Supplementary Material for Viral Kinetics of Primary Dengue Virus Infection in Non-Human Primates: A Systematic Review and Individual Pooled Analysis

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Dengue Virus Genotypes Represented

Figure S1 reports the genotypes represented in the identified studies. Genotype names are as reported as in the study.

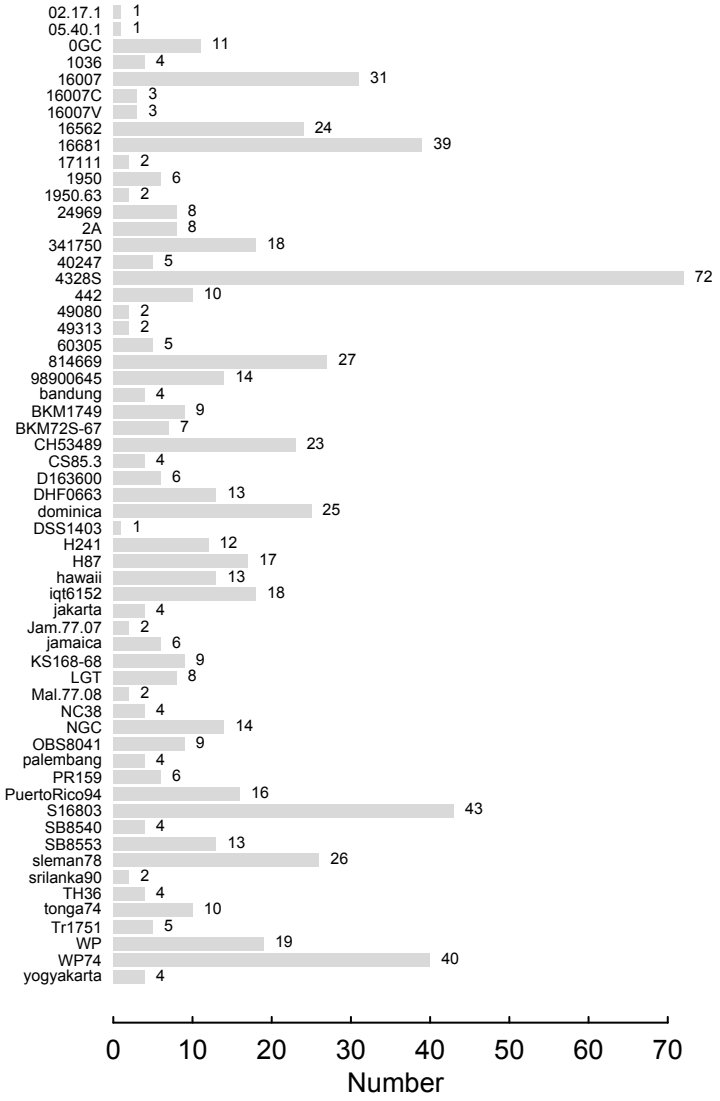

Figure S1: **Histrogram of DENV Genotypes Used in Studies**

Linear Regression Models

Tables S1 and S2 show univariate and multivariate linear regression results associating time to- and duration of viremia with serotype, species, assay, and inoculating dose. Ignoring the heterogeneity between studies results in many covariates being significantly associated with DENV viral kinetics.

