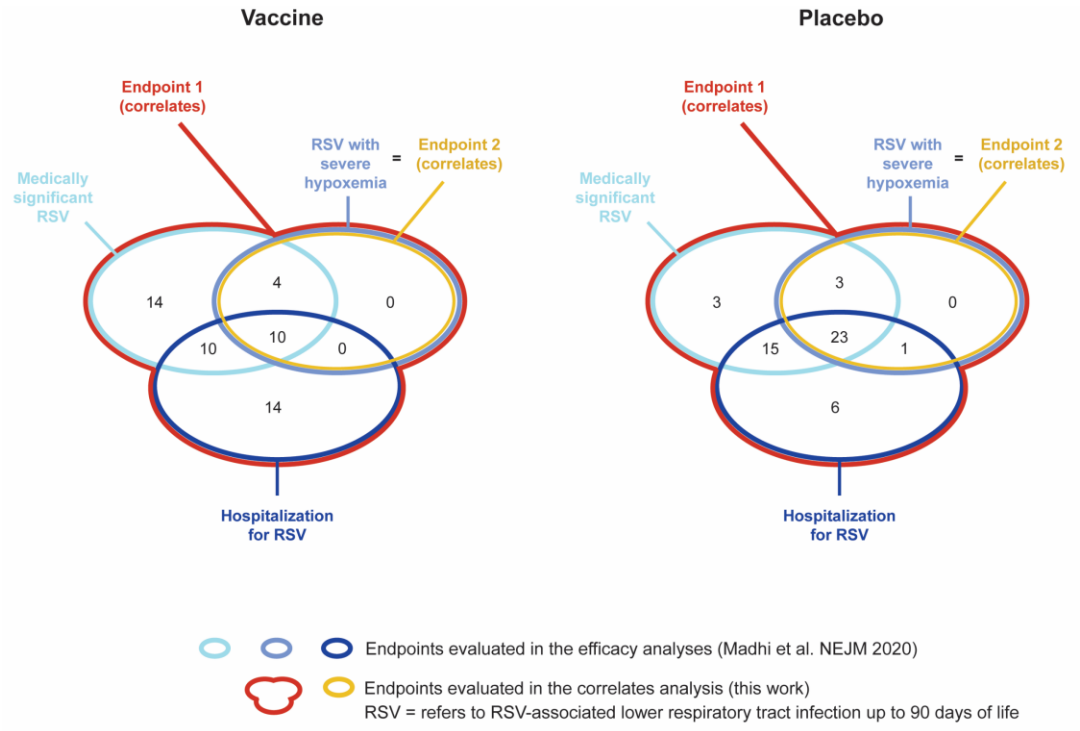
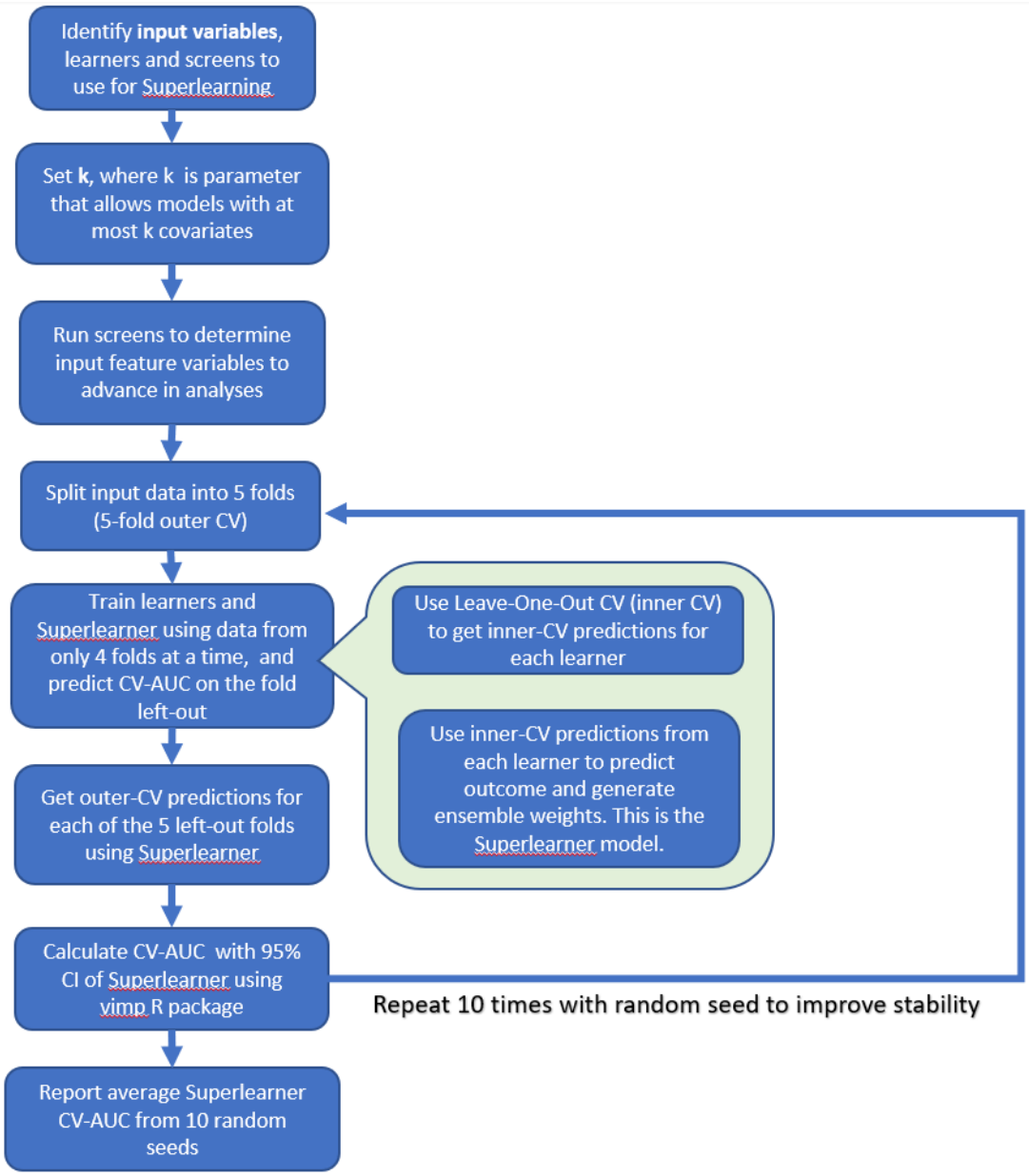
**Supplementary Material: Antibody Correlates of Protection from Severe RSV Disease in a Vaccine Efficacy Trial**

**Supplementary Figure 1.** Venn diagram showing the relationships between the prespecified endpoints evaluated in the correlates analysis and the endpoints defined in the efficacy analyses [1]. In each endpoint, "RSV" refers to RSV-associated lower respiratory tract infection (LRTI) up to 90 days of life. While the primary endpoint (medically significant) and secondary endpoints (severe hypoxemia, hospitalization) evaluated in the efficacy analyses are not nested, the endpoints evaluated in the correlates analysis are chosen to be nested. Endpoint numbers are shown using the expanded dataset, which included physical findings, pulse oximetry data, and RSV diagnoses extracted from the medical records of infants hospitalized for respiratory or infectious illness. [1]Follow-up efficacy analyses conducted by the Novavax team (unpublished) using the expanded data showed that the estimated efficacy against the primary endpoint using the expanded dataset is close to that using the site-only data (as was done in Madhi et al.) but has a narrower confidence interval: 40.9% (95% CI 15.9, 58.5%) vs 39.4% (95% CI 5.3, 61.2%). Endpoint numbers shown are only those from the South Africa subset of the trial.

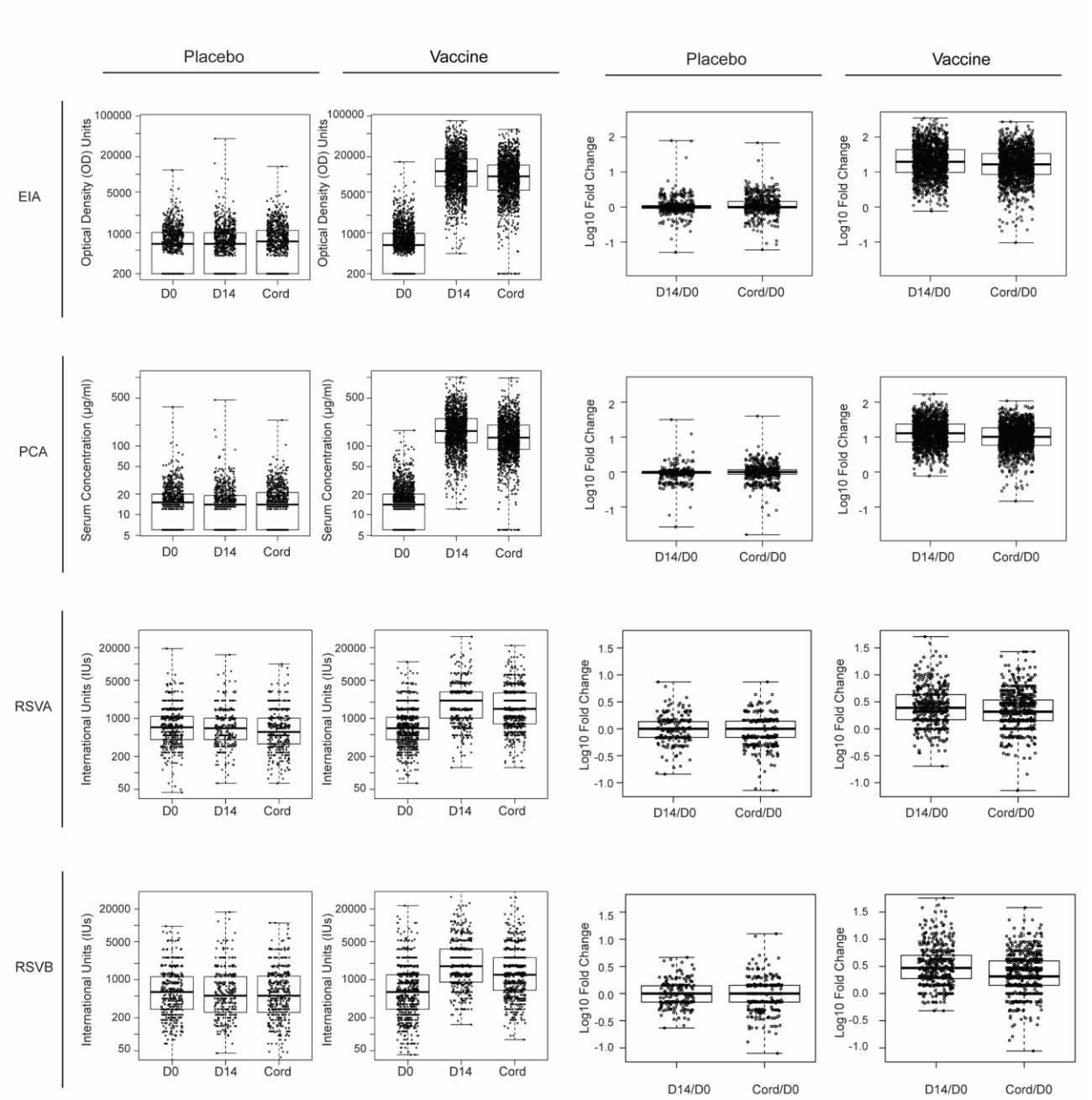
As in Madhi et al. [1]:
- Medically significant RSV-associated LRTI was defined as at least one manifestation of LRTI (cough, nasal flaring, indrawing of the lower chest wall, subcostal retractions, stridor, rales, rhonchi, wheezing, crackles or crepitations, or observed apnea) plus hypoxemia (peripheral oxygen saturation of <95% at sea level or of <92% at an altitude of >1800 m) or tachypnea (≥70 breaths per minute from 0 to 59 days of age and ≥60 breaths per minute at 60 days of age or older).
- RSV-associated LRTI with severe hypoxemia was defined as the presence of one of the following criteria: a peripheral oxygen saturation lower than 92% at sea level or lower than 87% at an altitude greater than 1800 m or the use of high-flow nasal cannula, continuous positive airway pressure, bilevel positive airway pressure, bubble continuous positive airway pressure, bag-mask ventilation, intubation with subsequent mechanical (or manual) ventilation, or extracorporeal membrane oxygenation.
- Hospitalization for RSV = RSV-associated LRTI with documented hospitalization.



