CoVPN COVID-19 Correlates Analysis

the CoVPN Biostatistics Team

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Chapter 1

Day 57 Univariate CoR: Cox Models of Risk

The main regression model is the Cox proportional hazards model. All plots are made with Cox models fit unless specified otherwise.

1.1 Hazard ratios

Table 1.1: 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 1	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	0.24	(0.18 - 0.31)	< 0.001	< 0.001	< 0.001
PsV-nAb ID80	72/13,254	0.38	(0.28 - 0.51)	< 0.001	< 0.001	< 0.001

^{*}Baseline covariates adjusted for: age in years, at risk or not, community of color or not **No. at-risk = number of per-protocol baseline negative vaccine recipients at-risk for COVID at 7 days post Day 57 visit; no. cases = number of this cohort with an observed COVID endpoints.

Table 1.2: 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	Tertile	No. cases /	Attack	Haz	. Ratio	P-value	Overall P-	Overall q-	Overall
Immunologic Marker		No. at-risk**	rate	Pt. Est.	95% CI	(2-sided)	value***	value	FWER
Spike IgG (IU/ml)	Lower	67/4,425	0.0151	1	N/A	N/A	< 0.001	< 0.001	< 0.001
	Middle	4/4,403	0.0009	0.04	(0.01-0.11)	< 0.001			
	Upper	1/4,426	0.0002	0.00	(0.00-0.03)	< 0.001			
RBD IgG (IU/ml)	Lower	45/4,437	0.0101	1	N/A	N/A	< 0.001	< 0.001	< 0.001
	Middle	19/4,398	0.0043	0.24	(0.13-0.43)	< 0.001			
	Upper	8/4,420	0.0018	0.05	(0.02 - 0.12)	< 0.001			
PsV-nAb ID50	Lower	56/4,443	0.0126	1	N/A	N/A	< 0.001	< 0.001	< 0.001
	Middle	9/4,382	0.0021	0.10	(0.05-0.22)	< 0.001			
	Upper	6/4,429	0.0014	0.05	(0.02 - 0.11)	< 0.001			
PsV-nAb ID80	Lower	40/4,434	0.0090	1	N/A	N/A	< 0.001	< 0.001	< 0.001
	Middle	21/4,400	0.0048	0.43	(0.24 - 0.79)	0.006			
	Upper	11/4,420	0.0025	0.17	(0.08 - 0.34)	< 0.001			
Placebo		713/13,271	0.0537						

^{*}Baseline covariates adjusted for: age in years, at risk or not, community of color or not . Average follow-up time 172 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 7 days post Day 57 visit; 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.

1.1. HAZARD RATIOS

Binding Antibody to Spike: Day 57

Group	No. E	vents											HR (95% CI)
All baseline negative, vaccine	72		-										0.08 (0.05, 0.12)
Age >= 65	37	-	-										0.10 (0.06, 0.17)
Age < 65, At risk	27	-	-										0.06 (0.03, 0.11)
Age < 65, Not at risk	8	•-											0.01 (0.00, 0.06)
				١.								1	
		0	0.2	0.4	0.6	0.8	1	1.2	1.4	1.6	1.8	2	

Binding Antibody to RBD: Day 57

Group	No. Ev	vents	HR (95% CI)
All baseline negative, vacci	ne 72		0.17 (0.12, 0.25)
Age >= 65	37		0.23 (0.15, 0.36)
Age < 65, At risk	27	-	0.11 (0.07, 0.18)
Age < 65, Not at risk	8	_	0.10 (0.02, 0.54)
		0 0.2 0.4 0.6 0.8 1 1.2	1.4 1.6 1.8 2

PsV Neutralization 50% Titer: Day 57

Group	No. Ev	ents	HR (95% CI)									
All baseline negative, vaccin	ne 72		-	_								0.24 (0.18, 0.31)
Age >= 65	37		-	_								0.25 (0.18, 0.36)
Age < 65, At risk	27		-									0.23 (0.13, 0.39)
Age < 65, Not at risk	8	_	•									0.11 (0.05, 0.29)
		0	0.2	0.4	0.6	0.8	1	1.2	1.4	1.6	1.8	2

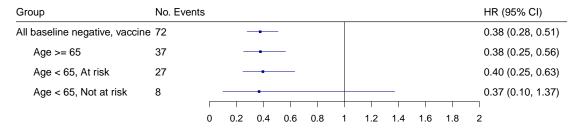


Figure 1.1: Forest plots of hazard ratios among baseline seronegative vaccine recipients and subgroups with 95% point-wise confidence intervals.