Covariate	Univariate	95% CI	p	Multivariate	95% CI	p
DENV-4	ref.			ref.		
DENV-1	0.25	(-0.08, 0.59)	0.139	0.46	(0.14, 0.77)	0.005
DENV-2	-0.28	(-0.59, 0.03)	0.078	-0.24	(-0.54, 0.05)	0.101
DENV-3	-0.28	(-0.65, 0.09)	0.140	0.28	(-0.06, 0.62)	0.111
rhesus macaque (*Macaca mulatta*)	ref.					
chimpanzee (*Pan troglodytes*)	-0.05	(-0.71, 0.61)	0.878	-0.58	(-1.20, 0.05)	0.070
common marmoset (*Callithrix jacchus*)	-1.36	(-2.05, -0.67)	< 0.001	-0.83	(-1.59, -0.08)	0.031
cynomolgus macaques (*Macaca fascicularis*)	0.34	(-0.37, 1.04)	0.353	0.39	(-0.30, 1.07)	0.266
green monkey (*Chlorocebus aethiops sabaeus*)	-0.43	(-1.05, 0.20)	0.179	-0.61	(-1.35, 0.13)	0.109
owl monkeys (*Aotus nancymaae*)	-0.30	(-0.78, 0.18)	0.216	0.28	(-0.24, 0.79)	0.291
patas (*Erythrocebus patas*)	4.16	(2.41, 5.91)	< 0.001	3.85	(2.21, 5.48)	< 0.001
pig-tailed macaques (*Macaca nemestrina*)	-1.14	(-1.71, -0.57)	< 0.001	-0.85	(-1.55, -0.14)	0.018
spider monkey (*Ateles geoffroyi*)	-1.51	(-2.02, -0.99)	< 0.001	-2.50	(-3.99, -1.01)	0.001
squirrel monkey (*Saimiri sciureus*)	-0.31	(-1.67, 1.05)	0.659	-1.24	(-2.52, 0.04)	0.058
white handed gibbon (*Hylobates lar*)	0.40	(-0.14, 0.95)	0.148	-0.51	(-1.10, 0.09)	0.096
plaque count	ref.					
ELISA	-0.85	(-1.84, 0.15)	0.097	0.13	(-1.03, 1.30)	0.821
FFA	0.04	(-0.82, 0.91)	0.921	0.23	(-0.60, 1.06)	0.589
IFA	-1.23	(-1.50, -0.97)	< 0.001	-1.48	(-1.77, -1.18)	< 0.001
RTPCR	-1.05	(-1.38, -0.72)	< 0.001	-0.67	(-1.09, -0.25)	0.002
suckling mice	-1.76	(-2.25, -1.27)	< 0.001	0.31	(-1.11, 1.73)	0.673
$\log_{10}$ dose	-0.22	(-0.34, -0.11)	< 0.001	-0.15	(-0.29, -0.02)	0.022

Table S1: **Linear Associations with the Time to Viremia** Table reports the results of the univariate and multivariate linear regression calculating associations between serotype, species, viremia assay used, and $\log_{10}$ inoculating dose and time to viremia. Estimates are differences in days of viremia for each covariate from rhesus monkeys infected with DENV-2 assayed using plaque count.