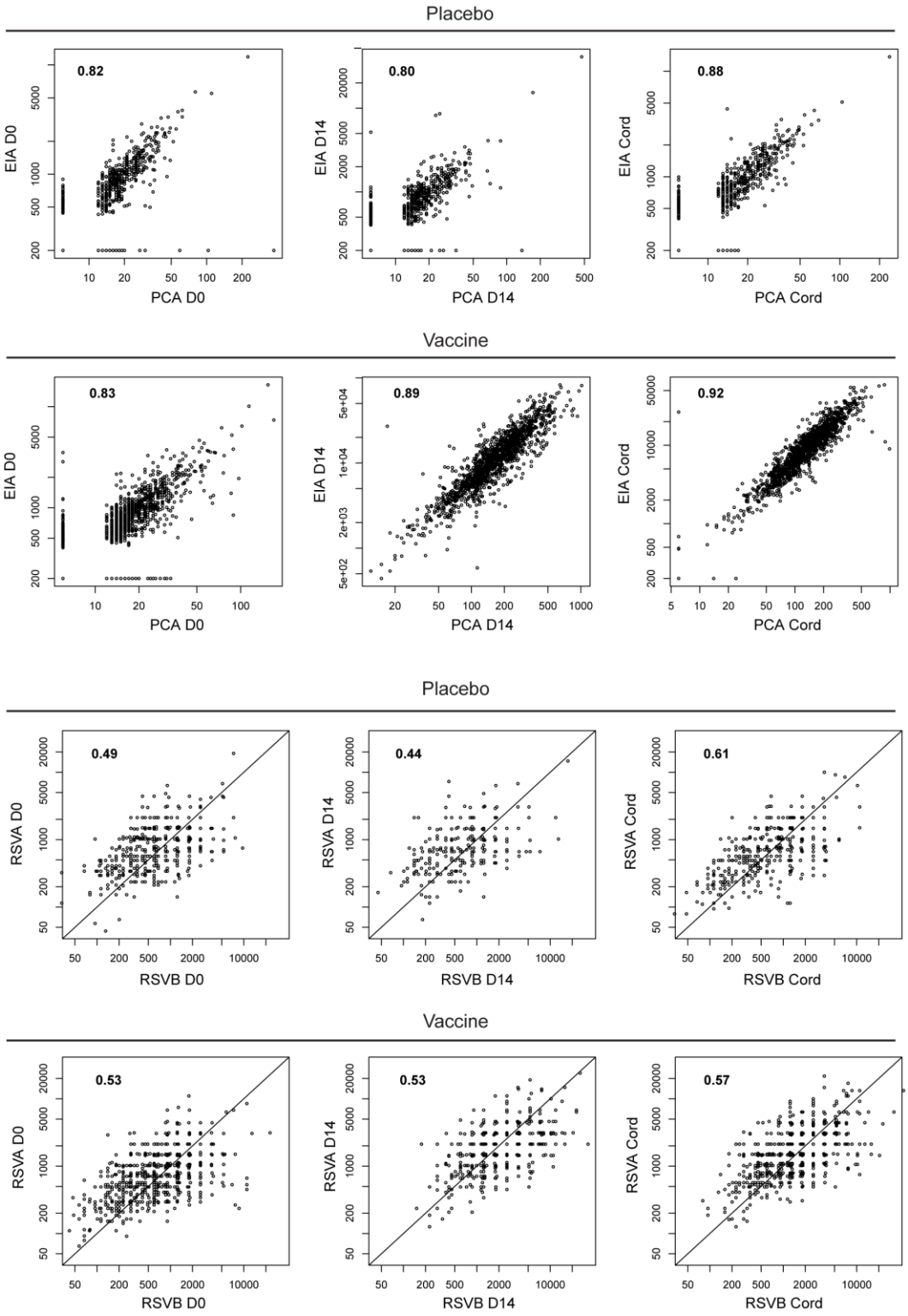
**Supplementary Figure 2.** Superlearner ensemble machine learning framework applied to (a) generate risk scores and to (b) conduct multivariable antibody marker correlates analyses. For (a), input variables were maternal enrollment variables or delivery/birth Superlearner ensemble machine learning framework applied to (a) generate risk scores variables, and the k parameter ranged from 1 to 8. For (b), the superlearning was implemented in the same way except with the following differences: 1) the input variables were one of the 29 input marker variable sets (Supp Table 2); 2) the k parameter was held constant at 6, except when a quantitative fold-rise marker was included as a covariate in the variable set and passed the screen, in which case the indicator of both a 2-fold and 4-fold rise were included along (the 2-fold and 4-fold rise indicator variables were not part of the variable screening process); 3) Estimated CV-AUC with 95% confidence intervals was weighted using empirical inverse probability weights to account for the two-phase sampling design.



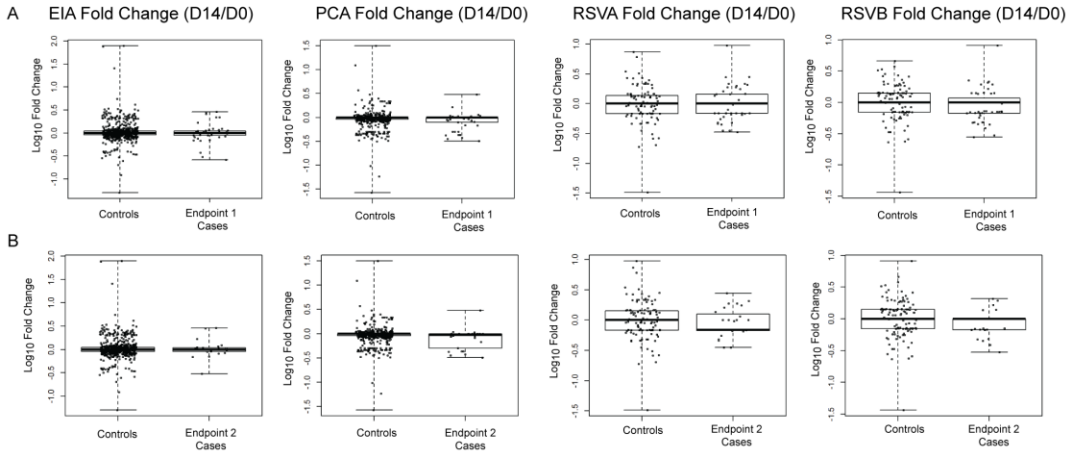
**Supplementary Figure 3.** Levels of the EIA, PCA, RSVA, and RSVB antibody markers in controls at Day 0 (D0), Day 14 (D14), and at birth (Cord), as well as fold-change from enrollment to D14 (D14/D0) and from enrollment to birth (Cord/D0), in the placebo and in the vaccine arms. The Cord/D0 analysis was post-hoc.

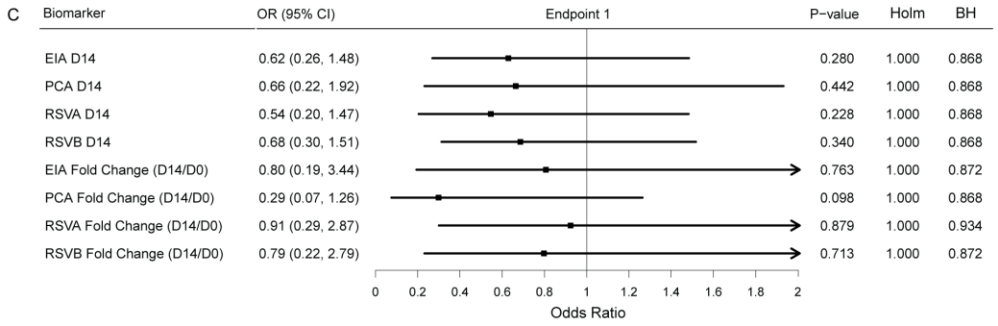


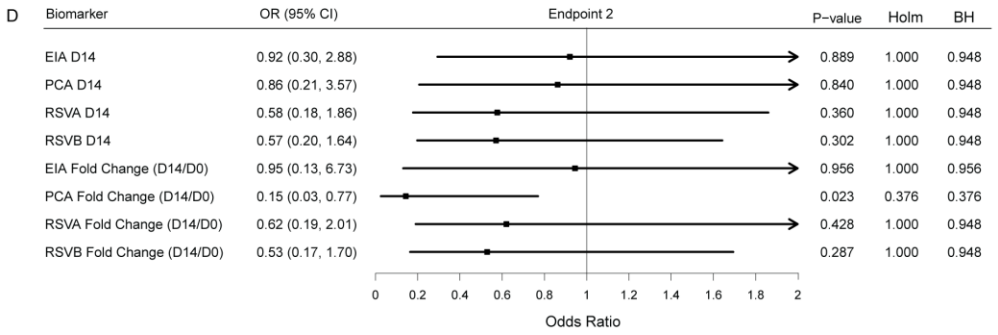
**Supplementary Figure 4.** Correlations between the EIA and PCA (top two rows) and RSVA and RSVB (bottom two rows) antibody markers in controls at each of the three time points, in the vaccine and placebo arms separately. The number in the upper left of each plot is the Spearman correlation coefficient.



**Supplementary Figure 5.** A, B) Boxplots of EIA, PCA, RSVA, and RSVB D14/D0 fold-change by case/control status (A, endpoint 1 cases; B, endpoint 2 cases) in the placebo arm. C, D) Odds ratios (ORs) in the placebo arm of experiencing RSV disease defined by (C) endpoint 1 or (D) endpoint 2 per 10-fold increase in the designated immunologic biomarker, based on logistic regression modeling adjusting for maternal risk score and number of days from vaccination to birth. Cases were defined as infants in the correlates analysis cohort with an RSV illness defined by endpoint 1 or endpoint 2 (as appropriate) through 90 days of age in the expanded data set. Controls were defined as infants who did not experience RSV disease defined by endpoint 1 or endpoint 2 (as appropriate) through to 90 days of age in the expanded data set. Endpoint 1 was defined as medically significant RSV-associated lower respiratory tract infection (LRTI), RSV-associated LRTI with hospitalization, or RSV-associated LRTI with severe hypoxemia (51 placebo endpoints). Endpoint 2 was defined as RSV-associated LRTI with severe hypoxemia (27 placebo endpoints). Holm = family-wise error rate (Holm-Bonferroni); BH = false-discovery rate (q-value, Benjamini-Hochberg) adjustment applied separately for the placebo arm. CI, confidence interval.

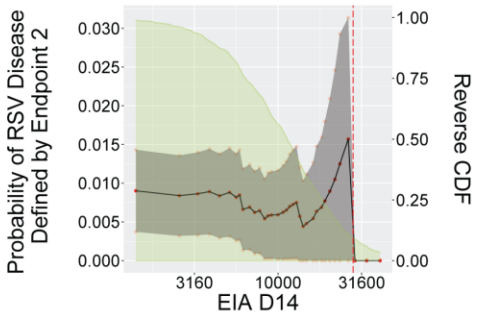


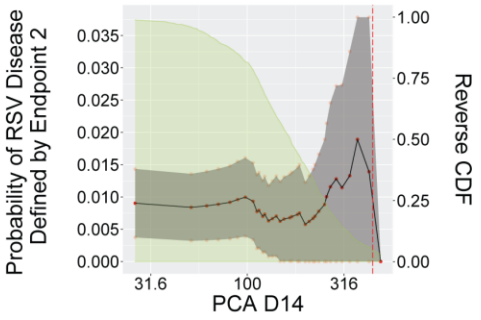
**Supplementary Figure 6.** Risk of RSV disease (defined by endpoint 2) in vaccine arm subgroups defined by antibody marker exceeding threshold s with antibody marker defined by (A) EIA D14, (B) PCA D14, (C) RSVA D14, or (D) RSVB D14 with covariate adjustment. The gray shaded region is pointwise 95% confidence intervals and the green shaded region is the area under the reverse cumulative distribution function. The vertical dashed red line marks the estimated threshold of zero risk. CDF, cumulative distribution function. Endpoint 2 was defined as RSV-associated lower respiratory tract infection with severe hypoxemia (14 vaccine endpoints).

A



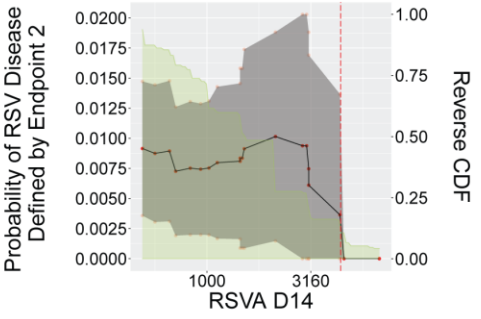

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 1420 | 0.009 (0.004 to 0.014) |
| 4450 | 0.008 (0.003 to 0.014) |
| 6190 | 0.007 (0.001 to 0.012) |
| 7830 | 0.006 (0.001 to 0.012) |
| 9890 | 0.006 (0.000 to 0.012) |
| 12400 | 0.007 (0.000 to 0.014) |
| 15000 | 0.005 (0.000 to 0.011) |
| 18200 | 0.007 (0.000 to 0.016) |
| 23700 | 0.012 (0.000 to 0.029) |
| 41100 | 0.000 (0.000 to 1.000) |

B



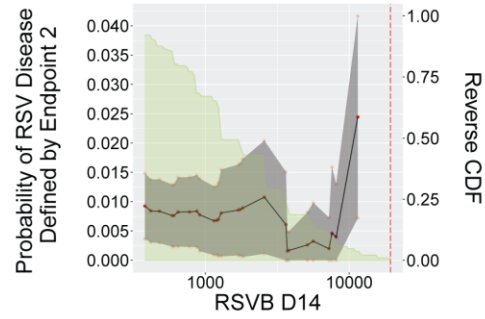

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 26.3 | 0.009 (0.004 to 0.014) |
| 80.8 | 0.009 (0.004 to 0.015) |
| 111 | 0.008 (0.002 to 0.013) |
| 124 | 0.007 (0.001 to 0.013) |
| 148 | 0.006 (0.000 to 0.012) |
| 180 | 0.007 (0.000 to 0.015) |
| 218 | 0.007 (0.000 to 0.014) |
| 249 | 0.009 (0.000 to 0.019) |
| 308 | 0.011 (0.000 to 0.027) |
| 486 | 0.000 (0.000 to 1.000) |

