CoP SAP 6.5 and 6.6

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6.5 Percent of Variance Explained by Virus Specific Antibody

This section aims to answer the question: how much of the variance of the viral load is explained by the virus-specific antibody, compared to models with vaccine type and vaccine dose additionally included? First a variable is defined, PVE: the Percentage of the Variance of the viral load Explained by the virus-specific antibody apart from the vaccine type and dose. This approach will only be used if it is confirmed that the dose is related to viral load (Section 6.3). If the dose is related to viral load, then the PVE equals 0 if the virus-specific antibody explains none of the variability of the viral load, and the PVE will equal 100 if the virus-specific antibody explains as much of the variability as the more expansive model with effects for vaccine type and dose added (in other words, PVE=100 means that all of the effect of the vaccine acts through the virus-specific antibody). If the PVE is substantial, then that virus-specific antibody acts as a correlate of protection (CoP). A dose-response causal effect for the vaccines will likely have already been established in Section 6.3. However, a mechanistic meaning is not assigned to the CoP, as it may or may not be a mediator in the biological pathway to protection (Plotkin and Gilbert, 2012).

Numeric viral load

We first describe this analysis in its most basic form. The first step is to describe the association between the virus-specific antibody and the viral load with two models: the base model and the base + dose model. The base model predicts the viral load using the virus-specific antibody. The model is explained for the linear model, although more complicated models (see Section 6.4) may be used if feasible. For a continuous viral load like that described in Section 6.4.2, a linear model is fit with an intercept and a linear term for the virus-specific antibody. To measure how much of the variance of the viral load is explained by the model an adjusted R square value is employed such that,

$R_a^2 = 1 - \frac{(n-1)(1-R^2)}{(n-p)}$

where n is the sample size, and p is the number of parameters (including the intercept). The base + dose model is a linear model that allows a separate line of prediction of viral load by virus-specific antibody for each dose score (the single-dose halved dose score is used and dose scores were not adjusted). We get an adjusted R squared for the base + dose model. Then the percentage of variance explained by the virus-specific antibody apart from the dose (PVE) is 100 times the adjusted R square value from the base model over the adjusted R squared values from the base + dose model.

Confidence intervals on the PVE are calculated by using bias-adjusted nonparametric bootstrap methods (using 5000 replicates) as in Fay et al., (2012).

Table 6.5.1: Percent of Variance Explained by Immune Virus-Specific Antibodies - Numeric Viral Load

