RSV correlates analysis report

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Correlates of risk objective 1

Cox PH model-based analyses

In this objective we assessed the association of each of the 16 immunologic biomarkers, one-at-a-time, with each of the three endpoints within each study arm. All markers were on the log10 scale unless otherwise specified.

For maternal time points (D0, D14), the analyses adjusted for the maternal risk score and the indicator for whether the number of days from vaccination to birth was greater than or equal to 30 days; for cord blood markers, the analyses adjusted for the maternal risk score alone.

Results for EIA and PCA were estimated from phase 1 data using the glm function. Results for RSVA and RSVB were estimated from phase 2 data using the osDesign package (@breslow1997maximum) for endpoint 1 and the survey package (@lumley2010complex) for endpoints 2 and 3.

osDesign was the specified regression method in the SAP. In the terminology used by osDesign, there were 20 strata in our design, 10 in vaccine and 10 in placebo (crossing 5 regions with time from vaccination to birth less than 30 days (<30d)). The numbers of cases and controls in these strata were input to osDesign::tps; no counts can be zero, otherwise we obtained a "zero cell frequency at phase I" error. For endpoint 1, there were no cases in the stratum SS/<30d in both the placebo arm and the vaccine arm. These two had small strata: 11 controls in the placebo arm (out of 784 total) and 18 controls in the vaccine arm (out of 1553 total) and 2 controls from each stratum were sampled for biomarkers measurements. We thus removed these two strata from the analyses for endpoint 1.

An alternative method for making inference based on phase 2 data is to use the svyglm function from the survey package. Results for RSVA and RSVB for endpoint 1 using the survey package (not shown) were close to the results obtained using the osDesign package. For endpoints 2 and 3, four out of ten strata in placebo and five out of ten strata in vaccine are empty, so we used the survey package for endpoints 2 and 3. For the survey package, when a stratum has only one sample, "there is no contribution to the variance from the first stage of sampling in this stratum," (https://r-survey.r-forge.r-project.org/survey/exmample-lonely.html), the survey package offers several options, and the best option to us seems to be options(survey.lonely.psu="adjust"), by which "the stratum contribution to the variance is taken to be the average of all the strata with more than one primary sampling unit. This might be appropriate if the lonely PSUs were due to data missing at random rather than to design deficiencies. Other options include removing the strata or ignore the first stage sampling variance in those strata."

Based on logistic regression modeling, there was no evidence for a correlate of risk of endpoint 1 for any of the markers for either treatment arm (Figures 0.14 and 0.15). In contrast, for endpoint 2, fold-rise of each of the 4 markers EIA, PCA, RSVA, RSVB was inversely associated with outcome, with odds ratios for the vaccine arm of 0.13, 0.19, 0.19, 0.21 per 10-fold increase of RSVA, RSVB, EIA, and PCA, respectively (Figure 0.16). The precision of the correlate was greater for EIA and PCA than for RSVA and RSVB, with narrower confidence intervals about the odds ratios. Figure 0.17 shows results for endpoint 2 and the placebo arm.

For CoR objective 1, the only marker that passed the preset criterion of either q value of 0.1 or the more stringent Holm-adjusted p value of 0.05 was EIA fold change (d14 over d0) for endpoint 2 in the vaccine arm, which had a P value of 0.005 and q value of 0.085 (Table 0.2). In fact, Table 0.1 shows that not just EIA, but also PCA and RSVB fold change, have an inverse association with risk for endpoint 2 in the vaccine arm that was significant before multiplicity adjustment, and RSVA also has a trend. The point and 95% confidence interval estimates of odds ratios support substantial inverse associations of each antibody marker with RSV risk. Therefore, the message from the results is that for all four assays, fold-rise in vaccine

recipients was consistently an inverse correlate of risk of endpoint 2 with a large estimated effect size. Given there were only 14 vaccine breakthrough type 2 endpoints, these consistent results with the 95% confidence intervals generally lying below one (e.g., 95% CI 0.06 to 0.62 around the odds ratio estimate of 0.21 for the fold-rise EIA marker) highlights the strong correlates effect sizes. Point estimates for the D14 versions of the markers, and the cord blood versions of the markers, indicated inverse associations, but with odds ratio estimates much closer to one.

In the placebo arm, the log10 d0 measurements for the four assays showed no association with outcome. In the vaccine arm, the log10 d0 measurements showed trends toward direct associations with RSV risk; this can be explained as an induced association because d0 measurement is inversely associated with fold change. (When we include both d0 and fold change EIA in the same model for endpoint 2 and the vaccine arm, both are inversely correlated with risk. But to see the effect of fold change, we should not adjust for baseline, because baseline is associated with fold change. Leaving baseline out is justified because in the placebo arm it is not associated with risk.)

EIA or PCA were fitted using phase 2 data in order to compare with RSVA and RSVB to see which ones appeared to be stronger correlates on a more fair footing. The results suggest that EIA was better than RSVA and RSVB, which in turn were better than PCA. It is interesting that EIA and PCA were highly correlated (Pearson 0.95 in phase 2) and yet their performances as correlates of risk differed.

For endpoint 2 and the vaccine arm, the single marker regression p value for EIA fold change was 0.00627; the multiplicity Holm and BH adjusted p values were 0.100 and 0.100. The multiplicity adjustment approach we took may have been conservative because it did not account for the correlation between markers, and all markers were included in the multiplicity adjustment. Alternative less-conservative approaches to multiplicity adjustment would be the following:

1) Due to correlation between markers, a permutation-based procedure may be worth doing.
2) We could be more selective in which markers to include in the multiplicity adjustment. For example, we may exclude cord blood markers, baseline markers, or both from multiplicity adjustment and treat them as secondary objectives.

Some post-hoc exploratory preliminary Westfall and Young permutation-based multiplicity adjusted p values (@westfall1989p) for endpoint 2 and the vaccine arm are shown in Table 0.3. The permutation procedure can be potentially improved because the fact that we have a mix of phase 1 and phase 2 analyses presents a challenge. Furthermore, p.FWER is 0.0443 if cord blood is dropped, and 0.0311 if cord blood and baseline are dropped. These results are preliminary because the way permutation is done is complicated by the fact that some markers are phase 1 and some are phase 2. In these results, these facts were ignored when permuting and fit glm for all markers.

Endpoint 1

Vaccine arm

	RSVA	RSVB	EIA	PCA
log10 d0	1.28 (CI=0.57,2.90, p=0.549)	1.45 (CI=0.75,2.82, p=0.275)	1.47 (CI=0.68,3.16, p=0.328)	1.60 (CI=0.61,4.17, p=0.340)
log10 d14	1.49 (CI=0.64,3.48, p=0.352)	1.61 (CI=0.84,3.08, p=0.153)	0.81 (CI=0.36,1.79, p=0.598)	1.23 (CI=0.46,3.33, p=0.681)
log10d14overd0	1.13 (CI=0.49,2.61, p=0.769)	1.18 (CI=0.51,2.72, p=0.696)	0.69 (CI=0.37,1.27, p=0.230)	0.85 (CI=0.41,1.80, p=0.679)
log10 cord	1.48 (CI=0.65,3.34, p=0.349)	1.59 (CI=0.81,3.13, p=0.181)	1.34 (CI=0.59,3.04, p=0.486)	1.27 (CI=0.48,3.34, p=0.626)

Placebo arm

	RSVA	RSVB	EIA	PCA
log10 d0	0.76 (CI=0.30,1.94, p=0.565)	0.80 (CI=0.36,1.79, p=0.592)	0.77 (CI=0.34,1.75, p=0.539)	1.24 (CI=0.45,3.38, p=0.676)
log10 d14	0.68 (CI=0.26,1.80, p=0.438)	0.70 (CI=0.32,1.55, p=0.380)	0.62 (CI=0.26,1.48, p=0.280)	0.66 (CI=0.22,1.92, p=0.442)
log10d14overd0	0.87 (CI=0.26,2.86, p=0.814)	0.60 (CI=0.14,2.60, p=0.491)	0.80 (CI=0.19,3.44, p=0.763)	0.29 (CI=0.07,1.26, p=0.098)
log10 cord	0.50 (CI=0.18,1.40, p=0.186)	0.70 (CI=0.33,1.49, p=0.349)	1.04 (CI=0.44,2.42, p=0.934)	1.32 (CI=0.48,3.64, p=0.597)

Endpoint 2

Vaccine arm

	RSVA	RSVB	EIA	PCA
log10 d0	2.04 (CI=0.44,9.45, p=0.363)	1.68 (CI=0.63,4.51, p=0.303)	3.60 (CI=0.83,15.60, p=0.087)	3.77 (CI=0.62,22.82, p=0.148)
log10 d14	0.97 (CI=0.23,4.15, p=0.970)	0.76 (CI=0.21,2.74, p=0.677)	0.26 (CI=0.06,1.06, p=0.060)	0.27 (CI=0.05,1.51, p=0.136)
log10d14overd0	0.40 (CI=0.07,2.24, p=0.300)	0.25 (CI=0.04,1.69, p=0.157)	0.19 (CI=0.06,0.62, p=0.006)**	0.21 (CI=0.05,0.85, p=0.029)*
log10 cord	0.58 (CI=0.22,1.54, p=0.275)	0.86 (CI=0.31,2.39, p=0.767)	0.56 (CI=0.15,1.99, p=0.366)	0.40 (CI=0.09,1.72, p=0.218)

Placebo arm

	RSVA	RSVB	EIA	PCA
log10 d0	0.96 (CI=0.26,3.56, p=0.953)	0.77 (CI=0.22,2.69, p=0.686)	1.09 (CI=0.37,3.20, p=0.879)	2.38 (CI=0.65,8.76, p=0.193)
log10 d14	0.60 (CI=0.21,1.74, p=0.347)	0.56 (CI=0.19,1.65, p=0.295)	0.92 (CI=0.30,2.88, p=0.889)	0.86 (CI=0.21,3.57, p=0.840)
log10d14overd0	0.50 (CI=0.14,1.84, p=0.301)	0.36 (CI=0.06,2.05, p=0.252)	0.95 (CI=0.13,6.73, p=0.956)	0.15 (CI=0.03,0.77, p=0.023)*
log10 cord	0.53 (CI=0.14,2.01, p=0.354)	0.75 (CI=0.23,2.41, p=0.627)	1.20 (CI=0.38,3.79, p=0.755)	1.59 (CI=0.41,6.24, p=0.505)

Endpoint 3

Vaccine arm

	RSVA	RSVB	EIA	PCA
log10 d0	2.76 (CI=0.56,13.72, p=0.215)	2.11 (CI=0.75,5.97, p=0.161)	4.63 (CI=0.94,22.80, p=0.059)	4.84 (CI=0.70,33.70, p=0.111)
log10 d14	1.25 (CI=0.27,5.64, p=0.776)	1.14 (CI=0.33,3.89, p=0.838)	0.36 (CI=0.08,1.71, p=0.198)	0.41 (CI=0.06,2.74, p=0.357)
log10d14overd0	0.35 (CI=0.05,2.56, p=0.300)	0.32 (CI=0.04,2.37, p=0.267)	0.20 (CI=0.06,0.73, p=0.015)*	0.24 (CI=0.05,1.07, p=0.060)
log10 cord	0.66 (CI=0.23,1.85, p=0.427)	1.23 (CI=0.44,3.40, p=0.697)	0.66 (CI=0.16,2.75, p=0.563)	0.43 (CI=0.09,2.12, p=0.298)

Placebo arm

	RSVA	RSVB	EIA	PCA
log10 d0	1.40 (CI=0.43,4.59, p=0.582)	0.94 (CI=0.28,3.13, p=0.920)	1.25 (CI=0.42,3.74, p=0.694)	2.86 (CI=0.77,10.66, p=0.117)
log10 d14	0.76 (CI=0.29,2.00, p=0.579)	0.66 (CI=0.24,1.83, p=0.424)	1.08 (CI=0.34,3.42, p=0.896)	1.02 (CI=0.24,4.25, p=0.983)
log10d14overd0	0.44 (CI=0.12,1.65, p=0.224)	0.34 (CI=0.06,2.07, p=0.245)	0.98 (CI=0.13,7.14, p=0.985)	0.14 (CI=0.03,0.73, p=0.020)*
log10 cord	0.69 (CI=0.19,2.47, p=0.572)	0.95 (CI=0.32,2.81, p=0.924)	1.44 (CI=0.44,4.68, p=0.545)	1.91 (CI=0.48,7.66, p=0.361)

Table 0.1: CoR objective 1. Each cell corresponds to one model. RSVA and RSVB models are fitted to phase 2 data, PCA and EIA models are fitted to phase 1 data. Time from vaccination to birth is adjusted for in analyses of maternal markers but not in analyses of infant markers. All models adjust for maternal risk score. Phase 1 data are used for EIA and PCA.

