COVID correlates analysis report CoR

2021-02-05

1 Univariate CoR: Cox Proportional Hazards Modeling of Relative and Absolute Risk

All analyses for D57 markers are run on the population with EventTimePrimaryD57>=7. The main regression model is the Cox proportional hazards model. All plots are made with Cox models fit unless specified otherwise. The trichotomized variables in Table 1 are defined with respect to inverse probability weighted quantiles computed using the Hmisc::wtd.quantile function.

Table 1: Inference for Day 57 antibody marker covariate-adjusted correlates of risk of COVID in the vaccine group: Hazard ratios per 10-fold increment in the marker*

| Mock | No. cases / | HR per 10-fold incr. | | P-value | q-value | FWER |
Immunologic Marker	No. at-risk**	Pt. Est.	95% CI	(2-sided)		
Spike IgG (IU/ml)	72/13,254	0.08	(0.05-0.12)	<0.001	<0.001	<0.001
RBD IgG (IU/ml)	72/13,254	0.17	(0.12-0.25)	<0.001	<0.001	<0.001
PsV-nAb ID50	72/13,254	0.26	(0.20-0.34)	<0.001	<0.001	<0.001
PsV-nAb ID80	72/13,254	0.39	(0.29-0.52)	<0.001	<0.001	<0.001

*Baseline covariates adjusted for: age in years, at risk or not, community of color or not, baseline risk score. Average follow-up time 175 days, maximum follow-up time 185 days.

**No. at-risk = number of per-protocol baseline negative vaccine recipients at-risk for COVID at Day 57; no. cases = number of this cohort with an observed COVID endpoints.

Table 2: Inference for Day 57 antibody marker covariate-adjusted correlates of risk of COVID in the vaccine group: Hazard ratios for Middle vs. Upper tertile vs. Lower tertile*

Mock Immunologic Marker	Tertile	No. cases / No. at-risk**	Attack rate	Haz. Ratio Pt. Est.	Haz. Ratio 95% CI	P-value (2-sided)	Overall P-value***	Overall q-value	Overall FWER
Spike IgG (IU/ml)	Lower	67/4,373	0.0153	1	N/A	N/A	<0.001	<0.001	<0.001
	Middle	4/4,449	0.0009	0.04	(0.01-0.11)	<0.001			
	Upper	1/4,422	0.0002	0.00	(0.00-0.03)	<0.001			
RBD IgG (IU/ml)	Lower	45/4,395	0.0102	1	N/A	N/A	<0.001	<0.001	<0.001
	Middle	19/4,433	0.0043	0.24	(0.13-0.43)	<0.001			
	Upper	8/4,416	0.0018	0.05	(0.02-0.12)	<0.001			
PsV-nAb ID50	Lower	56/4,440	0.0126	1	N/A	N/A	<0.001	<0.001	<0.001
	Middle	9/4,416	0.0020	0.10	(0.05-0.22)	<0.001			
	Upper	6/4,388	0.0014	0.05	(0.02-0.11)	<0.001			
PsV-nAb ID80	Lower	40/4,392	0.0091	1	N/A	N/A	<0.001	<0.001	<0.001
	Middle	21/4,436	0.0047	0.43	(0.24-0.78)	0.005			
	Upper	11/4,417	0.0025	0.16	(0.08-0.34)	<0.001			
Placebo		713/13,299	0.0536						

*Baseline covariates adjusted for: age in years, at risk or not, community of color or not, baseline risk score. Average follow-up time 175 days, maximum follow-up time 185 days. Cutpoints: Spike IgG (IU/ml) [6.09, 6.7), RBD IgG (IU/ml) [5.68, 6.38), PsV-nAb ID50 [2.8, 3.66), PsV-nAb ID80 [3.08, 3.82).

**No. at-risk = number of per-protocol baseline negative vaccine recipients at-risk for COVID at Day 57; no. cases = number of this cohort with an observed COVID endpoints.

