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

USG COVID-19 Response Biostatistics Team

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 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. 27
- 2.2 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. 27

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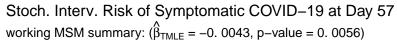
Chapter 1

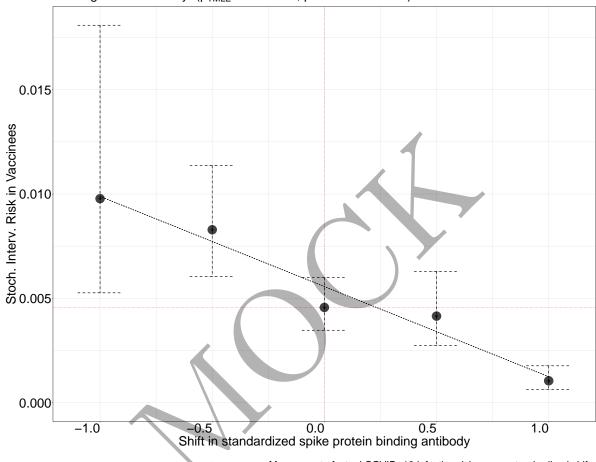
Stochastic Interventional Vaccine Efficacy

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 $\{-1, -0.5, 0, 0.5, 1\}$, 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).

1.1 Figures for Stochastic Interventional CoPs for Day 57

1.1.1 Stoch interv. risk: spike protein binding antibody

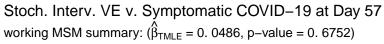


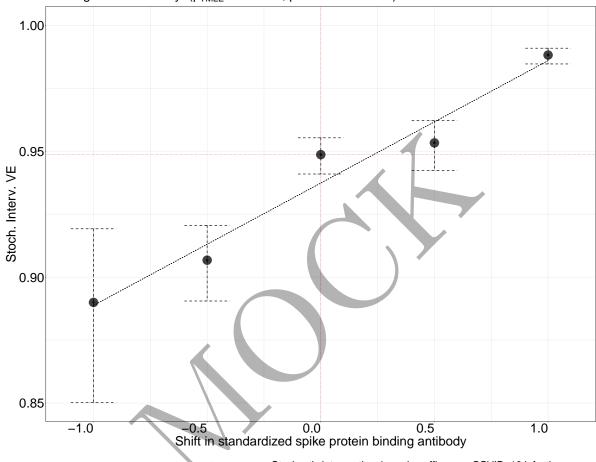


Mean counterfactual COVID–19 infection risk across standardized shifts in spike protein binding antibody levels, summarized by projection of causal dose–response curve onto a linear working model.

Figure 1.1: Stochastic interventional risk estimates, with confidence intervals, for spike protein binding antibody at Day 57

1.1.2 Stoch. interv. VE: spike protein binding antibody





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.

Figure 1.2: Stochastic interventional VE estimates, with confidence intervals, for spike protein binding antibody at Day 57

1.1.3 Stoch. interv. risk: RBD binding antibody

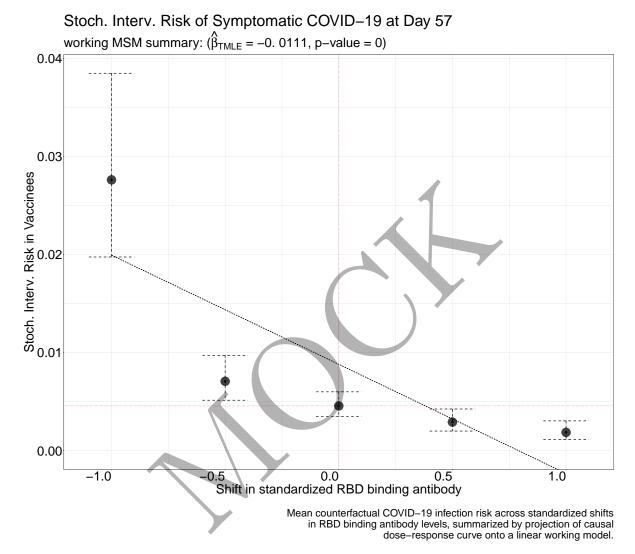


Figure 1.3: Stochastic interventional risk estimates, with confidence intervals, for RBD binding antibody at Day 57