Endpoint 1

	pvals	Holm	BH
RSVA.d0.p.value	0.549	1.000	0.742
RSVA.d14.p.value	0.352	1.000	0.703
RSVA.log10d14overd0.p.value	0.769	1.000	0.769
RSVA.cord.p.value	0.349	1.000	0.703
RSVB.d0.p.value	0.275	1.000	0.703
RSVB.d14.p.value	0.153	1.000	0.703
RSVB.log10d14overd0.p.value	0.696	1.000	0.742
RSVB.cord.p.value	0.181	1.000	0.703
EIA.d0.p.value	0.328	1.000	0.703
EIA.d14.p.value	0.598	1.000	0.742
EIA.log10d14overd0.p.value	0.230	1.000	0.703
EIA.cord.p.value	0.486	1.000	0.742
PCA.d0.p.value	0.340	1.000	0.703
PCA.d14.p.value	0.681	1.000	0.742
PCA.log10d14overd0.p.value	0.679	1.000	0.742
PCA.cord.p.value	0.626	1.000	0.742

	pvals	Holm	BH
RSVA.d0.p.value	0.565	1.000	0.796
RSVA.d14.p.value	0.438	1.000	0.796
RSVA.log10d14overd0.p.value	0.814	1.000	0.868
RSVA.cord.p.value	0.186	1.000	0.796
RSVB.d0.p.value	0.592	1.000	0.796
RSVB.d14.p.value	0.380	1.000	0.796
RSVB.log10d14overd0.p.value	0.491	1.000	0.796
RSVB.cord.p.value	0.349	1.000	0.796
EIA.d0.p.value	0.539	1.000	0.796
EIA.d14.p.value	0.280	1.000	0.796
EIA.log10d14overd0.p.value	0.763	1.000	0.868
EIA.cord.p.value	0.934	1.000	0.934
PCA.d0.p.value	0.676	1.000	0.832
PCA.d14.p.value	0.442	1.000	0.796
PCA.log10d14overd0.p.value	0.098	1.000	0.796
PCA.cord.p.value	0.597	1.000	0.796

Endpoint 2

	pvals	Holm	BH
RSVA.d0.p.value	0.363	1.000	0.451
RSVA.d14.p.value	0.970	1.000	0.970
RSVA.log10d14overd0.p.value	0.300	1.000	0.441
RSVA.cord.p.value	0.275	1.000	0.441
RSVB.d0.p.value	0.303	1.000	0.441
RSVB.d14.p.value	0.677	1.000	0.774
RSVB.log10d14overd0.p.value	0.157	1.000	0.358
RSVB.cord.p.value	0.767	1.000	0.818
EIA.d0.p.value	0.087	1.000	0.349
EIA.d14.p.value	0.060	0.845	0.322
EIA.log10d14overd0.p.value	0.006	0.100	0.100
EIA.cord.p.value	0.366	1.000	0.451
PCA.d0.p.value	0.148	1.000	0.358
PCA.d14.p.value	0.136	1.000	0.358
PCA.log10d14overd0.p.value	0.029	0.428	0.228
PCA.cord.p.value	0.218	1.000	0.436

	pvals	Holm	BH
RSVA.d0.p.value	0.953	1.000	0.956
RSVA.d14.p.value	0.347	1.000	0.809
RSVA.log10d14overd0.p.value	0.301	1.000	0.809
RSVA.cord.p.value	0.354	1.000	0.809
RSVB.d0.p.value	0.686	1.000	0.956
RSVB.d14.p.value	0.295	1.000	0.809
RSVB.log10d14overd0.p.value	0.252	1.000	0.809
RSVB.cord.p.value	0.627	1.000	0.956
EIA.d0.p.value	0.879	1.000	0.956
EIA.d14.p.value	0.889	1.000	0.956
EIA.log10d14overd0.p.value	0.956	1.000	0.956
EIA.cord.p.value	0.755	1.000	0.956
PCA.d0.p.value	0.193	1.000	0.809
PCA.d14.p.value	0.840	1.000	0.956
PCA.log10d14overd0.p.value	0.023	0.376	0.376
PCA.cord.p.value	0.505	1.000	0.956

Endpoint 3

	pvals	Holm	BH
RSVA.d0.p.value	0.215	1.000	0.480
RSVA.d14.p.value	0.776	1.000	0.828
RSVA.log10d14overd0.p.value	0.300	1.000	0.480
RSVA.cord.p.value	0.427	1.000	0.569
RSVB.d0.p.value	0.161	1.000	0.480
RSVB.d14.p.value	0.838	1.000	0.838
RSVB.log10d14overd0.p.value	0.267	1.000	0.480
RSVB.cord.p.value	0.697	1.000	0.796
EIA.d0.p.value	0.059	0.889	0.323
EIA.d14.p.value	0.198	1.000	0.480
EIA.log10d14overd0.p.value	0.015	0.241	0.241
EIA.cord.p.value	0.563	1.000	0.694
PCA.d0.p.value	0.111	1.000	0.443
PCA.d14.p.value	0.357	1.000	0.519
PCA.log10d14overd0.p.value	0.060	0.889	0.323
PCA.cord.p.value	0.298	1.000	0.480

	pvals	Holm	BH
RSVA.d0.p.value	0.582	1.000	0.932
RSVA.d14.p.value	0.579	1.000	0.932
RSVA.log10d14overd0.p.value	0.224	1.000	0.932
RSVA.cord.p.value	0.572	1.000	0.932
RSVB.d0.p.value	0.920	1.000	0.985
RSVB.d14.p.value	0.424	1.000	0.932
RSVB.log10d14overd0.p.value	0.245	1.000	0.932
RSVB.cord.p.value	0.924	1.000	0.985
EIA.d0.p.value	0.694	1.000	0.985
EIA.d14.p.value	0.896	1.000	0.985
EIA.log10d14overd0.p.value	0.985	1.000	0.985
EIA.cord.p.value	0.545	1.000	0.932
PCA.d0.p.value	0.117	1.000	0.932
PCA.d14.p.value	0.983	1.000	0.985
PCA.log10d14overd0.p.value	0.020	0.319	0.319
PCA.cord.p.value	0.361	1.000	0.932

Table 0.2: P-values multiplicity adjustment for CoR objective 1. Vaccine arm on the left and placebo arm on the right. Phase 1 data are used for EIA and PCA.

	p.unadj	p.FWER	p.FDR
EIA.log10d14overd0	0.006	0.062	0.086
RSVB.log10d14overd0	0.027	0.243	0.124
PCA.log10d14overd0	0.029	0.243	0.124
RSVA.log10d14overd0	0.036	0.281	0.124
RSVA.log10d0	0.040	0.292	0.124
EIA.log10d14	0.060		
EIA.log10d0	0.087		
PCA.log10d14	0.136		
PCA.log10d0	0.148		
RSVA.log10d14	0.232		
RSVB.log10d0	0.335		
RSVB.log10d14	0.348		
PCA.log10cord	0.388		
RSVA.log10cord	0.550		
EIA.log10cord	0.565		
RSVB.log10cord	0.834		

Table 0.3: CoR objective 1, endpoint 2, vaccine arm. Westfall and Young permutation-based multiplicity adjustment. Permutation is done by tethering the end point and the clinical covariates together and permuting the marker only.

Endpoint 1

Vaccine arm

	RSVA	RSVB	EIA	PCA
log10 d0	1.28 (CI=0.57,2.90, p=0.549)	1.45 (CI=0.75,2.82, p=0.275)	1.29 (CI=0.55,3.02, p=0.551)	1.17 (CI=0.39,3.57, p=0.777)
log10 d14	1.49 (CI=0.64,3.48, p=0.352)	1.61 (CI=0.84,3.08, p=0.153)	0.86 (CI=0.36,2.09, p=0.742)	2.13 (CI=0.68,6.67, p=0.194)
log10d14overd0	1.13 (CI=0.49,2.61, p=0.769)	1.18 (CI=0.51,2.72, p=0.696)	0.77 (CI=0.39,1.54, p=0.463)	1.39 (CI=0.60,3.25, p=0.446)
log10 cord	1.48 (CI=0.65,3.34, p=0.349)	1.59 (CI=0.81,3.13, p=0.181)	1.81 (CI=0.76,4.32, p=0.179)	1.42 (CI=0.51,3.95, p=0.504)

Placebo arm

	RSVA	RSVB	EIA	PCA
log10 d0	0.76 (CI=0.30,1.94, p=0.565)	0.80 (CI=0.36,1.79, p=0.592)	0.45 (CI=0.16,1.28, p=0.134)	0.67 (CI=0.18,2.45, p=0.549)
log10 d14	0.68 (CI=0.26,1.80, p=0.438)	0.70 (CI=0.32,1.55, p=0.380)	0.35 (CI=0.12,0.97, p=0.044)*	0.30 (CI=0.08,1.18, p=0.085)
log10d14overd0	0.87 (CI=0.26,2.86, p=0.814)	0.60 (CI=0.14,2.60, p=0.491)	0.50 (CI=0.10,2.43, p=0.392)	0.10 (CI=0.01,1.18, p=0.068)
log10 cord	0.50 (CI=0.18,1.40, p=0.186)	0.70 (CI=0.33,1.49, p=0.349)	0.82 (CI=0.29,2.35, p=0.710)	0.71 (CI=0.19,2.66, p=0.607)

Endpoint 2

Vaccine arm

	RSVA	RSVB	EIA	PCA
log10 d0	2.04 (CI=0.44,9.45, p=0.363)	1.68 (CI=0.63,4.51, p=0.303)	4.27 (CI=0.65,27.86, p=0.131)	3.53 (CI=0.48,26.18, p=0.218)
log10 d14	0.97 (CI=0.23,4.15, p=0.970)	0.76 (CI=0.21,2.74, p=0.677)	0.32 (CI=0.07,1.45, p=0.141)	0.47 (CI=0.05,4.06, p=0.490)
log10d14overd0	0.40 (CI=0.07,2.24, p=0.300)	0.25 (CI=0.04,1.69, p=0.157)	0.20 (CI=0.07,0.52, p=0.001)**	0.32 (CI=0.09,1.22, p=0.098)
log10 cord	0.58 (CI=0.22,1.54, p=0.275)	0.86 (CI=0.31,2.39, p=0.767)	0.72 (CI=0.31,1.64, p=0.434)	0.46 (CI=0.17,1.24, p=0.127)

Placebo arm

	RSVA	RSVB	EIA	PCA
log10 d0	0.96 (CI=0.26,3.56, p=0.953)	0.77 (CI=0.22,2.69, p=0.686)	0.77 (CI=0.24,2.44, p=0.658)	1.46 (CI=0.26,8.17, p=0.670)
log10 d14	0.60 (CI=0.21,1.74, p=0.347)	0.56 (CI=0.19,1.65, p=0.295)	0.61 (CI=0.22,1.74, p=0.359)	0.51 (CI=0.12,2.24, p=0.378)
log10d14overd0	0.50 (CI=0.14,1.84, p=0.301)	0.36 (CI=0.06,2.05, p=0.252)	0.53 (CI=0.09,3.02, p=0.476)	0.02 (CI=0.00,1.25, p=0.066)
log10 cord	0.53 (CI=0.14,2.01, p=0.354)	0.75 (CI=0.23,2.41, p=0.627)	0.84 (CI=0.25,2.81, p=0.778)	0.69 (CI=0.17,2.70, p=0.590)

Endpoint 3

Vaccine arm

	RSVA	RSVB	EIA	PCA
log10 d0	2.76 (CI=0.56,13.72, p=0.215)	2.11 (CI=0.75,5.97, p=0.161)	6.05 (CI=0.79,46.43, p=0.085)	4.89 (CI=0.63,38.14, p=0.131)
log10 d14	1.25 (CI=0.27,5.64, p=0.776)	1.14 (CI=0.33,3.89, p=0.838)	0.47 (CI=0.10,2.29, p=0.351)	0.79 (CI=0.08,7.43, p=0.834)
log10d14overd0	0.35 (CI=0.05,2.56, p=0.300)	0.32 (CI=0.04,2.37, p=0.267)	0.22 (CI=0.08,0.61, p=0.004)**	0.38 (CI=0.09,1.63, p=0.194)
log10 cord	0.66 (CI=0.23,1.85, p=0.427)	1.23 (CI=0.44,3.40, p=0.697)	0.84 (CI=0.33,2.15, p=0.712)	0.49 (CI=0.16,1.50, p=0.215)

Placebo arm

	RSVA	RSVB	EIA	PCA
log10 d0	1.40 (CI=0.43,4.59, p=0.582)	0.94 (CI=0.28,3.13, p=0.920)	0.89 (CI=0.29,2.80, p=0.848)	1.85 (CI=0.33,10.40, p=0.484)
log10 d14	0.76 (CI=0.29,2.00, p=0.579)	0.66 (CI=0.24,1.83, p=0.424)	0.73 (CI=0.27,1.99, p=0.539)	0.63 (CI=0.15,2.69, p=0.536)
log10d14overd0	0.44 (CI=0.12,1.65, p=0.224)	0.34 (CI=0.06,2.07, p=0.245)	0.57 (CI=0.10,3.40, p=0.540)	0.02 (CI=0.00,1.22, p=0.065)
log10 cord	0.69 (CI=0.19,2.47, p=0.572)	0.95 (CI=0.32,2.81, p=0.924)	1.01 (CI=0.30,3.43, p=0.987)	0.84 (CI=0.21,3.33, p=0.799)

Table 0.4: CoR objective 1. Each cell corresponds to one model. All marker models are fitted to phase 2 data. Time from vaccination to birth is adjusted for in analyses of maternal markers but not in analyses of infant markers. All models adjust for maternal risk score. Phase 2 data are used for EIA and PCA.

