

CoP SAP 6.3

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6.3 Dose-Response Effects of Vaccine Product on Virus Specific Antibody or Viral Load

The expectation is that there will be a significant dose-response effect for both the virus-specific antibodies and the viral load. For each virus-specific antibody or viral load, a test for a dose response will be performed. Since each vaccine product will have its own set of dose dilutions, we define a separate dose score for each vaccine. Let D_{Aj} be the j^{th} dose for vaccine A, and let $D_{A,min}$ be the minimum dose (i.e., the most diluted dose) of vaccine A, then the corresponding dose score is:

$$d_{Aj} = \log_{10}\left(\frac{10 * D_{Aj}}{D_{A,min}}\right)$$

Thus, the dose score associated with the minimum dose will always be 1, and the dose 10 times larger will be 2, etc. We define the dose score for the placebo group to be 0, which is functionally equivalent to a 10-fold dilution of the minimum dose for each vaccine. Most vaccines will be given as two immunizations. For those animals that are given as only 1 immunization, we will define two vaccine scores: (1) same as above (i.e., animals that are given 1 immunization of dose x, will have the same dose score as animals that have 2 immunizations [prime+boost] of dose x), or (2) the values associated with one scheduled immunization have their dose divided by 2 (because the cumulative dose is half as much as those that get two scheduled immunizations). Alternatively, some analyses may leave out animal groups that only received one immunization.

For the remainder of this report, the dose score calculated in the normal way will be referred to as the “original dose score”, and the dose score where the single dose group has the dose divided by 2 will be referred to as the “single dose halved dose score”.

Initially, within each vaccine product a Spearman correlation (i.e., rank correlation) of the dose score with the virus-specific antibody or viral load will be performed. This is a check that the virus-specific antibody and viral load are associated with vaccine dose in a monotonic way. Then, the overall Spearman correlation with all vaccine product and the placebo arms included will be done.

We graphically plot the virus specific antibody and viral load by dose score, with geometric means and 95% confidence intervals within each dose score/vaccine product group, using the original dose score.

Next we fit a linear model on the log of the viral load, where the model for the mean will include an intercept, and the dose scores are treated as numeric allowing a different dose parameter for each vaccine product. This model will allow a calibration of each dose score to its vaccine product. Let y_{jk} , v_{jk} , and d_{jk} , be the numeric viral load, vaccine product, and dose score, respectively for the k^{th} animal in the j^{th} vaccine dose group (where a vaccine dose group is defined by a row in Table 1, except placebos that are all combined). Then the model is:

$$\log_{10}(y_{jk}) = \beta_0 + \beta_1 d_{jk} I(v_{jk} = A) + \beta_2 d_{jk} I(v_{jk} = B) + \beta_3 d_{jk} I(v_{jk} = C) + \beta_4 d_{jk} I(v_{jk} = D)$$

where $I(S) = 1$ if statement S is true, and 0 otherwise.

This will be fit with a generalized estimating equation (GEE) model with the data clustered by challenge day groupings (see groups defined in Table 3) using a working independence variance model. Because the GEE model uses a sandwich estimator of variance, it allows for misspecification of the model. Typically, the GEE

models are presumed as misspecifying the variance with a “working variance” model; however, sandwich estimators also work for misspecifying the mean (see e.g., White, 1996). For example, if the models for the CoR predicting the viral load are similar but slightly different for different vaccine product, then the model without vaccine product information will be misspecified and will measure a kind of average effect. Because GEE methods are typically anti-conservative, inferences adjusted for small samples will be made using the `saws` R package with the default method (Fay and Graubard, 2001).

A: Janssen

B: Moderna

C: Novavax

D: Sanofi

For binary variables, when possible (i.e., when not all of the binary responses are the same), within each vaccine product a dose-response will be evaluated by a Wilcoxon-Mann-Whitney (WMW) test comparing the dose score of animals with a positive signal to those with a negative signal. NA is indicated when the binary responses are the same. Then, the overall MW test with all vaccine product and the placebo arms included will be done.

We graphically plot the virus-specific antibody for each vaccine product, stratified by animals with a positive signal and animals with a negative signal.

As a combined analysis, a GEE logistic regression will be used when possible. The linear predictor portion of the model will be the same as numeric viral load. The model will be fit with a GEE model with the data clustered by challenge day groupings using a working independence variance model and the `saws` adjustment for small samples as with numeric viral load.

Dose Response on Virus Specific Antibody

Correlations

By Vaccine Product

Table 6.3.1: Spearman Correlation of Dose Score with Virus Specific Antibody By Vaccine

	Janssen Original Dose Score	Janssen Single Dose Halved Dose Score	Janssen Single Dose Removed	Moderna	Novavax	Sanofi
log MN 2 weeks prior challenge	0.43 (0.09, 0.68)	0.55 (0.25, 0.75)	-0.43 (-0.83, 0.27)	0.81 (0.62, 0.91)	0.34 (-0.06, 0.64)	0.31 (-0.09, 0.62)
log MN day challenge	0.33 (-0.02, 0.61)	0.46 (0.13, 0.7)	0.37 (-0.34, 0.81)	0.76 (0.53, 0.89)	0.32 (-0.08, 0.63)	0.15 (-0.25, 0.51)
log MSD ECL 2 weeks prior challenge	0.53 (0.22, 0.74)	0.64 (0.38, 0.81)	0.43 (-0.28, 0.83)	0.85 (0.69, 0.93)	0.17 (-0.23, 0.52)	0.52 (0.16, 0.75)
log MSD ECL day challenge	0.57 (0.28, 0.77)	0.63 (0.37, 0.8)	0 (-0.63, 0.63)	0.86 (0.71, 0.93)	0.24 (-0.16, 0.58)	0.6 (0.28, 0.8)
log PsVNA ID50 2 weeks prior challenge	0.42 (0.08, 0.67)	0.57 (0.27, 0.76)	0.5 (-0.19, 0.86)	0.8 (0.59, 0.9)	0.17 (-0.23, 0.52)	0.35 (-0.05, 0.65)
log PsVNA ID50 day challenge	0.46 (0.13, 0.7)	0.6 (0.31, 0.78)	0.43 (-0.28, 0.83)	0.74 (0.49, 0.87)	0.28 (-0.12, 0.6)	0.33 (-0.06, 0.64)
log PsVNA ID80 2 weeks prior challenge	0.6 (0.31, 0.78)	0.71 (0.47, 0.85)	0.57 (-0.1, 0.88)	0.81 (0.62, 0.91)	0.21 (-0.2, 0.55)	0.43 (0.05, 0.7)
log PsVNA ID80 day challenge	0.63 (0.37, 0.81)	0.74 (0.52, 0.86)	0.5 (-0.19, 0.86)	0.84 (0.67, 0.93)	0.27 (-0.13, 0.59)	0.39 (0, 0.67)

Overall

Table 6.3.2: Spearman Correlation of Dose Score with Virus-Specific Antibody Overall

	Original Dose Score	Single Dose Halved Dose Score	Single Dose Group Removed
log MN 2 weeks prior challenge	0.69 (0.58, 0.77)	0.7 (0.6, 0.78)	0.68 (0.56, 0.77)
log MN day challenge	0.65 (0.54, 0.74)	0.68 (0.57, 0.76)	0.66 (0.54, 0.76)
log MSD ECL 2 weeks prior challenge	0.7 (0.59, 0.78)	0.7 (0.59, 0.78)	0.72 (0.61, 0.8)
log MSD ECL day challenge	0.71 (0.62, 0.79)	0.71 (0.61, 0.79)	0.72 (0.61, 0.8)
log PsVNA ID50 2 weeks prior challenge	0.63 (0.51, 0.72)	0.63 (0.51, 0.72)	0.69 (0.57, 0.78)
log PsVNA ID50 day challenge	0.61 (0.49, 0.71)	0.61 (0.48, 0.71)	0.65 (0.53, 0.75)
log PsVNA ID80 2 weeks prior challenge	0.69 (0.59, 0.77)	0.7 (0.6, 0.78)	0.72 (0.61, 0.8)
log PsVNA ID80 day challenge	0.7 (0.59, 0.78)	0.7 (0.6, 0.78)	0.69 (0.57, 0.78)

Plots

Displayed below are geometric means and the corresponding 95% confidence intervals.