1.1.4 Stoch. interv. VE: RBD binding antibody

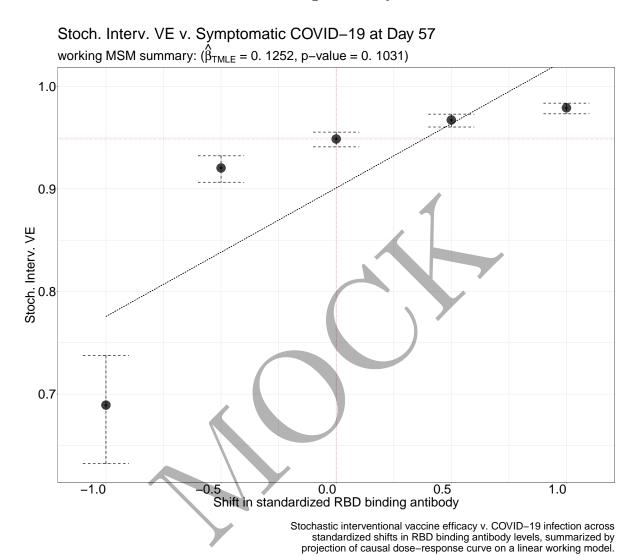
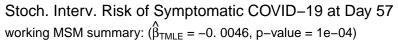
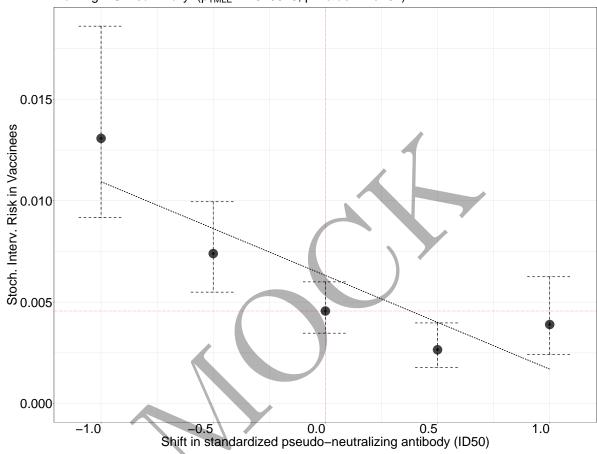


Figure 1.4: Stochastic interventional VE estimates, with confidence intervals, for RBD binding antibody at Day 57

1.1.5 Stoch. interv. risk: pseudo-neutralizing antibody (ID50)

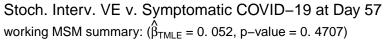


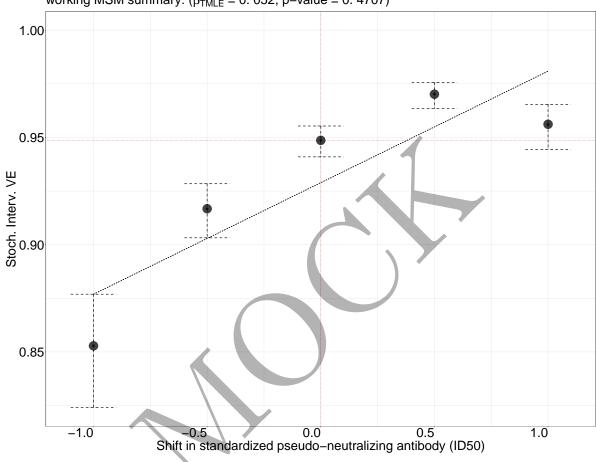


Mean counterfactual COVID–19 infection risk across standardized shifts in pseudo–neutralizing antibody (ID50) levels, summarized by projection of causal dose–response curve onto a linear working model.

