Time-to-event model of vivax recurrence

James Watson & Aimee Taylor

```
## Loading required package: lme4
## Loading required package: Matrix
## Loading required package: plyr
## Loading required package: dplyr
##
## Attaching package: 'dplyr'
## The following objects are masked from 'package:plyr':
##
##     arrange, count, desc, failwith, id, mutate, rename, summarise,
##     summarize
## The following objects are masked from 'package:stats':
##
##     filter, lag
## The following objects are masked from 'package:base':
##
##     intersect, setdiff, setequal, union
## Loading required package: gtools
## Loading required package: tictoc
## Loading required package: doParallel
## Loading required package: foreach
## Loading required package: iterators
## Loading required package: parallel
## Loading required package: matrixStats
##
## Attaching package: 'matrixStats'
## The following object is masked from 'package:dplyr':
##
##     count
## The following object is masked from 'package:plyr':
##
##     count
## Loading required package: igraph
##
## Attaching package: 'igraph'
## The following object is masked from 'package:gtools':
##
##     permute
```

```
## The following objects are masked from 'package:dplyr':
##
##     as_data_frame, groups, union

## The following objects are masked from 'package:stats':
##
##     decompose, spectrum

## The following object is masked from 'package:base':
##
##     union

## Loading required package: RColorBrewer

## Loading required package: knitr

## Loading required package: bindrcpp

## Loading required package: rstan

## Loading required package: StanHeaders

## Loading required package: ggplot2

## rstan (Version 2.19.2, GitRev: 2e1f913d3ca3)

## For execution on a local, multicore CPU with excess RAM we recommend calling
## options(mc.cores = parallel::detectCores()).
## To avoid recompilation of unchanged Stan programs, we recommend calling
## rstan_options(auto_write = TRUE)

## Loading required package: boot

##
## Attaching package: 'boot'

## The following objects are masked from 'package:gtools':
##
##     inv.logit, logit

## Loading required package: gdata

## gdata: read.xls support for 'XLS' (Excel 97-2004) files ENABLED.

##

## gdata: read.xls support for 'XLSX' (Excel 2007+) files ENABLED.

##
## Attaching package: 'gdata'

## The following objects are masked from 'package:dplyr':
##
##     combine, first, last

## The following object is masked from 'package:stats':
##
##     nobs

## The following object is masked from 'package:utils':
##
##     object.size
```

```
## The following object is masked from 'package:base':
##
##     startsWith
```

```
## Loading required package: loo
```

```
## This is loo version 2.1.0.
## **NOTE: As of version 2.0.0 loo defaults to 1 core but we recommend using as many as possible. Use t
```

```
##
## Attaching package: 'loo'
```

```
## The following object is masked from 'package:rstan':
##
##     loo
```

```
## The following object is masked from 'package:igraph':
##
##     compare
```

```
## Loading required package: devtools
```

```
## Loading required package: truncnorm
```

```
##         lme4         plyr        dplyr       gtools       tictoc
##         TRUE         TRUE         TRUE         TRUE         TRUE
##   doParallel     parallel    iterators      foreach       Matrix
##         TRUE         TRUE         TRUE         TRUE         TRUE
##  matrixStats       igraph RColorBrewer        knitr     bindrcpp
##         TRUE         TRUE         TRUE         TRUE         TRUE
##        rstan  StanHeaders      ggplot2         boot        gdata
##         TRUE         TRUE         TRUE         TRUE         TRUE
##          loo        stats     graphics    grDevices        utils
##         TRUE         TRUE         TRUE         TRUE         TRUE
##     datasets      methods         base     devtools    truncnorm
##         TRUE         TRUE         TRUE         TRUE         TRUE
```

Preliminaries

Stan models

Model 1: Mixture of three components

- ReInfections occur at 'random' (exponential distribution). A random effects term is used to adjust for inter-individual variability in propensity to be reinfected.
- Recrudescences can happen in the first couple of weeks (exponential distribution, high rate parameter).
- Relapses are broken into two components. The fast/periodic relapse component happens as described by a Weibull with blood-stage drug dependent parameters (same as in Model 1). The slow/random relapse component is described by an exponential disrtibution.
- Primaquine is assumed to have 100% efficacy.

Model 2: Mixture of three components and reLapses after PMQ

This is the final model reported in the paper.

- ReInfections occur at 'random' (exponential distribution). A random effects term is used to adjust for inter-individual variability in propensity to be reinfected.
- Recrudescences are exponentially distributed
- Relapses are broken into two components (same as in Model 2).
- Primaquine is not assumed to have 100% efficacy and a random effects term describes the propensity to relapse after primaquine.

Model 3: Adding seasonality

Here we explore whether a seasonality term is useful to explain some reinfections

The seasonal term is given in units of weeks by $\exp(\beta_1 \sin(\frac{2\pi t}{T} + \beta_1))$ where $T = 365/7$ (number of weeeks in the year). This increases the reinfection mixing proportion $p_{(n)}$ for each drug treatment.

This model is still in development and not currently functional.

VHX and BPD pooled data set

```
load('../RData/TimingModel/Combined_Time_Event.RData')
# Get rid of the very short durations
Combined_Time_Data = filter(Combined_Time_Data, Censored > -1, Time_to_event >= 5)
# Turn drug into a numeric vector
Combined_Time_Data$numeric_drug = as.integer(revalue(Combined_Time_Data$arm_num,
                                                     c('AS'='0','CHQ'='1','CHQ/PMQ'='2')))
# deal with non-integer ids
Combined_Time_Data$patientid = factor(Combined_Time_Data$patientid)

# Convert ID to integer
Combined_Time_Data$ID = as.integer(Combined_Time_Data$patientid)
Combined_Time_Data = arrange(Combined_Time_Data, ID, episode)
# We sort the ids so that ids go from 1...N
ids = unique(Combined_Time_Data$ID)
N = as.integer(length(ids))

# Create a vector that maps the nth person to 0 (always received Primaquine)
# or to their rank for those who didn't receive primaquine
noPMQ_ind = which(Combined_Time_Data$arm_num != "CHQ/PMQ")
N_noPMQ = length(unique(Combined_Time_Data$ID[noPMQ_ind])) #number of IDs without PMQ
ID_mapped_to_noPMQ_rank = rep(0, N)


index = 1
for(id in 1:N){
  ind = which(Combined_Time_Data$ID==id)
  if(!2 %in% Combined_Time_Data$numeric_drug[ind]){
    ID_mapped_to_noPMQ_rank[id] = index
    index = index + 1
```

```
  }
}


# Create a vector that maps the nth person to 0 (always received Primaquine) or
PMQ_ind = which(Combined_Time_Data$arm_num == "CHQ/PMQ")
N_PMQ = length(unique(Combined_Time_Data$ID[PMQ_ind])) #number of IDs with PMQ
ID_mapped_to_PMQ_rank = rep(0, N)


index = 1
for(id in 1:N){
  ind = which(Combined_Time_Data$ID==id)
  if(2 %in% Combined_Time_Data$numeric_drug[ind]){
    ID_mapped_to_PMQ_rank[id] = index
    index = index + 1
  }
}


ind = !duplicated(Combined_Time_Data$ID)
drug_received = Combined_Time_Data$numeric_drug[ind]
```

Prior specification

```
# The hierachical parameters defining the prior distributions for model 1
Prior_params_M1 = list(Hyper_lambda_shape = 50,
                       Hyper_lambda_rate = 50*900,
                       Hyper_gamma_shape = 50,
                       Hyper_gamma_rate = 50*100,
                       Hyper_lambda_recrud_shape = 100,
                       Hyper_lambda_recrud_rate = 100*10,
                       Hyper_AS_shape_mean = 5,
                       Hyper_AS_shape_sd = .5,
                       Hyper_AS_scale_mean = 27,
                       Hyper_AS_scale_sd = 1,
                       Hyper_CQ_shape_mean = 5,
                       Hyper_CQ_shape_sd = .5,
                       Hyper_CQ_scale_mean = 45,
                       Hyper_CQ_scale_sd = 1,
                       Hyper_logit_mean_p_mean = logit(0.3),
                       Hyper_logit_mean_p_sd = .5,
                       Hyper_logit_sd_p_lambda = 1,
                       Hyper_logit_c1_mean = logit(0.01),
                       Hyper_logit_c1_sd = .25,
                       Early_L_logit_mean = 0,
                       Early_L_logit_sd = .25,
                       Hyper_mean_rate_decrease = 0.66,
                       Hyper_sd_rate_decrease = 0.15)
# Model 2: extra parameters
Prior_params_M2 = c(Prior_params_M1,
```

```
                    Hyper_logit_mean_pPMQ_mean = logit(0.95),
                    Hyper_logit_mean_pPMQ_sd = .25,
                    Hyper_logit_sd_pPMQ_lambda = 1)

writeLines(sprintf('The prior specification for Model 2 is a PMQ+ failure rate of %s%% (%s-%s)',
                   round(100*inv.logit(Prior_params_M2$Hyper_logit_mean_pPMQ_mean),1),
                   round(100 - 100*inv.logit(Prior_params_M2$Hyper_logit_mean_pPMQ_mean +
                                               1.96*Prior_params_M2$Hyper_logit_mean_pPMQ_sd), 1),
                   round(100 - 100*inv.logit(Prior_params_M2$Hyper_logit_mean_pPMQ_mean -
                                               1.96*Prior_params_M2$Hyper_logit_mean_pPMQ_sd), 1)))
```

```
## The prior specification for Model 2 is a PMQ+ failure rate of 95% (3.1-7.9)
```

Run Model

Set up parameters for the MCMC runs.

```
# remove this once models 1-2 conform with augmented data (including Censored == -1)
Combined_Time_Data = filter(Combined_Time_Data, Censored > -1)
# Choose as many chains as available cores
Chains = 8
options(mc.cores = Chains)
IT = 10^5
WarmUp = .5*IT
thin = 400

# put the data into stan format
# For model 1
Time_data_1 =list(N         = N,
                  #Number of individuals
                  Neps      = as.integer(nrow(Combined_Time_Data)),
                  #Number of durations
                  N_noPMQ   = as.integer(N_noPMQ),
                  # Number of individuals who do not recieve PMQ
                  N_PMQ     = as.integer(N_PMQ),
                  # Number of individuals who do not recieve PMQ
                  Durations = as.double(Combined_Time_Data$Time_to_event),
                  #Time to reinfection or time to censoring
                  Censored  = as.integer(Combined_Time_Data$Censored),
                  #If the duration is right censored or not
                  Drug      = Combined_Time_Data$numeric_drug,
                  # drug coded as an integer
                  ID_of_Patient = Combined_Time_Data$ID,
                  # the ID corresponding to each time interval
                  ID_mapped_to_noPMQ_rank = ID_mapped_to_noPMQ_rank,
                  # the index mapping PMQ individuals to their rank
                  Study_Period = as.integer(Combined_Time_Data$Study_Period)
)
# For model 2
Time_data_2 =list(N         = N,
                  #Number of individuals
                  Neps      = as.integer(nrow(Combined_Time_Data)),
                  #Number of durations
```

```
                    N_noPMQ   = N_noPMQ,
                    # Number of individuals who do not recieve PMQ
                    N_PMQ     = N_PMQ,
                    # Number of individuals who do not recieve PMQ
                    Durations = as.double(Combined_Time_Data$Time_to_event),
                    #Time to reinfection or time to censoring
                    Censored  = as.integer(Combined_Time_Data$Censored),
                    #If the duration is right censored or not
                    Drug      = Combined_Time_Data$numeric_drug,
                    # drug coded as an integer
                    ID_of_Patient   = Combined_Time_Data$ID,
                    # the index of the individual for each time interval
                    ID_mapped_to_noPMQ_rank = ID_mapped_to_noPMQ_rank,
                    # the index mapping no PMQ individuals to their rank
                    ID_mapped_to_PMQ_rank = ID_mapped_to_PMQ_rank,
                    # the index mapping PMQ individuals to their rank
                    Study_Period = as.integer(Combined_Time_Data$Study_Period))
```

Run with `{r} Chains` parallel chains. The choice of this number depends on compute power.

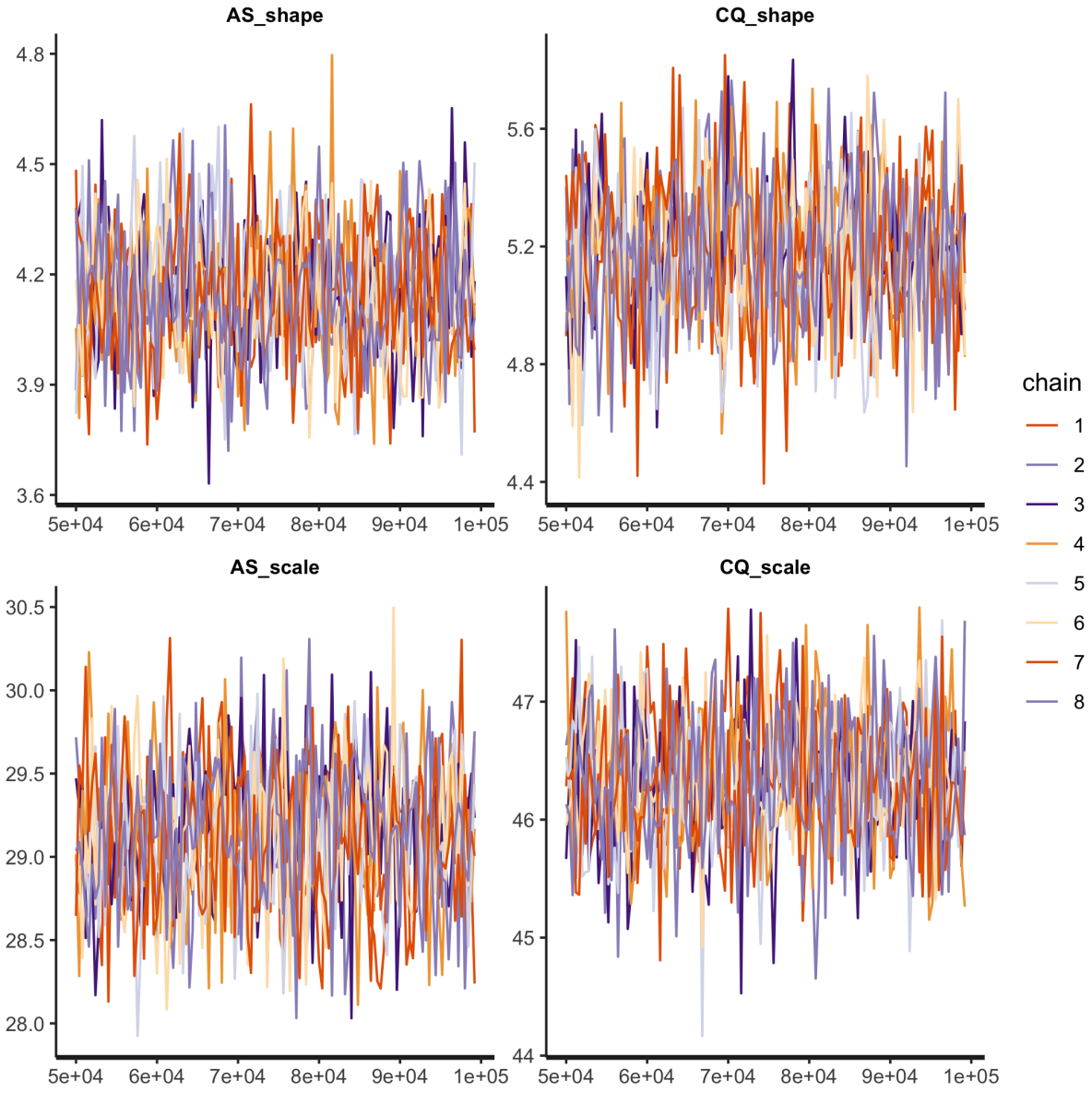
Plot output

Let's make some nice colors for the plotting

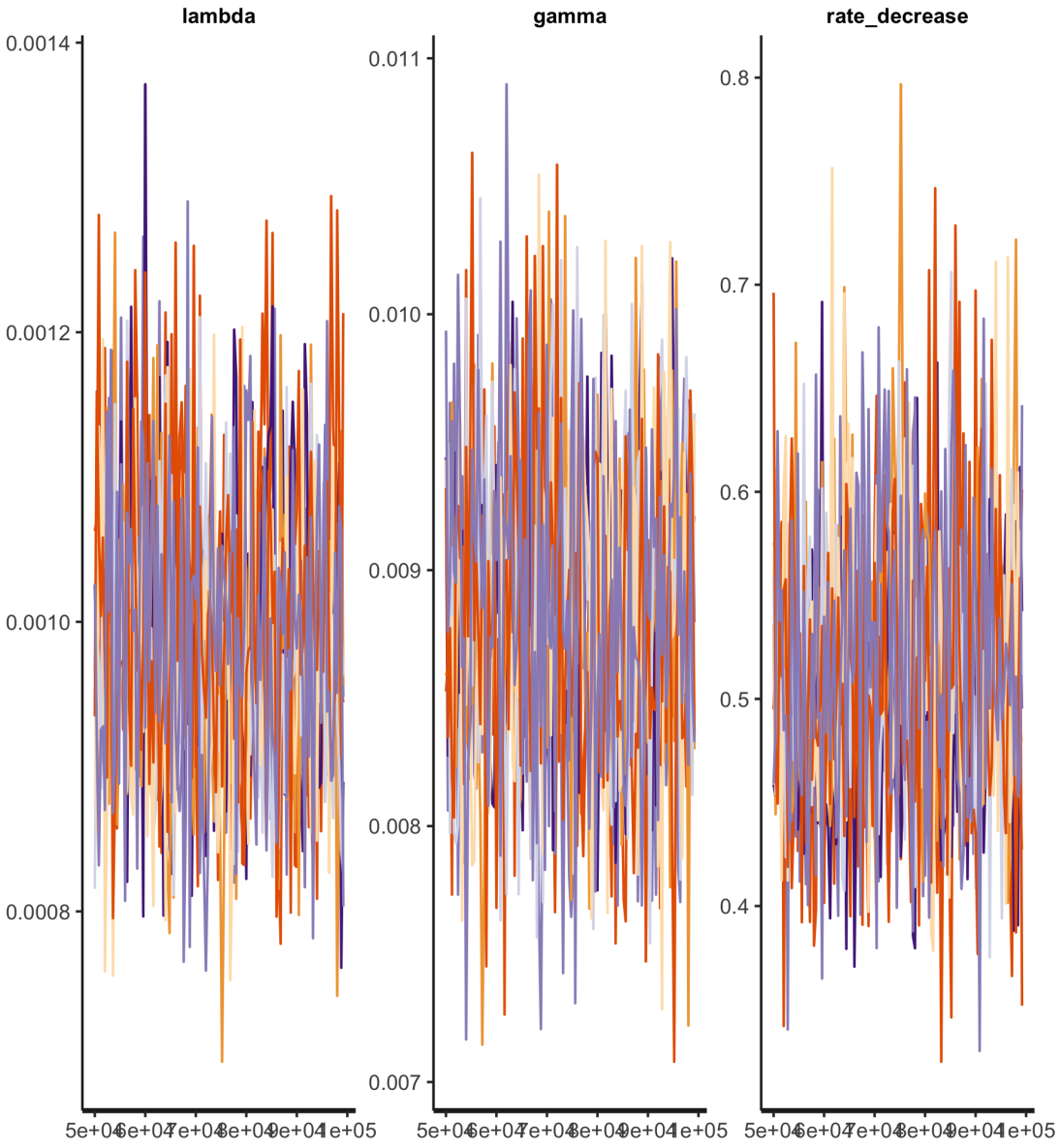
```
# Colour scheme
# Previous Set1 not colourblind friendly: display.brewer.all(colorblindFriendly = T)
Dark2 = brewer.pal(8, 'Dark2')
Set2 = brewer.pal(8, 'Set2')

drug_cols3 = array(Dark2[c(4,6,1)], dim = 3, dimnames = list(c('AS','CHQ','CHQ/PMQ')))
drug_cols2 = array(Dark2[c(2,2,1)], dim = 3, dimnames = list(c('AS','CHQ','CHQ/PMQ')))
drug_cols_light2 = array(Set2[c(2,2,1)], dim = 3, dimnames = list(c('AS','CHQ','CHQ/PMQ')))

# Vector of states
states = c(relapse = 'L', reinfection = 'I', recrudescence = 'C')

#mycols = brewer.pal(n=3, name = 'Set1')
# Do we include censored time intervals in the plots:
PLOT_Censored_Obs = F
if(PLOT_Censored_Obs){
  ind_plotting = which(Combined_Time_Data$Censored > -1)
} else {
  ind_plotting = which(Combined_Time_Data$Censored == 0)
}
```