Endpoint 1

	pvals	Holm	BH
RSVA.d0.p.value	0.549	1.000	0.735
RSVA.d14.p.value	0.352	1.000	0.735
RSVA.log10d14overd0.p.value	0.769	1.000	0.777
RSVA.cord.p.value	0.349	1.000	0.735
RSVB.d0.p.value	0.275	1.000	0.735
RSVB.d14.p.value	0.153	1.000	0.735
RSVB.log10d14overd0.p.value	0.696	1.000	0.777
RSVB.cord.p.value	0.181	1.000	0.735
EIA.d0.p.value	0.551	1.000	0.735
EIA.d14.p.value	0.742	1.000	0.777
EIA.log10d14overd0.p.value	0.463	1.000	0.735
EIA.cord.p.value	0.179	1.000	0.735
PCA.d0.p.value	0.777	1.000	0.777
PCA.d14.p.value	0.194	1.000	0.735
PCA.log10d14overd0.p.value	0.446	1.000	0.735
PCA.cord.p.value	0.504	1.000	0.735

	pvals	Holm	BH
RSVA.d0.p.value	0.565	1.000	0.694
RSVA.d14.p.value	0.438	1.000	0.694
RSVA.log10d14overd0.p.value	0.814	1.000	0.814
RSVA.cord.p.value	0.186	1.000	0.595
RSVB.d0.p.value	0.592	1.000	0.694
RSVB.d14.p.value	0.380	1.000	0.694
RSVB.log10d14overd0.p.value	0.491	1.000	0.694
RSVB.cord.p.value	0.349	1.000	0.694
EIA.d0.p.value	0.134	1.000	0.537
EIA.d14.p.value	0.044	0.707	0.451
EIA.log10d14overd0.p.value	0.392	1.000	0.694
EIA.cord.p.value	0.710	1.000	0.758
PCA.d0.p.value	0.549	1.000	0.694
PCA.d14.p.value	0.085	1.000	0.451
PCA.log10d14overd0.p.value	0.068	1.000	0.451
PCA.cord.p.value	0.607	1.000	0.694

Endpoint 2

	pvals	Holm	BH
RSVA.d0.p.value	0.363	1.000	0.528
RSVA.d14.p.value	0.970	1.000	0.970
RSVA.log10d14overd0.p.value	0.300	1.000	0.485
RSVA.cord.p.value	0.275	1.000	0.485
RSVB.d0.p.value	0.303	1.000	0.485
RSVB.d14.p.value	0.677	1.000	0.774
RSVB.log10d14overd0.p.value	0.157	1.000	0.418
RSVB.cord.p.value	0.767	1.000	0.818
EIA.d0.p.value	0.131	1.000	0.418
EIA.d14.p.value	0.141	1.000	0.418
EIA.log10d14overd0.p.value	0.001	0.018	0.018
EIA.cord.p.value	0.434	1.000	0.579
PCA.d0.p.value	0.218	1.000	0.485
PCA.d14.p.value	0.490	1.000	0.603
PCA.log10d14overd0.p.value	0.098	1.000	0.418
PCA.cord.p.value	0.127	1.000	0.418

	pvals	Holm	BH
RSVA.d0.p.value	0.953	1.000	0.953
RSVA.d14.p.value	0.347	1.000	0.755
RSVA.log10d14overd0.p.value	0.301	1.000	0.755
RSVA.cord.p.value	0.354	1.000	0.755
RSVB.d0.p.value	0.686	1.000	0.784
RSVB.d14.p.value	0.295	1.000	0.755
RSVB.log10d14overd0.p.value	0.252	1.000	0.755
RSVB.cord.p.value	0.627	1.000	0.784
EIA.d0.p.value	0.658	1.000	0.784
EIA.d14.p.value	0.359	1.000	0.755
EIA.log10d14overd0.p.value	0.476	1.000	0.784
EIA.cord.p.value	0.778	1.000	0.830
PCA.d0.p.value	0.670	1.000	0.784
PCA.d14.p.value	0.378	1.000	0.755
PCA.log10d14overd0.p.value	0.066	1.000	0.755
PCA.cord.p.value	0.590	1.000	0.784

Endpoint 3

	pvals	Holm	BH
RSVA.d0.p.value	0.215	1.000	0.492
RSVA.d14.p.value	0.776	1.000	0.838
RSVA.log10d14overd0.p.value	0.300	1.000	0.534
RSVA.cord.p.value	0.427	1.000	0.621
RSVB.d0.p.value	0.161	1.000	0.492
RSVB.d14.p.value	0.838	1.000	0.838
RSVB.log10d14overd0.p.value	0.267	1.000	0.534
RSVB.cord.p.value	0.697	1.000	0.838
EIA.d0.p.value	0.085	1.000	0.492
EIA.d14.p.value	0.351	1.000	0.562
EIA.log10d14overd0.p.value	0.004	0.068	0.068
EIA.cord.p.value	0.712	1.000	0.838
PCA.d0.p.value	0.131	1.000	0.492
PCA.d14.p.value	0.834	1.000	0.838
PCA.log10d14overd0.p.value	0.194	1.000	0.492
PCA.cord.p.value	0.215	1.000	0.492

	pvals	Holm	BH
RSVA.d0.p.value	0.582	1.000	0.847
RSVA.d14.p.value	0.579	1.000	0.847
RSVA.log10d14overd0.p.value	0.224	1.000	0.847
RSVA.cord.p.value	0.572	1.000	0.847
RSVB.d0.p.value	0.920	1.000	0.986
RSVB.d14.p.value	0.424	1.000	0.847
RSVB.log10d14overd0.p.value	0.245	1.000	0.847
RSVB.cord.p.value	0.924	1.000	0.986
EIA.d0.p.value	0.848	1.000	0.986
EIA.d14.p.value	0.539	1.000	0.847
EIA.log10d14overd0.p.value	0.540	1.000	0.847
EIA.cord.p.value	0.987	1.000	0.987
PCA.d0.p.value	0.484	1.000	0.847
PCA.d14.p.value	0.536	1.000	0.847
PCA.log10d14overd0.p.value	0.065	1.000	0.847
PCA.cord.p.value	0.799	1.000	0.986

Table 0.5: P-values multiplicity adjustment for CoR objective 1. Vaccine arm on the left and placebo arm on the right. Phase 2 data are used for EIA and PCA.

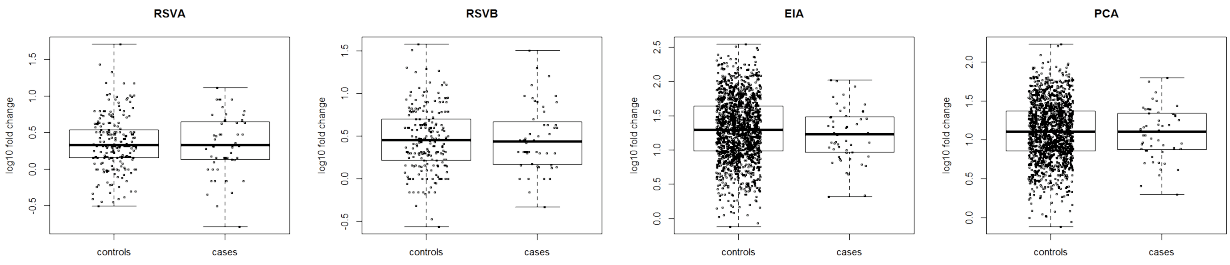

Figure 0.1: Boxplots of fold change (D14 over D0) by endpoint 1 status in the vaccine arm

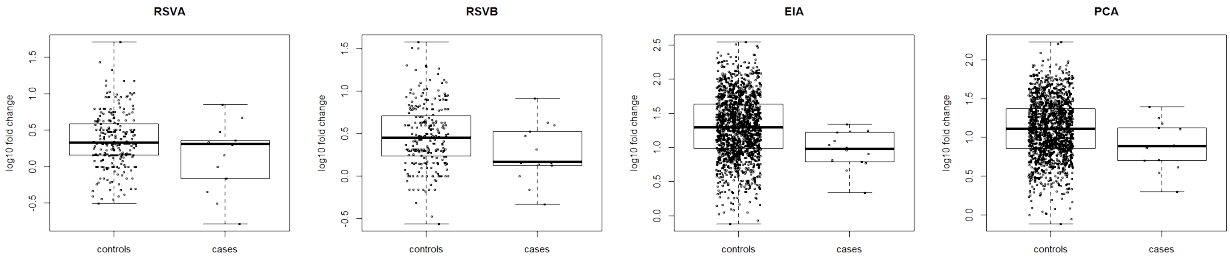

Figure 0.2: Boxplots of fold change (D14 over D0) by endpoint 2 status in the vaccine arm

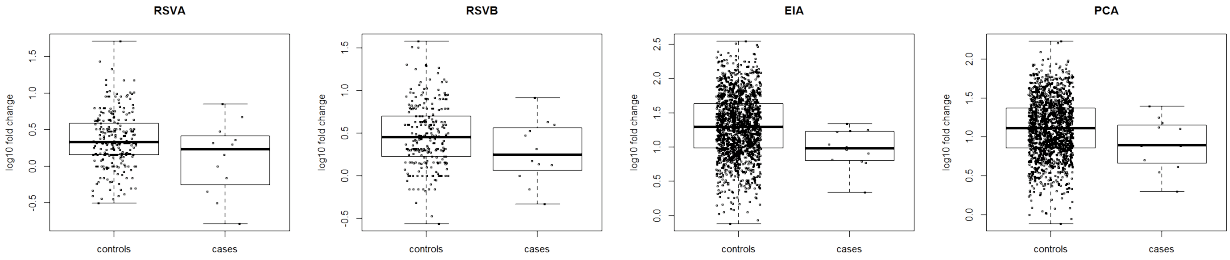

Figure 0.3: Boxplots of fold change (D14 over D0) by endpoint 3 status in the vaccine arm

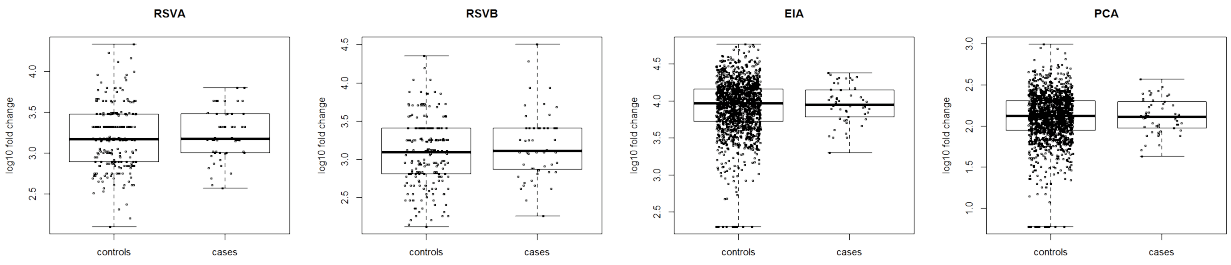

Figure 0.4: Boxplots of cord by endpoint 1 status in the vaccine arm

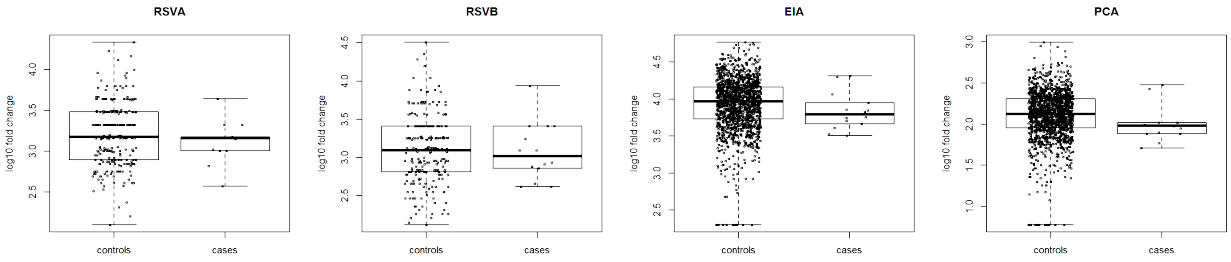

Figure 0.5: Boxplots of cord by endpoint 2 status in the vaccine arm

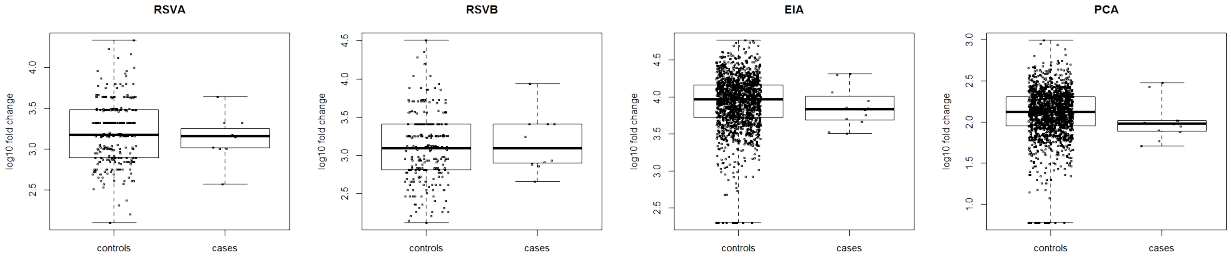

Figure 0.6: Boxplots of cord by endpoint 3 status in the vaccine arm

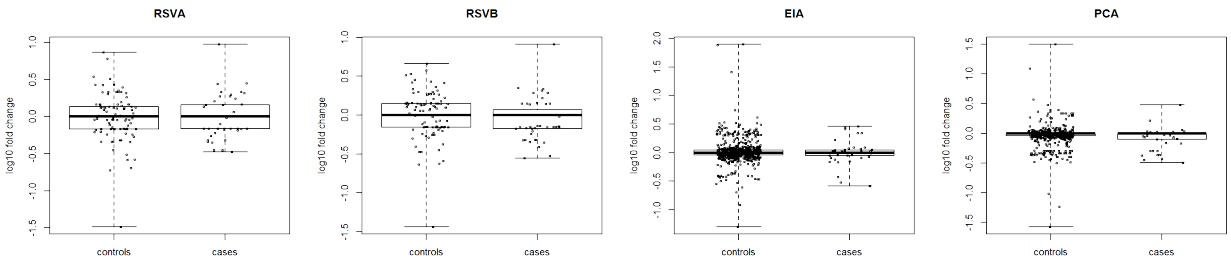

Figure 0.7: Boxplots of fold change (D14 over D0) by endpoint 1 status in the placebo arm

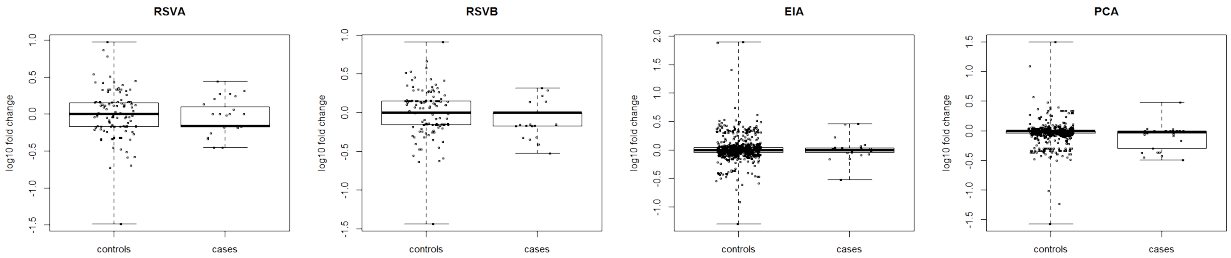

Figure 0.8: Boxplots of fold change (D14 over D0) by endpoint 2 status in the placebo arm