Covariate	Univariate	95% CI	p	Multivariate	95% CI	p
DENV-4	ref.			ref.		
DENV-1	0.87	(0.40, 1.34)	< 0.001	0.80	(0.35, 1.25)	0.001
DENV-2	1.30	(0.86, 1.73)	< 0.001	1.48	(1.07, 1.90)	< 0.001
DENV-3	0.02	(-0.49, 0.54)	0.928	-0.26	(-0.75, 0.23)	0.297
rhesus macaque (*Macaca mulatta*)	ref.					
chimpanzee (*Pan troglodytes*)	0.03	(-0.95, 1.02)	0.949	0.83	(-0.06, 1.73)	0.067
common marmoset (*Callithrix jacchus*)	0.13	(-0.90, 1.16)	0.802	-2.39	(-3.47, -1.31)	< 0.001
cynomolgus macaques (*Macaca fascicularis*)	0.24	(-0.81, 1.30)	0.653	-0.22	(-1.20, 0.75)	0.656
green monkey (*Chlorocebus aethiops sabaeus*)	-1.61	(-2.53, -0.68)	0.001	-1.91	(-2.97, -0.85)	< 0.001
owl monkeys (*Aotus nancymaae*)	-0.35	(-1.07, 0.36)	0.330	-1.35	(-2.08, -0.62)	< 0.001
patas (*Erythrocebus patas*)	-2.97	(-5.58, -0.35)	0.026	-2.56	(-4.89, -0.24)	0.031
pig-tailed macaques (*Macaca nemestrina*)	-0.03	(-0.88, 0.82)	0.937	-1.15	(-2.15, -0.15)	0.025
spider monkey (*Ateles geoffroyi*)	-0.83	(-1.60, -0.06)	0.035	0.64	(-1.49, 2.76)	0.557
squirrel monkey (*Saimiri sciureus*)	-1.57	(-3.60, 0.46)	0.130	-1.02	(-2.84, 0.81)	0.276
white handed gibbon (*Hylobates lar*)	0.27	(-0.54, 1.09)	0.508	0.46	(-0.39, 1.30)	0.290
plaque count	ref.					
ELISA	0.18	(-1.29, 1.65)	0.808	1.56	(-0.10, 3.23)	0.066
FFA	0.65	(-0.62, 1.93)	0.316	0.42	(-0.77, 1.60)	0.493
IFA	1.04	(0.65, 1.43)	< 0.001	1.49	(1.07, 1.91)	< 0.001
RTPCR	1.91	(1.42, 2.39)	< 0.001	2.91	(2.31, 3.51)	< 0.001
suckling mice	-0.09	(-0.81, 0.63)	0.803	-0.51	(-2.53, 1.52)	0.624
$\log_{10}$ dose	0.00	(0.00, 0.00)	0.114	-0.31	(-0.49, -0.12)	0.002

Table S2: **Linear Associations with the Duration of Viremia** Table reports the results of the univariate and multivariate linear regression calculating associations between serotype, species, viremia assay used, and $\log_{10}$ inoculating dose and duration of viremia. Estimates are differences in days of viremia for each covariate from rhesus monkeys infected with DENV-2 assayed using plaque count.

Model Selection

Table S3 reports Akaike information criterion (AIC) values for the linear and random effects models and likelihood ratio tests for differences between models. We find random effects models are universally favored over linear models.

	Time to viremia			**Duration**		
Covariate	Lin. AIC	R.E. AIC	p	Lin. AIC	R.E. AIC	p
Serotype	2680.42	2504.07	< 0.0001	3150.95	2975.66	< 0.0001
Species	2622.85	2485.22	< 0.0001	3184.89	2994.60	< 0.0001
Assay	2581.47	2508.01	< 0.0001	3128.07	2995.30	< 0.0001
$\log_{10}$ Dose	2674.08	2510.47	< 0.0001	3188.44	2998.25	< 0.0001
Multivariate	2521.66	2472.55	< 0.0001	3020.60	2941.05	< 0.0001

Table S3: **Model Selection** Table reports the reports AIC values for the linear ("Lin.") and random effects ("R.E.") models and likelihood ratio tests for differences between models.

Additional Regression Results

Table S4 reports the results of the multivariate random effects regression for duration of viremia with DENV-2 as the reference serotype. We find durations of DENV-1, -3, and -4 viremia are significantly shorter than DENV-2 after adjusting for study, species, assay and $\log_{10}$ dose.