Model 1

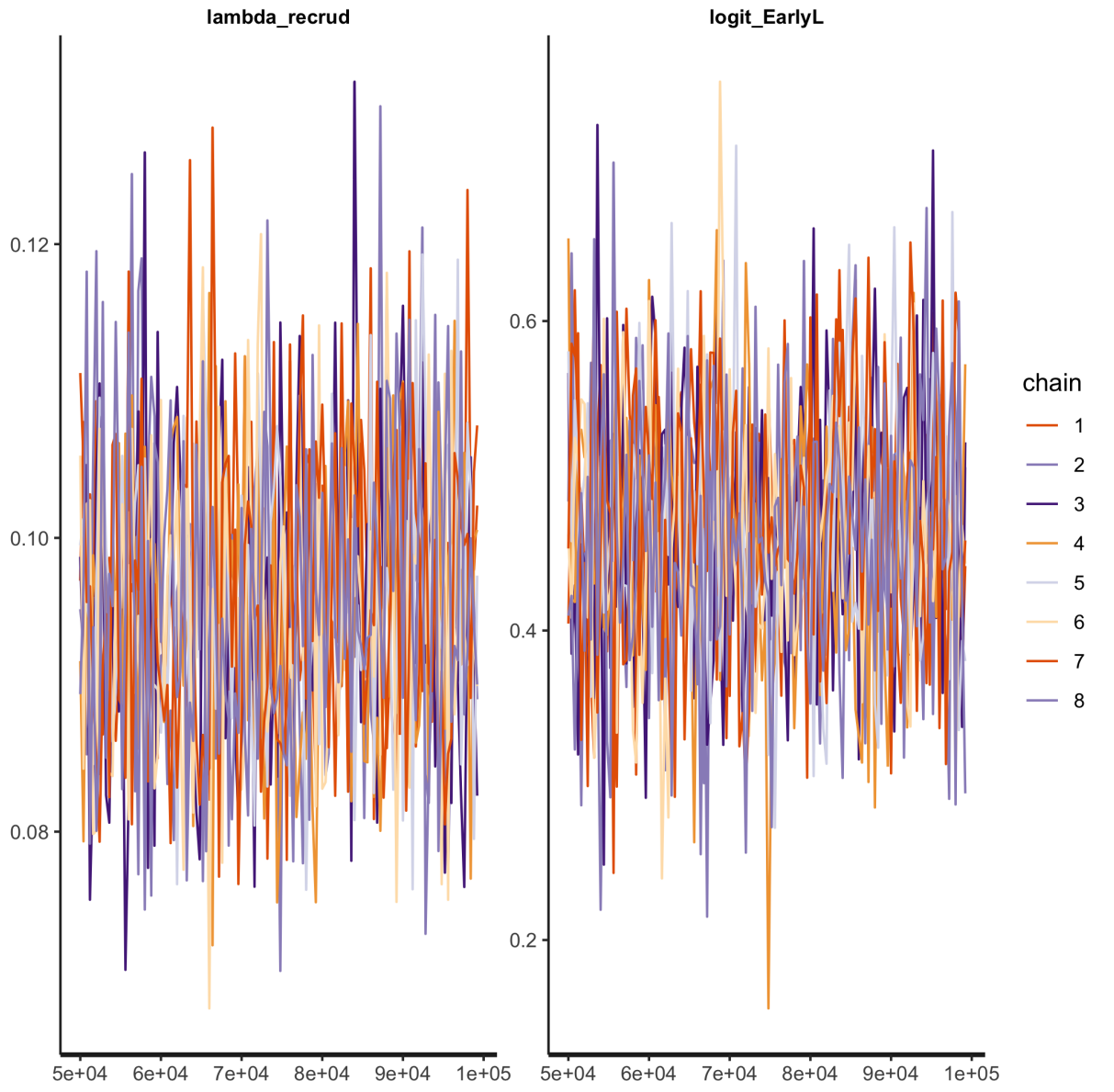
```
par(las=1)
traceplot(mod1_Fit,c('AS_shape', 'CQ_shape', 'AS_scale', 'CQ_scale'))
```



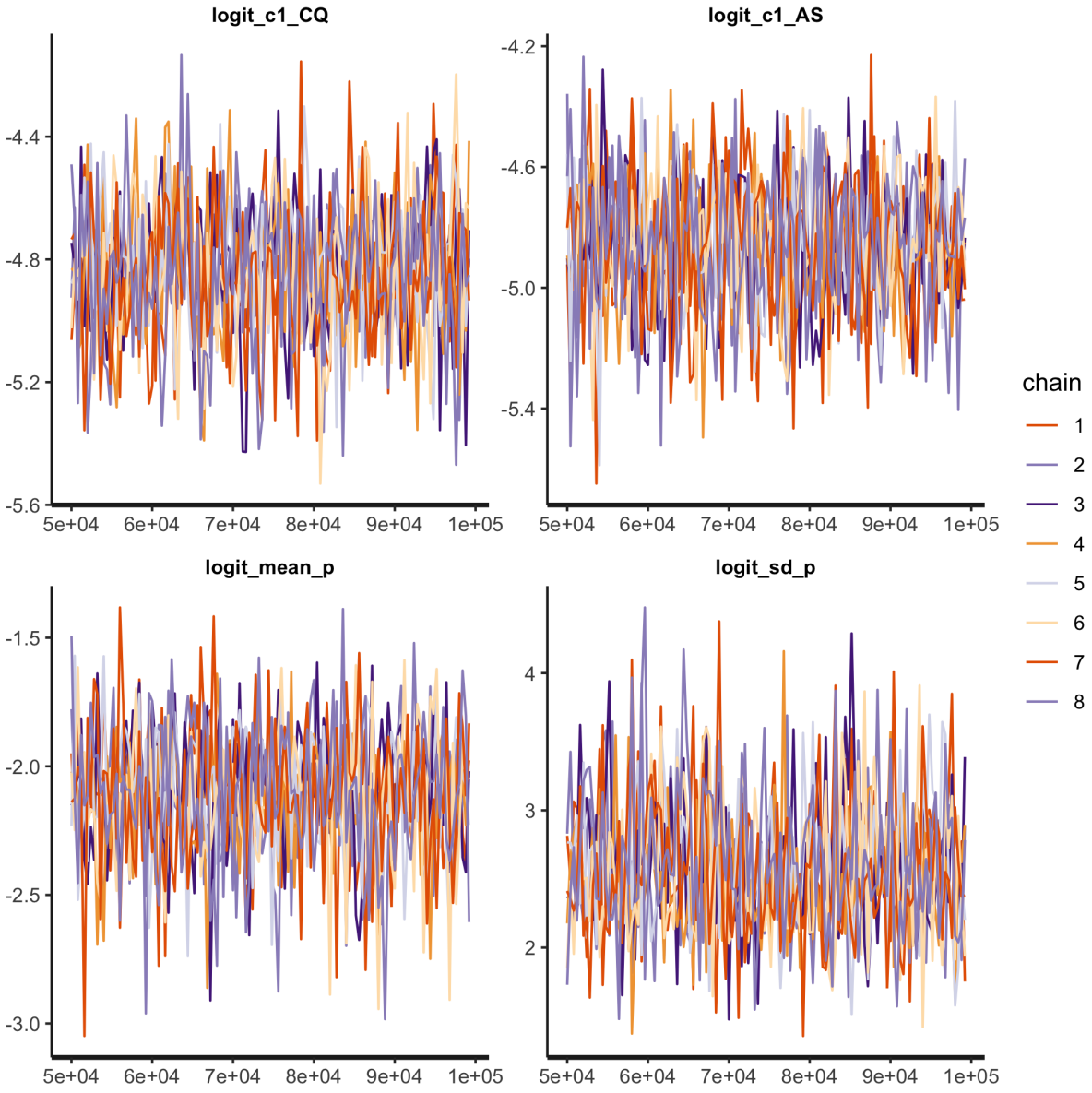

```
traceplot(mod1_Fit, c('lambda','gamma','rate_decrease'))
```




```
traceplot(mod1_Fit, c('lambda_recrud','logit_EarlyL'))
```

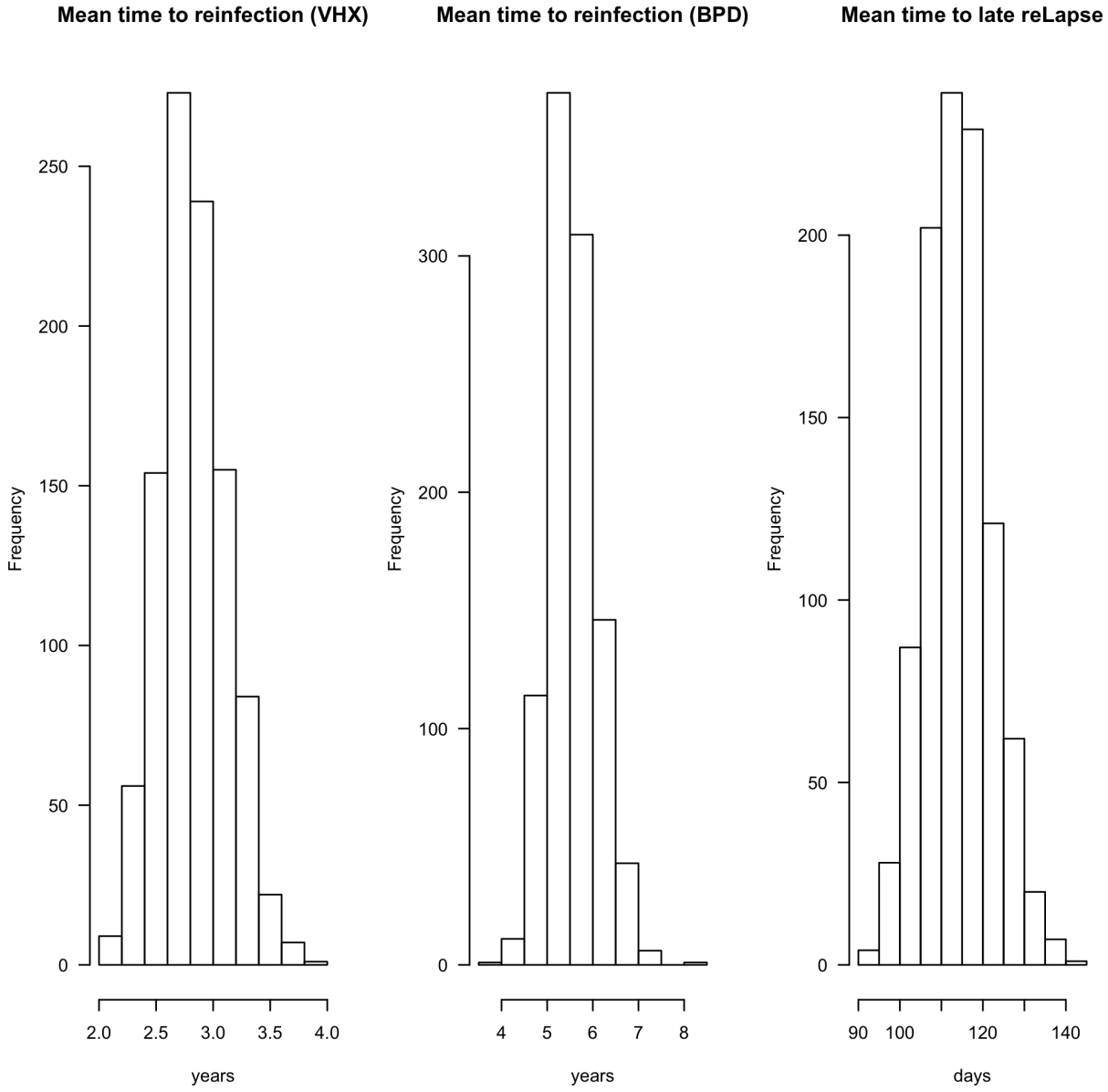



```
traceplot(mod1_Fit, c('logit_c1_CQ','logit_c1_AS','logit_mean_p','logit_sd_p'))
```

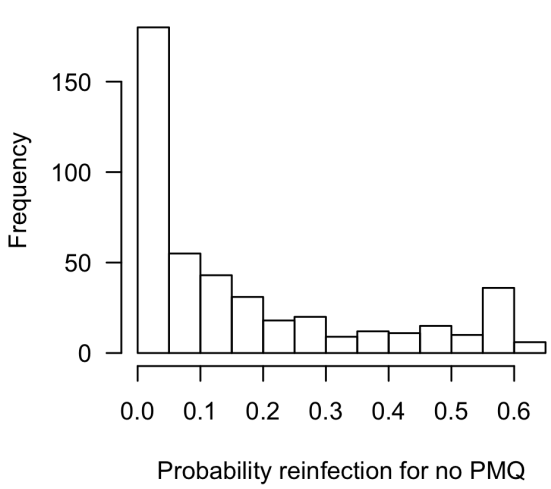


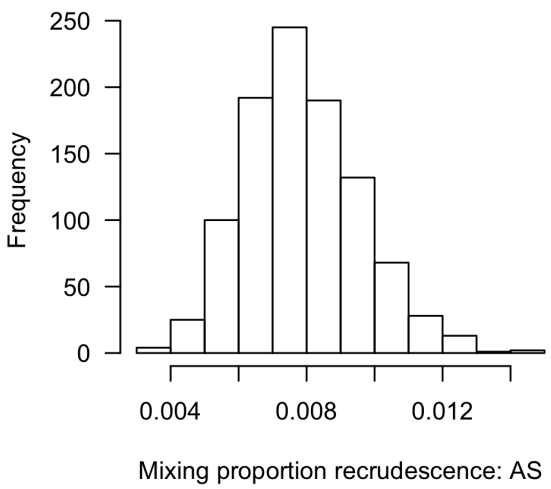

```
thetas_mod1 = extract(mod1_Fit)
```

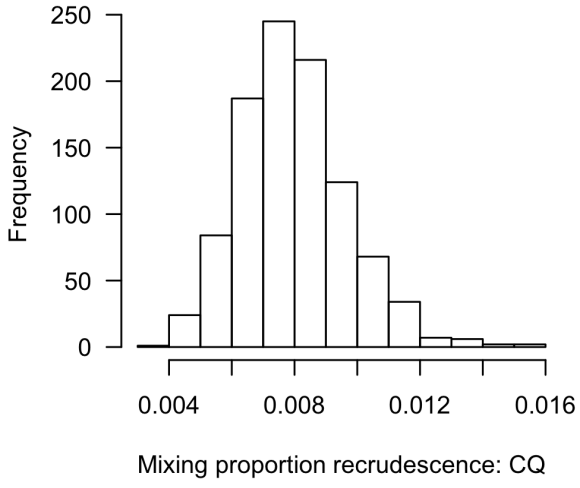
```
par(las=1)
par(mfrow=c(1,3))
hist((1/thetas_mod1$lambda)/360, main='Mean time to reinfection (VHX)', xlab='years')
hist((1/(thetas_mod1$lambda*thetas_mod1$rate_decrease))/360,
     main='Mean time to reinfection (BPD)', xlab='years')
hist(1/thetas_mod1$gamma, main='Mean time to late reLapse', xlab='days')
```

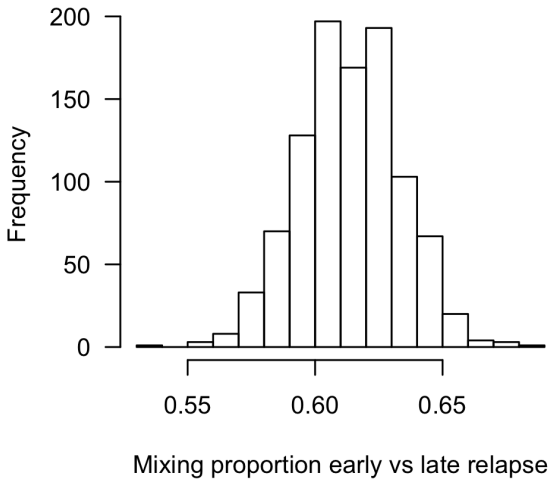



```r
par(las=1, mfrow=c(2,2))

hist(inv.logit(apply(thetas_mod1$logit_p,2,mean)),
     xlab = 'Probability reinfection for no PMQ', main = '')

hist(inv.logit(thetas_mod1$logit_c1_AS),
     xlab = 'Mixing proportion recrudescence: AS', main='')
hist(inv.logit(thetas_mod1$logit_c1_CQ),
     xlab = 'Mixing proportion recrudescence: CQ', main='')
hist(inv.logit(thetas_mod1$logit_EarlyL),
     xlab = 'Mixing proportion early vs late relapse', main='')
```



