

PLATCOV Statistical Analysis

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TODO list:

- Flow diagram output

Preamble

This is the analysis of the Ivermectin arm of the PLATCOV study

Data preparation is done in a different R script called `data_prep.R`. This Markdown script assumes that the data are saved in a `.csv` file `interim_dat.csv` in long format. The file `interim_dat.csv` contains the patient clinical and viral load data with the following column headers:

- ID: anonymised patient id code
- Time: time from randomisation
- Trt: treatment allocation as written in CRF
- Site: site at enrolment
- Timepoint_ID: Day of study (integer 0 to 14)
- BARCODE: unique sample id code (in the following format: PLT-site-number-swab type-timepoint)
- Swab_ID: RTS or TSL (right versus left tonsil)
- Plate: unique Plate ID for the PCR assay (matching with plate identifiers in `interim_control_dat.csv`)
- Rand_date: date of randomisation
- Any_dose: (0/1) any doses of any manufacturer received
- N_dose: integer number of doses received (any manufacturer)
- Antibody_test: 0/1 (negative/positive for SARS-CoV-2 antibody rapid test)
- Weight (kg)
- BMI: kg/weight^2
- Age: (years - has to be between 18-50)
- Sex: 0/1 (male: 1; female/other: 0)
- Symptom_onset: time since onset of symptoms (days)
- Variant: variant of concern (using standard WHO terminology for the main lineages, reference will be the predominant variant in the dataset at the start of the study)
- CT_NS: observed CT value for the N/S gene
- CT_RNaseP: observed CT value for the human RNase P gene

- Per_protocol_sample: whether at the time of sampling the patient was still in per protocol with respect to drug dosing
- IgG: + IgG band on the LFT
- IgM: + IgM band on the LFT
- log10_viral_load: log10 number of viral copies per mL (estimated from control samples using a mixed effects model)
- log10_cens_vl: censoring value

Computational setup

```
## 
## platform      -x86_64-apple-darwin17.0
## arch         x86_64
## os           darwin17.0
## system       x86_64, darwin17.0
## status
## major        4
## minor        0.2
## year         2020
## month        06
## day          22
## svn rev     78730
## language     R
## version.string R version 4.0.2 (2020-06-22)
## nickname     Taking Off Again

## R version 4.0.2 (2020-06-22)
## Platform: x86_64-apple-darwin17.0 (64-bit)
## Running under: macOS 10.16
##
## Matrix products: default
## BLAS: /Library/Frameworks/R.framework/Versions/4.0/Resources/lib/libRblas.dylib
## LAPACK: /Library/Frameworks/R.framework/Versions/4.0/Resources/lib/libRlapack.dylib
##
## locale:
## [1] en_GB.UTF-8/en_GB.UTF-8/en_GB.UTF-8/C/en_GB.UTF-8/en_GB.UTF-8
##
## attached base packages:
## [1] stats      graphics   grDevices  utils      datasets   methods    base
##
## other attached packages:
## [1] plotrix_3.8-2      dplyr_1.0.7      reshape2_1.4.4
## [4] tictoc_1.0.1       censReg_0.5-32   maxLik_1.5-2
## [7] miscTools_0.6-26   RColorBrewer_1.1-2 loo_2.4.1
## [10] rstanarm_2.21.1    Rcpp_1.0.7       lme4_1.1-27.1
## [13] Matrix_1.3-4      rstan_2.21.2     ggplot2_3.3.5
## [16] StanHeaders_2.21.0-7
##
## loaded via a namespace (and not attached):
## [1] plm_2.6-0          minqa_1.2.4      colorspace_2.0-2 ellipsis_0.3.2
## [5] ggridges_0.5.3     rsconnect_0.8.24  markdown_1.1     base64enc_0.1-3
## [9] rstudioapi_0.13    glmmML_1.1.1     DT_0.19        fansi_0.5.0
## [13] codetools_0.2-18   splines_4.0.2     knitr_1.34      shinythemes_1.2.0
## [17] bayesplot_1.8.1    Formula_1.2-4    jsonlite_1.7.2  nloptr_1.2.2.2
## [21] shiny_1.6.0         compiler_4.0.2    backports_1.2.1 assertthat_0.2.1
```

```

## [25] fastmap_1.1.0      cli_3.0.1        later_1.3.0      htmltools_0.5.2
## [29] prettyunits_1.1.1   tools_4.0.2       igraph_1.2.6     gtable_0.3.0
## [33] glue_1.4.2         V8_3.4.2        vctrs_0.3.8     nlme_3.1-153
## [37] crosstalk_1.1.1    lmtest_0.9-38    xfun_0.26       stringr_1.4.0
## [41] rbibutils_2.2.7    ps_1.6.0        collapse_1.7.6  mime_0.11
## [45] miniUI_0.1.1.1     lifecycle_1.0.0  gtools_3.9.2     MASS_7.3-54
## [49] zoo_1.8-9          scales_1.1.1     colourpicker_1.1.0 promises_1.2.0.1
## [53] parallel_4.0.2      sandwich_3.0-1   inline_0.3.19   shinystan_2.5.0
## [57] yaml_2.2.1         curl_4.3.2       gridExtra_2.3   bdsmatrix_1.3-4
## [61] stringi_1.7.4      dygraphs_1.1.1.6 checkmate_2.0.0  boot_1.3-28
## [65] pkgbuild_1.2.0      Rdpack_2.1.3     rlang_0.4.11    pkgconfig_2.0.3
## [69] matrixStats_0.61.0   evaluate_0.14   lattice_0.20-44 purrr_0.3.4
## [73] rstantools_2.1.1    htmlwidgets_1.5.4 processx_3.5.2   tidyselect_1.1.1
## [77] plyr_1.8.6          magrittr_2.0.1   R6_2.5.1       generics_0.1.0
## [81] DBI_1.1.1           pillar_1.6.2     withr_2.4.2    xts_0.12.1
## [85] survival_3.2-13     tibble_3.1.4     crayon_1.4.1   utf8_1.2.2
## [89] rmarkdown_2.11       grid_4.0.2       callr_3.7.0    threejs_0.3.3
## [93] digest_0.6.27       xtable_1.8-4    httpuv_1.6.3   RcppParallel_5.1.4
## [97] stats4_4.0.2        munsell_0.5.0   shinyjs_2.0.0

```

Warning in checkStrict(make_stan_inputs): global variables used: log10_cens_vl,
log10_viral_load

Load data

```

## ITT population:
##   Favipiravir   Fluoxetine   Ivermectin No study drug   Regeneron
##   45            3             46            45            40
##   Remdesivir
##   45

## These IDs are in the ITT database but are not in the PCR database:
## [1] "PLT-TH1-003"  "PLT-TH1-005"  "PLT-TH1-006"  "PLT-TH1-012"  "PLT-TH1-013"
## [6] "PLT-TH1-016"  "PLT-TH1-019"  "PLT-TH1-022"  "PLT-TH1-025"  "PLT-TH1-027"
## [11] "PLT-TH1-029"  "PLT-TH1-030"  "PLT-TH1-031"  "PLT-TH1-033"  "PLT-TH1-039"
## [16] "PLT-TH1-042"  "PLT-TH1-044"  "PLT-TH1-046"  "PLT-TH1-048"  "PLT-TH1-052"
## [21] "PLT-TH1-054"  "PLT-TH1-055"  "PLT-TH1-056"  "PLT-TH1-057"  "PLT-TH1-059"
## [26] "PLT-TH1-060"  "PLT-TH1-061"  "PLT-TH1-062"  "PLT-TH1-063"  "PLT-TH1-064"
## [31] "PLT-TH1-065"  "PLT-TH1-067"  "PLT-TH1-070"  "PLT-TH1-071"  "PLT-TH1-073"
## [36] "PLT-TH1-074"  "PLT-TH1-076"  "PLT-TH1-078"  "PLT-TH1-079"  "PLT-TH1-082"
## [41] "PLT-TH1-083"  "PLT-TH1-084"  "PLT-TH1-087"  "PLT-TH1-089"  "PLT-TH1-090"
## [46] "PLT-TH1-091"  "PLT-TH1-092"  "PLT-TH1-095"  "PLT-TH1-096"  "PLT-TH1-097"
## [51] "PLT-TH1-100"  "PLT-TH1-101"  "PLT-TH1-102"  "PLT-TH1-103"  "PLT-TH1-106"
## [56] "PLT-TH1-108"  "PLT-TH1-109"  "PLT-TH1-110"  "PLT-TH1-112"  "PLT-TH1-113"
## [61] "PLT-TH1-114"  "PLT-TH1-117"  "PLT-TH1-118"  "PLT-TH1-119"  "PLT-TH1-121"
## [66] "PLT-TH1-122"  "PLT-TH1-125"  "PLT-TH1-126"  "PLT-TH1-127"  "PLT-TH1-130"
## [71] "PLT-TH1-131"  "PLT-TH1-132"  "PLT-TH1-135"  "PLT-TH1-136"  "PLT-TH1-138"
## [76] "PLT-TH1-140"  "PLT-TH1-143"  "PLT-TH1-145"  "PLT-TH1-146"  "PLT-TH1-147"
## [81] "PLT-TH1-148"  "PLT-TH1-150"  "PLT-TH1-151"  "PLT-TH1-152"  "PLT-TH1-153"
## [86] "PLT-TH1-154"  "PLT-TH1-155"  "PLT-TH1-163"  "PLT-TH1-164"  "PLT-TH1-166"
## [91] "PLT-TH1-167"  "PLT-TH1-169"  "PLT-TH1-170"  "PLT-TH1-171"  "PLT-TH1-172"
## [96] "PLT-TH1-174"  "PLT-TH1-177"  "PLT-TH1-178"  "PLT-TH1-181"  "PLT-TH1-182"
## [101] "PLT-TH1-184"  "PLT-TH1-186"  "PLT-TH1-190"  "PLT-TH1-192"  "PLT-TH1-193"
## [106] "PLT-TH1-194"  "PLT-TH1-196"  "PLT-TH1-197"  "PLT-TH1-198"  "PLT-TH1-199"

```

```

## [111] "PLT-TH1-200"  "PLT-TH1-201"  "PLT-TH1-203"  "PLT-TH1-204"  "PLT-TH58-001"
## [116] "PLT-TH58-003" "PLT-TH58-005" "PLT-TH58-007" "PLT-TH58-009" "PLT-TH57-004"
## [121] "PLT-TH57-005" "PLT-TH57-006" "PLT-TH57-007" "PLT-TH57-008"

## [1] TRUE

## Missing time for following samples: PLT-TH57-001
## Missing time for following samples: PLT-TH57-002
## Missing time for following samples: PLT-TH57-003
## Missing time for following samples: PLT-TH58-004
## Missing time for following samples: PLT-TH58-002
## Missing time for following samples: PLT-TH58-006
## Missing time for following samples: PLT-TH58-008

## Negative time for following samples: PLT-TH57-009
## Negative time for following samples: PLT-TH57-010

## All negative samples for id: PLT-TH1-128