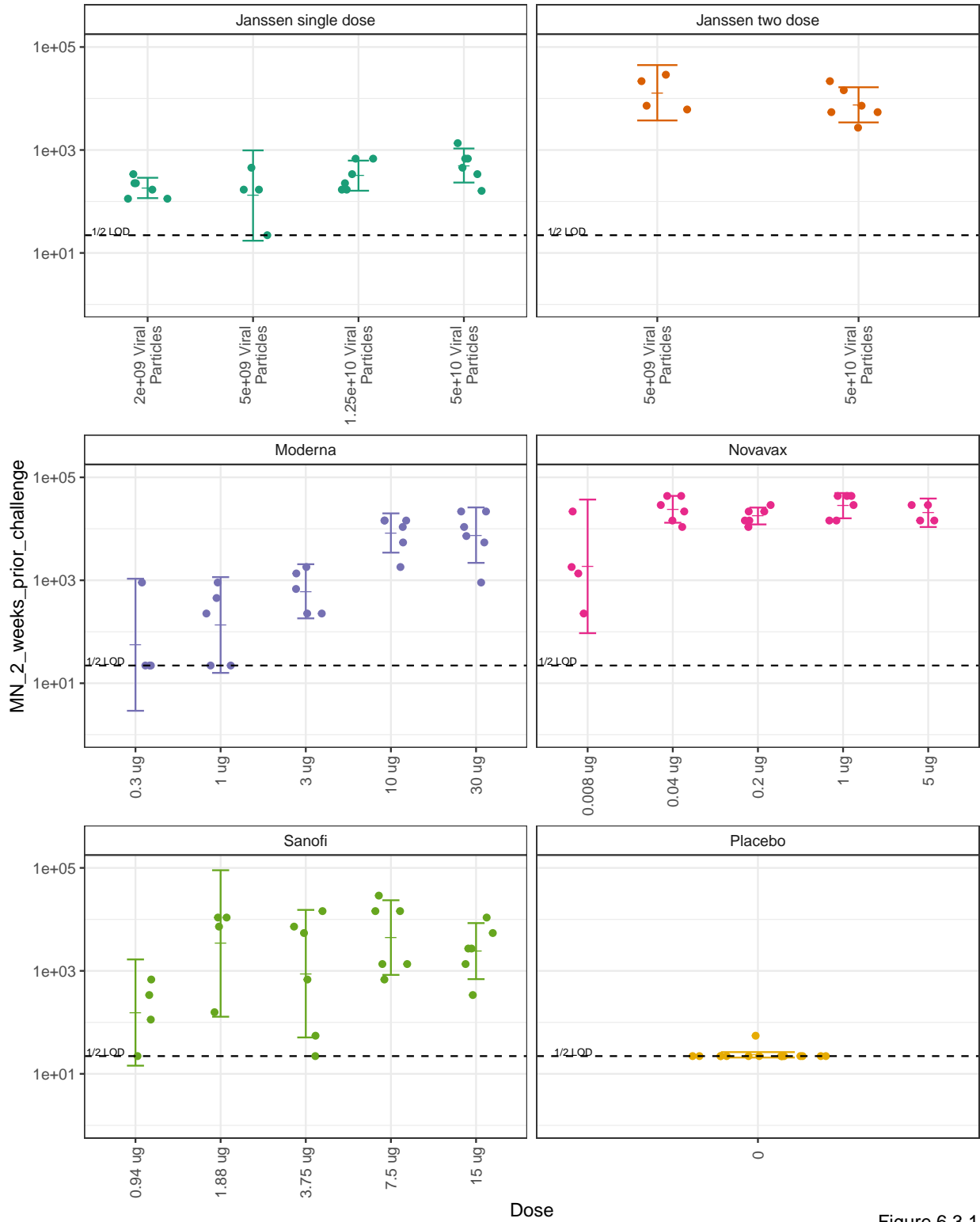


Figure 6.3.1

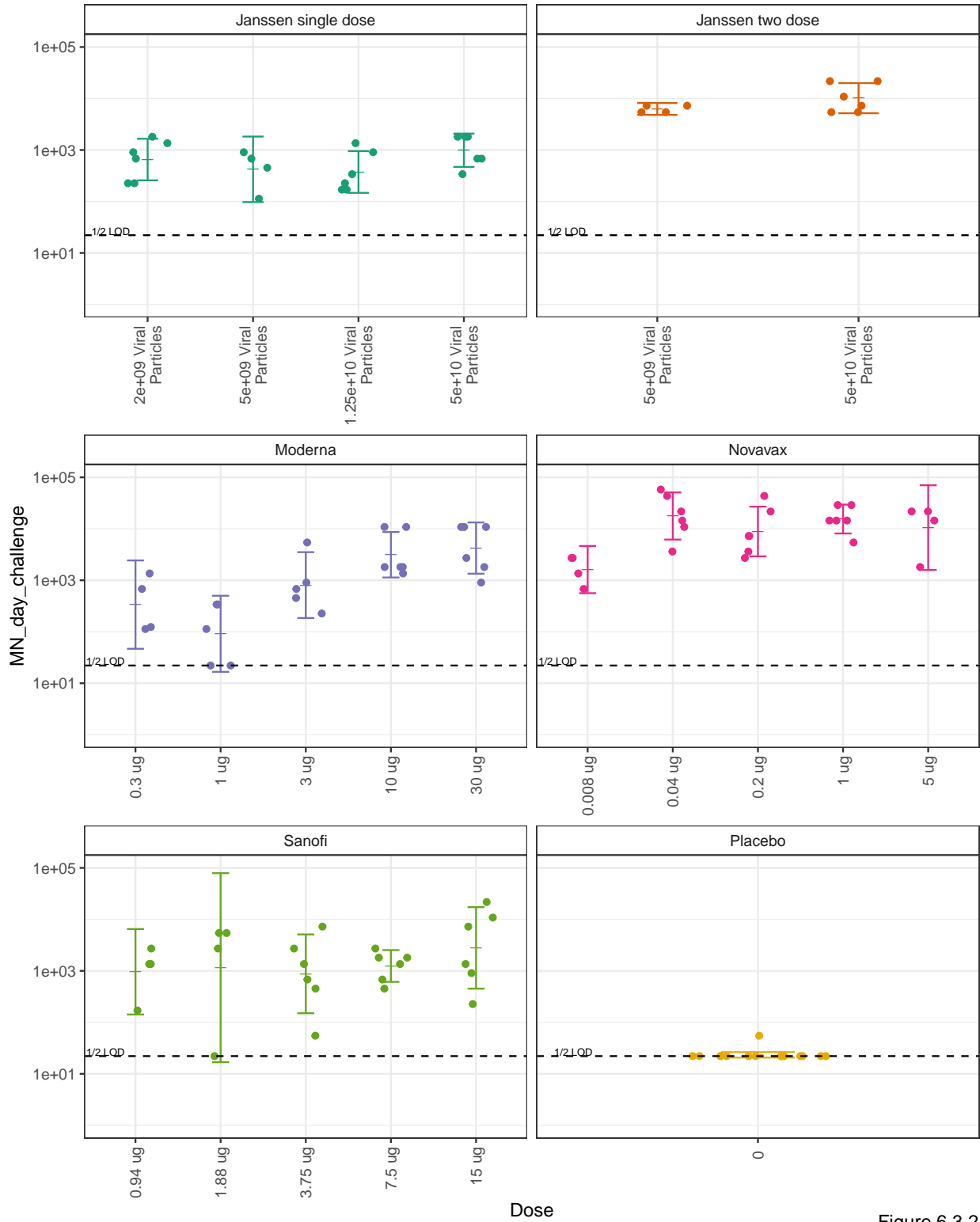


Figure 6.3.2

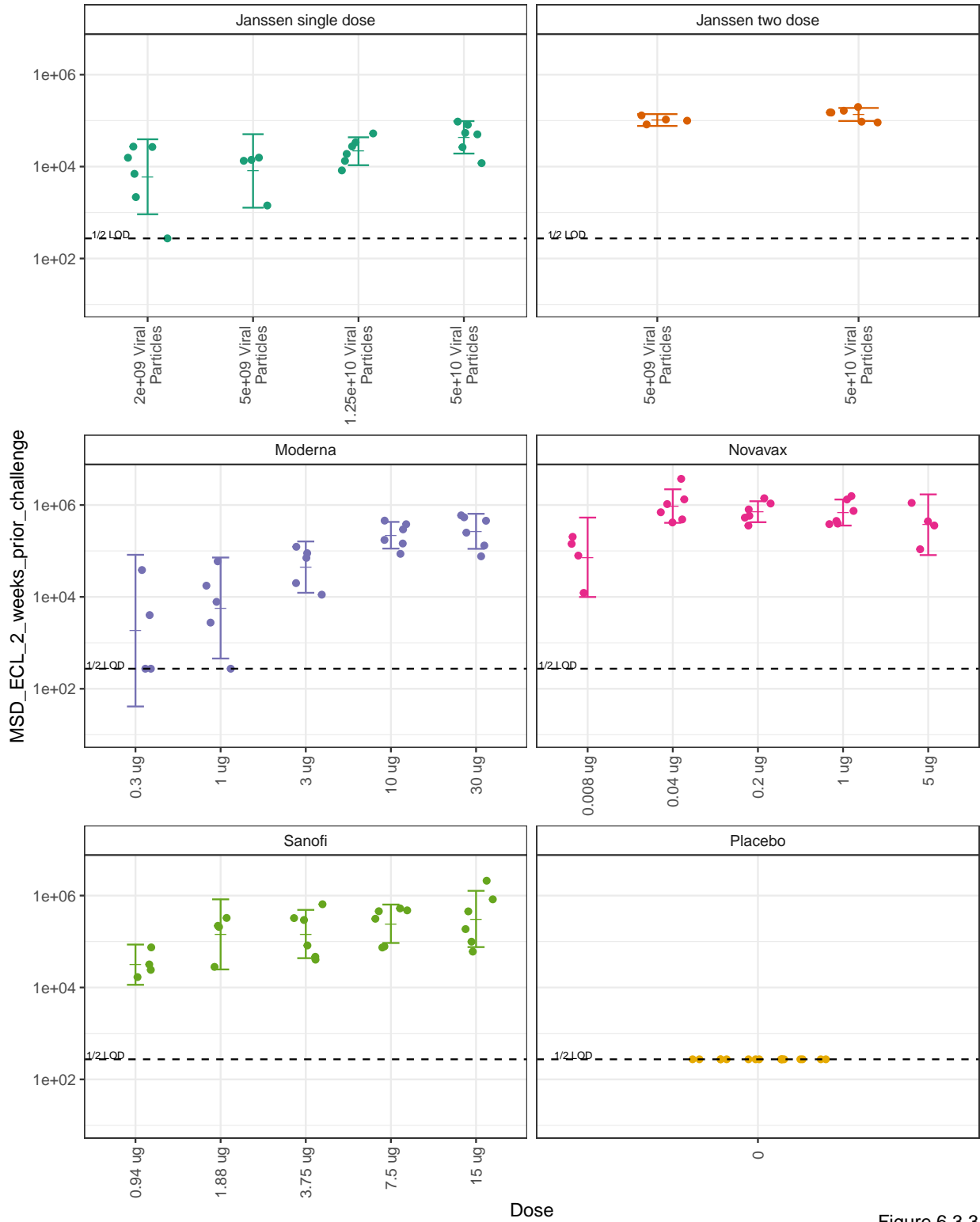


Figure 6.3.3

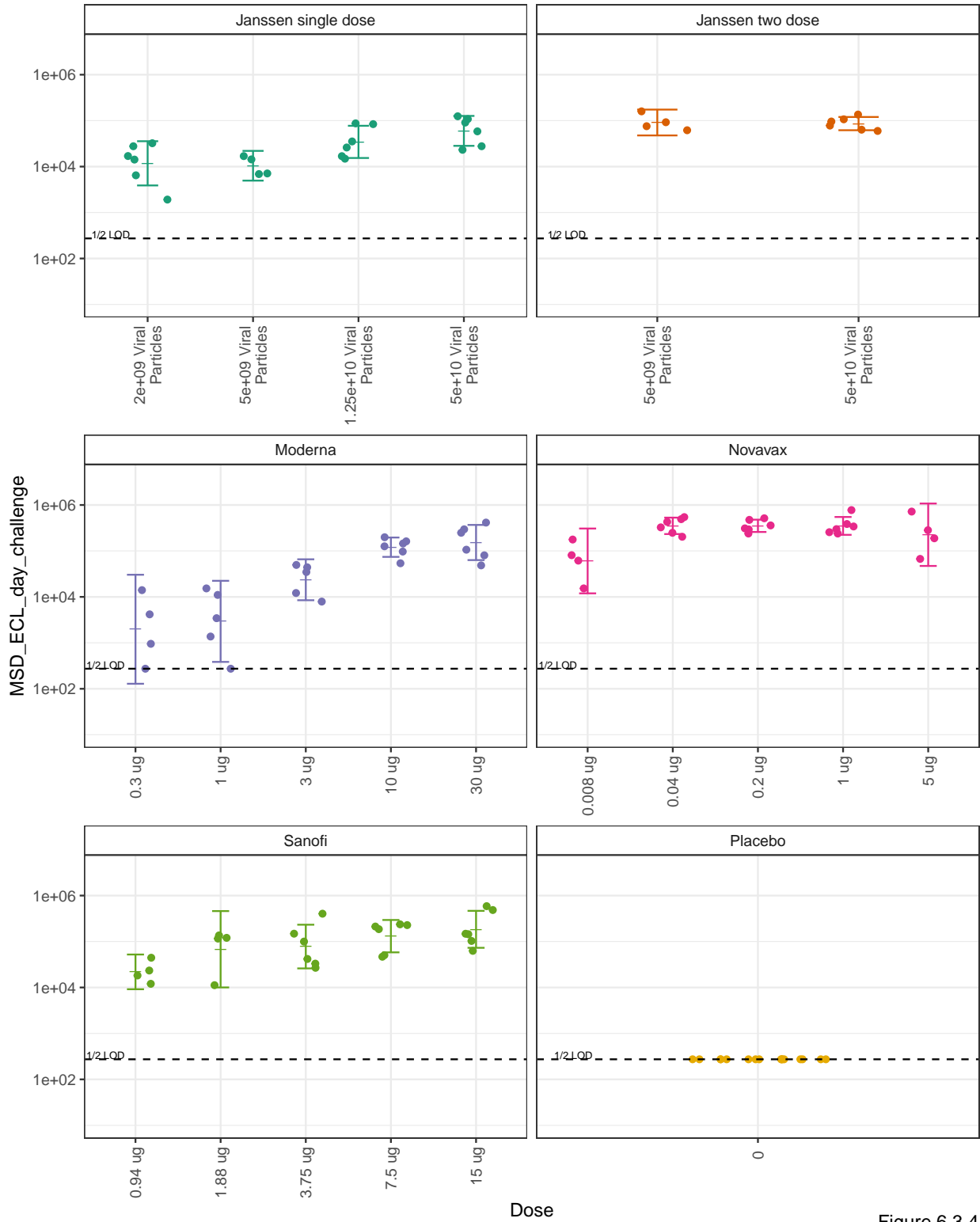


Figure 6.3.4

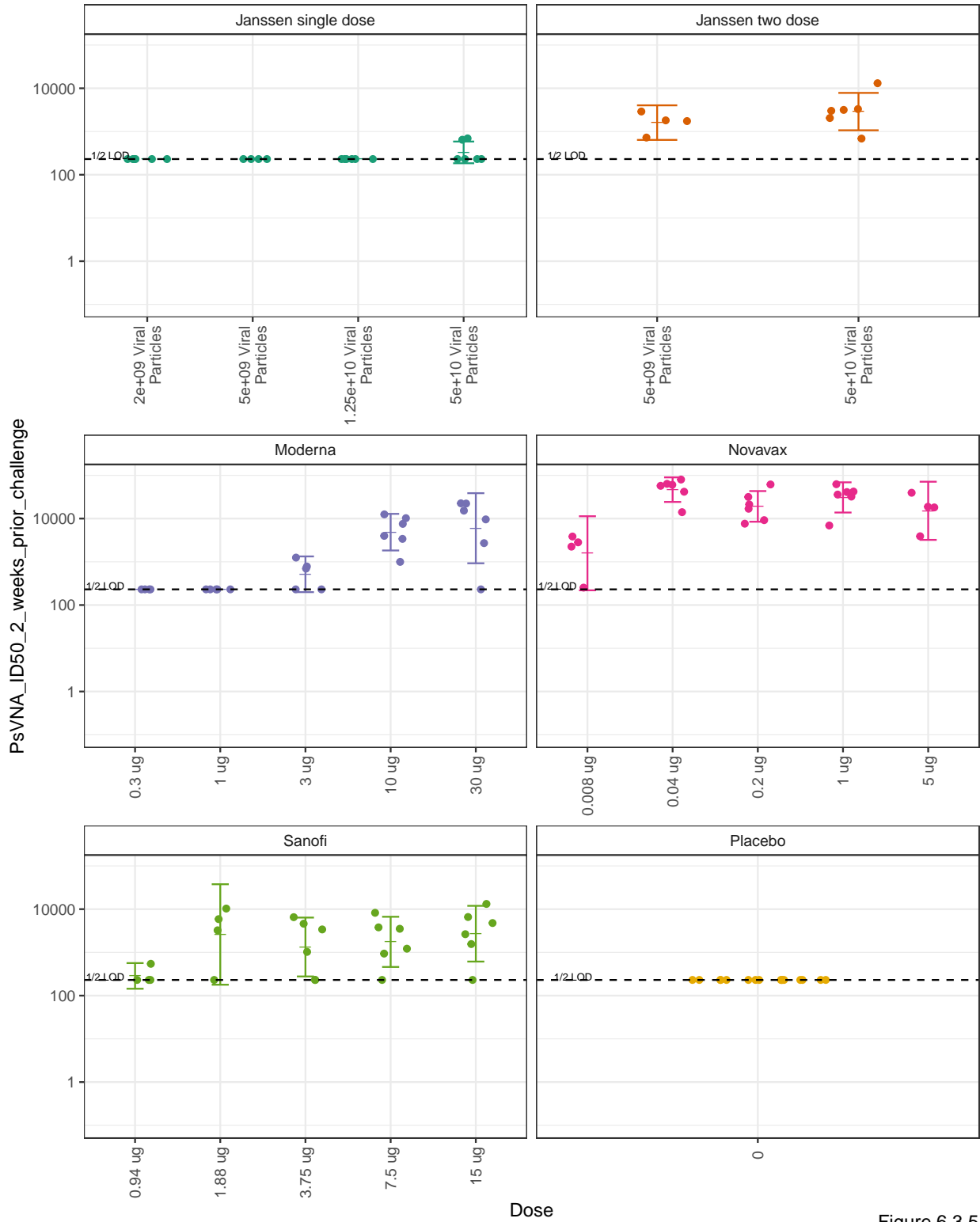


Figure 6.3.5

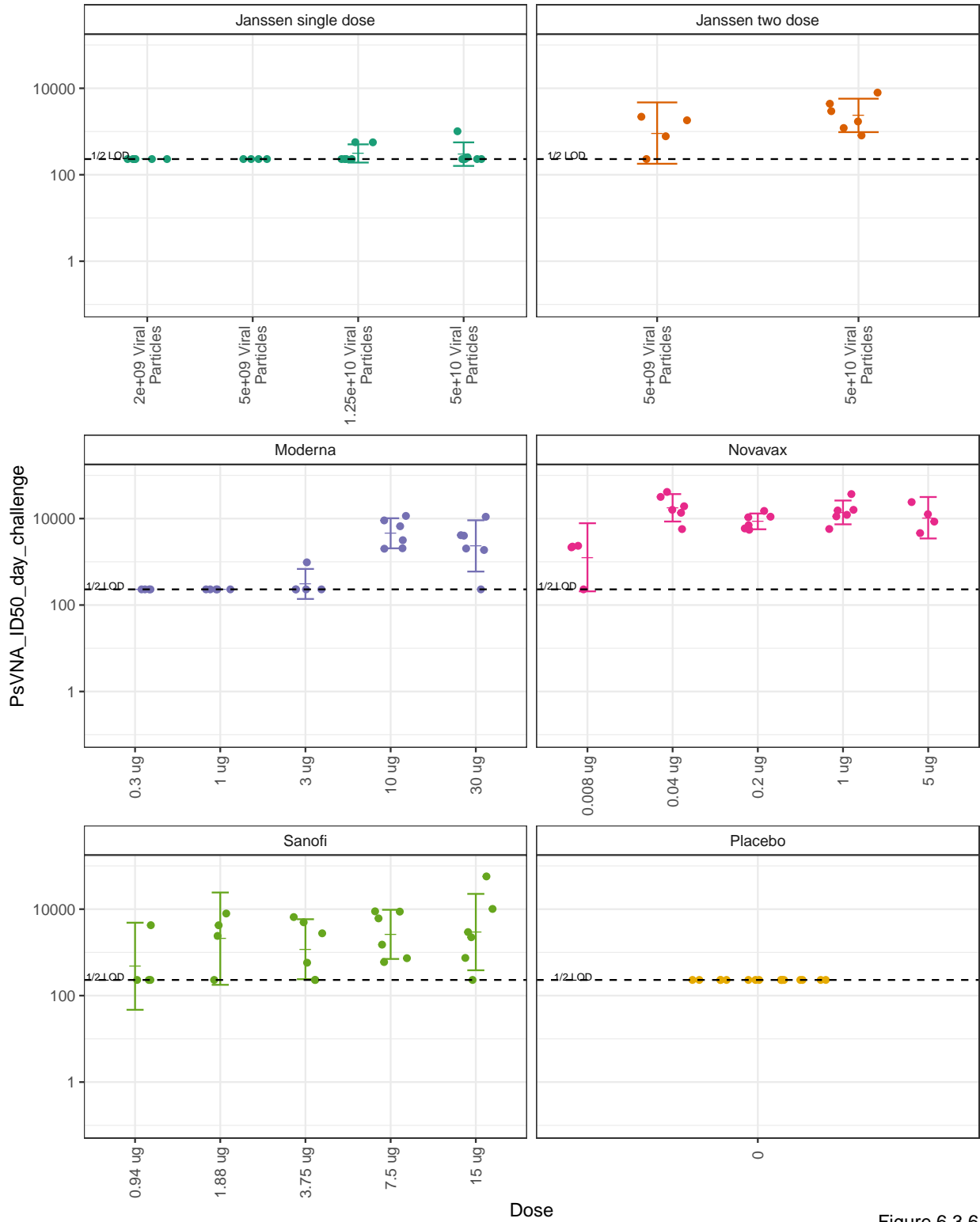


Figure 6.3.6

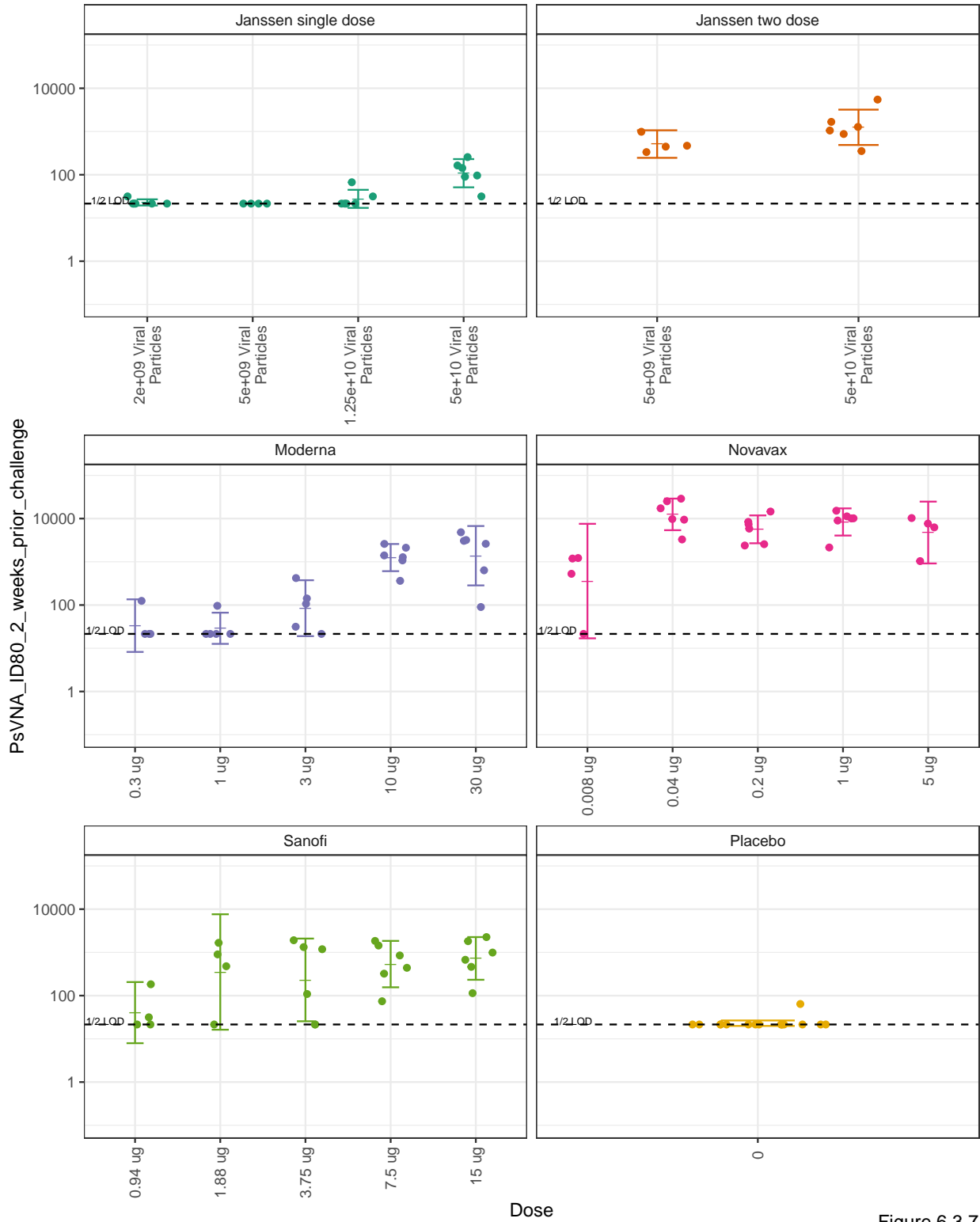


Figure 6.3.7

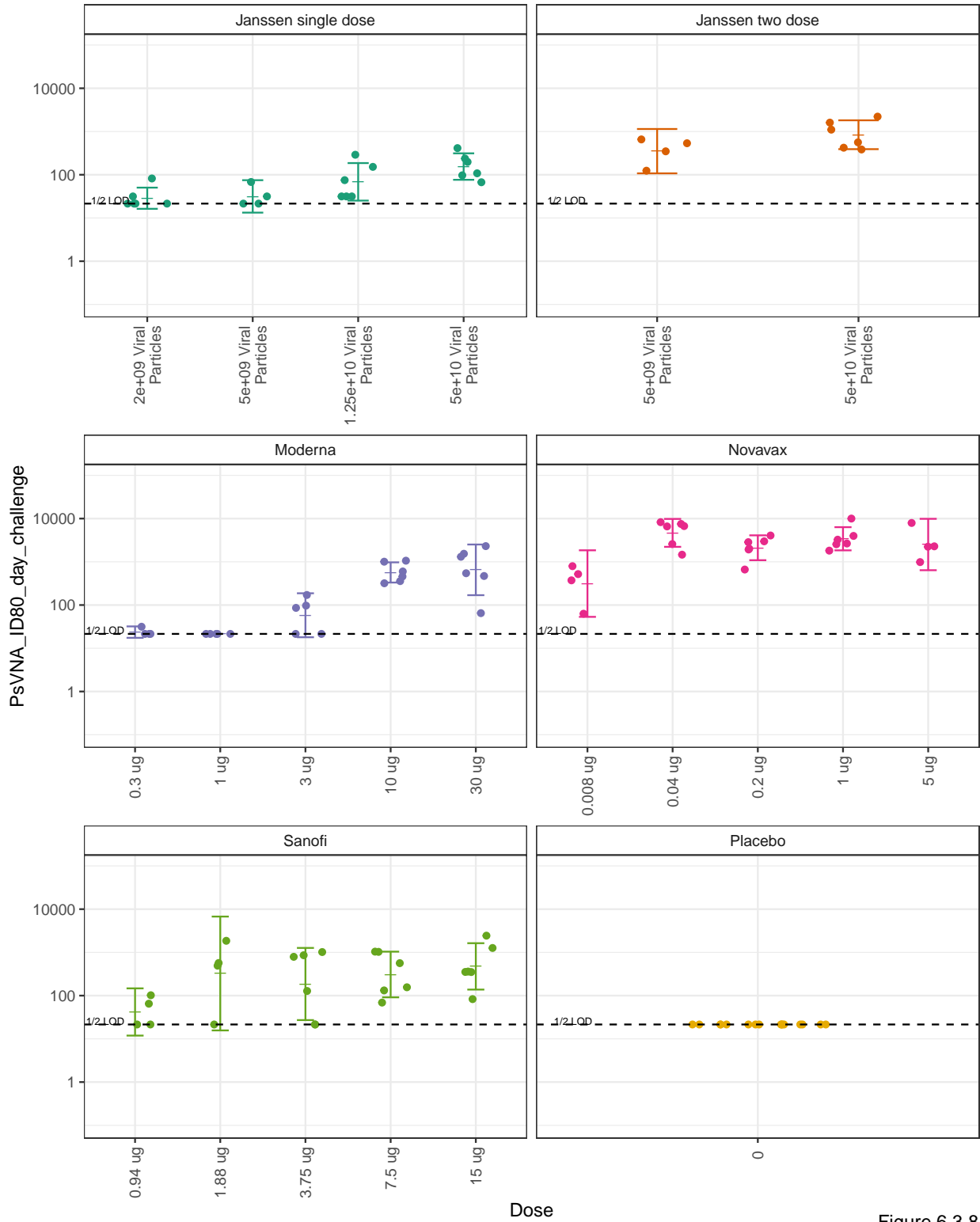


Figure 6.3.8

Dose Response on Viral Load - Numeric

Correlations

By Vaccine Product

Table 6.3.3: Spearman Correlation of Dose Score with Viral Load By Vaccine

	Janssen Original Dose Score	Janssen Single Dose Halved Dose Score	Janssen Single Dose Removed	Moderna	Novavax	Sanofi
AUC BAL N1	0 (-0.35, 0.35)	-0.09 (-0.42, 0.27)	0.11 (-0.56, 0.69)	-0.27 (-0.59, 0.14)	-0.1 (-0.47, 0.3)	-0.17 (-0.53, 0.23)
AUC BAL Subgenomic	0.1 (-0.25, 0.44)	0.04 (-0.31, 0.38)	0.23 (-0.47, 0.75)	-0.37 (-0.66, 0.02)	-0.09 (-0.46, 0.31)	-0.08 (-0.45, 0.32)
AUC Nasal Swab N1	-0.21 (-0.52, 0.15)	-0.28 (-0.57, 0.07)	-0.36 (-0.8, 0.35)	-0.54 (-0.77, -0.2)	-0.21 (-0.55, 0.2)	-0.26 (-0.59, 0.14)
AUC Nasal Swab Subgenomic	-0.22 (-0.53, 0.14)	-0.28 (-0.57, 0.08)	-0.21 (-0.74, 0.48)	-0.53 (-0.76, -0.19)	-0.23 (-0.57, 0.17)	-0.14 (-0.5, 0.26)
AUC OP Swab N1	-0.2 (-0.52, 0.15)	-0.26 (-0.56, 0.1)	-0.14 (-0.71, 0.54)	-0.34 (-0.64, 0.06)	-0.19 (-0.53, 0.22)	-0.19 (-0.54, 0.22)
AUC OP Swab Subgenomic	-0.27 (-0.56, 0.09)	-0.3 (-0.59, 0.06)	-0.14 (-0.71, 0.54)	-0.29 (-0.61, 0.11)	-0.09 (-0.46, 0.31)	-0.26 (-0.59, 0.14)
log VL Day2 PostChallenge BAL N1	0.24 (-0.12, 0.54)	0.16 (-0.2, 0.48)	0.11 (-0.56, 0.69)	-0.24 (-0.58, 0.17)	-0.03 (-0.41, 0.36)	-0.1 (-0.47, 0.3)
log VL Day2 PostChallenge BAL Subgenomic	0.17 (-0.19, 0.49)	0.11 (-0.24, 0.45)	0.23 (-0.47, 0.75)	-0.36 (-0.66, 0.04)	-0.11 (-0.48, 0.29)	-0.09 (-0.46, 0.31)
log VL Day2 PostChallenge OPswab N1	-0.02 (-0.37, 0.33)	-0.07 (-0.41, 0.28)	0.61 (-0.04, 0.89)	-0.18 (-0.53, 0.23)	-0.23 (-0.57, 0.17)	-0.23 (-0.57, 0.17)
log VL Day2 PostChallenge OPswab Subgenomic	-0.12 (-0.45, 0.24)	-0.19 (-0.5, 0.17)	0.76 (0.25, 0.94)	-0.28 (-0.6, 0.12)	-0.16 (-0.51, 0.24)	-0.32 (-0.63, 0.08)
log VL Day2 PostChallenge NasalSwab N1	-0.3 (-0.59, 0.06)	-0.42 (-0.67, -0.09)	0 (-0.63, 0.63)	-0.52 (-0.75, -0.16)	-0.17 (-0.52, 0.23)	-0.28 (-0.6, 0.12)
log VL Day2 PostChallenge NasalSwab Subgenomic	-0.26 (-0.56, 0.1)	-0.38 (-0.64, -0.04)	0.36 (-0.35, 0.81)	-0.5 (-0.74, -0.14)	-0.1 (-0.47, 0.3)	-0.33 (-0.63, 0.07)

Overall

Table 6.3.4: Spearman Correlation of Dose Score with Viral Load Overall

	Original Dose Score	Single Dose Halved Dose Score	Single Dose Group Removed
AUC BAL N1	-0.42 (-0.55, -0.26)	-0.43 (-0.56, -0.28)	-0.46 (-0.6, -0.29)
AUC BAL Subgenomic	-0.39 (-0.53, -0.23)	-0.4 (-0.54, -0.24)	-0.45 (-0.59, -0.28)
AUC Nasal Swab N1	-0.51 (-0.63, -0.37)	-0.52 (-0.64, -0.38)	-0.55 (-0.67, -0.4)
AUC Nasal Swab Subgenomic	-0.52 (-0.64, -0.38)	-0.53 (-0.64, -0.39)	-0.54 (-0.66, -0.38)
AUC OP Swab N1	-0.48 (-0.6, -0.33)	-0.48 (-0.61, -0.34)	-0.51 (-0.64, -0.35)
AUC OP Swab Subgenomic	-0.45 (-0.58, -0.3)	-0.45 (-0.58, -0.3)	-0.47 (-0.61, -0.3)
log VL Day2 PostChallenge BAL N1	-0.33 (-0.48, -0.17)	-0.34 (-0.49, -0.18)	-0.42 (-0.56, -0.24)
log VL Day2 PostChallenge BAL Subgenomic	-0.34 (-0.49, -0.18)	-0.36 (-0.5, -0.19)	-0.43 (-0.57, -0.25)
log VL Day2 PostChallenge OPswab N1	-0.25 (-0.4, -0.07)	-0.26 (-0.42, -0.09)	-0.24 (-0.42, -0.05)
log VL Day2 PostChallenge OPswab Subgenomic	-0.3 (-0.45, -0.13)	-0.31 (-0.46, -0.14)	-0.28 (-0.45, -0.09)
log VL Day2 PostChallenge NasalSwab N1	-0.55 (-0.66, -0.41)	-0.56 (-0.67, -0.43)	-0.57 (-0.68, -0.42)
log VL Day2 PostChallenge NasalSwab Subgenomic	-0.54 (-0.65, -0.4)	-0.56 (-0.67, -0.42)	-0.55 (-0.67, -0.4)

Plots

Displayed below are geometric means and the corresponding 95% confidence intervals.