Covariate	Multivariate	95% CI	p
DENV-2	ref.		
DENV-1	-1.21	(-1.65, -0.77)	< 0.001
DENV-3	-0.47	(-0.93, -0.02)	0.026
DENV-4	-1.51	(-1.99, -1.04)	< 0.001
rhesus macaque (*Macaca mulatta*)	ref.		
chimpanzee (*Pan troglodytes*)	0.26	(-1.06, 1.59)	0.624
common marmoset (*Callithrix jacchus*)	-1.80	(-5.09, 1.49)	0.185
cynomolgus macaques (*Macaca fascicularis*)	0.00	(-1.24, 1.24)	0.941
green monkey (*Chlorocebus aethiops sabaeus*)	-1.48	(-3.08, 0.12)	0.050
owl monkeys (*Aotus nancymaae*)	-1.29	(-3.23, 0.66)	0.125
patas (*Erythrocebus patas*)	-2.35	(-4.45, -0.25)	0.026
pig-tailed macaques (*Macaca nemestrina*)	-0.64	(-3.16, 1.88)	0.514
spider monkey (*Ateles geoffroyi*)	0.34	(-3.77, 4.46)	0.834
squirrel monkey (*Saimiri sciureus*)	-1.39	(-3.36, 0.59)	0.170
white handed gibbon (*Hylobates lar*)	0.09	(-3.09, 3.28)	0.932
plaque count	ref.		
ELISA	1.34	(-1.61, 4.30)	0.304
FFA	0.27	(-2.22, 2.75)	0.788
IFA	1.34	(0.05, 2.64)	0.018
RTPCR	2.52	(1.19, 3.85)	< 0.001
suckling mice	-0.37	(-3.92, 3.18)	0.807
$\log_{10}$ dose	-0.44	(-0.69, -0.18)	< 0.001
Intercept (β_0)	6.24	(4.72, 7.77)	< 0.001
Random Effect (σ)	2.32	(-0.67, 5.30)	

Table S4: **Associations with Duration of Viremia, DENV-2 as Reference** Table reports the results of the multivariate mixed effects regression calculating associations between serotype, species, viremia assay used, and $\log_{10}$ inoculating dose and duration of viremia with DENV-2 as the reference category. Mixed effects models included random effect for study. Estimates are differences in days of viremia for each covariate from rhesus monkeys infected with DENV-2 assayed using plaque count. P-values calculated using likelihood ratio tests. Durations of DENV-1, -3, and -4 viremia are significantly shorter than DENV-2 after adjusting for study, species, assay and $\log_{10}$ dose. Estimates of the fixed intercept (β_0) and variance of the random intercept are presented (σ).

Distribution of Time to– and Duration of Viremia

Figures S2 and S3 show histograms of the time to– and duration of DENV-1–4 viremia, respectively, pooled across non-human primates with maximum likelihood log-normal fits.