***Generalized Wald-test p-value of the null hypothesis that the hazard rate is constant across the Lower, Middle, and Upper tertile groups.
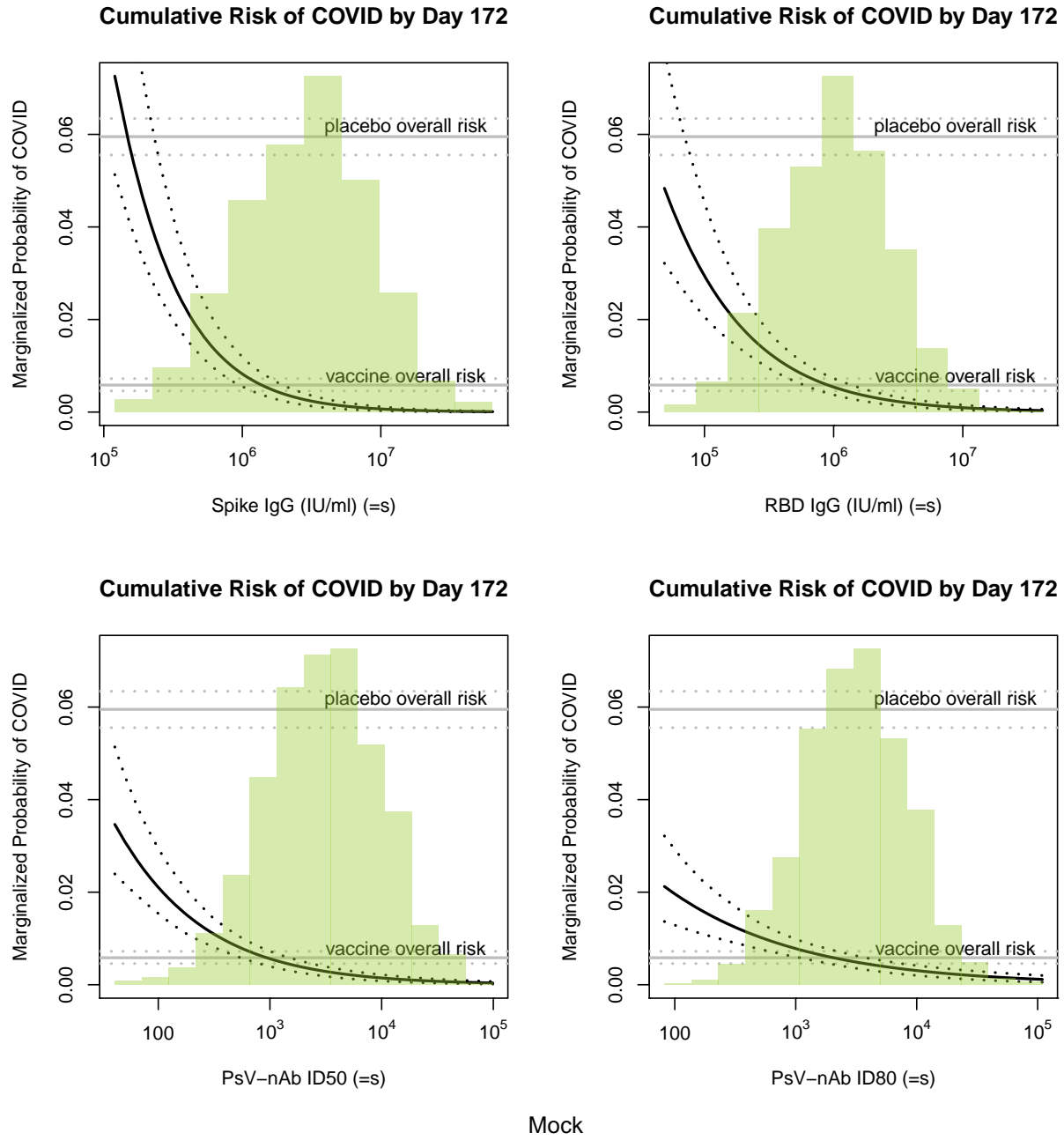
Figure 1: Marginalized cumulative risk by Day 172 as functions of Day 57 markers (=s) among baseline seronegative vaccine recipients with 95% bootstrap point-wise confidence bands. The horizontal lines indicate the overall cumulative risk of the placebo and vaccine arms by Day 172 and its 95% point-wise confidence interval. Histograms of the immunological markers in the vaccine arm are overlaid.

Figure 2: Marginalized cumulative risk by Day 172 as functions of Day 57 markers above a threshold (>=s) among baseline seronegative vaccine recipients with 95% bootstrap point-wise confidence bands (at least 5 cases are required). The horizontal lines indicate the overall cumulative risk of the vaccine arm by Day 172 and its 95% point-wise confidence interval. Histograms of the immunological markers in the vaccine arm are overlaid.