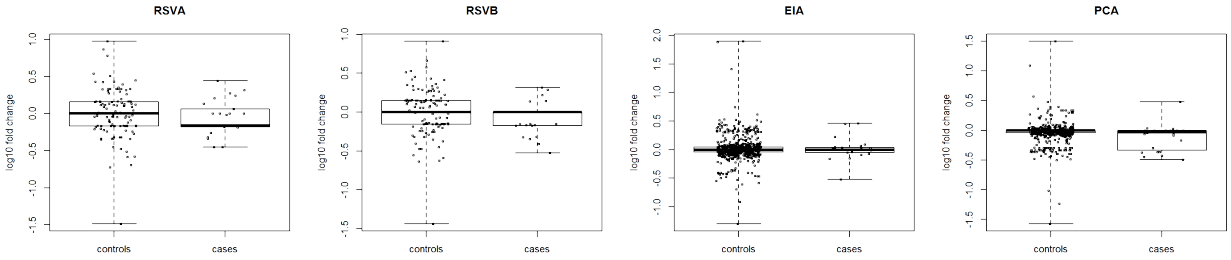

Figure 0.9: Boxplots of fold change (D14 over D0) by endpoint 3 status in the placebo arm

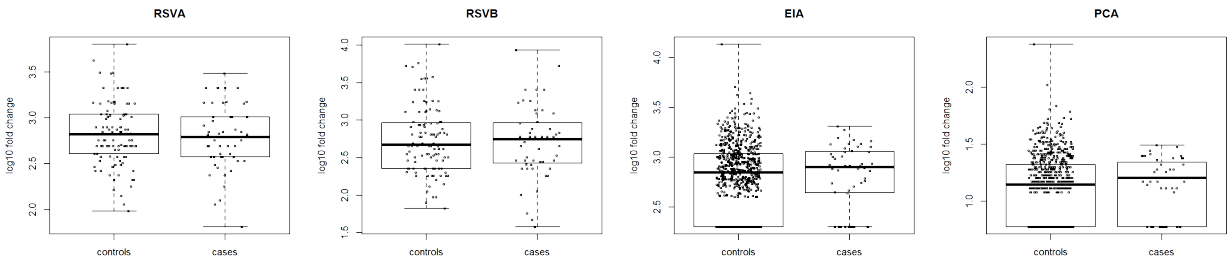

Figure 0.10: Boxplots of cord by endpoint 1 status in the placebo arm

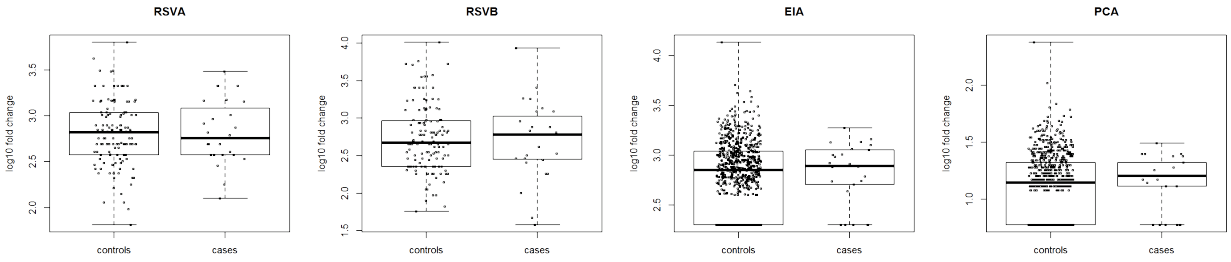

Figure 0.11: Boxplots of cord by endpoint 2 status in the placebo arm

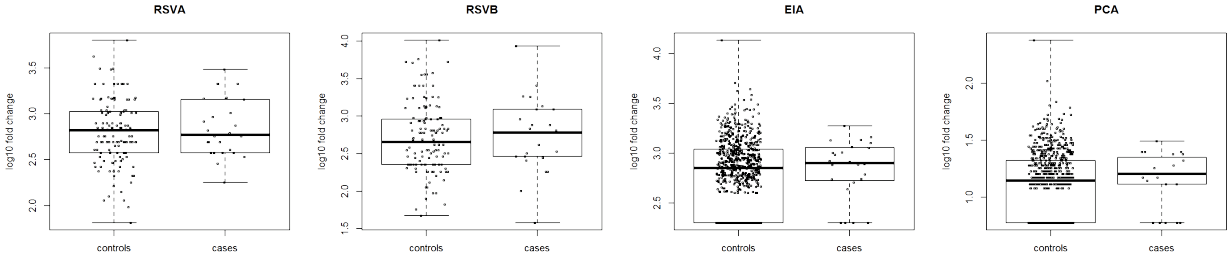

Figure 0.12: Boxplots of cord by endpoint 3 status in the placebo arm

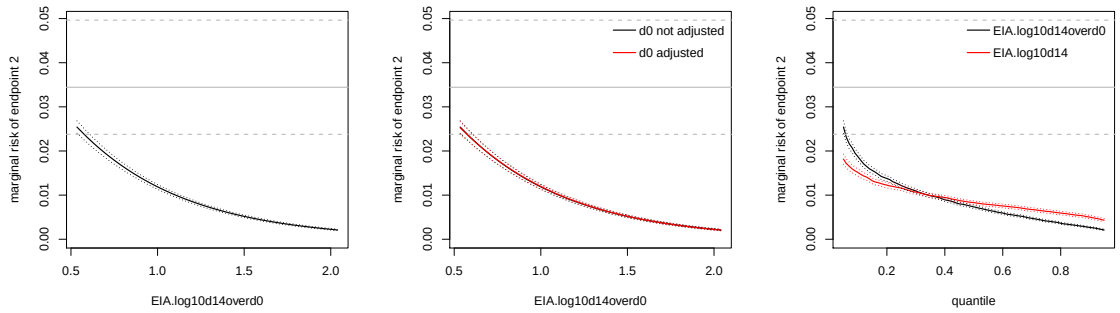

Figure 0.13: Marginalized risk plots in the vaccine arm. These plots are based on the risk regression model, averaging over the distribution of maternal risk score and number of days between vaccination and birth. The horizontal lines indicate the overall risk in the placebo arm. 95% bootstrap confidence bands are shown. Left: not adjusted for baseline concentration; middle: showing both adjusted and not adjusted for baseline concentration; right: comparing D14 and fold rise (not adjusted for baseline concentration).

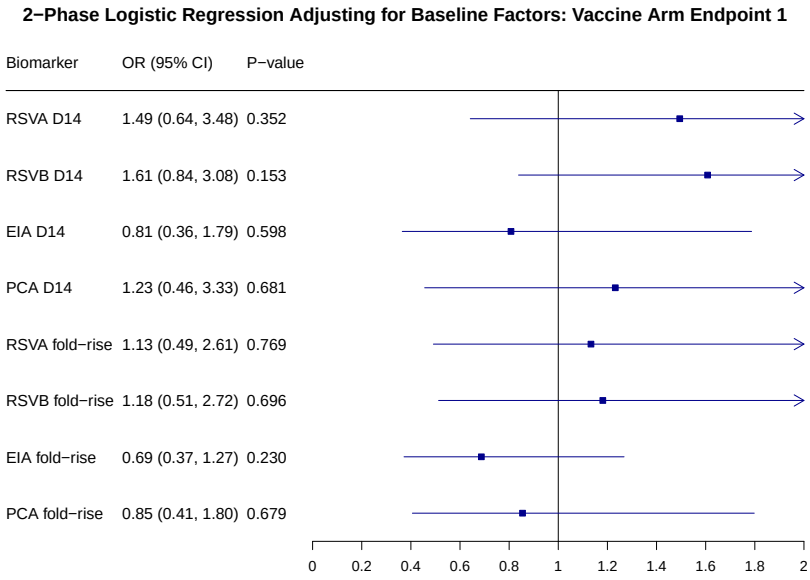

Figure 0.14: Forest plots of odds ratios of Day 14 and fold rise markers for endpoint 1 in the vaccine arm.

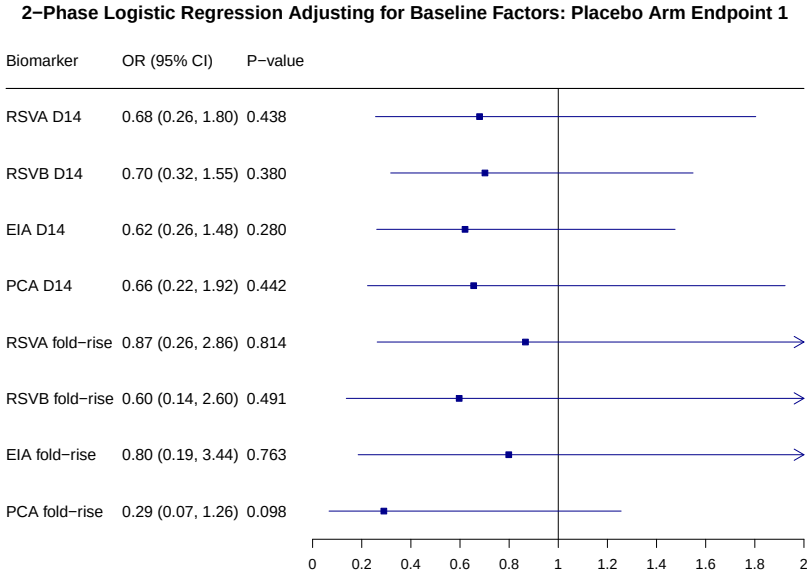

Figure 0.15: Forest plots of odds ratios of Day 14 and fold rise markers for endpoint 1 in the placebo arm.

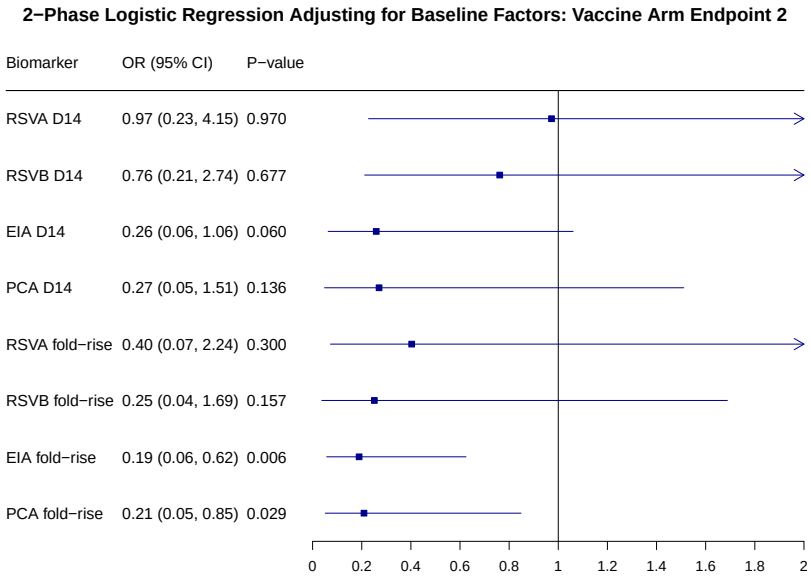

Figure 0.16: Forest plots of odds ratios of Day 14 and fold rise markers for endpoint 2 in the vaccine arm.

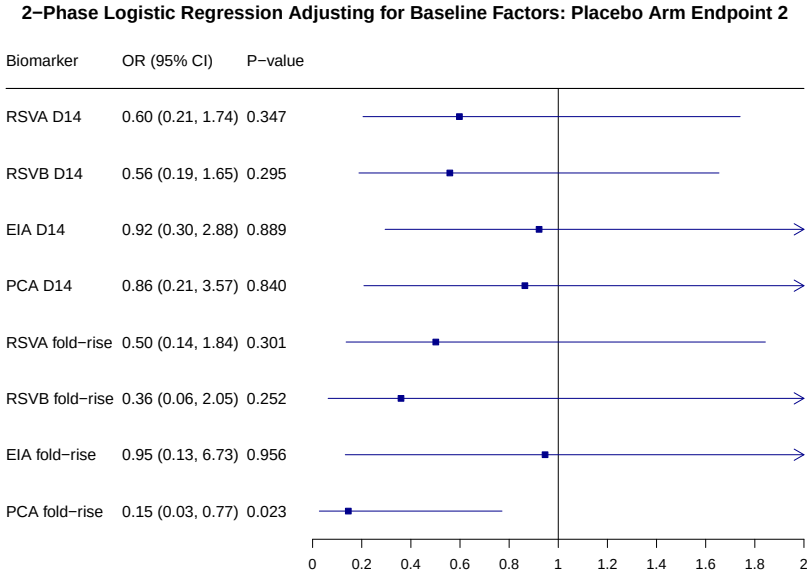

Figure 0.17: Forest plots of odds ratios of Day 14 and fold rise markers for endpoint 2 in the placebo arm.

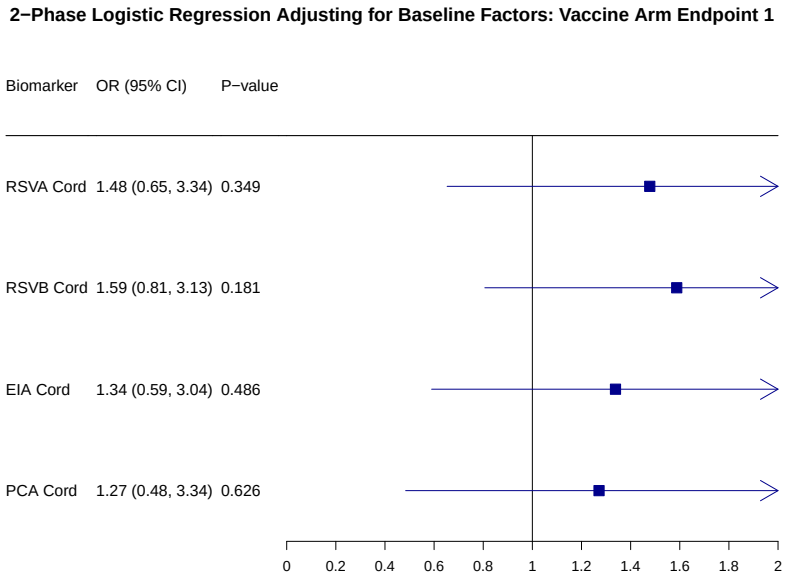

Figure 0.18: Forest plots of odds ratios of cord blood markers for endpoint 1 in the vaccine arm.