C




| Threshold | Risk Estimate (95% CI) |
|---|---|
| 491 | 0.009 (0.004 to 0.015) |
| 663 | 0.009 (0.003 to 0.015) |
| 828 | 0.008 (0.002 to 0.013) |
| 1020 | 0.008 (0.002 to 0.013) |
| 1440 | 0.008 (0.002 to 0.015) |
| 1520 | 0.009 (0.001 to 0.017) |
| 2910 | 0.009 (0.000 to 0.021) |
| 3060 | 0.007 (0.000 to 0.019) |
| 4410 | 0.004 (0.000 to 0.014) |
| 6780 | 0.000 (0.000 to 1.000) |

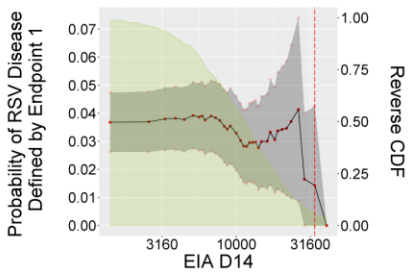
D




| Threshold | Risk Estimate (95% CI) |
|---|---|
| 378 | 0.009 (0.004 to 0.015) |
| 595 | 0.008 (0.002 to 0.013) |
| 784 | 0.008 (0.002 to 0.014) |
| 908 | 0.008 (0.002 to 0.014) |
| 1240 | 0.007 (0.001 to 0.013) |
| 1750 | 0.009 (0.001 to 0.016) |
| 3630 | 0.006 (0.000 to 0.015) |
| 3760 | 0.002 (0.000 to 0.005) |
| 7260 | 0.002 (0.000 to 0.007) |
| 11500 | 0.024 (0.007 to 0.042) |

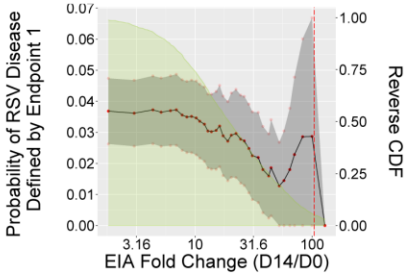
**Supplementary Figure 7.** Risk of RSV disease (defined by endpoint 1) in vaccine arm subgroups defined by antibody marker exceeding threshold s with antibody marker defined by (A) EIA D14, (B) EIA D14/D0 fold-change, (C) EIA Cord, (D) PCA D14, (E) PCA D14/D0 fold-change, or (F) PCA Cord with covariate adjustment. The gray shaded region is pointwise 95% confidence intervals and the green shaded region is the area under the reverse cumulative distribution function. The vertical dashed red line marks the estimated threshold of zero risk. CDF, cumulative distribution function. Endpoint 1 was defined as medically significant RSV-associated lower respiratory tract infection (LRTI), RSV-associated LRTI with hospitalization, or RSV-associated LRTI with severe hypoxemia (52 vaccine endpoints).

A



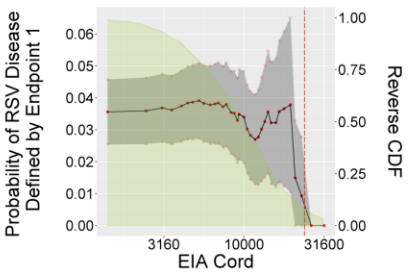

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 1420 | 0.037 (0.026 to 0.047) |
| 4450 | 0.038 (0.026 to 0.049) |
| 6190 | 0.038 (0.025 to 0.050) |
| 7830 | 0.037 (0.025 to 0.050) |
| 9890 | 0.033 (0.020 to 0.046) |
| 12400 | 0.030 (0.016 to 0.043) |
| 15000 | 0.030 (0.014 to 0.046) |
| 18200 | 0.031 (0.012 to 0.049) |
| 23700 | 0.037 (0.010 to 0.064) |
| 41100 | 0.000 (0.000 to 1.000) |

B



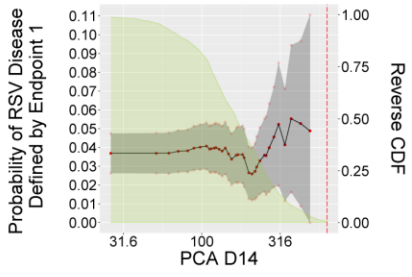

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 1.82 | 0.037 (0.026 to 0.047) |
| 6.16 | 0.037 (0.026 to 0.048) |
| 9.31 | 0.035 (0.023 to 0.047) |
| 12.0 | 0.033 (0.021 to 0.045) |
| 16.1 | 0.032 (0.019 to 0.045) |
| 22.3 | 0.030 (0.015 to 0.044) |
| 31.0 | 0.022 (0.008 to 0.037) |
| 42.2 | 0.016 (0.002 to 0.030) |
| 64.5 | 0.018 (0.000 to 0.038) |
| 129 | 0.000 (0.000 to 1.000) |

C



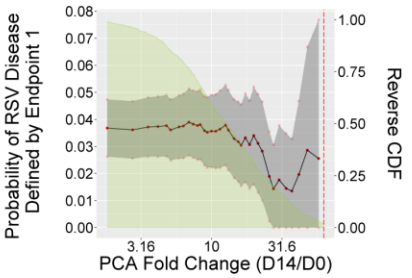

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 1420 | 0.036 (0.025 to 0.046) |
| 4090 | 0.037 (0.026 to 0.049) |
| 5620 | 0.038 (0.026 to 0.050) |
| 6910 | 0.038 (0.026 to 0.051) |
| 8620 | 0.035 (0.022 to 0.048) |
| 10600 | 0.030 (0.016 to 0.044) |
| 12900 | 0.030 (0.014 to 0.046) |
| 14700 | 0.032 (0.013 to 0.051) |
| 19400 | 0.038 (0.011 to 0.065) |
| 31300 | 0.000 (0.000 to 1.000) |

D



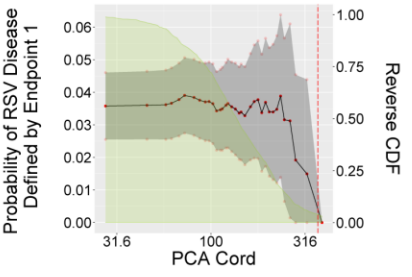

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 26.3 | 0.037 (0.026 to 0.047) |
| 80.8 | 0.038 (0.027 to 0.050) |
| 111 | 0.039 (0.027 to 0.051) |
| 124 | 0.040 (0.027 to 0.053) |
| 148 | 0.037 (0.023 to 0.050) |
| 180 | 0.036 (0.021 to 0.051) |
| 218 | 0.027 (0.012 to 0.042) |
| 249 | 0.036 (0.016 to 0.055) |
| 308 | 0.052 (0.020 to 0.085) |
| 486 | 0.049 (0.000 to 0.118) |

E




| Threshold | Risk Estimate (95% CI) |
|---|---|
| 1.80 | 0.037 (0.026 to 0.047) |
| 4.75 | 0.038 (0.026 to 0.049) |
| 6.94 | 0.039 (0.027 to 0.051) |
| 8.35 | 0.038 (0.025 to 0.051) |
| 10.7 | 0.036 (0.022 to 0.049) |
| 14.5 | 0.033 (0.018 to 0.047) |
| 18.7 | 0.031 (0.014 to 0.047) |
| 22.8 | 0.028 (0.010 to 0.046) |
| 33.7 | 0.014 (0.000 to 0.035) |
| 57.3 | 0.026 (0.000 to 0.077) |

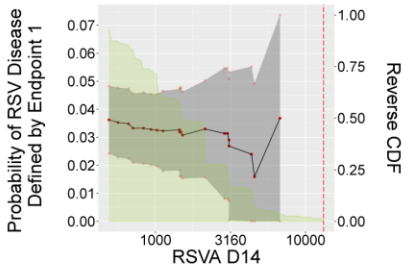
F




| Threshold | Risk Estimate (95% CI) |
|---|---|
| 27.7 | 0.036 (0.026 to 0.046) |
| 67.0 | 0.038 (0.027 to 0.049) |
| 92.6 | 0.037 (0.025 to 0.049) |
| 106 | 0.034 (0.022 to 0.046) |
| 124 | 0.037 (0.023 to 0.050) |
| 146 | 0.034 (0.019 to 0.049) |
| 177 | 0.038 (0.020 to 0.056) |
| 205 | 0.034 (0.014 to 0.054) |
| 247 | 0.032 (0.006 to 0.057) |
| 386 | 0.000 (0.000 to 1.000) |

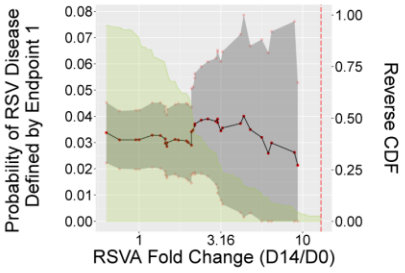
**Supplementary Figure 8.** Risk of RSV disease (defined by endpoint 1) in vaccine arm subgroups defined by antibody marker exceeding threshold s with antibody marker defined by (A) RSVA D14, (B) RSVA D14/D0 fold-change, (C) RSVA Cord, (D) RSVB D14, (E) RSVB D14/D0 fold-change, or (F) RSVB Cord with covariate adjustment. The gray shaded region is pointwise 95% confidence intervals and the green shaded region is the area under the reverse cumulative distribution function. The vertical dashed red line marks the estimated threshold of zero risk. CDF, cumulative distribution function. Endpoint 1 was defined as medically significant RSV-associated lower respiratory tract infection (LRTI), RSV-associated LRTI with hospitalization, or RSV-associated LRTI with severe hypoxemia (52 vaccine endpoints).

A



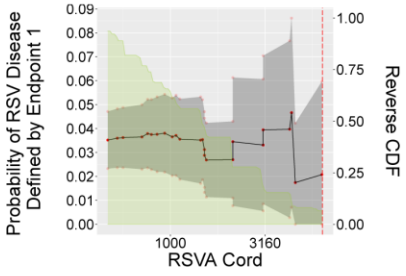

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 491 | 0.036 (0.024 to 0.048) |
| 663 | 0.035 (0.022 to 0.047) |
| 828 | 0.033 (0.020 to 0.046) |
| 1020 | 0.033 (0.020 to 0.045) |
| 1440 | 0.033 (0.018 to 0.047) |
| 1520 | 0.031 (0.015 to 0.046) |
| 2910 | 0.031 (0.008 to 0.055) |
| 3060 | 0.029 (0.007 to 0.051) |
| 4410 | 0.024 (0.000 to 0.055) |
| 6780 | 0.037 (0.000 to 0.118) |

B



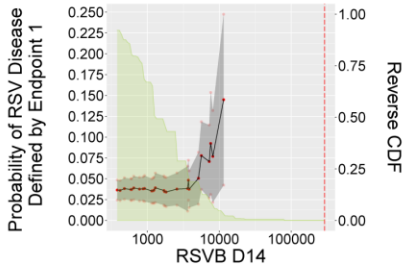

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 0.638 | 0.034 (0.022 to 0.045) |
| 1.20 | 0.033 (0.020 to 0.045) |
| 1.44 | 0.030 (0.018 to 0.042) |
| 1.72 | 0.031 (0.017 to 0.045) |
| 2.08 | 0.034 (0.018 to 0.050) |
| 2.19 | 0.037 (0.018 to 0.056) |
| 3.00 | 0.039 (0.013 to 0.065) |
| 4.18 | 0.037 (0.003 to 0.071) |
| 5.57 | 0.032 (0.000 to 0.069) |
| 9.25 | 0.021 (0.000 to 0.053) |

C



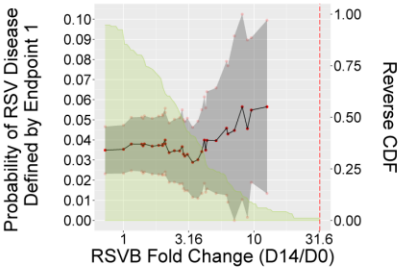

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 466 | 0.035 (0.023 to 0.047) |
| 707 | 0.036 (0.023 to 0.050) |
| 790 | 0.038 (0.023 to 0.052) |
| 1020 | 0.037 (0.020 to 0.053) |
| 1130 | 0.036 (0.019 to 0.052) |
| 1500 | 0.031 (0.015 to 0.047) |
| 1550 | 0.027 (0.011 to 0.042) |
| 3060 | 0.033 (0.006 to 0.061) |
| 4240 | 0.040 (0.003 to 0.077) |
| 6350 | 0.021 (0.000 to 0.060) |

D



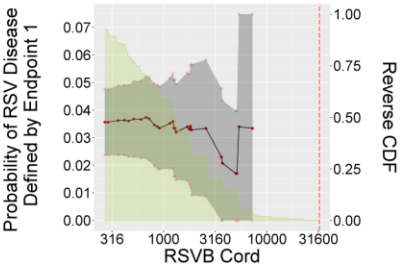

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 378 | 0.036 (0.024 to 0.048) |
| 595 | 0.037 (0.024 to 0.050) |
| 784 | 0.038 (0.023 to 0.052) |
| 908 | 0.038 (0.023 to 0.054) |
| 1240 | 0.036 (0.021 to 0.052) |
| 1750 | 0.034 (0.017 to 0.052) |
| 3630 | 0.038 (0.011 to 0.065) |
| 3760 | 0.037 (0.015 to 0.059) |
| 7260 | 0.071 (0.027 to 0.115) |
| 11500 | 0.145 (0.042 to 0.247) |