Figure 1.5: Stochastic interventional risk estimates, with confidence intervals, for pseudo-neutralizing antibody (ID50) at Day 57

1.1.6 Stoch. interv. VE: pseudo-neutralizing antibody (ID50)

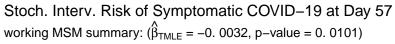


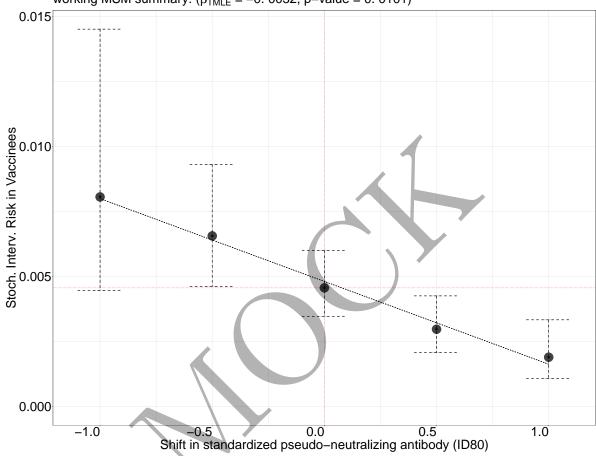


Stochastic interventional vaccine efficacy v. COVID-19 infection across standardized shifts in pseudo-neutralizing antibody (ID50) levels, summarized by projection of causal dose-response curve on a linear working model.

Figure 1.6: Stochastic interventional VE estimates, with confidence intervals, for pseudo-neutralizing antibody (ID50) at Day 57

1.1.7 Stoch. interv. risk: pseudo-neutralizing antibody (ID80)

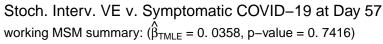


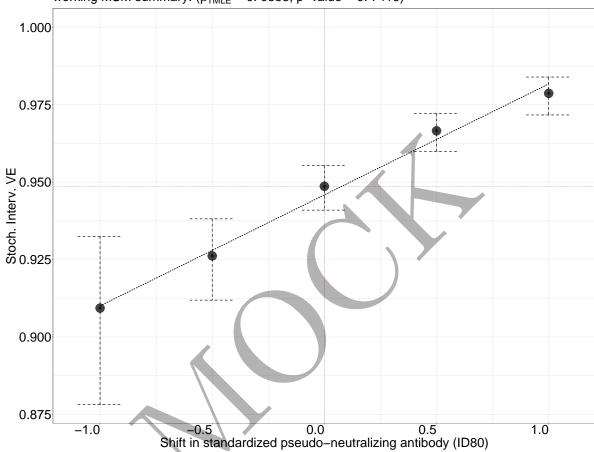


Mean counterfactual COVID–19 infection risk across standardized shifts in pseudo–neutralizing antibody (ID80) levels, summarized by projection of causal dose–response curve onto a linear working model.

Figure 1.7: Stochastic interventional risk estimates, with confidence intervals, for pseudo-neutralizing antibody (ID80) at Day 57

1.1.8 Stoch. interv. VE: pseudo-neutralizing antibody (ID80)





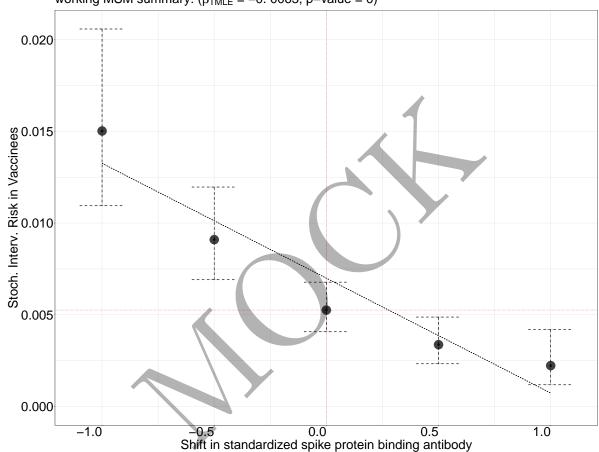
Stochastic interventional vaccine efficacy v. COVID–19 infection across standardized shifts in pseudo–neutralizing antibody (ID80) levels, summarized by projection of causal dose–response curve on a linear working model.