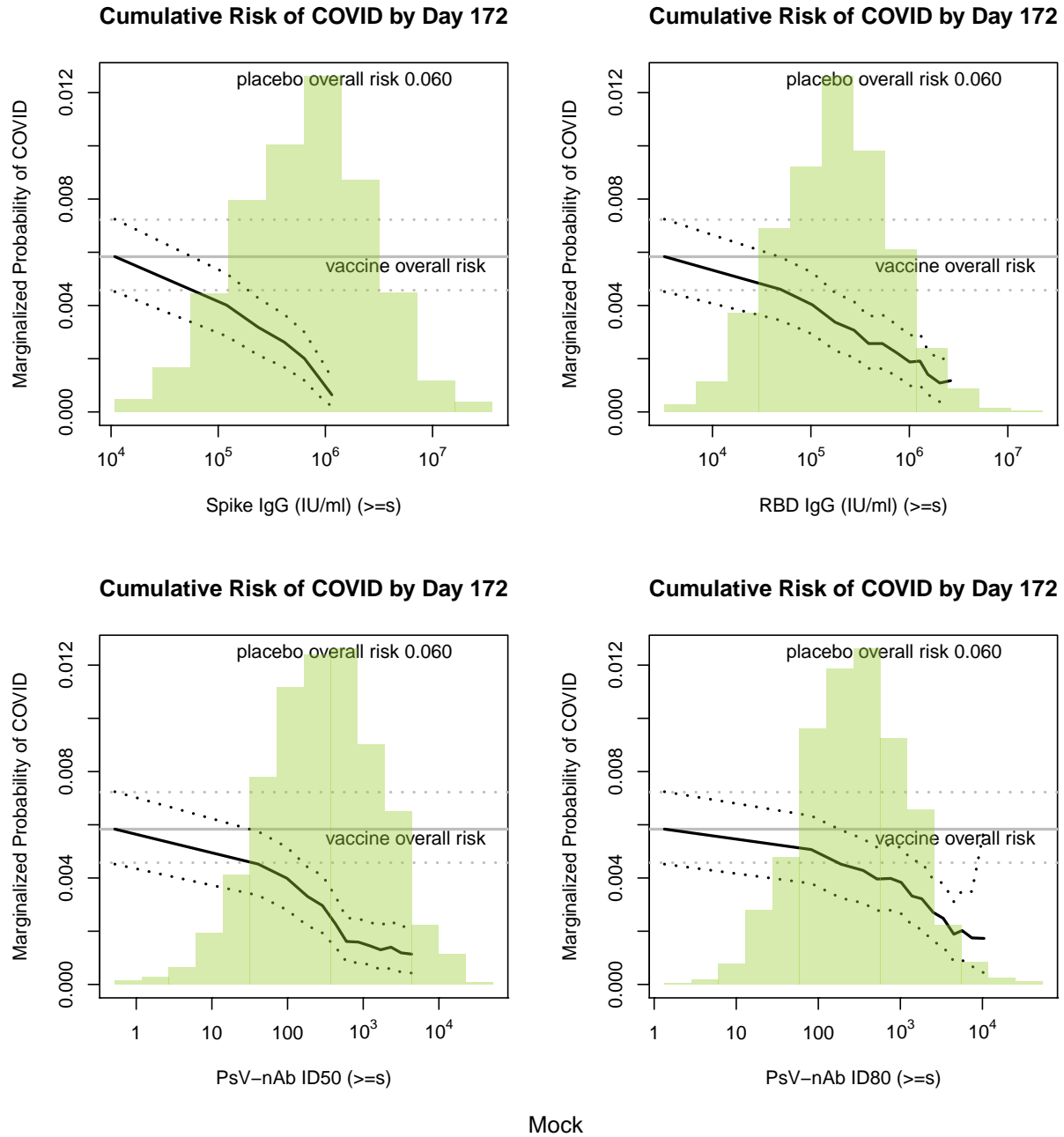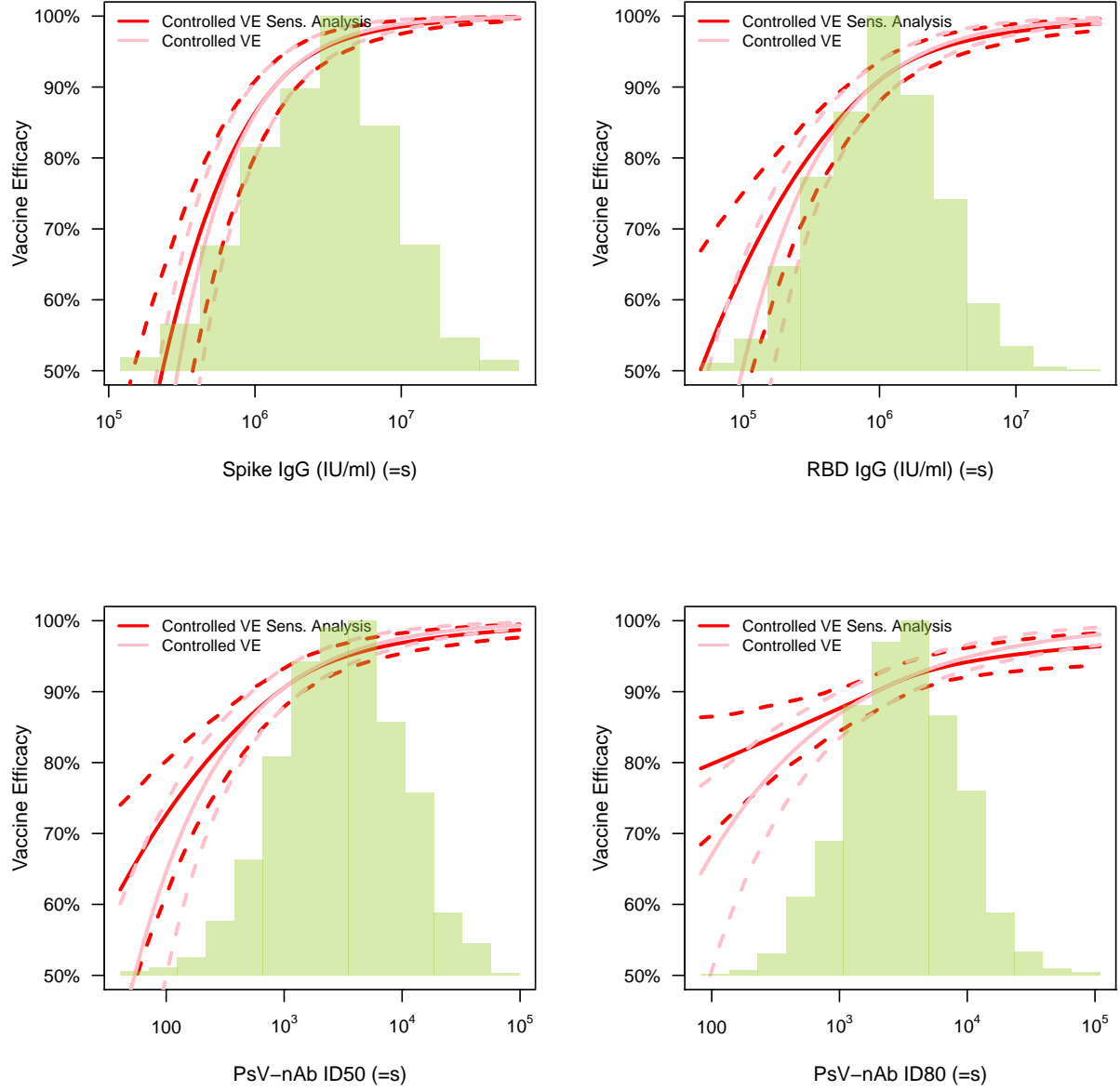Figure 3: Controlled VE with sensitivity analysis as functions of Day 57 markers (=s) among baseline seronegative vaccine recipients with 95% bootstrap point-wise confidence bands. Histograms of the immunological markers in the vaccine arm are overlaid.