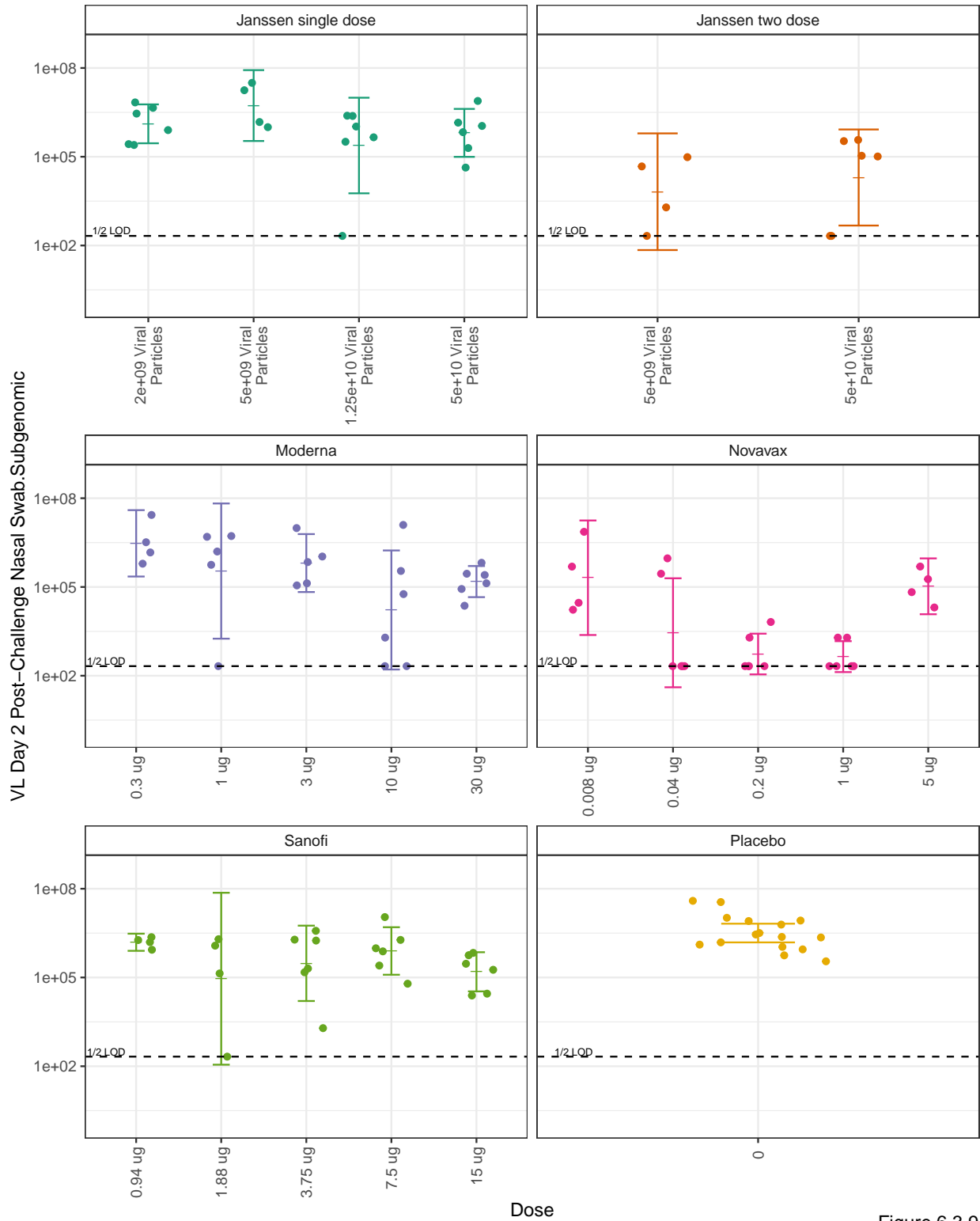
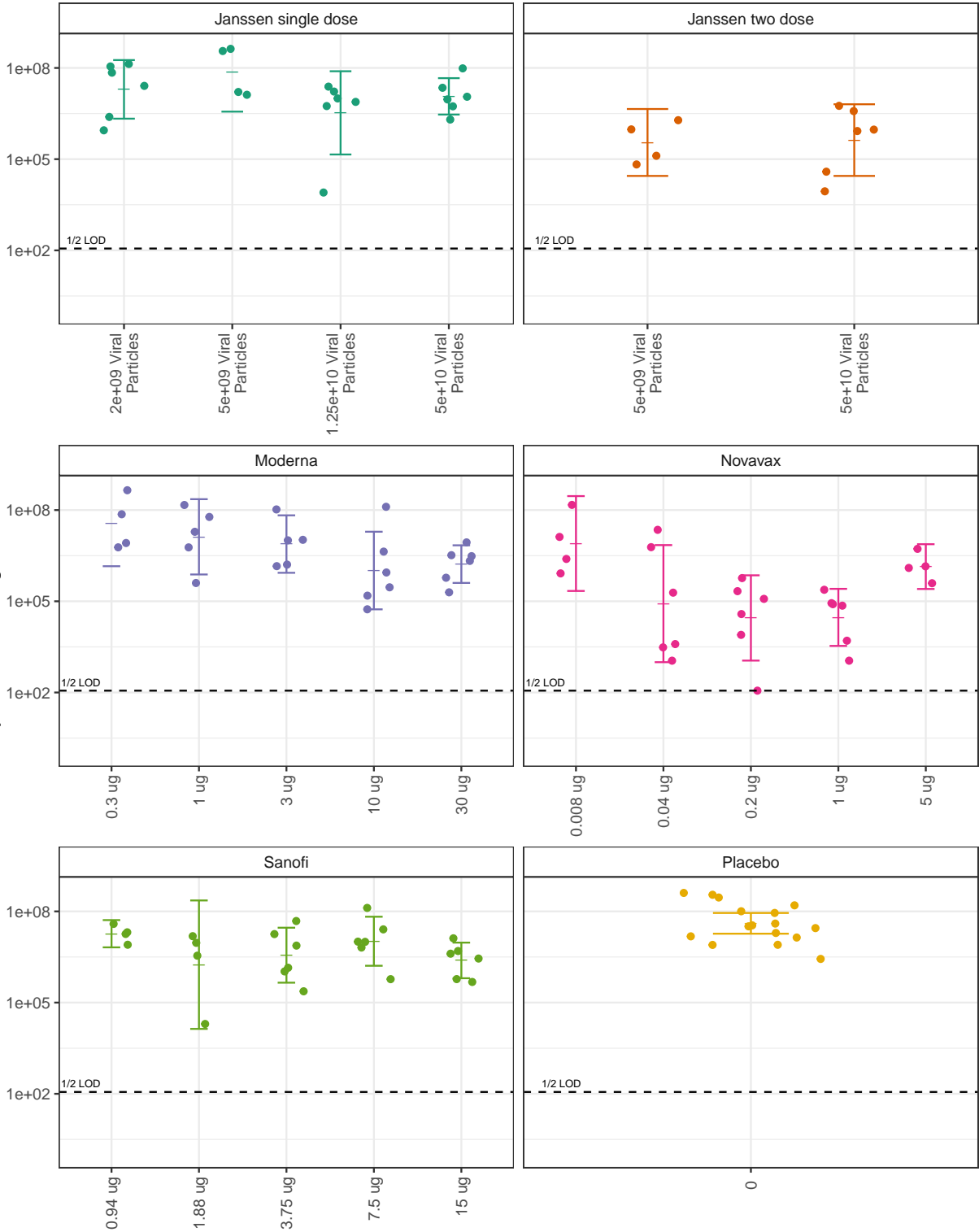