E



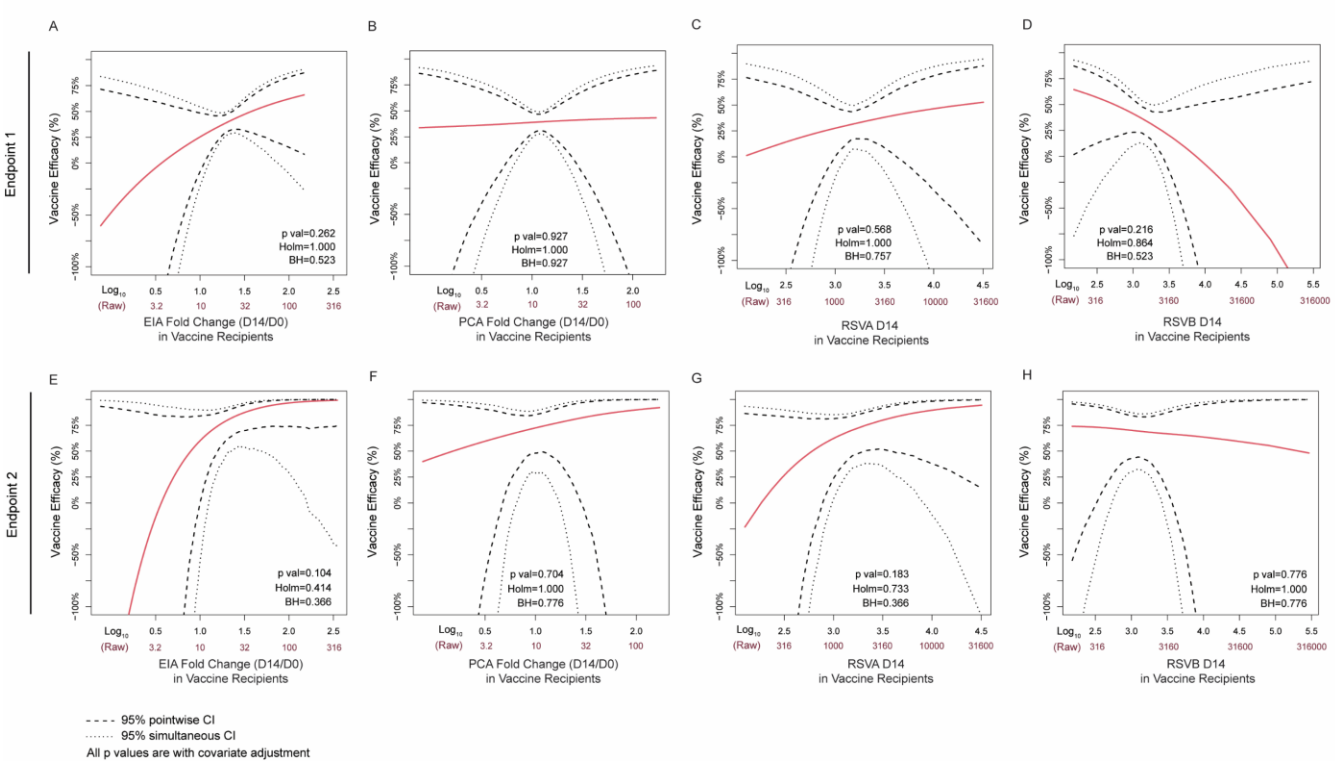

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 0.733 | 0.035 (0.023 to 0.047) |
| 1.42 | 0.037 (0.023 to 0.051) |
| 1.88 | 0.037 (0.023 to 0.052) |
| 2.07 | 0.038 (0.023 to 0.054) |
| 2.70 | 0.035 (0.018 to 0.051) |
| 3.12 | 0.033 (0.015 to 0.051) |
| 4.00 | 0.034 (0.013 to 0.055) |
| 5.07 | 0.040 (0.013 to 0.066) |
| 7.1 | 0.045 (0.000 to 0.092) |
| 12.7 | 0.056 (0.013 to 0.100) |

F




| Threshold | Risk Estimate (95% CI) |
|---|---|
| 267 | 0.036 (0.024 to 0.048) |
| 416 | 0.036 (0.024 to 0.049) |
| 599 | 0.037 (0.022 to 0.051) |
| 813 | 0.035 (0.020 to 0.050) |
| 1140 | 0.035 (0.019 to 0.052) |
| 1280 | 0.033 (0.016 to 0.051) |
| 1780 | 0.033 (0.013 to 0.053) |
| 2570 | 0.033 (0.009 to 0.058) |
| 4990 | 0.017 (0.000 to 0.040) |
| 7260 | 0.033 (0.000 to 0.110) |

**Supplementary Figure 9.** Point and 95% confidence interval estimates of vaccine efficacy against RSV disease defined by endpoint 1 (top row) or endpoint 2 (bottom row) as a function of (A,E) EIA D14/D0 fold-change, (B,F) PCA D14/D0 fold-change, (C,G) RSVA D14, and (D,H) RSVB D14 in vaccine recipients, denoted S(1). p val = two-sided p-value based on the Wald-test for interaction between treatment and S(1) in the risk model, which evaluate whether VE changes over subgroups defined by S(1). Holm = family-wise error rate (Holm-Bonferroni); BH = false-discovery rate (q-value, Benjamini-Hochberg) adjustment. Analyses were performed as in Figure 5, except that the model additionally adjusted for baseline marker level. Endpoint 1 was defined as medically significant RSV-associated lower respiratory tract infection (LRTI), RSV-associated LRTI with hospitalization, or RSV-associated LRTI with severe hypoxemia (52 vaccine endpoints). Endpoint 2 was defined as RSV-associated LRTI with severe hypoxemia (14 vaccine endpoints).



**Supplementary Table 1.** Learner-screen combinations used in the superlearner model (a) to build a maternal enrollment risk score and a birth variable risk score, and (b) to conduct the antibody marker multivariable correlates of risk analyses. The k parameter ranges from 1:8 for (a) and is fixed at 6 for (b), and allows models with at most k covariates, and is appended at the end of the screen name.

| **Learner (learner name in the Superlearner R package)** | **Screen*** |
|---|---|
| Intercept model (SL.mean) | all_k |
| Logistic regression (SL.glm) | all_k |
| | glmnet_k |
| | univar_logistic_pval_k |
| | highcor_random_k |
| Logistic regression with all 2-way interaction terms (SL.glm.interaction) | all_k |
| | glmnet_k |
| | univar_logistic_pval_k |
| | highcor_random_k |
| Bayesian logistic regression (SL.bayesglm) | all_k |
| | glmnet_k |
| | univar_logistic_pval_k |
| | highcor_random_k |
| Logistic regression with step-wise model selection with AIC (SL.step) | glmnet_k |
| | univar_logistic_pval_k |
| | highcor_random_k |
| L1-penalized lasso with default tuning parameters (SL.glmnet) | glmnet_k |
| | univar_logistic_pval_k |
| | highcor_random_k |
| Generalized additive model with default tuning parameters (SL.gam) | glmnet_k |
| | univar_logistic_pval_k |
| | highcor_random_k |
| Random forests with default tuning parameters SL.cforest | glmnet_k |
| | univar_logistic_pval_k |
| | highcor_random_k |
| Gradient boosting with default tuning parameters (SL.xgboost) | glmnet_k |
| | univar_logistic_pval_k |
| | highcor_random_k |

***Screen details:**
**all_k:** includes all variables
**glmnet_k:** includes variables with non-zero coefficients in the standard/default implementation of SL.glmnet that optimizes the lasso tuning parameter via cross-validation
**univar_logistic_pval_k:** Wald test 2-sided p-value in a logistic regression model < 0.10
**highcor_random_k:** if pairs of quantitative variables with Spearman rank correlation > 0.90, select one of the variables at random

**Supplementary Table 2.** The 29 variable sets on which an estimated optimal surrogate was built with Superlearner.

| Variable Set Name | Variables included in the set |
|---|---|
| 1_only_matvars | Maternal baseline demographic covariates only (Reference model) |
| 2_varset_EIA.log10d0 | Maternal covariates + EIA marker at Day 0 |
| 3_varset_EIA.log10d14 | Maternal covariates + EIA marker at Day 14 |
| 4_varset_EIA.log10d14overd0 | Maternal covariates + EIA marker fold-rise |
| 5_varset_EIA.log10cord | Maternal covariates + EIA marker at birth (cord) |
| 6_varset_PCA.log10d0 | Maternal covariates + PCA marker at Day 0 |
| 7_varset_PCA.log10d14 | Maternal covariates + PCA marker at Day 14 |
| 8_varset_PCA.log10d14overd0 | Maternal covariates + PCA marker fold-rise |
| 9_varset_PCA.log10cord | Maternal covariates + PCA marker at birth (cord) |
| 10_varset_RSVA.log10d0 | Maternal covariates + RSVA marker at Day 0 |
| 11_varset_RSVA.log10d14 | Maternal covariates + RSVA marker at Day 14 |
| 12_varset_RSVA.log10d14overd0 | Maternal covariates + RSVA marker fold-rise |
| 13_varset_RSVA.log10cord | Maternal covariates + RSVA marker at birth (cord) |
| 14_varset_RSVB.log10d0 | Maternal covariates + RSVB marker at Day 0 |
| 15_varset_RSVB.log10d14 | Maternal covariates + RSVB marker at Day 14 |
| 16_varset_RSVB.log10d14overd0 | Maternal covariates + RSVB marker fold-rise |
| 17_varset_RSVB.log10cord | Maternal covariates + RSVB marker at birth (cord) |
| 18_varset_d0_all4 | Maternal covariates + all 4 markers at Day 0 |
| 19_varset_d14_all4 | Maternal covariates + all 4 markers at Day 14 |
| 20_varset_d14overd0_all4 | Maternal covariates + all 4 markers fold-rise |
| 21_varset_cord_all4 | Maternal covariates + all 4 markers at birth (cord) |
| 22_varset_EIA_all4 | Maternal covariates + all 4 EIA markers (Days 0, 14, fold-rise and cord) |
| 23_varset_PCA_all4 | Maternal covariates + all 4 PCA markers |
| 24_varset_RSVA_all4 | Maternal covariates + all 4 RSVA markers |
| 25_varset_RSVB_all4 | Maternal covariates + all 4 RSVB markers |
| 26_varset_d0_d14 | Maternal covariates + all 4 markers at Day 0 and Day 14 |
| 27_varset_d0_foldrise | Maternal covariates + all 4 markers at Day 0 and their fold-rise |
| 28_varset_d0_cord | Maternal covariates + all 4 markers at Day 0 and birth (cord) |
| 29_varset_all16 | Maternal covariates + all 4 markers at Day 0, 14, at birth and their fold-rise |

Note: If the quantitative fold-rise marker passed the screen, it was included along with both a 2-fold and 4-fold rise (d0 to d14) indicator. The 2-fold and 4-fold rise indicator variables were not part of the variable screening process.

**Supplementary Table 3.** Post-hoc analysis reporting odds ratios (95% confidence intervals) and p values in (A) the vaccine arm or (B) the placebo arm of experiencing RSV disease defined by endpoint 4, medically significant RSV-associated lower respiratory tract infection only, per 10-fold increase in the designated immunologic biomarker, based on logistic regression modeling adjusting for maternal risk score and number of days from vaccination to birth. Cases were defined as infants in the correlates analysis cohort with an RSV illness defined by endpoint 4 through 90 days of age in the expanded data set. Controls were defined as infants who did not experience RSV disease defined by endpoint 4 through to 90 days of age in the expanded data set. Endpoint 4 was defined as medically significant RSV-associated lower respiratory tract infection (LRTI) (38 vaccine endpoints, 44 placebo endpoints). No multiplicity adjustment was applied.

A.

Vaccine arm

| | EIA | PCA | RSVA | RSVB |
|---|---|---|---|---|
| D0 | 2.12 (0.87, 5.17, p=0.099) | 2.30 (0.76, 6.99, p=0.141) | 1.35 (0.55, 3.27, p=0.512) | 1.71 (0.72, 4.05, p=0.224) |
| D14 | 0.74 (0.29, 1.87, p=0.527) | 1.00 (0.32, 3.13, p=0.996) | 1.65 (0.68, 4.00, p=0.268) | 1.67 (0.74, 3.77, p=0.219) |
| Fold-change (D14/D0) | 0.52 (0.25, 1.06, p=0.072) | 0.61 (0.26, 1.45, p=0.265) | 1.20 (0.42, 3.41, p=0.739) | 0.95 (0.35, 2.58, p=0.913) |
| Cord | 1.14 (0.46, 2.85, p=0.775) | 1.02 (0.35, 3.00, p=0.965) | 1.44 (0.68, 3.03, p=0.342) | 1.38 (0.65, 2.93, p=0.406) |

B.