Binding Antibody to Spike: Day 57

cutpoints : 1.2×10^6, 5.0×10^6

Cumulative COVID Rate vs Days Since Day 57 Visit

Legend: Vaccine low, Vaccine medium, Vaccine high, Placebo

No. at risk

	0	30	60	90	120	150	172
Low:	4373	4326	4223	4151	4062	3974	3456
Med:	4449	4417	4411	4366	4312	4299	4044
High:	4422	4406	4381	4375	4359	4309	3695

Cumulative No. of Overall infections

Low:	0	7	20	34	46	59	67
Med:	0	0	0	1	1	2	4
High:	0	0	1	1	1	1	1

Binding Antibody to RBD: Day 57

cutpoints : 4.8×10^5, 2.4×10^6

Cumulative COVID Rate vs Days Since Day 57 Visit

Legend: Vaccine low, Vaccine medium, Vaccine high, Placebo

No. at risk

	0	30	60	90	120	150	172
Low:	4395	4347	4265	4212	4128	4058	3522
Med:	4433	4404	4378	4354	4295	4284	3903
High:	4416	4399	4373	4326	4308	4239	3770

Cumulative No. of Overall infections

Low:	0	5	15	22	29	37	45
Med:	0	1	3	9	14	19	19
High:	0	1	3	5	5	6	8

PsV Neutralization 50% Titer: Day 57

cutpoints : 6.3×10^2, 4.5×10^3

Cumulative COVID Rate vs Days Since Day 57 Visit

Legend: Vaccine low, Vaccine medium, Vaccine high, Placebo

No. at risk

	0	30	60	90	120	150	172
Low:	4440	4384	4337	4231	4176	4110	3533
Med:	4416	4392	4367	4357	4295	4237	3909
High:	4388	4373	4311	4304	4261	4235	3752

Cumulative No. of Overall infections

Low:	0	6	19	29	38	49	56
Med:	0	0	1	5	7	9	9
High:	0	1	1	2	2	4	6

PsV Neutralization 80% Titer: Day 57

cutpoints : 1.2×10^3, 6.6×10^3

Cumulative COVID Rate vs Days Since Day 57 Visit

Legend: Vaccine low, Vaccine medium, Vaccine high, Placebo

No. at risk

	0	30	60	90	120	150	172
Low:	4392	4341	4297	4210	4090	4025	3575
Med:	4436	4407	4381	4363	4344	4278	3790
High:	4417	4402	4337	4320	4297	4278	3829