	log MN 2 weeks prior challenge	log MN day challenge	log MSD ECL 2 weeks prior challenge	log MSD ECL day challenge	log PsVNA ID50 2 weeks prior challenge	log PsVNA ID50 day challenge	log PsVNA ID80 2 weeks prior challenge	log PsVNA ID80 day challenge
AUC BAL N1	88.02 (87, 100)	93.85 (94.06, 100)	77.9 (69.81, 95.75)	88.31 (87.86, 100)	70.3 (65.7, 96.07)	67.22 (60.51, 93.81)	73.64 (69.72, 93.96)	84.71 (84.36, 96.88)
AUC BAL Subgenomic	86.36 (84.7, 100)	100 (98.8, 100)	88.81 (84.98, 100)	99.67 (100, 100)	67.25 (62.08, 100)	64.64 (59.3, 100)	75.82 (71.09, 100)	86.42 (85.81, 100)
AUC Nasal Swab N1	83.83 (81, 98.41)	91.63 (94.44, 100)	78.01 (73.56, 91.07)	81.13 (78.98, 91.7)	77.62 (72.14, 93.89)	84.23 (82.72, 95.34)	85.16 (83.39, 97.67)	94.23 (94.44, 100)
AUC Nasal Swab Subgenomic	89.2 (88.49, 100)	90.08 (91.34, 100)	72.63 (65.43, 92.07)	72.72 (66.79, 91.75)	77.2 (72.59, 91.11)	84.77 (82.65, 100)	81.41 (77.26, 94.18)	93.86 (94.41, 100)
AUC OP Swab N1	100 (95.3, 100)	100 (97.92, 100)	97.28 (97.35, 100)	100 (99.83, 100)	92.54 (89.2, 100)	77.79 (71.16, 100)	97.98 (98.01, 100)	100 (90.45, 100)
AUC OP Swab Subgenomic	100 (74.63, 100)	100 (82.74, 100)	100 (87.04, 100)	100 (83.04, 100)	100 (89.48, 100)	78.2 (70.52, 100)	100 (85.48, 100)	100 (75.52, 100)
log VL Day2 PostChallenge BAL N1	74.6 (71.62, 100)	94.18 (100, 100)	66.58 (62.35, 89.36)	74.48 (74.93, 100)	89.17 (91.26, 100)	72.51 (73.04, 91.34)	92.81 (98.95, 100)	93.29 (100, 100)
log VL Day2 PostChallenge BAL Subgenomic	92.5 (96.18, 100)	100 (100, 100)	77.77 (73.93, 100)	86.43 (89.18, 100)	98.77 (100, 100)	80.97 (79.39, 100)	100 (100, 100)	98.07 (100, 100)
log VL Day2 PostChallenge OPswab N1	49.78 (42.52, 75.02)	39.26 (29.35, 67.19)	46.41 (39.59, 68.47)	42.27 (33.46, 72.52)	60.64 (54.11, 96.76)	49.3 (43.14, 80.05)	66.21 (65.18, 93.69)	73.09 (76.78, 100)
log VL Day2 PostChallenge OPswab Subgenomic	59.22 (53.41, 81.71)	49.23 (40.71, 76.65)	51.03 (40.81, 88)	47.32 (34.93, 78.47)	65.94 (58, 98.21)	61.25 (55.92, 88.75)	69.1 (66.4, 91.43)	79.11 (82.55, 100)
log VL Day2 PostChallenge NasalSwab N1	92.5 (94.87, 100)	73.23 (69.61, 95.15)	73.9 (71.06, 94.38)	71.96 (71.02, 90.78)	95.18 (96.61, 100)	79.73 (77.35, 96.57)	97.6 (100, 100)	93.22 (95.02, 100)
log VL Day2 PostChallenge NasalSwab Subgenomic	82.09 (83.21, 92.65)	70.83 (69.08, 86.72)	65.98 (64.34, 79.11)	64.45 (63.65, 76.62)	83.49 (81.82, 97.03)	72.19 (65.34, 89.26)	79.95 (76.81, 92.34)	82.91 (80.75, 100)

Binary viral load

For binary viral load there is a slight variation of the method. Logistic regression is used to predict the viral load in the two models, and the adjusted coefficient of discrimination (an analog to the adjusted R squared for use with logistic regression). More complicated models, regardless of what was selected by the cross-validation procedure in section 6.4.2, are not used. The case with the binary viral load was used in Fay et al (2012), where the PVE statistic was called the percent of prediction explained (PPE) and the base model was called “Model 1” and the base + dose model was called “Model 3”.

Confidence intervals on the PVE are calculated by using bias-adjusted nonparametric bootstrap methods, if possible, as in Fay et al., (2012). If bias-adjusted bootstrap confidence intervals were not able to be calculated, then percentile confidence intervals were used.

Table 6.5.2: Percent of Variance Explained by Immune Virus Specific Antibodies - Binary Viral Load

	log MN 2 weeks prior challenge	log MN day challenge	log MSD ECL 2 weeks prior challenge	log MSD ECL day challenge	log PsVNA ID50 2 weeks prior challenge	log PsVNA ID50 day challenge	log PsVNA ID80 2 weeks prior challenge	log PsVNA ID80 day challenge
bin VL Day2 PostChallenge BAL N1	100 (56.1, 100)	63.4 (36.59, 100)	0 (0, 100)	26.58 (4.28, 100)	100 (50.29, 100)	40.6 (15.98, 100)	0 (0, 100)	100 (55.68, 100)
bin VL Day2 PostChallenge BAL Subgenomic	70.06 (65.03, 100)	75.74 (73.25, 100)	41.21 (20.3, 100)	51.84 (35.8, 100)	100 (86.75, 100)	62.22 (46.4, 100)	100 (100, 100)	55.48 (33.96, 100)
bin VL Day2 PostChallenge OPswab N1	66.99 (34.36, 100)	100 (81.23, 100)	100 (68.21, 100)	98.14 (65, 100)	57.95 (32.54, 100)	100 (59.28, 100)	100 (63.69, 100)	100 (54.65, 100)
bin VL Day2 PostChallenge OPswab Subgenomic	35.93 (22.35, 100)	20.59 (7.53, 100)	23.76 (7.11, 100)	19.22 (0.77, 86.09)	43.24 (29.36, 100)	42.63 (30.77, 100)	36.31 (23.37, 100)	46.97 (36.6, 100)
bin VL Day2 PostChallenge NasalSwab N1	0 (0, 100)	17.42 (4.34, 53.78)	4.19 (0.94, 12.1)	4.38 (1.02, 10.43)	1.07 (0, 100)	1.16 (0.08, 3.31)	1.31 (0, 100)	0 (0, 100)
bin VL Day2 PostChallenge NasalSwab Subgenomic	41.45 (25.81, 100)	47.95 (32.05, 100)	29.74 (4.35, 98.07)	62.78 (38.37, 100)	30.47 (0, 66.35)	48.39 (28.33, 100)	70.92 (59.84, 100)	100 (74.36, 100)