1.2 1.4

1.6 1.8

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) 35 Age < 65 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) 44 0.06 (0.04, 0.11) White Non-Hispanic 39 0.07 (0.04, 0.13) Men Women 33 0.07 (0.04, 0.14)

Binding Antibody to Spike: Day 57

Figure 1.2: 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.

0.6 0.8

0.2 0.4

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) 35 0.11 (0.07, 0.18) Age < 65 52 At risk 0.18 (0.12, 0.27) 0.13 (0.07, 0.27) Not at risk 20 Comm. of color 28 0.21 (0.13, 0.33) White Non-Hispanic 44 0.15 (0.08, 0.26) 39 0.23 (0.15, 0.35) Men Women 33 0.11 (0.06, 0.22)

Binding Antibody to RBD: Day 57

Figure 1.3: Forest plots of hazard ratios of Day57binding Ab to RBD markers among baseline seronegative vaccine recipients (top row) and eight subpopulations (row 2-9) with 95% point-wise confidence intervals.

0.6

0.8

1.2 1.4

1.6

1.8 2

0.2 0.4

Group (Baseline Negativ	HR (95% CI)		
All Vaccine	72		0.24 (0.18, 0.31)
Age >= 65	37		0.25 (0.18, 0.36)
Age < 65	35	-	0.21 (0.14, 0.34)
At risk	52		0.25 (0.18, 0.34)
Not at risk	20		0.19 (0.10, 0.35)
Comm. of color	28		0.26 (0.18, 0.39)
White Non-Hispanic	44		0.21 (0.14, 0.32)
Men	39		0.21 (0.13, 0.33)
Women	33		0.27 (0.18, 0.39)
		0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6 1.8	2

Figure 1.4: 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.

Group (Baseline Negativ	nts									HR (95% CI)					
All Vaccine	72											0.38 (0.28, 0.51)			
Age >= 65	37		_		_							0.38 (0.25, 0.56)			
Age < 65	35		_	-								0.39 (0.25, 0.61)			
At risk	52		-	-	_							0.39 (0.27, 0.54)			
Not at risk	20										0.38 (0.22, 0.66)				
Comm. of color	28											0.32 (0.21, 0.48)			
White Non-Hispanic	44			-								0.43 (0.28, 0.66)			
Men	39											0.29 (0.18, 0.46)			
Women	33					-						0.47 (0.32, 0.70)			
			1												
		0	0.2	0.4	0.6	8.0	1	1.2	1.4	1.6	1.8	2			

Figure 1.5: 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.

1.2 Marginalized risk and controlled vaccine efficacy plots

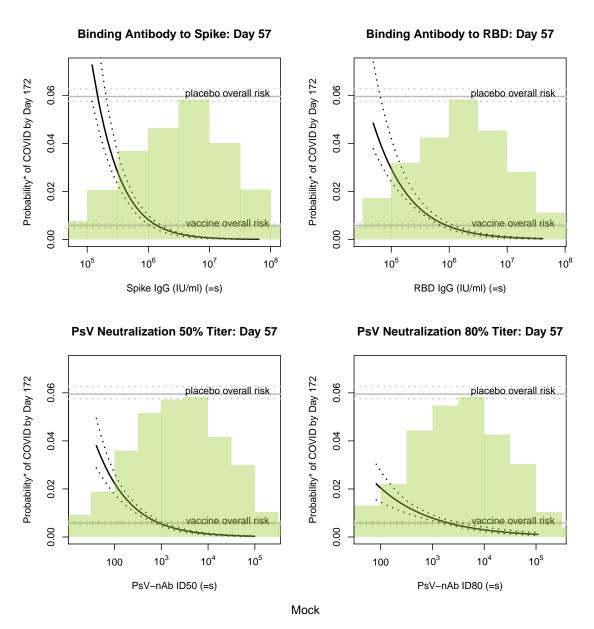


Figure 1.6: Marginalized cumulative risk by Day 172 as functions of Day 57 markers (=s) among baseline seronegative vaccine recipients with 95% bootstrap point-wise confidence bands. The horizontal lines indicate the overall cumulative risk of the placebo and vaccine arms by Day 172 and its 95% point-wise confidence interval. Histograms of the immunological markers in the vaccine arm are overlaid. lod: lower limit of detection.