Cumulative No. of Overall infections

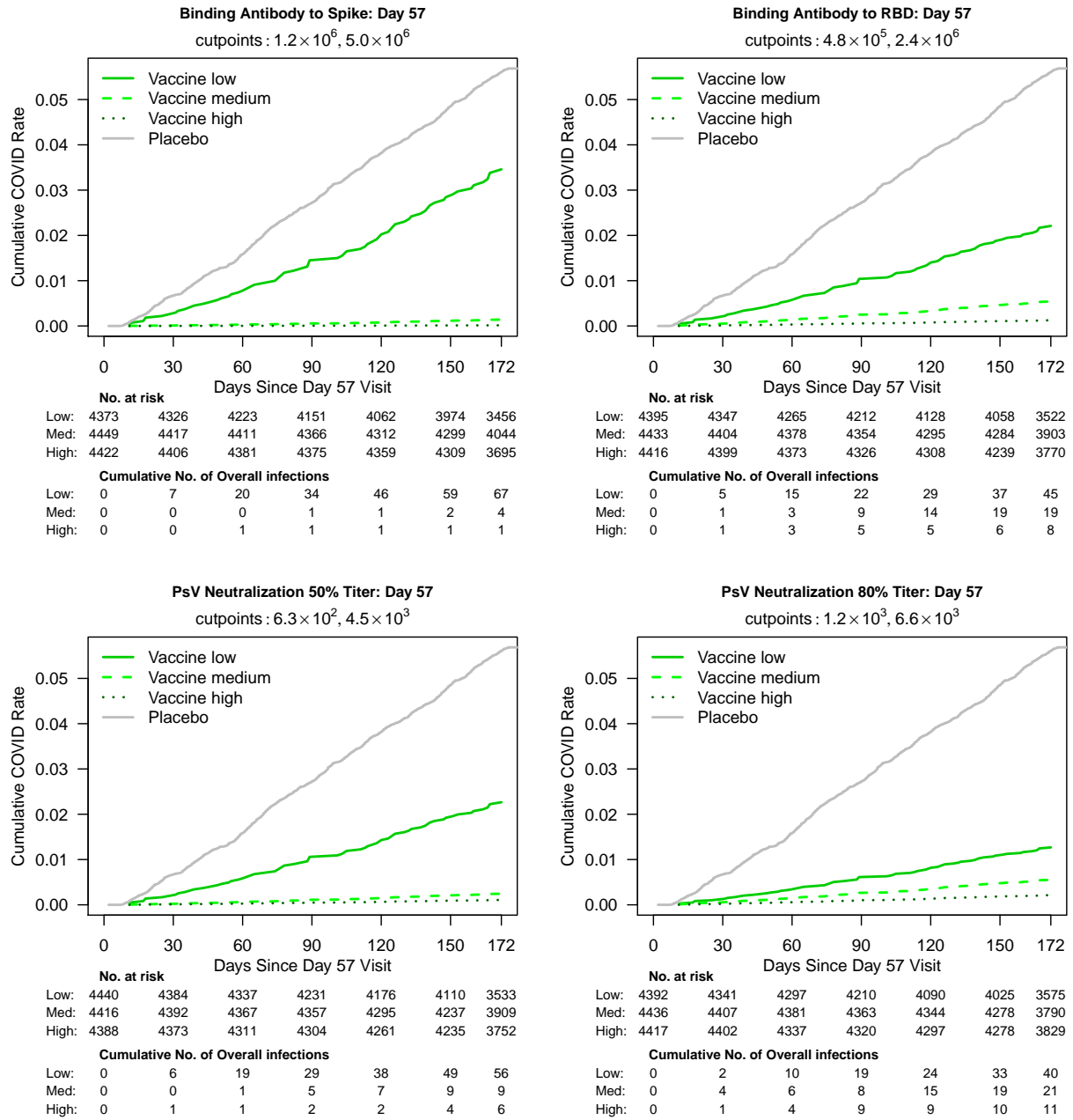|							
Low:	0	2	10	19	24	33	40
Med:	0	4	6	8	15	19	21
High:	0	1	4	9	9	10	11

Figure 4: Marginalized cumulative incidence rate curves for trichotomized Day 57 markers among baseline seronegative vaccine recipients. The gray line is the overall cumulative incidence rate curve in the placebo arm.

Mock

Group	No. Events		HR (95% CI)
All baseline negative, vaccine	72		0.08 (0.05, 0.12)
Age >= 65	37		0.10 (0.07, 0.15)
Age < 65, At risk	27		0.07 (0.03, 0.15)
Age < 65, Not at risk	8		0.01 (0.00, 0.04)

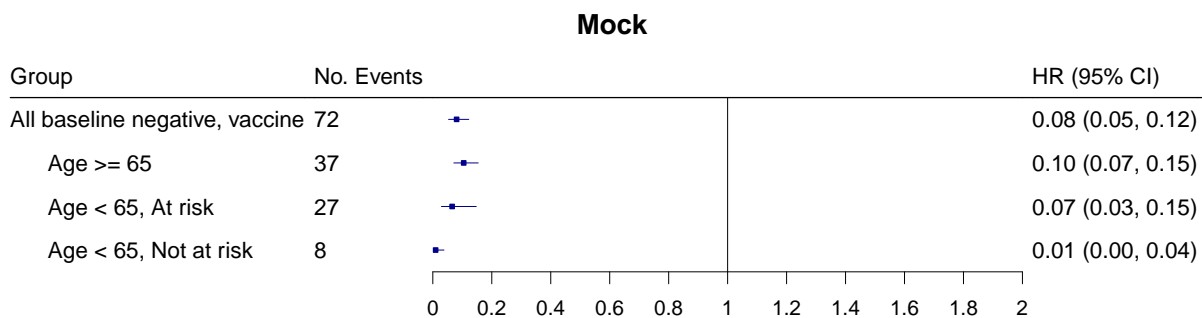0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6 1.8 2

Figure 5: Forest plots of hazard ratios of Day 57 binding Ab to spike markers among baseline seronegative vaccine recipients (top row) and each of the 3 randomization strata with 95% point-wise confidence intervals.