Placebo arm

| | EIA | PCA | RSVA | RSVB |
|---|---|---|---|---|
| D0 | 1.09 (0.46, 2.58, p=0.840) | 2.00 (0.70, 5.72, p=0.198) | 1.03 (0.33, 3.23, p=0.961) | 0.86 (0.30, 2.45, p=0.782) |
| D14 | 0.85 (0.34, 2.11, p=0.729) | 0.95 (0.31, 2.92, p=0.932) | 0.76 (0.28, 2.10, p=0.602) | 0.72 (0.29, 1.77, p=0.477) |
| Fold-change (D14/D0) | 0.81 (0.17, 3.97, p=0.798) | 0.24 (0.05, 1.10, p=0.066) | 0.65 (0.19, 2.19, p=0.491) | 0.55 (0.12, 2.62, p=0.455) |
| Cord | 1.52 (0.61, 3.81, p=0.367) | 1.99 (0.68, 5.85, p=0.212) | 0.63 (0.20, 1.99, p=0.429) | 0.75 (0.27, 2.04, p=0.570) |

**Supplementary Table 4.** Results of post hoc analyses calculating: A) Odds ratios (95% confidence intervals) of RSV disease defined by endpoint 2 per 10-fold increase in fold-change from maternal baseline to cord blood, for each of the four antibody markers. B) Odds ratios (95% confidence intervals) of RSV disease defined by endpoint 2 per SD-increase in fold-change from maternal baseline to D14, and from maternal baseline to cord blood, for each of the four antibody markers. Each cell corresponds to one model. RSVA and RSVB models were fit to phase 2 data, PCA and EIA models were fit to phase 1 data. Time from vaccination to birth was adjusted for in analyses of maternal markers but not in analyses of infant markers. All models adjusted for maternal risk score. Endpoint 2 was defined as RSV-associated lower respiratory tract infection with severe hypoxemia. * = p< 0.05; ** = p<0.01.

A.

*Vaccine arm*

| | EIA | PCA | RSVA | RSVB |
|---|---|---|---|---|
| Fold-change (Cord/D0) | 0.36 (0.14, 0.94, p=0.038)* | 0.29 (0.09, 0.94, p=0.039)* | 0.22 (0.07, 0.73, p=0.014)* | 0.37 (0.13, 1.03, p=0.058) |

*Placebo arm*

| | EIA | PCA | RSVA | RSVB |
|---|---|---|---|---|
| Fold-change (Cord/D0) | 1.31 (0.28, 6.01, p=0.731) | 0.51 (0.10, 2.59, p=0.416) | 0.40 (0.04, 3.70, p=0.419) | 1.31 (0.28, 6.01, p=0.731) |

B.

Vaccine arm

| | EIA | PCA | RSVA | RSVB |
|---|---|---|---|---|
| Fold-change (D14/D0) | 0.47 (0.27, 0.81, p=0.006)** | 0.56 (0.33, 0.94, p=0.029)* | 0.71 (0.37, 1.35, p=0.300) | 0.61 (0.30, 1.21, p=0.157) |
| Fold-change (Cord/D0) | 0.62 (0.40, 0.97, p=0.038)* | 0.62 (0.40, 0.98, p=0.039) | 0.60 (0.40, 0.90, p=0.014)* | 0.71 (0.51, 1.01, p=0.058) |

**Supplementary Table 5.** p-values and multiplicity adjustment for 16 multivariable models for each treatment arm including (top) EIA and PCA in each model and the indicated variable; (bottom) D0, D14, and Cord time points in each model and the indicated variable. Vaccine arm, left; placebo arm, right. Each p value is a generalized Wald test p value testing whether the set of antibody markers correlates with endpoint. BH, Benjamini-Hochberg.

| | Vaccine | | | Placebo | | |
|---|---|---|---|---|---|---|
| | p value | Holm | BH | p value | Holm | BH |
| EIA and PCA in Each Model | | | | | | |
| | Endpoint 1 | | | | | |
| D0 | 0.905 | 1.000 | 0.980 | 0.664 | 1.000 | 0.935 |
| D14 | 0.324 | 1.000 | 0.980 | 0.882 | 1.000 | 0.935 |
| D14/D0 Fold-change | 0.537 | 1.000 | 0.980 | 0.581 | 1.000 | 0.935 |
| Cord | 0.980 | 1.000 | 0.980 | 0.935 | 1.000 | 0.935 |
| | Endpoint 2 | | | | | |
| D0 | 0.570 | 1.000 | 0.761 | 0.463 | 1.000 | 0.925 |
| D14 | 0.430 | 1.000 | 0.761 | 1.000 | 1.000 | 1.000 |
| D14/D0 Fold-change | 0.099 | 0.397 | 0.397 | 0.222 | 0.890 | 0.890 |
| Cord | 0.763 | 1.000 | 0.763 | 0.947 | 1.000 | 1.000 |
| D0, D14, and Cord in Each Model | | | | | | |
| | Endpoint 1 | | | | | |
| EIA | 0.550 | 1.000 | 0.879 | 0.786 | 1.000 | 0.900 |
| PCA | 0.849 | 1.000 | 0.879 | 0.591 | 1.000 | 0.900 |
| RSVA | 0.879 | 1.000 | 0.879 | 0.704 | 1.000 | 0.900 |
| RSVB | 0.504 | 1.000 | 0.879 | 0.900 | 1.000 | 0.900 |
| | Endpoint 2 | | | | | |
| EIA | 0.117 | 0.463 | 0.234 | 1.000 | 1.000 | 1.000 |
| PCA | 0.251 | 0.501 | 0.334 | 0.280 | 1.000 | 1.000 |
| RSVA | 0.116 | 0.463 | 0.234 | 0.816 | 1.000 | 1.000 |
| RSVB | 0.340 | 0.501 | 0.340 | 0.654 | 1.000 | 1.000 |

**Supplementary Table 6.** Risk of RSV disease (defined by endpoint 2) in vaccine arm subgroups defined by antibody marker exceeding threshold s with antibody marker defined by fold change (D14/D0) in (A) EIA, (B) PCA, (C) RSVA, or (D) RSVB; fold change (Cord/D0) in (E) EIA, (F) PCA, (G) RSVA, or (H) RSVA; or Cord levels of (I) EIA, (J) PCA, (K) RSVA, (L) or RSVB, with adjustment for covariates. The Cord/D0 fold-change analyses were post-hoc. 95% confidence intervals are given in parentheses. Endpoint 2 was defined as RSV-associated lower respiratory tract infection with severe hypoxemia (14 vaccine endpoints). These tables accompany the corresponding panels in Figure 4.

A) EIA Fold Change (D14/D0)

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 1.82 | 0.009 (0.004 to 0.014) |
| 6.16 | 0.007 (0.002 to 0.012) |
| 9.31 | 0.005 (0.001 to 0.010) |
| 12 | 0.004 (0.000 to 0.008) |
| 16.1 | 0.005 (0.000 to 0.010) |
| 22.3 | 0.000 (0.000 to 1.000) |
| 31 | 0.000 (0.000 to 1.000) |
| 42.2 | 0.000 (0.000 to 1.000) |
| 64.5 | 0.000 (0.000 to 1.000) |
| 129 | 0.000 (0.000 to 1.000) |

B) PCA Fold Change (D14/D0)

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 1.8 | 0.009 (0.004 to 0.014) |
| 4.75 | 0.008 (0.003 to 0.014) |
| 6.94 | 0.008 (0.003 to 0.014) |
| 8.35 | 0.006 (0.001 to 0.011) |
| 10.7 | 0.007 (0.001 to 0.014) |
| 14.5 | 0.005 (0.000 to 0.011) |
| 18.7 | 0.003 (0.000 to 0.008) |
| 22.8 | 0.003 (0.000 to 0.009) |
| 33.7 | 0.000 (0.000 to 1.000) |
| 57.3 | 0.000 (0.000 to 1.000) |

C RSVA Fold Change (D14/D0)

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 0.638 | 0.007 (0.002 to 0.012) |
| 1.2 | 0.006 (0.002 to 0.011) |
| 1.44 | 0.006 (0.001 to 0.011) |
| 1.72 | 0.007 (0.002 to 0.013) |
| 2.08 | 0.007 (0.001 to 0.014) |
| 2.19 | 0.005 (0.000 to 0.011) |
| 3 | 0.005 (0.000 to 0.012) |
| 4.18 | 0.003 (0.000 to 0.010) |
| 5.57 | 0.000 (0.000 to 1.000) |
| 9.25 | 0.000 (0.000 to 1.000) |

D) RSVB Fold Change (D14/D0)

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 0.733 | 0.007 (0.002 to 0.012) |
| 1.42 | 0.007 (0.002 to 0.013) |
| 1.88 | 0.005 (0.001 to 0.010) |
| 2.07 | 0.007 (0.001 to 0.012) |
| 2.7 | 0.006 (0.000 to 0.012) |
| 3.12 | 0.006 (0.000 to 0.012) |
| 4 | 0.005 (0.000 to 0.012) |
| 5.07 | 0.000 (0.000 to 1.000) |
| 7.1 | 0.000 (0.000 to 1.000) |
| 12.7 | 0.000 (0.000 to 1.000) |

E) EIA Fold Change (Cord/D0)

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 1.52 | 0.009 (0.004 to 0.014) |
| 5.31 | 0.006 (0.002 to 0.011) |
| 8.86 | 0.005 (0.001 to 0.010) |
| 10.9 | 0.005 (0.000 to 0.009) |
| 14.6 | 0.001 (0.000 to 0.004) |
| 19.3 | 0.000 (0.000 to 1.000) |
| 26.1 | 0.000 (0.000 to 1.000) |
| 34.1 | 0.000 (0.000 to 1.000) |
| 50.6 | 0.000 (0.000 to 1.000) |
| 97.7 | 0.000 (0.000 to 1.000) |

F) PCA Fold Change (Cord/D0)

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 1.57 | 0.009 (0.004 to 0.014) |
| 4.16 | 0.007 (0.002 to 0.012) |
| 5.84 | 0.005 (0.001 to 0.010) |
| 7.33 | 0.005 (0.000 to 0.010) |
| 9.21 | 0.004 (0.000 to 0.009) |
| 11.5 | 0.004 (0.000 to 0.009) |
| 15.4 | 0.000 (0.000 to 1.000) |
| 18.7 | 0.000 (0.000 to 1.000) |
| 26.6 | 0.000 (0.000 to 1.000) |
| 43.1 | 0.000 (0.000 to 1.000) |

G) RSVA Fold Change (Cord/D0)

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 0.694 | 0.008 (0.003 to 0.013) |
| 1.18 | 0.005 (0.001 to 0.009) |
| 1.44 | 0.004 (0.000 to 0.009) |
| 1.93 | 0.002 (0.000 to 0.006) |
| 2.08 | 0.003 (0.000 to 0.007) |
| 2.36 | 0.004 (0.000 to 0.009) |
| 3 | 0.005 (0.000 to 0.012) |
| 3.75 | 0.000 (0.000 to 1.000) |
| 4.83 | 0.000 (0.000 to 1.000) |
| 8 | 0.000 (0.000 to 1.000) |

H) RSVB Fold Change (Cord/D0)

| Threshold | Risk Estimate (95% CI) |
|---|---|
| 0.695 | 0.008 (0.003 to 0.013) |
| 1 | 0.008 (0.003 to 0.014) |
| 1.44 | 0.008 (0.002 to 0.014) |
| 1.94 | 0.006 (0.000 to 0.012) |
| 2.07 | 0.005 (0.000 to 0.010) |
| 2.58 | 0.003 (0.000 to 0.007) |
| 2.98 | 0.002 (0.000 to 0.007) |
| 3.75 | 0.003 (0.000 to 0.009) |
| 4.76 | 0.000 (0.000 to 1.000) |
| 7.81 | 0.000 (0.000 to 1.000) |

I) EIA Cord

| Threshold (OD Units) | Risk Estimate (95% CI) |
|---|---|
| 1420 | 0.009 (0.004 to 0.014) |
| 4090 | 0.009 (0.004 to 0.015) |
| 5620 | 0.007 (0.002 to 0.013) |
| 6910 | 0.006 (0.001 to 0.011) |
| 8620 | 0.004 (0.000 to 0.009) |
| 10600 | 0.004 (0.000 to 0.009) |
| 12900 | 0.005 (0.000 to 0.012) |
| 14700 | 0.007 (0.000 to 0.016) |
| 19400 | 0.011 (0.000 to 0.027) |
| 31300 | 0.000 (0.000 to 1.000) |

J) PCA Cord

| Threshold (Serum μg/ml) | Risk Estimate (95% CI) |
|---|---|
| 27.7 | 0.009 (0.004 to 0.014) |
| 67 | 0.009 (0.004 to 0.015) |
| 92.6 | 0.008 (0.002 to 0.013) |
| 106 | 0.002 (0.000 to 0.006) |
| 124 | 0.003 (0.000 to 0.007) |
| 146 | 0.004 (0.000 to 0.009) |
| 177 | 0.005 (0.000 to 0.012) |
| 205 | 0.007 (0.000 to 0.017) |
| 247 | 0.013 (0.000 to 0.030) |
| 386 | 0.000 (0.000 to 1.000) |

K) RSVA Cord

| Threshold (IUs) | Risk Estimate (95% CI) |
|---|---|
| 466 | 0.009 (0.003 to 0.014) |
| 707 | 0.010 (0.003 to 0.016) |
| 790 | 0.010 (0.003 to 0.017) |
| 1020 | 0.011 (0.003 to 0.019) |
| 1130 | 0.009 (0.002 to 0.017) |
| 1500 | 0.005 (0.000 to 0.010) |
| 1550 | 0.004 (0.000 to 0.008) |
| 3060 | 0.002 (0.000 to 0.008) |
| 4240 | 0.007 (0.000 to 0.019) |
| 6350 | 0.000 (0.000 to 1.000) |

