Mathematical Modeling of Antiviral Drug Mechanisms, GHP-88309 and ERDRP-0518, for Measles Treatment

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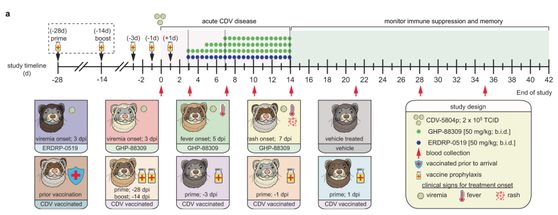
Background

- After the COVID-19 pandemic, over 40 million children worldwide are at risk for measles (MeV).
- The lasting immunosuppression presents a major health threat, especially for low and middle income countries, and treatment options are needed.
- Currently, experimental insight is lacking into the time window for prevention of MeV.
- The manuscript by Cox et al. uses a canine distemper virus model as a surrogate for measles, and treats them with GHP-88309, ERDRP-0519, or therapeutic vaccination.
- We aim to characterize the infection and efficacy of the drug treatments.

Experimental Setup



(Taken from Cox et al. (2024) Nat. Comm.)

Mathematical Model

$$\begin{aligned}\frac{dT}{dt} &= \lambda T\left(1-\frac{T}{K}\right)-\beta TV\\ \frac{dE}{dt} &= \beta TV - kE\\ \frac{dI}{dt} &= kE-\delta I\\ \frac{dV}{dt} &= pI-cV.\end{aligned}$$

- Uninfected target cells, T, infected with virus, V at infection rate, β.
- Target cells replicate with growth rate λ up to carrying capacity, K.
- After infection, cells enter eclipse phase, E, (infected, not virus producing).
- After time $1/k$, cells become infectious, I and produce virus at production rate, p.

Determining Parameters

The mathematical model was fitted to the experimental data

- PBMC associated viremia titers of CDV infected ferrets.
- Lymphocyte counts from infected ferrets The virus and target cell curves will be used to determine the parameters of the model.

Fitting was done via the minimization of the sum of squared residuals (SSR), given by

$$\mathrm{SSR}=\sum_{i=1}^{n}\left(y_i-f(t_i;\theta)\right)^2.$$

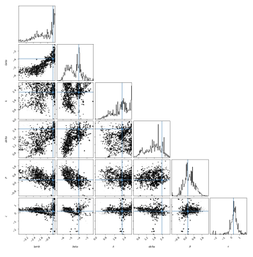
Monte Carlo Markov Chain

Errors in the parameter fits were estimated through MCMC.

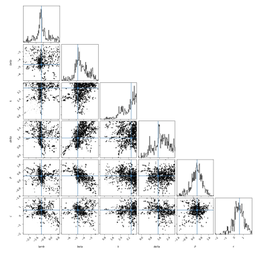
- Monte Carlo: performs simulation to generate lots of samples to approximate a quantity.
- Markov Chain: probability of next event depends only on the current event.
- In this case we use the process to find combinations of parameters that would fit our data to within the same error
- MCMC provides a range of values where the true parameter lies, allowing for an overall more accurate estimation of parameters

Conducting MCMC

Corner plots are generated to show the relationships between different parameters estimated through MCMC sampling.



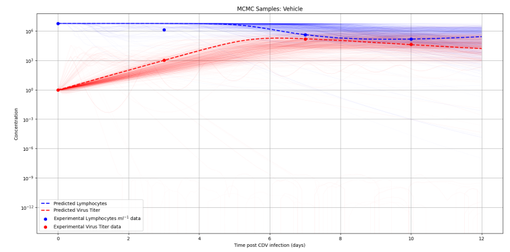
ERDRP-0519 (3 dpi) (n=3)



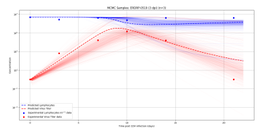
GHP-88309 (3 dpi) (n=3)

Distribution of Possible Fits

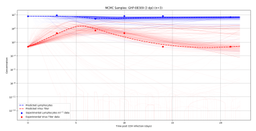
MCMC-generated lines represent distribution of possible fits



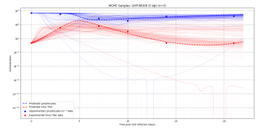
Vehicle (n=3)



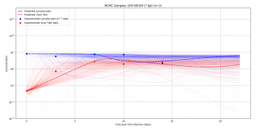
ERDRP-0519 (3 dpi) (n=3)



GHP-88309 (3 dpi) (n=3)



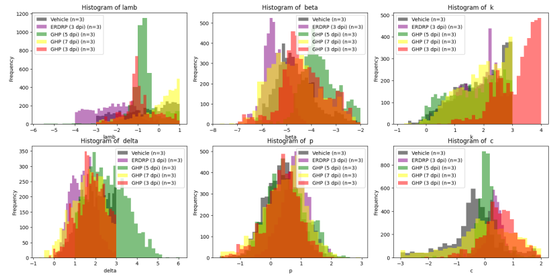
GHP-88309 (5 dpi) (n=3)



GHP-88309 (7 dpi) (n=3)

Visualizing Parameter Distributions

Using histograms, we can show the estimated parameters across MCMC trials for each dataset. By looking at the differences in parameter values between the datasets, we can directly compare how each treatment influences infection dynamics.



Key Comparisons

- λ, cell growth rate, was lower in vehicle and ERDRP-0519 groups, suggesting GHP-88309 enhances cell growth rate
- ERDRP-0519 showed lower β, infection rate, indicating potential blocking of viral entry into the cell
- GHP-88309 (3 dpi) showed a significant increase in k value, suggesting faster transition from eclipse phase to actively infectious
- Lower δ for GHP-88309 (5 dpi) indicates higher rate of infected cell death
- GHP-88309 treatments and ERDRP-0519 had higher c values, suggesting enhanced viral clearance

Conclusions

- Both drugs are potentially effective measles treatment options, with ERDRP-0519 having a direct antiviral effect and GHP-88309 aiding in immune recovery
- These insights provide a foundation for optimizing treatment strategies and highlight the potential for both drugs to combat measles and related morbillivirus infections

Future Directions

- We can conduct a Mann-Whitney U test to compare the parameter values from the control (vehicle) dataset to those from each antiviral treatment
- This allows us to test whether there is a statistically significant difference between the parameters of the control and treatment groups
- Overall, this would provide more insight into how effective an antiviral drug is

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With millions of children at risk of measles after the COVID-19 pandemic, treatments options are urgently needed. We analyzed data from a ferret-based model to evaluate two antiviral drug treatments. Using a mathematical model, we revealed that GHP-88309 aided in body recovery, cell-growth, and virus clearance while ERDRP-0519 prevented entry of virus. These findings enhance measles treatment strategies.