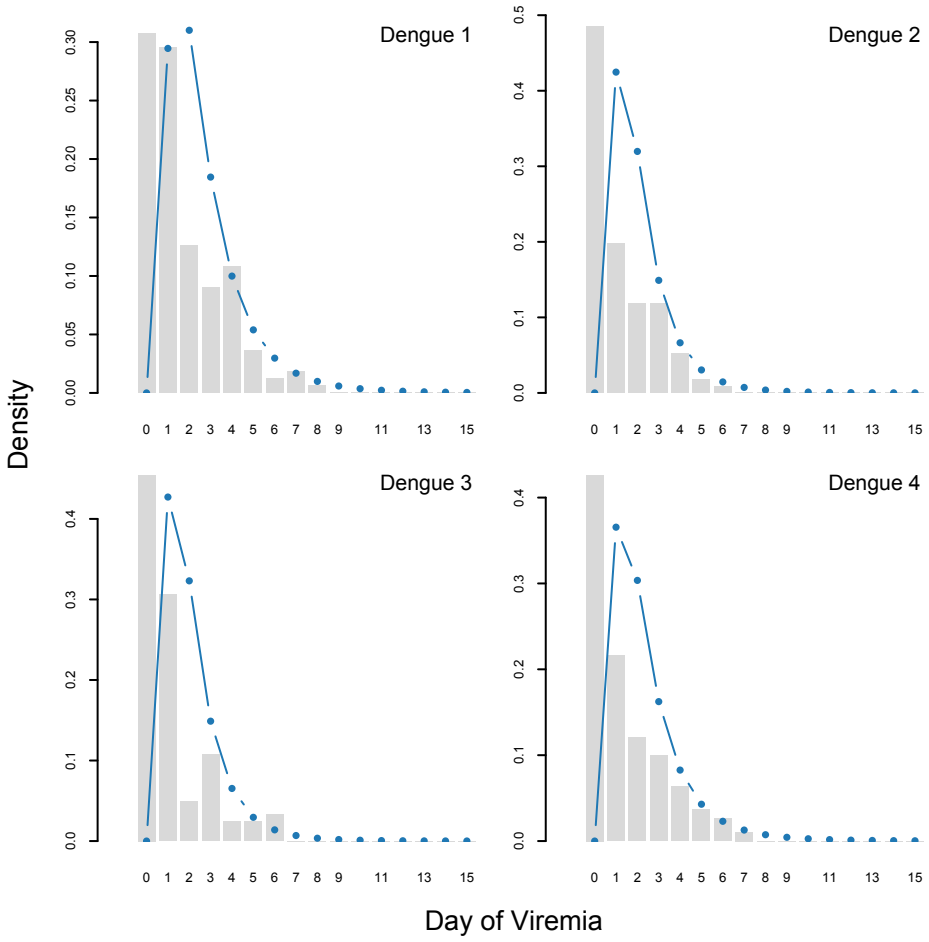

Figure S2: **Histogram of Time of DENV Viremia Pooled Across Primates** Figure shows histograms of the days to viremia by serotype pooled across non-human primates. Lines are log-normal maximum likelihood fits.

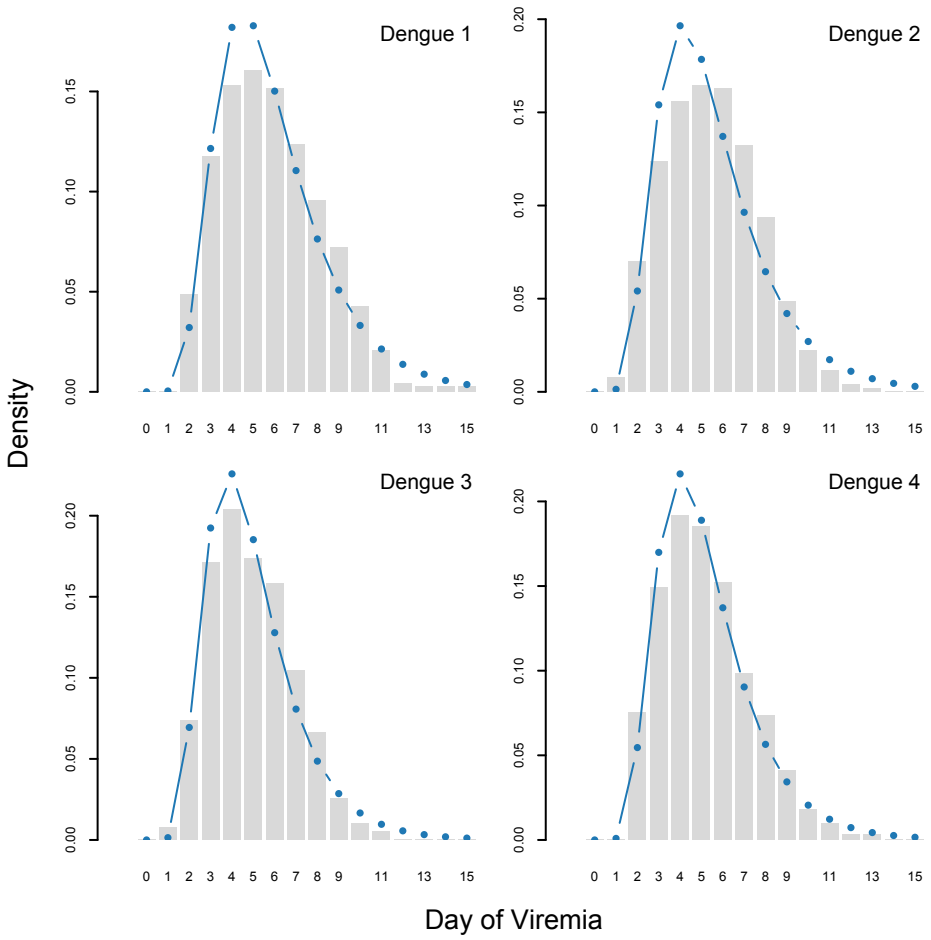

Figure S3: **Histogram of Duration of DENV Viremia Pooled Across Primates** Figure shows histograms of the days of viremia by serotype pooled across non-human primates. Lines are log-normal maximum likelihood fits.

