

Introduction

Background

- Lassa fever is an hemorrhagic fever caused by Lassa virus. No vaccine is approved and only ribavirin (RBV) is recommended despite limited efficacy (1).
- Favipiravir (FPV) showed a high viral efficacy, with 100% survival obtained in an otherwise fully lethal non-human primate model of Lassa fever (2).

Objectives

- The aim of this work was to characterize with mathematical models the host-pathogen-drugs interaction, determine modes of action of the drugs and extrapolate the findings to human setting.

Methods

Data

- 24 female cynomolgus macaques infected with Lassa virus, Strain Josiah. 8 treated with RBV, 8 with FPV for 14 days, starting at D4 post-infection.
- Measurements of RNA viral load and infectious virus (TCID₅₀)

PK-VK model selection

- Models to describe LASV disease dynamics:
 - Target-cell limited model with immune compartment F rendering cells refractory to the infection
 - Determination of FPV and RBV mode of action against LASV: Evaluation of 4 structural models, in which FPV and RBV were supposed to either block viral production or decrease infectious virus proportion.
 - Challenging initial hypothesis of a refractory effect of the immune response
- At each step the model providing the best improvement of the likelihood of the viral load data was selected.
- Model averaging (3) was performed to take into account model uncertainty on FPV Hill coefficient κ .
- Parameter estimation was performed using non-linear mixed effect models with SAEM algorithm implemented in Monolix (4).

Results

Viral kinetic model, immune response and drug's modes of action

- A model assuming that both FPV and RBV decreased infectious virus provided the best description of LASV viral load and TCID₅₀ as well as TCID₅₀/RNA ratio.
- Assumption that innate response (F compartment) rendered cells refractory to the infection consistently improved data fitting over all other tested immune response effect.

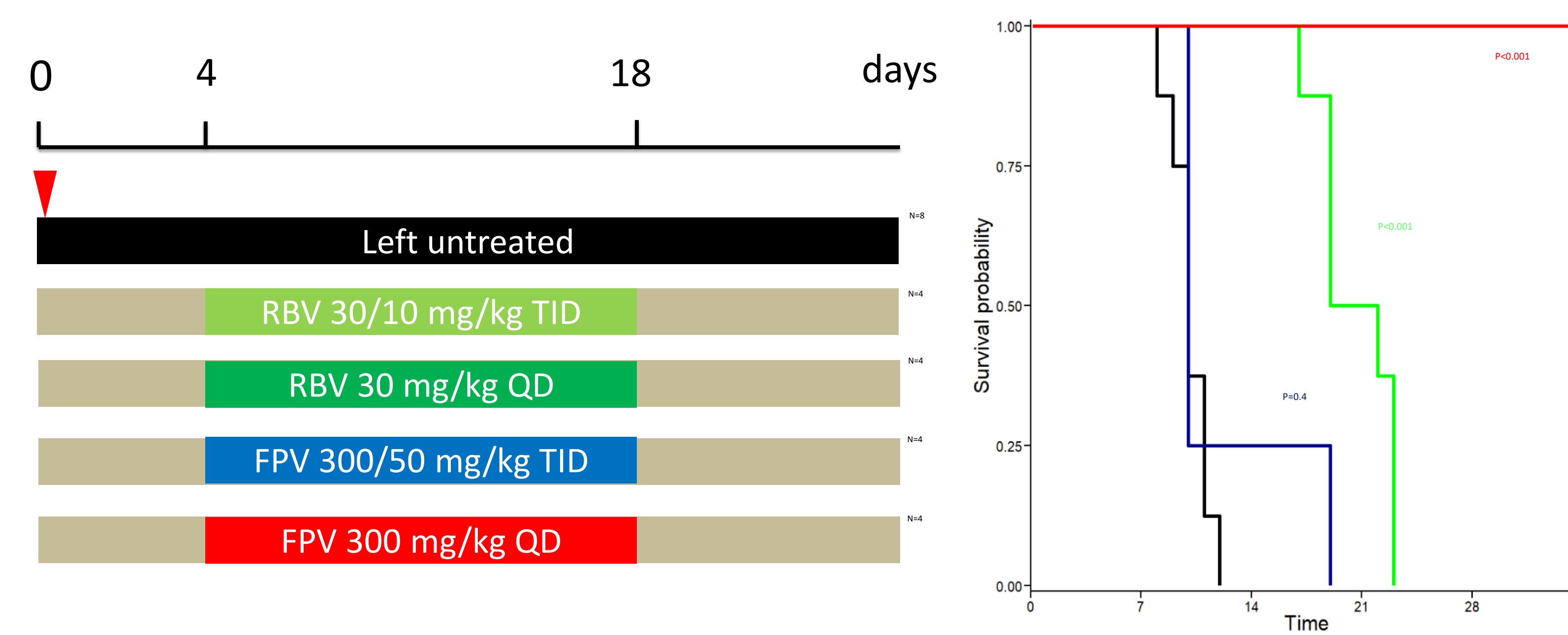


Figure 1. Left: design of the NHP experiment. Right: Survival curves. Log-rank test was performed to evaluate survival differences against control group.