L) RSVB Cord

| Threshold (IUs) | Risk Estimate (95% CI) |
|---|---|
| 267 | 0.009 (0.003 to 0.015) |
| 416 | 0.010 (0.003 to 0.016) |
| 599 | 0.009 (0.003 to 0.015) |
| 813 | 0.008 (0.002 to 0.014) |
| 1140 | 0.008 (0.001 to 0.015) |
| 1280 | 0.007 (0.000 to 0.014) |
| 1780 | 0.007 (0.000 to 0.014) |
| 2570 | 0.008 (0.000 to 0.018) |
| 4990 | 0.002 (0.000 to 0.007) |
| 7260 | 0.013 (0.000 to 0.041) |

**Supplementary Table 7.** Performance of Superlearner (SL) and the top-performing learner-screen combinations [CV-AUCs with 95% confidence intervals (CIs)] for each of the 29 variable sets in the vaccine arm with endpoint 1 as outcome. The same learner-screen combinations used for risk score development were used and a constraint of no more than k=6 input variables was applied to all learners. Endpoint 1 was defined as medically significant RSV-associated lower respiratory tract infection (LRTI), RSV-associated LRTI with hospitalization, or RSV-associated LRTI with severe hypoxemia (52 vaccine endpoints). CV-AUC, cross-validated area under the receiver operating characteristic curve. The asterisk denotes the learner and variable set with the highest CV-AUC (and, in the case of a tie, the highest CV-AUC with the narrowest 95% CI).

| Variable Set | SL CV-AUC (95% CI) | Best Learner | Screen | CV-AUC (95% CI) |
|---|---|---|---|---|
| 1_only_matvars | 0.842 [0.728, 0.911] | SL.cforest | univar_logistic_pval | 0.886 [0.736, 0.950] |
| 2_varset_EIA.log10d0 | 0.836 [0.724, 0.906] | SL.cforest | glmnet | 0.891 [0.740, 0.954] |
| 3_varset_EIA.log10d14 | 0.839 [0.716, 0.912] | SL.cforest | glmnet | 0.893 [0.740, 0.957] |
| 4_varset_EIA.log10d14overd0 | 0.859 [0.734, 0.929] | SL.cforest | glmnet | 0.891 [0.742, 0.955] |
| 5_varset_EIA.log10cord | 0.850 [0.723, 0.922] | SL.cforest | glmnet | 0.903 [0.737, 0.964] |
| 6_varset_PCA.log10d0 | 0.862 [0.740, 0.929] | SL.cforest | glmnet | 0.894 [0.738, 0.956] |
| 7_varset_PCA.log10d14 | 0.870 [0.730, 0.940] | SL.cforest | univar_logistic_pval | 0.904 [0.742, 0.967] |
| 8_varset_PCA.log10d14overd0 | 0.871 [0.731, 0.938]* | SL.cforest | glmnet | 0.901 [0.725, 0.963] |
| 9_varset_PCA.log10cord | 0.857 [0.729, 0.928] | SL.cforest | glmnet | 0.910 [0.704, 0.968] |
| 10_varset_RSVA.log10d0 | 0.833 [0.713, 0.905] | SL.cforest | glmnet | 0.894 [0.738, 0.957] |
| 11_varset_RSVA.log10d14 | 0.834 [0.722, 0.904] | SL.cforest | glmnet | 0.890 [0.728, 0.952] |
| 12_varset_RSVA.log10d14overd0 | 0.851 [0.724, 0.922] | SL.cforest | glmnet | 0.889 [0.684, 0.950] |
| 13_varset_RSVA.log10cord | 0.833 [0.717, 0.905] | SL.cforest | univar_logistic_pval | 0.891 [0.736, 0.952] |
| 14_varset_RSVB.log10d0 | 0.857 [0.733, 0.925] | SL.cforest | univar_logistic_pval | 0.894 [0.737, 0.955] |
| 15_varset_RSVB.log10d14 | 0.856 [0.732, 0.927] | SL.cforest | glmnet | 0.888 [0.732, 0.954] |
| 16_varset_RSVB.log10d14overd0 | 0.854 [0.730, 0.922] | SL.cforest | glmnet | 0.889 [0.746, 0.954] |
| 17_varset_RSVB.log10cord | 0.846 [0.726, 0.917] | SL.cforest | univar_logistic_pval | 0.892 [0.726, 0.955] |
| 18_varset_d0_all4 | 0.847 [0.725, 0.916] | SL.cforest | glmnet | 0.892 [0.738, 0.957] |
| 19_varset_d14_all4 | 0.871 [0.663, 0.937] | SL.cforest | glmnet | 0.893 [0.659, 0.953] |
| 20_varset_d14overd0_all4 | 0.860 [0.732, 0.930] | SL.cforest | glmnet | 0.898 [0.734, 0.961] |
| 21_varset_cord_all4 | 0.851 [0.709, 0.924] | SL.cforest | glmnet | 0.906 [0.731, 0.967] |
| 22_varset_EIA_all4 | 0.851 [0.718, 0.924] | SL.cforest | glmnet | 0.911 [0.722, 0.970] |
| 23_varset_PCA_all4 | 0.864 [0.711, 0.933] | SL.cforest | glmnet | 0.911 [0.638, 0.968] |
| 24_varset_RSVA_all4 | 0.851 [0.724, 0.922] | SL.cforest | glmnet | 0.891 [0.740, 0.954] |
| 25_varset_RSVB_all4 | 0.847 [0.715, 0.917] | SL.cforest | univar_logistic_pval | 0.892 [0.730, 0.955] |
| 26_varset_d0_d14 | 0.854 [0.712, 0.929] | SL.cforest | univar_logistic_pval | 0.898 [0.737, 0.963] |
| 27_varset_d0_foldrise | 0.845 [0.719, 0.917] | SL.cforest | glmnet | 0.899 [0.725, 0.962] |
| 28_varset_d0_cord | 0.848 [0.708, 0.922] | SL.cforest | univar_logistic_pval | 0.903 [0.680, 0.961] |
| 29_varset_all16 | 0.827 [0.694, 0.904] | SL.cforest | glmnet | 0.914 [0.587, 0.967]* |

**Supplementary Table 8.** Performance of Superlearner (SL) and the top-performing learner-screen combinations [CV-AUCs with 95% confidence intervals (CIs)] for each of the 29 variable sets in the placebo arm with endpoint 1 as outcome. A constraint of no more than k=6 input variables was applied to all learners. Endpoint 1 was defined as medically significant RSV-associated lower respiratory tract infection (LRTI), RSV-associated LRTI with hospitalization, or RSV-associated LRTI with severe hypoxemia (51 placebo endpoints). CV-AUC, cross-validated area under the receiver operating characteristic curve. The asterisk denotes the learner and variable set with the highest CV-AUC (and, in the case of a tie, the highest CV-AUC with the narrowest 95% CI).

| Variable Set | SL CV-AUC (95% CI) | Best Learner | Screen | CV-AUC (95% CI) |
|---|---|---|---|---|
| 1_only_matvars | 0.853 [0.636, 0.948] | SL.xgboost | univar_logistic_pval | 0.894 [0.584, 0.978] |
| 2_varset_EIA.log10d0 | 0.856 [0.631, 0.948] | SL.xgboost | univar_logistic_pval | 0.900 [0.566, 0.979] |
| 3_varset_EIA.log10d14 | 0.873 [0.622, 0.961] | SL.xgboost | univar_logistic_pval | 0.941 [0.382, 0.990] |
| 4_varset_EIA.log10d14overd0 | 0.890 [0.604, 0.968]* | SL.xgboost | univar_logistic_pval | 0.931 [0.451, 0.990] |
| 5_varset_EIA.log10cord | 0.853 [0.635, 0.946] | SL.xgboost | univar_logistic_pval | 0.895 [0.574, 0.978] |
| 6_varset_PCA.log10d0 | 0.838 [0.618, 0.936] | SL.xgboost | univar_logistic_pval | 0.895 [0.531, 0.976] |
| 7_varset_PCA.log10d14 | 0.861 [0.617, 0.954] | SL.cforest | univar_logistic_pval | 0.935 [0.433, 0.992] |
| 8_varset_PCA.log10d14overd0 | 0.888 [0.646, 0.969] | SL.cforest | univar_logistic_pval | 0.944 [0.414, 0.992]* |
| 9_varset_PCA.log10cord | 0.849 [0.609, 0.944] | SL.xgboost | glmnet | 0.892 [0.492, 0.977] |
| 10_varset_RSVA.log10d0 | 0.840 [0.628, 0.939] | SL.cforest | univar_logistic_pval | 0.883 [0.536, 0.967] |
| 11_varset_RSVA.log10d14 | 0.825 [0.617, 0.927] | SL.xgboost | glmnet | 0.895 [0.401, 0.973] |
| 12_varset_RSVA.log10d14overd0 | 0.850 [0.596, 0.942] | SL.cforest | univar_logistic_pval | 0.893 [0.534, 0.973] |
| 13_varset_RSVA.log10cord | 0.834 [0.605, 0.936] | SL.xgboost | univar_logistic_pval | 0.878 [0.556, 0.969] |
| 14_varset_RSVB.log10d0 | 0.857 [0.633, 0.947] | SL.xgboost | univar_logistic_pval | 0.898 [0.566, 0.979] |
| 15_varset_RSVB.log10d14 | 0.859 [0.619, 0.952] | SL.cforest | univar_logistic_pval | 0.888 [0.571, 0.972] |
| 16_varset_RSVB.log10d14overd0 | 0.858 [0.608, 0.948] | SL.xgboost | univar_logistic_pval | 0.896 [0.562, 0.978] |
| 17_varset_RSVB.log10cord | 0.844 [0.636, 0.941] | SL.xgboost | univar_logistic_pval | 0.901 [0.574, 0.981] |
| 18_varset_d0_all4 | 0.843 [0.591, 0.939] | SL.xgboost | univar_logistic_pval | 0.882 [0.563, 0.969] |
| 19_varset_d14_all4 | 0.880 [0.604, 0.966] | SL.cforest | univar_logistic_pval | 0.924 [0.407, 0.986] |
| 20_varset_d14overd0_all4 | 0.886 [0.635, 0.970] | SL.cforest | univar_logistic_pval | 0.927 [0.516, 0.989] |
| 21_varset_cord_all4 | 0.839 [0.612, 0.939] | SL.xgboost | univar_logistic_pval | 0.907 [0.521, 0.982] |
| 22_varset_EIA_all4 | 0.882 [0.540, 0.963] | SL.xgboost | univar_logistic_pval | 0.943 [0.367, 0.992] |
| 23_varset_PCA_all4 | 0.869 [0.604, 0.960] | SL.cforest | univar_logistic_pval | 0.928 [0.415, 0.986] |
| 24_varset_RSVA_all4 | 0.840 [0.606, 0.941] | SL.xgboost | univar_logistic_pval | 0.889 [0.588, 0.974] |
| 25_varset_RSVB_all4 | 0.871 [0.598, 0.957] | SL.xgboost | univar_logistic_pval | 0.910 [0.540, 0.984] |
| 26_varset_d0_d14 | 0.873 [0.619, 0.963] | SL.cforest | univar_logistic_pval | 0.923 [0.456, 0.986] |
| 27_varset_d0_foldrise | 0.883 [0.618, 0.969] | SL.xgboost | univar_logistic_pval | 0.927 [0.544, 0.990] |
| 28_varset_d0_cord | 0.830 [0.616, 0.934] | SL.xgboost | univar_logistic_pval | 0.891 [0.582, 0.974] |
| 29_varset_all16 | 0.849 [0.597, 0.945] | SL.cforest | univar_logistic_pval | 0.918 [0.427, 0.981] |

**Supplementary Table 9.** Performance of Superlearner (SL) and the top-performing learner-screen combinations [CV-AUCs with 95% confidence intervals (CIs)] for each of the 29 variable sets in the vaccine arm with endpoint 2 as outcome. A constraint of no more than k=6 input variables was applied to all learners. Endpoint 2 was defined as RSV-associated lower respiratory tract infection with severe hypoxemia (14 vaccine endpoints). CV-AUC, cross-validated area under the receiver operating characteristic curve. The asterisk denotes the learner and variable set with the highest CV-AUC (and, in the case of a tie, the highest CV-AUC with the narrowest 95% CI).