Figure 1.8: Stochastic interventional VE estimates, with confidence intervals, for pseudo-neutralizing antibody (ID80) at Day 57

1.2 Figures for Stochastic Interventional CoPs for Day 29

1.2.1 Stoch. interv. risk: spike protein binding antibody

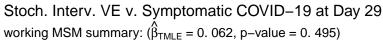
Stoch. Interv. Risk of Symptomatic COVID–19 at Day 29 working MSM summary: ($\hat{\beta}_{TMLE} = -0.0063$, p-value = 0)

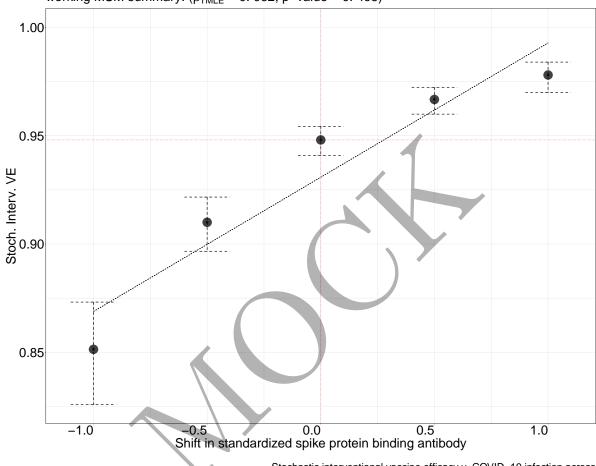


Mean counterfactual COVID–19 infection risk across standardized shifts in spike protein binding antibody levels, summarized by projection of causal dose–response curve onto a linear working model.

Figure 1.9: Stochastic interventional risk estimates, with confidence intervals, for spike protein binding antibody at Day 29

1.2.2 Stoch. interv. VE: spike protein binding antibody





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.

Figure 1.10: Stochastic interventional VE estimates, with confidence intervals, for spike protein binding antibody at Day 29

1.2.3 Stoch. interv. risk: RBD binding antibody

Stoch. Interv. Risk of Symptomatic COVID–19 at Day 29 working MSM summary: ($\hat{\beta}_{TMLE} = 0.0044$, p–value = 0.0935)

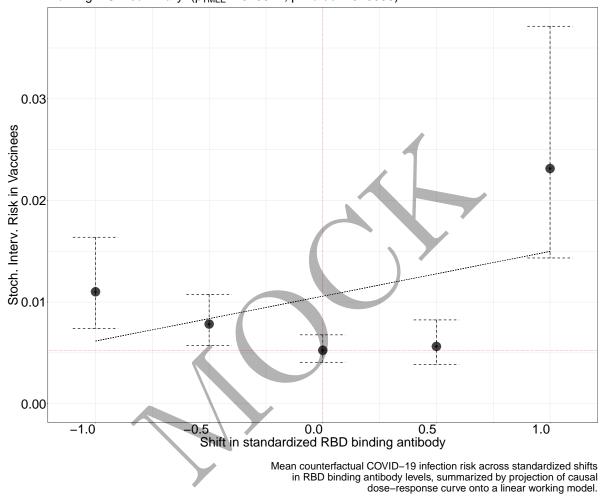


Figure 1.11: Stochastic interventional risk estimates, with confidence intervals, for RBD binding antibody at Day 29

1.2.4 Stoch. interv. VE: RBD binding antibody

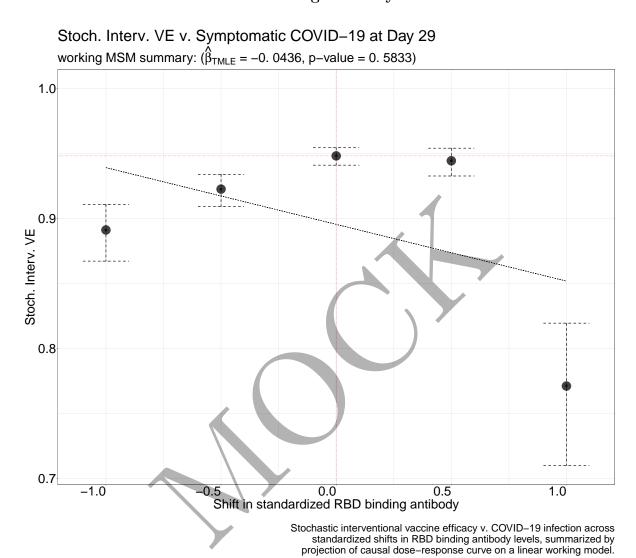
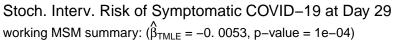
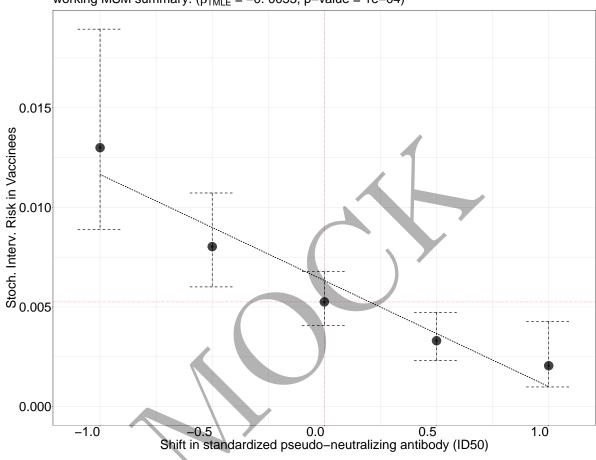