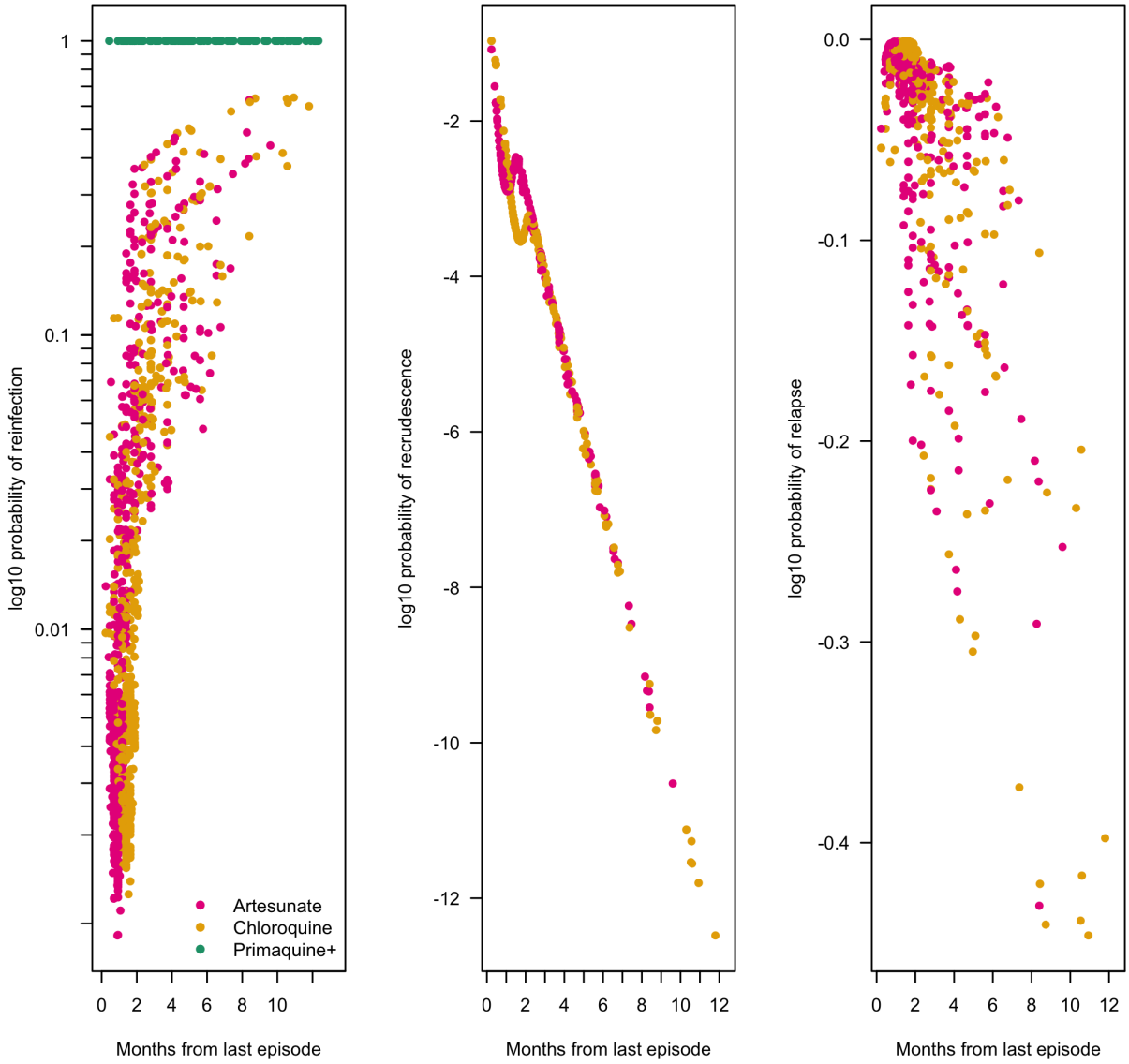







```
par(las=1, mfrow=c(1,3))
# Plot the outcome of the predicted labels
#***************************** Reinfection ******************************
labels = extract(mod1_Fit, 'prob_labels')$prob_labels
mean_labels_Reinfection = apply(labels[,ind_plotting,1,drop=T], 2, mean)
plot(Combined_Time_Data$Time_to_event[ind_plotting], log10(mean_labels_Reinfection),
     col = drug_cols3[Combined_Time_Data$numeric_drug[ind_plotting]+1],
     pch = as.numeric(Combined_Time_Data$Censored[ind_plotting])+16,
     ylab='log10 probability of reinfection', yaxt='n',xaxt='n',
     xlab='Months from last episode', xlim=c(0,400))
axis(1, at = seq(0, 420, by=60), labels = seq(0, 420, by=60)/30)
axis(2, at = -2:0, labels= 10^(-2:0))
axis(2, at = log10(seq(.1,1,by=.1)), labels = NA)
axis(2, at = log10(seq(.01,.1,by=.01)), labels = NA)
```

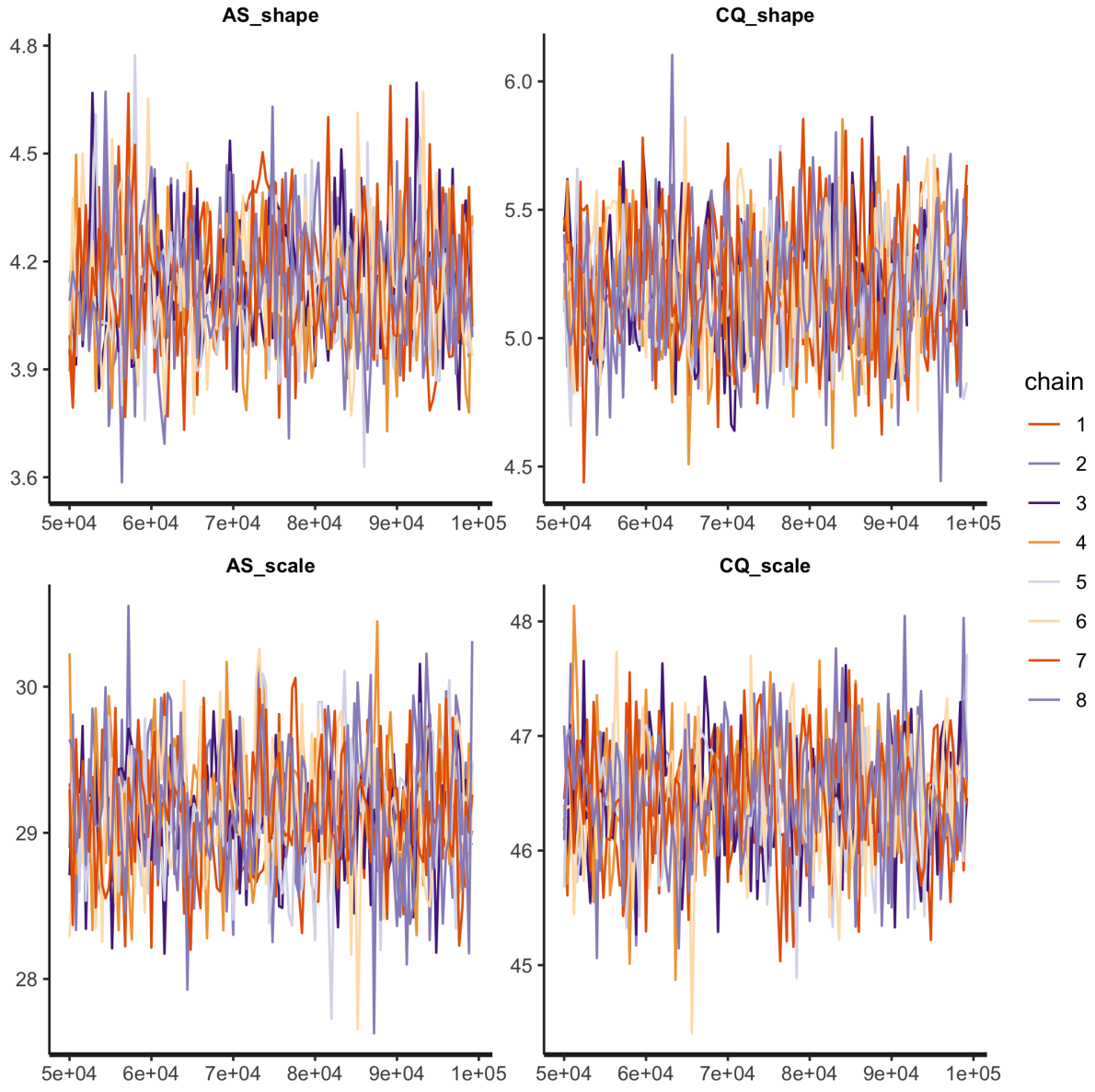
```r
axis(2, at = log10(seq(.001,.01,by=.001)), labels = NA)
legend('bottomright',legend = c('Artesunate','Chloroquine','Primaquine+'),
       col=drug_cols3,pch = rep(20,3), bty='n',lwd=2,lty=NA)


#***************************** Recrudescence ***************************
mean_labels_ReCrud = apply(labels[,ind_plotting,4,drop=T], 2, mean)
plot(Combined_Time_Data$Time_to_event[ind_plotting], log10(mean_labels_ReCrud),
     col = drug_cols3[Combined_Time_Data$numeric_drug[ind_plotting]+1], xaxt='n',
     pch = as.numeric(Combined_Time_Data$Censored[ind_plotting])+16,
     ylab='log10 probability of recrudescence',
     xlab='Months from last episode')
axis(1, at = seq(0,360,by=30), labels = seq(0,360,by=30)/30)


#***************************** Relapse ***************************
mean_labels_ReLap1 = apply(labels[,ind_plotting,2,drop=T], 2, mean)
mean_labels_ReLap2 = apply(labels[,ind_plotting,3,drop=T], 2, mean)
mean_labels_ReLap = mean_labels_ReLap1 + mean_labels_ReLap2
plot(Combined_Time_Data$Time_to_event[ind_plotting], log10(mean_labels_ReLap),
     col = drug_cols3[Combined_Time_Data$numeric_drug[ind_plotting]+1], xaxt='n',
     pch = as.numeric(Combined_Time_Data$Censored[ind_plotting])+16,
     ylab='log10 probability of relapse',
     xlab='Months from last episode')
axis(1, at = seq(0, 420, by= 60), labels = seq(0, 420, by=60)/30)
```



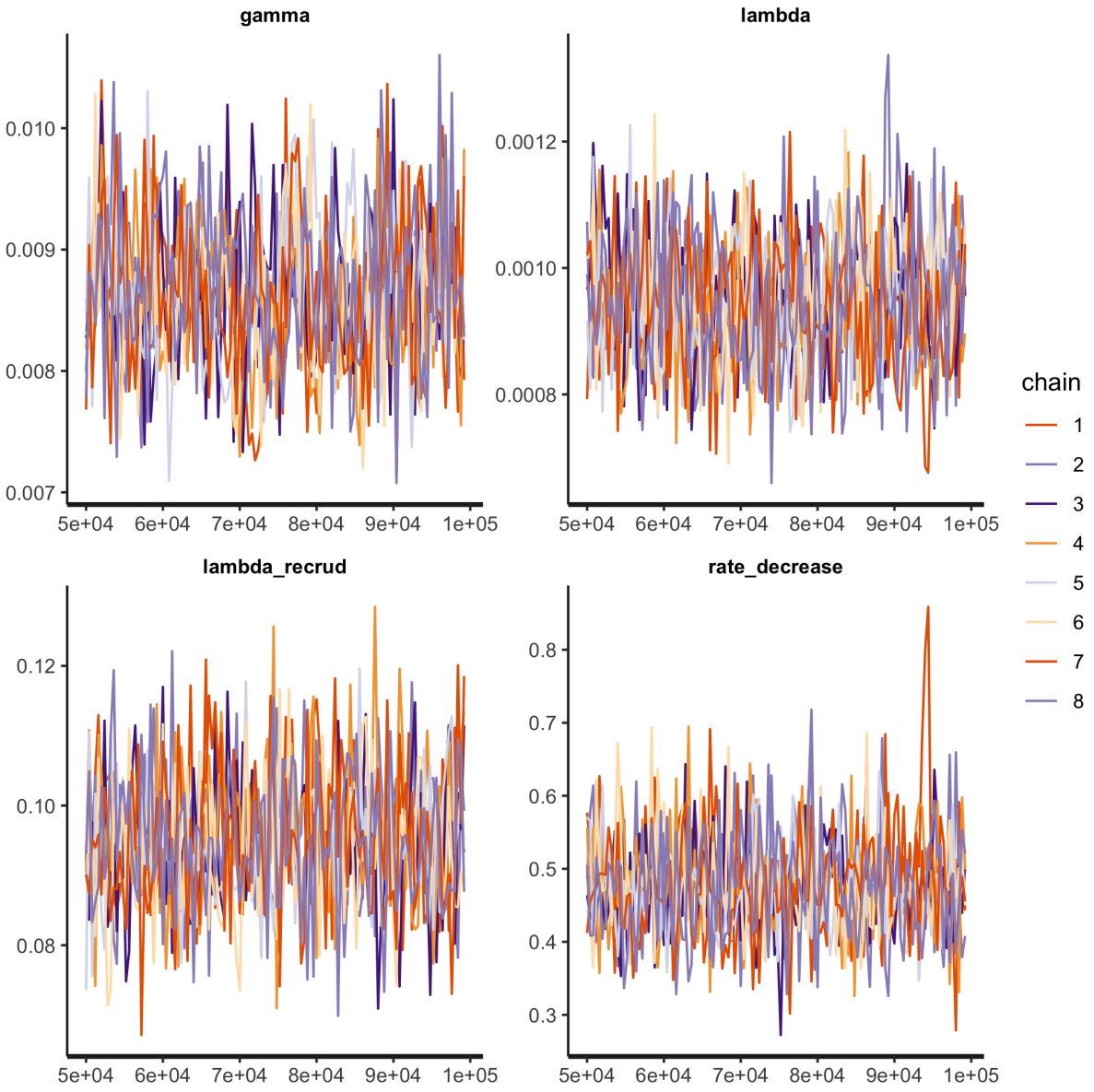
Model 2

Traceplots and posterior distributions:

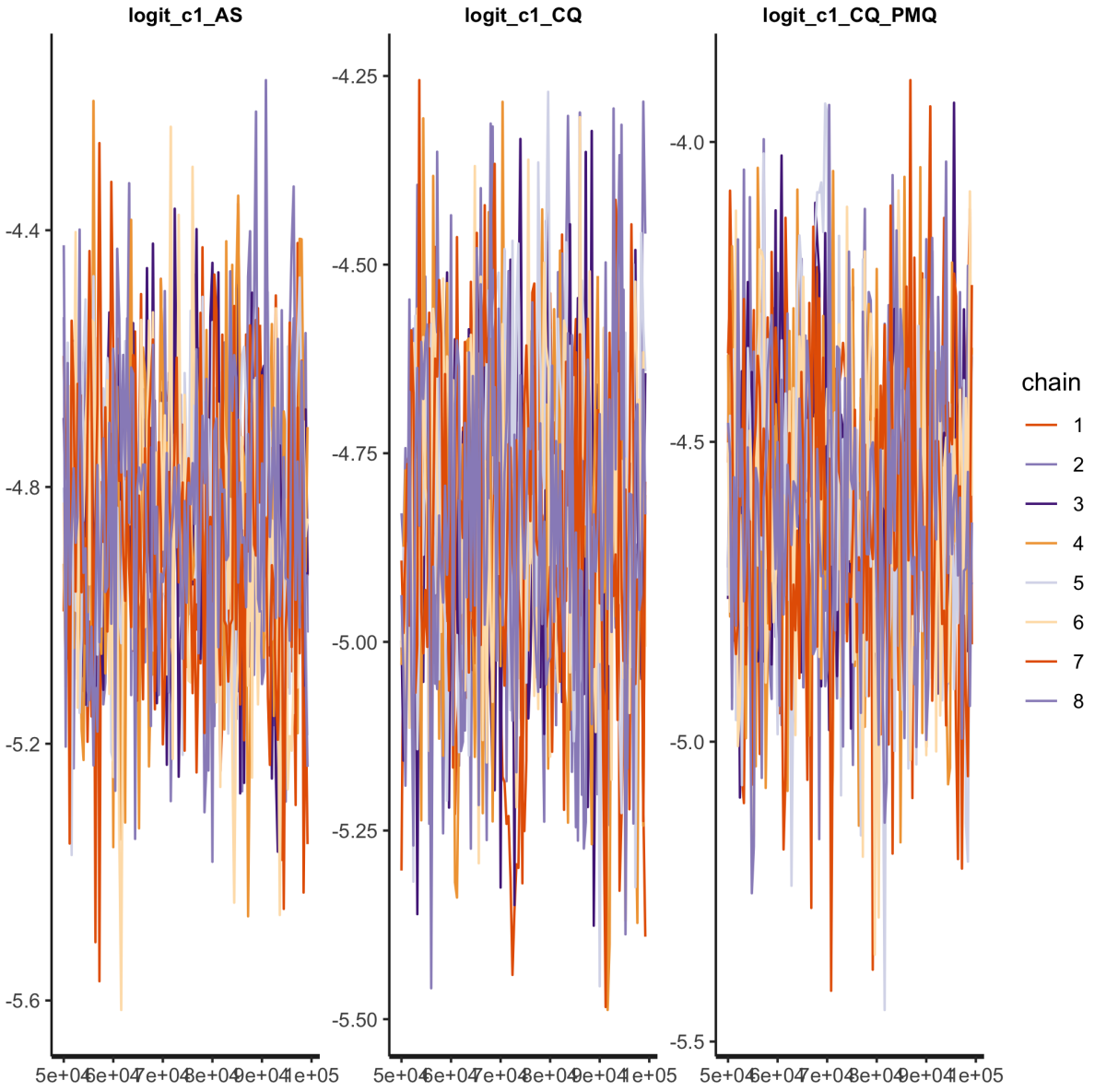
```
traceplot(mod2_Fit,c('AS_shape', 'CQ_shape', 'AS_scale', 'CQ_scale'))
```



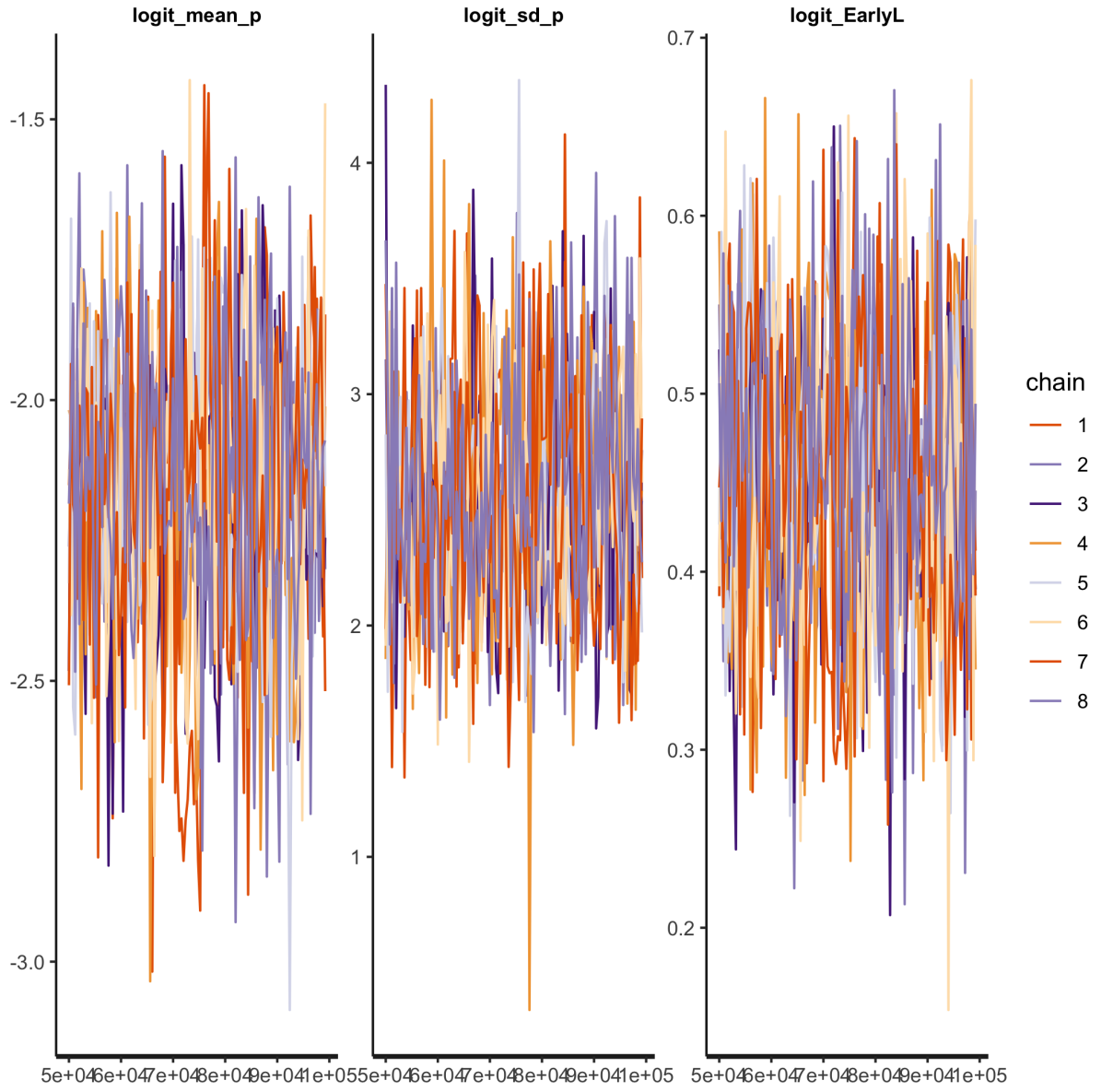

```
traceplot(mod2_Fit, c('gamma','lambda','lambda_recrud','rate_decrease'))
```




```
traceplot(mod2_Fit, c('logit_c1_AS','logit_c1_CQ','logit_c1_CQ_PMQ'))
```




```
traceplot(mod2_Fit, c('logit_mean_p','logit_sd_p','logit_EarlyL'))
```