| Variable Set | SL CV-AUC (95% CI) | Best Learner | Screen | CV-AUC (95% CI) |
|---|---|---|---|---|
| 1_only_matvars | 0.715 [0.571, 0.819] | SL.bayesglm | all | 0.780 [0.644, 0.868] |
| 2_varset_EIA.log10d0 | 0.724 [0.573, 0.831] | SL.bayesglm | all | 0.784 [0.642, 0.876] |
| 3_varset_EIA.log10d14 | 0.691 [0.556, 0.798] | SL.bayesglm | all | 0.784 [0.659, 0.866] |
| 4_varset_EIA.log10d14overd0 | 0.747 [0.611, 0.844] | SL.glm | all | 0.815 [0.679, 0.898]* |
| 5_varset_EIA.log10cord | 0.712 [0.559, 0.824] | SL.bayesglm | all | 0.777 [0.645, 0.865] |
| 6_varset_PCA.log10d0 | 0.697 [0.559, 0.803] | SL.bayesglm | all | 0.772 [0.642, 0.860] |
| 7_varset_PCA.log10d14 | 0.677 [0.530, 0.789] | SL.xgboost | glmnet | 0.758 [0.597, 0.864] |
| 8_varset_PCA.log10d14overd0 | 0.691 [0.555, 0.798] | SL.bayesglm | all | 0.771 [0.647, 0.857] |
| 9_varset_PCA.log10cord | 0.757 [0.620, 0.852]* | SL.bayesglm | all | 0.780 [0.645, 0.865] |
| 10_varset_RSVA.log10d0 | 0.725 [0.570, 0.831] | SL.bayesglm | all | 0.781 [0.629, 0.874] |
| 11_varset_RSVA.log10d14 | 0.735 [0.593, 0.838] | SL.xgboost | glmnet | 0.785 [0.604, 0.890] |
| 12_varset_RSVA.log10d14overd0 | 0.696 [0.557, 0.803] | SL.bayesglm | all | 0.761 [0.625, 0.854] |
| 13_varset_RSVA.log10cord | 0.703 [0.556, 0.812] | SL.glm | all | 0.776 [0.638, 0.864] |
| 14_varset_RSVB.log10d0 | 0.690 [0.544, 0.800] | SL.bayesglm | all | 0.787 [0.645, 0.877] |
| 15_varset_RSVB.log10d14 | 0.723 [0.574, 0.831] | SL.bayesglm | all | 0.791 [0.655, 0.877] |
| 16_varset_RSVB.log10d14overd0 | 0.710 [0.568, 0.817] | SL.bayesglm | all | 0.778 [0.644, 0.866] |
| 17_varset_RSVB.log10cord | 0.718 [0.565, 0.830] | SL.glm | all | 0.779 [0.645, 0.867] |
| 18_varset_d0_all4 | 0.673 [0.526, 0.790] | SL.bayesglm | all | 0.759 [0.609, 0.862] |
| 19_varset_d14_all4 | 0.704 [0.568, 0.805] | SL.glm | all | 0.754 [0.630, 0.842] |
| 20_varset_d14overd0_all4 | 0.699 [0.567, 0.802] | SL.xgboost | glmnet | 0.791 [0.635, 0.885] |
| 21_varset_cord_all4 | 0.735 [0.595, 0.835] | SL.glm | all | 0.773 [0.632, 0.859] |
| 22_varset_EIA_all4 | 0.746 [0.616, 0.841] | SL.glm | all | 0.810 [0.669, 0.896] |
| 23_varset_PCA_all4 | 0.707 [0.574, 0.810] | SL.xgboost | univar_logistic_pval | 0.756 [0.587, 0.864] |
| 24_varset_RSVA_all4 | 0.672 [0.534, 0.782] | SL.xgboost | univar_logistic_pval | 0.745 [0.589, 0.851] |
| 25_varset_RSVB_all4 | 0.722 [0.579, 0.830] | SL.bayesglm | all | 0.777 [0.637, 0.868] |
| 26_varset_d0_d14 | 0.677 [0.543, 0.785] | SL.bayesglm | all | 0.742 [0.603, 0.841] |
| 27_varset_d0_foldrise | 0.701 [0.557, 0.812] | SL.xgboost | univar_logistic_pval | 0.785 [0.632, 0.881] |
| 28_varset_d0_cord | 0.709 [0.548, 0.826] | SL.bayesglm | all | 0.768 [0.620, 0.865] |
| 29_varset_all16 | 0.700 [0.562, 0.805] | SL.xgboost | univar_logistic_pval | 0.780 [0.629, 0.875] |

**Supplementary Table 10.** Performance of Superlearner (SL) and the top-performing learner-screen combinations [CV-AUCs with 95% confidence intervals (CIs)] for each of the 29 variable sets in the placebo arm with endpoint 2 as outcome. A constraint of no more than k=6 input variables was applied to all learners. Endpoint 2 was defined as RSV-associated lower respiratory tract infection with severe hypoxemia (27 placebo endpoints). CV-AUC, cross-validated area under the receiver operating characteristic curve. The asterisk denotes the learner and variable set with the highest CV-AUC (and, in the case of a tie, the highest CV-AUC with the narrowest 95% CI).

| Variable Set | SL CV-AUC (95% CI) | Best Learner | Screen | CV-AUC (95% CI) |
|---|---|---|---|---|
| 1_only_matvars | 0.727 [0.548, 0.851] | SL.glm | all | 0.761 [0.583, 0.876] |
| 2_varset_EIA.log10d0 | 0.726 [0.555, 0.848] | SL.bayesglm | all | 0.763 [0.585, 0.878] |
| 3_varset_EIA.log10d14 | 0.713 [0.543, 0.837] | SL.bayesglm | all | 0.763 [0.589, 0.878] |
| 4_varset_EIA.log10d14overd0 | 0.746 [0.582, 0.860] | SL.bayesglm | all | 0.775 [0.599, 0.886] |
| 5_varset_EIA.log10cord | 0.718 [0.548, 0.842] | SL.bayesglm | all | 0.768 [0.594, 0.881] |
| 6_varset_PCA.log10d0 | 0.719 [0.548, 0.842] | SL.glm | all | 0.773 [0.595, 0.885] |
| 7_varset_PCA.log10d14 | 0.718 [0.542, 0.843] | SL.bayesglm | all | 0.761 [0.584, 0.876] |
| 8_varset_PCA.log10d14overd0 | 0.748 [0.577, 0.862]* | SL.glmnet | glmnet | 0.811 [0.638, 0.910] |
| 9_varset_PCA.log10cord | 0.715 [0.545, 0.838] | SL.glm | all | 0.768 [0.588, 0.882] |
| 10_varset_RSVA.log10d0 | 0.719 [0.546, 0.844] | SL.glm | all | 0.772 [0.592, 0.885] |
| 11_varset_RSVA.log10d14 | 0.726 [0.554, 0.847] | SL.bayesglm | all | 0.766 [0.592, 0.879] |
| 12_varset_RSVA.log10d14overd0 | 0.732 [0.555, 0.854] | SL.glm | all | 0.754 [0.586, 0.868] |
| 13_varset_RSVA.log10cord | 0.724 [0.550, 0.847] | SL.bayesglm | all | 0.769 [0.596, 0.882] |
| 14_varset_RSVB.log10d0 | 0.719 [0.547, 0.842] | SL.bayesglm | all | 0.758 [0.581, 0.874] |
| 15_varset_RSVB.log10d14 | 0.717 [0.542, 0.843] | SL.bayesglm | all | 0.760 [0.582, 0.874] |
| 16_varset_RSVB.log10d14overd0 | 0.706 [0.532, 0.834] | SL.bayesglm | all | 0.747 [0.577, 0.863] |
| 17_varset_RSVB.log10cord | 0.711 [0.535, 0.838] | SL.glm | all | 0.761 [0.583, 0.877] |
| 18_varset_d0_all4 | 0.722 [0.549, 0.845] | SL.xgboost | glmnet | 0.750 [0.528, 0.884] |
| 19_varset_d14_all4 | 0.726 [0.547, 0.850] | SL.bayesglm | all | 0.753 [0.580, 0.870] |
| 20_varset_d14overd0_all4 | 0.733 [0.558, 0.854] | SL.bayesglm | glmnet | 0.805 [0.629, 0.908] |
| 21_varset_cord_all4 | 0.729 [0.555, 0.851] | SL.xgboost | glmnet | 0.752 [0.536, 0.883] |
| 22_varset_EIA_all4 | 0.704 [0.540, 0.828] | SL.xgboost | glmnet | 0.771 [0.558, 0.897] |
| 23_varset_PCA_all4 | 0.737 [0.571, 0.853] | SL.bayesglm | glmnet | 0.821 [0.645, 0.918]* |
| 24_varset_RSVA_all4 | 0.716 [0.538, 0.843] | SL.xgboost | univar_logistic_pval | 0.751 [0.554, 0.877] |
| 25_varset_RSVB_all4 | 0.686 [0.518, 0.813] | SL.bayesglm | all | 0.731 [0.564, 0.850] |
| 26_varset_d0_d14 | 0.727 [0.551, 0.851] | SL.bayesglm | all | 0.740 [0.570, 0.858] |
| 27_varset_d0_foldrise | 0.721 [0.557, 0.841] | SL.glm | glmnet | 0.808 [0.627, 0.911] |
| 28_varset_d0_cord | 0.722 [0.549, 0.844] | SL.xgboost | univar_logistic_pval | 0.745 [0.547, 0.873] |
| 29_varset_all16 | 0.734 [0.558, 0.857] | SL.glmnet | glmnet | 0.801 [0.617, 0.906] |

**Supplementary Methods**

**Antibody assays**

Four different assays were used to measure antibody responses:

• Anti-F IgG (EIA) concentration as measured by ELISA [2], reported in ELISA units/mL, with a negative response defined by a readout below the Lower Limit of Quantification (LLOQ) of 400; such readouts are set to 200 for analysis.

• Palivizumab-competitive antibody (PCA) concentration, reported as serum concentration of palivizumab-like antibodies (μg/ml) corresponding to 50% reduction in binding of labelled palivizumab to immobilized F protein as detected by ELISA [2], with a negative response defined by a readout below the LLOQ of 12; such readouts are set to 6 for analysis. These antibodies bind to the RSV F protein site II epitope [3].

• Microneutralization (MN) 50% antibody titer to RSV/A on HEp-2 cells [4], reported as the reciprocal of the serum dilution at which > 50% reduction in viral cytopathic effect (CPE) is observed. Titers were reported in International Units (IU) with an LLOQ of 13 IUs; titers below this value were set to 6.5 IUs.

• MN 50% antibody titer to RSV/B on HEp-2 cells [4], defined and reported similarly as for RSV/A, with a LLOQ of 8 for RSV/B. Titers below the LLOQ were set to 4 IU.

**Two-phase sampling design for measuring antibody markers**

The study cohort was divided into 10 strata by five clusters of study sites and by whether the interval between vaccination and birth was less than 30 days within each treatment arm. For every case in a placebo stratum, two controls were sampled; for every case in a vaccine stratum, four controls were sampled. (Endpoint 1 was used to define cases and controls, with definitions the same as in "Methods" of the main text.) If a placebo stratum had no cases, two controls were sampled; if a vaccine stratum had no cases, four controls were sampled. For the sampled participants, the lab assays occasionally produced missing values. In such cases, a single multivariate imputation was done using the mice R package [5], with default method "pmm". Imputation was performed separately within the two treatment arms. Within each treatment arm, imputation was done together for the four assays and the three time points (D0, D14, Cord).

**Development of risk scores (maternal baseline risk score and infant birth/delivery risk score)**

The analysis to develop a maternal baseline risk score (considering both endpoints 1 and 2) was carried out using data from the placebo arm. The maternal enrollment variable set contained n=11 variables, but development of the maternal enrollment risk score was based on only n=9, as detailed below:

1. age.at.trt.cat: Indicator of age > 28 (coded as 1 if age > 28; 0 otherwise)
2. age.at.trt: Age as continuous variable
3. bmi: BMI
4. mshmopr: Smoker status
5. m.ast: Asthma status
6. child5: Indicator of other children < 5 years of age in home
7. season: RSV season intensity score at time of birth
8. smoker: Indicator of infant living with smoker
9. daycare: Indicator of daycare, or infant living in home with daycare attendee
10. prebrth: Number of previous children [this variable was dropped before development of the maternal enrollment risk score because data missing for 349/784 (44%) of mother-infant pairs]

11. hiv: HIV [this variable was also dropped before development of the maternal enrollment risk score because all non-NA values were negative]

An infant birth/delivery risk score was also developed, based on the following n=8 covariates:

1. p.sex: Infant sex
2. iwt: Birthweight (continuous)
3. p.lbw: Birthweight (low vs. not low)
4. iwtlen: Ratio of length to birthweight
5. hdcirc: Frontal occipital head circumference
6. ga: Estimated gestational age at birth in days (count variable)
7. p.small: Small for gestational age
8. p.igr: Intrauterine growth retardation

For both sets (the maternal enrollment variable set and the birth variable set), missing covariate values were imputed using a multivariable regression method (mice package in R). All variables had less than 5% missing values, with the exception of the child5 covariate in the maternal enrollment variable set, which had 8.9% missing values. Nevertheless, the child5 variable was included in the analysis as it was found to have a significant association with RSV disease in the placebo arm.
For both sets, all included covariates were pre-scaled to have a mean of 0 and standard deviation of 1 (including binary, count, and continuous variables).

Note, as detailed below, all immune correlates analyses adjusted for maternal baseline risk score and for the number of days between vaccination and birth, but not for infant birth/delivery risk score.

**Use of superlearner ensemble modeling to define the risk score**
We applied the super learner ensemble machine learning framework [6] to build a model for predicting the RSV disease endpoints. A super learner is an ensemble of individual learners with ensemble weights chosen to minimize a cross-validated measure of risk, which we take to be negative log likelihood for our binary outcome of interest. The super learner approach was used because we lack *a priori* knowledge as to which learning algorithm might provide the best predictions. All Super Learner-based analyses were performed with the open source SuperLearner R package.