Figure 6.3.9

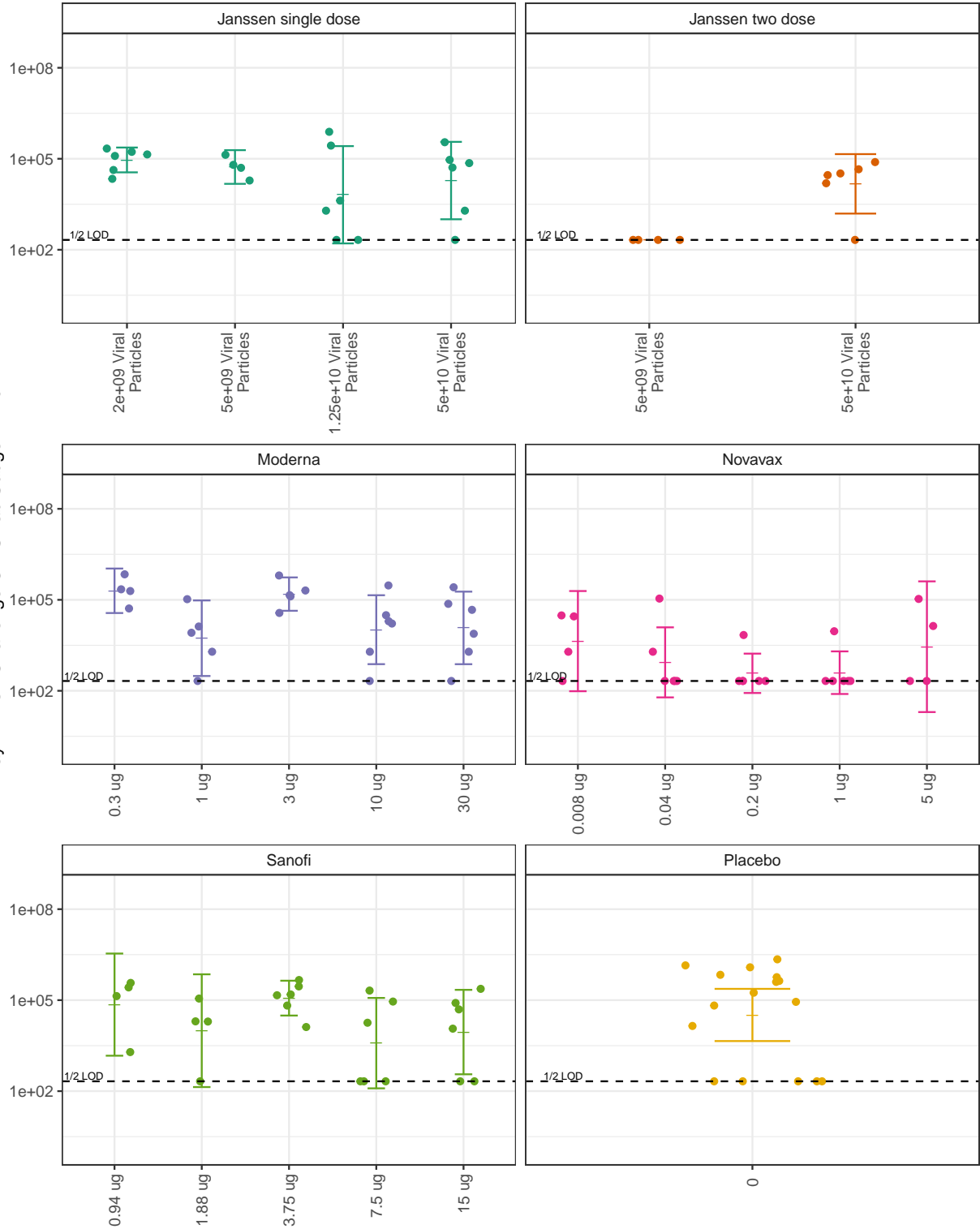
VL Day 2 Post-Challenge Nasal Swab, N1



Dose

Figure 6.3.10

VL Day 2 Post-Challenge OP Swab.Subgenomic



Dose

Figure 6.3.11

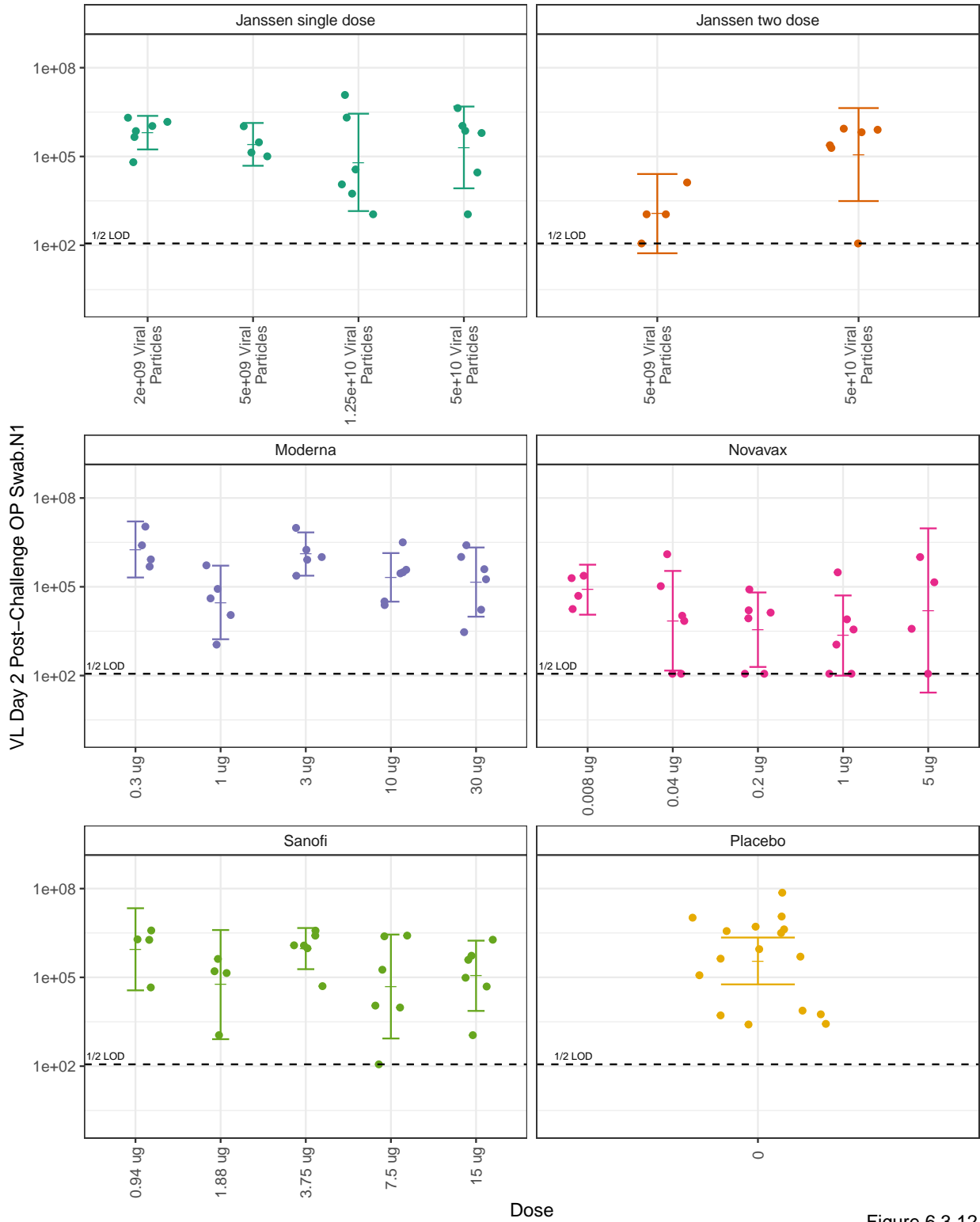


Figure 6.3.12

VL Day 2 Post-Challenge BAL: Subgenomic

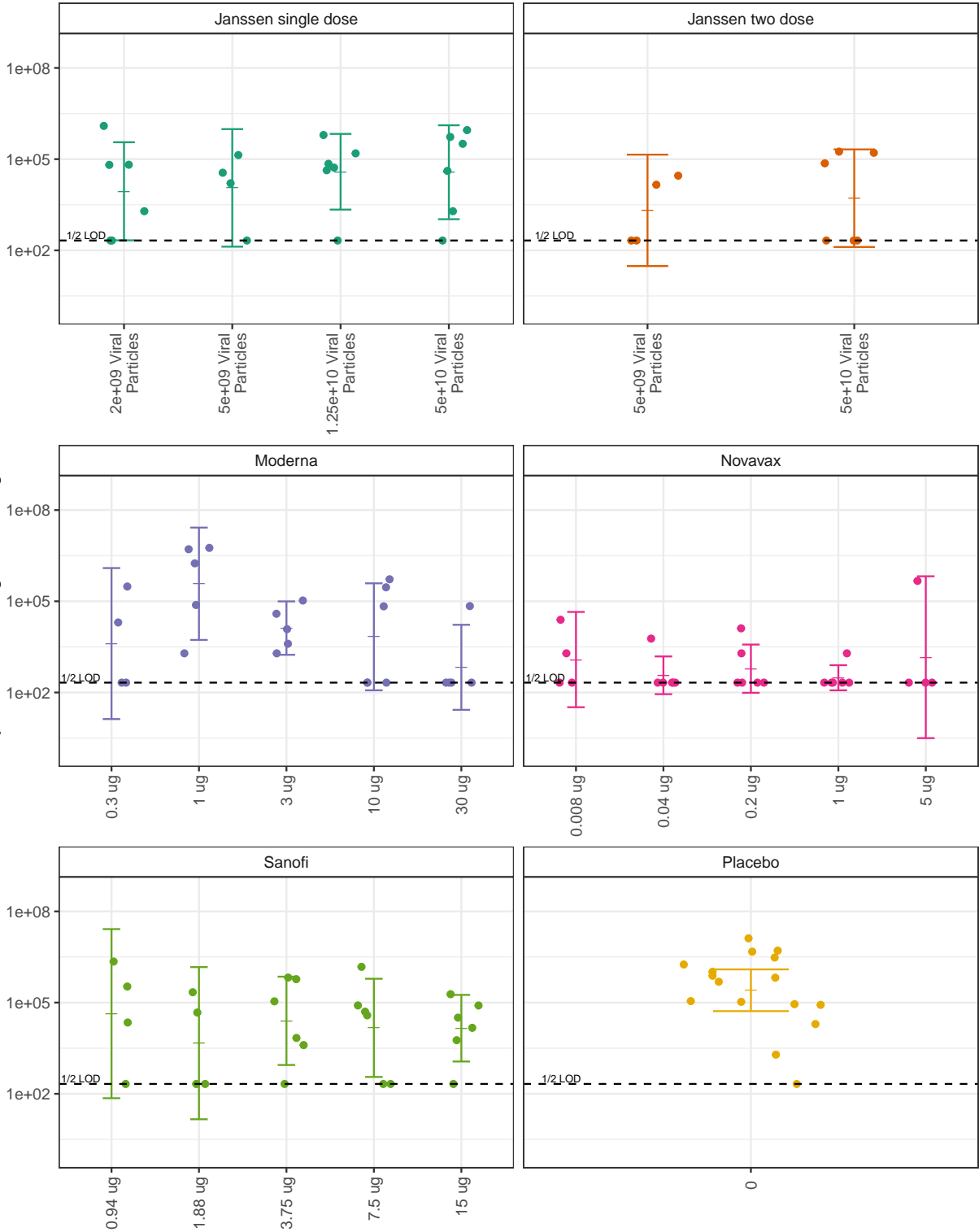


Figure 6.3.13

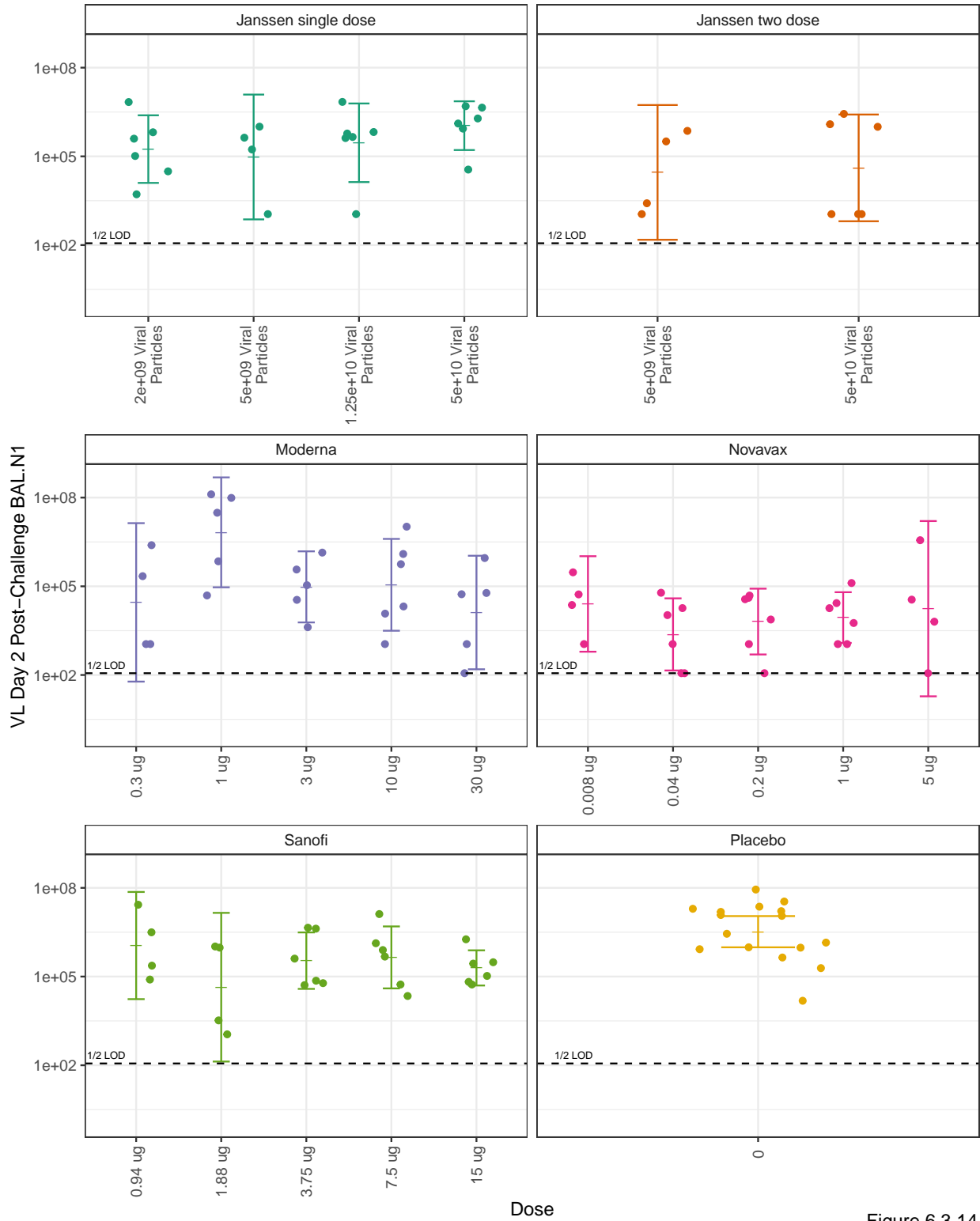


Figure 6.3.14

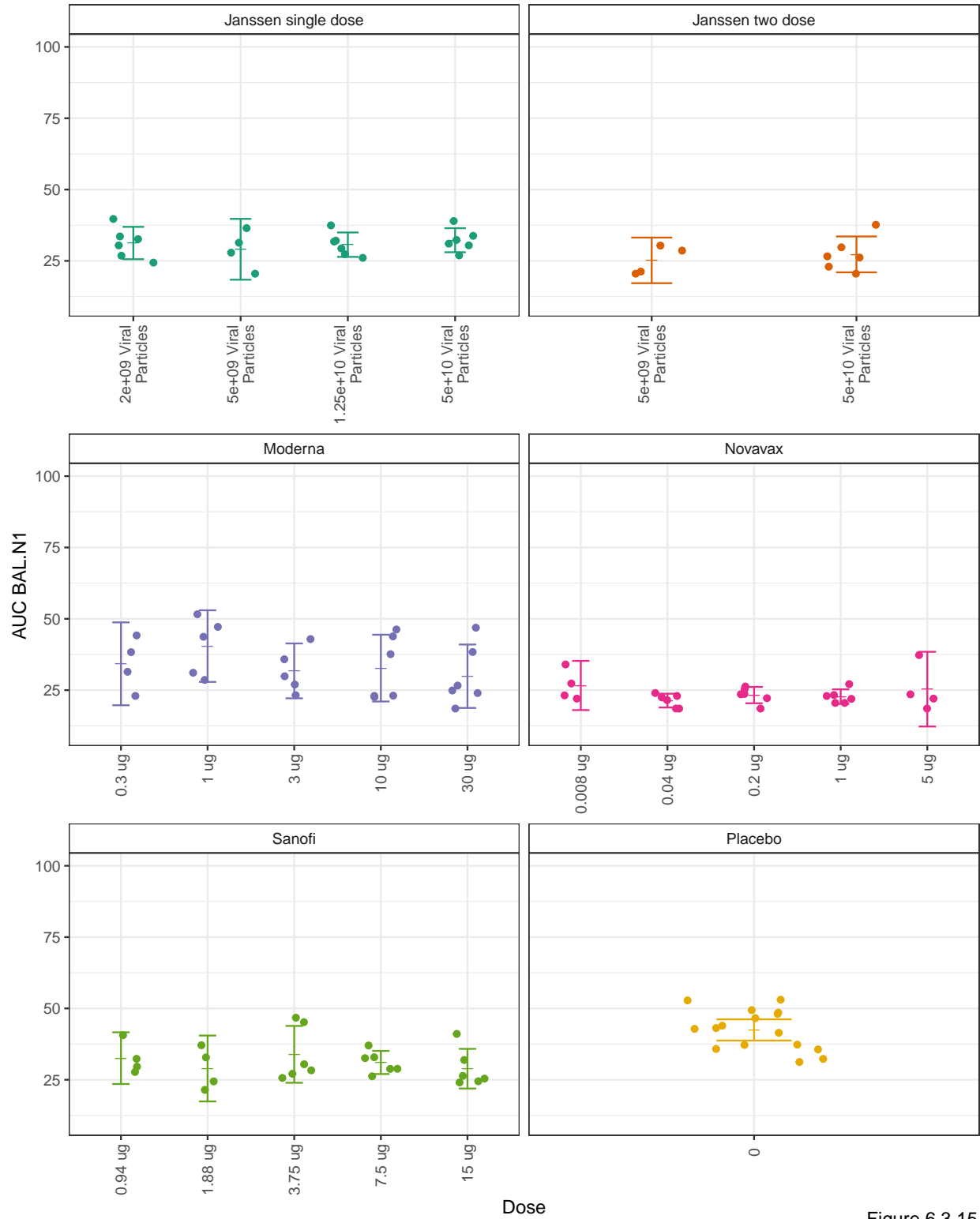


Figure 6.3.15

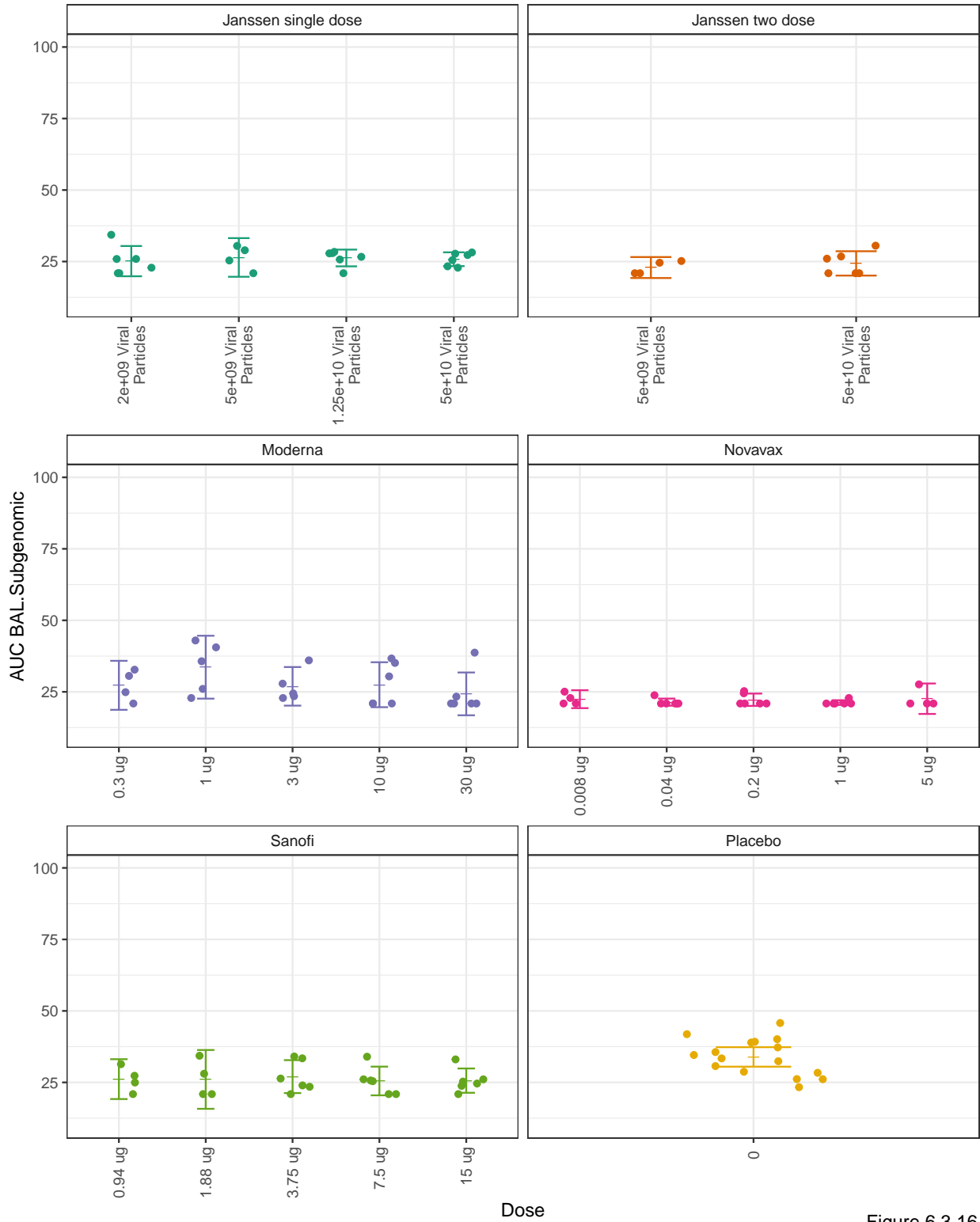


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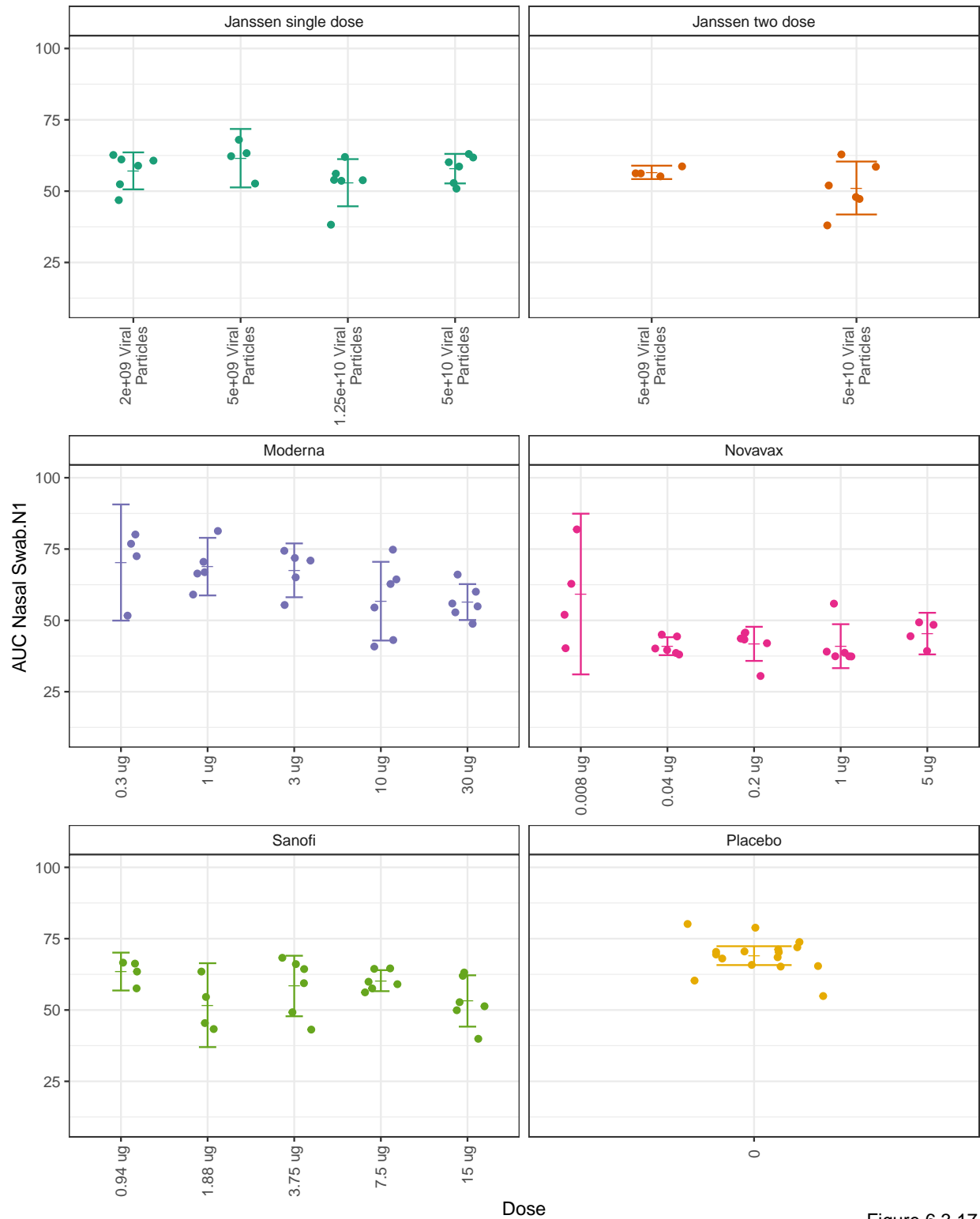


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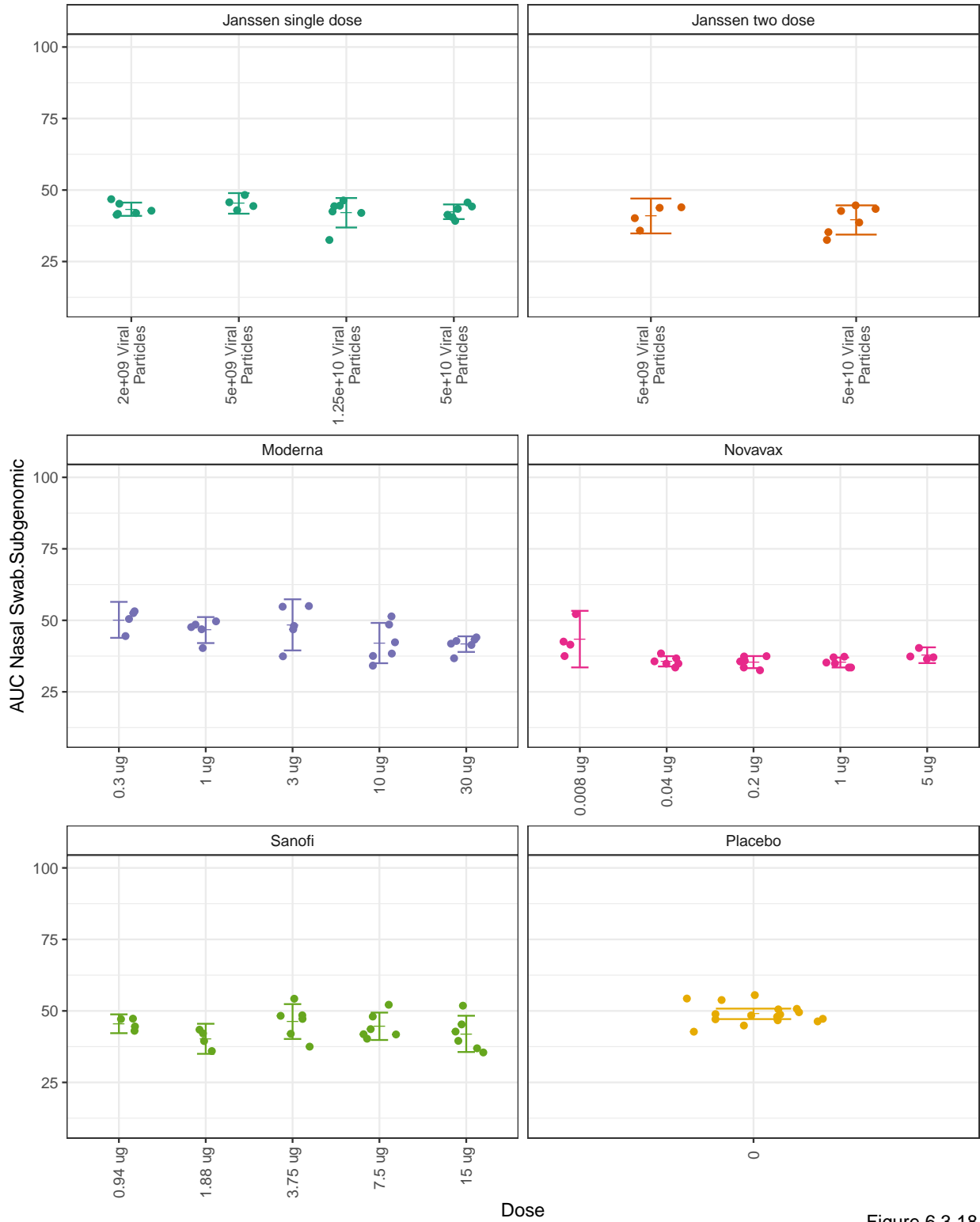


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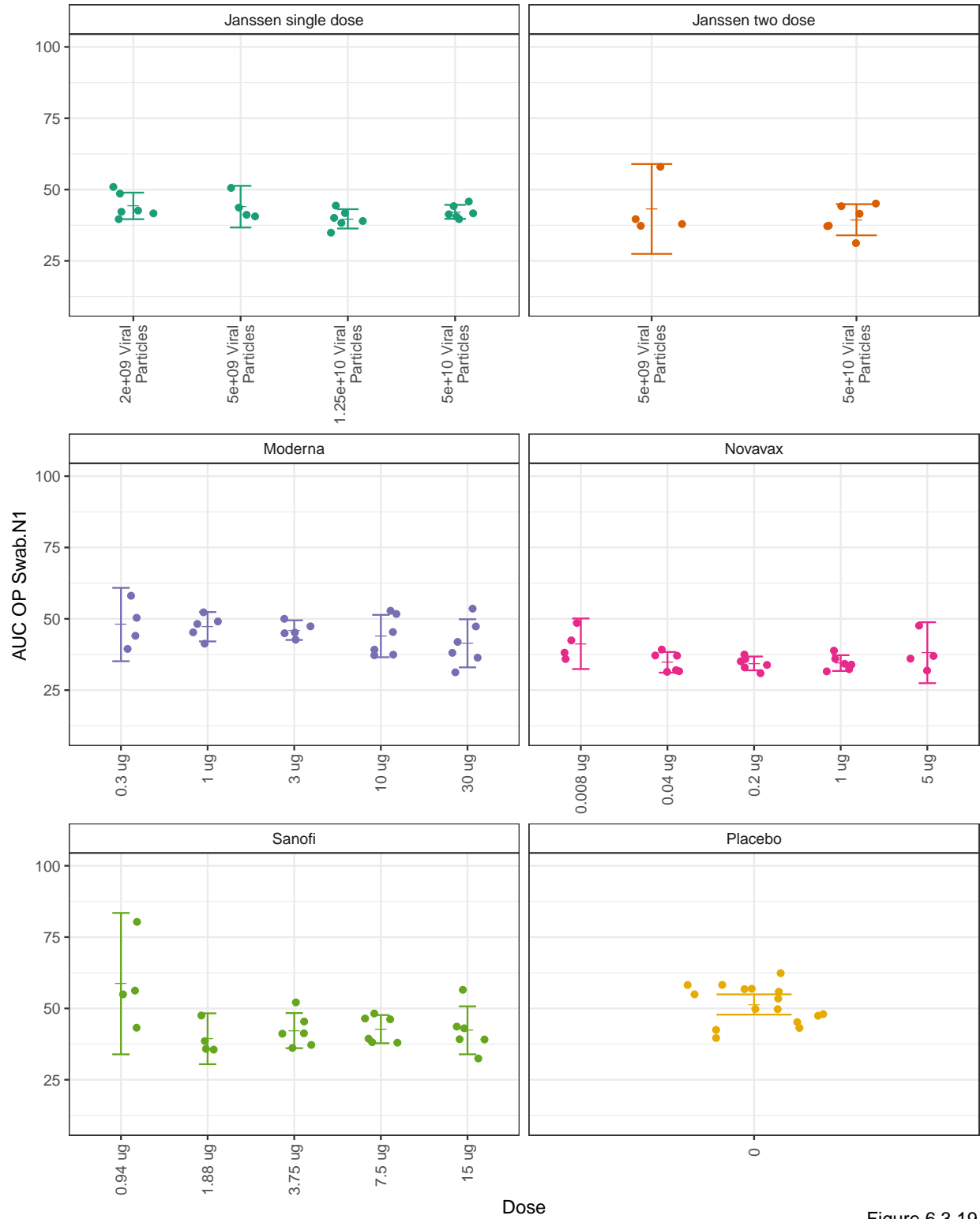