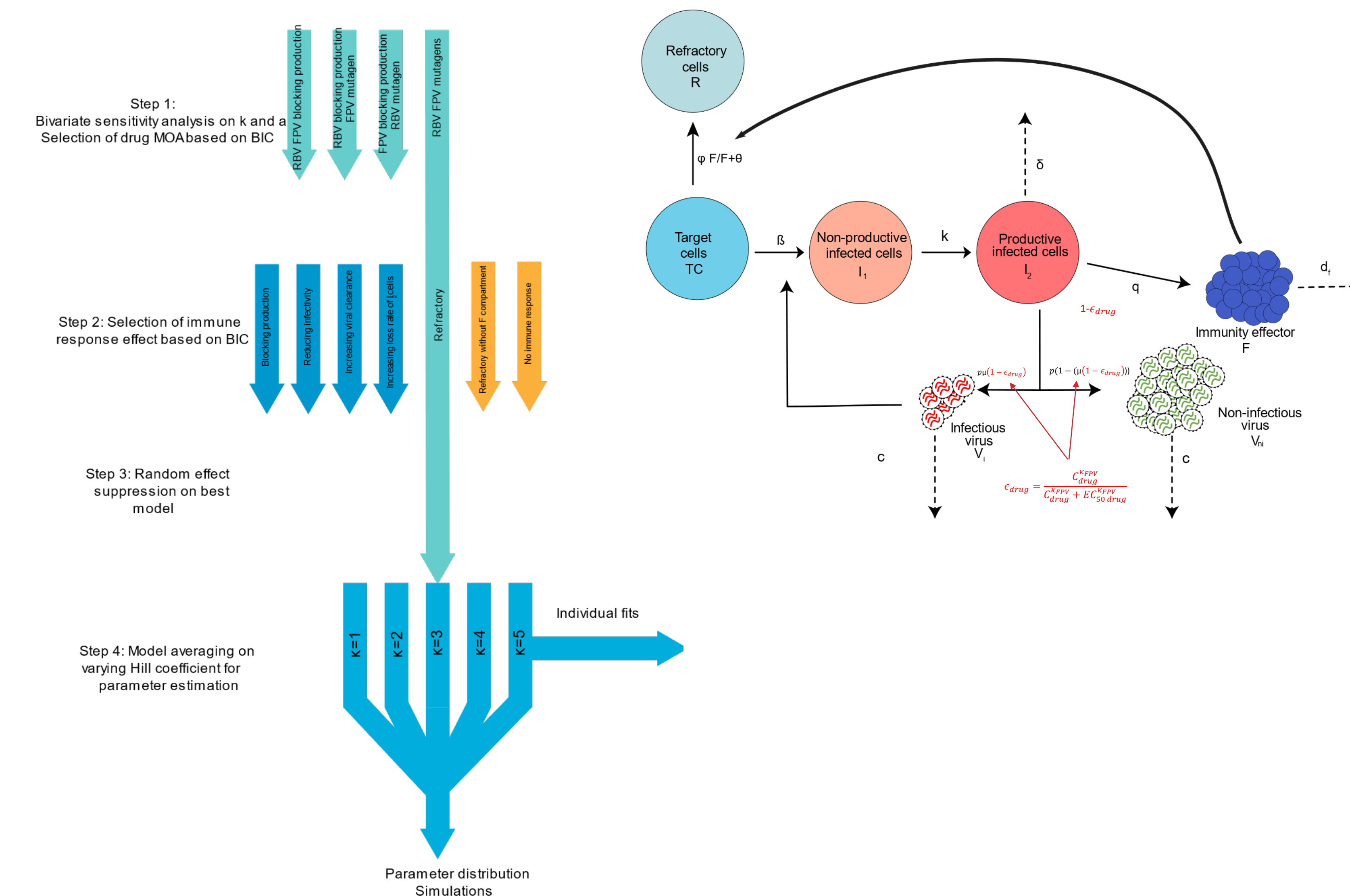


Figure 2. Model building strategy.

Figure 3. Final PK-VK model of LASV infection in cynomolgus macaques treated by favipiravir or ribavirin.