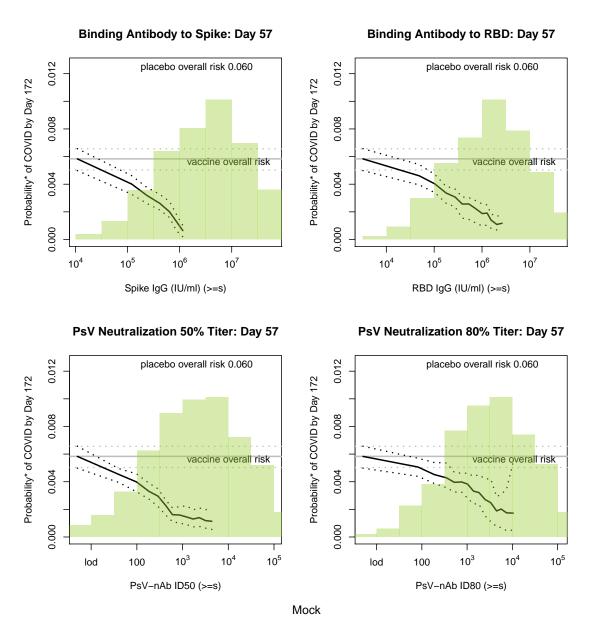


Figure 1.7: Marginalized cumulative risk by Day 57 as functions of Day 57 markers above a threshold $(\geq s)$ among baseline seronegative vaccine recipients with 95% bootstrap point-wise confidence bands (at least 5 cases are required). The horizontal lines indicate the overall cumulative risk of the vaccine arm by Day 172and its 95% point-wise confidence interval. Histograms of the immunological markers in the vaccine arm are overlaid. lod: lower limit of detection.

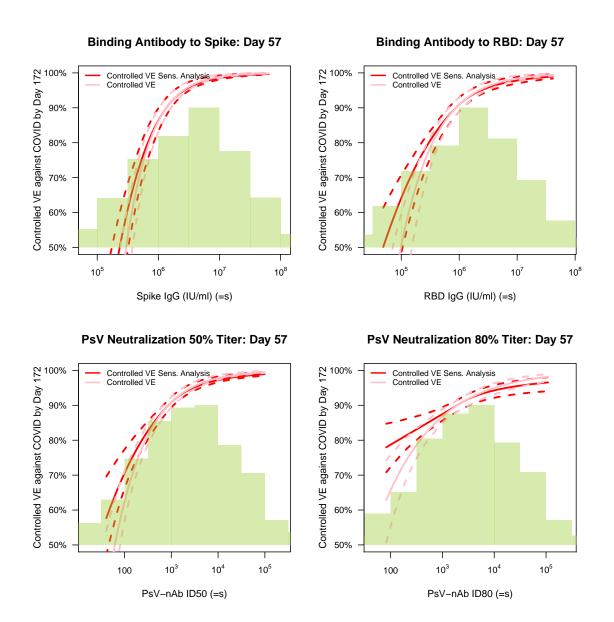


Figure 1.8: Controlled VE with sensitivity analysis as functions of Day 57 markers (=s) among baseline seronegative vaccine recipients with 95% bootstrap point-wise confidence bands. Histograms of the immunological markers in the vaccine arm are overlaid. lod: lower limit of detection.