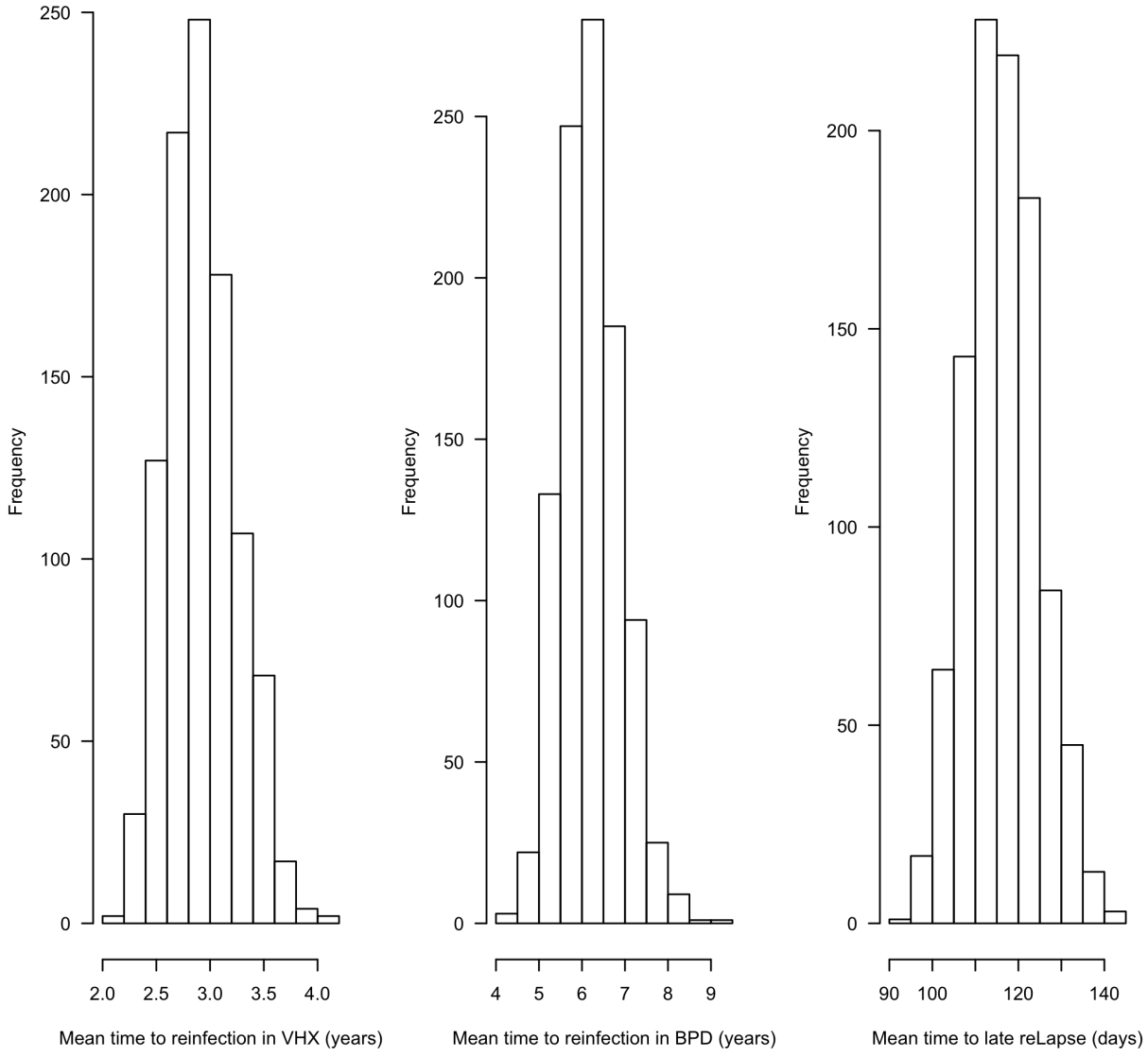



```
thetas_mod2 = extract(mod2_Fit)
```

```
# save a set of posterior parameter values for posterior predictive simulation
parameter_names = names(generate_inital_values_M2(Prior_params_M2,10,10))
parameter_names = parameter_names[!parameter_names %in% c('logit_p','logit_p_PMQ')]
N_samples = 200
thetas2_matrix = array(dim = c(N_samples, length(parameter_names)))
colnames(thetas2_matrix) = parameter_names
for(p in parameter_names){
  thetas2_matrix[,which(p==parameter_names)] = sample(thetas_mod2[[p]],size = N_samples)
}
save(thetas2_matrix, file = '../RData/TimingModel/Posterior_theta_samples.RData')
```

```
par(mfrow=c(1,3),las=1)
hist((1/thetas_mod2$lambda)/365, xlab='Mean time to reinfection in VHX (years)', main='')
```

```r
hist((1/(thetas_mod2$lambda*thetas_mod2$rate_decrease))/365,
     xlab='Mean time to reinfection in BPD (years)', main='')
hist((1/thetas_mod2$gamma), xlab='Mean time to late reLapse (days)', main='')
```




```r
par(mfrow=c(3,2),las=1)
# distribution of individual mixing proportions
hist(inv.logit(apply(thetas_mod2$logit_p,2,mean)),
     main = 'no PMQ', xlab = 'Individual mixing weights p',
     yaxt='n',ylab='')
hist(inv.logit(apply(thetas_mod2$logit_p_PMQ,2,mean)),
     main = 'PMQ+', xlab = 'Individual mixing weights p',
     yaxt='n',ylab='')

# posterior distribution of hierachical mixing proportions
```

```r
hist(inv.logit(thetas_mod2$logit_mean_p),
     xlab = 'Mean reinfection mixing weight', main = 'no PMQ',
     yaxt='n',ylab='')
round(100*quantile(inv.logit(thetas_mod2$logit_mean_p), probs = c(0.025,0.5,0.975)))
```

```
##  2.5%   50% 97.5%
##     6    10    16
```

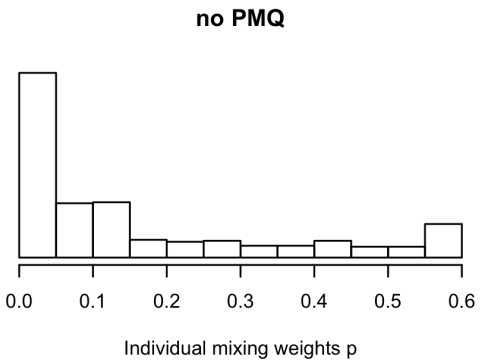
```r
hist(inv.logit(thetas_mod2$logit_mean_p_PMQ),
     xlab = 'Mean reinfection mixing weight', main = 'PMQ+',
     yaxt='n',ylab='')
round(100*quantile(inv.logit(thetas_mod2$logit_mean_p_PMQ), probs = c(0.025,0.975)))
```

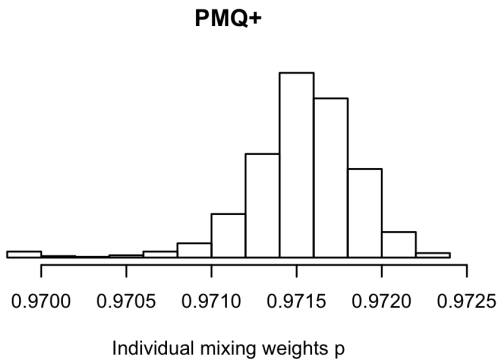
```
##  2.5% 97.5%
##    96    98
```

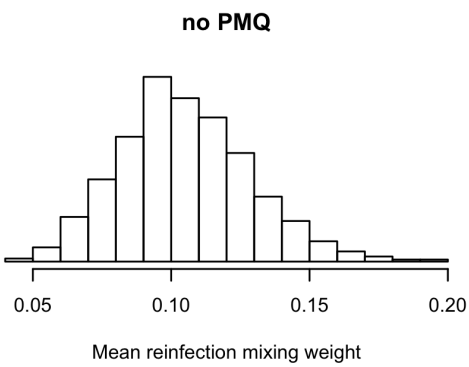
```r
# posterior distribution of hierachical mixing proportions
hist(inv.logit(thetas_mod2$logit_sd_p),
     xlab = 'SD of reinfection mixing weight', main = 'no PMQ',
     yaxt='n',ylab='')
round(quantile(inv.logit(thetas_mod2$logit_sd_p), probs = c(0.025,0.5,0.975)),2)
```

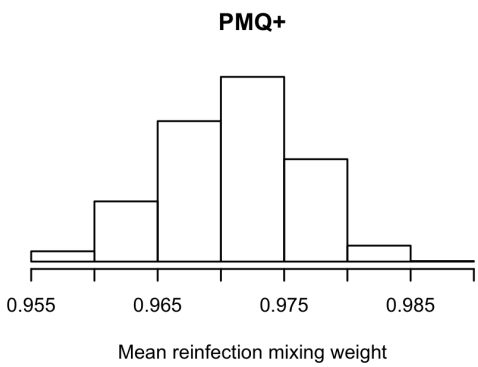
```
##  2.5%   50% 97.5%
##  0.84  0.93  0.97
```

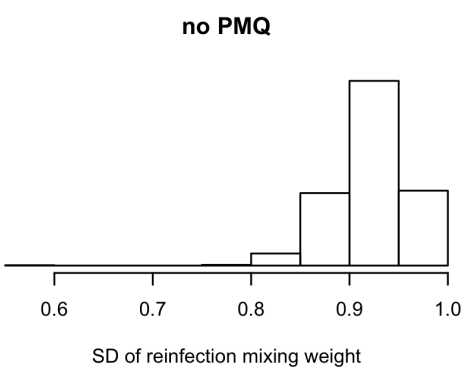
```r
hist(inv.logit(thetas_mod2$logit_sd_p_PMQ),
     xlab = 'SD of reinfection mixing weight', main = 'PMQ+',
     yaxt='n',ylab='')
```

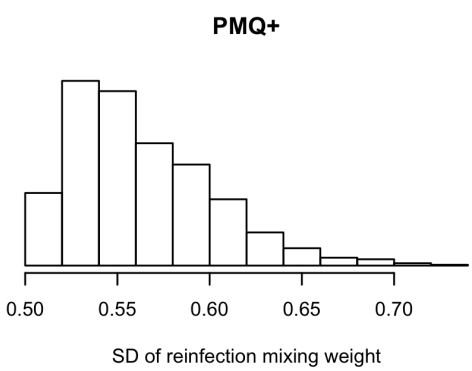








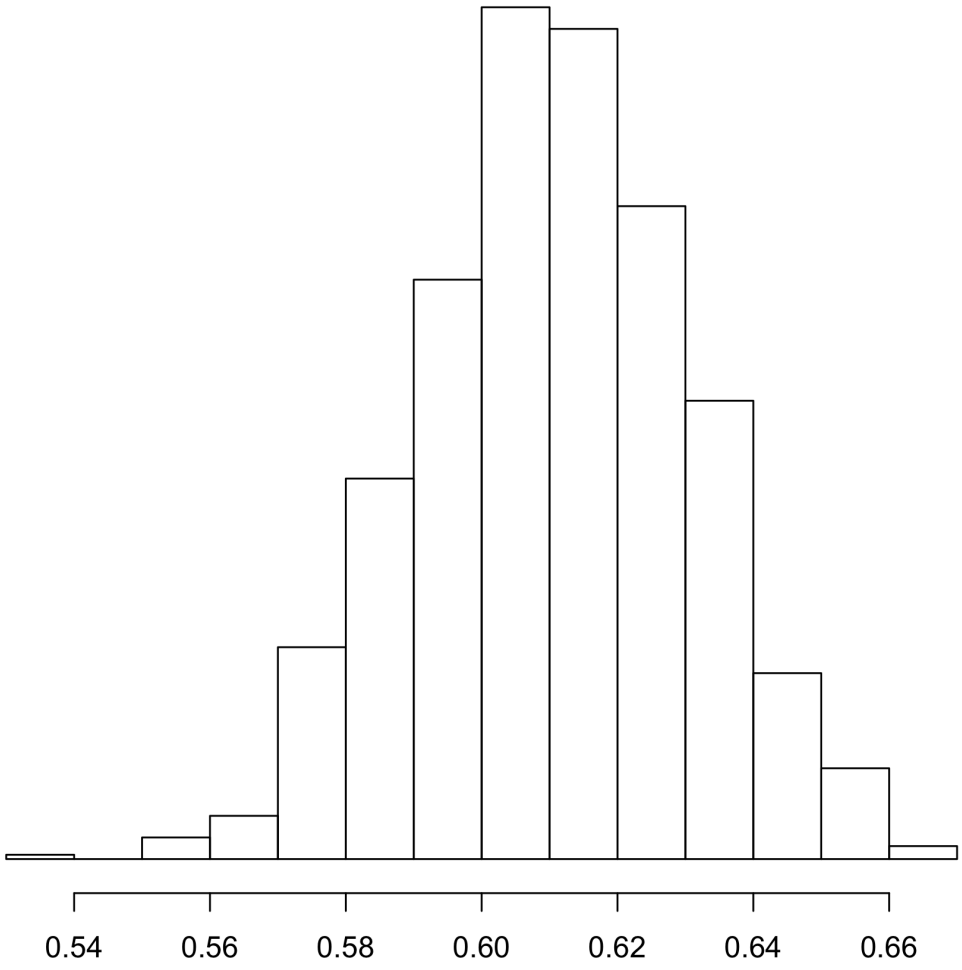





```
quantile(inv.logit(thetas_mod2$logit_sd_p_PMQ), probs = c(0.025,0.975),2)
```