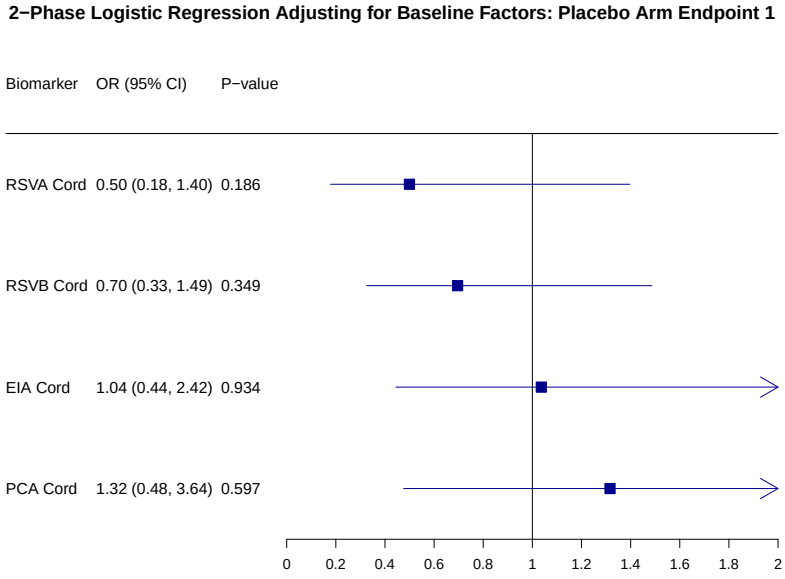

Figure 0.19: Forest plots of odds ratios of cord blood markers for endpoint 1 in the placebo arm.

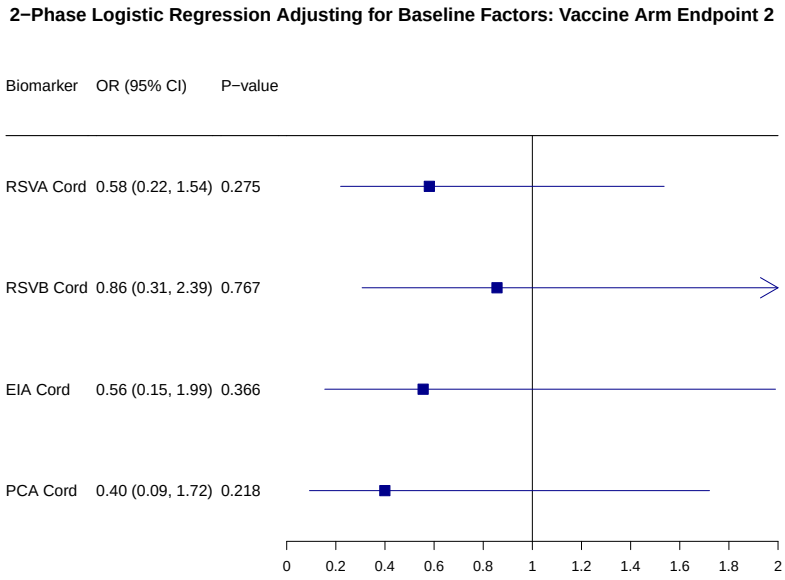

Figure 0.20: Forest plots of odds ratios of cord blood markers for endpoint 2 in the vaccine arm.

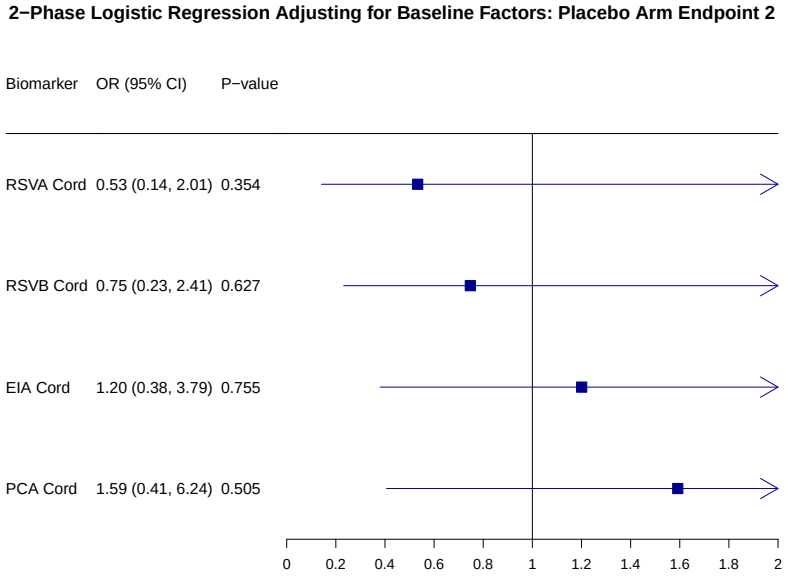

Figure 0.21: Forest plots of odds ratios of cord blood markers for endpoint 2 in the placebo arm.

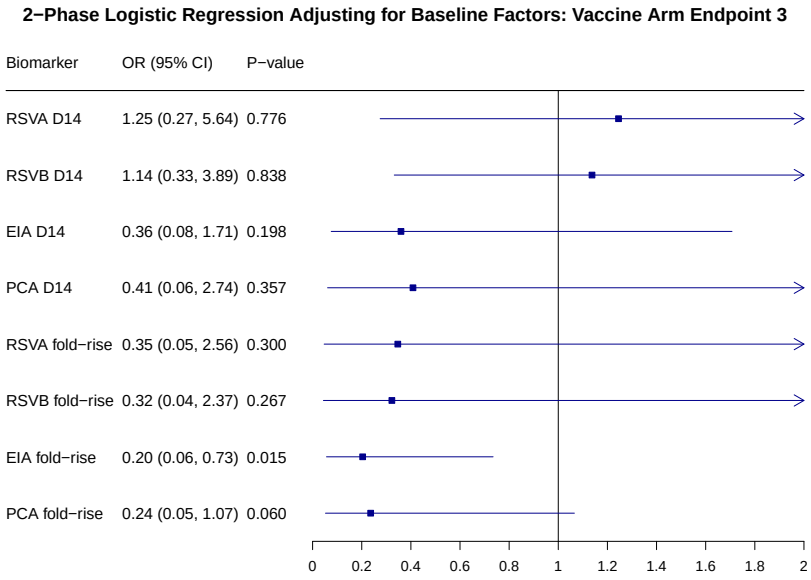

Figure 0.22: Forest plots of odds ratios of Day 14 and fold rise markers for endpoint 3 in the vaccine arm.

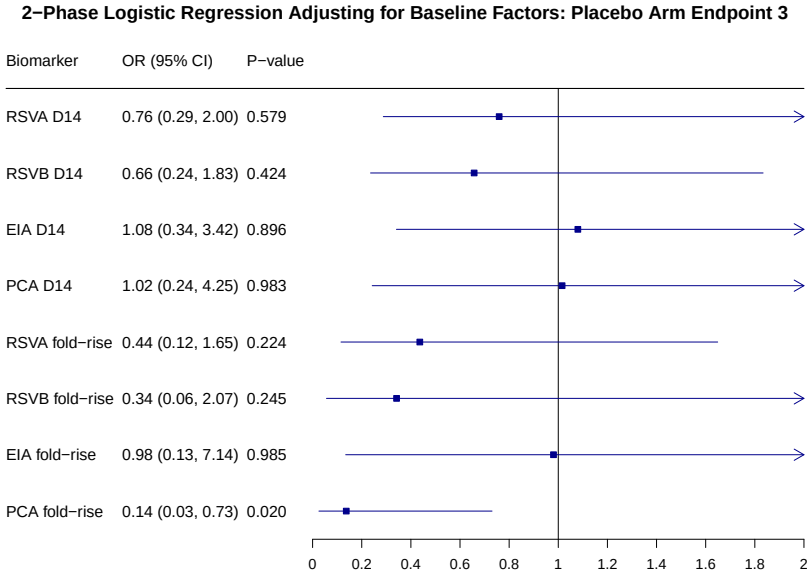

Figure 0.23: Forest plots of odds ratios of Day 14 and fold rise markers for endpoint 3 in the placebo arm.

Correlates of risk objective 2

For CoR objective 2a1, multi-assay models without baseline marker adjustment fit to the phase 2 data, d14 markers are significant by Holm FWER adjustment for all endpoints, in the vaccine arm but not the placebo arm (Table 0.7). If we remove RSVA and RSVB, the models are still significant; since the model now only contains EIA and PCA, we can fit it to the phase 1 data. The results are not significant (Table 0.9). It is also worth noting that there is a very high collinearity between EIA and PCA at D14 in the vaccine arm (Pearson correlation 0.96).

CoR objective 2a2 repeats objective 2a1 but adds adjustment of baseline RSVA/RSVB average. The results and conclusions are similar (Table 0.6).

For CoR objective 2b, multi-time points models, there are two ways to model the data. Since fold change can be expressed as the difference between d14 and d0 on the log scale, we can either include d0, d14, and cord blood (Table 0.6 and 0.7) or d0, fold change, and cord blood (Table 0.10 and 0.11). There are no significant results.

Endpoint 1

Vaccine arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
RSVA	.83 (CI=.27,2.57, p=.749)	0.72 (CI=.22,2.33, p=.588)	0.90 (CI=.34, 2.42, p=.842)	1.01 (CI=.33, 3.12, p=.982)
RSVB	1.59 (CI=.68,3.70, p=.283)	2.05 (CI=.87,4.87, p=.103)	1.13 (CI=.42, 3.08, p=.810)	1.74 (CI=.65, 4.61, p=.268)
EIA	1.51 (CI=.24,9.44, p=.660)	0.02 (CI=.00,.19, p=.001)**	0.09 (CI=.02, 0.47, p=.004)**	9.20 (CI=.44,191.69, p=.152)
PCA	.58 (CI=.06,5.36, p=.635)	>100 (CI= , , p=.000)**	19.58 (CI=2.78,137.99, p=.003)**	.06 (CI=.00, 2.67, p=.149)

Placebo arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
RSVA	.72 (CI=.22, 2.32, p=.576)	.89 (CI=.27,2.99, p=.857)	1.12 (CI=.28,4.38, p=.875)	.78 (CI=.23, 2.65, p=.689)
RSVB	1.00 (CI=.37, 2.70, p=.996)	.98 (CI=.38,2.52, p=.971)	.89 (CI=.20,3.99, p=.884)	.97 (CI=.38, 2.51, p=.953)
EIA	.39 (CI=.06, 2.56, p=.329)	.29 (CI=.05,1.59, p=.155)	.26 (CI=.04,1.63, p=.149)	3.66 (CI=.46,28.86, p=.219)
PCA	1.95 (CI=.21,17.99, p=.554)	.61 (CI=.07,5.34, p=.658)	.04 (CI=.00,.59, p=.020)*	.15 (CI=.01, 2.04, p=.152)

Endpoint 2

Vaccine arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
RSVA	0.89 (CI=.15, 5.21, p=.900)	0.70 (CI=.05, 10.64, p=.797)	0.32 (CI=.02, 4.62, p=.404)	0.67 (CI=.19, 2.42, p=.543)
RSVB	1.29 (CI=.50, 3.35, p=.595)	1.53 (CI=.28, 8.44, p=.629)	0.25 (CI=.04, 1.76, p=.166)	1.60 (CI=.37, 6.96, p=.534)
EIA	14.69 (CI=.06,3729.15, p=.342)	0.05 (CI=.00, 2.05, p=.114)	0.02 (CI=.00, 1.44, p=.074)	81.54 (CI=.19,34109.33, p=.154)
PCA	0.15 (CI=.00, 107.55, p=.576)	16.67 (CI=.20,1366.82, p=.212)	72.73 (CI=.22,24107.00, p=.149)	0.00 (CI=.00, 3.11, p=.097)

Placebo arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
RSVA	1.00 (CI=.15, 6.83, p=.997)	.89 (CI=.21,3.88, p=.882)	.57 (CI=.12,2.63, p=.472)	1.06 (CI=.21, 5.42, p=.944)
RSVB	.74 (CI=.17, 3.28, p=.689)	.68 (CI=.20,2.25, p=.529)	.99 (CI=.20,4.91, p=.985)	.95 (CI=.20, 4.50, p=.953)
EIA	.27 (CI=.02, 3.49, p=.316)	.83 (CI=.13,5.41, p=.843)	.58 (CI=.08,4.19, p=.589)	4.75 (CI=.27,84.80, p=.292)
PCA	7.00 (CI=.17,287.49, p=.306)	.62 (CI=.05,8.54, p=.725)	.01 (CI=.00,.58, p=.028)*	.09 (CI=.00, 4.88, p=.236)

Endpoint 3

Vaccine arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
RSVA	1.07 (CI=.16, 7.32, p=.942)	0.43 (CI=.02, 8.75, p=.580)	0.17 (CI=.01, 3.52, p=.255)	0.54 (CI=.15, 1.99, p=.357)
RSVB	1.44 (CI=.62, 3.32, p=.398)	2.30 (CI=.43, 12.25, p=.330)	0.31 (CI=.04, 2.74, p=.295)	2.69 (CI=.61,11.87, p=.191)
EIA	20.63 (CI=.03,15429.23, p=.371)	0.06 (CI=.00, 3.05, p=.160)	0.02 (CI=.00, 2.28, p=.106)	>100 (CI= , , p=.119)
PCA	0.12 (CI=.00, 296.71, p=.594)	22.74 (CI=.23,2270.16, p=.185)	98.77 (CI=.13,72819.61, p=.174)	0.00 (CI=.00, 1.80, p=.069)

Placebo arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
RSVA	1.52 (CI=.25, 9.37, p=.655)	1.09 (CI=.25,4.64, p=.910)	.46 (CI=.10,2.19, p=.331)	1.20 (CI=.23, 6.32, p=.826)
RSVB	.79 (CI=.17, 3.69, p=.760)	.74 (CI=.22,2.42, p=.613)	1.04 (CI=.20,5.45, p=.961)	1.17 (CI=.25, 5.38, p=.841)
EIA	.21 (CI=.01, 2.88, p=.243)	.88 (CI=.13,6.14, p=.901)	.65 (CI=.08,4.98, p=.678)	6.26 (CI=.29,133.23, p=.242)
PCA	9.37 (CI=.20,428.59, p=.253)	.62 (CI=.04,8.85, p=.727)	.01 (CI=.00,.46, p=.022)*	.06 (CI=.00, 4.41, p=.205)

Table 0.6: Correlates objective 2a1. Each column corresponds to one model with four assay markers from the same time point. All models are fitted to the phase 2 data. The models for maternal marker time points (D0, D14) adjust for time from vaccination to birth whereas the models for the infant time point (cord blood) do not. All models adjust for the maternal risk score.