Mock

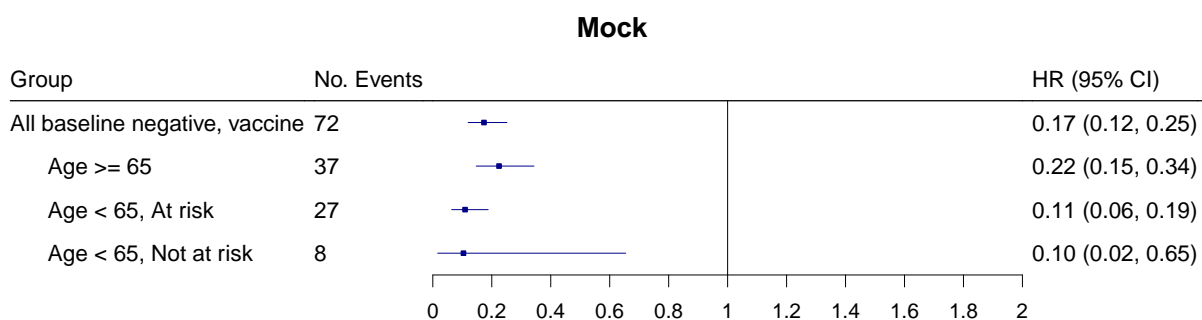| Group	No. Events		HR (95% CI)
All baseline negative, vaccine	72		0.17 (0.12, 0.25)
Age >= 65	37		0.22 (0.15, 0.34)
Age < 65, At risk	27		0.11 (0.06, 0.19)
Age < 65, Not at risk	8		0.10 (0.02, 0.65)

0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6 1.8 2

Figure 6: Forest plots of hazard ratios of Day 57 binding Ab to RBD markers among baseline seronegative vaccine recipients (top row) and each of the 3 randomization strata with 95% point-wise confidence intervals.

Mock

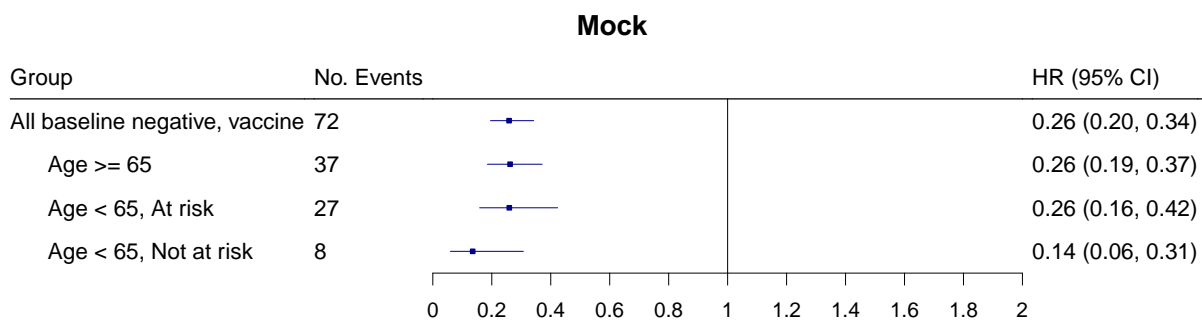| Group	No. Events		HR (95% CI)
All baseline negative, vaccine	72		0.26 (0.20, 0.34)
Age >= 65	37		0.26 (0.19, 0.37)
Age < 65, At risk	27		0.26 (0.16, 0.42)
Age < 65, Not at risk	8		0.14 (0.06, 0.31)

0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6 1.8 2

Figure 7: Forest plots of hazard ratios of Day 57 pseudo neut ID50 markers among baseline seronegative vaccine recipients (top row) and each of the 3 randomization strata with 95% point-wise confidence intervals.

Mock

Group	No. Events		HR (95% CI)
All baseline negative, vaccine	72		0.39 (0.29, 0.52)
Age >= 65	37		0.40 (0.27, 0.58)
Age < 65, At risk	27		0.45 (0.29, 0.69)
Age < 65, Not at risk	8		0.33 (0.08, 1.44)

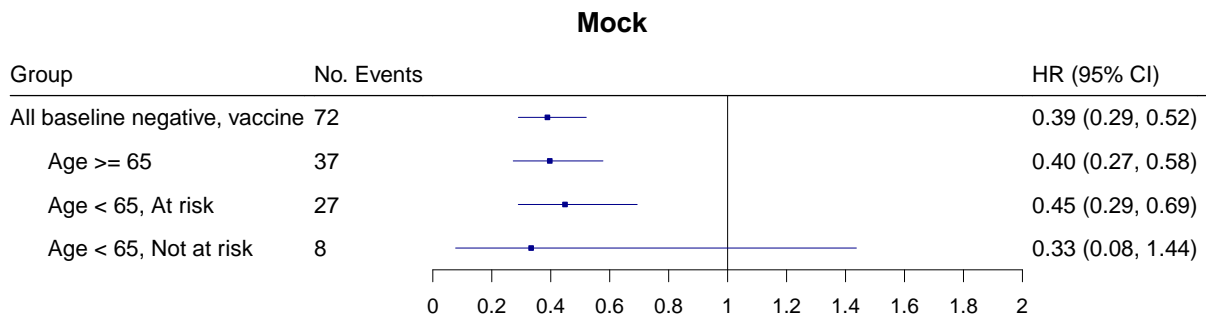0   0.2   0.4   0.6   0.8   1   1.2   1.4   1.6   1.8   2

Figure 8: Forest plots of hazard ratios of Day 57 pseudo neut ID80 markers among baseline seronegative vaccine recipients (top row) and each of the 3 randomization strata with 95% point-wise confidence intervals.