6.6 Examining Differential Vaccine Effect

One way of examining differential vaccine effects is to create two models to predict viral load using the combined data. The base + dose model uses the immune virus-specific antibody plus the dose of the vaccine with a degree of freedom for each dose score (see Section 6.3 for definition of the dose score). Single-dose halved dose scores were used. In the base + dose model, information regarding the identity of the vaccine administered is not included in the analysis, except in information captured in the dose score. For the second model, termed the base + dose + vacc model, separate effects for each specific vaccine/dose score combination (i.e., a different parameter for each specific vaccine/dose) will be included. Linear models for numeric viral load (e.g., Section 6.4.1) or logistic models for binary viral load (more complicated models, regardless of what was selected by the cross-validation procedure in section 6.4.2, are not used) will be employed. In either case, the base + dose model is a special case of the base + dose + vacc model when the vaccine effects are the same. Thus, we can test if the specific vaccine information significantly improves the fit by using a likelihood ratio test. However, as with Section 4, whether there is a significant difference or not is not as important as how large the difference in effects is. To measure how large that difference is we use the Percent of Variance Explained (PVE) as was done in Section 6.5, except now the base + dose model replaces the base model and the base + dose + vacc model replaces the base + dose model. Inferences on the PVE will use bias-adjusted nonparametric bootstrap (with 5000 replicates) as in Section 6.5. If bias-adjusted bootstrap confidence intervals were not able to be calculated, then percentile confidence intervals were used.