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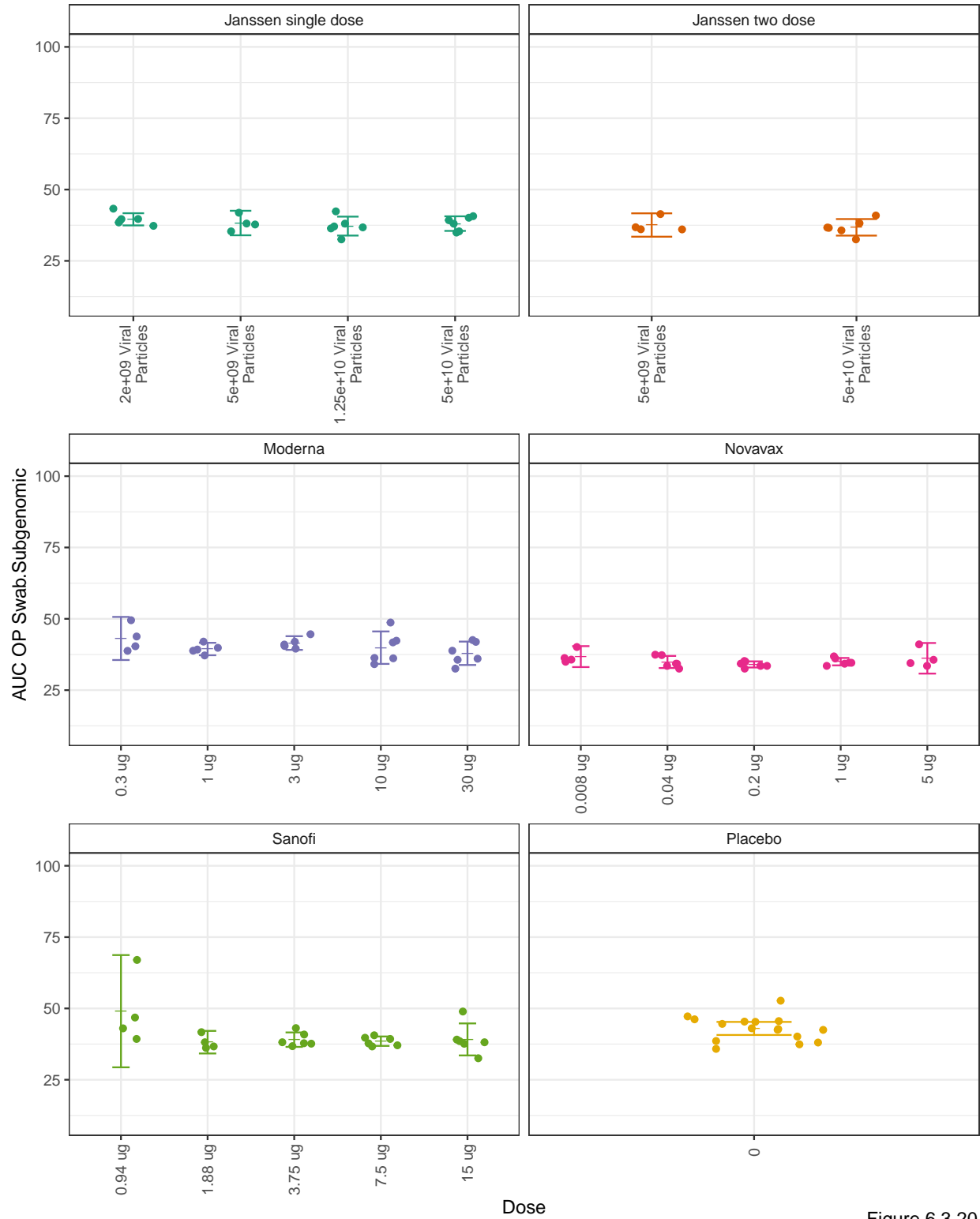


Figure 6.3.20

Linear GEE

Original dose score:

Table 6.3.5: Linear GEE Results, Original Dose Score AUC BAL.N1

	Estimate	Lower	Upper	p
Intercept	38.13	35.10	41.16	<0.001
Janssen dose score	-4.41	-6.89	-1.93	0.005
Moderna dose score	-2.29	-5.52	0.95	0.133
Novavax dose score	-5.33	-7.61	-3.05	0.002
Sanofi dose score	-4.07	-6.17	-1.97	0.003

Table 6.3.6: Linear GEE Results, Original Dose Score AUC BAL.Subgenomic

	Estimate	Lower	Upper	p
Intercept	31.03	28.55	33.52	<0.001
Janssen dose score	-3.00	-4.38	-1.62	0.002
Moderna dose score	-1.66	-3.64	0.33	0.086
Novavax dose score	-3.33	-4.41	-2.25	0.001
Sanofi dose score	-2.84	-4.41	-1.27	0.004

Table 6.3.7: Linear GEE Results, Original Dose Score AUC Nasal Swab.N1

	Estimate	Lower	Upper	p
Intercept	67.03	62.30	71.77	<0.001
Janssen dose score	-6.01	-9.28	-2.74	0.004
Moderna dose score	-2.47	-4.64	-0.30	0.032
Novavax dose score	-8.62	-12.73	-4.50	0.003
Sanofi dose score	-5.68	-8.79	-2.56	0.004

Table 6.3.8: Linear GEE Results, Original Dose Score AUC Nasal Swab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	47.91	45.06	50.76	<0.001
Janssen dose score	-3.13	-4.75	-1.51	0.003
Moderna dose score	-1.54	-2.92	-0.17	0.034
Novavax dose score	-4.16	-6.37	-1.95	0.005
Sanofi dose score	-2.36	-4.51	-0.20	0.037

Table 6.3.9: Linear GEE Results, Original Dose Score AUC OP Swab.N1

	Estimate	Lower	Upper	p
Intercept	49.74	46.12	53.37	<0.001
Janssen dose score	-4.24	-6.40	-2.09	0.003
Moderna dose score	-2.35	-4.74	0.03	0.052
Novavax dose score	-5.08	-7.43	-2.72	0.003
Sanofi dose score	-3.49	-6.15	-0.83	0.018

Table 6.3.10: Linear GEE Results, Original Dose Score AUC OP Swab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	42.27	39.61	44.94	<0.001
Janssen dose score	-2.36	-3.79	-0.93	0.007
Moderna dose score	-1.10	-2.56	0.36	0.113
Novavax dose score	-2.60	-3.93	-1.27	0.004
Sanofi dose score	-1.42	-2.73	-0.12	0.037

Table 6.3.11: Linear GEE Results, Original Dose Score log VL Day2 PostChallenge BAL.N1

	Estimate	Lower	Upper	p
Intercept	5.91	5.47	6.35	<0.001
Janssen dose score	-0.36	-0.88	0.17	0.15
Moderna dose score	-0.41	-0.97	0.16	0.129
Novavax dose score	-0.73	-1.12	-0.33	0.005
Sanofi dose score	-0.27	-0.62	0.08	0.106

Table 6.3.12: Linear GEE Results, Original Dose Score log VL Day2 PostChallenge BAL.Subgenomic

	Estimate	Lower	Upper	p
Intercept	4.84	4.35	5.33	<0.001
Janssen dose score	-0.37	-0.80	0.05	0.076
Moderna dose score	-0.44	-0.94	0.06	0.074
Novavax dose score	-0.76	-1.11	-0.40	0.003
Sanofi dose score	-0.36	-0.72	-0.01	0.048

Table 6.3.13: Linear GEE Results, Original Dose Score log VL Day2 PostChallenge OPswab.N1

	Estimate	Lower	Upper	p
Intercept	5.45	4.43	6.48	<0.001
Janssen dose score	-0.24	-0.64	0.17	0.196
Moderna dose score	-0.04	-0.40	0.32	0.793
Novavax dose score	-0.61	-1.00	-0.22	0.011
Sanofi dose score	-0.14	-0.60	0.32	0.489

Table 6.3.14: Linear GEE Results, Original Dose Score log VL Day2 PostChallenge OPswab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	4.47	3.48	5.46	<0.001
Janssen dose score	-0.20	-0.58	0.19	0.254
Moderna dose score	-0.07	-0.42	0.28	0.623
Novavax dose score	-0.56	-1.01	-0.12	0.023
Sanofi dose score	-0.16	-0.64	0.32	0.446

Table 6.3.15: Linear GEE Results, Original Dose Score log VL Day2 PostChallenge NasalSwab.N1

	Estimate	Lower	Upper	p
Intercept	7.44	6.75	8.13	<0.001
Janssen dose score	-0.46	-0.94	0.02	0.059
Moderna dose score	-0.40	-0.78	-0.02	0.043
Novavax dose score	-0.85	-1.51	-0.19	0.021
Sanofi dose score	-0.44	-0.83	-0.06	0.031

Table 6.3.16: Linear GEE Results, Original Dose Score log VL Day2 PostChallenge NasalSwab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	6.22	5.46	6.99	<0.001
Janssen dose score	-0.49	-0.99	0.01	0.052
Moderna dose score	-0.45	-0.94	0.05	0.068
Novavax dose score	-0.98	-1.80	-0.15	0.028
Sanofi dose score	-0.41	-0.80	-0.01	0.046

Single dose halved dose score:

Also shown are geometric means and the corresponding 95% confidence intervals, along with the fitted line from the linear GEE model. Dashed horizontal lines are the placebo estimate from the model.

Table 6.3.17: Linear GEE Results, Single Dose Halved Dose Score AUC BAL.N1

	Estimate	Lower	Upper	p
Intercept	38.23	35.40	41.06	<0.001
Janssen dose score	-4.28	-6.33	-2.23	0.002
Moderna dose score	-2.33	-5.43	0.77	0.114
Novavax dose score	-5.37	-7.60	-3.13	0.002
Sanofi dose score	-4.13	-6.12	-2.14	0.002

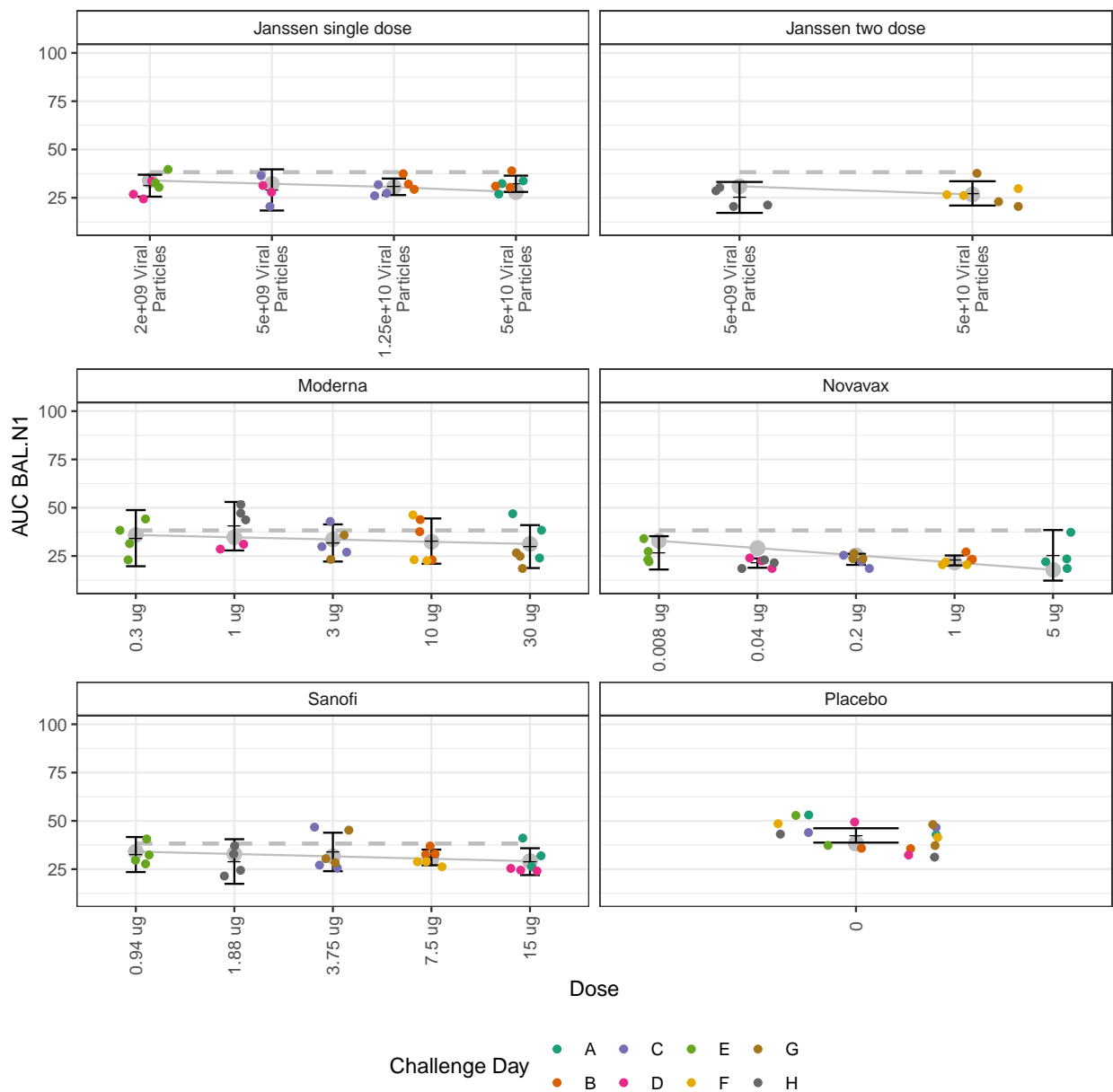


Figure 6.3.21

Table 6.3.18: Linear GEE Results, Single Dose Halved Dose Score AUC BAL.Subgenomic

	Estimate	Lower	Upper	p
Intercept	31.06	28.61	33.52	<0.001
Janssen dose score	-2.87	-4.09	-1.66	0.001
Moderna dose score	-1.67	-3.57	0.24	0.075
Novavax dose score	-3.34	-4.41	-2.27	0.001
Sanofi dose score	-2.86	-4.39	-1.32	0.004

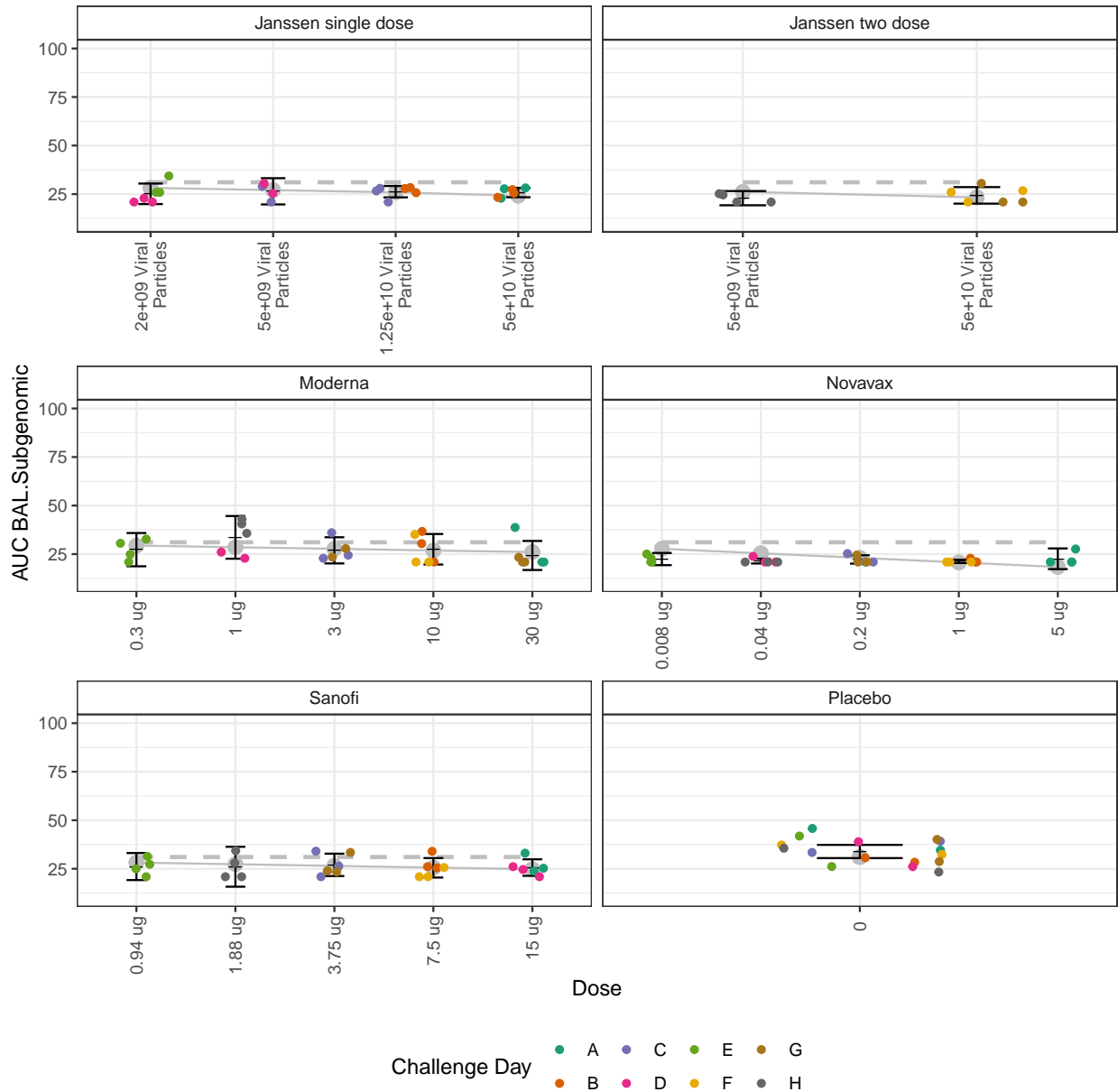


Figure 6.3.22

Table 6.3.19: Linear GEE Results, Single Dose Halved Dose Score AUC Nasal Swab.N1

	Estimate	Lower	Upper	p
Intercept	67.05	62.50	71.60	<0.001
Janssen dose score	-5.72	-8.56	-2.88	0.003
Moderna dose score	-2.47	-4.58	-0.36	0.029
Novavax dose score	-8.62	-12.68	-4.57	0.003
Sanofi dose score	-5.69	-8.73	-2.64	0.004

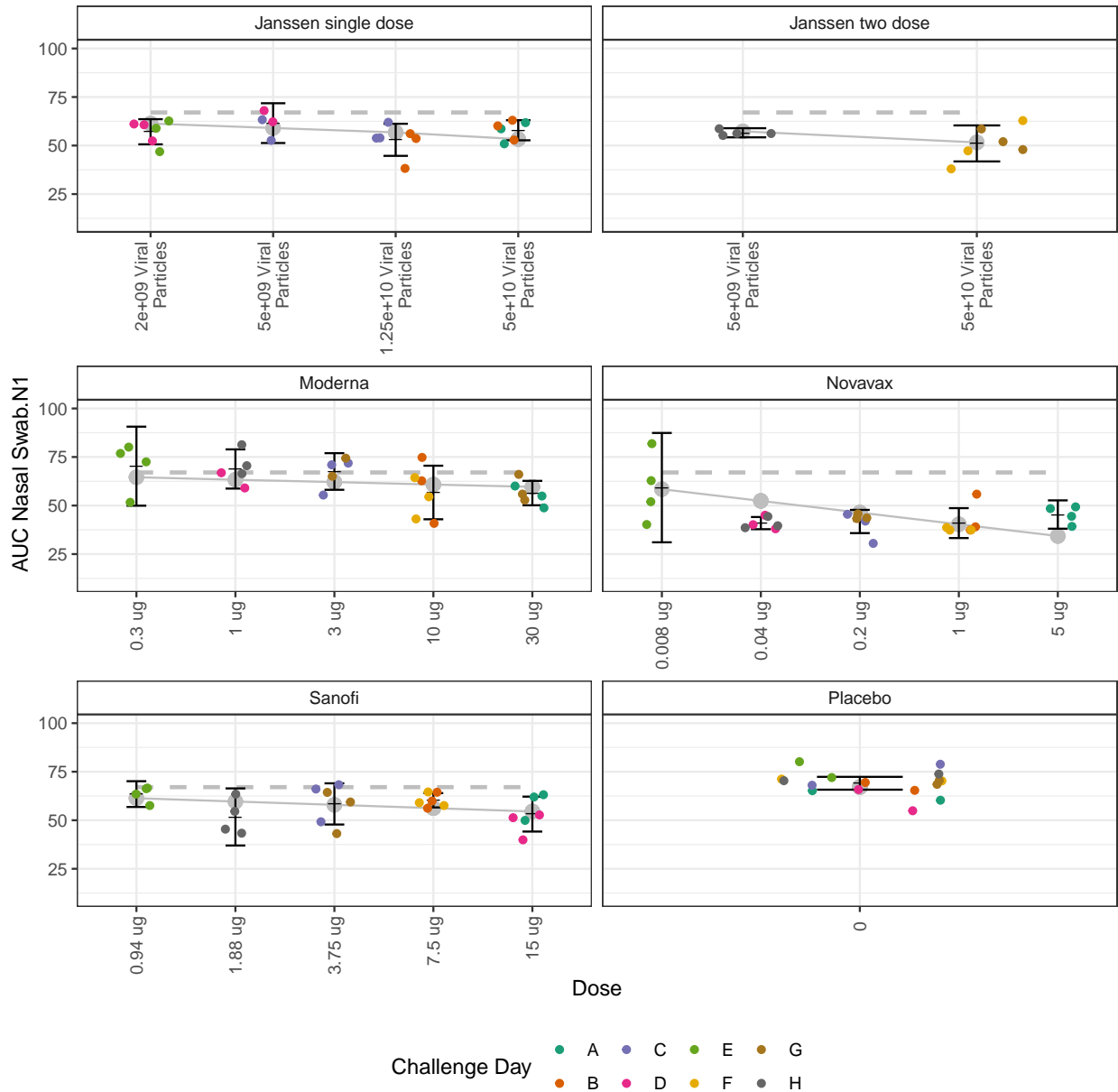


Figure 6.3.23

Table 6.3.20: Linear GEE Results, Single Dose Halved Dose Score AUC Nasal Swab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	47.96	45.21	50.71	<0.001
Janssen dose score	-3.02	-4.46	-1.57	0.002
Moderna dose score	-1.56	-2.89	-0.23	0.029
Novavax dose score	-4.18	-6.36	-1.99	0.005
Sanofi dose score	-2.38	-4.50	-0.26	0.033