```

Data summaries

Display the per protocol matrix

```

## Number of patients per arm in modified intention to treat analysis

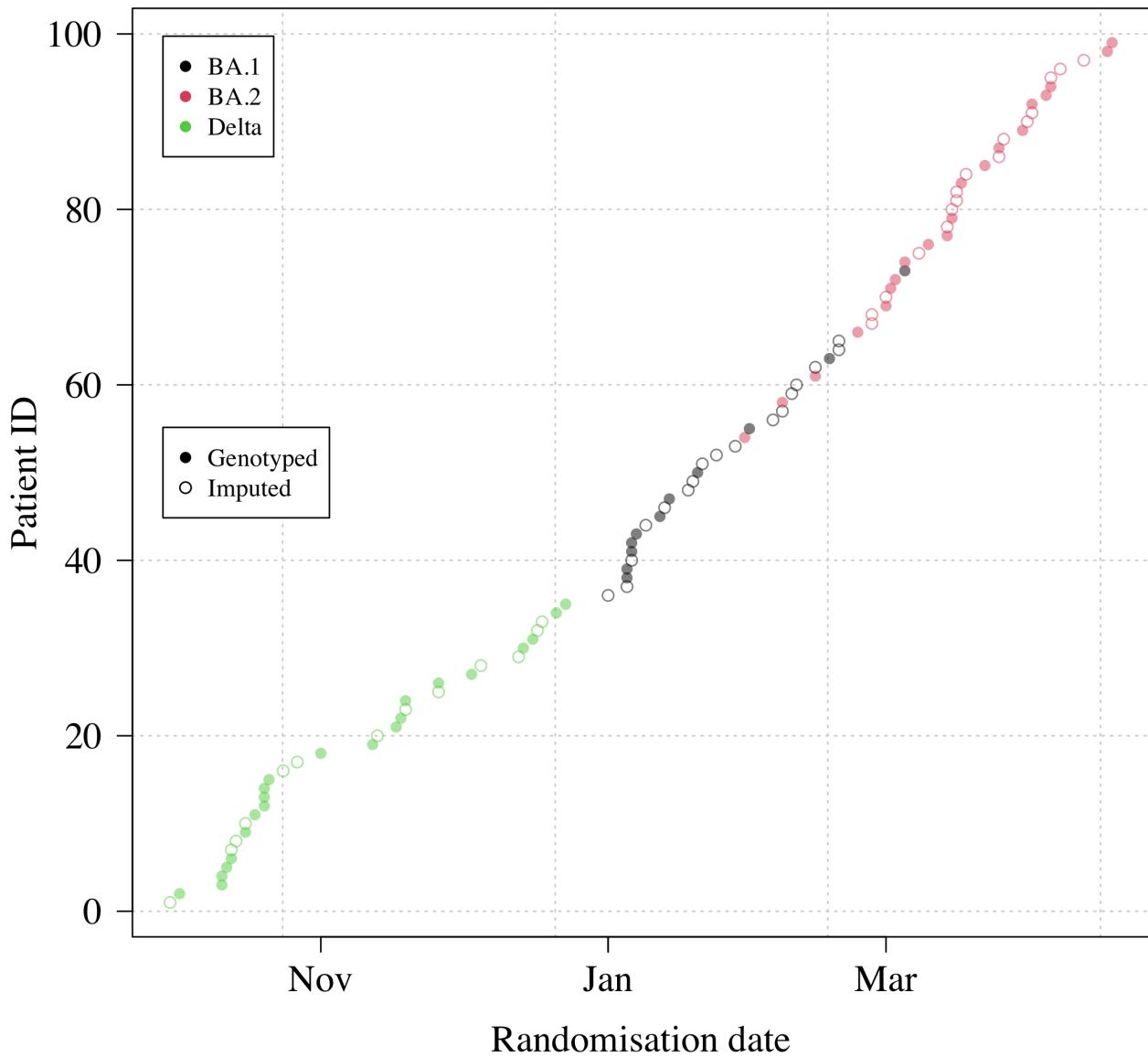
##                                     Include_mITT
##                               FALSE  TRUE
## Casirivimab\nimdevimab      0   10
## Ivermectin                  1   45
## No study drug                3   41

## Number of swabs per protocol per treatment

##                                     PP_swabs
##                               6   8   12  18  20
## Casirivimab\nimdevimab    0   0   0   0  10
## Ivermectin                  1   1   3   0  41
## No study drug                2   0   0   2  40

## We have 1988 PCR datapoints on 99 patients from 3 sites between 2021-09-30 and 2022-04-18

```



```

## [1] TRUE
## The analysis dataset contains 96 patients. The geometric mean baseline (defined as samples taken with
## Summary table
## [1] "Ivermectin"           "Casirivimab\nimdevimab" "No study drug"

```

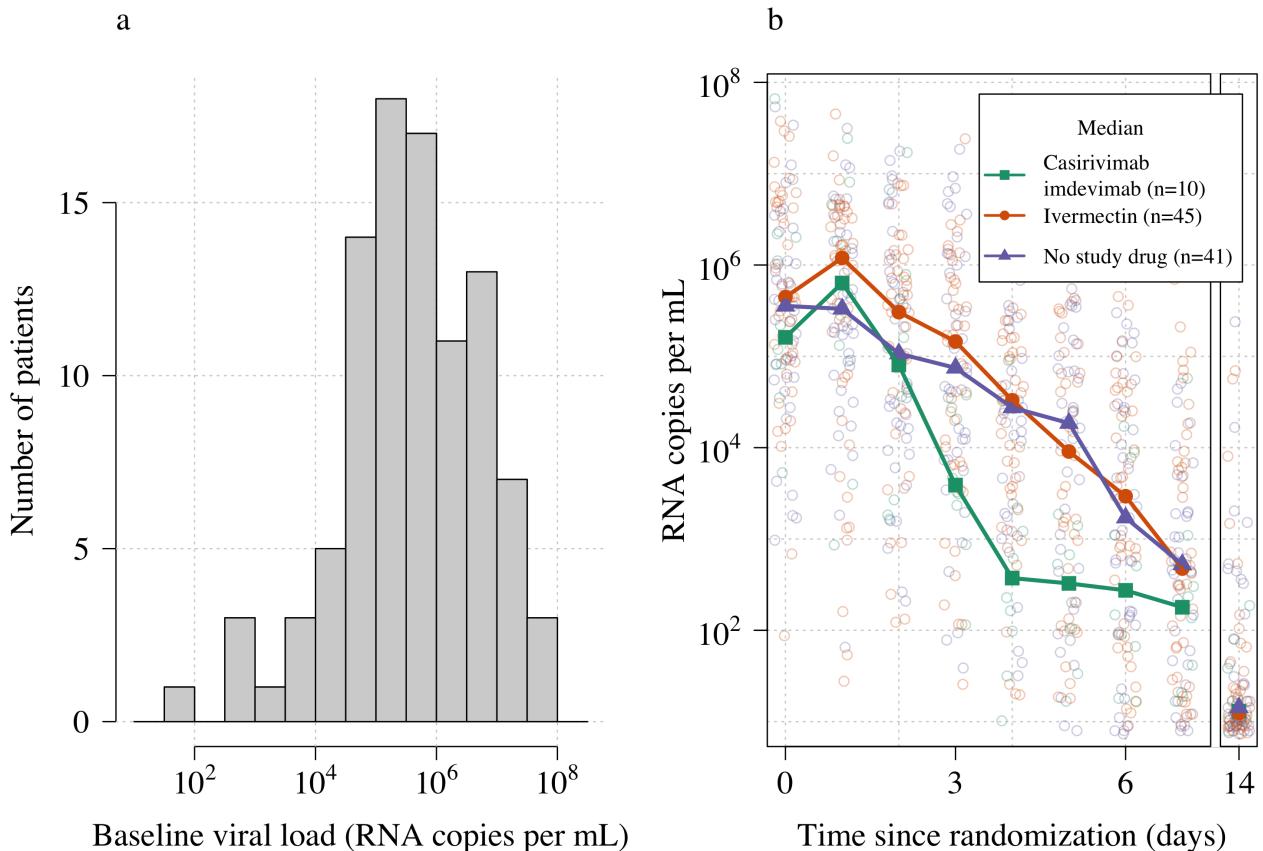
Table 1: Summary of patient characteristics included in the current interim analysis (n= 96). Age: median (range); baseline viral load (log₁₀ copies per mL: mean (range)); vaccinated: % with any number of doses; number of vaccine doses: median (range); antibody data are from rapid tests done at screening (+ is presence of IgM or IgG band).

Arm	n	Age	Baseline viral load (log ₁₀)	Vaccinated (%)	Number of vaccine doses	Antibody +	Male (%)	th001 (%)	th057 (%)	th058 (%)
Casirivimab										

Arm	n	Age	Baseline viral load (log10)	Vaccinated (%)	Number of vaccine doses	Antibody+ (%)	Male (%)	th001	th057	th058
imdevimab	10	26.5 (18-31)	5.5 (3.7-7.8)	80	2 (0-3)	50	20	10	0	0
Ivermectin	45	29 (19-45)	5.7 (1.9-7.6)	98	2 (0-4)	78	47	41	2	2
No study drug	41	27 (20-43)	5.5 (3-7.7)	100	2 (2-4)	90	44	36	3	2

Summary data plot

Plotting data for 96 individuals



Model fitting

Specify priors

Prepare model

Make stan data set.

Covariates that we use in model 2:

- Vaccination (number of doses)
- Age (standardised to have mean=0 and sd=1)
- Time since symptom onset (days, between 0 and 4)
- Variant (WHO variants of concern) - when available (this is replaced by epoch until we have variant data)

- Serology rapid test (+/-)
- Serum antibody: not yet decided which antibody will be measured - expected May/June 2022

```

## Total number of datapoints up until day 8 is 1700
## Number of patients per arm in analysis:
##
##           No study drug Casirivimab\nimdevimab          Ivermectin
##                  41                           10                      45
## There are a total of 96 patients in the database with a total of 1700 PCRs analysable
## 7.12% of samples are below LOD
## check stan data formatting:
```

Setup model runs

We fit a sequence of Bayesian hierarchical models. To make sure there are no bugs in the code (all stan code is written specifically for this trial analysis), I fit the following sequence of five models of increasing complexity:

- Model 0: vanilla student-t regression with left censoring at 0 and with individual random effects for slope and intercept;
- Model 1: add the RNaseP measurements;
- Model 2: Add covariate adjustment;
- Model 3: Non-linear model (up and then down) with RNaseP adjustment.

```

## [1] ".../Stan_models/Linear_model_basic.stan"
## [2] ".../Stan_models/Linear_model_RNaseP.stan"
## [3] ".../Stan_models/Nonlinear_model_RNaseP.stan"

## We are running all models with 4 chains and 10000 samples for each chain, discarding half for burn-in
```