Endpoint 1

	pvals	Holm	BH
d0	0.799	0.799	0.799
d14	0.004	0.016	0.016
log10d14overd0	0.049	0.147	0.098
cord	0.281	0.561	0.374

	pvals	Holm	BH
d0	0.703	1.000	0.703
d14	0.080	0.259	0.160
log10d14overd0	0.065	0.259	0.160
cord	0.650	1.000	0.703

Endpoint 2

	pvals	Holm	BH
d0	0.531	0.731	0.531
d14	0.015	0.059	0.059
log10d14overd0	0.045	0.135	0.090
cord	0.365	0.731	0.487

	pvals	Holm	BH
d0	0.846	1.000	0.846
d14	0.748	1.000	0.846
log10d14overd0	0.162	0.647	0.647
cord	0.616	1.000	0.846

Endpoint 3

	pvals	Holm	BH
d0	0.374	0.374	0.374
d14	0.018	0.071	0.071
log10d14overd0	0.085	0.255	0.148
cord	0.111	0.255	0.148

	pvals	Holm	BH
d0	0.799	1.000	0.886
d14	0.886	1.000	0.886
log10d14overd0	0.134	0.537	0.537
cord	0.728	1.000	0.886

Table 0.7: CoR objective 2a1 p-values multiplicity adjustment. Vaccine arm on the left and placebo arm on the right. Each p value is a generalized Wald test p value for the four assays.

Endpoint 1

Vaccine arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
EIA	1.27 (CI=.33,4.83, p=.730)	.15 (CI=.03, 0.87, p=.034)*	.34 (CI=.10, 1.16, p=.085)	1.63 (CI=.20,13.36, p=.650)
PCA	1.25 (CI=.23,6.72, p=.793)	9.93 (CI=1.13,87.11, p=.038)*	2.70 (CI=.61,12.04, p=.193)	.75 (CI=.06, 8.89, p=.817)

Placebo arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
EIA	.44 (CI=.14, 1.33, p=.146)	.60 (CI=.16,2.23, p=.441)	1.29 (CI=.27,6.10, p=.746)	.53 (CI=.10, 2.76, p=.454)
PCA	2.64 (CI=.67,10.31, p=.164)	1.07 (CI=.21,5.54, p=.935)	.26 (CI=.05,1.28, p=.098)	2.54 (CI=.34,19.07, p=.364)

Endpoint 2

Vaccine arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
EIA	3.55 (CI=.25,50.44, p=.350)	.12 (CI=.00, 3.12, p=.203)	.11 (CI=.01, 1.11, p=.062)	1.98 (CI=.11,34.39, p=.640)
PCA	1.02 (CI=.04,26.09, p=.990)	2.76 (CI=.05,144.20, p=.615)	1.99 (CI=.14,29.30, p=.615)	.19 (CI=.01, 5.14, p=.325)

Placebo arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
EIA	.44 (CI=.11, 1.70, p=.232)	1.02 (CI=.17,6.09, p=.981)	2.12 (CI=.31,14.50, p=.446)	.53 (CI=.06, 5.05, p=.581)
PCA	4.74 (CI=.95,23.60, p=.058)	.85 (CI=.09,7.79, p=.883)	.11 (CI=.02, 0.68, p=.018)*	3.09 (CI=.20,48.21, p=.421)

Endpoint 3

Vaccine arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
EIA	4.66 (CI=.26,84.40, p=.297)	.14 (CI=.00, 4.84, p=.276)	.11 (CI=.01, 1.21, p=.071)	3.13 (CI=.22,43.80, p=.397)
PCA	.99 (CI=.03,32.82, p=.996)	3.57 (CI=.05,269.91, p=.564)	2.40 (CI=.14,41.85, p=.548)	.13 (CI=.01, 2.50, p=.176)

Placebo arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
EIA	.47 (CI=.12, 1.83, p=.274)	1.18 (CI=.19,7.29, p=.858)	2.29 (CI=.33,16.02, p=.403)	.63 (CI=.06, 6.43, p=.696)
PCA	5.32 (CI=1.06,26.71, p=.042)*	.87 (CI=.09,8.27, p=.901)	.10 (CI=.01, 0.62, p=.014)*	3.10 (CI=.19,51.57, p=.431)

Table 0.8: Correlates objective 2a1 variant. Each column corresponds to one model with both EIA and PCA from the same time point. All models are fitted to the phase 1 data. The models for maternal marker time points (D0, D14) adjust for time from vaccination to birth whereas the models for the infant time point (cord blood) do not. All models adjust for the maternal risk score.

Endpoint 1

	pvals	Holm	BH
d0	0.905	1.000	0.980
d14	0.324	1.000	0.980
log10d14overd0	0.537	1.000	0.980
cord	0.980	1.000	0.980

	pvals	Holm	BH
d0	0.664	1.000	0.935
d14	0.882	1.000	0.935
log10d14overd0	0.581	1.000	0.935
cord	0.935	1.000	0.935

Endpoint 2

	pvals	Holm	BH
d0	0.570	1.000	0.761
d14	0.430	1.000	0.761
log10d14overd0	0.099	0.397	0.397
cord	0.763	1.000	0.763

	pvals	Holm	BH
d0	0.463	1.000	0.925
d14	1.000	1.000	1.000
log10d14overd0	0.222	0.890	0.890
cord	0.947	1.000	1.000

Endpoint 3

	pvals	Holm	BH
d0	0.469	1.000	0.730
d14	0.730	1.000	0.730
log10d14overd0	0.173	0.692	0.692
cord	0.709	1.000	0.730

	pvals	Holm	BH
d0	0.383	1.000	0.765
d14	1.000	1.000	1.000
log10d14overd0	0.191	0.763	0.763
cord	0.914	1.000	1.000

Table 0.9: CoR objective 2a1 variant p-values multiplicity adjustment. Vaccine arm on the left and placebo arm on the right. Each p value is a generalized Wald testp value for the two assays.

Endpoint 1

Vaccine arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
RSVA	.83 (CI=.27,2.57, p=.749)	0.65 (CI=.19, 2.23, p=.489)	0.98 (CI=.36, 2.67, p=.969)	1.04 (CI=.32, 3.35, p=.947)
RSVB	1.59 (CI=.68,3.70, p=.283)	1.76 (CI=.63, 4.87, p=.278)	1.23 (CI=.44, 3.40, p=.696)	1.84 (CI=.56, 5.98, p=.313)
EIA	1.51 (CI=.24,9.44, p=.660)	0.02 (CI=.00, 0.19, p=.001)**	0.10 (CI=.02, 0.51, p=.006)**	9.06 (CI=.43,189.37, p=.155)
PCA	.58 (CI=.06,5.36, p=.635)	>100 (CI= , , p=.000)**	18.31 (CI=2.56,130.86, p=.004)**	.06 (CI=.00, 2.63, p=.147)
RSVA/B.log10d0		1.37 (CI=.44, 4.26, p=.582)	1.41 (CI=.59, 3.37, p=.438)	.91 (CI=.29, 2.83, p=.867)

Placebo arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
RSVA	.72 (CI=.22, 2.32, p=.576)	0.68 (CI=.18, 2.57, p=.572)	.89 (CI=.21, 3.71, p=.874)	.89 (CI=.24, 3.36, p=.865)
RSVB	1.00 (CI=.37, 2.70, p=.996)	0.73 (CI=.24, 2.24, p=.585)	.74 (CI=.16, 3.49, p=.707)	1.09 (CI=.38, 3.12, p=.869)
EIA	.39 (CI=.06, 2.56, p=.329)	0.25 (CI=.05, 1.38, p=.113)	.23 (CI=.04, 1.46, p=.120)	3.87 (CI=.48,31.07, p=.204)
PCA	1.95 (CI=.21, 17.99, p=.554)	0.58 (CI=.07, 5.08, p=.626)	.04 (CI=.00, 0.59, p=.020)*	.15 (CI=.01, 2.07, p=.155)
RSVA/B.log10d0		2.17 (CI=.44, 10.73, p=.342)	.48 (CI=.16, 1.47, p=.198)	.69 (CI=.17, 2.87, p=.609)

Endpoint 2

Vaccine arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
RSVA	0.89 (CI=.15, 5.21, p=.900)	0.22 (CI=.01, 6.11, p=.373)	0.31 (CI=.02, 4.29, p=.385)	0.49 (CI=.18, 1.37, p=.177)
RSVB	1.29 (CI=.50, 3.35, p=.595)	0.59 (CI=.09, 3.69, p=.574)	0.25 (CI=.04, 1.72, p=.158)	0.85 (CI=.18, 4.10, p=.844)
EIA	14.69 (CI=.06,3729.15, p=.342)	0.07 (CI=.00, 3.44, p=.181)	0.02 (CI=.00, 1.32, p=.068)	>100 (CI= , , p=.147)
PCA	0.15 (CI=.00, 107.55, p=.576)	22.01 (CI=.18,2641.24, p=.207)	73.76 (CI=.24,22302.34, p=.141)	0.00 (CI=.00, 4.25, p=.111)
RSVA/B.log10d0		9.65 (CI=.60, 154.91, p=.111)	0.90 (CI=.23, 3.46, p=.876)	3.28 (CI=.70,15.36, p=.132)

Placebo arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
RSVA	1.00 (CI=.15, 6.83, p=.997)	.72 (CI=.15, 3.42, p=.679)	.49 (CI=.10, 2.32, p=.373)	1.09 (CI=.17, 6.78, p=.929)
RSVB	.74 (CI=.17, 3.28, p=.689)	.47 (CI=.13, 1.74, p=.260)	.91 (CI=.19, 4.43, p=.910)	.97 (CI=.20, 4.82, p=.973)
EIA	.27 (CI=.02, 3.49, p=.316)	.63 (CI=.09, 4.65, p=.652)	.52 (CI=.07, 3.67, p=.515)	4.86 (CI=.22,106.42, p=.318)
PCA	7.00 (CI=.17,287.49, p=.306)	.66 (CI=.05, 9.41, p=.759)	.01 (CI=.00, 0.52, p=.025)*	.09 (CI=.00, 5.26, p=.244)
RSVA/B.log10d0		2.74 (CI=.40,18.62, p=.304)	.56 (CI=.11, 2.90, p=.489)	.93 (CI=.15, 5.90, p=.940)

Endpoint 3

Vaccine arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
RSVA	1.07 (CI=.16, 7.32, p=.942)	0.12 (CI=.00, 5.26, p=.269)	0.18 (CI=.01, 3.49, p=.261)	0.41 (CI=.15, 1.17, p=.096)
RSVB	1.44 (CI=.62, 3.32, p=.398)	0.74 (CI=.11, 5.07, p=.755)	0.33 (CI=.04, 2.95, p=.323)	1.29 (CI=.24, 6.96, p=.769)
EIA	20.63 (CI=.03,15429.23, p=.371)	0.08 (CI=.00, 5.32, p=.240)	0.02 (CI=.00, 2.24, p=.106)	>100 (CI= , , p=.109)
PCA	0.12 (CI=.00, 296.71, p=.594)	33.50 (CI=.23,4963.33, p=.170)	95.67 (CI=.14,66841.76, p=.174)	0.00 (CI=.00, 2.20, p=.075)
RSVA/B.log10d0		13.47 (CI=.54, 336.79, p=.115)	1.24 (CI=.31, 4.91, p=.761)	3.62 (CI=.62,21.17, p=.154)

Placebo arm

	log10(d0)	log10(d14)	log10d14overd0	log10(cord)
RSVA	1.52 (CI=.25, 9.37, p=.655)	.84 (CI=.18, 4.00, p=.827)	.45 (CI=.09,2.23, p=.327)	1.14 (CI=.18, 7.29, p=.890)
RSVB	.79 (CI=.17, 3.69, p=.760)	.45 (CI=.12, 1.71, p=.242)	1.03 (CI=.20,5.21, p=.972)	1.12 (CI=.22, 5.63, p=.889)
EIA	.21 (CI=.01, 2.88, p=.243)	.61 (CI=.08, 4.81, p=.643)	.64 (CI=.08,4.83, p=.662)	5.92 (CI=.23,155.75, p=.288)
PCA	9.37 (CI=.20,428.59, p=.253)	.67 (CI=.04,10.11, p=.772)	.01 (CI=.00,.45, p=.021)*	.07 (CI=.00, 4.91, p=.218)
RSVA/B.log10d0		3.88 (CI=.59,25.42, p=.160)	.89 (CI=.21,3.79, p=.880)	1.17 (CI=.19, 7.29, p=.864)

Table 0.10: Correlates objective 2a2. Each column corresponds to one model with four assay markers from the same time point. All models are fitted to the phase 2 data. The models for maternal marker time points (D0, D14) adjust for time from vaccination to birth whereas the models for the infant time point (cord blood) do not. All models adjust for the maternal risk score.

Endpoint 1

	pvals	Holm	BH
d0	0.799	0.799	0.799
d14	0.005	0.022	0.022
log10d14overd0	0.055	0.164	0.109
cord	0.395	0.790	0.527

	pvals	Holm	BH
d0	0.703	1.000	0.721
d14	0.077	0.230	0.153
log10d14overd0	0.047	0.189	0.153
cord	0.721	1.000	0.721

Endpoint 2

	pvals	Holm	BH
d0	0.531	0.531	0.531
d14	0.019	0.077	0.062
log10d14overd0	0.031	0.094	0.062
cord	0.139	0.278	0.186

	pvals	Holm	BH
d0	0.846	1.000	0.846
d14	0.492	1.000	0.815
log10d14overd0	0.127	0.509	0.509
cord	0.611	1.000	0.815

Endpoint 3

	pvals	Holm	BH
d0	0.374	0.374	0.374
d14	0.031	0.122	0.122
log10d14overd0	0.064	0.192	0.128
cord	0.128	0.257	0.171

	pvals	Holm	BH
d0	0.799	1.000	0.799
d14	0.523	1.000	0.799
log10d14overd0	0.131	0.522	0.522
cord	0.645	1.000	0.799

Table 0.11: CoR objective 2a2 p-values multiplicity adjustment. Vaccine arm on the left and placebo arm on the right. Each p value is a generalized Wald test p value for the four assays.