Combined Estimates of Vireima

Table S5 reports the doubly-interval censored estimates and bootstrap confidence intervals of time to- and duration of viremia pooled across all non-human primates.

Serotype	Percentile	Time to viremia Days (95% CI)	Duration Days (95% CI)
1	5th	1.47 (1.30, 1.64)	1.73 (1.50, 2.02)
n = 166	25th	2.34 (2.14, 2.52)	2.98 (2.70, 3.28)
	50th	3.23 (3.00, 3.45)	4.33 (4.03, 4.67)
	75th	4.47 (4.14, 4.77)	6.31 (5.87, 6.73)
	95th	7.12 (6.42, 7.76)	10.85 (9.75, 11.87)
2	5th	0.88 (0.73, 1.03)	1.84 (1.60, 2.12)
n = 227	25th	1.60 (1.41, 1.79)	3.25 (2.97, 3.55)
	50th	2.44 (2.22, 2.65)	4.84 (4.52, 5.15)
	75th	3.71 (3.44, 3.94)	7.19 (6.75, 7.60)
	95th	6.78 (6.26, 7.31)	12.72 (11.64, 13.84)
3	5th	1.33 (1.17, 1.54)	1.17 (0.99, 1.41)
n = 121	25th	2.10 (1.92, 2.31)	2.17 (1.92, 2.46)
	50th	2.89 (2.67, 3.11)	3.34 (3.01, 3.68)
	75th	3.96 (3.64, 4.30)	5.12 (4.69, 5.61)
	95th	6.25 (5.55, 7.07)	9.49 (8.47, 10.51)
4	5th	1.46 (1.34, 1.59)	1.19 (1.05, 1.38)
n = 190	25th	2.31 (2.17, 2.46)	2.15 (1.96, 2.38)
	50th	3.17 (2.98, 3.37)	3.24 (3.01, 3.51)
	75th	4.36 (4.07, 4.65)	4.88 (4.54, 5.24)
	95th	6.88 (6.29, 7.46)	8.81 (7.97, 9.64)

Table S5: **Summary of DENV Virus Kinetics Pooled Across Primates** Table reports median days of DENV viremia with 95% confidence intervals for 5th, 25th, 50th, 75th, and 95th percentile.