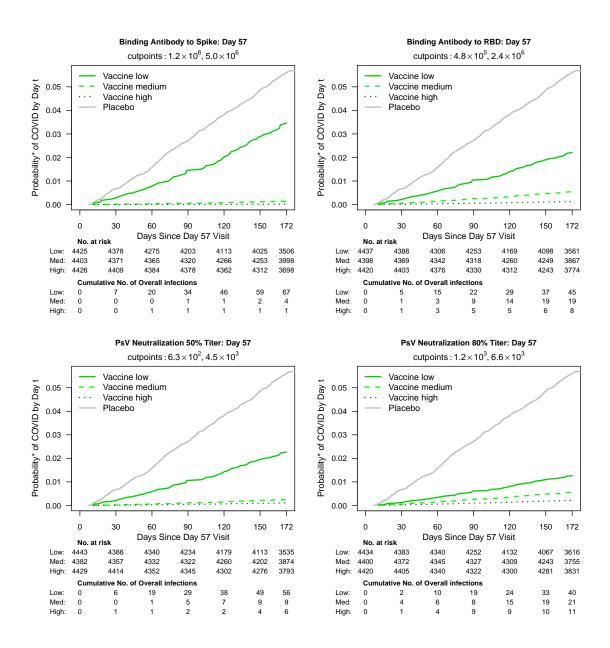


Figure 1.9: Marginalized cumulative incidence rate curves for trichotomized Day 57 markers among baseline seronegative vaccine recipients. The gray line is the overall cumulative incidence rate curve in the placebo arm.

Chapter 2

Day 29 Univariate CoR: Cox Models of Risk

The main regression model is the Cox proportional hazards model. All plots are made with Cox models fit unless specified otherwise.

2.1 Hazard ratios

Table 2.1: Inference for Day 29 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 1	10-fold incr.	P-value	q-value	FWER
Immunologic Marker	No. at-risk**	Pt. Est.	95% CI	(2-sided)		
Spike IgG (IU/ml)	83/13,271	0.09	(0.05 - 0.16)	< 0.001	< 0.001	< 0.001
RBD IgG (IU/ml)	83/13,271	0.25	(0.16 - 0.38)	< 0.001	< 0.001	< 0.001
PsV-nAb ID50	83/13,271	0.32	(0.23 - 0.46)	< 0.001	< 0.001	< 0.001
PsV-nAb ID80	83/13,271	0.57	(0.43 - 0.75)	< 0.001	< 0.001	< 0.001

^{*}Baseline covariates adjusted for: age in years, at risk or not, community of color or not **No. at-risk = number of per-protocol baseline negative vaccine recipients at-risk for COVID at 7 days post Day 29 visit; no. cases = number of this cohort with an observed COVID endpoints.

Table 2.2: Inference for Day 29 antibody marker covariate-adjusted correlates of risk of COVID in the vaccine group: Hazard ratios for Middle vs. Upper tertile vs. Lower tertile*

Mock	Tertile	No. cases /	Attack	Haz	. Ratio	P-value	Overall P-	Overall q-	Overall
Immunologic Marker		No. at-risk**	rate	Pt. Est.	95% CI	(2-sided)	value***	value	FWER
Spike IgG (IU/ml)	Lower	54/4,422	0.0122	1	N/A	N/A	< 0.001	< 0.001	< 0.001
	Middle	24/4,423	0.0054	0.20	(0.11-0.37)	< 0.001			
	Upper	5/4,427	0.0011	0.02	(0.01 - 0.06)	< 0.001			
RBD IgG (IU/ml)	Lower	46/4,419	0.0104	1	N/A	N/A	< 0.001	< 0.001	< 0.001
	Middle	25/4,428	0.0056	0.30	(0.17 - 0.55)	< 0.001			
	Upper	12/4,424	0.0027	0.08	(0.04-0.17)	< 0.001			
PsV-nAb ID50	Lower	47/4,403	0.0107	1	N/A	N/A	< 0.001	< 0.001	< 0.001
	Middle	24/4,420	0.0054	0.33	(0.19 - 0.59)	< 0.001			
	Upper	12/4,448	0.0027	0.12	(0.06-0.25)	< 0.001			
PsV-nAb ID80	Lower	30/4,416	0.0068	1	N/A	N/A	0.001	< 0.001	< 0.001
	Middle	36/4,429	0.0081	0.94	(0.55-1.62)	0.834			
	Upper	$17/4,\!426$	0.0038	0.33	(0.17 - 0.64)	0.001			
Placebo		821/13,299	0.0617						

^{*}Baseline covariates adjusted for: age in years, at risk or not, community of color or not . Average follow-up time 200 days, maximum follow-up time 213 days. Cutpoints: Spike IgG (IU/ml) [4.38, 4.94), RBD IgG (IU/ml) [4.11, 4.66), PsV-nAb ID50 [1.67, 2.38), PsV-nAb ID80 [1.97, 2.64) **No. at-risk = number of per-protocol baseline negative vaccine recipients at-risk for COVID at 7 days post Day 29 visit; 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.