Figure 1.12: Stochastic interventional VE estimates, with confidence intervals, for RBD binding antibody at Day 29

1.2.5 Stoch. interv. risk: pseudo-neutralizing antibody (ID50)

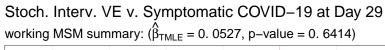


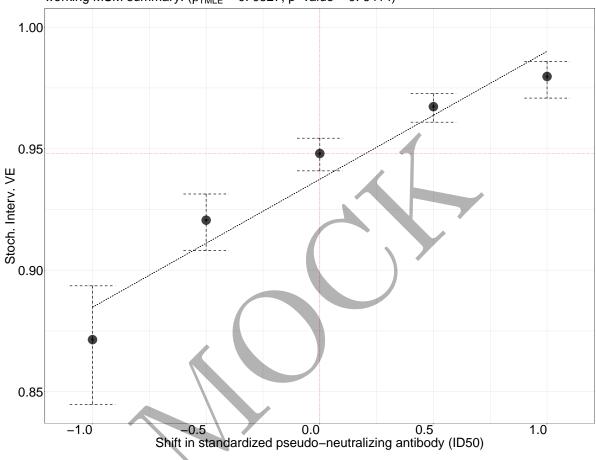


Mean counterfactual COVID–19 infection risk across standardized shifts in pseudo–neutralizing antibody (ID50) levels, summarized by projection of causal dose–response curve onto a linear working model.

Figure 1.13: Stochastic interventional risk estimates, with confidence intervals, for pseudo-neutralizing antibody (ID50) at Day 29

1.2.6 Stoch. interv. VE: pseudo-neutralizing antibody (ID50)

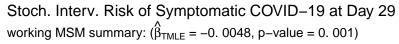


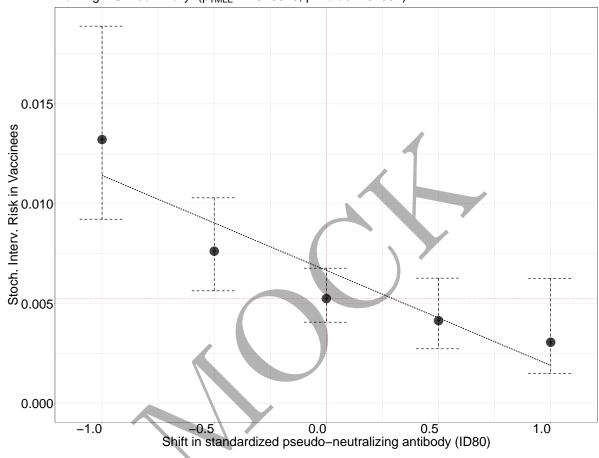


Stochastic interventional vaccine efficacy v. COVID-19 infection across standardized shifts in pseudo-neutralizing antibody (ID50) levels, summarized by projection of causal dose-response curve on a linear working model.