Load model fits

Model fits: summaries

Model comparisons using loo

Results

Estimated treatment effects under the 4 models

Posterior distributions over the treatment effects for the interventions. Red: no effect; blue: median inferred effect.

```

##
## ****
## Mean estimated treatment effects (multiplicative):
##
##           Casirivimab\nimdevimab Ivermectin
## [1,]          1.606569  0.9057598
## [2,]          1.552534  0.9119189
## [3,]          1.479141  0.9129407
## [4,]          1.682005  0.9254563
## [5,]          1.562946  0.9110849
## [6,]          1.546228  0.9221675
## [7,]          1.465852  0.9220199
## [8,]          1.668224  0.9312359
## [9,]          1.521437  0.9145647
```

```

##  

## *****  

## Probability of super-superiority:  

##  

##      Casirivimab\Ivermectin  

## [1,] 96.2     3.2  

## [2,] 96.8     2.4  

## [3,] 93.7     1.4  

## [4,] 97.7     5.1  

## [5,] 96.2     1.4  

## [6,] 95.2     3.9  

## [7,] 93.8     2.2  

## [8,] 95.8     4.4  

## [9,] 96.2     2.3  

Overall effects  

##  

##      mean        sd       2.5%      97.5%    n_eff  

## trt_effect[1] 0.439888637 0.17934459 0.09960327 0.7962699 1254.1722  

## trt_effect[2] -0.092204211 0.11091826 -0.31184301 0.1165217 1293.0637  

## alpha_0        5.376053376 0.20737297 4.97711203 5.7713613 1202.6199  

## beta_0         -0.393258717 0.05308808 -0.50397721 -0.2993492 923.8939  

## sigma_logvl   0.918595705 0.03082043 0.85824143 0.9824783 1239.7395  

## sigmasq_u[1]  0.944248379 0.08594156 0.79412882 1.1260287 1111.5958  

## sigmasq_u[2]  0.491408783 0.05762955 0.38986451 0.6233133 1148.9370  

## t_dof          6.406923088 1.15074675 4.61178316 9.1687686 1155.5419  

## gamma_rnasep  0.212751834 0.02973523 0.15754763 0.2717516 1189.6898  

## slope_coefs[1] 0.036787854 0.14932143 -0.25367176 0.3354384 1168.3910  

## slope_coefs[2] -0.049529172 0.16025225 -0.35438203 0.2742960 1144.4142  

## slope_coefs[3] 0.402033598 0.24506979 -0.07397654 0.8623881 1182.4303  

## slope_coefs[4] 0.004732043 0.30463116 -0.61702613 0.5948953 1157.6187  

## intercept_coefs[1] 0.929006765 0.25498617 0.42861423 1.4514274 1188.0568  

## intercept_coefs[2] 0.301949535 0.26267776 -0.19173216 0.8233794 1189.7200  

## intercept_coefs[3] -0.430171778 0.42821058 -1.26408866 0.4022732 1191.5614  

## intercept_coefs[4] -0.676360801 0.46784331 -1.56210113 0.2542441 1259.7549  

##  

##      Rhat  

## trt_effect[1] 0.9974927  

## trt_effect[2] 0.9979626  

## alpha_0        1.0001441  

## beta_0         0.9991269  

## sigma_logvl   0.9978665  

## sigmasq_u[1]  0.9994497  

## sigmasq_u[2]  0.9984864  

## t_dof          0.9983689  

## gamma_rnasep  0.9989161  

## slope_coefs[1] 0.9978297  

## slope_coefs[2] 0.9985918  

## slope_coefs[3] 1.0030934  

## slope_coefs[4] 0.9994791  

## intercept_coefs[1] 0.9981466  

## intercept_coefs[2] 1.0025176  

## intercept_coefs[3] 0.9997953  

## intercept_coefs[4] 0.9979061  

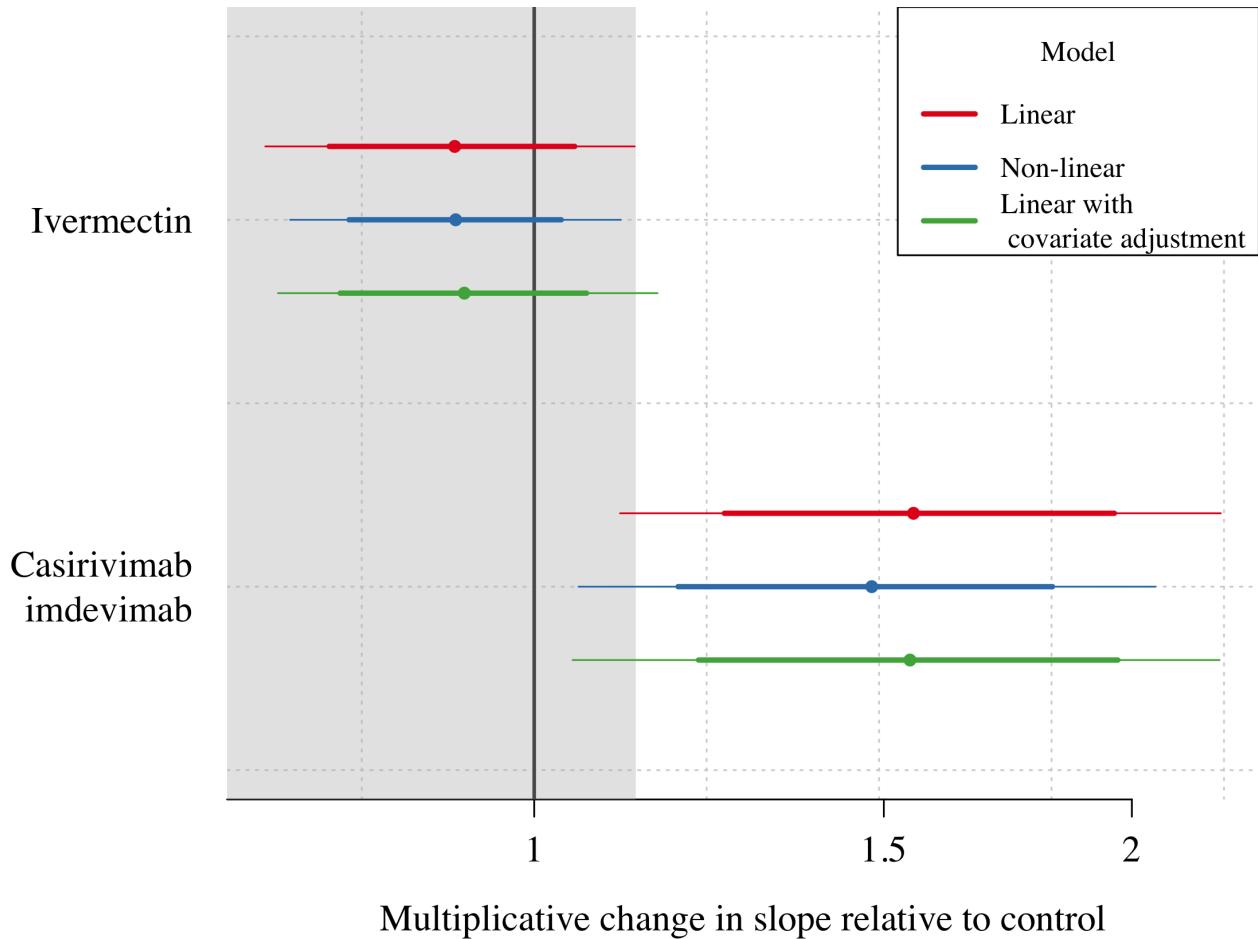
  

## Under model 2 the treatment effect for ivermectin is 0.91 (95% 0.73 to 1.1)

```

```
## Under model 2 the treatment effect for Regeneron is 1.6 (95% 1.1 to 2.2)
```

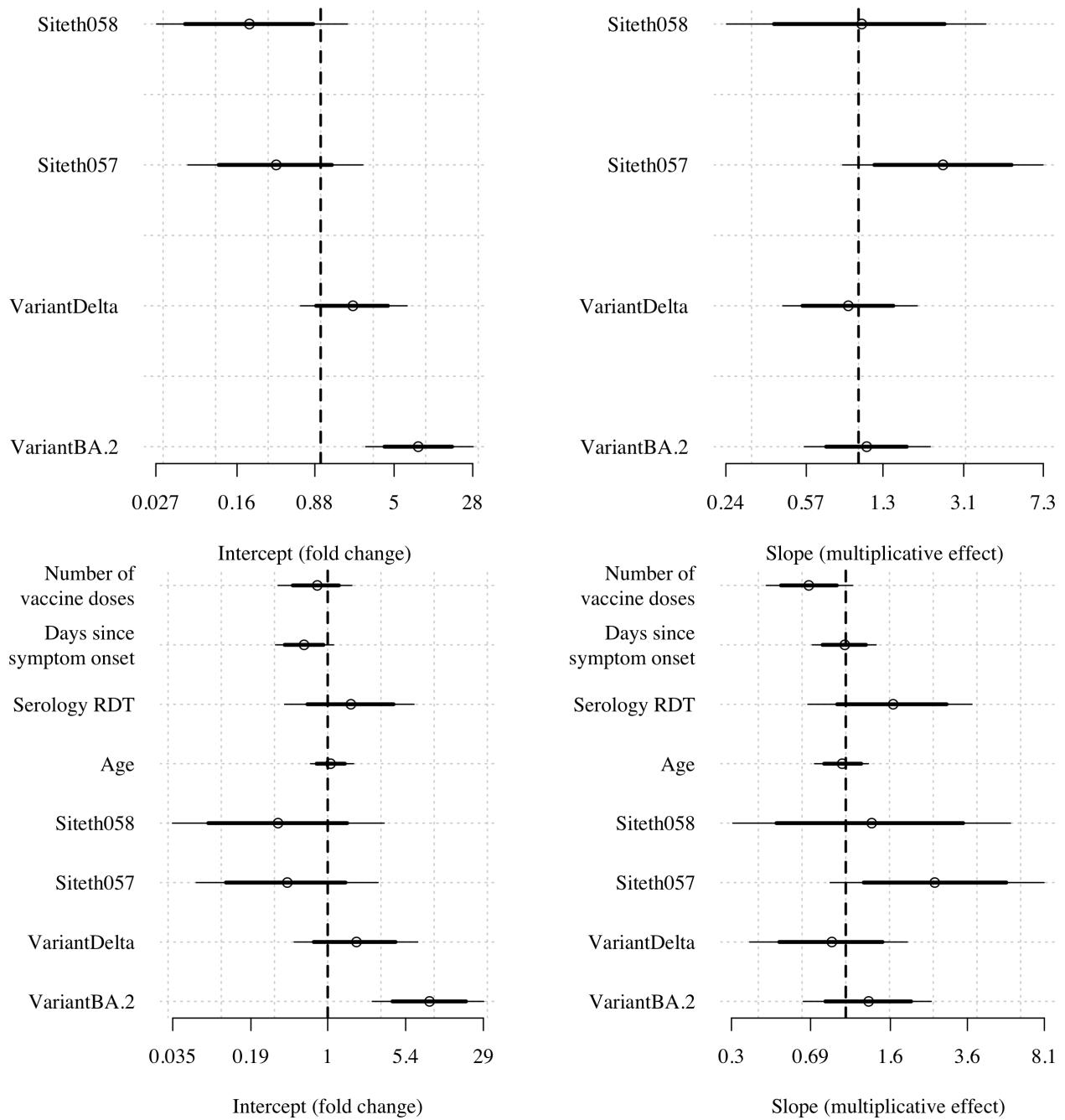
```
## The main 3 models with weakly informative priors:
```