Mock

Group (Baseline Negative)	No. Events		HR (95% CI)
All Vaccine	72		0.08 (0.05, 0.12)
Age >= 65	37		0.10 (0.06, 0.17)
Age < 65	35		0.05 (0.03, 0.09)
At risk	52		0.11 (0.07, 0.16)
Not at risk	20		0.03 (0.01, 0.07)
Comm. of color	28		0.10 (0.06, 0.18)
White Non–Hispanic	44		0.06 (0.04, 0.11)
Men	39		0.07 (0.04, 0.13)
Women	33		0.07 (0.04, 0.14)

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0   0.2  0.4  0.6  0.8  1  1.2  1.4  1.6  1.8  2
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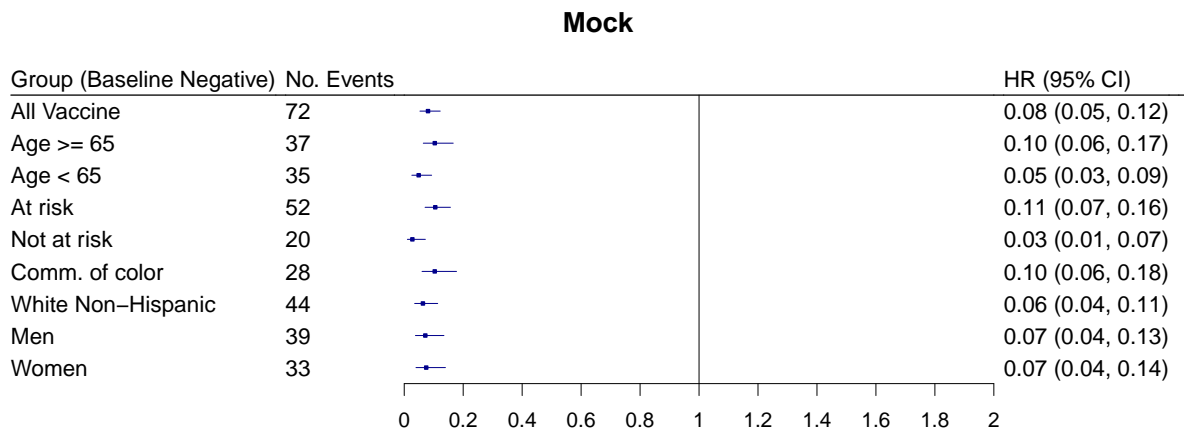
Figure 9: Forest plots of hazard ratios of Day 57 binding Ab to spike markers among baseline seronegative vaccine recipients (top row) and eight subpopulations (row 2-9) with 95% point-wise confidence intervals.

Mock

Group (Baseline Negative)	No. Events		HR (95% CI)
All Vaccine	72		0.17 (0.12, 0.25)
Age >= 65	37		0.23 (0.15, 0.36)
Age < 65	35		0.11 (0.07, 0.18)
At risk	52		0.18 (0.12, 0.27)
Not at risk	20		0.13 (0.07, 0.27)
Comm. of color	28		0.21 (0.13, 0.33)
White Non–Hispanic	44		0.15 (0.08, 0.26)
Men	39		0.23 (0.15, 0.35)
Women	33		0.11 (0.06, 0.22)

```
0   0.2  0.4  0.6  0.8  1  1.2  1.4  1.6  1.8  2
```
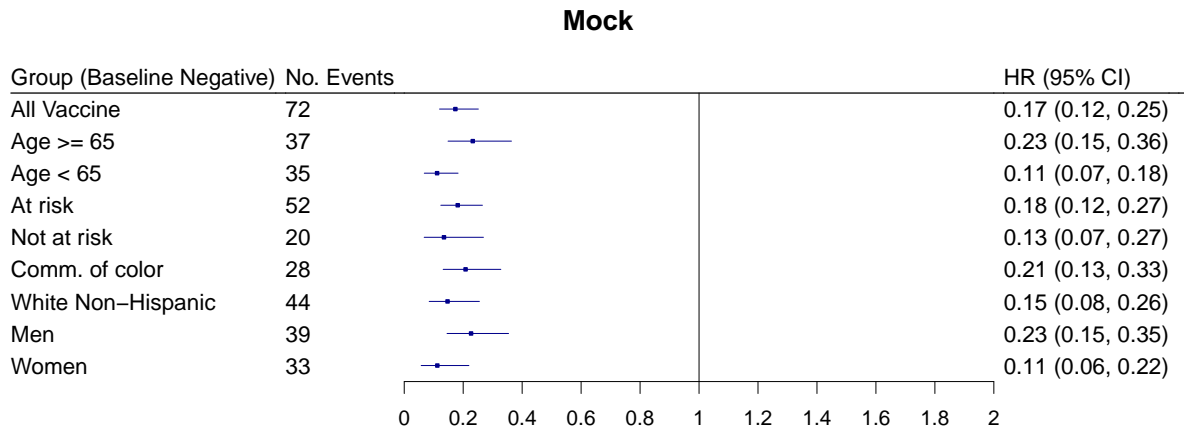
Figure 10: Forest plots of hazard ratios of Day 57 binding Ab to RBD markers among baseline seronegative vaccine recipients (top row) and eight subpopulations (row 2-9) with 95% point-wise confidence intervals.