2.1. HAZARD RATIOS

Binding Antibody to Spike: Day 29

23

Group	No. Eve	ents										HR (9	5% CI)
All baseline negative, vacci	ne 83	-	_									0.09 (0	0.05, 0.16)
Age >= 65	40	-	-									0.08 (0	0.04, 0.16)
Age < 65, At risk	30	-										0.05 (0	0.02, 0.17)
Age < 65, Not at risk	13											0.11 (0	0.01, 0.79)
		0	0.2	0.4	0.6	0.8	1	1.2	1.4	1.6	1.0		

Binding Antibody to RBD: Day 29

Group	No. Ev	No. Events										HR (95% CI)
All baseline negative, vacci	ne 83		-									0.25 (0.16, 0.38)
Age >= 65	40		-									0.23 (0.12, 0.45)
Age < 65, At risk	30											0.22 (0.11, 0.46)
Age < 65, Not at risk	13				_							0.24 (0.09, 0.65)
		0	0.2	0.4	0.6	0.8	1	1.2	1.4	1.6	1.8	2

PsV Neutralization 50% Titer: Day 29

Group	No. Ever	No. Events										HR (95% CI)
All baseline negative, vacci	ne 83		_	•								0.32 (0.23, 0.46)
Age >= 65	40		_									0.28 (0.17, 0.46)
Age < 65, At risk	30			•								0.32 (0.17, 0.60)
Age < 65, Not at risk	13		-									0.48 (0.27, 0.86)
		0	0.2	0.4	0.6	0.8	1	1.2	1.4	1.6	1.8	2

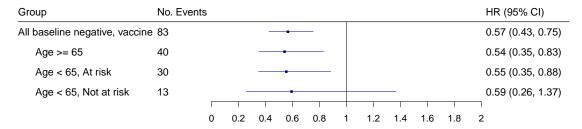


Figure 2.1: Forest plots of hazard ratios among baseline seronegative vaccine recipients and subgroups with 95% point-wise confidence intervals.

1.2 1.4

1.6 1.8

Group (Baseline Negative) No. Events HR (95% CI) All Vaccine 83 0.09 (0.05, 0.16) Age >= 65 40 0.08 (0.04, 0.16) Age < 65 43 0.07 (0.03, 0.18) At risk 55 0.10 (0.05, 0.18) Not at risk 28 0.06 (0.02, 0.15) Comm. of color 32 0.12 (0.06, 0.26) White Non-Hispanic 51 0.07 (0.03, 0.15) 0.09 (0.04, 0.17) Men 46 Women 37 0.09 (0.03, 0.22)

Binding Antibody to Spike: Day 29

Figure 2.2: Forest plots of hazard ratios of Day 29 binding Ab to spike markers among baseline seronegative vaccine recipients (top row) and eight subpopulations (row 2-9) with 95% point-wise confidence intervals.

0.6 0.8

0.2 0.4

Binding Antibody to RBD: Day 29

Group (Baseline Negativ	e) No. Eve	ents	HR (95% CI)
All Vaccine	83		0.25 (0.16, 0.38)
Age >= 65	40		0.23 (0.12, 0.45)
Age < 65	43		0.23 (0.13, 0.42)
At risk	55		0.27 (0.17, 0.45)
Not at risk	28		0.18 (0.09, 0.39)
Comm. of color	32		0.27 (0.16, 0.48)
White Non-Hispanic	51		0.24 (0.13, 0.43)
Men	46		0.28 (0.17, 0.47)
Women	37		0.20 (0.10, 0.43)
		0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6 1.8	2

Figure 2.3: Forest plots of hazard ratios of Day29binding Ab to RBD markers among baseline seronegative vaccine recipients (top row) and eight subpopulations (row 2-9) with 95% point-wise confidence intervals.