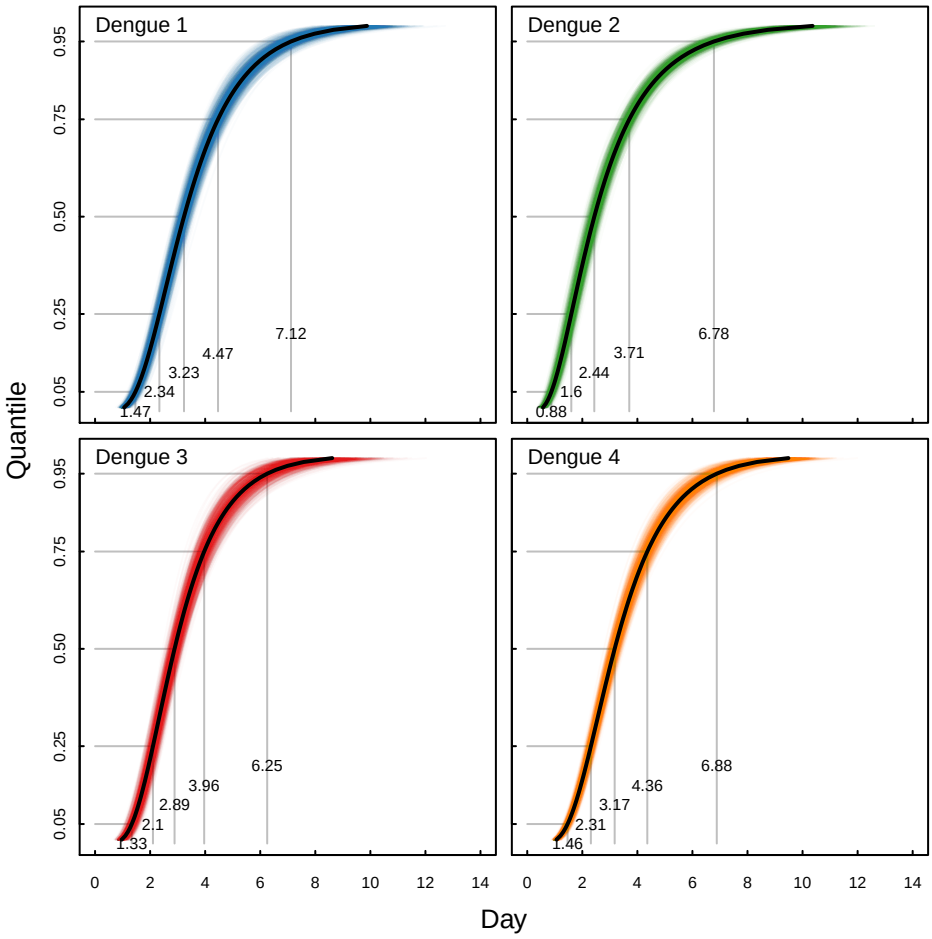

Figure S4: **Time to Viremia for DENV Pooled Across Primates** Figure shows estimates of the time to viremia (time from inoculation to positive isolation of virus) for DENV-1–4 pooled across all non-human primate species. Black lines indicate estimates from full dataset and light colored lines indicate bootstrap replicates. Grey lines indicate the 5th, 25th, 50th, 75th and 95th quantiles.