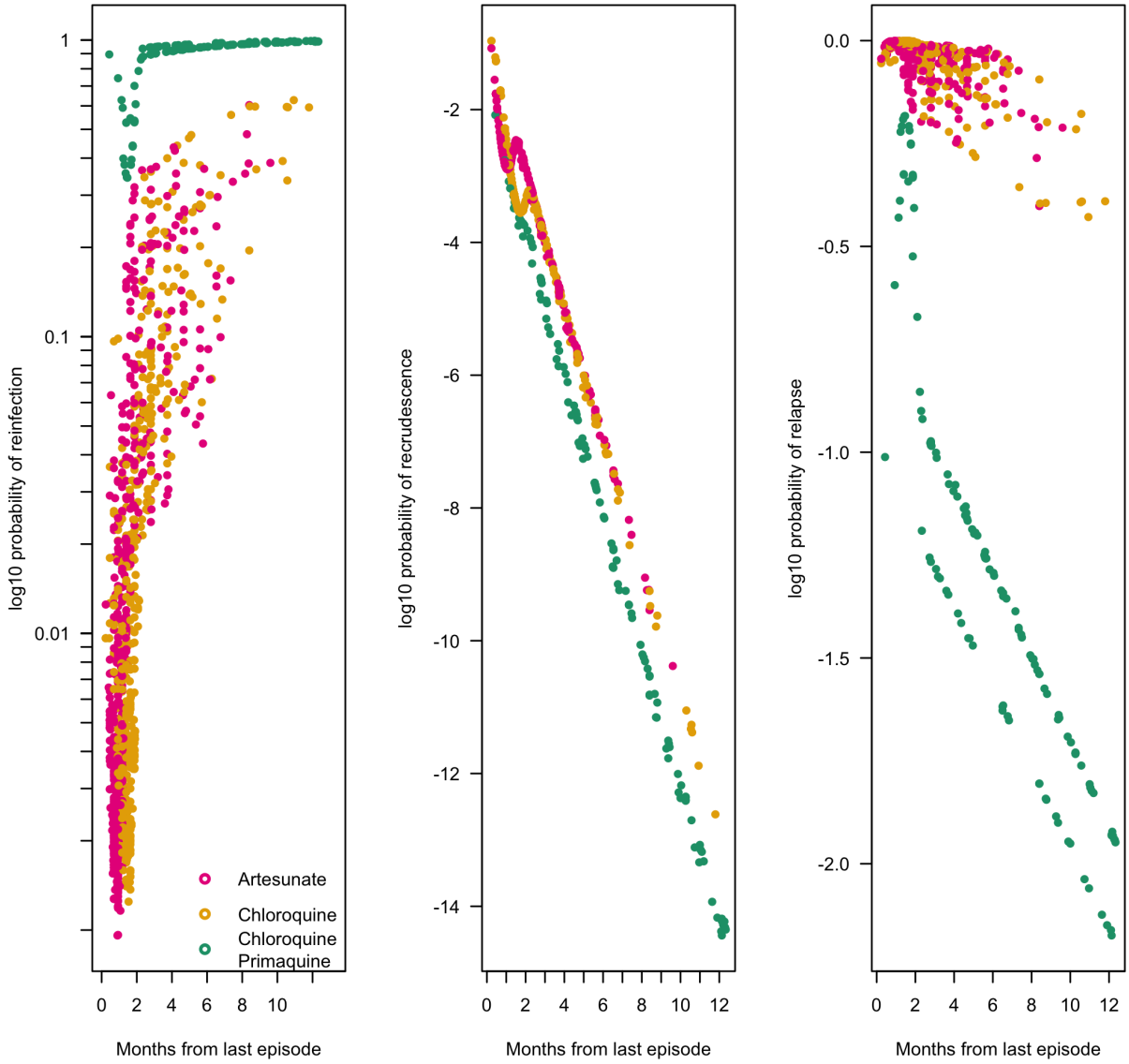
```
##      2.5%     97.5%
## 0.5131797 0.6582314
```

```
par(mfrow=c(1,1))
hist(inv.logit(thetas_mod2$logit_EarlyL), xlab = 'Mixing weight: early versus late relapse',
     main='',yaxt='n',ylab='')
```




```
par(las=1, mfrow=c(1,3))
# Plot the outcome of the predicted labels
#***************************** Reinfection ******************************
labels2 = extract(mod2_Fit, 'prob_labels')$prob_labels
mean_labels_Reinfection = apply(labels2[,ind_plotting,1,drop=T], 2, mean)
plot(Combined_Time_Data$Time_to_event[ind_plotting], log10(mean_labels_Reinfection),
     col = drug_cols3[Combined_Time_Data$numeric_drug[ind_plotting]+1],
     pch = as.numeric(Combined_Time_Data$Censored[ind_plotting])+16,
     ylab='log10 probability of reinfection', yaxt='n',xaxt='n',
     xlab='Months from last episode', xlim=c(0,400))
axis(1, at = seq(0, 420, by=60), labels = seq(0, 420, by=60)/30)
axis(2, at = -2:0, labels= 10^(-2:0))
axis(2, at = log10(seq(.1,1,by=.1)), labels = NA)
axis(2, at = log10(seq(.01,.1,by=.01)), labels = NA)
```

```
axis(2, at = log10(seq(.001,.01,by=.001)), labels = NA)
legend('bottomright',legend = c('Artesunate','Chloroquine','Chloroquine\nPrimaquine'),
       col=c(drug_cols3),pch = rep(1,3), bty='n',lwd=2,lty=NA)


#***************************** Recrudescence ***************************
mean_labels_ReCrud = apply(labels2[,ind_plotting,4,drop=T], 2, mean)
plot(Combined_Time_Data$Time_to_event[ind_plotting], log10(mean_labels_ReCrud),
     col = drug_cols3[Combined_Time_Data$numeric_drug[ind_plotting]+1], xaxt='n',
     pch = as.numeric(Combined_Time_Data$Censored[ind_plotting])+16,
     ylab='log10 probability of recrudescence',
     xlab='Months from last episode')
axis(1, at = seq(0,360,by=30), labels = seq(0,360,by=30)/30)

#***************************** Relapse ***************************
mean_labels_ReLap1 = apply(labels2[,ind_plotting,2,drop=T], 2, mean)
mean_labels_ReLap2 = apply(labels2[,ind_plotting,3,drop=T], 2, mean)
mean_labels_ReLap = mean_labels_ReLap1 + mean_labels_ReLap2
plot(Combined_Time_Data$Time_to_event[ind_plotting], log10(mean_labels_ReLap),
     col = drug_cols3[Combined_Time_Data$numeric_drug[ind_plotting]+1], xaxt='n',
     pch = as.numeric(Combined_Time_Data$Censored[ind_plotting])+16,
     ylab='log10 probability of relapse',
     xlab='Months from last episode')
axis(1, at = seq(0, 420, by= 60), labels = seq(0, 420, by=60)/30)
```




```
writeLines(sprintf('The estimated decrease in reinfection rate from the VHX to BPD studies is %s%% (95 C
                   round(100-100*quantile(thetas_mod2$rate_decrease,probs = .5)),
                   round(100-100*quantile(thetas_mod2$rate_decrease,probs = .975)),
                   round(100-100*quantile(thetas_mod2$rate_decrease,probs = 0.025))
))
```

```
## The estimated decrease in reinfection rate from the VHX to BPD studies is 53% (95 CI 37%-64%)
```

```
writeLines(sprintf('The mean time to reinfection in the VHX study is estimated as %s years (95 CI %s-%s
                   round((1/quantile(thetas_mod2$lambda,probs = .5))/365,1),
                   round((1/quantile(thetas_mod2$lambda,probs = .975))/365,1),
                   round((1/quantile(thetas_mod2$lambda,probs = .025))/365,1)
))
```

```
## The mean time to reinfection in the VHX study is estimated as 2.9 years (95 CI 2.4-3.6)
```

```
writeLines(sprintf('The mean time to reinfection in the BPD study is estimated as %s years (95 CI %s-%s
                   round((1/quantile(thetas_mod2$lambda*thetas_mod2$rate_decrease,
                                     probs = .5))/365,1),
                   round((1/quantile(thetas_mod2$lambda*thetas_mod2$rate_decrease,
                                     probs = .975))/365,1),
                   round((1/quantile(thetas_mod2$lambda*thetas_mod2$rate_decrease,
                                     probs = .025))/365,1)
))
```

```
## The mean time to reinfection in the BPD study is estimated as 6.2 years (95 CI 5-7.6)
```

Model Evaluation

Model Comparison

```
library(loo)
log_lik1 = extract_log_lik(mod1_Fit)
log_lik2 = extract_log_lik(mod2_Fit)

loo_2 = loo(log_lik2)
```

```
## Warning: Relative effective sample sizes ('r_eff' argument) not specified.
## For models fit with MCMC, the reported PSIS effective sample sizes and
## MCSE estimates will be over-optimistic.
```

```
## Warning: Some Pareto k diagnostic values are too high. See help('pareto-k-diagnostic') for details.
```

```
loo_1 = loo(log_lik1)
```

```
## Warning: Relative effective sample sizes ('r_eff' argument) not specified.
## For models fit with MCMC, the reported PSIS effective sample sizes and
## MCSE estimates will be over-optimistic.
```

```
## Warning: Some Pareto k diagnostic values are too high. See help('pareto-k-diagnostic') for details.
```

```
loo::compare(loo_1,loo_2)
```

```
## elpd_diff        se
##      -4.0       3.3
```

The simpler model (model 1) has higher predictive accuracy.

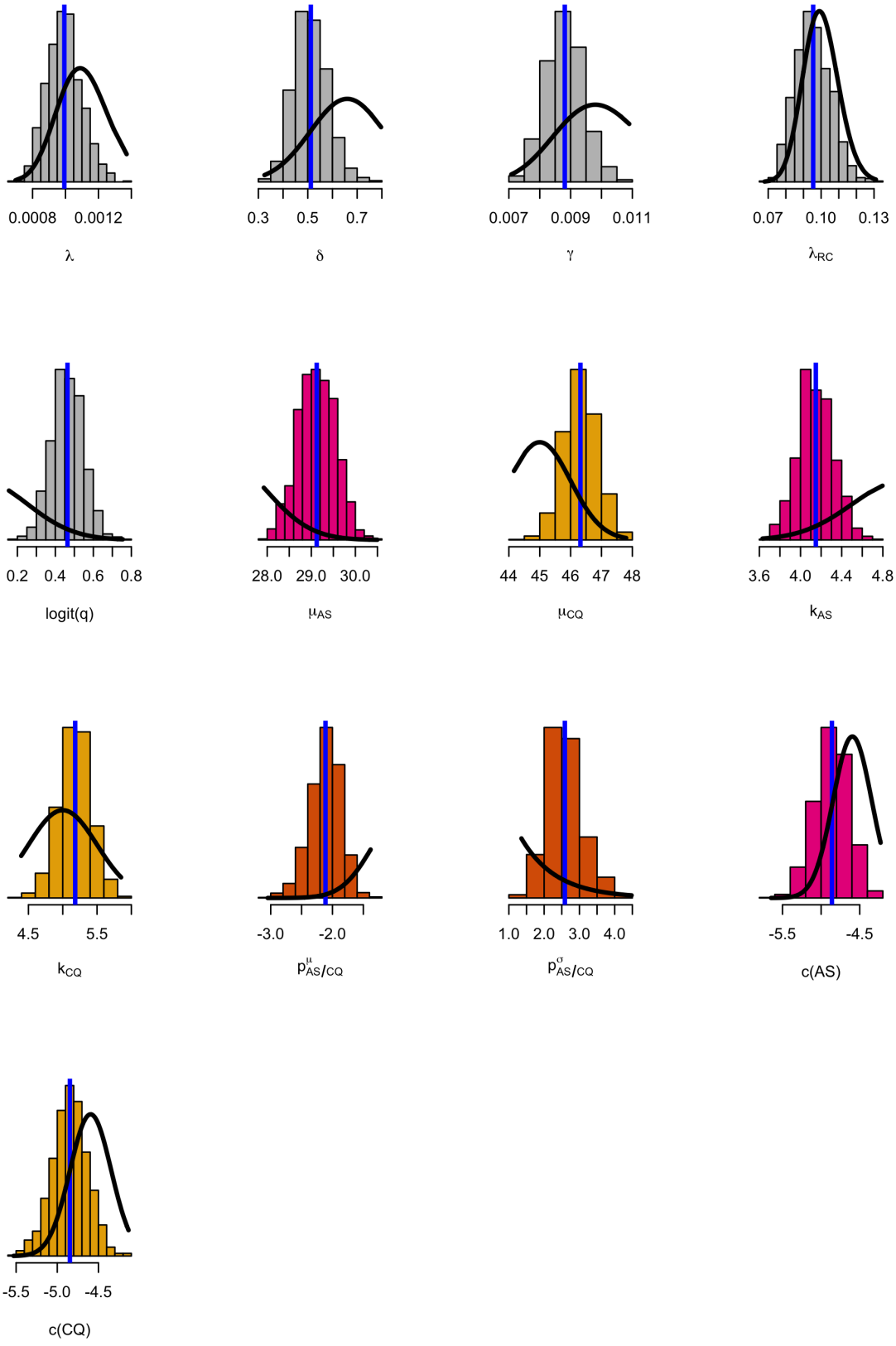
Prior to Posterior plots

```
par(mfrow=c(4,4))
# lambda: reinfection rate in VHX
hist(thetas_mod1$lambda,freq = FALSE, main='',yaxt='n',
     xlab=expression(lambda), ylab = '', col='grey', breaks=10)
xs = quantile(thetas_mod1$lambda, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod1$lambda),lwd=3,col='blue')
lines(xs, dgamma(x = xs,shape = Prior_params_M1$Hyper_lambda_shape,
                 rate = Prior_params_M1$Hyper_lambda_rate),
      col='black',lwd=3)
```

```
# delta: decrease in reinfection rate in BPD
hist(thetas_mod1$rate_decrease,freq = FALSE, main='',yaxt='n',
     xlab=expression(delta), ylab = '', col='grey', breaks=10)
xs = quantile(thetas_mod1$rate_decrease, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod1$rate_decrease),lwd=3,col='blue')
lines(xs, dnorm(x = xs,mean = Prior_params_M1$Hyper_mean_rate_decrease,
                sd = Prior_params_M1$Hyper_sd_rate_decrease),
      col='black',lwd=3)

# gamma: late relapse rate
hist(thetas_mod1$gamma,freq = FALSE, main='',
     xlab=expression(gamma), ylab = '', yaxt='n',
     col='grey', breaks=10)
xs = quantile(thetas_mod1$gamma, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod1$gamma),lwd=3,col='blue')
lines(xs, dgamma(x = xs,shape = Prior_params_M1$Hyper_gamma_shape,
                 rate = Prior_params_M1$Hyper_gamma_rate),
      col='black',lwd=3)

# lambda_RC:recrudescence rate
hist(thetas_mod1$lambda_recrud,freq = FALSE, main='',
     xlab=expression(lambda[RC]), ylab = '', yaxt='n',
     col='grey', breaks=10)
xs = quantile(thetas_mod1$lambda_recrud, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod1$lambda_recrud),lwd=3,col='blue')
lines(xs, dgamma(x = xs,shape = Prior_params_M1$Hyper_lambda_recrud_shape,
                 rate = Prior_params_M1$Hyper_lambda_recrud_rate),
      col='black',lwd=3)

# mixing weight: early versus late relapse
hist(thetas_mod1$logit_EarlyL, freq = F, main='',
     xlab= 'logit(q)', yaxt='n', ylab='', col='grey', breaks=10)
xs = quantile(thetas_mod1$logit_EarlyL, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod1$logit_EarlyL),lwd=3,col='blue')
lines(xs, dnorm(x = xs, mean = Prior_params_M1$Early_L_logit_mean,
                sd = Prior_params_M1$Early_L_logit_sd),
      col='black',lwd=3)

# AS_scale (Weibull scale parameter for AS monotherapy)
hist(thetas_mod1$AS_scale, freq = F, main='',
     xlab= expression(mu[AS]), yaxt='n', ylab='', col=drug_cols3['AS'], breaks=10)
xs = quantile(thetas_mod1$AS_scale, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod1$AS_scale),lwd=3,col='blue')
lines(xs, dnorm(x = xs, mean = Prior_params_M1$Hyper_AS_scale_mean,
                sd = Prior_params_M1$Hyper_AS_scale_sd),
      col='black',lwd=3)

# CQ_scale (Weibull scale parameter for CQ with or without PMQ)
hist(thetas_mod1$CQ_scale, freq = F, main='',
     xlab= expression(mu[CQ]), yaxt='n', ylab='', col=drug_cols3['CHQ'], breaks=10)
xs = quantile(thetas_mod1$CQ_scale, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod1$CQ_scale),lwd=3,col='blue')
lines(xs, dnorm(x = xs,mean = Prior_params_M1$Hyper_CQ_scale_mean,
```

```
                sd = Prior_params_M1$Hyper_CQ_scale_sd),
      col='black',lwd=3)

# AS_shape (Weibull shape parameter for AS monotherapy)
hist(thetas_mod1$AS_shape, freq = F, main='',
     xlab= expression(k[AS]), yaxt='n', ylab='', col=drug_cols3['AS'], breaks=10)
xs = quantile(thetas_mod1$AS_shape, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod1$AS_shape),lwd=3,col='blue')
lines(xs, dnorm(x = xs,mean = Prior_params_M1$Hyper_AS_shape_mean,
                sd = Prior_params_M1$Hyper_AS_shape_sd),
      col='black',lwd=3)

# CQ_shape (Weibull shape parameter for CQ with or without PMQ)
hist(thetas_mod1$CQ_shape,  freq = F, main='',
     xlab= expression(k[CQ]), yaxt='n', ylab='', col=drug_cols3['CHQ'], breaks=10)
xs = quantile(thetas_mod1$CQ_shape, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod1$CQ_shape),lwd=3,col='blue')
lines(xs, dnorm(x = xs,mean = Prior_params_M1$Hyper_CQ_shape_mean,
                sd = Prior_params_M1$Hyper_CQ_shape_sd),
      col='black',lwd=3)

# Mean logit p (hierachical mean reinfection proportion): no PMQ
hist(thetas_mod1$logit_mean_p, freq = F, main='',
     xlab= expression(p[AS/CQ]^mu), yaxt='n', ylab='', col=drug_cols2['AS'], breaks=10)
xs = quantile(thetas_mod1$logit_mean_p, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod1$logit_mean_p),lwd=3,col='blue')
lines(xs, dnorm(x = xs, mean = Prior_params_M1$Hyper_logit_mean_p_mean,
                sd = Prior_params_M1$Hyper_logit_mean_p_sd),
      col='black',lwd=3)


# SD logit p (hierachical sd reinfection proportion): no PMQ
hist(thetas_mod1$logit_sd_p, freq = F, main='',
     xlab= expression(p[AS/CQ]^sigma), yaxt='n', ylab='', col=drug_cols2['AS'], breaks=10)
xs = quantile(thetas_mod1$logit_sd_p, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod1$logit_sd_p),lwd=3,col='blue')
lines(xs, dexp(x = xs, rate = Prior_params_M1$Hyper_logit_sd_p_lambda),
      col='black',lwd=3)


# Mean c1 AS : mixing weight for recrudescence following AS
hist(thetas_mod1$logit_c1_AS, freq = F, main='',
     xlab= 'c(AS)', yaxt='n', ylab='', col=drug_cols3['AS'], breaks=10)
xs = quantile(thetas_mod1$logit_c1_AS, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod1$logit_c1_AS),lwd=3,col='blue')
lines(xs, dnorm(x = xs, mean = Prior_params_M1$Hyper_logit_c1_mean,
                sd = Prior_params_M1$Hyper_logit_c1_sd),
      col='black',lwd=3)

# Mean c1 CQ : mixing weight for recrudescence following CQ
hist(thetas_mod1$logit_c1_CQ, freq = F, main='',
     xlab= 'c(CQ)', yaxt='n', ylab='', col=drug_cols3['CHQ'], breaks=10)
xs = quantile(thetas_mod1$logit_c1_CQ, probs = seq(0,1,by = 0.001))
```

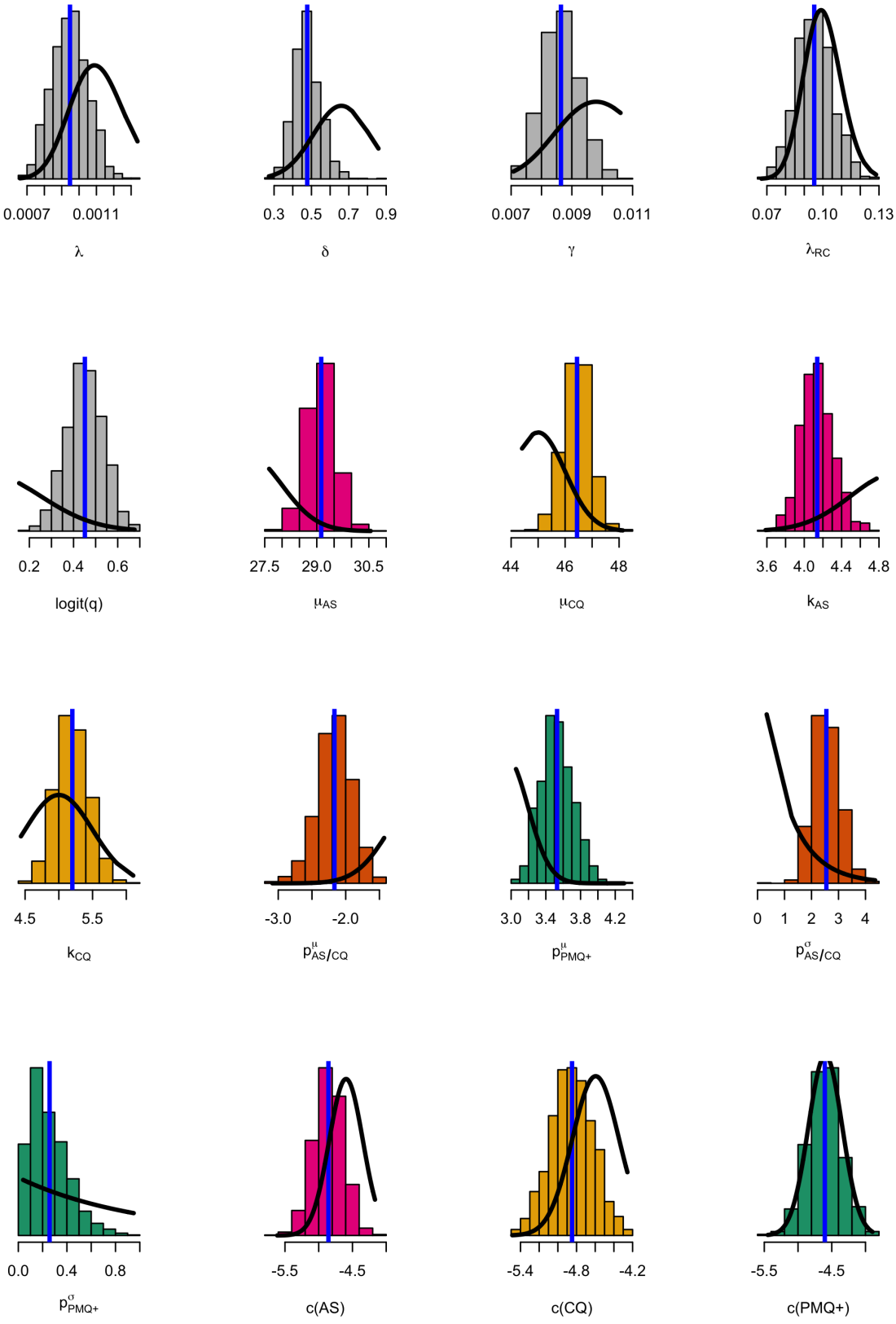
```r
abline(v=mean(thetas_mod1$logit_c1_CQ),lwd=3,col='blue')
lines(xs, dnorm(x = xs, mean = Prior_params_M1$Hyper_logit_c1_mean,
                sd = Prior_params_M1$Hyper_logit_c1_sd),
      col='black',lwd=3)
```