Parameter estimation

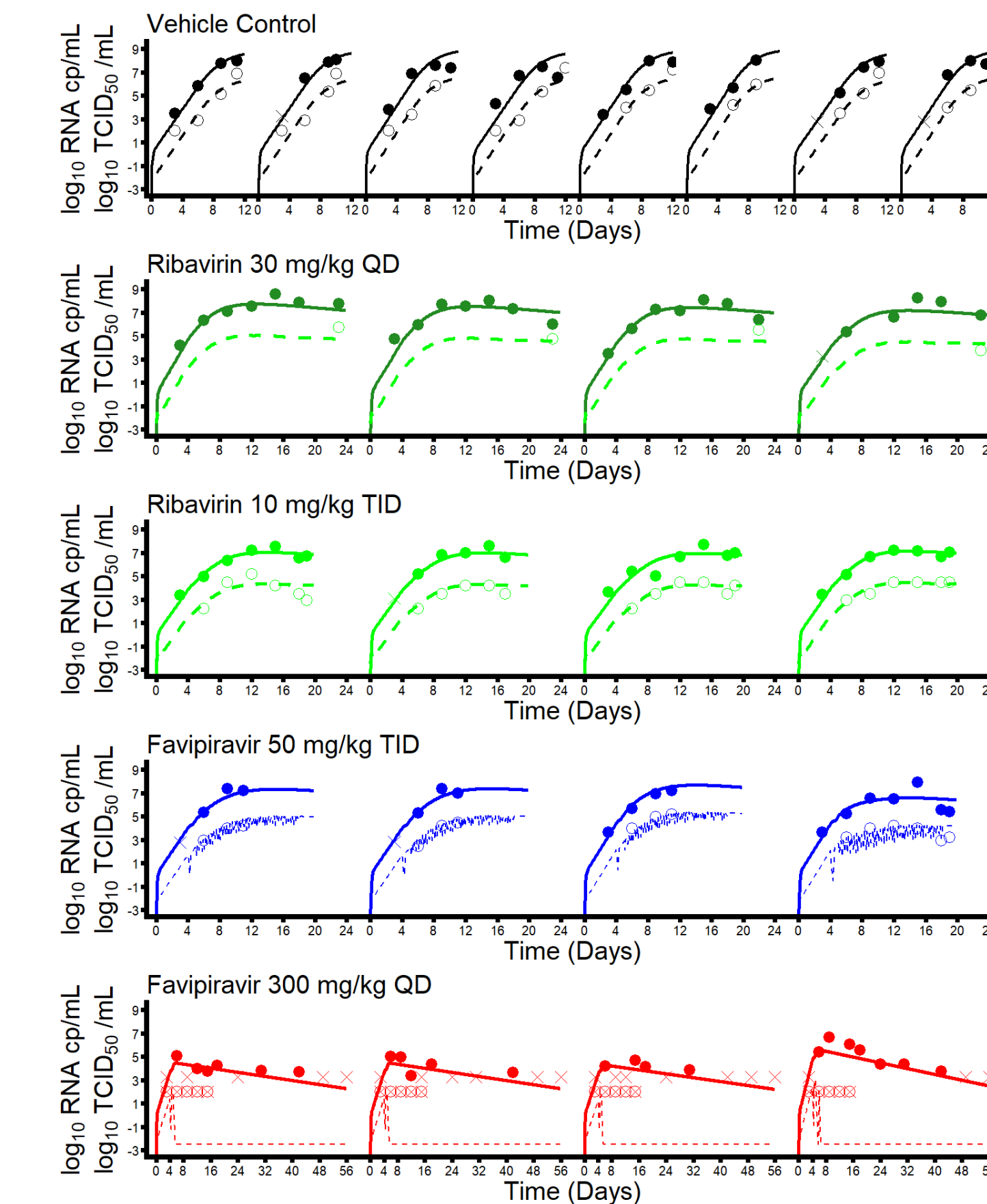
- In vivo* EC₅₀ of RBV and FPV were estimated at 2.96 and 2.89 $\mu\text{g/mL}$, giving average efficacies of 80 and 91% for RBV and high dose FPV respectively, in reducing infectious virus proportion.

Results

- FPV was associated with a high sigmoidicity ($\kappa = 5$ providing the best fit of the data).
- Cure boundary (no more infections when infectious virus < 1 TCID₅₀ in the whole blood volume) was reached at D5 post infection (D2 of treatment)

Figure 4. Individual fits of viral load (plain lines) and viral titers (dashed line) for best model considered.

Plain circles represent observed viral loads and empty circles represent observed viral TCID₅₀. Data below the limit of detection were represented by crosses (RNA viral load) or crossed empty circles (viral titers).



Model simulations

- Clinically relevant concentrations of FPV (5) would have a great impact on infectious viral load (Figure 5).
- Treatment initiated early would make infectious viral load reach cure boundary.