Endpoint 1

Vaccine arm

	RSVA	RSVB	EIA	PCA
log10(d0)	.96 (CI=.34,2.72, p=.940)	.87 (CI=.31,2.41, p=.787)	1.74 (CI=.79,3.85, p=.172)	1.72 (CI=.64,4.60, p=.283)
log10(d14)	.81 (CI=.26,2.50, p=.718)	1.28 (CI=.49,3.31, p=.616)	.51 (CI=.16,1.62, p=.256)	1.32 (CI=.36,4.89, p=.676)
log10(cord)	1.79 (CI=.55,5.83, p=.332)	1.71 (CI=.61,4.79, p=.307)	1.63 (CI=.49,5.48, p=.427)	.81 (CI=.24,2.77, p=.740)
riskScore.mat.endpoint1	1.32 (CI=.99,1.75, p=.062)	1.33 (CI=1.00,1.77, p=.054)	1.44 (CI=1.11,1.88, p=.007)**	1.44 (CI=1.11,1.87, p=.007)**

Placebo arm

	RSVA	RSVB	EIA	PCA
log10(d0)	.63 (CI=.14, 2.74, p=.535)	1.17 (CI=.28,4.92, p=.827)	.72 (CI=.13,4.07, p=.710)	2.77 (CI=.56,13.67, p=.211)
log10(d14)	.46 (CI=.11, 2.02, p=.305)	.55 (CI=.13,2.32, p=.416)	.59 (CI=.10,3.34, p=.549)	.22 (CI=.04, 1.41, p=.111)
log10(cord)	1.90 (CI=.36,10.02, p=.448)	1.10 (CI=.31,3.88, p=.881)	1.65 (CI=.48,5.70, p=.425)	1.62 (CI=.37, 7.10, p=.524)
riskScore.mat.endpoint1	1.62 (CI=1.12, 2.35, p=.011)*	1.49 (CI=1.04,2.14, p=.031)*	1.69 (CI=1.23,2.32, p=.001)**	1.66 (CI=1.21, 2.28, p=.002)**

Endpoint 2

Vaccine arm

	RSVA	RSVB	EIA	PCA
log10(d0)	7.32 (CI=.78,68.90, p=.083)	6.47 (CI=1.15,36.26, p=.035)*	4.95 (CI=1.12,21.79, p=.035)*	4.91 (CI=.78,30.76, p=.089)
log10(d14)	.26 (CI=.02, 3.13, p=.289)	.27 (CI=.05, 1.52, p=.139)	.19 (CI=.03, 1.38, p=.101)	.40 (CI=.04, 3.78, p=.423)
log10(cord)	.52 (CI=.16, 1.73, p=.289)	.69 (CI=.25, 1.95, p=.489)	.92 (CI=.13, 6.47, p=.934)	.40 (CI=.06, 2.83, p=.361)
riskScore.mat.endpoint2	1.52 (CI=.93, 2.49, p=.093)	1.46 (CI=.94, 2.28, p=.092)	1.47 (CI=.86, 2.51, p=.161)	1.47 (CI=.86, 2.51, p=.155)

Placebo arm

	RSVA	RSVB	EIA	PCA
log10(d0)	.93 (CI=.16, 5.51, p=.938)	1.39 (CI=.26,7.47, p=.698)	.92 (CI=.10,8.72, p=.942)	6.87 (CI=1.13,41.75, p=.036)*
log10(d14)	.35 (CI=.06, 1.92, p=.226)	.41 (CI=.12,1.43, p=.163)	.94 (CI=.10,8.43, p=.955)	.14 (CI=.01, 1.43, p=.097)
log10(cord)	2.05 (CI=.23,18.59, p=.523)	1.18 (CI=.30,4.65, p=.816)	1.01 (CI=.17,6.14, p=.990)	1.33 (CI=.17,10.20, p=.786)
riskScore.mat.endpoint2	1.37 (CI=.88, 2.13, p=.165)	1.28 (CI=.82,2.01, p=.282)	1.18 (CI=.93,1.49, p=.165)	1.16 (CI=.92, 1.47, p=.216)

Endpoint 3

Vaccine arm

	RSVA	RSVB	EIA	PCA
log10(d0)	11.19 (CI=.91,137.32, p=.060)	6.00 (CI=.88,41.09, p=.069)	5.80 (CI=1.18,28.45, p=.030)*	5.96 (CI=.82,43.27, p=.077)
log10(d14)	0.23 (CI=.01, 4.01, p=.315)	.35 (CI=.05, 2.29, p=.273)	.28 (CI=.03, 2.50, p=.252)	.72 (CI=.07, 7.68, p=.782)
log10(cord)	0.50 (CI=.14, 1.86, p=.303)	.90 (CI=.30, 2.64, p=.845)	.86 (CI=.10, 7.14, p=.887)	.32 (CI=.05, 2.18, p=.243)
riskScore.mat.endpoint2	1.55 (CI=.92, 2.62, p=.100)	1.46 (CI=.93, 2.31, p=.105)	1.48 (CI=.83, 2.63, p=.182)	1.49 (CI=.84, 2.65, p=.176)

Placebo arm

	RSVA	RSVB	EIA	PCA
log10(d0)	1.34 (CI=.25, 7.11, p=.734)	1.55 (CI=.27,8.76, p=.622)	.91 (CI=.09,8.96, p=.933)	7.72 (CI=1.25,47.61, p=.028)*
log10(d14)	.39 (CI=.07, 2.11, p=.274)	.38 (CI=.11,1.39, p=.148)	1.03 (CI=.11,9.35, p=.982)	.14 (CI=.01, 1.48, p=.103)
log10(cord)	1.88 (CI=.20,17.59, p=.582)	1.47 (CI=.38,5.66, p=.576)	1.16 (CI=.18,7.27, p=.876)	1.50 (CI=.19,11.81, p=.703)
riskScore.mat.endpoint2	1.43 (CI=.92, 2.23, p=.115)	1.36 (CI=.87,2.12, p=.186)	1.20 (CI=.95,1.50, p=.120)	1.18 (CI=.94, 1.49, p=.162)

Table 0.12: Correlates objective 2b1. Each column corresponds to one model with three time point (d0, d14, cord blood) markers for the same assay. RSVA and RSVB models are fitted to the phase 2 data, EIA and PCA data are fitted to the phase 1 data. The models do not adjust for time from vaccination to birth. The models adjust for maternal risk score.

Endpoint 1

	pvals	Holm	BH
RSVA	0.879	1.000	0.879
RSVB	0.504	1.000	0.879
EIA	0.550	1.000	0.879
PCA	0.849	1.000	0.879

	pvals	Holm	BH
RSVA	0.704	1.000	0.900
RSVB	0.900	1.000	0.900
EIA	0.786	1.000	0.900
PCA	0.591	1.000	0.900

Endpoint 2

	pvals	Holm	BH
RSVA	0.116	0.463	0.234
RSVB	0.340	0.501	0.340
EIA	0.117	0.463	0.234
PCA	0.251	0.501	0.334

	pvals	Holm	BH
RSVA	0.816	1.000	1.000
RSVB	0.654	1.000	1.000
EIA	1.000	1.000	1.000
PCA	0.280	1.000	1.000

Endpoint 3

	pvals	Holm	BH
RSVA	0.137	0.547	0.403
RSVB	0.415	0.629	0.415
EIA	0.201	0.604	0.403
PCA	0.314	0.629	0.415

	pvals	Holm	BH
RSVA	0.861	1.000	1.000
RSVB	0.679	1.000	1.000
EIA	1.000	1.000	1.000
PCA	0.233	0.932	0.932

Table 0.13: CoR objective 2b1 p-values multiplicity adjustment. Vaccine arm on the left and placebo arm on the right. Each p value is a generalized Wald test p value for the three time points.

Endpoint 1

Vaccine arm

	RSVA	RSVB	EIA	PCA
log10(d0)	.78 (CI=.20,3.03, p=.721)	1.11 (CI=.38,3.23, p=.850)	.89 (CI=.23,3.46, p=.869)	2.27 (CI=.45,11.32, p=.318)
log10d14overd0	.81 (CI=.26,2.50, p=.718)	1.28 (CI=.49,3.31, p=.616)	.51 (CI=.16,1.62, p=.256)	1.32 (CI=.36, 4.89, p=.676)
log10(cord)	1.79 (CI=.55,5.83, p=.332)	1.71 (CI=.61,4.79, p=.307)	1.63 (CI=.49,5.48, p=.427)	.81 (CI=.24, 2.77, p=.740)
riskScore.mat.endpoint1	1.32 (CI=.99,1.75, p=.062)	1.33 (CI=1.00,1.77, p=.054)	1.44 (CI=1.11,1.88, p=.007)**	1.44 (CI=1.11, 1.87, p=.007)**

Placebo arm

	RSVA	RSVB	EIA	PCA
log10(d0)	.29 (CI=.05, 1.74, p=.175)	.65 (CI=.16,2.55, p=.533)	.42 (CI=.12,1.55, p=.194)	.62 (CI=.12,3.14, p=.563)
log10d14overd0	.46 (CI=.11, 2.02, p=.305)	.55 (CI=.13,2.32, p=.416)	.59 (CI=.10,3.34, p=.549)	.22 (CI=.04,1.41, p=.111)
log10(cord)	1.90 (CI=.36,10.02, p=.448)	1.10 (CI=.31,3.88, p=.881)	1.65 (CI=.48,5.70, p=.425)	1.62 (CI=.37,7.10, p=.524)
riskScore.mat.endpoint1	1.62 (CI=1.12, 2.35, p=.011)*	1.49 (CI=1.04,2.14, p=.031)*	1.69 (CI=1.23,2.32, p=.001)**	1.66 (CI=1.21,2.28, p=.002)**

Endpoint 2

Vaccine arm

	RSVA	RSVB	EIA	PCA
log10(d0)	1.90 (CI=.22,16.55, p=.563)	1.75 (CI=.44,6.93, p=.425)	.94 (CI=.10, 9.17, p=.957)	1.96 (CI=.12,31.09, p=.634)
log10d14overd0	.26 (CI=.02, 3.13, p=.289)	.27 (CI=.05,1.52, p=.139)	.19 (CI=.03, 1.38, p=.101)	.40 (CI=.04, 3.78, p=.423)
log10(cord)	.52 (CI=.16, 1.73, p=.289)	.69 (CI=.25,1.95, p=.489)	.92 (CI=.13, 6.47, p=.934)	.40 (CI=.06, 2.83, p=.361)
riskScore.mat.endpoint2	1.52 (CI=.93, 2.49, p=.093)	1.46 (CI=.94,2.28, p=.092)	1.47 (CI=.86, 2.51, p=.161)	1.47 (CI=.86, 2.51, p=.155)

Placebo arm

	RSVA	RSVB	EIA	PCA
log10(d0)	.32 (CI=.03, 3.61, p=.360)	.57 (CI=.13,2.38, p=.439)	.86 (CI=.14,5.50, p=.877)	.97 (CI=.11, 8.74, p=.977)
log10d14overd0	.35 (CI=.06, 1.92, p=.226)	.41 (CI=.12,1.43, p=.163)	.94 (CI=.10,8.43, p=.955)	.14 (CI=.01, 1.43, p=.097)
log10(cord)	2.05 (CI=.23,18.59, p=.523)	1.18 (CI=.30,4.65, p=.816)	1.01 (CI=.17,6.14, p=.990)	1.33 (CI=.17,10.20, p=.786)
riskScore.mat.endpoint2	1.37 (CI=.88, 2.13, p=.165)	1.28 (CI=.82,2.01, p=.282)	1.18 (CI=.93,1.49, p=.165)	1.16 (CI=.92, 1.47, p=.216)

Endpoint 3

Vaccine arm

	RSVA	RSVB	EIA	PCA
log10(d0)	2.57 (CI=.27,24.95, p=.415)	2.08 (CI=.48,9.12, p=.331)	1.60 (CI=.13,20.13, p=.717)	4.27 (CI=.22,83.97, p=.340)
log10d14overd0	.23 (CI=.01, 4.01, p=.315)	.35 (CI=.05,2.29, p=.273)	.28 (CI=.03, 2.50, p=.252)	.72 (CI=.07, 7.68, p=.782)
log10(cord)	.50 (CI=.14, 1.86, p=.303)	.90 (CI=.30,2.64, p=.845)	.86 (CI=.10, 7.14, p=.887)	.32 (CI=.05, 2.18, p=.243)
riskScore.mat.endpoint2	1.55 (CI=.92, 2.62, p=.100)	1.46 (CI=.93,2.31, p=.105)	1.48 (CI=.83, 2.63, p=.182)	1.49 (CI=.84, 2.65, p=.176)

Placebo arm

	RSVA	RSVB	EIA	PCA
log10(d0)	.51 (CI=.05, 5.21, p=.575)	.59 (CI=.14,2.55, p=.485)	.93 (CI=.14,6.05, p=.939)	1.10 (CI=.12,10.21, p=.932)
log10d14overd0	.39 (CI=.07, 2.11, p=.274)	.38 (CI=.11,1.39, p=.148)	1.03 (CI=.11,9.35, p=.982)	.14 (CI=.01, 1.48, p=.103)
log10(cord)	1.88 (CI=.20,17.59, p=.582)	1.47 (CI=.38,5.66, p=.576)	1.16 (CI=.18,7.27, p=.876)	1.50 (CI=.19,11.81, p=.703)
riskScore.mat.endpoint2	1.43 (CI=.92, 2.23, p=.115)	1.36 (CI=.87,2.12, p=.186)	1.20 (CI=.95,1.50, p=.120)	1.18 (CI=.94, 1.49, p=.162)

Table 0.14: Correlates objective 2b2. Each column corresponds to one model with three time point (d0, d14/d0, cord blood) markers for the same assay fitted to the phase 2 data. Results for endpoint 1 are obtained using the osDesign package and results for endpoints 2 and 3 are obtained using the survey package. The models do not adjust for time from vaccination to birth. The models adjust for maternal risk score.