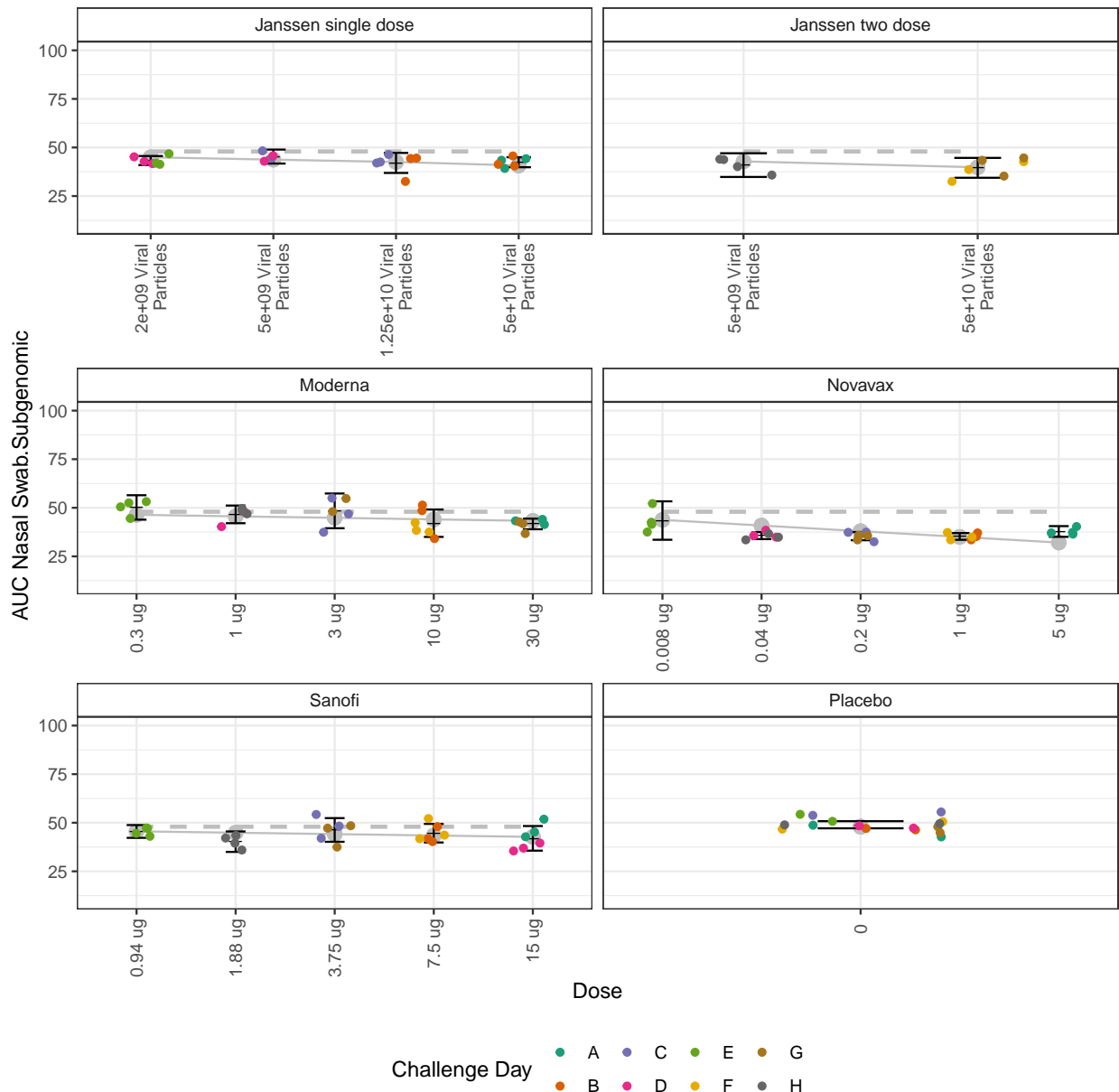


Figure 6.3.24

Table 6.3.21: Linear GEE Results, Single Dose Halved Dose Score AUC OP Swab.N1

	Estimate	Lower	Upper	p
Intercept	49.71	46.25	53.17	<0.001
Janssen dose score	-3.99	-5.90	-2.08	0.002
Moderna dose score	-2.34	-4.66	-0.02	0.049
Novavax dose score	-5.06	-7.36	-2.77	0.002
Sanofi dose score	-3.47	-6.06	-0.88	0.017

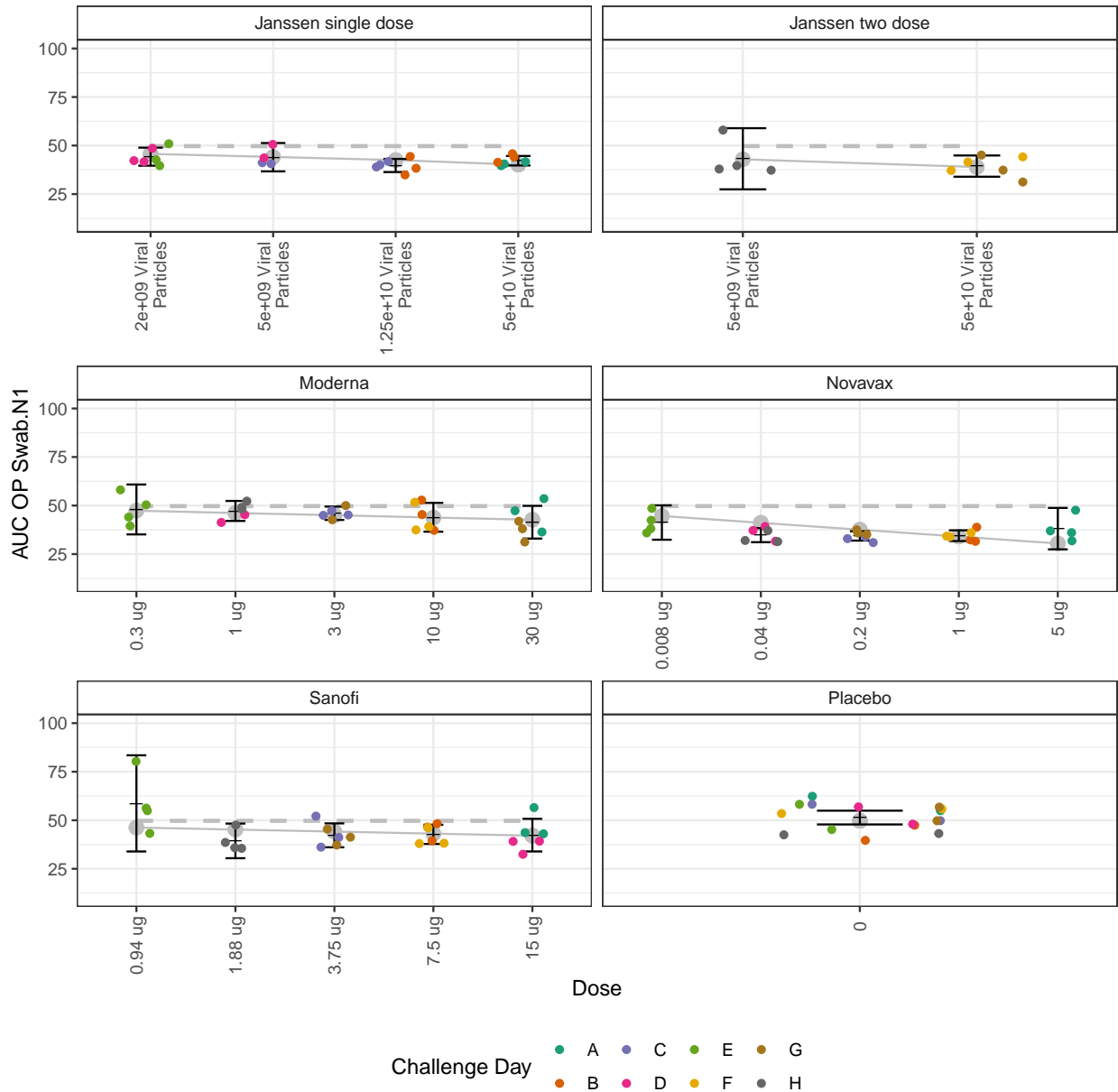


Figure 6.3.25

Table 6.3.22: Linear GEE Results, Single Dose Halved Dose Score AUC OP Swab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	42.27	39.72	44.82	<0.001
Janssen dose score	-2.24	-3.50	-0.97	0.005
Moderna dose score	-1.10	-2.51	0.31	0.104
Novavax dose score	-2.60	-3.89	-1.31	0.004
Sanofi dose score	-1.42	-2.66	-0.19	0.031

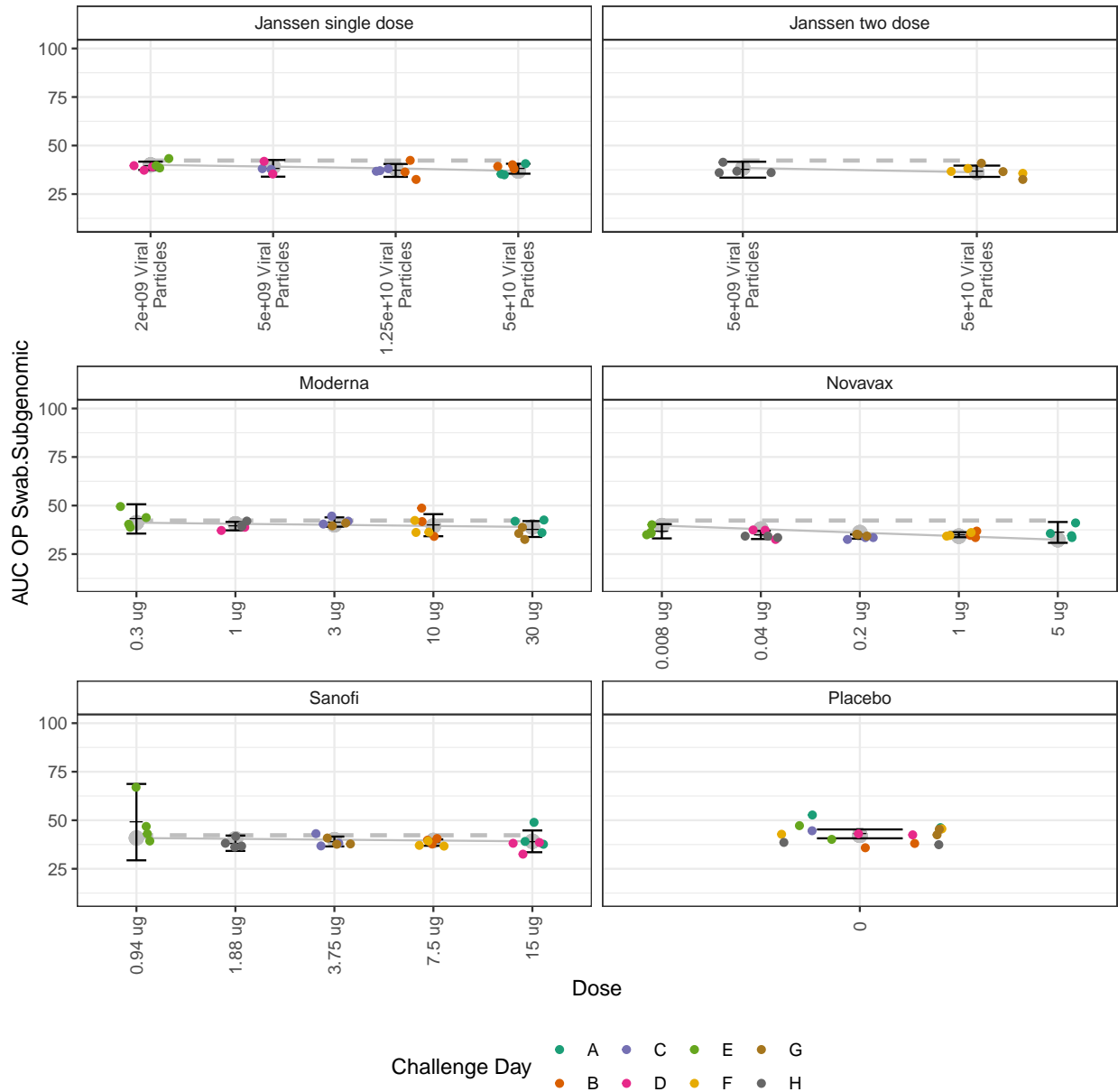


Figure 6.3.26

Table 6.3.23: Linear GEE Results, Single Dose Halved Dose Score log VL Day2 PostChallenge BAL.N1

	Estimate	Lower	Upper	p
Intercept	5.95	5.52	6.37	<0.001
Janssen dose score	-0.37	-0.84	0.10	0.104
Moderna dose score	-0.42	-0.98	0.14	0.114
Novavax dose score	-0.74	-1.13	-0.35	0.004
Sanofi dose score	-0.29	-0.63	0.05	0.085

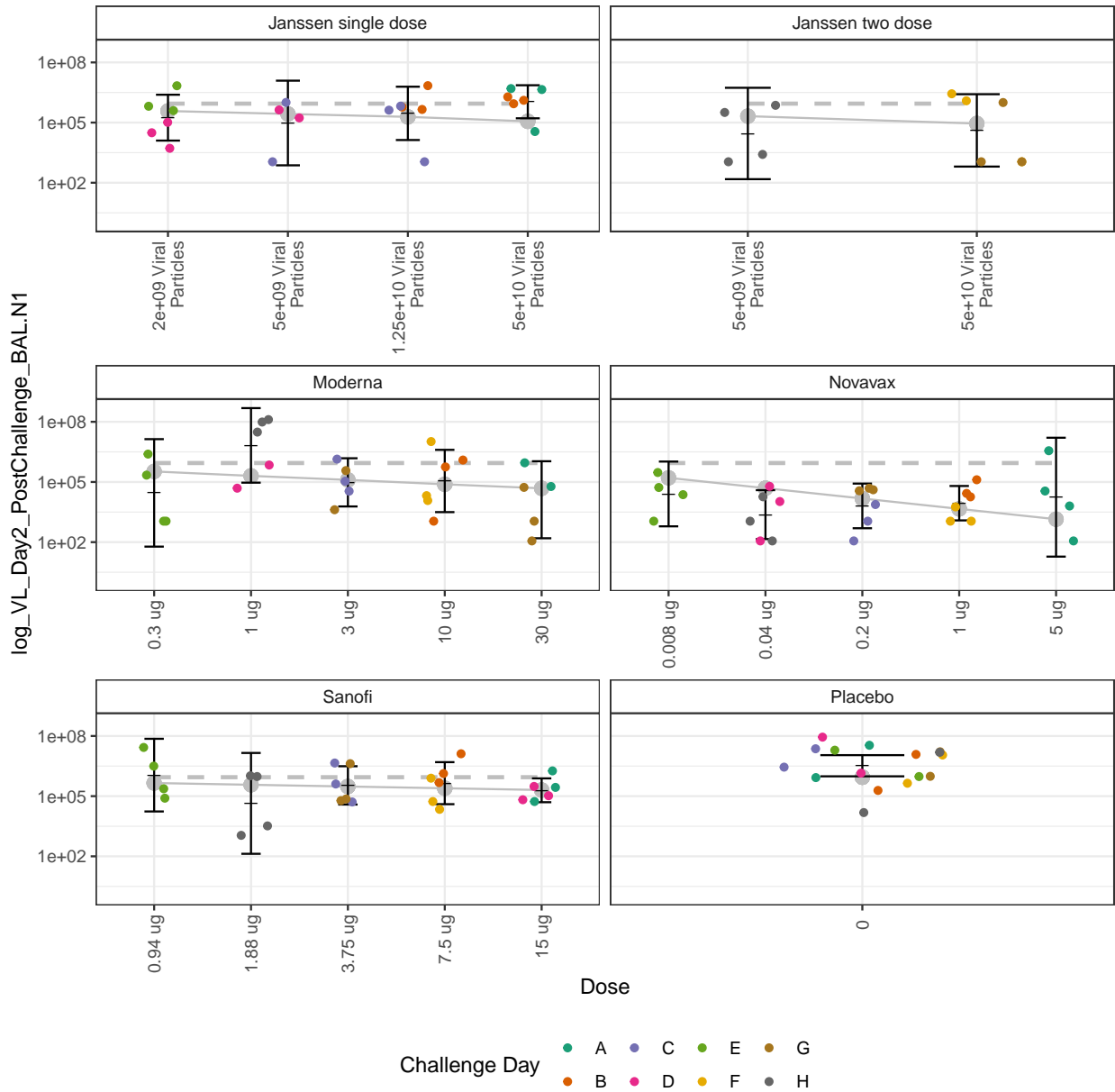


Figure 6.3.27

Table 6.3.24: Linear GEE Results, Single Dose Halved Dose Score log VL Day2 PostChallenge BAL.Subgenomic

	Estimate	Lower	Upper	p
Intercept	4.87	4.40	5.34	<0.001
Janssen dose score	-0.38	-0.76	0.00	0.052
Moderna dose score	-0.45	-0.93	0.03	0.062
Novavax dose score	-0.76	-1.11	-0.41	0.002
Sanofi dose score	-0.38	-0.72	-0.03	0.037

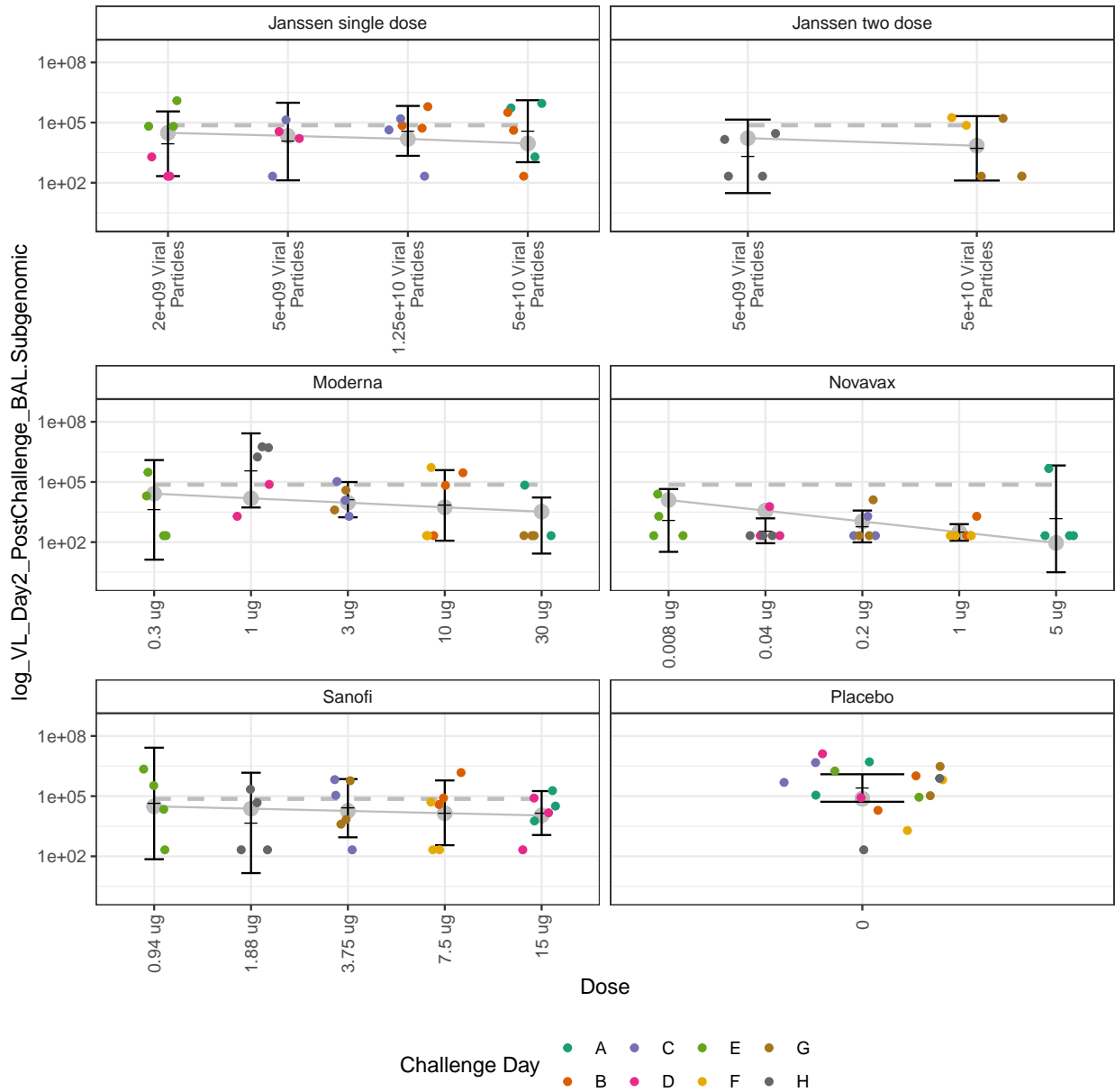


Figure 6.3.28

Table 6.3.25: Linear GEE Results, Single Dose Halved Dose Score log VL Day2 PostChallenge OPswab.N1