Figure 1.14: Stochastic interventional VE estimates, with confidence intervals, for pseudo-neutralizing antibody (ID50) at Day 29

1.2.7 Stoch. interv. risk: pseudo-neutralizing antibody (ID80)

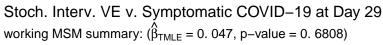


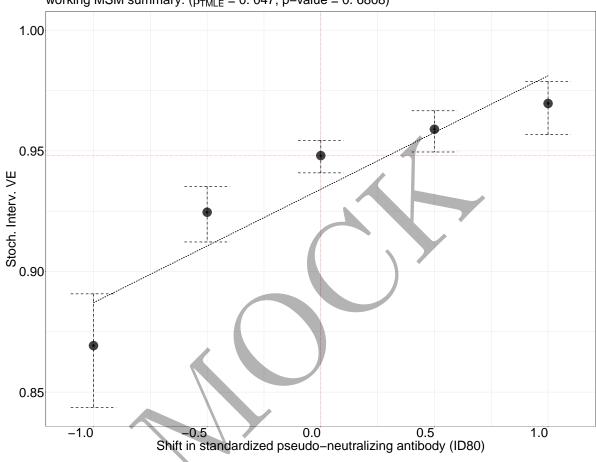


Mean counterfactual COVID–19 infection risk across standardized shifts in pseudo–neutralizing antibody (ID80) levels, summarized by projection of causal dose–response curve onto a linear working model.

Figure 1.15: Stochastic interventional risk estimates, with confidence intervals, for pseudo-neutralizing antibody (ID80) at Day 29

1.2.8 Stoch. interv. VE: pseudo-neutralizing antibody (ID80)





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.

Figure 1.16: Stochastic interventional VE estimates, with confidence intervals, for pseudo-neutralizing antibody (ID80) at Day 29



Chapter 2

Mediators of Vaccine Efficacy

Table 2.1: 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	$0.441 \ (0.396, \ 0.482)$	$0.894\ (0.865,\ 0.917)$	$0.794\ (0.824,\ 0.765)$
Day 29	PsV Neutralization 80% Titer	$0.915 \ (0.713, \ 0.975)$	$0.301 \ (-1.356, \ 0.793)$	$0.127 \ (0.556, -0.303)$

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

Table 2.2: 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	0.914 (0.861, 0.947)	$0.302\ (0.003,\ 0.512)$	0.128 (0.257, -0.002)
Day 57	Binding Antibody to RBD	$0.940 \ (0.898, \ 0.965)$	$0.006 \; (-0.522, 0.350)$	$0.002 \ (0.153, -0.149)$
Day 57	PsV Neutralization 50% Titer	$0.916 \ (0.852, \ 0.952)$	0.292 (-0.106, 0.547)	$0.122\ (0.284, -0.039)$
Day 57	PsV Neutralization 80% Titer	$0.920\ (0.873,\ 0.949)$	0.255 (-0.049, 0.471)	$0.104 \ (0.228, -0.019)$
Day 29	Binding Antibody to Spike	0.944 (0.894, 0.970)	-0.062 (-0.816, 0.379)	-0.021 (0.168, -0.211)
Day 29	Binding Antibody to RBD	$0.934\ (0.887,\ 0.962)$	0.095 (-0.416, 0.421)	$0.035 \ (0.194, -0.124)$
Day 29	PsV Neutralization 50% Titer	$0.914\ (0.856,\ 0.948)$	$0.314 \ (-0.026, \ 0.541)$	$0.133\ (0.278, -0.012)$
Day 29	PsV Neutralization 80% Titer	$0.924 \ (0.883, \ 0.950)$	$0.221 \ (-0.088, \ 0.442)$	$0.088 \ (0.207, -0.031)$



Chapter 3

Appendix

- This report was built from the CoVPN/correlates_reporting repository with commit hash 72f994596bc358e8c097920f5e575e118a2791bc. A diff of the changes introduced by that commit may be viewed at https://github.com/CoVPN/correlates_reporting/commit/72f994596bc358e8c097920f5e575e118a2791bc
- \bullet The sha256 hash sum of the raw input file, "COVID_VEtrial_practicedata_primarystage1.csv": 45 ff85033 ffbc717462 d678b41bc4060a12c7bc60952e2cb72297bb5500b97b9
- $\bullet \ \ The sha256 \ hash \ sum \ of the \ processed \ file, "practice_data.csv": \ aaf 466d 62ce 6f 25c 7c 8cd 2adf bd 6805 ad 3cb 140a 363f 3cb 4b 5cb 4b$