Endpoint 1

	pvals	Holm	BH
RSVA	0.879	1.000	0.879
RSVB	0.504	1.000	0.879
EIA	0.550	1.000	0.879
PCA	0.849	1.000	0.879

	pvals	Holm	BH
RSVA	0.704	1.000	0.900
RSVB	0.900	1.000	0.900
EIA	0.786	1.000	0.900
PCA	0.591	1.000	0.900

Endpoint 2

	pvals	Holm	BH
RSVA	0.116	0.463	0.234
RSVB	0.340	0.501	0.340
EIA	0.117	0.463	0.234
PCA	0.251	0.501	0.334

	pvals	Holm	BH
RSVA	0.816	1.000	1.000
RSVB	0.654	1.000	1.000
EIA	1.000	1.000	1.000
PCA	0.280	1.000	1.000

Endpoint 3

	pvals	Holm	BH
RSVA	0.137	0.547	0.403
RSVB	0.415	0.629	0.415
EIA	0.201	0.604	0.403
PCA	0.314	0.629	0.415

	pvals	Holm	BH
RSVA	0.861	1.000	1.000
RSVB	0.679	1.000	1.000
EIA	1.000	1.000	1.000
PCA	0.233	0.932	0.932

Table 0.15: CoR objective 2b2 p-values multiplicity adjustment. Vaccine arm on the left and placebo arm on the right. Each p value is a generalized Wald test p value for the three time points.

Posthoc exploratory analyses

Baseline positivity

To further investigate the differential between D14 and fold rise markers performance, we look at fold rise more closely in the spaghetti plots that show the markers longitudinally from baseline to D14. Based on the plots, we divide the volunteers into baseline positive and baseline negative and fit regression models including baseline positivity. The results do not support the baseline positivity being a statistically significant effect modifier, probably due to the small sample size.

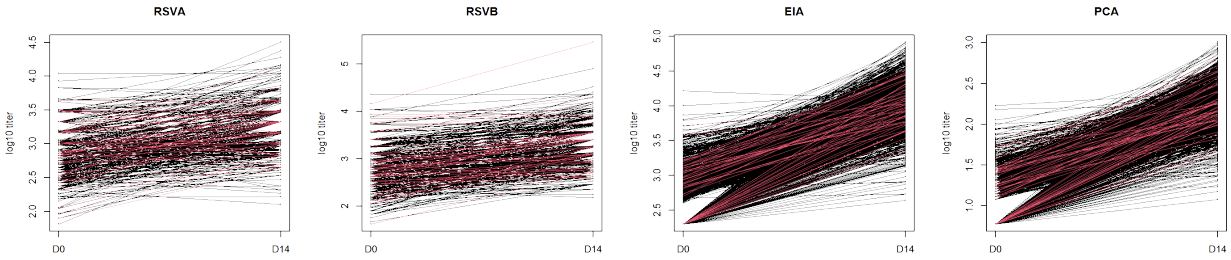

Figure 0.24: Change from D0 to D14. Endpoint 1 cases are shown in red. Vaccine arm

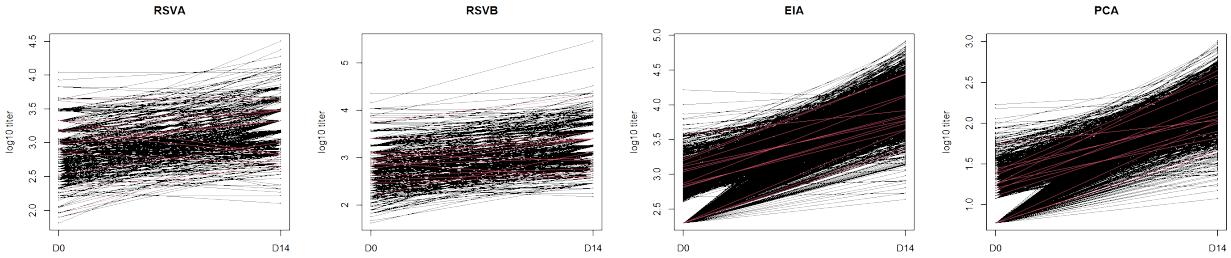

Figure 0.25: Change from D0 to D14. Endpoint 2 cases are shown in red. Vaccine arm

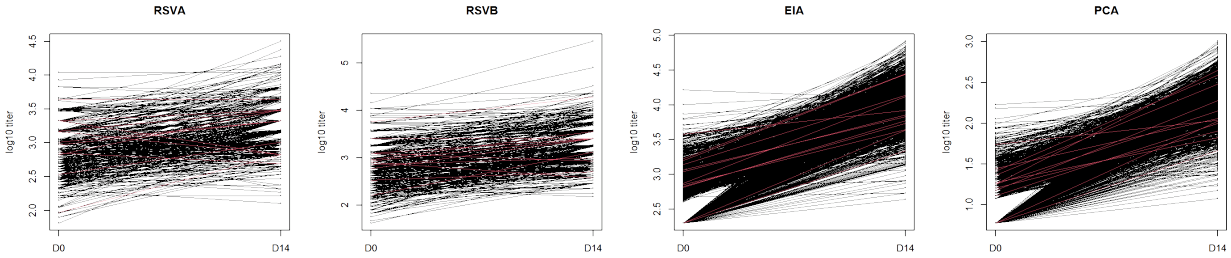

Figure 0.26: Change from D0 to D14. Endpoint 3 cases are shown in red. Vaccine arm

	D0 pos+neg	D0 pos	D0 neg	main	itxn
riskScore.mat.endpoint2	1.43 (0.190)	1.37 (0.318)	1.64 (0.434)	1.45 (0.181)	1.44 (0.191)
vacc2birth	0.98 (0.167)	0.97 (0.096)	1.00 (0.888)	0.98 (0.163)	0.98 (0.149)
EIA.log10d14overd0	0.19 (0.006)**	0.25 (0.075)	0.05 (0.028)*	0.16 (0.008)**	0.04 (0.024)*
EIA.d0pos				0.69 (0.623)	0.09 (0.201)
EIA.log10d14overd0:EIA.d0pos					5.72 (0.276)

Table 0.16: OR and p-values from models to investigate the impact of baseline positivity. Baseline EIA positivity is defined by a cutoff of 2.5, which is based on the fact that the distribution of D0 is a mixed distribution of point mass and a continuous distribution. Endpoint 2, vaccine arm, EIA, fold change.

	D0 pos+neg	D0 pos	D0 neg	main	itxn
riskScore.mat.endpoint2	1.49 (0.143)	1.36 (0.320)	1.64 (0.434)	1.44 (0.188)	1.43 (0.196)
vacc2birth	0.98 (0.152)	0.97 (0.092)	1.00 (0.888)	0.98 (0.157)	0.98 (0.145)
EIA.log10d14	0.26 (0.060)	0.39 (0.306)	0.05 (0.028)*	0.20 (0.035)*	0.04 (0.024)*
EIA.d0pos				2.34 (0.204)	0.00 (0.229)
EIA.log10d14:EIA.d0pos					9.14 (0.185)

Table 0.17: OR and p-values from models to investigate the impact of baseline positivity. Baseline EIA positivity is defined by a cutoff of 2.5, which is based on the fact that the distribution of D0 is a mixed distribution of point mass and a continuous distribution. Endpoint 2, vaccine arm, EIA, D14.

	D0 pos+neg	D0 pos	D0 neg	main	itxn
riskScore.mat.endpoint2	1.45 (0.173)	1.17 (0.632)	3.31 (0.066)	1.45 (0.176)	1.45 (0.178)
vacc2birth	0.98 (0.152)	0.97 (0.091)	1.00 (0.956)	0.98 (0.152)	0.98 (0.144)
PCA.log10d14overd0	0.21 (0.029)*	0.42 (0.366)	0.03 (0.030)*	0.22 (0.064)	0.04 (0.034)*
PCA.d0pos				1.09 (0.912)	0.08 (0.190)
PCA.log10d14overd0:PCA.d0pos					11.89 (0.181)

Table 0.18: OR and p-values from models to investigate the impact of baseline positivity. Baseline PCA positivity is defined by a cutoff of 1.0, which is based on the fact that the distribution of D0 is a mixed distribution of point mass and a continuous distribution. Endpoint 2, vaccine arm, PCA, fold change.

	D0 pos+neg	D0 pos	D0 neg	main	itxn
riskScore.mat.endpoint2	1.48 (0.148)	1.16 (0.638)	3.31 (0.066)	1.43 (0.188)	1.45 (0.182)
vacc2birth	0.98 (0.153)	0.97 (0.091)	1.00 (0.956)	0.98 (0.148)	0.98 (0.143)
PCA.log10d14	0.27 (0.136)	0.51 (0.553)	0.03 (0.030)*	0.22 (0.097)	0.04 (0.034)*
PCA.d0pos				2.45 (0.177)	0.01 (0.239)
PCA.log10d14:PCA.d0pos					14.90 (0.163)

Table 0.19: OR and p-values from models to investigate the impact of baseline positivity. Baseline PCA positivity is defined by a cutoff of 1.0, which is based on the fact that the distribution of D0 is a mixed distribution of point mass and a continuous distribution. Endpoint 2, vaccine arm, PCA, D14.

	D0 pos+neg	D0 pos	D0 neg	main	itxn
riskScore.mat.endpoint1	1.38 (0.014)*	1.30 (0.106)	1.50 (0.072)	1.39 (0.012)*	1.39 (0.012)*
vacc2birth	1.00 (0.881)	0.98 (0.056)	1.04 (0.019)*	1.00 (0.862)	1.00 (0.857)
EIA.log10d14overd0	0.69 (0.230)	0.63 (0.324)	0.50 (0.261)	0.57 (0.129)	0.47 (0.224)
EIA.d0pos				0.72 (0.357)	0.48 (0.513)
EIA.log10d14overd0:EIA.d0pos					1.34 (0.709)

Table 0.20: OR and p-values from models to investigate the impact of baseline positivity. Baseline EIA positivity is defined by a cutoff of 2.5, which is based on the fact that the distribution of D0 is a mixed distribution of point mass and a continuous distribution. Endpoint 1, vaccine arm, EIA, fold change.

	D0 pos+neg	D0 pos	D0 neg	main	itxn
riskScore.mat.endpoint1	1.39 (0.012)*	1.30 (0.112)	1.50 (0.072)	1.39 (0.013)*	1.39 (0.013)*
vacc2birth	1.00 (0.894)	0.98 (0.056)	1.04 (0.019)*	1.00 (0.874)	1.00 (0.858)
EIA.log10d14	0.81 (0.598)	1.18 (0.767)	0.50 (0.261)	0.79 (0.575)	0.47 (0.224)
EIA.d0pos				1.00 (0.989)	0.03 (0.271)
EIA.log10d14:EIA.d0pos					2.49 (0.270)

Table 0.21: OR and p-values from models to investigate the impact of baseline positivity. Baseline EIA positivity is defined by a cutoff of 2.5, which is based on the fact that the distribution of D0 is a mixed distribution of point mass and a continuous distribution. Endpoint 1, vaccine arm, EIA, D14.

	D0 pos+neg	D0 pos	D0 neg	main	itxn
riskScore.mat.endpoint1	1.39 (0.013)*	1.21 (0.245)	1.68 (0.019)*	1.39 (0.013)*	1.39 (0.013)*
vacc2birth	1.00 (0.875)	0.98 (0.078)	1.03 (0.055)	1.00 (0.873)	1.00 (0.863)
PCA.log10d14overd0	0.85 (0.679)	0.96 (0.938)	0.65 (0.561)	0.80 (0.621)	0.59 (0.474)
PCA.d0pos				0.91 (0.789)	0.51 (0.565)
PCA.log10d14overd0:PCA.d0pos					1.62 (0.607)

Table 0.22: OR and p-values from models to investigate the impact of baseline positivity. Baseline PCA positivity is defined by a cutoff of 1.0, which is based on the fact that the distribution of D0 is a mixed distribution of point mass and a continuous distribution. Endpoint 1, vaccine arm, PCA, fold change.

	D0 pos+neg	D0 pos	D0 neg	main	itxn
riskScore.mat.endpoint1	1.39 (0.012)*	1.21 (0.244)	1.68 (0.019)*	1.39 (0.013)*	1.39 (0.013)*
vacc2birth	1.00 (0.909)	0.98 (0.080)	1.03 (0.055)	1.00 (0.892)	1.00 (0.870)
PCA.log10d14	1.23 (0.681)	2.18 (0.256)	0.65 (0.561)	1.23 (0.688)	0.59 (0.474)
PCA.d0pos				0.99 (0.979)	0.06 (0.192)
PCA.log10d14:PCA.d0pos					3.71 (0.190)

Table 0.23: OR and p-values from models to investigate the impact of baseline positivity. Baseline PCA positivity is defined by a cutoff of 1.0, which is based on the fact that the distribution of D0 is a mixed distribution of point mass and a continuous distribution. Endpoint 1, vaccine arm, PCA, D14.

Cord fold change markers

Endpoint 2
Vaccine arm

	RSVA	RSVB	EIA	PCA
log10cordoverd0	0.22 (CI=0.07,0.73, p=0.014)*	0.37 (CI=0.13,1.03, p=0.058)	0.36 (CI=0.14,0.94, p=0.038)*	0.29 (CI=0.09,0.94, p=0.039)*

Placebo arm

	RSVA	RSVB	EIA	PCA
log10cordoverd0	0.40 (CI=0.04,3.70, p=0.419)	0.89 (CI=0.23,3.42, p=0.860)	1.31 (CI=0.28,6.01, p=0.731)	0.51 (CI=0.10,2.59, p=0.416)

Table 0.24: CoR objective 1. Each cell corresponds to one model. RSVA and RSVB models are fitted to phase 2 data, PCA and EIA models are fitted to phase 1 data. Time from vaccination to birth is adjusted for in analyses of maternal markers but not in analyses of infant markers. All models adjust for maternal risk score.

	RSVA	RSVB	EIA	PCA
log10d14overd0	0.71 (CI=0.37,1.35, p=0.300)	0.61 (CI=0.30,1.21, p=0.157)	0.47 (CI=0.27,0.81, p=0.006)**	0.56 (CI=0.33,0.94, p=0.029)*
log10cordoverd0	0.60 (CI=0.40,0.90, p=0.014)*	0.71 (CI=0.51,1.01, p=0.058)	0.62 (CI=0.40,0.97, p=0.038)*	0.62 (CI=0.40,0.98, p=0.039)*

Table 0.25: OR per SD changes for the two fold change markers in the vaccine arm.