For building each risk score (maternal and birth), the superlearner ensemble model was fit using the input variables listed above. The library of learners used in the ensemble was defined by a set of 'learner-screen' combinations, where by "learner" we mean a type of binary outcome regression modeling approach that was used, where we included the following learners, with superlearner R package function indicated: logistic regression (SL.glm), Bayesian logistic regression (SL.bayesglm), L1 penalized lasso regression (SL.glmnet), step-wise BIC model-selection with logistic regression (SL.step), generalized additive models (SL.gam), gradient boosting (SL.xgboost), and random forests (SL.cforest). By "screen" we mean an initial screening component of a candidate learner that determines whether to advance an input feature for consideration in the model. Screens employed were none, L1 penalized lasso regression where only variables with non-zero coefficient estimate were retained, and a p-value < 0.10 from a univariable p-value in a logistic regression model; moreover a high correlation screen was always applied that selected one variable at random from pairs of quantitative variables having Spearman rank correlation > 0.90. Note that except for the highcor_random screen, variables passing the screens were further ranked by univariate p-value and the highest-ranking variables were selected up to a cap of k variables. Variables

passing the highcor_random screen, in contrast, were selected at random. Thus, the performance of learners with the highcor_random screen was generally lower in comparison to the other three screens. Supplementary Table 1 lists all of the learner-screen combinations that were used in the superlearner for developing each risk score (the maternal enrollment risk score and the birth variable risk score).

Two levels of cross-validation (CV) were used in the generation of the superlearner ensemble model:
1. Outer level: CV-AUC was computed over 5-fold CV and used to estimate performance of the ensemble.
This was repeated 10 times to improve stability. Note that once the screens were set up, the selected covariates remained constant for the superlearner job (over the 5 outer folds). The variability in the 10 random seeds was generated in the way superlearner split the data into the 5 outer folds.
2. Inner level: leave-one-out CV was used to estimate individual learner performance and ensemble weights.

Eight superlearner models were fit for each endpoint and variable set with model k (among k=1, . . . , 8) only allowing models with at most k covariates in the model. The eight superlearner models were compared by CV-AUC and the most parsimonious model (i.e., the model with smallest value of k) with estimated CV-AUC no more than 0.01 less than the superlearner model with highest estimated CV-AUC was selected for each endpoint. Larger models were not considered based on the available sample size.

The selected superlearner models were subsequently used to derive the risk scores defined as the logit of the predicted probability of outcome for each participant. The risk scores for the vaccine recipients were predicted using the selected superlearner models (trained using data from the placebo arm). The risk scores for the placebo recipients were derived upon splitting the data into 5 folds. For each of the 5 folds, SL (for the selected k) was trained on the rest of the placebo data and used to predict the probability of outcome. The 5-fold split was repeated 10 times and the probabilities were averaged.

For endpoint 1 as outcome, the selected superlearner model had the child5 covariate (indicator for other children < 5 years of age in home) as a major predictor and gave a CV-AUC of 0.60 for the placebo arm and an AUC of 0.59 for the vaccine arm. For endpoint 2 as outcome, the selected superlearner model had the child5 and maternal asthma status covariates as the major predictors and gave a CV-AUC of 0.60 for the placebo arm and an AUC of 0.56 for the vaccine arm. The infant birth/delivery variables had no ability to predict RSV disease outcome (CV-AUCs < 0.5). Therefore, all immune correlates analyses adjusted for maternal baseline risk score but not for an infant birth/delivery risk score. In addition, all immune correlates analyses adjusted for the number of days between vaccination and birth.

Supplementary Figure 3 provides a flowchart illustrating how superlearner was implemented for building the two risk scores, where the same flowchart also illustrates how superlearner was used for conducting the multivariable antibody marker correlates of risk analysis.

**Preparation for antibody marker correlates analyses: unsupervised analysis**

Supplementary Figure 5 shows correlations between the EIA and PCA readouts, and between the RSVA and RSVB readouts, at each of the three timepoints. The D14 EIA and PCA readouts were highly correlated (r = 0.9) yet have different interpretations and thus were both analyzed. The neutralization readouts RSVA and RSVB were moderately correlated with each other (r = 0.5) and with EIA and PCA (r = 0.4 ~ 0.5). The correlation between D0 and D14 readouts in the placebo arm was 0.9 for RSVB/EIA/PCA and 0.7 for RSVA, suggesting that RSVA measurement error was higher than for the other three assays. The correlation between D14 and cord blood readouts in the placebo arm was 0.8 for RSVB/EIA/PCA and 0.7 for RSVA. All four assays were advanced for assessment as immune correlates.

**Correlates analyses**

All correlates analyses are based on actual treatment received.

**Logistic regression correlates of risk modeling:** Results for RSVA and RSVB were estimated from case/control (phase 2) data via maximum likelihood estimation for endpoint 1 (implemented in the osDesign R package [7]) and via inverse probability weighting complete-case for endpoints 2 and 3 (implemented in the survey R package [8]). osDesign requires every stratum has non-zero cases and non-zero controls. For endpoint 1, there were no cases in the stratum SS & <30d in both the placebo arm and the vaccine arm. Since these two strata were small – 11 controls in the placebo arm (out of 784 total) and 18 controls in the vaccine arm (out of 1553 total) – we removed these two strata from the analyses for endpoint 1.

**Nonparametric threshold correlates of risk modeling:** Targeted maximum likelihood estimation was applied to estimate, for each antibody marker, the "threshold-response" function that is the risk of RSV endpoint 1 or 2 for the subgroup of vaccine recipients with antibody marker above a given threshold and repeating the analysis over all possible thresholds [9]. This threshold-response function adjusts for baseline covariates W through direct standardization, with threshold response function defined by $E_W[P(Y=1|A=a,S>=v,W)]$, where Y is the indicator of the RSV endpoint during follow-up, A is randomization assignment to vaccine (a=1) or placebo (a=0), S is the antibody marker, and v is the fixed antibody threshold that is varied, where $E_W$ is expectation over the marginal distribution of W. The data analysis adjusted for W taken to be maternal baseline risk score and the number of days between vaccination and birth, and results are reported as plots of point estimates and pointwise 95% confidence interval estimates of the threshold-response function for each RSV endpoint 1 and 2. The plots also include estimates of reverse cumulative distribution functions of the antibody marker S, calculated using inverse probability of sampling weighting.

**Multiple hypothesis testing adjustment:** For the univariable correlate of risk analyses of the 16 antibody marker variables, family-wise error rate (Holm-Bonferroni) and false-discovery rate (q-values; Benjamini-Hochberg) adjustment was applied, separately for the vaccine and placebo groups. Multiplicity adjustment was applied separately for each of the three time points maternal baseline, maternal Day 14, and delivery/birth, where the adjustment was over all studied antibody markers at the given time point. The reason for this approach is that assessment of correlates of risk at each of these time points can be viewed as separate study question. For each analysis the unadjusted p-value, the FWER-adjusted p-value, and the q-value is reported for a Wald test of whether the odds ratio differs from 1. All p-values and q-values are 2-sided. As a guideline for interpreting correlate of risk findings (but not meant to be a rigid gateway), results with unadjusted p-value $\leq 0.05$ and q-value $\leq 0.10$ are flagged as having statistical

evidence for being a correlate of risk. Results with FWER-adjusted p-value $\leq 0.05$ are flagged as having more robust statistical evidence for being a correlate of risk.

For the principal stratification analyses, family-wise error rate (Holm-Bonferroni) and false-discovery rate (q-values; Benjamini-Hochberg) adjustment was applied. Multiplicity adjustment was applied across the four biomarkers used in PS analyses (i.e., D14/D0 fold-change EIA and PCA and D14 RSVA and RSVB) and for each endpoint separately.

**Machine learning superlearner ensemble multivariable correlates of risk analysis**

Superlearner modeling of models including the antibody markers was implemented in a similar way as described for building the risk scores as described in Section "**Use of superlearner ensemble modeling to define the risk score**." This includes the same procedures for inner and outer cross-validation, use of the same set of learner types, and use of the same set of variable screens, except that instead of allowing at most k=8 covariates in each model at most k=6 covariates were allowed in each model. Fewer variables were allowed due to the further reduced sample size when restricting to participants with antibody markers measured. Regarding the requirement of at most k=6 covariates in the model, one exception was allowed: when a quantitative fold-change marker was included in the variable set and passed the screen, the indicators of a 2-fold rise and of a 4-fold rise (from D0 to D14) were also included. The 2-fold and 4-fold rise indicator variables were not part of the variable screening process.

Supplementary Table 7 lists all of the variable sets and the top-performing learner-screen combinations from amongst the library of learners used for the superlearner multivariable correlates of risk analyses for endpoint 1 and the vaccine arm. Supplementary Table 8 lists the same information for endpoint 1 and the placebo arm. Supplementary Tables 9 and 10 list the same information for endpoint 2 and the vaccine arm, and for endpoint 2 and the placebo arm, respectively. Supplementary Table 2 defines the 29 input variable sets that are used for each of these four sets of outputs. For each input variable set, each supplementary table 7-10 reports the CV-AUC both for the superlearner model and for the best performing model, and it is important to note that the CV-AUC for the superlearner model is the most useful metric for quantifying the classification accuracy achieved by the input variable set. By always using the pre-specified model choice superlearner (that is fit and evaluated by two layers of cross-validation), the results provide an honest/accurate estimate of classification accuracy, whereas in contrast the best performing individual model's CV-AUC will tend to be too high as it is susceptible to over-fitting. The best performing individual model results are included for the purpose of providing insights on what type of model tended to perform best. When CV-AUC results are cited in the text, we always cite the superlearner model CV-AUC.

The learners were implemented with the same empirical inverse probability weights that were used for the logistic regression modeling to account for the two-phase sampling design. Estimation of CV-AUC with 95% confidence intervals using the empirical inverse probability weights for each variable set was implemented using the R package vimp [10].

**Principal stratification correlate of VE CoP analysis:** EIA D14/D0 (log10 fold-change), PCA D14/D0 (log10 fold-change), D14 RSVA, and D14 RSVB, for each of endpoints 1 and 2, were assessed based on the SAP that stated only markers meeting a pre-specified benchmark for sufficient correlation with the baseline measurement of the antibody marker would be included. For each pair of antibody marker (S(1)) and endpoint, VE curves were constructed utilizing corresponding baseline antibody markers as the baseline immunogenicity predictor, based on a probit risk model conditional on S(1), treatment,

interaction between treatment and S(1), after adjusting for potential confounders (indicator of less than 30 days between vaccination and birth, maternal risk score). Complementary analyses further adjusting for baseline antibody marker level in the risk model were also conducted. VE curves for EIA and PCA were constructed using the whole cohort (phase 1 data) samples, whereas VE curves for RSVA and RSVB were constructed using case/control (phase 2) samples. VE curves were presented together with 95% pointwise and simultaneous confidence intervals based on 1,000 bootstrap samples (stratified on case/control sampling strata). Also shown in the figures are two-sided p-values based on Wald-test for interaction between treatment and S(1) in the risk model, which evaluate whether VE changes over subgroups defined by the antibody marker S(1).

**Prentice surrogate endpoint evaluation CoP analysis:** Based on the logistic regression modeling, an antibody marker is supported to meet the Prentice criteria if all of the following conditions are met, all after adjustment for baseline potential confounding variables: (1) there is no evidence of an interaction between treatment and the marker; (2) in a main effects model taking out the interaction term, there is an association of the antibody marker with outcome; (3) in this main effects model, there is no evidence of an association of the treatment/randomization assignment with outcome (i.e., after accounting for the marker, treatment contains no additional information about risk).

## References


1. Madhi SA, Polack FP, Piedra PA, et al. Respiratory Syncytial Virus Vaccination during Pregnancy and Effects in Infants. N Engl J Med **2020**; 383:426-39.
2. August A, Glenn GM, Kpamegan E, et al. A Phase 2 randomized, observer-blind, placebo-controlled, dose-ranging trial of aluminum-adjuvanted respiratory syncytial virus F particle vaccine formulations in healthy women of childbearing age. Vaccine **2017**; 35:3749-59.
3. Rossey I, McLellan JS, Saelens X, Schepens B. Clinical Potential of Prefusion RSV F-specific Antibodies. Trends Microbiol **2018**; 26:209-19.
4. Piedra PA, Jewell AM, Cron SG, Atmar RL, Glezen WP. Correlates of immunity to respiratory syncytial virus (RSV) associated-hospitalization: establishment of minimum protective threshold levels of serum neutralizing antibodies. Vaccine **2003**; 21:3479-82.
5. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med **1999**; 18:681-94.
6. van der Laan MJ, Polley EC, Hubbard AE. Super learner. Stat Appl Genet Mol Biol **2007**; 6:Article25.
7. Breslow NE, Holubkov R. Maximum likelihood estimation of logistic regression parameters under two-phase, outcome-dependent sampling. J Roy Stat Soc B Met **1997**; 59:447-61.
8. Lumley T. *Complex Surveys: A Guide to Analysis Using R*. Vol. 565. John Wiley & Sons. **2010**.
9. van der Laan L, Zhang W, Gilbert PB. Efficient nonparametric estimation of the covariate-adjusted threshold-response function, a support-restricted stochastic intervention. arXiv:2107.11459 [stat.ME]. **2021**.
10. Williamson BD, Gilbert PB, Simon NR, Carone M. A general framework for inference on algorithm-agnostic variable importance. Posted online 9 Nov 2021. https://doi.org/10.1080/01621459.2021.2003200. Journal of the American Statistical Association **2021**:1-38.

**Statistical Analysis Plan**

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| Protocol Title: | A Phase 3, Randomized, Observer-blind, Placebo-Controlled, Group-Sequential Study to Determine the Immunogenicity and Safety of a Respiratory Syncytial Virus (RSV) F Nanoparticle Vaccine with Aluminum in Healthy Third-Trimester Pregnant, Women, and Safety and Efficacy of Maternally Transferred Antibodies in Preventing RSV Disease in Their Infants |
| Protocol Number: | RSV-M-301 |
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| Date: | 30 April 2020 |
| SAP Version: | v2.0 |