0.0008 0.0012
λ
0.3 0.5 0.7
δ
0.007 0.009 0.011
γ
0.07 0.10 0.13
λRC
0.2 0.4 0.6 0.8
logit(q)
28.0 29.0 30.0
μAS
44 45 46 47 48
μCQ
3.6 4.0 4.4 4.8
kAS
4.5 5.5
kCQ
-3.0 -2.0
p^μ AS/CQ
1.0 2.0 3.0 4.0
p^σ AS/CQ
-5.5 -4.5
c(AS)
-5.5 -5.0 -4.5
c(CQ)

```
par(mfrow=c(4,4))
# lambda: reinfection rate in VHX
hist(thetas_mod2$lambda,freq = FALSE, main='',yaxt='n',
     xlab=expression(lambda), ylab = '', col='grey', breaks=10)
xs = quantile(thetas_mod2$lambda, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$lambda),lwd=3,col='blue')
lines(xs, dgamma(x = xs,shape = Prior_params_M2$Hyper_lambda_shape,
                 rate = Prior_params_M2$Hyper_lambda_rate),
      col='black',lwd=3)

# delta: decrease in reinfection rate in BPD
hist(thetas_mod2$rate_decrease,freq = FALSE, main='',yaxt='n',
     xlab=expression(delta), ylab = '', col='grey', breaks=10)
xs = quantile(thetas_mod2$rate_decrease, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$rate_decrease),lwd=3,col='blue')
lines(xs, dnorm(x = xs,mean = Prior_params_M2$Hyper_mean_rate_decrease,
                sd = Prior_params_M2$Hyper_sd_rate_decrease),
      col='black',lwd=3)

# gamma: late relapse rate
hist(thetas_mod2$gamma,freq = FALSE, main='',
     xlab=expression(gamma), ylab = '', yaxt='n',
     col='grey', breaks=10)
xs = quantile(thetas_mod2$gamma, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$gamma),lwd=3,col='blue')
lines(xs, dgamma(x = xs,shape = Prior_params_M2$Hyper_gamma_shape,
                 rate = Prior_params_M2$Hyper_gamma_rate),
      col='black',lwd=3)

# lambda_RC:recrudescence rate
hist(thetas_mod2$lambda_recrud,freq = FALSE, main='',
     xlab=expression(lambda[RC]), ylab = '', yaxt='n',
     col='grey', breaks=10)
xs = quantile(thetas_mod2$lambda_recrud, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$lambda_recrud),lwd=3,col='blue')
lines(xs, dgamma(x = xs,shape = Prior_params_M2$Hyper_lambda_recrud_shape,
                 rate = Prior_params_M2$Hyper_lambda_recrud_rate),
      col='black',lwd=3)

# mixing weight: early versus late relapse
hist(thetas_mod2$logit_EarlyL, freq = F, main='',
     xlab= 'logit(q)', yaxt='n', ylab='', col='grey', breaks=10)
xs = quantile(thetas_mod2$logit_EarlyL, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$logit_EarlyL),lwd=3,col='blue')
lines(xs, dnorm(x = xs, mean = Prior_params_M2$Early_L_logit_mean,
                sd = Prior_params_M2$Early_L_logit_sd),
      col='black',lwd=3)

# AS_scale (Weibull scale parameter for AS monotherapy)
hist(thetas_mod2$AS_scale, freq = F, main='',
     xlab= expression(mu[AS]), yaxt='n', ylab='', col=drug_cols3['AS'], breaks=10)
xs = quantile(thetas_mod2$AS_scale, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$AS_scale),lwd=3,col='blue')
```

```
lines(xs, dnorm(x = xs, mean = Prior_params_M2$Hyper_AS_scale_mean,
                sd = Prior_params_M2$Hyper_AS_scale_sd),
      col='black',lwd=3)

# CQ_scale (Weibull scale parameter for CQ with or without PMQ)
hist(thetas_mod2$CQ_scale, freq = F, main='',
     xlab= expression(mu[CQ]), yaxt='n', ylab='', col=drug_cols3['CHQ'], breaks=10)
xs = quantile(thetas_mod2$CQ_scale, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$CQ_scale),lwd=3,col='blue')
lines(xs, dnorm(x = xs,mean = Prior_params_M2$Hyper_CQ_scale_mean,
                sd = Prior_params_M2$Hyper_CQ_scale_sd),
      col='black',lwd=3)

# AS_shape (Weibull shape parameter for AS monotherapy)
hist(thetas_mod2$AS_shape, freq = F, main='',
     xlab= expression(k[AS]), yaxt='n', ylab='', col=drug_cols3['AS'], breaks=10)
xs = quantile(thetas_mod2$AS_shape, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$AS_shape),lwd=3,col='blue')
lines(xs, dnorm(x = xs,mean = Prior_params_M2$Hyper_AS_shape_mean,
                sd = Prior_params_M2$Hyper_AS_shape_sd),
      col='black',lwd=3)

# CQ_shape (Weibull shape parameter for CQ with or without PMQ)
hist(thetas_mod2$CQ_shape,  freq = F, main='',
     xlab= expression(k[CQ]), yaxt='n', ylab='', col=drug_cols3['CHQ'], breaks=10)
xs = quantile(thetas_mod2$CQ_shape, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$CQ_shape),lwd=3,col='blue')
lines(xs, dnorm(x = xs,mean = Prior_params_M2$Hyper_CQ_shape_mean,
                sd = Prior_params_M2$Hyper_CQ_shape_sd),
      col='black',lwd=3)

# Mean logit p (hierachical mean reinfection proportion): no PMQ
hist(thetas_mod2$logit_mean_p, freq = F, main='',
     xlab= expression(p[AS/CQ]^mu), yaxt='n', ylab='', col=drug_cols2['AS'], breaks=10)
xs = quantile(thetas_mod2$logit_mean_p, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$logit_mean_p),lwd=3,col='blue')
lines(xs, dnorm(x = xs, mean = Prior_params_M2$Hyper_logit_mean_p_mean,
                sd = Prior_params_M2$Hyper_logit_mean_p_sd),
      col='black',lwd=3)

# Mean logit p PMQ+ (hierachical mean reinfection proportion): PMQ+
hist(thetas_mod2$logit_mean_p_PMQ, freq = F, main='',
     xlab= expression(p['PMQ+']^mu), yaxt='n', ylab='', col=drug_cols3['CHQ/PMQ'], breaks=10)
xs = quantile(thetas_mod2$logit_mean_p_PMQ, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$logit_mean_p_PMQ),lwd=3,col='blue')
lines(xs, dnorm(x = xs, mean = Prior_params_M2$Hyper_logit_mean_pPMQ_mean,
                sd = Prior_params_M2$Hyper_logit_mean_pPMQ_sd),
      col='black',lwd=3)

# SD logit p (hierachical sd reinfection proportion): no PMQ
hist(thetas_mod2$logit_sd_p, freq = F, main='',
     xlab= expression(p[AS/CQ]^sigma), yaxt='n', ylab='', col=drug_cols2['AS'], breaks=10)
xs = quantile(thetas_mod2$logit_sd_p, probs = seq(0,1,by = 0.001))
```

```
abline(v=mean(thetas_mod2$logit_sd_p),lwd=3,col='blue')
lines(xs, dexp(x = xs, rate = Prior_params_M2$Hyper_logit_sd_p_lambda),
      col='black',lwd=3)

# SD logit p PMQ+ (hierachical sd reinfection proportion): PMQ+
hist(thetas_mod2$logit_sd_p_PMQ, freq = F, main='',
     xlab= expression(p['PMQ+']^sigma), yaxt='n', ylab='', col=drug_cols2['CHQ/PMQ'], breaks=10)
xs = quantile(thetas_mod2$logit_sd_p_PMQ, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$logit_sd_p_PMQ),lwd=3,col='blue')
lines(xs, dexp(x = xs, rate = Prior_params_M2$Hyper_logit_sd_pPMQ_lambda),
      col='black',lwd=3)

# Mean c1 AS : mixing weight for recrudescence following AS
hist(thetas_mod2$logit_c1_AS, freq = F, main='',
     xlab= 'c(AS)', yaxt='n', ylab='', col=drug_cols3['AS'], breaks=10)
xs = quantile(thetas_mod2$logit_c1_AS, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$logit_c1_AS),lwd=3,col='blue')
lines(xs, dnorm(x = xs, mean = Prior_params_M2$Hyper_logit_c1_mean,
                sd = Prior_params_M2$Hyper_logit_c1_sd),
      col='black',lwd=3)

# Mean c1 CQ : mixing weight for recrudescence following CQ
hist(thetas_mod2$logit_c1_CQ, freq = F, main='',
     xlab= 'c(CQ)', yaxt='n', ylab='', col=drug_cols3['CHQ'], breaks=10)
xs = quantile(thetas_mod2$logit_c1_CQ, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$logit_c1_CQ),lwd=3,col='blue')
lines(xs, dnorm(x = xs, mean = Prior_params_M2$Hyper_logit_c1_mean,
                sd = Prior_params_M2$Hyper_logit_c1_sd),
      col='black',lwd=3)

# Mean c1 PMQ+ : mixing weight for recrudescence following PMQ+
hist(thetas_mod2$logit_c1_CQ_PMQ, freq = F, main='',
     xlab= 'c(PMQ+)', yaxt='n', ylab='', col=drug_cols3['CHQ/PMQ'], breaks=10)
xs = quantile(thetas_mod2$logit_c1_CQ_PMQ, probs = seq(0,1,by = 0.001))
abline(v=mean(thetas_mod2$logit_c1_CQ_PMQ),lwd=3,col='blue')
lines(xs, dnorm(x = xs, mean = Prior_params_M2$Hyper_logit_c1_mean,
                sd = Prior_params_M2$Hyper_logit_c1_sd),
      col='black',lwd=3)
```


0.0007
0.0011
λ
0.3
0.5
0.7
0.9
δ
0.007
0.009
0.011
γ
0.07
0.10
0.13
λRC
0.2
0.4
0.6
logit(q)
27.5
29.0
30.5
μAS
44
46
48
μCQ
3.6
4.0
4.4
4.8
kAS
4.5
5.5
kCQ
-3.0
-2.0
p^μ_AS/CQ
3.0
3.4
3.8
4.2
p^μ_PMQ+
0
1
2
3
4
p^σ_AS/CQ
0.0
0.4
0.8
p^σ_PMQ+
-5.5
-4.5
c(AS)
-5.4
-4.8
-4.2
c(CQ)
-5.5
-4.5
c(PMQ+)

Posterior summaries of parameters

Model 2 posterior median values with 95% CIs:

```
writeLines(sprintf('lambda: %s [%s;%s]', round(median(thetas_mod2$lambda),5),
                   round(quantile(thetas_mod2$lambda, 0.025),5),
                   round(quantile(thetas_mod2$lambda, 0.975),5)))
```

```
## lambda: 0.00095 [0.00077;0.00115]
```

```
writeLines(sprintf('delta: %s [%s;%s]', round(median(thetas_mod2$rate_decrease),2),
                   round(quantile(thetas_mod2$rate_decrease, 0.025),2),
                   round(quantile(thetas_mod2$rate_decrease, 0.975),2)))
```

```
## delta: 0.47 [0.36;0.63]
```

```
writeLines(sprintf('gamma: %s [%s;%s]', round(median(thetas_mod2$gamma),4),
                   round(quantile(thetas_mod2$gamma, 0.025),4),
                   round(quantile(thetas_mod2$gamma, 0.975),4)))
```

```
## gamma: 0.0086 [0.0075;0.0099]
```

```
writeLines(sprintf('lambda_RC: %s [%s;%s]', round(median(thetas_mod2$lambda_recrud),3),
                   round(quantile(thetas_mod2$lambda_recrud, 0.025),3),
                   round(quantile(thetas_mod2$lambda_recrud, 0.975),3)))
```

```
## lambda_RC: 0.095 [0.077;0.115]
```

```
writeLines(sprintf('logit(q): %s [%s;%s]', round(median(thetas_mod2$logit_EarlyL),2),
                   round(quantile(thetas_mod2$logit_EarlyL, 0.025),2),
                   round(quantile(thetas_mod2$logit_EarlyL, 0.975),2)))
```

```
## logit(q): 0.45 [0.29;0.61]
```

```
writeLines(sprintf('mu_AS: %s [%s;%s]', round(median(thetas_mod2$AS_scale),0),
                   round(quantile(thetas_mod2$AS_scale, 0.025),0),
                   round(quantile(thetas_mod2$AS_scale, 0.975),0)))
```

```
## mu_AS: 29 [28;30]
```

```
writeLines(sprintf('mu_CQ: %s [%s;%s]', round(median(thetas_mod2$CQ_scale),0),
                   round(quantile(thetas_mod2$CQ_scale, 0.025),0),
                   round(quantile(thetas_mod2$CQ_scale, 0.975),0)))
```

```
## mu_CQ: 46 [45;47]
```

```
writeLines(sprintf('k_AS: %s [%s;%s]', round(median(thetas_mod2$AS_shape),1),
                   round(quantile(thetas_mod2$AS_shape, 0.025),1),
                   round(quantile(thetas_mod2$AS_shape, 0.975),1)))
```

```
## k_AS: 4.1 [3.8;4.5]
```

```
writeLines(sprintf('k_CQ: %s [%s;%s]', round(median(thetas_mod2$CQ_shape),1),
                   round(quantile(thetas_mod2$CQ_shape, 0.025),1),
                   round(quantile(thetas_mod2$CQ_shape, 0.975),1)))
```

```
## k_CQ: 5.2 [4.8;5.7]
```

```
writeLines(sprintf('p_n: %s [%s;%s]', round(median(apply(thetas_mod2$logit_p,1,median)),1),
                   round(median(apply(thetas_mod2$logit_p,1,quantile, probs=0)),1),
                   round(median(apply(thetas_mod2$logit_p,1,quantile, probs=1)),1)))
```

```
## p_n: -2.3 [-9.8;5.2]
```

```
writeLines(sprintf('pPMQ_n: %s [%s;%s]', round(median(apply(thetas_mod2$logit_p_PMQ,1,median)),1),
                   round(median(apply(thetas_mod2$logit_p_PMQ,1,quantile, probs=0)),1),
                   round(median(apply(thetas_mod2$logit_p_PMQ,1,quantile, probs=1)),1)))
```

```
## pPMQ_n: 3.5 [2.8;4.2]
```

```
writeLines(sprintf('p^mu_AS/CQ: %s [%s;%s]', round(median(thetas_mod2$logit_mean_p),1),
                   round(quantile(thetas_mod2$logit_mean_p, 0.025),1),
                   round(quantile(thetas_mod2$logit_mean_p, 0.975),1)))
```

```
## p^mu_AS/CQ: -2.2 [-2.7;-1.7]
```

```
writeLines(sprintf('p^mu_PMQ: %s [%s;%s]', round(median(thetas_mod2$logit_mean_p_PMQ),1),
                   round(quantile(thetas_mod2$logit_mean_p_PMQ, 0.025),1),
                   round(quantile(thetas_mod2$logit_mean_p_PMQ, 0.975),1)))
```

```
## p^mu_PMQ: 3.5 [3.2;3.9]
```

```
writeLines(sprintf('p^sigma_AS/CQ: %s [%s;%s]', round(median(thetas_mod2$logit_sd_p),1),
                   round(quantile(thetas_mod2$logit_sd_p, 0.025),1),
                   round(quantile(thetas_mod2$logit_sd_p, 0.975),1)))
```

```
## p^sigma_AS/CQ: 2.5 [1.7;3.6]
```

```
writeLines(sprintf('p^sigma_PMQ: %s [%s;%s]', round(median(thetas_mod2$logit_sd_p_PMQ),1),
                   round(quantile(thetas_mod2$logit_sd_p_PMQ, 0.025),1),
                   round(quantile(thetas_mod2$logit_sd_p_PMQ, 0.975),1)))
```

```
## p^sigma_PMQ: 0.2 [0.1;0.7]
```

```
writeLines(sprintf('c1_AS: %s [%s;%s]', round(median(thetas_mod2$logit_c1_AS),1),
                   round(quantile(thetas_mod2$logit_c1_AS, 0.025),1),
                   round(quantile(thetas_mod2$logit_c1_AS, 0.975),1)))
```

```
## c1_AS: -4.9 [-5.3;-4.4]
```

```
writeLines(sprintf('c1_CQ: %s [%s;%s]', round(median(thetas_mod2$logit_c1_CQ),1),
                   round(quantile(thetas_mod2$logit_c1_CQ, 0.025),1),
                   round(quantile(thetas_mod2$logit_c1_CQ, 0.975),1)))
```

```
## c1_CQ: -4.8 [-5.3;-4.4]
```

```
writeLines(sprintf('c1_PMQ: %s [%s;%s]', round(median(thetas_mod2$logit_c1_CQ_PMQ),1),
                   round(quantile(thetas_mod2$logit_c1_CQ_PMQ, 0.025),1),
                   round(quantile(thetas_mod2$logit_c1_CQ_PMQ, 0.975),1)))
```

```
## c1_PMQ: -4.6 [-5.1;-4.1]
```