Covariate effects on the intercept (baseline viral load) and slope (viral clearance):

```
## The following `from` values were not present in `x`: Age_scaled, Antibody_test, Symptom_onset, N_dose
```

```
## The following `from` values were not present in `x`: Age_scaled, Antibody_test, Symptom_onset, N_dose
```



Slopes over time

Plot the absolute slope estimate for each individual over time

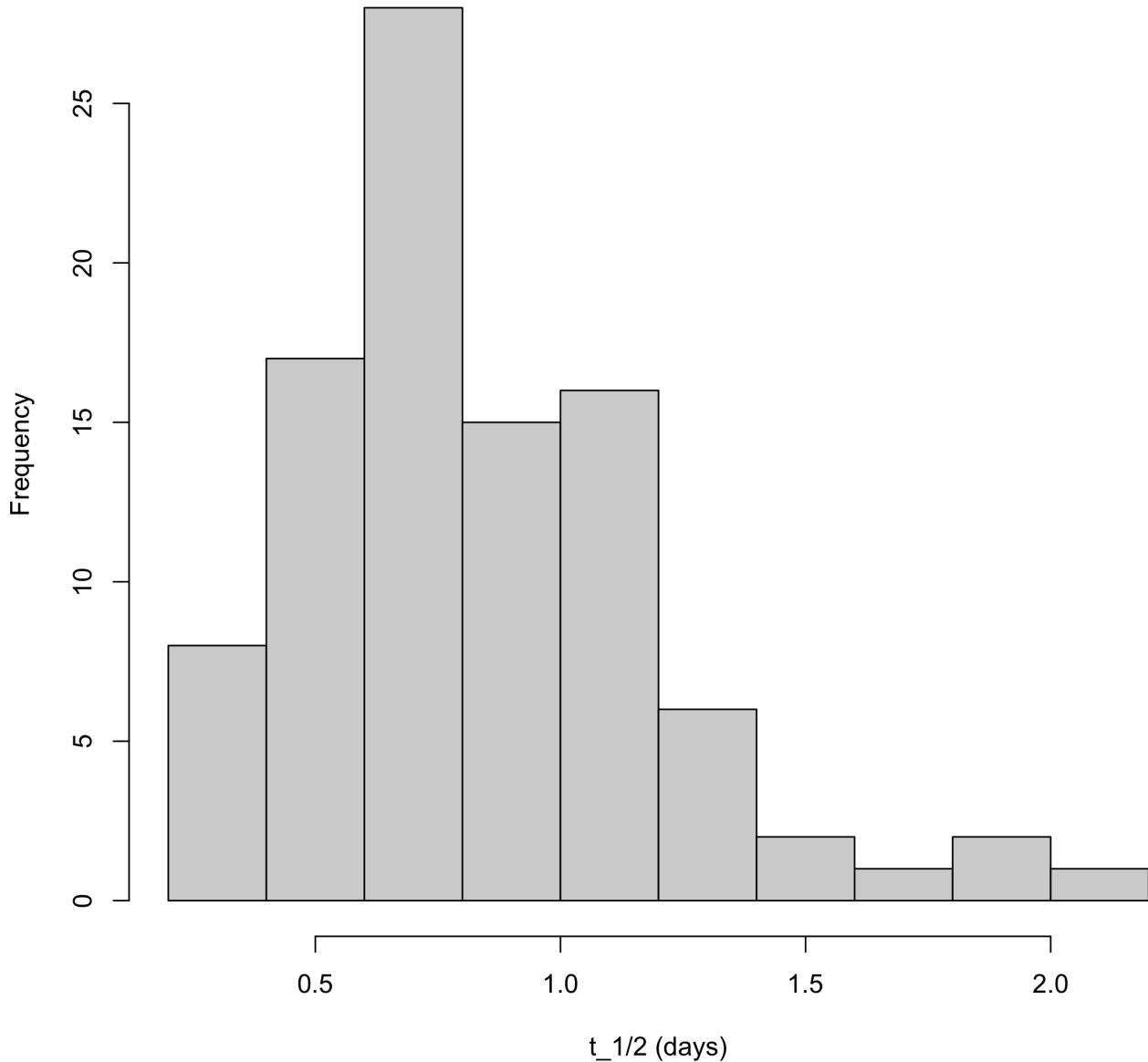
```
## The following `from` values were not present in `x`: PLT-TH1-018, PLT-TH1-020, PLT-TH1-105
## The following `from` values were not present in `x`: PLT-TH1-018, PLT-TH1-020, PLT-TH1-105
## The following `from` values were not present in `x`: PLT-TH1-018, PLT-TH1-020, PLT-TH1-105

## Slopes plot for model setting 2

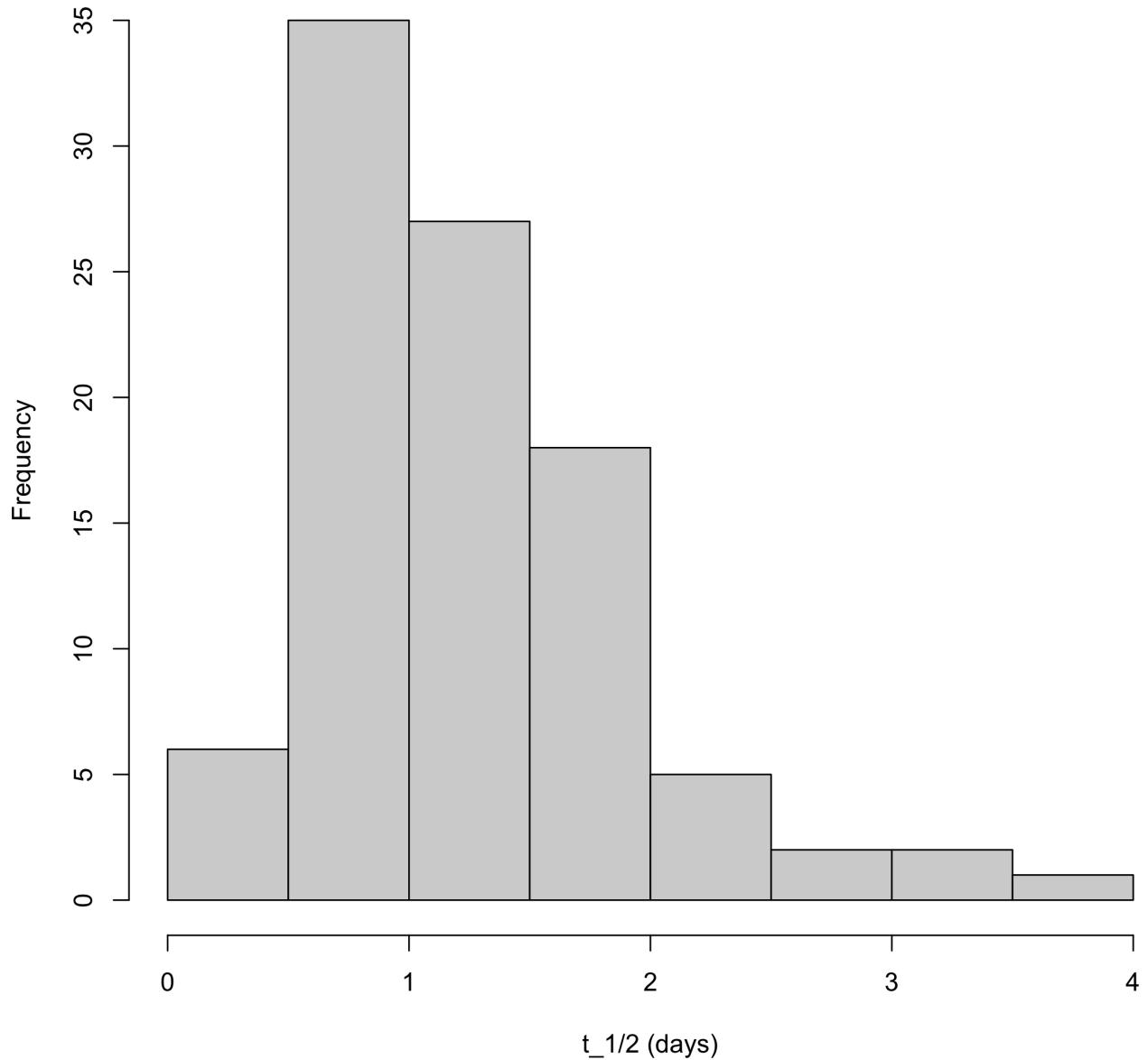
##                                     mod prior cov_matrices Niter Nwarmup
## 2 ./Stan_models/Linear_model_RNaseP.stan      1          1 10000    1000
##     Nthin Nchain
```

```
## 2      30      4
```

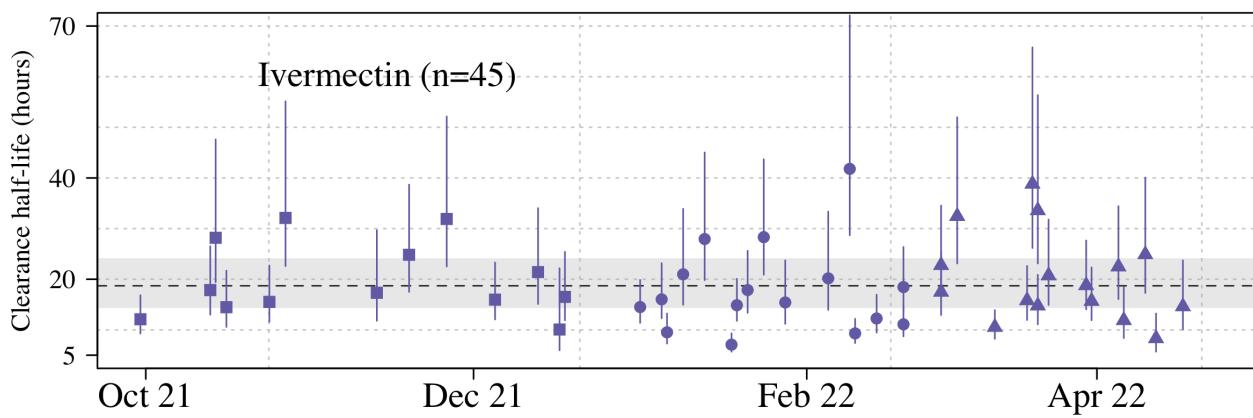
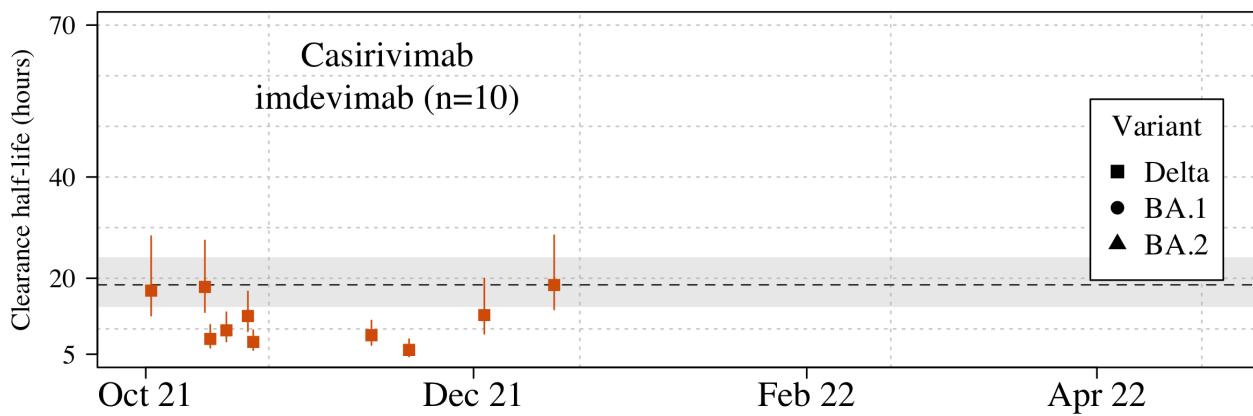
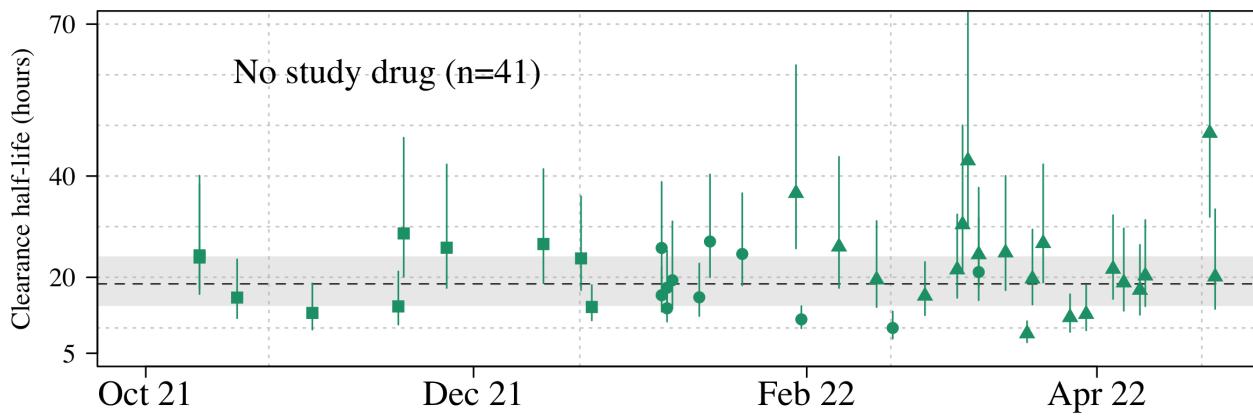
Median



