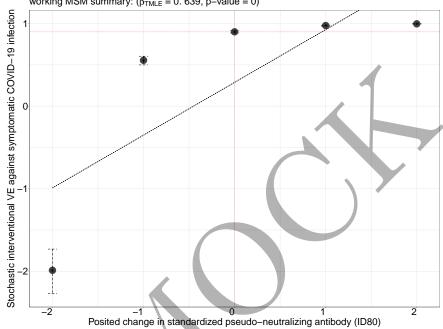


Mean counterfactual COVID-19 infection risk across standardized shifts in pseudo-neutralizing antibody (ID80) levels, summarized by projection of causal dose-response curve onto a linear working model.

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

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

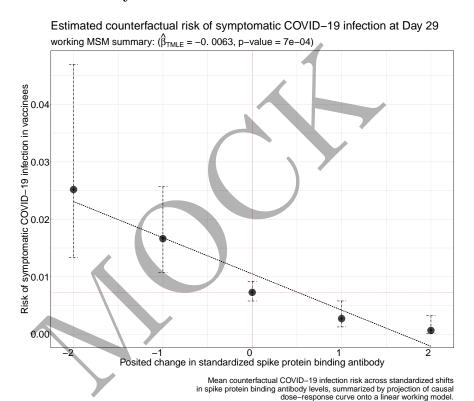
Estimated vaccine efficacy v. symptomatic COVID–19 infection at Day 57 working MSM summary: ( $\hat{\beta}_{TMLE}$  = 0. 639, p-value = 0)



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

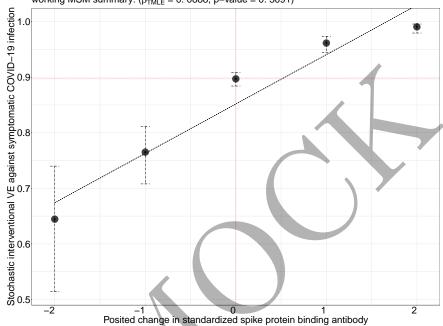
## 3.2.1 Stochastic interventional risk: spike protein binding antibody



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

## 3.2.2 Stochastic interventional VE: spike protein binding antibody

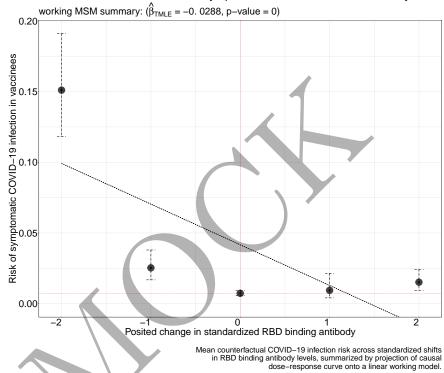
Estimated vaccine efficacy v. symptomatic COVID-19 infection at Day 29 working MSM summary: ( $\hat{\beta}_{TMLE}$  = 0. 0888, p-value = 0. 3091)



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

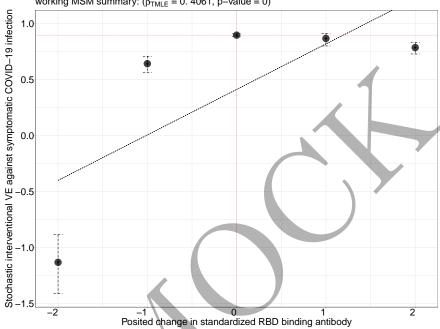




### $3.2.\ FIGURES\ WITH\ ESTIMATES\ AND\ CONFIDENCE\ INTERVALS\ FOR\ DAY\ 2925$

### 3.2.4 Stochastic interventional VE: RBD binding antibody

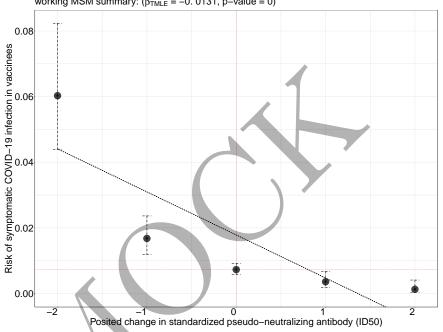
Estimated vaccine efficacy v. symptomatic COVID–19 infection at Day 29 working MSM summary: ( $\hat{\beta}_{TMLE}$  = 0. 4061, p–value = 0)



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)

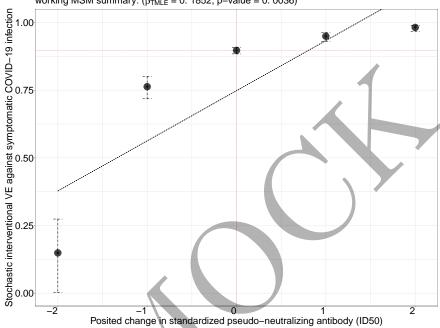


Mean counterfactual COVID-19 infection risk across standardized shifts in pseudo-neutralizing antibody (ID50) levels, summarized by projection of causal dose-response curve onto a linear working model.

#### 3.2. FIGURES WITH ESTIMATES AND CONFIDENCE INTERVALS FOR DAY 2927

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

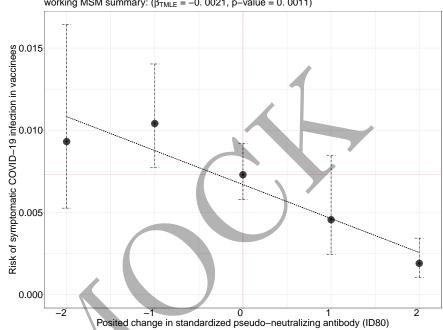
Estimated vaccine efficacy v. symptomatic COVID-19 infection at Day 29 working MSM summary: ( $\hat{\beta}_{TMLE}$  = 0. 1852, p-value = 0. 0036)



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)

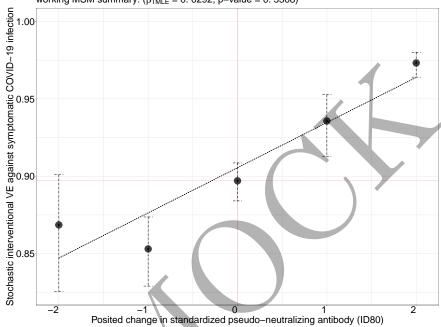


Mean counterfactual COVID-19 infection risk across standardized shifts in pseudo-neutralizing antibody (ID80) levels, summarized by projection of causal dose-response curve onto a linear working model.

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

## 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)

<sup>&</sup>lt;sup>a</sup> 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 446c7410246976e2912b2d55f09c7b51f9ab43e5. A diff of the changes introduced by that commit may be viewed at https://github.com/CoVPN/correlates\_reporting/commit/446c7410246976e2912b2d55f09c7b51f9ab43e5
- 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