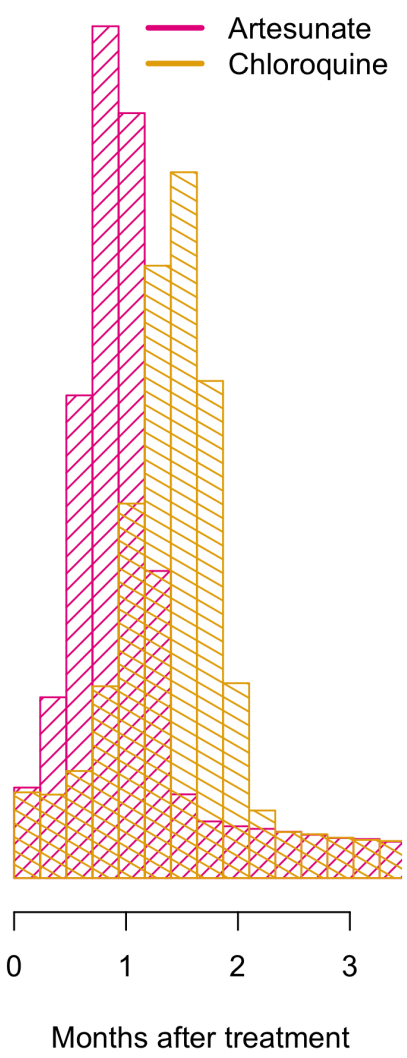
Interpretation of results

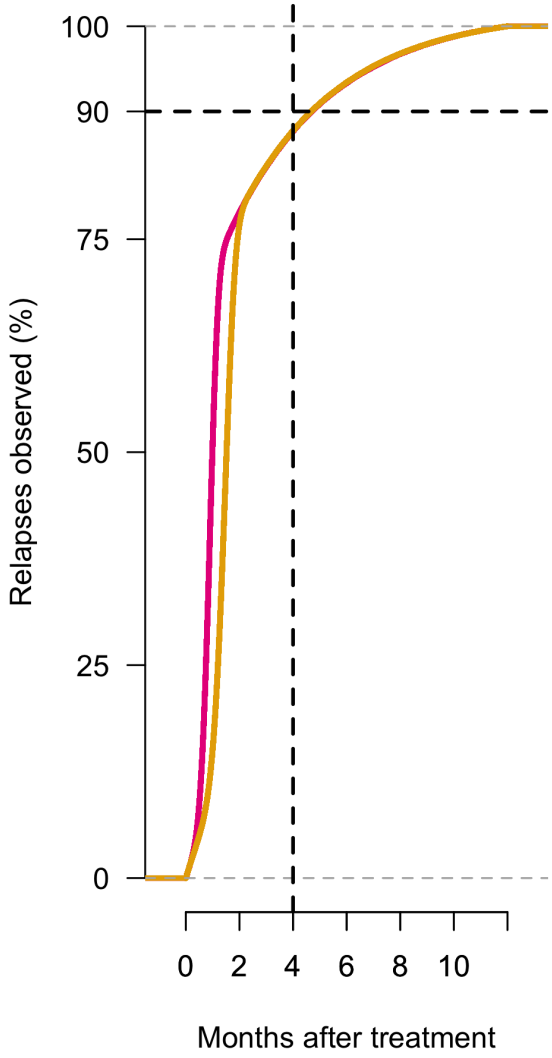
The cumulative probability of time to relapse. We draw from the posterior distribution to get a predicted time to relapse (in those who will relapse before they are reinfected).

```
thetas_mod2 = extract(mod2_Fit)
K = 500000
Early_relapse = sample(x = inv.logit(thetas_mod2$logit_EarlyL),replace = T, size = K)
Mixture = sapply(Early_relapse, FUN = function(x){
```

```
  sample(x = 1:2, replace = T, size = 1 , prob = c(x,1-x))
})
# Artesunate mono-therapy
T1s = rweibull(n = K, shape = sample(x = thetas_mod2$AS_shape, size = K, replace = T),
               scale = sample(x = thetas_mod2$AS_scale, size = K, replace = T))
T2s = rexp(n = K, rate =  sample(x = thetas_mod2$gamma, size = K, replace = T))
Times_RelapseAS = c(T1s[Mixture==1], T2s[Mixture==2])
```

```
par(mfrow=c(1,2), las=1)

# Chloroquine mono-therapy
T1s = rweibull(n = K, shape = sample(x = thetas_mod2$CQ_shape, size = K, replace = T),
               scale = sample(x = thetas_mod2$CQ_scale, size = K, replace = T))
T2s = rexp(n = K, rate =  sample(x = thetas_mod2$gamma, size = K, replace = T))
Times_RelapseCQ = c(T1s[Mixture==1], T2s[Mixture==2])

hist(Times_RelapseAS, breaks = seq(0,7000, by=7), xlim=c(0,100),
     main='', col=drug_cols3['AS'], density = 15, yaxt='n',ylab = '',
     xlab='Months after treatment', xaxt='n')
hist(Times_RelapseCQ, breaks = seq(0,7000, by=7), xlim=c(0,100),
     main='', add=T, density=15, col=drug_cols3['CHQ'], angle= -30)
axis(1, at = seq(0,90, by=30), labels =  seq(0,90, by=30)/30)
legend('topright', col=drug_cols3[1:2], lwd=3,bty='n',
       legend = c('Artesunate','Chloroquine'))

plot(ecdf(Times_RelapseAS[Times_RelapseAS<360]),
     col=drug_cols3['AS'], xaxt='n',main='',
     xlab='Months after treatment', bty='n', yaxt='n',
     ylab = 'Relapses observed (%)', lwd=3, lty=1)
axis(2, at = c(0,.25,.5,.75,.9,1),
     labels = 100*c(0,.25,.5,.75,.9,1))
axis(1, at = seq(0,360, by=60), labels =  seq(0,360, by=60)/30)
lines(ecdf(Times_RelapseCQ[Times_RelapseCQ<360]),
      col=drug_cols3['CHQ'], lwd=3, lty=1)
axis(1, at = seq(0,360, by=60), labels =  seq(0,360, by=60)/30)
abline(h=.9, lwd=2, lty=2)
abline(v=4*30, lwd=2, lty=2)
```






```
# Now we compute the fixed effect probabilities over time
Ts = 1:360
# AS
prob_labels_raw_AS = array(dim = c(4,length(Ts)))
# Reinfection
prob_labels_raw_AS[1,] =
  exp(mean(thetas_mod2$log_p))*
  dexp(Ts, rate = mean(thetas_mod2$lambda));
# Early Relapse
prob_labels_raw_AS[2,] =
  exp(mean(thetas_mod2$log_1m_p))*
  exp(mean(thetas_mod2$log_1m_c1_AS))*
  exp(mean(thetas_mod2$log_EarlyL))*
  dweibull(Ts , shape = mean(thetas_mod2$AS_shape),
```

```
          scale = mean(thetas_mod2$AS_scale))
# Late Relapse
prob_labels_raw_AS[3,] =
  exp(mean(thetas_mod2$log_1m_p))*
  exp(mean(thetas_mod2$log_1m_c1_AS))*
  exp(mean(thetas_mod2$log_1m_EarlyL))*
  dexp(Ts, rate = mean(thetas_mod2$gamma))
# Recrudescence
prob_labels_raw_AS[4,] =
  exp(mean(thetas_mod2$log_1m_p))*
  exp(mean(thetas_mod2$log_c1_AS))*
  dexp(Ts, rate = mean(thetas_mod2$lambda_recrud))

# CQ
prob_labels_raw_CQ = array(dim = c(4,length(Ts)))
# Reinfection
prob_labels_raw_CQ[1,] =
  exp(mean(thetas_mod2$log_p))*
  dexp(Ts, rate = mean(thetas_mod2$lambda));
# Early Relapse
prob_labels_raw_CQ[2,] =
  exp(mean(thetas_mod2$log_1m_p))*
  exp(mean(thetas_mod2$log_1m_c1_CQ))*
  exp(mean(thetas_mod2$log_EarlyL))*
  dweibull(Ts , shape = mean(thetas_mod2$CQ_shape),
          scale = mean(thetas_mod2$CQ_scale))
# Late Relapse
prob_labels_raw_CQ[3,] =
  exp(mean(thetas_mod2$log_1m_p))*
  exp(mean(thetas_mod2$log_1m_c1_CQ))*
  exp(mean(thetas_mod2$log_1m_EarlyL))*
  dexp(Ts, rate = mean(thetas_mod2$inv_gamma))
```

```
## Warning in mean.default(thetas_mod2$inv_gamma): argument is not numeric or
## logical: returning NA
```

```
# Recrudescence
prob_labels_raw_CQ[4,] =
  exp(mean(thetas_mod2$log_1m_p))*
  exp(mean(thetas_mod2$log_c1_CQ))*
  dexp(Ts, rate = mean(thetas_mod2$lambda_recrud))

# CQ+PMQ
prob_labels_raw_CQPMQ = array(dim = c(4,length(Ts)))
# Reinfection
prob_labels_raw_CQPMQ[1,] =
  exp(mean(thetas_mod2$log_p_PMQ))*
  dexp(Ts, rate = mean(thetas_mod2$lambda));
# Early Relapse
prob_labels_raw_CQPMQ[2,] =
  exp(mean(thetas_mod2$log_1m_p_PMQ))*
  exp(mean(thetas_mod2$log_1m_c1_CQ_PMQ))*
  exp(mean(thetas_mod2$log_EarlyL))*
  dweibull(Ts , shape = mean(thetas_mod2$CQ_shape),
```

```
          scale = mean(thetas_mod2$CQ_scale))
# Late Relapse
prob_labels_raw_CQPMQ[3,] =
  exp(mean(thetas_mod2$log_1m_p_PMQ))*
  exp(mean(thetas_mod2$log_1m_c1_CQ_PMQ))*
  exp(mean(thetas_mod2$log_1m_EarlyL))*
  dexp(Ts, rate = mean(thetas_mod2$gamma))
# Recrudescence
prob_labels_raw_CQPMQ[4,] =
  exp(mean(thetas_mod2$log_1m_p_PMQ))*
  exp(mean(thetas_mod2$log_c1_CQ_PMQ))*
  dexp(Ts, rate = mean(thetas_mod2$lambda_recrud))

for(i in 1:length(Ts)){
  prob_labels_raw_AS[,i] = prob_labels_raw_AS[,i]/sum(prob_labels_raw_AS[,i])
  prob_labels_raw_CQ[,i] = prob_labels_raw_CQ[,i]/sum(prob_labels_raw_CQ[,i])
  prob_labels_raw_CQPMQ[,i] = prob_labels_raw_CQPMQ[,i]/sum(prob_labels_raw_CQPMQ[,i])
}
```

Function to compute the conditional probability of each label given the time to event.

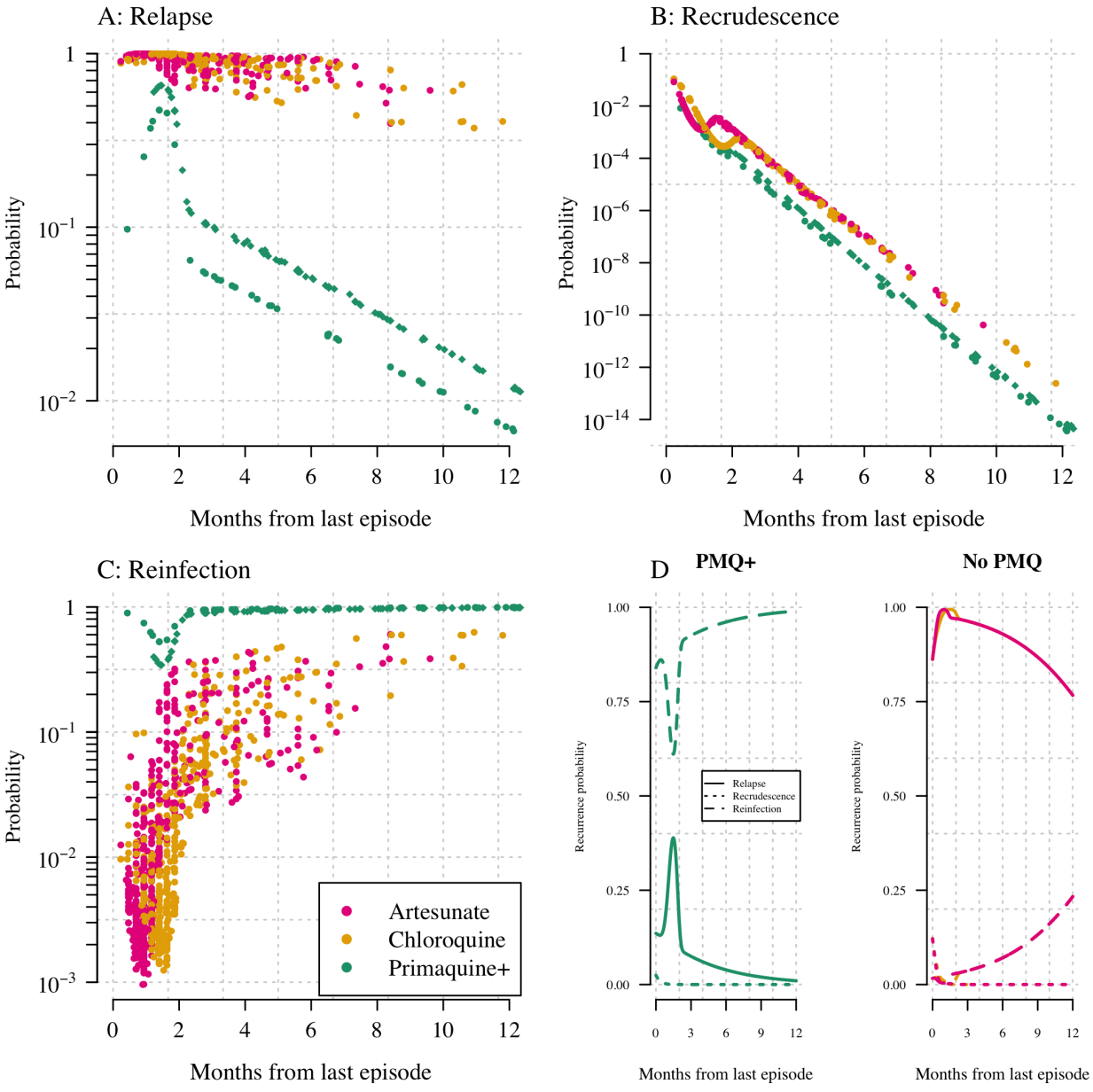
```
Label_probability = function(drug,t, thetas){

  # drug independent parameters
  q = inv.logit(mean(thetas$logit_EarlyL))

  if(drug == 'AS'){
    p = inv.logit(mean(thetas$logit_p))
    c = inv.logit(mean(thetas$logit_c1_AS))

    p_relapse = (1-p) * (1-c) * (q * dexp(x = t, rate = mean(thetas$gamma)) +
                                   (1-q) * dweibull(x = t,shape = mean(thetas$AS_shape),
                                                    scale = mean(thetas$AS_scale)))

    p_recrudes = (1-p) * c * dexp(x = t,rate = mean(thetas$lambda_recrud))

    p_reinfect = p * dexp(x = t,rate = mean(thetas$lambda))
  }
  if(drug == 'CHQ'){
    p = inv.logit(mean(thetas$logit_p))
    c = inv.logit(mean(thetas$logit_c1_CQ))

    p_relapse = (1-p) * (1-c) * (q * dexp(x = t, rate = mean(thetas$gamma)) +
                                   (1-q) * dweibull(x = t,shape = mean(thetas$CQ_shape),
                                                    scale = mean(thetas$CQ_scale)))

    p_recrudes = (1-p) * c * dexp(x = t,rate = mean(thetas$lambda_recrud))

    p_reinfect = p * dexp(x = t,rate = mean(thetas$lambda))

  }
  if(drug == 'PMQ+'){
    p = inv.logit(mean(thetas$logit_p_PMQ))
    c = inv.logit(mean(thetas$logit_c1_CQ_PMQ))
```

```
    p_relapse = (1-p) * (1-c) * (q * dexp(x = t, rate = mean(thetas$gamma)) +
                                   (1-q) * dweibull(x = t,shape = mean(thetas$CQ_shape),
                                                    scale = mean(thetas$CQ_scale)))

    p_recrudes = (1-p) * c * dexp(x = t,rate = mean(thetas$lambda_recrud))

    p_reinfect = p * dexp(x = t,rate = mean(thetas$lambda))

  }
  probs = data.frame(p_relapse=p_relapse,p_recrudes=p_recrudes,p_reinfect=p_reinfect)
  for(i in 1:nrow(probs)){
    probs[i,] = probs[i,]/sum(probs[i,])
  }

  return(probs)
}
```

```
labels2 = extract(mod2_Fit, 'prob_labels')$prob_labels

layout(mat = matrix(data = c(1,1,2,2,1,1,2,2,3,3,4,5,3,3,4,5),byrow = T,nrow = 4))
par(las=1,bty='n', cex.lab=1.3, cex.axis=1.3, mar=c(4,5,3,1), family = 'serif')

#***************************** Relapse *********************************
mean_labels_ReLap1= apply(labels2[,ind_plotting,2,drop=T], 2, mean)
mean_labels_ReLap2= apply(labels2[,ind_plotting,3,drop=T], 2, mean)
mean_labels_ReLap = mean_labels_ReLap1 + mean_labels_ReLap2
plot(Combined_Time_Data$Time_to_event[ind_plotting], log10(mean_labels_ReLap),
     col = drug_cols3[Combined_Time_Data$numeric_drug[ind_plotting]+1], xaxt='n',
     pch = mapvalues(x = Combined_Time_Data$Study_Period[ind_plotting],
                     from = 1:2,to = c(20,18)),
     cex=1,panel.first = grid(),
     ylab='',yaxt='n',
     xlab='', xlim=c(0,360))
mtext(text='A: Relapse', side = 3, adj = 0, line=0.5)
mtext(text = 'Probability',side = 2,line=3.5,cex=.8,las=3)
axis(side=2, at = -2:0, c(expression(10^-2, 10^-1),1))
axis(1, at = seq(0, 360, by=60), labels = seq(0, 360, by=60)/30)
axis(2, at = log10(seq(.1,1,by=.1)), labels = NA)
axis(2, at = log10(seq(.01,.1,by=.01)), labels = NA)
mtext(text = 'Months from last episode',side = 1,line=3,cex=.9)

#***************************** Recrudescence ***************************
mean_labels_ReCrud = apply(labels2[,ind_plotting,4,drop=T], 2, mean)
plot(Combined_Time_Data$Time_to_event[ind_plotting], log10(mean_labels_ReCrud),
     col = drug_cols3[Combined_Time_Data$numeric_drug[ind_plotting]+1], xaxt='n',
     pch = mapvalues(x = Combined_Time_Data$Study_Period[ind_plotting],
                     from = 1:2,to = c(20,18)),
     cex=1,panel.first = grid(),
     ylab='',yaxt='n',
     xlab='', xlim=c(0,360), ylim= c(min(log10(mean_labels_ReCrud)),0))
mtext(text='B: Recrudescence', side = 3, adj = 0, line=0.5)
mtext(text = 'Months from last episode',side = 1,line=3,cex=.9)
mtext(text = 'Probability',side = 2,line=3.5,cex=.8,las=3)
```

```
axis(1, at = seq(0,12,by=2)*30, labels = seq(0,12,by=2))
axis(side=2, at = c(-14, -12,-10,-8,-6,-4,-2,0),
     c(expression(10^-14,10^-12, 10^-10, 10^-8, 10^-6, 10^-4, 10^-2),1))

#***************************** Reinfection ****************************
mean_labels_Reinfection = apply(labels2[,ind_plotting,1,drop=T], 2, mean)
plot(Combined_Time_Data$Time_to_event[ind_plotting], log10(mean_labels_Reinfection),
     col = drug_cols3[Combined_Time_Data$numeric_drug[ind_plotting]+1],
     pch = mapvalues(x = Combined_Time_Data$Study_Period[ind_plotting],
                     from = 1:2,to = c(20,18)),
     cex=1,panel.first = grid(),
     ylab='', yaxt='n',xaxt='n',
     xlab='', xlim=c(0,360))
mtext(text = 'Probability',side = 2, las=3,line=3.5,cex=.8)
mtext(text = 'Months from last episode',side = 1,line=3,cex=.9)
mtext(text='C: Reinfection', side = 3, adj = 0, line=0.5)
axis(1, at = seq(0, 360, by=60), labels = seq(0, 360, by=60)/30)
axis(side=2, at = c(-3,-2,-1,0), c(expression(10^-3, 10^-2, 10^-1),1))
axis(2, at = log10(seq(.1,1,by=.1)), labels = NA)
axis(2, at = log10(seq(.01,.1,by=.01)), labels = NA)
axis(2, at = log10(seq(.001,.01,by=.001)), labels = NA)
legend('bottomright',family('serif'), inset = 0.01, lty=NA, cex=1.35,
       legend = c('Artesunate','Chloroquine','Primaquine+'),
       col=drug_cols3,pch = 20, bty='o',lwd=2,bg='white')


#******************** Plot of overall probability conditional on time to event ***********************
Recurrence_cols_PMQ = brewer.pal(4,'Greens')[2:4]
Recurrence_cols_noPMQ = brewer.pal(4,'Oranges')[2:4]

LinesTypes = c(1,3,2)
par(cex.lab=.7, cex.axis=.75)
t_points = seq(0,360,by=1)/30

# Behaviour for PMQ
PMQ_labels = Label_probability(drug = 'PMQ+',t = t_points*30, thetas = thetas_mod2)
plot(t_points, PMQ_labels[,1], lwd=2, type='l', ylim = c(0,1),
     main = 'PMQ+', col=drug_cols3['CHQ/PMQ'], panel.first = grid(),
     xlab='', ylab='Recurrence probability',yaxt='n',xaxt='n',lty=LinesTypes[1])
lines(t_points, PMQ_labels[,2], lwd=2,col=drug_cols3['CHQ/PMQ'], lty=LinesTypes[2])
lines(t_points, PMQ_labels[,3], lwd=2,col=drug_cols3['CHQ/PMQ'], lty=LinesTypes[3])
mtext(text='D', side = 3, adj = 0, line=0.5)
mtext(text = 'Months from last episode',side = 1,line=3,cex=.65)
axis(2, at = c(0,.25,.5,.75,1))
axis(1, at = c(0,3,6,9,12))

legend('right',inset = 0.01,col='black',pch = NA, bty='o',
       legend = c('Relapse','Recrudescence', 'Reinfection'),
       lwd=1,bg='white',lty=LinesTypes, cex=.6)

# Behaviour for CQ and AS
CQ_labels = Label_probability(drug = 'CHQ',t = t_points*30, thetas = thetas_mod2)
AS_labels = Label_probability(drug = 'AS',t = t_points*30, thetas = thetas_mod2)
```

```
plot(t_points, CQ_labels[,1], lwd=2, type='l', ylim = c(0,1),
     main = 'No PMQ', col=drug_cols3['CHQ'], xlab='',lty=LinesTypes[1],
     panel.first = grid(), ylab = 'Recurrence probability',xaxt='n',yaxt='n')
axis(2, at = c(0,.25,.5,.75,1))
axis(1, at = c(0,3,6,9,12))
lines(t_points, CQ_labels[,2], lwd=2,col=drug_cols3['CHQ'],lty=LinesTypes[2])
lines(t_points, CQ_labels[,3], lwd=2,col=drug_cols3['CHQ'],lty=LinesTypes[3])

lines(t_points, AS_labels[,1], lwd=2,col=drug_cols3['AS'],lty=LinesTypes[1])
lines(t_points, AS_labels[,2], lwd=2,col=drug_cols3['AS'],lty=LinesTypes[2])
lines(t_points, AS_labels[,3], lwd=2,col=drug_cols3['AS'],lty=LinesTypes[3])

mtext(text = 'Months from last episode',side = 1,line=3,cex=.65)
```