Upper 90th percentile



```
## In the no study drug arm the mean clearance half life was 21.6 (range 8.9 to 48.5)
## In the ivermectin arm the mean clearance half life was 19.3 (range 7.1 to 41.8)
## In the ivermectin arm the mean clearance half life was 12 (range 5.8 to 18.7)
## The model estimated population mean clearance half-life is 18.7 (95% CI 14.3-24.1)
```

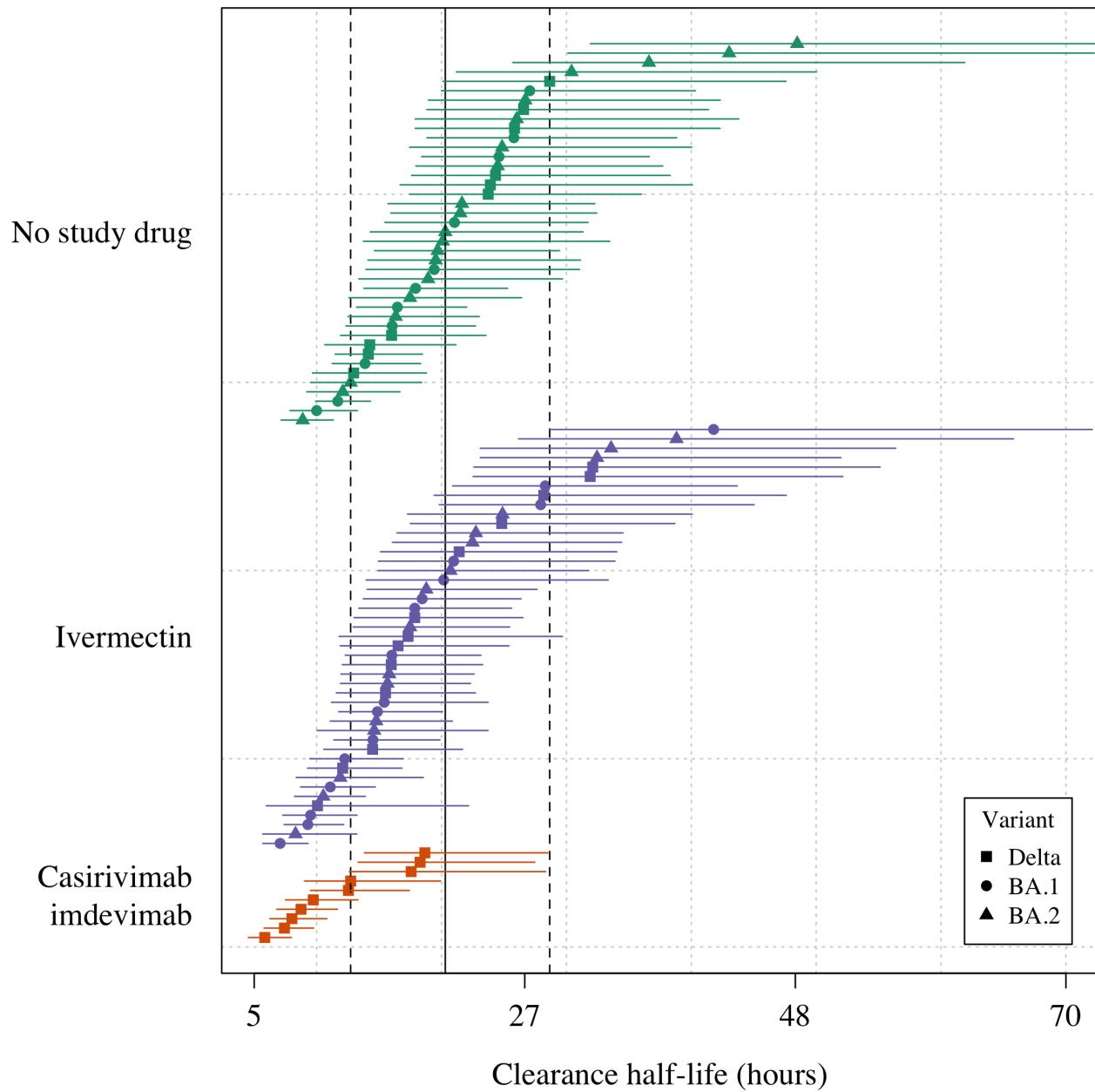


changes in half life

In the Ivermectin arm the mean change in half life is 1.8 (95% CI -2.4 to 6.3)

In the Regeneron arm the mean change in half life is -6.5 (95% CI -11 to -1.8)

Plot the individual slope estimates by group



Some exploratory covariate analyses

```
##
## Call:
## lm(formula = t_12 ~ trt, data = trt_summary_dat)
##
## Residuals:
##      Min       1Q   Median       3Q      Max 
## -12.682  -4.870  -1.628   4.243  26.917 
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)    
## (Intercept) 21.567     1.241  17.378 < 2e-16 ***
## trtCasirivimab\nimdevimab -9.610     2.803  -3.429 0.000906 ***
## trtIvermectin -2.292     1.716  -1.336 0.184921
##
```

```

## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 7.947 on 93 degrees of freedom
## Multiple R-squared: 0.1128, Adjusted R-squared: 0.09367
## F-statistic: 5.909 on 2 and 93 DF, p-value: 0.003838