Numeric viral load

Table 6.6.1: Differential Vaccine Effect - Numeric Viral Load

	log MN 2 weeks prior challenge	log MN day challenge	log MSD ECL 2 weeks prior challenge	log MSD ECL day challenge	log PsVNA ID50 2 weeks prior challenge	log PsVNA ID50 day challenge	log PsVNA ID80 2 weeks prior challenge	log PsVNA ID80 day challenge
AUC BAL N1	100 (91.74, 100)	100 (94.76, 100)	99.69 (97.03, 100)	100 (96.65, 100)	100 (94.26, 100)	100 (91.21, 100)	100 (96.06, 100)	100 (91.28, 100)
AUC BAL Subgenomic	100 (78.18, 100)	100 (85.35, 100)	100 (92.53, 100)	100 (89.14, 100)	100 (80.44, 100)	100 (77.44, 100)	100 (91.55, 100)	100 (80.72, 100)
AUC Nasal Swab N1	89.86 (75.61, 96.63)	85.06 (69.31, 95.32)	91.05 (79.13, 98.27)	91.77 (80.37, 98.65)	92.81 (82.34, 100)	90.33 (78.05, 98.67)	88.64 (75.57, 96.79)	86.79 (70.37, 95.41)
AUC Nasal Swab Subgenomic	97.87 (94.8, 100)	94.69 (88.5, 100)	96.3 (90.6, 100)	98.7 (95.62, 100)	94.47 (87.22, 100)	93.69 (85.23, 100)	93.76 (87.16, 100)	92.82 (83.96, 99.31)
AUC OP Swab N1	62.83 (20.39, 94.46)	63.37 (23.24, 94.45)	62.76 (23.17, 92.17)	59.21 (22.23, 89.69)	64.81 (27.47, 96.84)	63.17 (29.18, 92.12)	60.29 (22.94, 91.81)	63.29 (22.9, 93.11)
AUC OP Swab Subgenomic	41.85 (2.61, 93.53)	40.35 (5.3, 89.27)	38.19 (4.21, 83.39)	38.5 (4.33, 86.64)	41.22 (8.73, 93.63)	36.39 (7.61, 49.76)	36.51 (5.62, 75.07)	37.77 (4.81, 83.29)
log VL Day2 PostChallenge BAL N1	94.21 (84.34, 100)	92.97 (84.46, 100)	98.22 (95.09, 100)	98.17 (95, 100)	95.56 (87.67, 100)	96.13 (89.78, 100)	94.47 (86.99, 100)	97.14 (90.6, 100)
log VL Day2 PostChallenge BAL Subgenomic	96.55 (90.56, 100)	100 (96.69, 100)	100 (97.57, 100)	100 (96.41, 100)	100 (91.95, 100)	100 (96.45, 100)	95.51 (90.35, 100)	97.84 (94.8, 100)
log VL Day2 PostChallenge OPswab N1	100 (90.49, 100)	100 (79.1, 100)	100 (83.49, 100)	100 (87.88, 100)	100 (93.28, 100)	100 (97.09, 100)	100 (93.68, 100)	100 (86.2, 100)
log VL Day2 PostChallenge OPswab Subgenomic	100 (89.3, 100)	100 (85.04, 100)	100 (81, 100)	100 (89.66, 100)	100 (81.74, 100)	95.4 (83.79, 100)	100 (86.3, 100)	100 (84.43, 100)
log VL Day2 PostChallenge NasalSwab N1	100 (93.04, 100)	95.62 (90.18, 100)	100 (96.76, 100)	100 (96.05, 100)	100 (89.64, 100)	92.97 (79.9, 100)	100 (95.38, 100)	100 (96.83, 100)
log VL Day2 PostChallenge NasalSwab Subgenomic	100 (95.4, 100)	92.81 (85.13, 100)	100 (98.08, 100)	100 (97.76, 100)	98.18 (92.66, 100)	89.57 (75.55, 96.5)	97.86 (93.74, 100)	95.5 (89.26, 100)

Binary viral load

Table 6.6.2: Differential Vaccine Effect - Binary Viral Load

	log MN 2 weeks prior challenge	log MN day challenge	log MSD ECL 2 weeks prior challenge	log MSD ECL day challenge	log PsVNA ID50 2 weeks prior challenge	log PsVNA ID50 day challenge	log PsVNA ID80 2 weeks prior challenge	log PsVNA ID80 day challenge
bin VL Day2 PostChallenge BAL N1	70.12 (0, 100)	34.54 (0, 100)	74.79 (0, 100)	100 (55.33, 100)	5.63 (0, 100)	100 (0, 100)	5.35 (0, 100)	0 (0, 100)
bin VL Day2 PostChallenge BAL Subgenomic	88.83 (65.27, 100)	94.96 (77.04, 100)	100 (71.76, 100)	78.06 (0, 100)	100 (71.26, 100)	87.82 (31.28, 100)	97.96 (78.45, 100)	100 (80.78, 100)
bin VL Day2 PostChallenge OPswab N1	88.78 (0, 100)	22.81 (0, 73.31)	88.47 (0, 100)	100 (20.19, 100)	30.9 (0, 85.75)	2.12 (0, 64.74)	20.41 (0, 55.4)	9.9 (0, 64.8)
bin VL Day2 PostChallenge OPswab Subgenomic	97.32 (0, 100)	100 (0, 100)	100 (0, 100)	100 (0, 100)	97.03 (0, 100)	100 (54.6, 100)	100 (24.9, 100)	100 (0, 100)
bin VL Day2 PostChallenge NasalSwab N1	0 (0, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)	0 (0, 100)	100 (100, 100)	0 (0, 100)	8.92 (0, 100)
bin VL Day2 PostChallenge NasalSwab Subgenomic	100 (64.68, 100)	43.7 (0, 57.29)	100 (45.6, 100)	100 (32.48, 100)	100 (51.89, 100)	66.17 (0, 100)	44.04 (0, 58.72)	28.69 (0, 51.51)