Extract probabilistic information

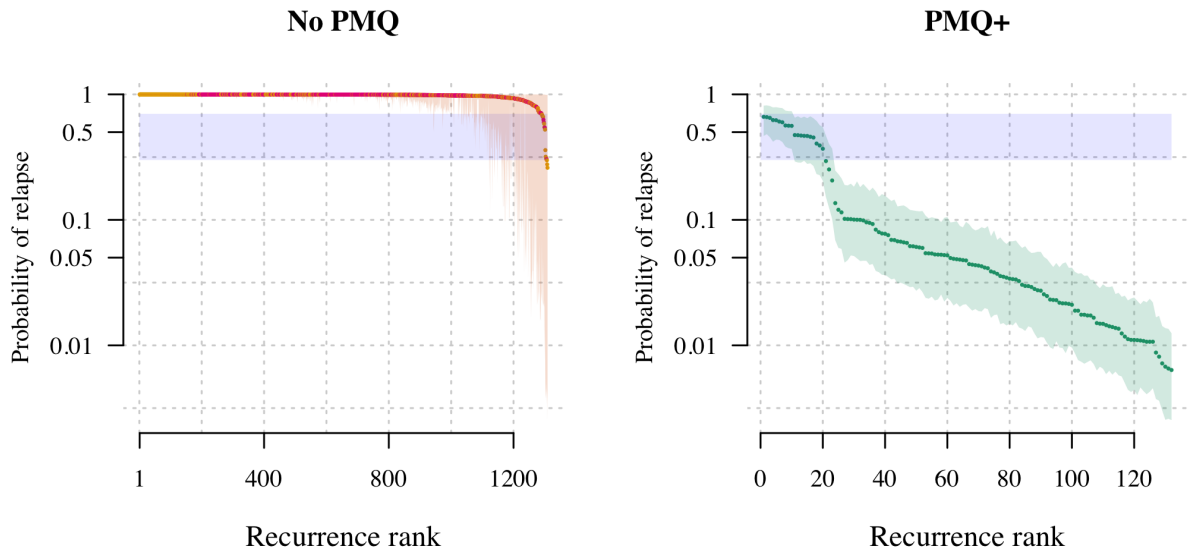
```
labels = extract(mod2_Fit, 'prob_labels')$prob_labels
# recrudescence
Combined_Time_Data$Recrudescence_mean_theta = apply(labels[,,4,drop=T],2,median)
Combined_Time_Data$Recrudescence_975_theta = apply(labels[,,4,drop=T],2,quantile,
                                                   probs = 0.975)
Combined_Time_Data$Recrudescence_025_theta = apply(labels[,,4,drop=T],2,quantile,
                                                   probs = 0.025)

# relapse
Relapse_labels = labels[,,2,drop=T] + labels[,,3,drop=T]
Combined_Time_Data$Relapse_mean_theta = apply(Relapse_labels,2,median)
Combined_Time_Data$Relapse_975_theta = apply(Relapse_labels,2,quantile, probs = 0.975)
Combined_Time_Data$Relapse_025_theta = apply(Relapse_labels,2,quantile, probs = 0.025)

# reinfection
Combined_Time_Data$ReInfection_mean_theta = apply(labels[,,1,drop=T],2,median)
Combined_Time_Data$ReInfection_975_theta = apply(labels[,,1,drop=T],2,quantile,
                                                 probs = 0.975)
Combined_Time_Data$ReInfection_025_theta = apply(labels[,,1,drop=T],2,quantile,
                                                 probs = 0.025)

# Save this for use by the genetic model
Mod2_ThetaEstimates = Combined_Time_Data
Mod2_ThetaEstimates$episode = as.integer(Mod2_ThetaEstimates$episode)
Mod2_ThetaEstimates$episode = Mod2_ThetaEstimates$episode
Mod2_ThetaEstimates$patientid = as.character(Mod2_ThetaEstimates$patientid)
Mod2_ThetaEstimates$Episode_Identifier =
  apply(Mod2_ThetaEstimates,
        1,
        function(x) {
          paste(x['patientid'], as.integer(x['episode']), sep = '_')
        } )
save(Mod2_ThetaEstimates, file = '../RData/TimingModel/MOD2_theta_estimates.RData')
```

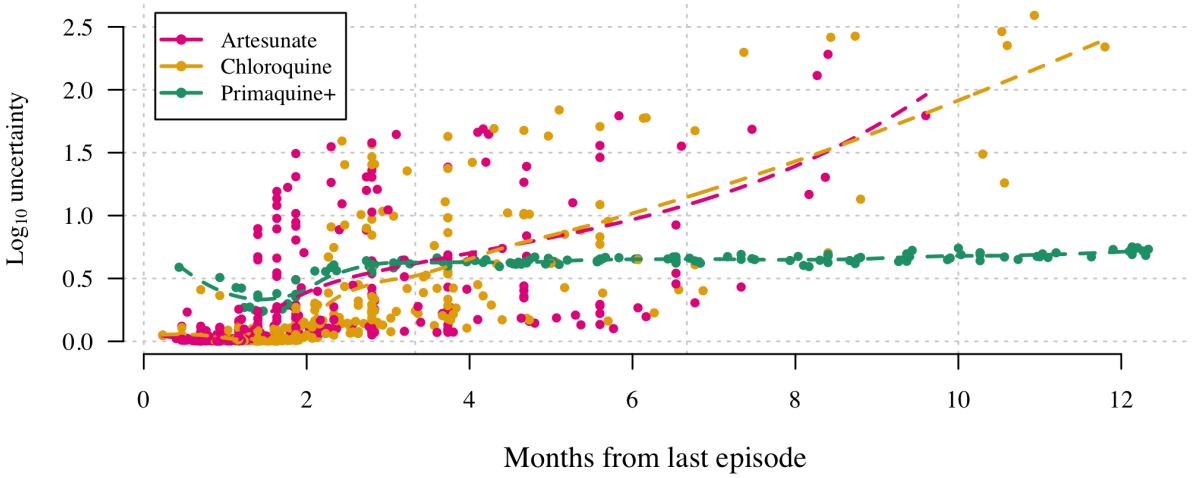
We also save a matrix of posterior samples to be used by the genetic model for full computation of the posterior:

```
labels = extract(mod2_Fit, 'prob_labels')$prob_labels
K_samples = min(100, dim(labels)[1])
random_ind = sample(1:dim(labels)[1], K_samples)
Relapse_labels = labels[random_ind,,2,drop=T] + labels[random_ind,,3,drop=T]
Post_samples_matrix = data.frame(cbind(t(labels[random_ind, ,4,drop=T]),
                                       t(Relapse_labels[, ]),
                                       t(labels[random_ind, ,1,drop=T])))
colnames(Post_samples_matrix) = c(sapply(c('C','L','I'), rep, K_samples))
Post_samples_matrix$Episode_Identifier = apply(Combined_Time_Data, 1,
                                               function(x) {
                                                 paste(x['patientid'], as.integer(x['episode']),
                                                       sep = '_')} )
save(Post_samples_matrix, file = '../RData/TimingModel/MOD2_Posterior_samples.RData')
```

```
## Threshold value for classification
Epsilon_upper = 0.7
Epsilon_lower = 0.3

transp_grey = adjustcolor('grey', alpha.f = 0.5)
transparent_blue_band = adjustcolor('blue', alpha.f = 0.1)

# Order by difference in posterior interval
Combined_Time_Data = Combined_Time_Data[order(-log10(Combined_Time_Data$Relapse_mean_theta)),]

par(las = 1, bty='n', family = 'serif')
layout(mat= matrix(data = c(1,2,3,3),nrow = 2,byrow = T))
## No PMQ group
ind = Combined_Time_Data$arm_num!='CHQ/PMQ' & !Combined_Time_Data$Censored
plot(log10(Combined_Time_Data$Relapse_mean_theta[ind]),
     ylim = c(min(log10(Combined_Time_Data$Relapse_025_theta[ind]),na.rm = T), 0),
     type='p',yaxt='n', main ='No PMQ',pch=20,cex=.3,
     ylab = 'Probability of relapse', xlab = '',panel.first = grid(),
     col = drug_cols3[Combined_Time_Data$arm_num[ind]], xaxt='n')
Nrecs = length(Combined_Time_Data$Relapse_mean_theta[ind])
polygon(x = c(0,Nrecs,Nrecs,0),
        y = log10(c(Epsilon_lower,Epsilon_lower,Epsilon_upper,Epsilon_upper)),
        col = transparent_blue_band, border = NA)
axis(1, at = c(1, 400, 800, 1200))
mtext(text = 'Recurrence rank',side = 1, line = 3)
axis(2, at = c(0:(-2),log10(0.5),log10(0.05)), labels = c(10^(0:(-2)),0.5,0.05))
polygon(c(1:sum(ind), rev(1:sum(ind))),
        y = c(log10(Combined_Time_Data$Relapse_025_theta[ind]),
              rev(log10(Combined_Time_Data$Relapse_975_theta[ind]))),
        border = NA, col = adjustcolor(drug_cols2[2],alpha.f = 0.2))

#PMQ group
ind = Combined_Time_Data$arm_num=='CHQ/PMQ' & !Combined_Time_Data$Censored
plot(log10(Combined_Time_Data$Relapse_mean_theta[ind]),
     ylim = c(min(log10(Combined_Time_Data$Relapse_025_theta[ind])), 0),
     type='p',cex=.3, yaxt='n', xlab = '',col=drug_cols2[3],
     ylab = 'Probability of relapse',panel.first = grid(),
     main = 'PMQ+', pch=20)
Nrecs = length(Combined_Time_Data$Relapse_mean_theta[ind])
polygon(x = c(0,Nrecs,Nrecs,0),
        y = log10(c(Epsilon_lower,Epsilon_lower,Epsilon_upper,Epsilon_upper)),
        col = transparent_blue_band, border = NA)
mtext(text = 'Recurrence rank',side = 1, line = 3)
axis(2, at = c(0:(-2),log10(c(0.5,0.05))), labels = c(10^(0:(-2)),0.5,0.05))
polygon(c(1:sum(ind), rev(1:sum(ind))),
        y = c(log10(Combined_Time_Data$Relapse_025_theta[ind]),
              rev(log10(Combined_Time_Data$Relapse_975_theta[ind]))),
        border = NA, col = adjustcolor(drug_cols2[3],alpha.f = 0.2))

####### Time of event versus uncertainty in the interval ******
# Time of event versus uncertainty in the interval
## No PMQ
ind = Combined_Time_Data$arm_num=='AS' & !Combined_Time_Data$Censored
```

```
df = data.frame(time=Combined_Time_Data$Time_to_event[ind],
                uncertainty=log10(Combined_Time_Data$Relapse_975_theta[ind]) -
                  log10(Combined_Time_Data$Relapse_025_theta[ind]),
                col = drug_cols3[Combined_Time_Data$arm_num[ind]], group=1)
ind = Combined_Time_Data$arm_num=='CHQ' & !Combined_Time_Data$Censored
df = rbind(df, data.frame(time=Combined_Time_Data$Time_to_event[ind],
                          uncertainty=log10(Combined_Time_Data$Relapse_975_theta[ind]) -
                            log10(Combined_Time_Data$Relapse_025_theta[ind]),
                          col = drug_cols3[Combined_Time_Data$arm_num[ind]], group=2))
ind = Combined_Time_Data$arm_num=='CHQ/PMQ' & !Combined_Time_Data$Censored
df = rbind(df, data.frame(time=Combined_Time_Data$Time_to_event[ind],
                          uncertainty=log10(Combined_Time_Data$Relapse_975_theta[ind]) -
                            log10(Combined_Time_Data$Relapse_025_theta[ind]),
                          col = drug_cols3[Combined_Time_Data$arm_num[ind]], group=3))
# permute the rows for better visualisation
set.seed(653467)
df = df[sample(1:nrow(df), size = nrow(df), replace = F),]

plot(df$time,df$uncertainty,  xaxt='n',
     ylab = expression('Log'[10]*' uncertainty'), panel.first = grid(),
     col = df$col,pch=20, xlab='', main = '')
axis(1, at = seq(0,360, by = 60), labels = seq(0,360,by=60)/30)
mtext(text = 'Months from last episode',side = 1, line = 3)

# add spline fits to show trends

f = loess(uncertainty ~ time, df[df$group==1,])
lines(0:400, predict(f, data.frame(time=0:400)),lwd=2,lty=2, col = drug_cols3['AS'])
f = loess(uncertainty ~ time, df[df$group==2,], span = .32)
lines((0:400), predict(f, data.frame(time=0:400)),lwd=2,lty=2, col = drug_cols3['CHQ'])
f = loess(uncertainty ~ time, df[df$group==3,], span = .32)
lines((0:400), predict(f, data.frame(time=0:400)),lwd=2,lty=2, col = drug_cols3['CHQ/PMQ'])

legend('topleft',legend = c('Artesunate',
                            'Chloroquine',
                            'Primaquine+'),
       col=drug_cols3,pch = 20, bty='o',lwd=2,bg='white',lty=1,
       family('serif'), inset = 0.03, cex=0.9)
```





Some rough calculations to make sure we're not completely off track with the model output

```
## No radical cure: episodes per year:  3.97
## Radical cure: episodes per year:  0.2
## AS patients had a total follow-up of 161 years and 722 observed recurrences
## CQ patients had a total follow-up of 169 years and 587 observed recurrences
## PMQ+ patients had a total follow-up of 677 years and 132 observed recurrences
## PMQ+ patients in VHX had a total follow-up of 155 years and 40 observed recurrences
## PMQ+ patients in BPD had a total follow-up of 522 years and 92 observed recurrences
```

We look at weighted averages of relapses, recrudescences and reinfections. We pick 500 random draws from the posterior to calculate credible intervals.

The labels on the observed recurrences along with 95% credible intervals:

```
## Relapses are approximately  96.1 ( 94.3 - 97.3 ) % of recurrences after AS
## Recrudescences are approximately  0.3 ( 0.2 - 0.5 ) % of recurrences after AS
## Reinfections are approximately  3.6 ( 2.4 - 5.4 ) % of recurrences after AS
## Relapses are approximately  95 ( 92.9 - 96.7 ) % of recurrences after CQ
## Recrudescences are approximately  0.2 ( 0.1 - 0.3 ) % of recurrences after CQ
## Reinfections are approximately  4.8 ( 3.1 - 6.9 ) % of recurrences after CQ
## Relapses are approximately  12.2 ( 9.2 - 15.5 ) % of recurrences after PMQ+
## Recrudescences are approximately  0.01 ( 0.01 - 0.02 ) % of recurrences after PMQ+
## Reinfections are approximately  87.8 ( 84.5 - 90.8 ) % of recurrences after PMQ+
##
## VHX: Relapses are approximately  9.2 ( 6.4 - 12.2 ) % of recurrences after PMQ+
## VHX: Recrudescences are approximately  0.03 ( 0.01 - 0.06 ) % of recurrences after PMQ+
## VHX: Reinfections are approximately  90.8 ( 87.8 - 93.6 ) % of recurrences after PMQ+
## BPD: Relapses are approximately  13.5 ( 10.1 - 17.3 ) % of recurrences after PMQ+
## BPD: Recrudescences are approximately  0.01 ( 0 - 0.01 ) % of recurrences after PMQ+
## BPD: Reinfections are approximately  86.5 ( 82.7 - 89.9 ) % of recurrences after PMQ+
```

```
toc()
```

```
## 84.561 sec elapsed
```