Mock

Group (Baseline Negative)	No. Events		HR (95% CI)
All Vaccine	72		0.26 (0.20, 0.34)
Age >= 65	37		0.27 (0.19, 0.39)
Age < 65	35		0.24 (0.16, 0.35)
At risk	52		0.27 (0.20, 0.37)
Not at risk	20		0.19 (0.10, 0.34)
Comm. of color	28		0.28 (0.19, 0.41)
White Non–Hispanic	44		0.24 (0.16, 0.35)
Men	39		0.22 (0.15, 0.33)
Women	33		0.29 (0.20, 0.42)

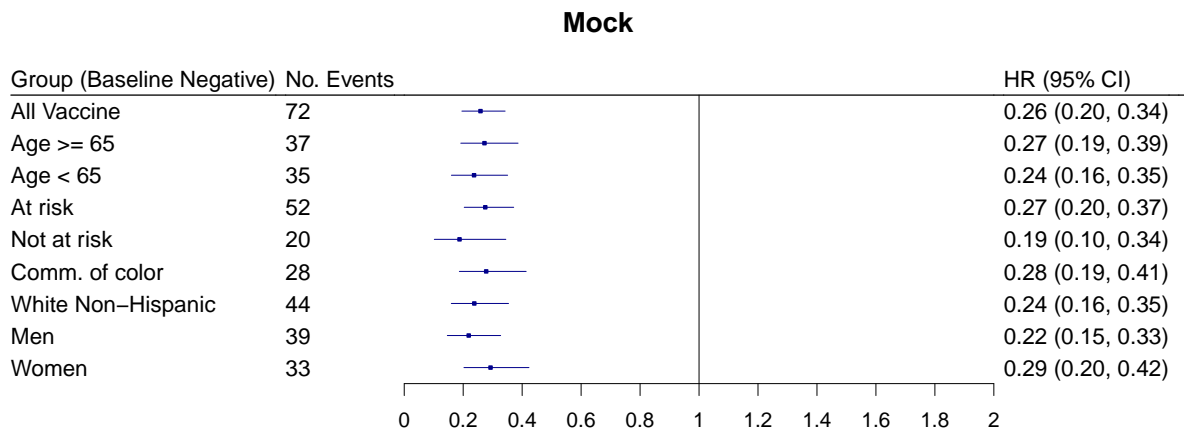0   0.2   0.4   0.6   0.8   1   1.2   1.4   1.6   1.8   2

Figure 11: Forest plots of hazard ratios of Day 57 pseudo neut ID50 markers among baseline seronegative vaccine recipients (top row) and eight subpopulations (row 2-9) with 95% point-wise confidence intervals.

Mock

Group (Baseline Negative)	No. Events		HR (95% CI)
All Vaccine	72		0.39 (0.29, 0.52)
Age >= 65	37		0.38 (0.26, 0.57)
Age < 65	35		0.41 (0.27, 0.63)
At risk	52		0.41 (0.29, 0.57)
Not at risk	20		0.38 (0.22, 0.66)
Comm. of color	28		0.36 (0.24, 0.53)
White Non–Hispanic	44		0.42 (0.28, 0.65)
Men	39		0.29 (0.18, 0.47)
Women	33		0.48 (0.33, 0.70)

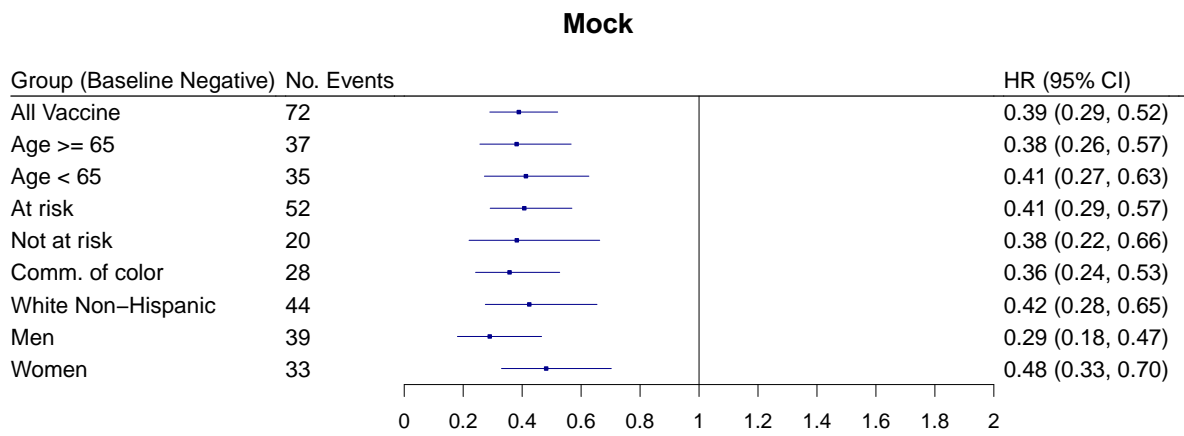0   0.2   0.4   0.6   0.8   1   1.2   1.4   1.6   1.8   2

Figure 12: Forest plots of hazard ratios of Day 57 pseudo neut ID80 markers among baseline seronegative vaccine recipients (top row) and eight subpopulations (row 2-9) with 95% point-wise confidence intervals.