	Estimate	Lower	Upper	p
Intercept	5.49	4.55	6.43	<0.001
Janssen dose score	-0.26	-0.61	0.09	0.121
Moderna dose score	-0.05	-0.39	0.28	0.69
Novavax dose score	-0.62	-1.00	-0.25	0.009
Sanofi dose score	-0.16	-0.57	0.26	0.384

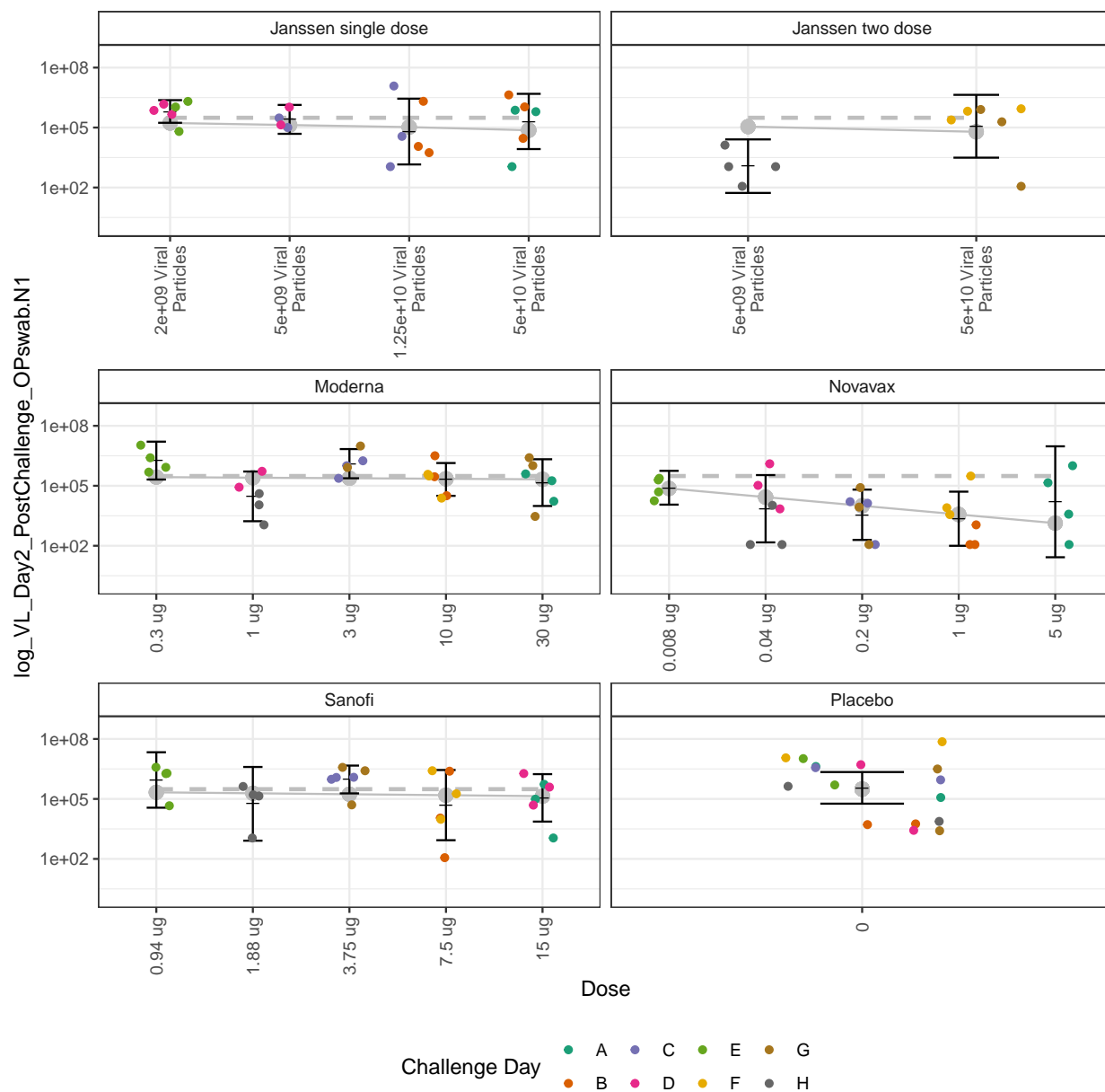


Figure 6.3.29

Table 6.3.26: Linear GEE Results, Single Dose Halved Dose Score log VL Day2 PostChallenge OP-swab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	4.50	3.58	5.43	<0.001
Janssen dose score	-0.22	-0.56	0.12	0.169
Moderna dose score	-0.09	-0.41	0.24	0.532
Novavax dose score	-0.58	-1.01	-0.15	0.019
Sanofi dose score	-0.18	-0.62	0.26	0.362

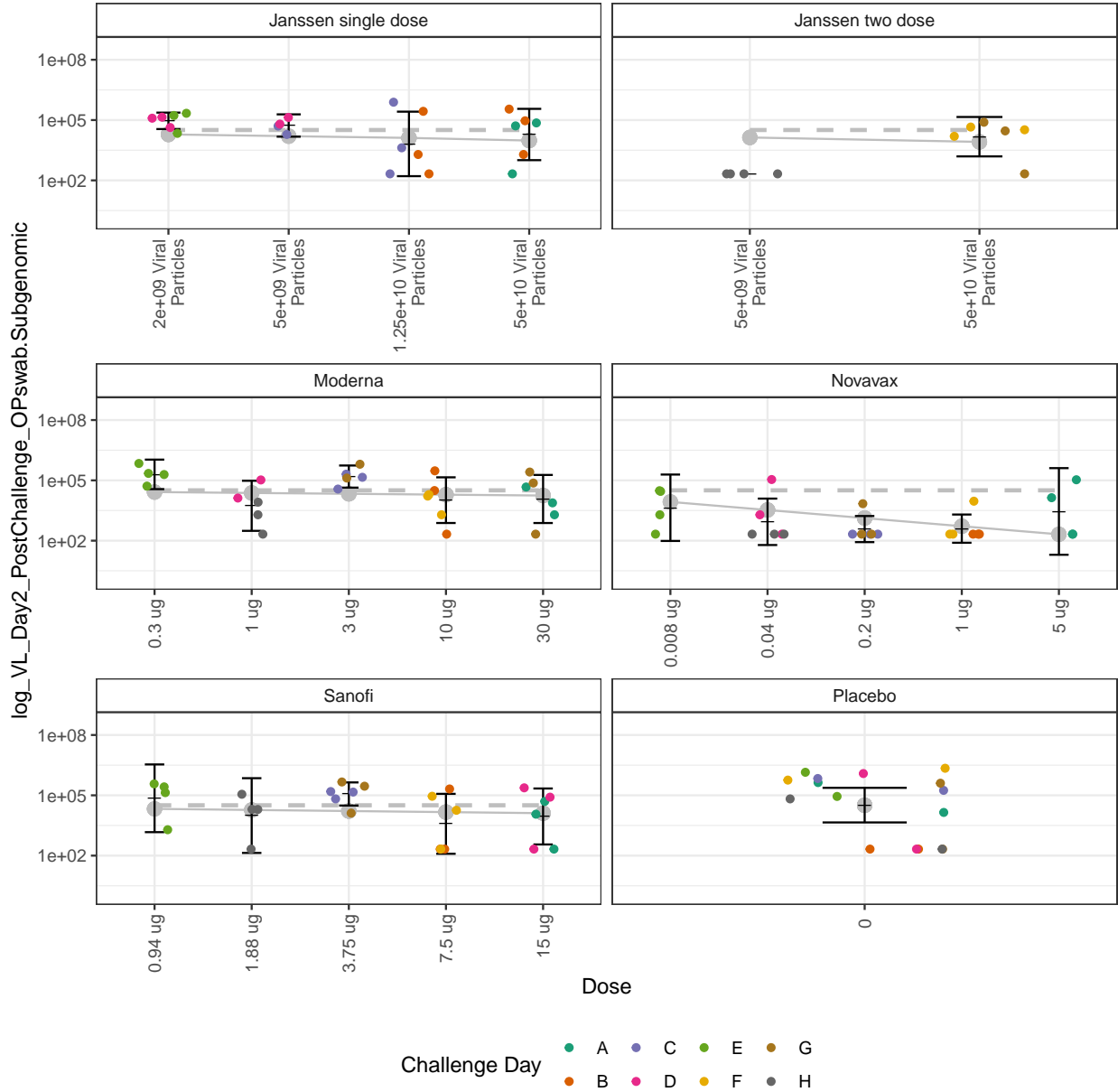


Figure 6.3.30

Table 6.3.27: Linear GEE Results, Single Dose Halved Dose Score log VL Day2 PostChallenge NasalSwab.N1

	Estimate	Lower	Upper	p
Intercept	7.48	6.83	8.14	<0.001
Janssen dose score	-0.48	-0.90	-0.05	0.033
Moderna dose score	-0.42	-0.79	-0.05	0.032
Novavax dose score	-0.87	-1.53	-0.20	0.02
Sanofi dose score	-0.47	-0.84	-0.09	0.022

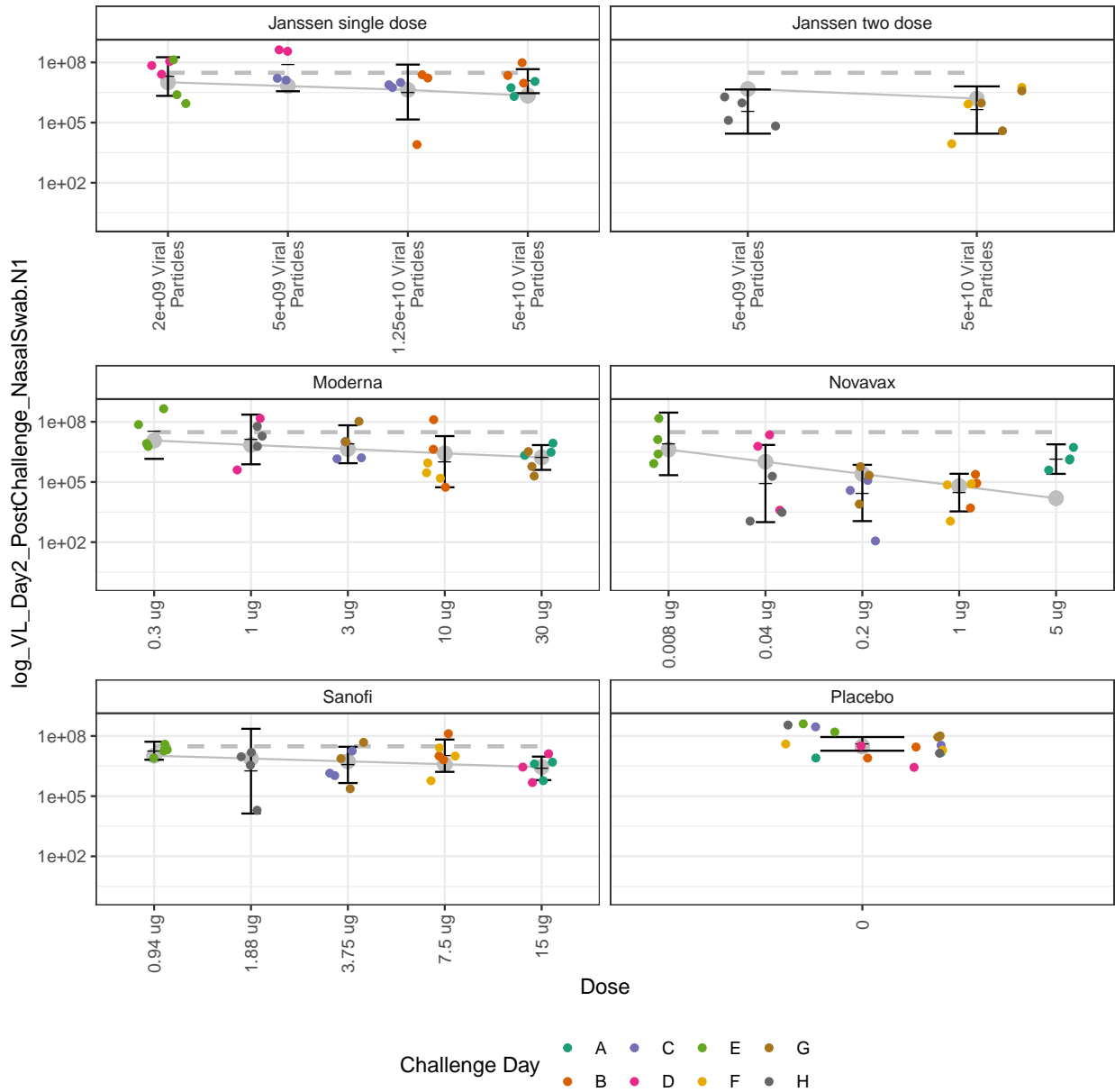


Figure 6.3.31

Table 6.3.28: Linear GEE Results, Single Dose Halved Dose Score log VL Day2 PostChallenge Nasal-Swab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	6.28	5.56	6.99	<0.001
Janssen dose score	-0.52	-0.96	-0.07	0.029
Moderna dose score	-0.47	-0.96	0.01	0.053
Novavax dose score	-1.00	-1.82	-0.17	0.027
Sanofi dose score	-0.44	-0.82	-0.06	0.031

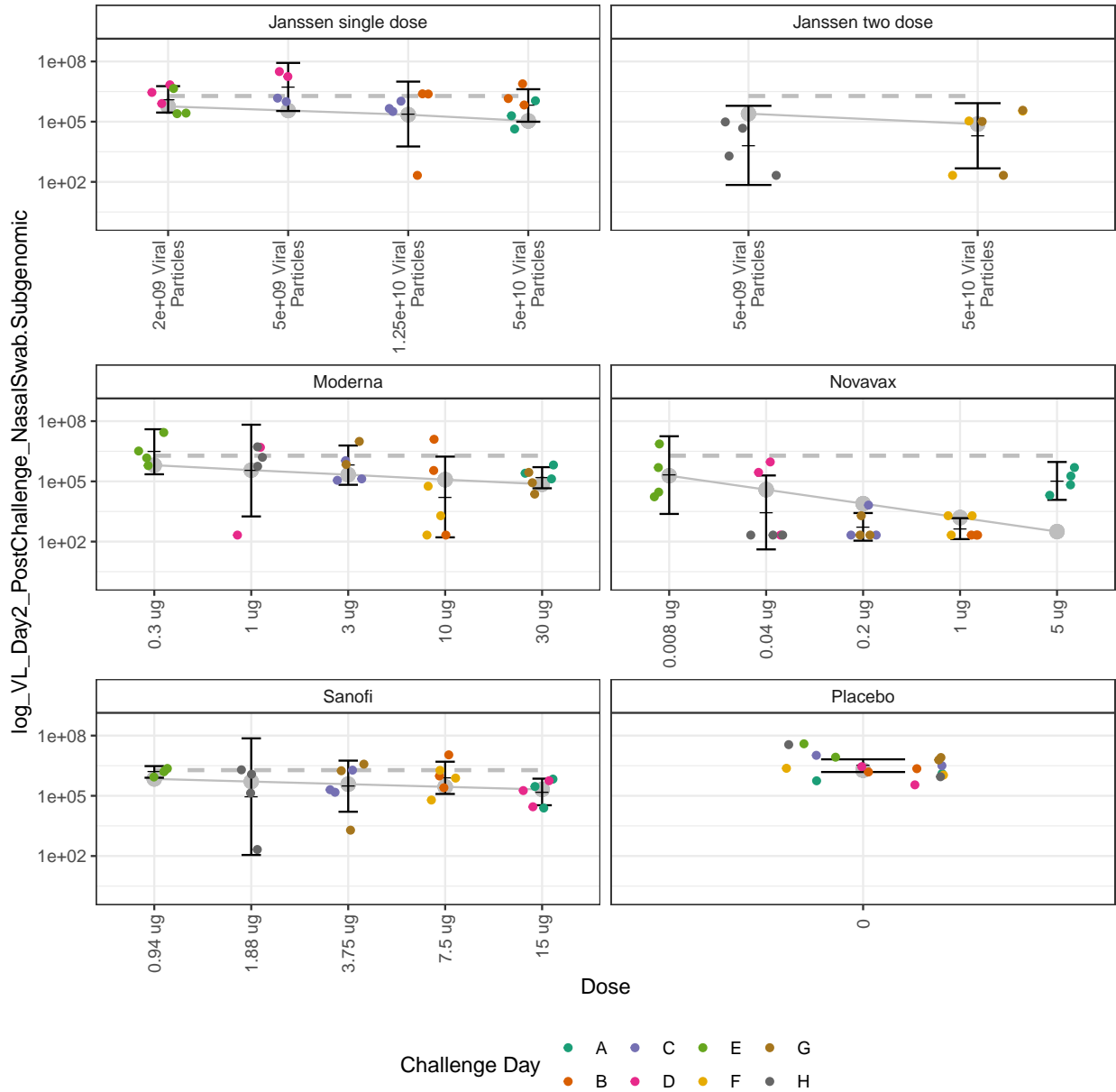


Figure 6.3.32

Single dose group removed:

Table 6.3.29: Linear GEE Results, Original Dose Score Single Dose Group Removed AUC BAL.N1

	Estimate	Lower	Upper	p
Intercept	38.59	35.49	41.69	<0.001
Janssen dose score	-6.76	-9.15	-4.38	0.002
Moderna dose score	-2.48	-5.78	0.82	0.114
Novavax dose score	-5.50	-7.79	-3.21	0.002
Sanofi dose score	-4.33	-6.44	-2.22	0.002

Table 6.3.30: Linear GEE Results, Original Dose Score Single Dose Group Removed AUC BAL.Subgenomic

	Estimate	Lower	Upper	p
Intercept	31.38	28.73	34.03	<0.001
Janssen dose score	-4.23	-6.54	-1.92	0.01
Moderna dose score	-1.80	-3.91	0.30	0.08
Novavax dose score	-3.45	-4.55	-2.36	0.001
Sanofi dose score	-3.03	-4.63	-1.44	0.003

Table 6.3.31: Linear GEE Results, Original Dose Score Single Dose Group Removed AUC Nasal Swab.N1

	Estimate	Lower	Upper	p
Intercept	67.57	62.37	72.76	<0.001
Janssen dose score	-8.63	-12.81	-4.45	0.007
Moderna dose score	-2.69	-5.05	-0.34	0.031
Novavax dose score	-8.81	-12.99	-4.64	0.003
Sanofi dose score	-5.98	-9.15	-2.81	0.003

Table 6.3.32: Linear GEE Results, Original Dose Score Single Dose Group Removed AUC Nasal Swab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	48.00	45.03	50.98	<0.001
Janssen dose score	-4.64	-7.39	-1.89	0.012
Moderna dose score	-1.58	-2.98	-0.18	0.033
Novavax dose score	-4.19	-6.43	-1.96	0.005
Sanofi dose score	-2.41	-4.64	-0.18	0.038

Table 6.3.33: Linear GEE Results, Original Dose Score Single Dose Group Removed AUC OP Swab.N1

	Estimate	Lower	Upper	p
Intercept	50.00	46.09	53.92	<0.001
Janssen dose score	-5.51	-8.25	-2.76	0.007
Moderna dose score	-2.47	-4.94	0.01	0.051
Novavax dose score	-5.17	-7.60	-2.75	0.003
Sanofi dose score	-3.64	-6.27	-1.00	0.015

Table 6.3.34: Linear GEE Results, Original Dose Score Single Dose Group Removed AUC OP Swab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	42.38	39.58	45.19	<0.001
Janssen dose score	-3.10	-4.71	-1.48	0.009
Moderna dose score	-1.15	-2.65	0.35	0.109
Novavax dose score	-2.64	-4.00	-1.28	0.004
Sanofi dose score	-1.49	-2.87	-0.10	0.039

Table 6.3.35: Linear GEE Results, Original Dose Score Single Dose Group Removed log VL Day2 PostChallenge BAL.N1

	Estimate	Lower	Upper	p
Intercept	5.99	5.50	6.47	<0.001
Janssen dose score	-0.81	-1.58	-0.04	0.044
Moderna dose score	-0.44	-1.00	0.12	0.103
Novavax dose score	-0.75	-1.16	-0.35	0.005
Sanofi dose score	-0.31	-0.67	0.04	0.075