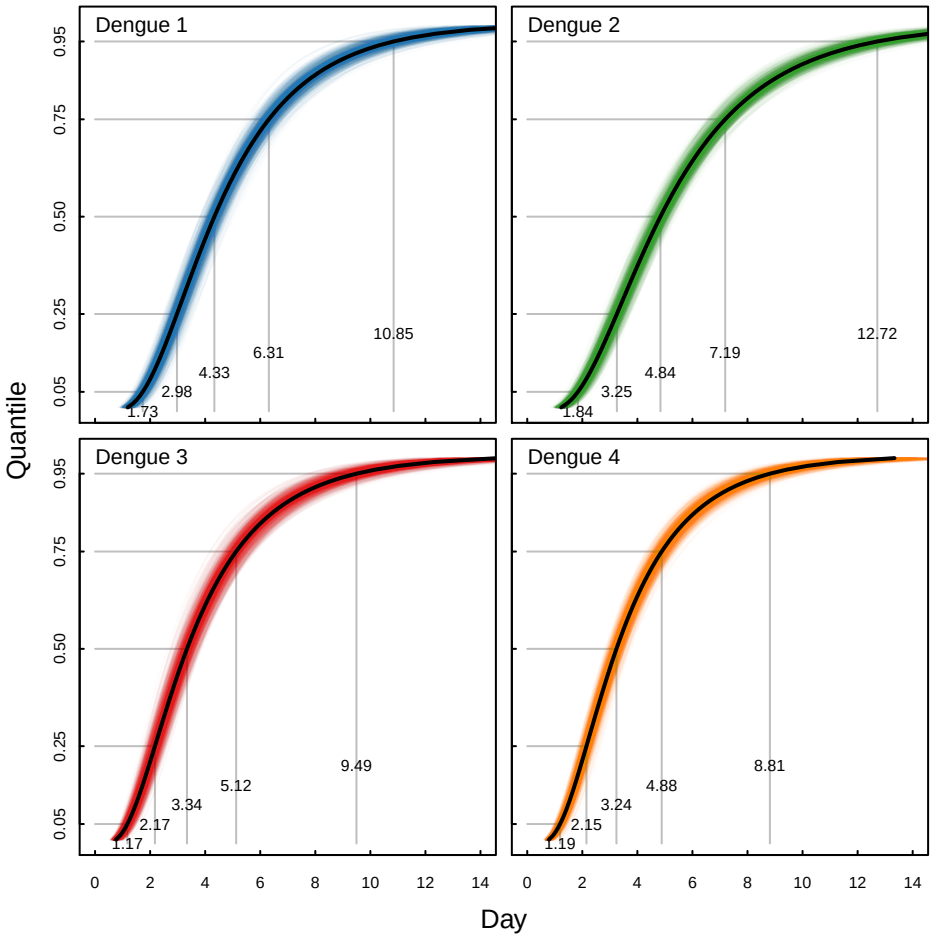

Figure S5: **Duration of DENV Infection Pooled Across Primates** Figure shows estimates of the duration of infection for DENV-1–4 pooled across all non-human primate species. Black lines indicate estimates from full dataset and light colored lines indicate bootstrap replicates. Grey lines indicate the 5th, 25th, 50th, 75th and 95th quantiles.

Sensitivity Analysis: Choice of Cutoff for Interval Censoring

Table S6 reports the doubly-interval censored estimates and bootstrap confidence intervals of duration of viremia for Rhesus macaques with day 14 and day 18 as assumed maximum duration of viremia. We find no qualitative differences from the 16 day cutoff as presented in the main text.

Serotype	Percentile	Day 14 Cutoff Days (95% CI)	Day 18 Cutoff Days (95% CI)
1	5th	2.03 (1.70, 2.46)	2.01 (1.70, 2.42)
n = 97	25th	3.31 (2.93, 3.76)	3.31 (2.94, 3.75)
	50th	4.66 (4.26, 5.10)	4.68 (4.27, 5.12)
	75th	6.55 (6.02, 7.07)	6.63 (6.02, 7.20)
	95th	10.69 (9.40, 11.85)	10.91 (9.49, 12.34)
2	5th	2.26 (1.97, 2.60)	2.23 (1.95, 2.56)
n = 155	25th	3.65 (3.33, 4.01)	3.65 (3.34, 3.98)
	50th	5.10 (4.75, 5.47)	5.15 (4.80, 5.53)
	75th	7.13 (6.64, 7.61)	7.27 (6.74, 7.80)
	95th	11.54 (10.32, 12.60)	11.92 (10.53, 13.28)
3	5th	1.04 (0.84, 1.32)	1.03 (0.84, 1.33)
n = 75	25th	2.02 (1.73, 2.40)	2.02 (1.72, 2.40)
	50th	3.22 (2.81, 3.67)	3.23 (2.80, 3.68)
	75th	5.12 (4.52, 5.72)	5.15 (4.46, 5.75)
	95th	10.00 (8.62, 11.26)	10.09 (8.57, 11.55)
4	5th	1.10 (0.95, 1.32)	1.09 (0.94, 1.31)
n = 139	25th	2.04 (1.82, 2.31)	2.04 (1.83, 2.30)
	50th	3.13 (2.84, 3.45)	3.14 (2.87, 3.45)
	75th	4.81 (4.39, 5.23)	4.83 (4.42, 5.29)
	95th	8.91 (8.02, 9.92)	8.99 (7.96, 10.06)

Table S6: **Sensitivity Analyses to Choice of Day of Maximum Viremia** Table reports mean days of DENV viremia with 95% bootstrap confidence intervals for 5th, 25th, 50th, 75th, and 95th percentile, for 14 and 18 day cutoffs..