Group (Baseline Negativ	e) No. Events		HR (95% CI)
All Vaccine	83		0.32 (0.23, 0.46)
Age >= 65	40		0.28 (0.17, 0.46)
Age < 65	43		0.36 (0.23, 0.57)
At risk	55		0.32 (0.21, 0.49)
Not at risk	28		0.33 (0.19, 0.57)
Comm. of color	32		0.40 (0.25, 0.65)
White Non-Hispanic	51		0.28 (0.17, 0.45)
Men	46		0.35 (0.22, 0.56)
Women	37		0.29 (0.17, 0.48)
			٦
		0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6 1.8	2

Figure 2.4: Forest plots of hazard ratios of Day 29 pseudo neut ID50 markers among baseline seronegative vaccine recipients (top row) and eight subpopulations (row 2-9) with 95% point-wise confidence intervals.

Group (Baseline Negative	e) No. Events	S										HR (95% CI)
All Vaccine	83			-	-	_						0.57 (0.43, 0.75)
Age >= 65	40				•							0.54 (0.35, 0.83)
Age < 65	43				•							0.57 (0.37, 0.85)
At risk	55			_	-							0.58 (0.42, 0.81)
Not at risk	28				•		-					0.50 (0.28, 0.92)
Comm. of color	32			_	-							0.67 (0.45, 1.01)
White Non-Hispanic	51				•	_						0.50 (0.34, 0.74)
Men	46			_	-							0.60 (0.42, 0.86)
Women	37			-	•							0.52 (0.33, 0.84)
					- 1	- 1			- 1			
		0	0.2	0.4	0.6	0.8	1	1.2	1.4	1.6	1.8	2

Figure 2.5: Forest plots of hazard ratios of Day 29 pseudo neut ID80 markers among baseline seronegative vaccine recipients (top row) and eight subpopulations (row 2-9) with 95% point-wise confidence intervals.

2.2 Marginalized risk and controlled vaccine efficacy plots

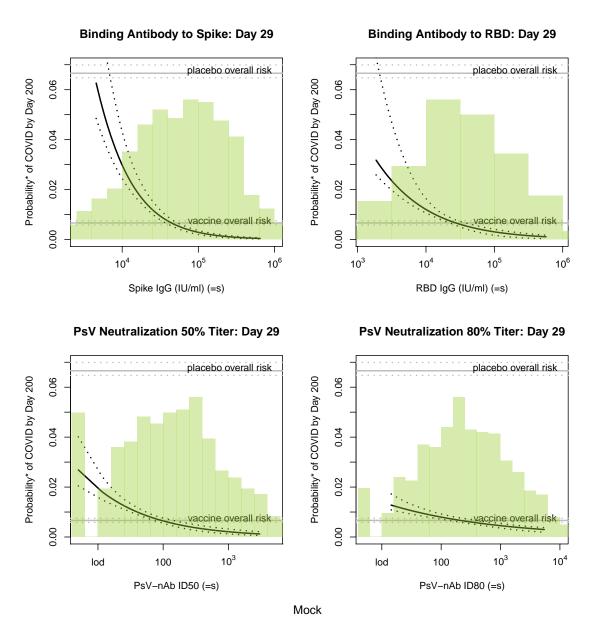


Figure 2.6: Marginalized cumulative risk by Day 200 as functions of Day 29 markers (=s) among baseline seronegative vaccine recipients with 95% bootstrap point-wise confidence bands. The horizontal lines indicate the overall cumulative risk of the placebo and vaccine arms by Day 200 and its 95% point-wise confidence interval. Histograms of the immunological markers in the vaccine arm are overlaid. lod: lower limit of detection.