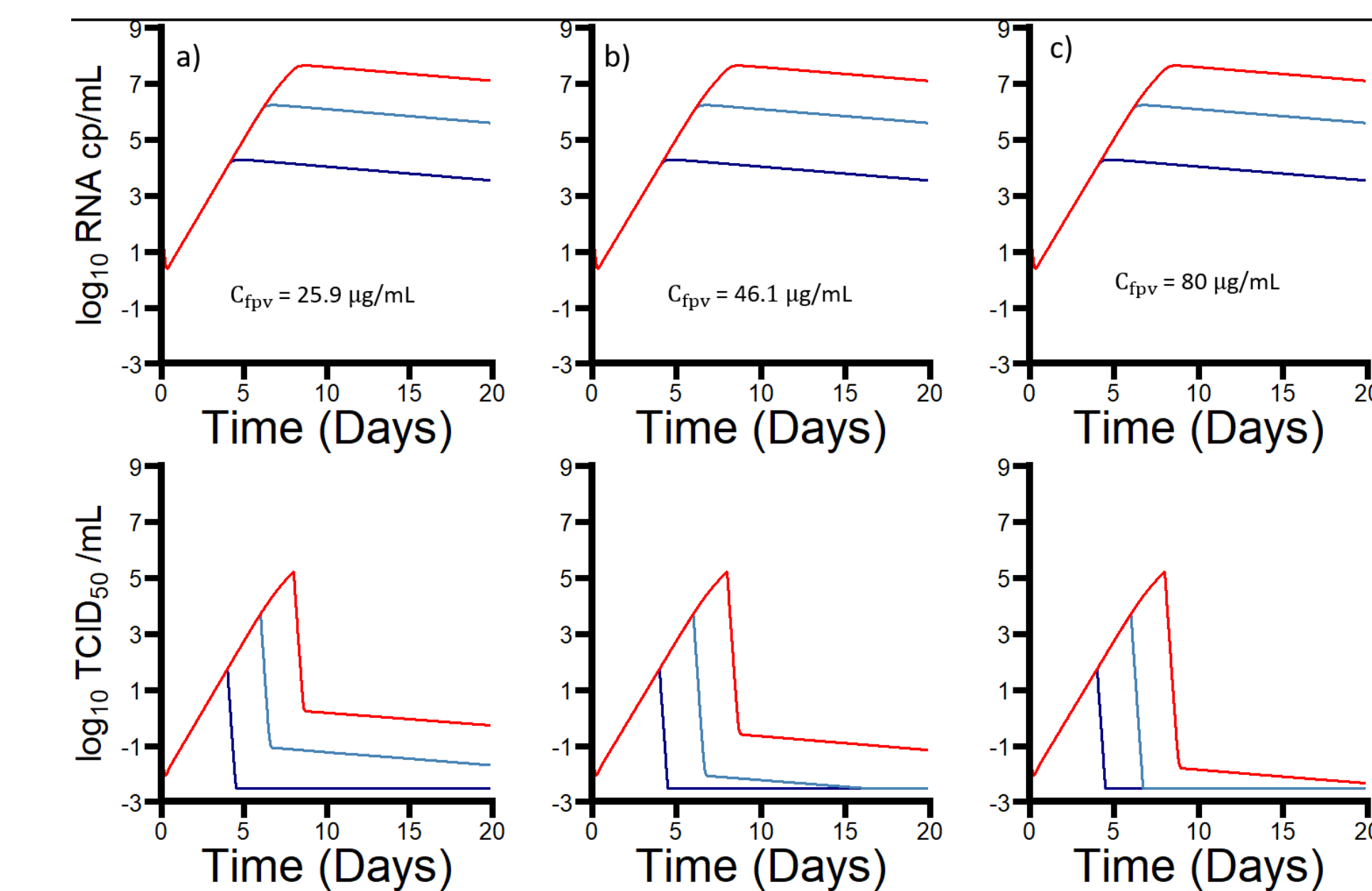


Figure 5. Mutagenesis model simulations. Constant favipiravir plasmatic concentration (a-c) or constant ribavirin plasmatic concentration (d). Treatment started at D4 (navy blue), D6 (blue), or D8 (red)

Conclusion

- High dose favipiravir initiated 4 days post-infection had a very consequent impact on infectious viral load and subsequent cell infection, with average $\epsilon \approx 91\%$ at 300 mg/kg QD.
- Best fit to the data was obtained when considering FPV and RBV to reduce the infectious viruses proportion, and with an immune response rendering target cells refractory to the infection.
- Model predicts that residual concentrations obtained in humans at 1200mg/kg BID would have a great antiviral efficacy, even when started late in the disease.