Table 6.3.36: Linear GEE Results, Original Dose Score Single Dose Group Removed log VL Day2 PostChallenge BAL.Subgenomic

	Estimate	Lower	Upper	p
Intercept	4.91	4.32	5.50	<0.001
Janssen dose score	-0.74	-1.47	-0.01	0.049
Moderna dose score	-0.47	-0.98	0.05	0.068
Novavax dose score	-0.78	-1.15	-0.41	0.003
Sanofi dose score	-0.40	-0.80	0.00	0.049

Table 6.3.37: Linear GEE Results, Original Dose Score Single Dose Group Removed log VL Day2 PostChallenge OPswab.N1

	Estimate	Lower	Upper	p
Intercept	5.35	4.23	6.47	<0.001
Janssen dose score	-0.45	-1.27	0.38	0.179
Moderna dose score	0.01	-0.39	0.40	0.972
Novavax dose score	-0.57	-0.98	-0.16	0.017
Sanofi dose score	-0.08	-0.61	0.45	0.731

Table 6.3.38: Linear GEE Results, Original Dose Score Single Dose Group Removed log VL Day2 PostChallenge OPswab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	4.34	3.29	5.39	<0.001
Janssen dose score	-0.36	-1.07	0.35	0.198
Moderna dose score	-0.02	-0.39	0.36	0.916
Novavax dose score	-0.52	-0.96	-0.07	0.031
Sanofi dose score	-0.09	-0.61	0.44	0.702

Table 6.3.39: Linear GEE Results, Original Dose Score Single Dose Group Removed log VL Day2 PostChallenge NasalSwab.N1

	Estimate	Lower	Upper	p
Intercept	7.34	6.63	8.05	<0.001
Janssen dose score	-0.99	-1.49	-0.49	0.007
Moderna dose score	-0.36	-0.73	0.02	0.058
Novavax dose score	-0.82	-1.46	-0.17	0.023
Sanofi dose score	-0.39	-0.76	-0.02	0.042

Table 6.3.40: Linear GEE Results, Original Dose Score Single Dose Group Removed log VL Day2 PostChallenge NasalSwab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	6.10	5.31	6.89	<0.001
Janssen dose score	-1.10	-1.75	-0.45	0.012
Moderna dose score	-0.40	-0.88	0.09	0.09
Novavax dose score	-0.93	-1.74	-0.12	0.032
Sanofi dose score	-0.34	-0.71	0.03	0.068

Dose Response on Viral Load - Binary

Wilcoxon-Mann-Whitney

By Vaccine Product:

Table 6.3.41: Wilcoxon Mann Whitney test p values of Dose Score with Binary Viral Load By Vaccine

	Janssen Original Dose Score	Janssen Single Dose Halved Dose Score	Janssen Single Dose Removed	Moderna	Novavax	Sanofi
bin VL Day2 PostChallenge BAL N1	NA	NA	NA	0.179	0.971	NA
bin VL Day2 PostChallenge BAL Subgenomic	0.916	0.853	1	0.064	0.535	0.616
bin VL Day2 PostChallenge OPswab N1	0.776	0.502	0.878	NA	0.535	0.633
bin VL Day2 PostChallenge OPswab Subgenomic	0.946	0.808	0.02	0.566	0.363	0.128
bin VL Day2 PostChallenge NasalSwab N1	NA	NA	NA	NA	1	NA
bin VL Day2 PostChallenge NasalSwab Subgenomic	0.389	0.193	0.894	0.935	1.000	0.376

Note:

NA is indicated when all animals for that vaccine manufacturer and viral load have a positive signal

Overall

Table 6.3.42: Wilcoxon-Mann-Whitney Test p-value of Dose Score with Binary Viral Load Overall

	Original Dose Score	Single Dose Halved Dose Score	Single Dose Group Removed
bin VL Day2 PostChallenge BAL N1	0.082	0.099	0.083
bin VL Day2 PostChallenge BAL Subgenomic	0.001	0.001	<0.001
bin VL Day2 PostChallenge OPswab N1	0.023	0.015	0.046
bin VL Day2 PostChallenge OPswab Subgenomic	0.068	0.042	0.153
bin VL Day2 PostChallenge NasalSwab N1	0.385	0.432	0.375
bin VL Day2 PostChallenge NasalSwab Subgenomic	0.004	0.004	0.008

Logistic GEE

Original dose score:

[1] “Model not fit for bin VL Day2 PostChallenge BAL.N1 due to the logistic model for probability has fitted value very close to 1. This occurs when at least one vaccine manufacturer has all positive responses.”

Table 6.3.43: Logistic GEE Results, Original Dose Score bin VL Day2 PostChallenge BAL.Subgenomic

	Estimate	Lower	Upper	p
Intercept	1.65	0.46	2.85	0.015
Janssen dose score	-0.43	-1.25	0.38	0.242
Moderna dose score	-0.57	-1.36	0.23	0.131
Novavax dose score	-1.08	-1.64	-0.52	0.003
Sanofi dose score	-0.33	-1.17	0.50	0.366

[1] “Model not fit for bin VL Day2 PostChallenge OPswab.N1 due to the logistic model for probability has fitted value very close to 1. This occurs when at least one vaccine manufacturer has all positive responses.”

Table 6.3.44: Logistic GEE Results, Original Dose Score bin VL Day2 PostChallenge OPswab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	1.06	-0.59	2.70	0.167
Janssen dose score	0.03	-0.70	0.76	0.918
Moderna dose score	0.38	-0.20	0.95	0.158
Novavax dose score	-0.69	-1.37	-0.01	0.047
Sanofi dose score	-0.01	-0.79	0.76	0.967

[1] “Model not fit for bin VL Day2 PostChallenge NasalSwab.N1 due to the logistic model for probability has fitted value very close to 1. This occurs when at least one vaccine manufacturer has all positive responses.”

Table 6.3.45: Logistic GEE Results, Original Dose Score bin VL Day2 PostChallenge NasalSwab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	2.35	0.54	4.17	0.020
Janssen dose score	-0.28	-1.31	0.75	0.534
Moderna dose score	-0.15	-1.26	0.95	0.740
Novavax dose score	-0.79	-1.97	0.38	0.143
Sanofi dose score	0.65	-0.48	1.78	0.211

Single Dose Halved Dose Score

The fitted line of predictions from the logistic GEE model is shown on the plots. Dashed horizontal lines are the placebo estimate from the model.

[1] “Model not fit for bin VL Day2 PostChallenge BAL.N1 due to the logistic model for probability has fitted value very close to 1. This occurs when at least one vaccine manufacturer has all positive responses.”

Table 6.3.46: Logistic GEE Results, Single Dose Halved Dose Score bin VL Day2 PostChallenge BAL.Subgenomic

	Estimate	Lower	Upper	p
Intercept	1.71	0.54	2.87	0.012
Janssen dose score	-0.46	-1.19	0.28	0.178
Moderna dose score	-0.59	-1.38	0.20	0.115
Novavax dose score	-1.10	-1.65	-0.55	0.002
Sanofi dose score	-0.37	-1.18	0.45	0.311

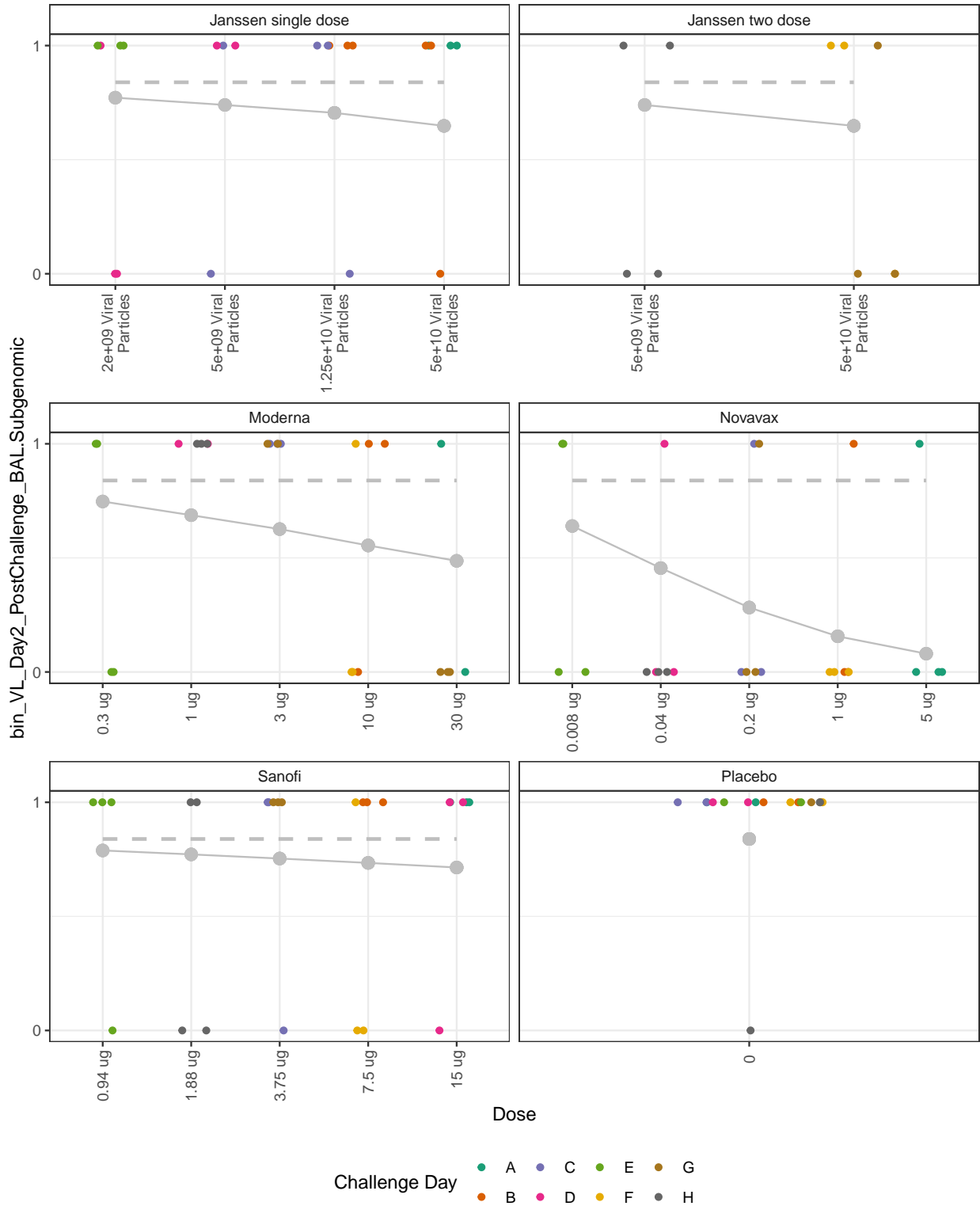


Figure 6.3.33

[1] “Model not fit for bin VL Day2 PostChallenge OPswab.N1 due to the logistic model for probability has fitted value very close to 1. This occurs when at least one vaccine manufacturer has all positive responses.”

Table 6.3.47: Logistic GEE Results, Single Dose Halved Dose Score bin VL Day2 PostChallenge OP-swab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	1.13	-0.44	2.71	0.129
Janssen dose score	-0.04	-0.74	0.66	0.894
Moderna dose score	0.34	-0.21	0.90	0.178
Novavax dose score	-0.72	-1.41	-0.04	0.041
Sanofi dose score	-0.06	-0.78	0.67	0.854

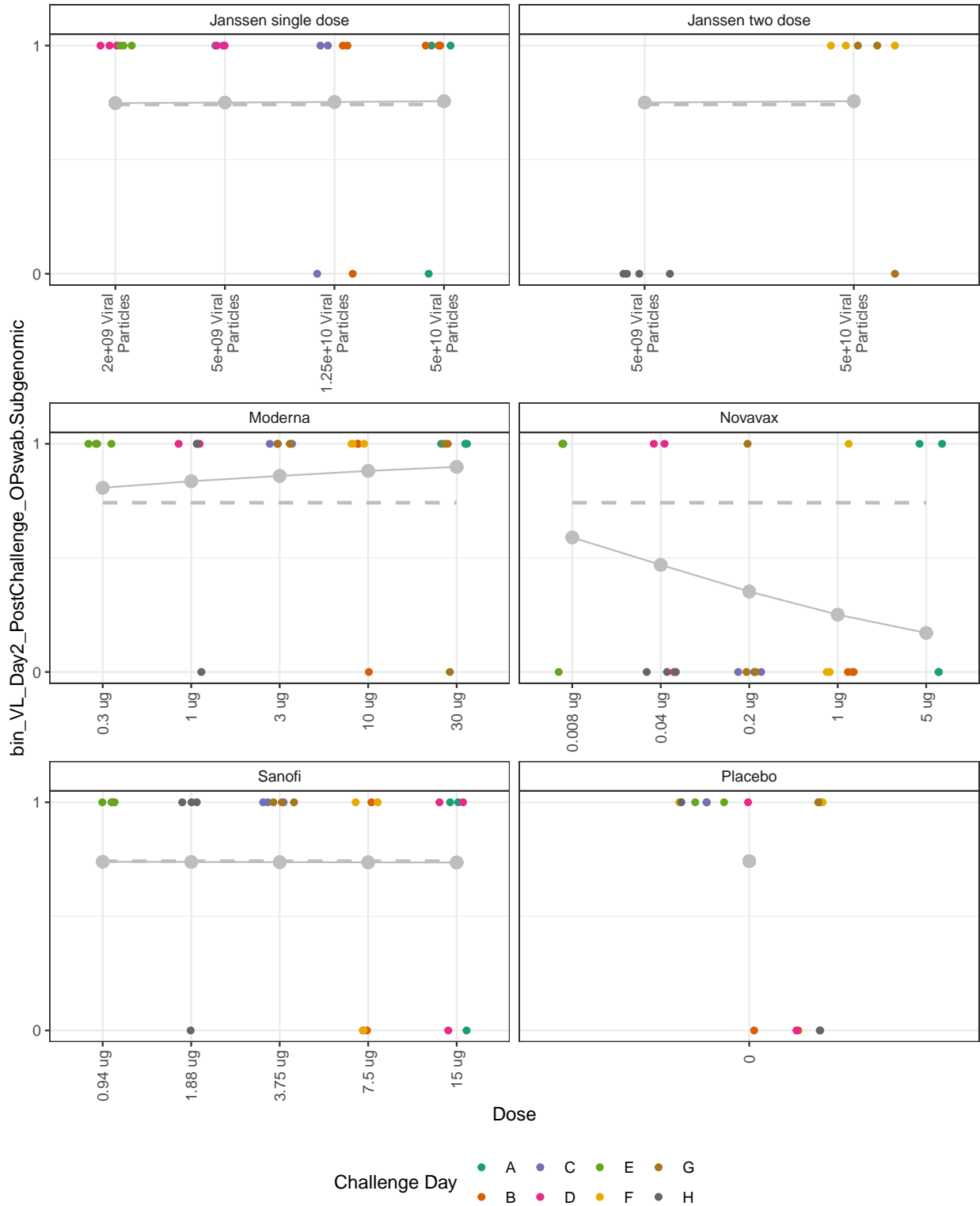


Figure 6.3.34

[1] “Model not fit for bin VL Day2 PostChallenge NasalSwab.N1 due to the logistic model for probability has fitted value very close to 1. This occurs when at least one vaccine manufacturer has all positive responses.”

Table 6.3.48: Logistic GEE Results, Single Dose Halved Dose Score bin VL Day2 PostChallenge Nasal-Swab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	2.44	0.62	4.26	0.017
Janssen dose score	-0.33	-1.28	0.62	0.423
Moderna dose score	-0.19	-1.29	0.91	0.682
Novavax dose score	-0.82	-2.01	0.37	0.135
Sanofi dose score	0.60	-0.54	1.74	0.248

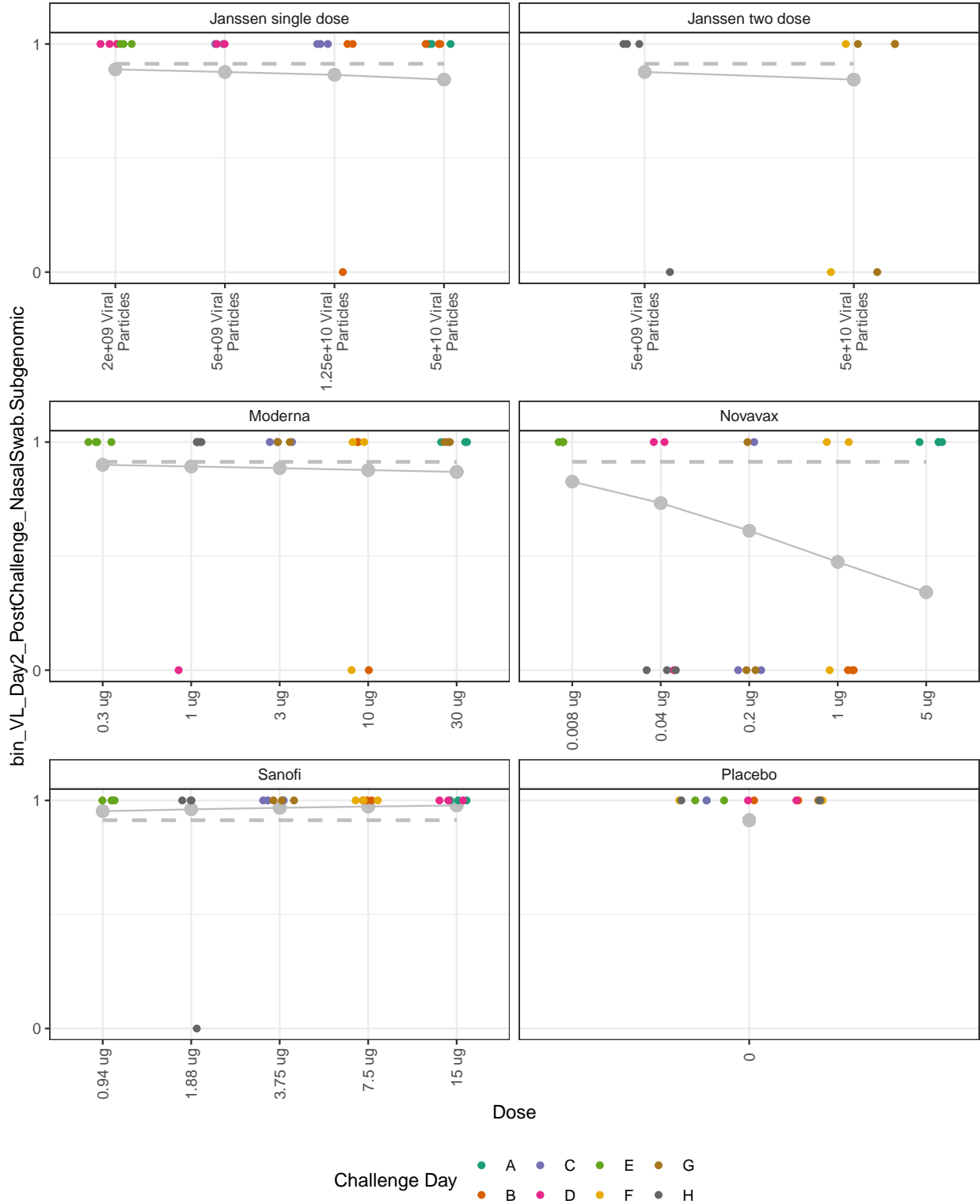


Figure 6.3.35

Single dose group removed:

[1] “Model not fit for bin VL Day2 PostChallenge BAL.N1 due to the logistic model for probability has fitted value very close to 1. This occurs when at least one vaccine manufacturer has all positive responses.”

Table 6.3.49: Logistic GEE Results, Original Dose Score Single Dose Group Removed bin VL Day2 PostChallenge BAL.Subgenomic

	Estimate	Lower	Upper	p
Intercept	1.71	0.34	3.08	0.023
Janssen dose score	-0.97	-1.99	0.05	0.056
Moderna dose score	-0.59	-1.40	0.22	0.122
Novavax dose score	-1.10	-1.69	-0.51	0.004
Sanofi dose score	-0.37	-1.25	0.52	0.352

[1] “Model not fit for bin VL Day2 PostChallenge OPswab.N1 due to the logistic model for probability has fitted value very close to 1. This occurs when at least one vaccine manufacturer has all positive responses.”

Table 6.3.50: Logistic GEE Results, Original Dose Score Single Dose Group Removed bin VL Day2 PostChallenge OPswab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	0.79	-0.77	2.35	0.262
Janssen dose score	-0.16	-1.57	1.25	0.742
Moderna dose score	0.50	-0.08	1.08	0.080
Novavax dose score	-0.59	-1.23	0.04	0.062
Sanofi dose score	0.14	-0.64	0.92	0.686

[1] “Model not fit for bin VL Day2 PostChallenge NasalSwab.N1 due to the logistic model for probability has fitted value very close to 1. This occurs when at least one vaccine manufacturer has all positive responses.”

Table 6.3.51: Logistic GEE Results, Original Dose Score Single Dose Group Removed bin VL Day2 PostChallenge NasalSwab.Subgenomic

	Estimate	Lower	Upper	p
Intercept	2.16	0.58	3.75	0.016
Janssen dose score	-0.77	-1.74	0.19	0.089
Moderna dose score	-0.07	-1.11	0.96	0.867
Novavax dose score	-0.72	-1.82	0.37	0.150
Sanofi dose score	0.77	-0.36	1.89	0.149