```

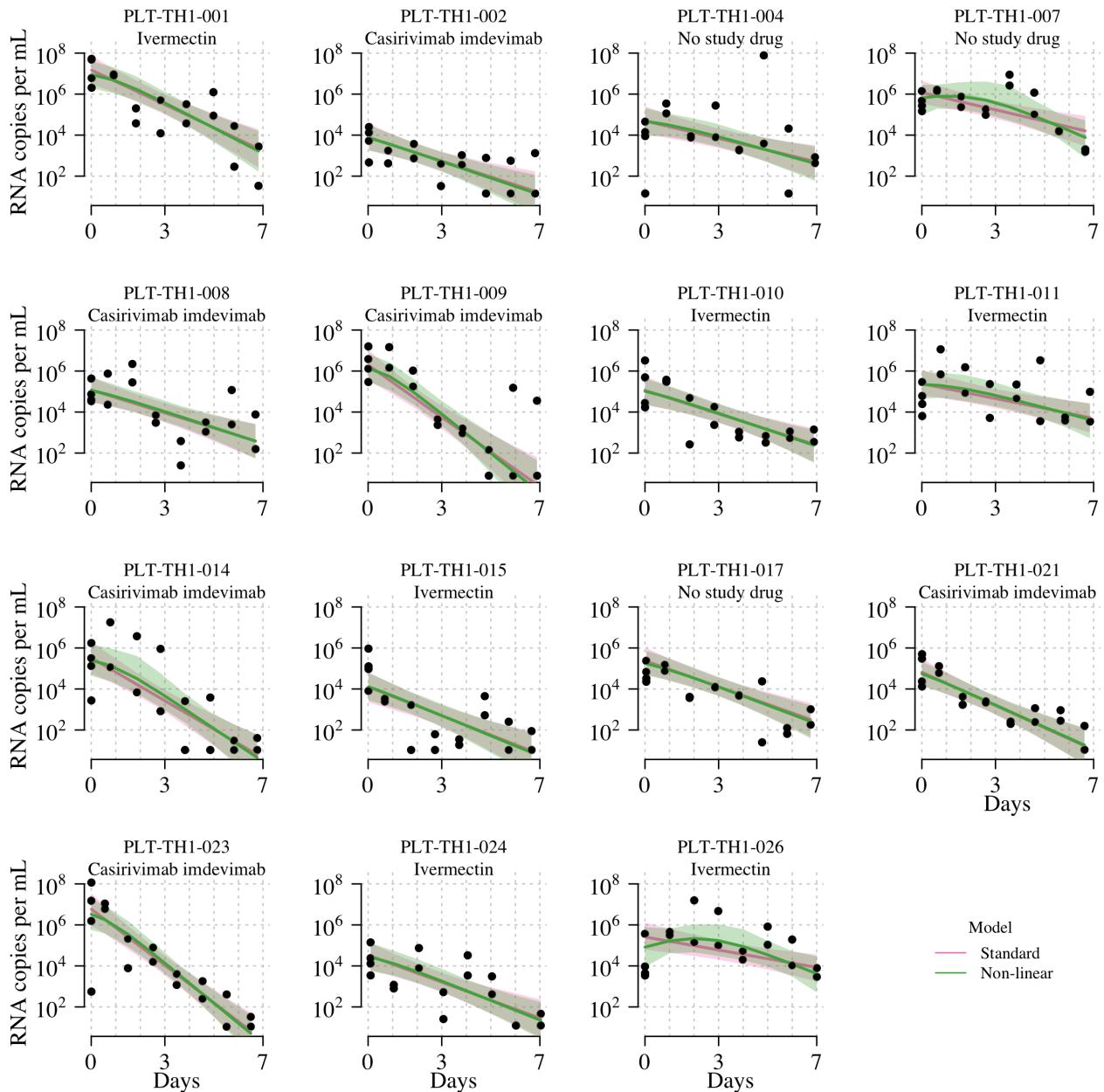
Individual plots

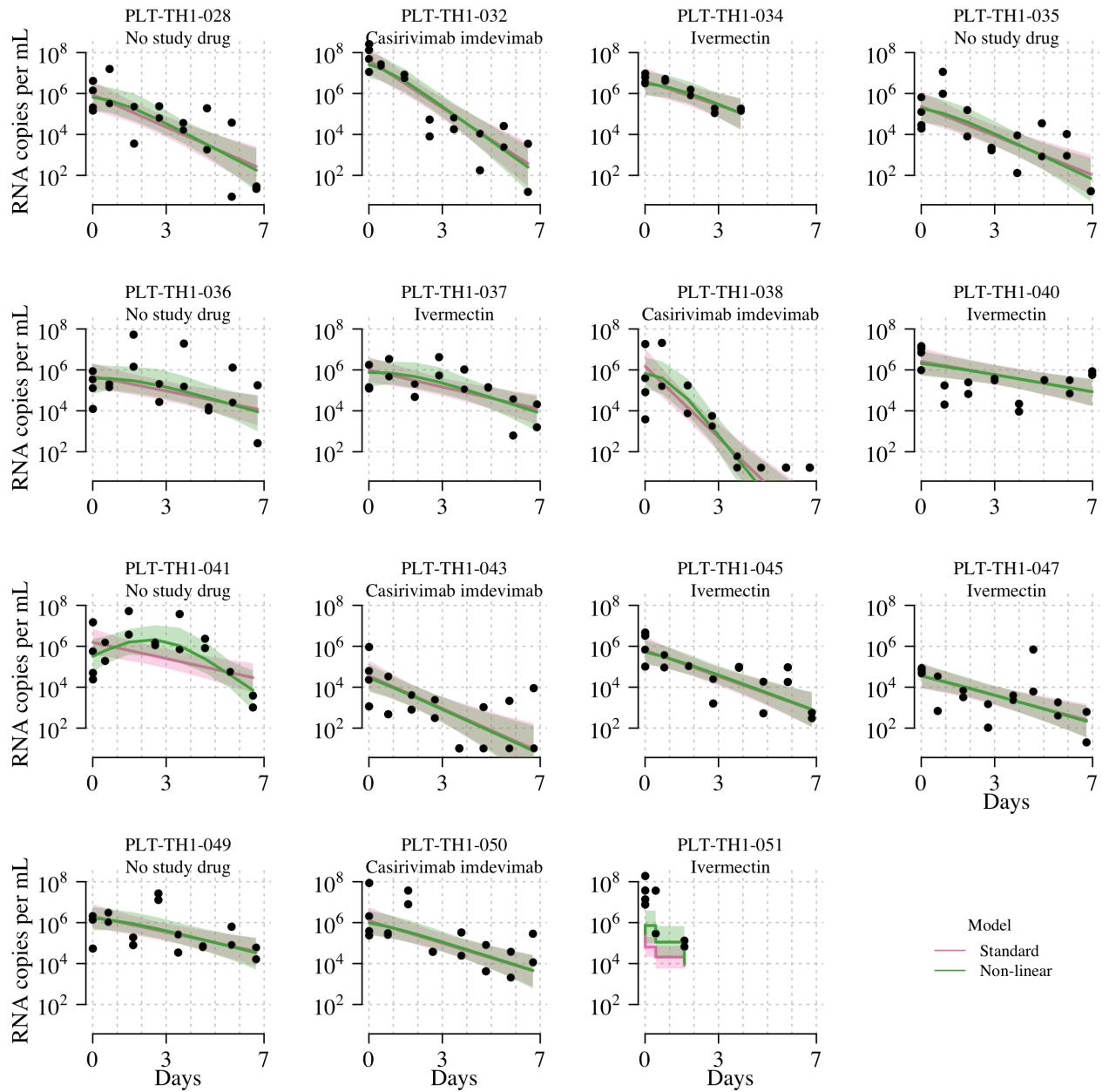
Individual plots colored by model

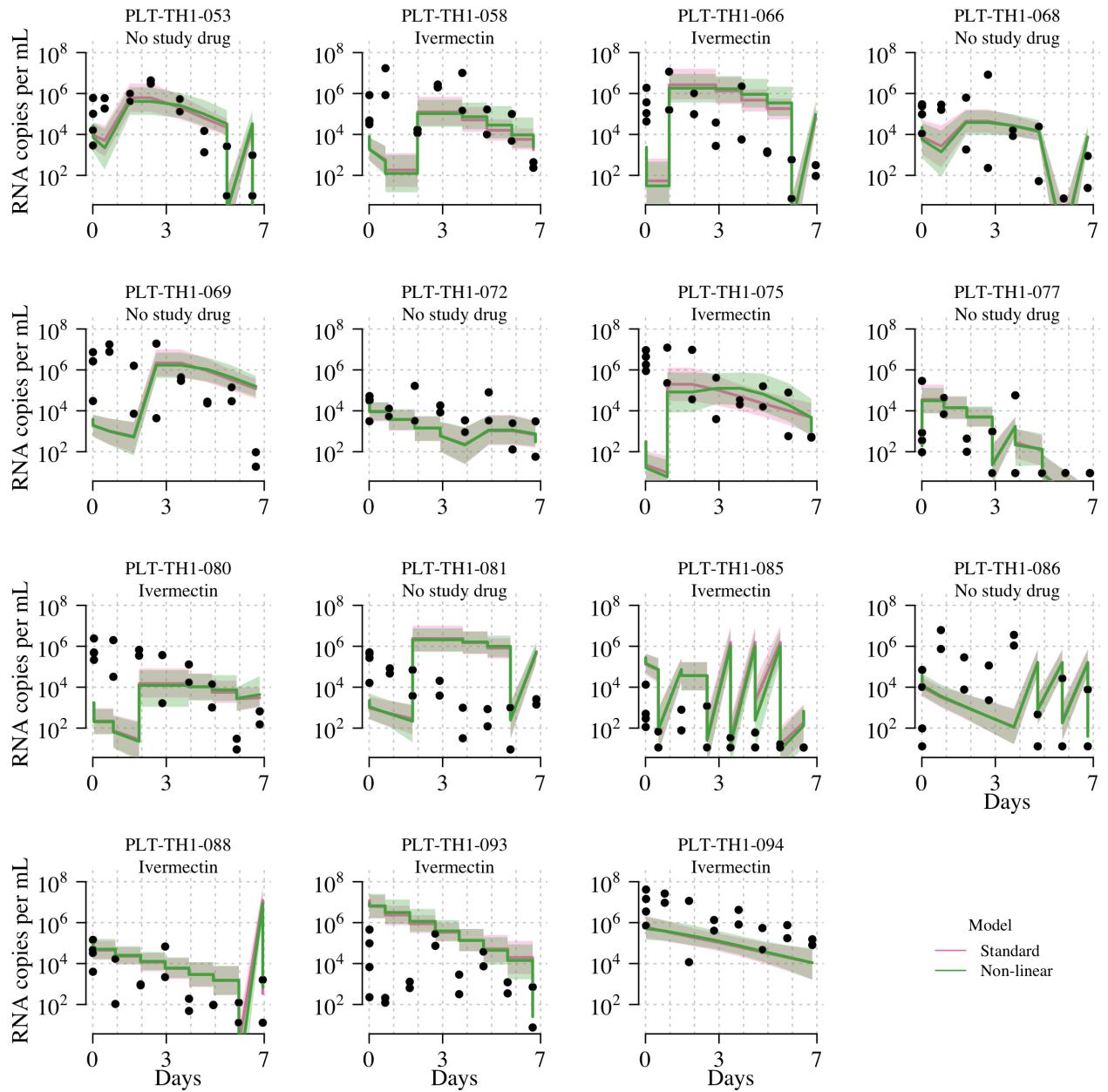
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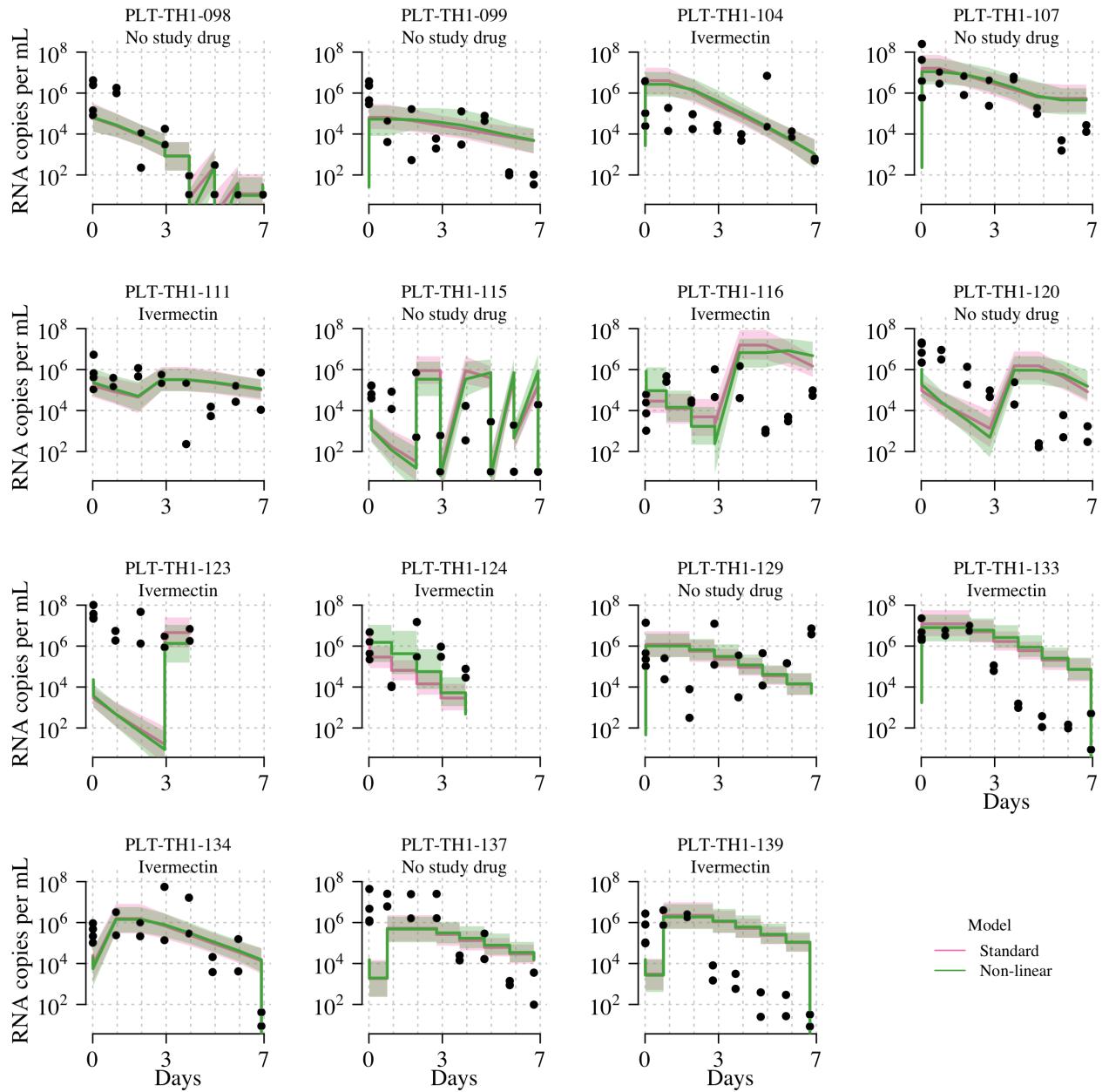
## The following `from` values were not present in `x`: PLT-TH1-018, PLT-TH1-020, PLT-TH1-105