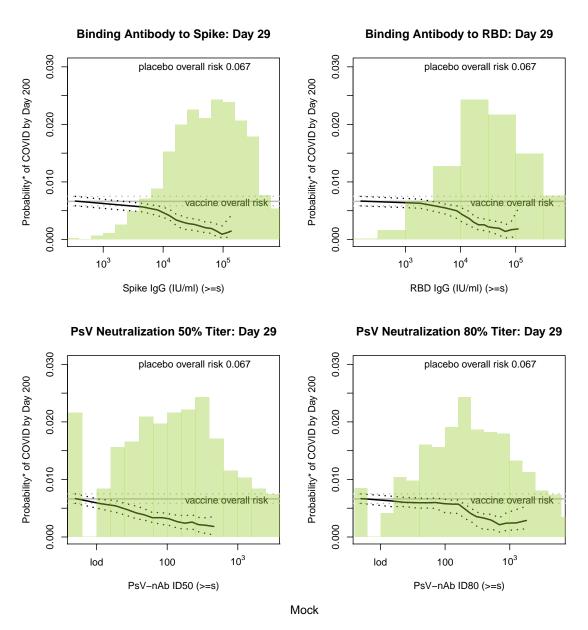


Figure 2.7: Marginalized cumulative risk by Day 29 as functions of Day 29 markers above a threshold $(\geq s)$ among baseline seronegative vaccine recipients with 95% bootstrap point-wise confidence bands (at least 5 cases are required). The horizontal lines indicate the overall cumulative risk of the vaccine arm by Day 200 and its 95% point-wise confidence interval. Histograms of the immunological markers in the vaccine arm are overlaid. lod: lower limit of detection.

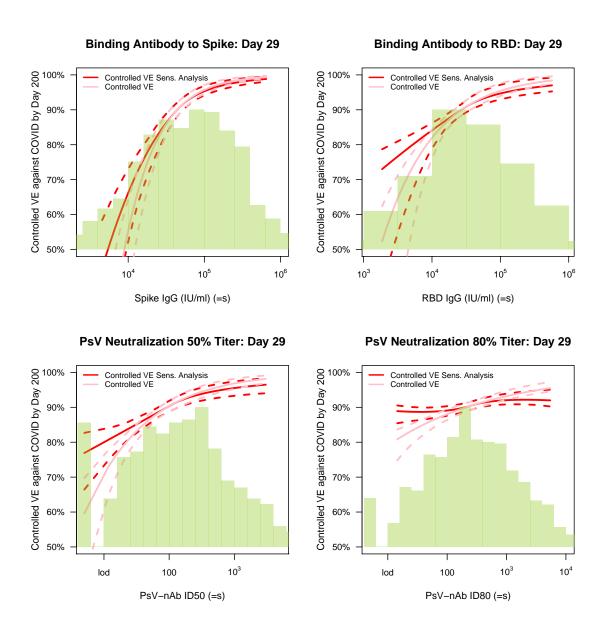


Figure 2.8: Controlled VE with sensitivity analysis as functions of Day 29 markers (=s) among baseline seronegative vaccine recipients with 95% bootstrap point-wise confidence bands. Histograms of the immunological markers in the vaccine arm are overlaid. lod: lower limit of detection.

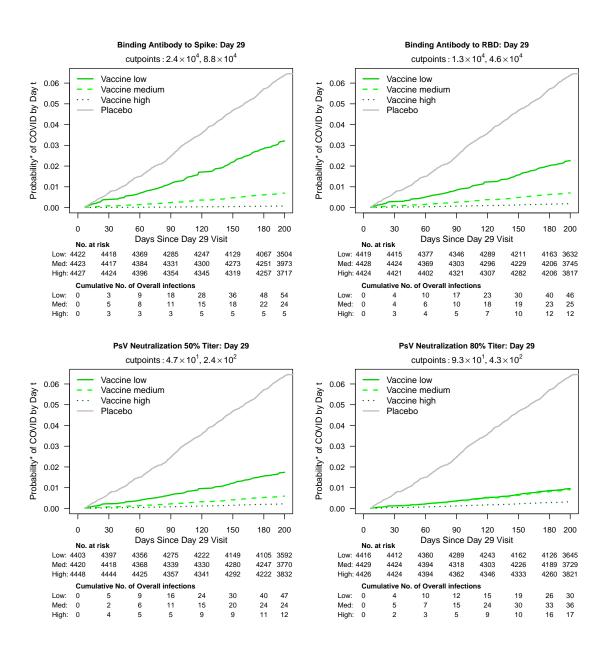


Figure 2.9: Marginalized cumulative incidence rate curves for trichotomized Day 29 markers among baseline seronegative vaccine recipients. The gray line is the overall cumulative incidence rate curve in the placebo arm.