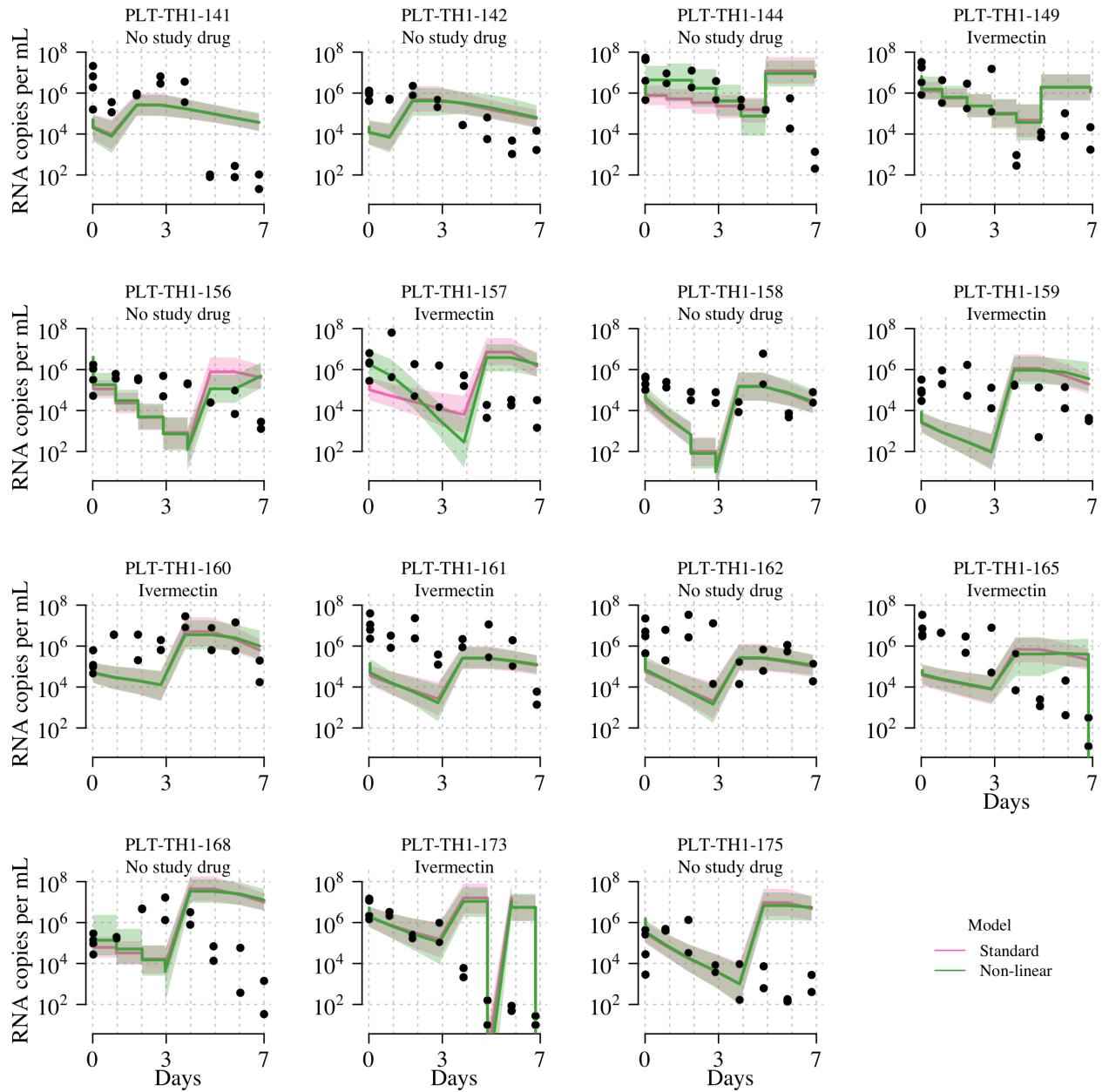
```

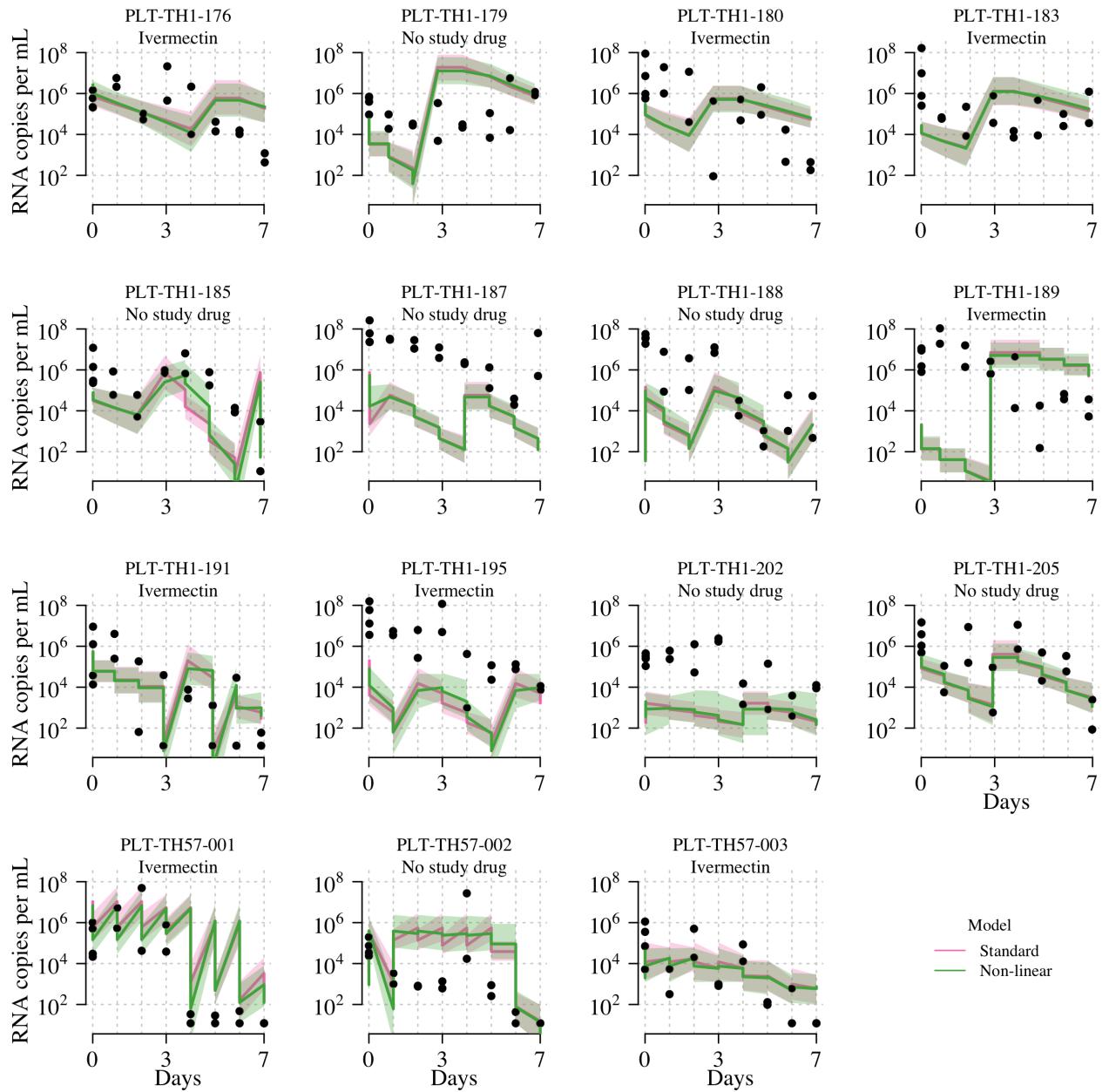


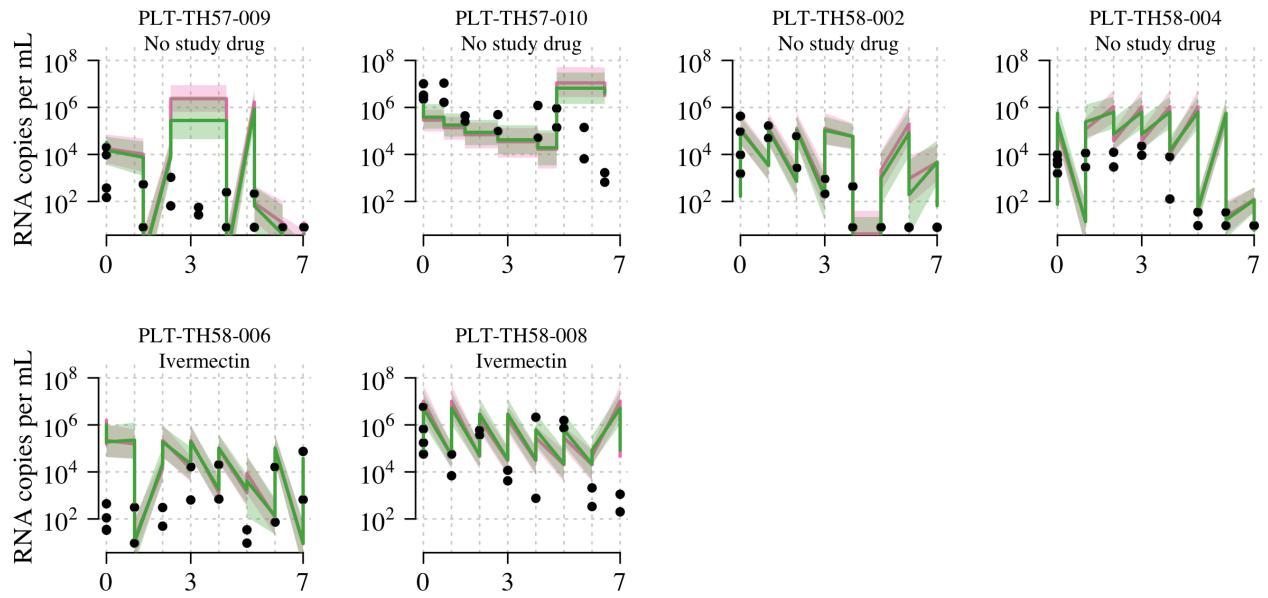






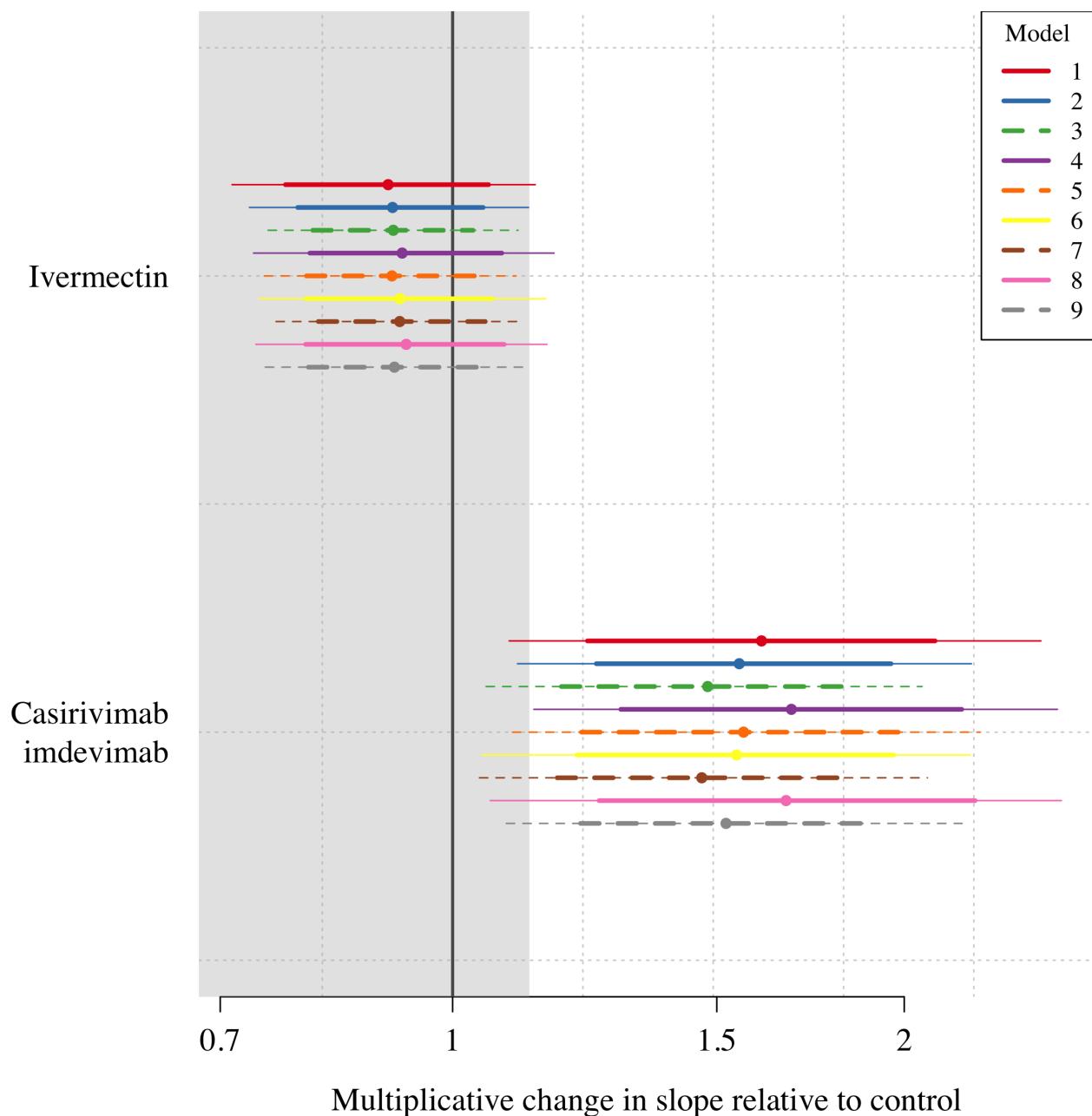




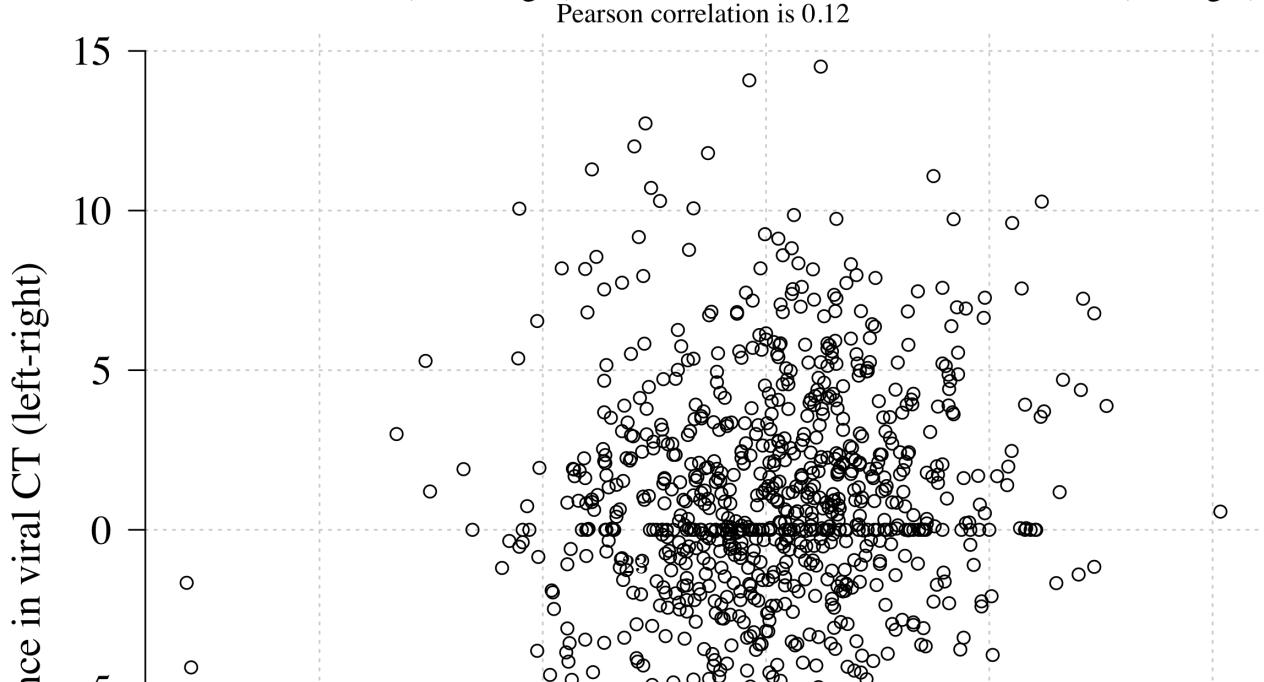
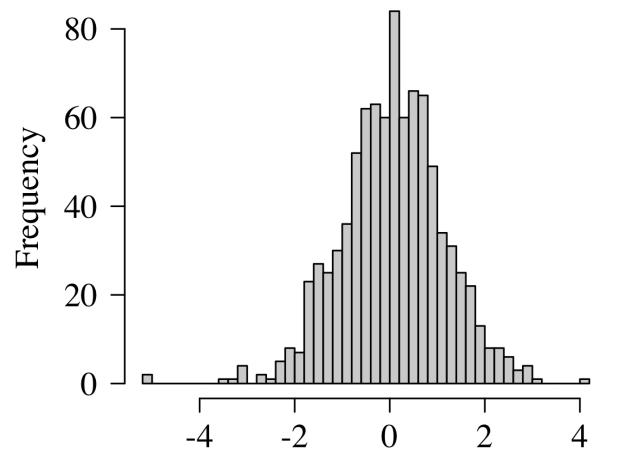
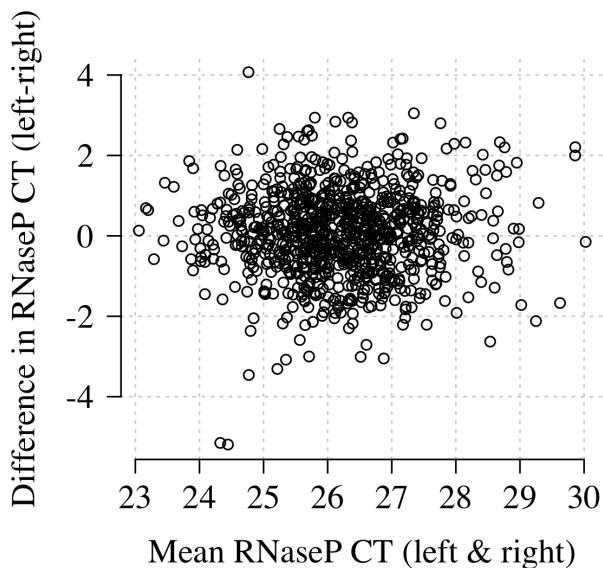
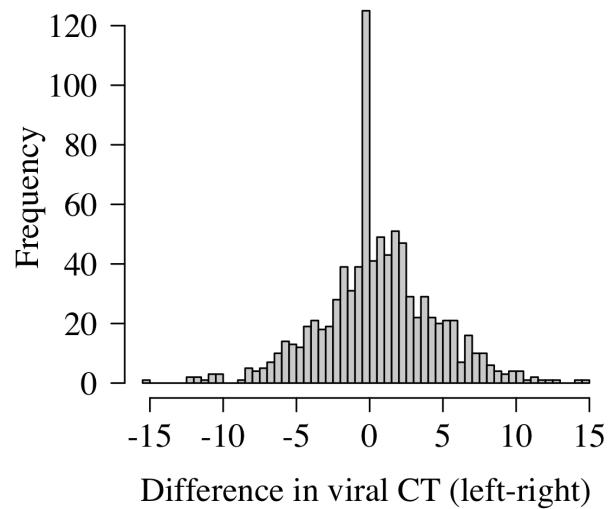
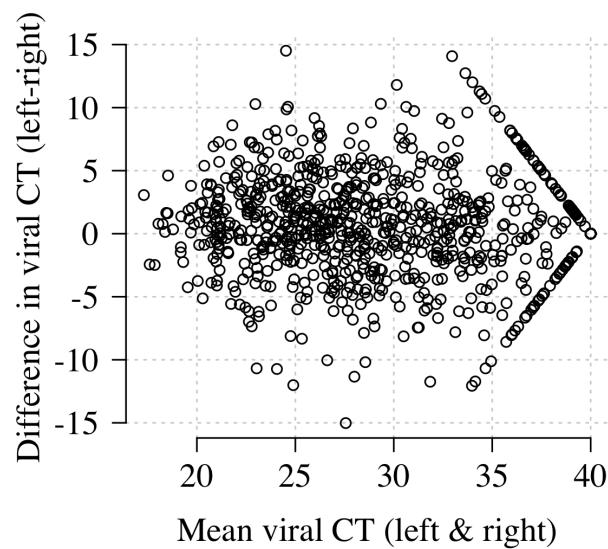


Sensitivity analysis

Treatment effects



Left vs right tonsil



Quality Control for PCR

SD of the intercept is 0.93

Maximum difference in CT values for a tenfold change in viral load is 0.69

